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Short communication

Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea

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ABSTRACT

The purpose of this study was to examine the physiological mechanisms of persistent dyspnoea in COVID-19 survivors. Non-critical patients (n = 116) with varying degrees of COVID-19 severity reported persistent symptoms using a standardized questionnaire and underwent pulmonary function and 6-minute walk testing between 30 and 90 days following the onset of acute COVID-19 symptoms. Patients were divided into those with (n = 70) and without (n = 46) persistent dyspnoea. Patients with persistent dyspnoea had significantly lower FVC (p = 0.03), FEV1 (p = 0.04), D LCO (p = 0.01), 6-minute walk distance (% predicted, p = 0.03), and end-exercise oxygen saturation (p < 0.001), and higher Borg 0-10 ratings of dyspnoea and fatigue (both p < 0.001) compared to patients without persistent dyspnoea. We have shown that dyspnoea is a common persistent symptom across varying degrees of initial COVID-19 severity. Patients with persistent dyspnoea had greater restriction on spirometry, lower D LCO, reduced functional capacity, and increased exertional desaturation and symptoms. This suggests that there is a true physiological mechanism that may explain persistent dyspnoea after COVID-19.

1. Introduction

Emerging research shows a burden of chronic symptoms and reduced quality of life in coronavirus disease 2019 (COVID-19) survivors (Carfi et al., 2020; Garrigues et al., 2020; Wong et al., 2020). Approximately half of patients recovering from COVID-19 report chronic dyspnoea 2–3 months after infection (Carfi et al., 2020; Garrigues et al., 2020; Wong et al., 2020). Dyspnoea is an independent predictor of morbidity and mortality in the general population and is associated with reduced functional capacity and adverse health-related quality-of-life (Laviolette et al., 2014). This complex and multidimensional symptom can result in a downward spiral of activity avoidance, deconditioning, and ultimately the inability to perform basic activities of daily living (Moxham and Jolley, 2009). Whether COVID-19 survivors with persistent dyspnoea ultimately enter this downward spiral is unknown. More research is needed to understand the mechanisms of persistent dyspnoea in survivors of COVID-19 in order to improve patient management following infection.

A growing body of literature indicates the presence of racial and ethnic disparities in COVID-19-related infections and hospitalizations (Mackey et al., 2020; Ogedegbe et al., 2020). A recent systematic review concluded that Hispanic populations experience a disproportionate burden of severe COVID-19 and have increased mortality (Mackey et al., 2020). Racial and ethnic disparities may be at least partly attributable to the higher rates of comorbidities that worsen COVID-19 outcomes. Mexico has a high prevalence of chronic non-communicable diseases (Parra-Rodriguez et al., 2020), with diabetes, obesity, and the presence

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of more than one comorbidity all being independently associated with laboratory-confirmed COVID-19, need for hospitalization, and adverse outcomes (Giannouchos et al., 2020). Unfortunately, there is limited data on persistent COVID-19 symptoms, and particularly dyspnoea, in this population. Understanding differences in pulmonary function, comorbidities, and functional capacity between those with and without persistent dyspnoea may provide insight into the mechanisms of this symptom in individuals who are susceptible to the negative lasting effects of COVID-19. Accordingly, the purpose of this study was to compare spirometry, diffusing capacity of the lungs for carbon monoxide (D\textsubscript{LCO}), and 6-minute walk distance (6MWD) in Mexican survivors of COVID-19 with and without persistent dyspnoea. We hypothesized that COVID-19 patients with persistent dyspnoea would have lower forced vital capacity (FVC), D\textsubscript{LCO}, and 6MWD compared to patients without persistent dyspnoea, suggesting a physiologic driver of this persistent symptom.

2. Material and methods

This study received ethical approval (#2020-024) from the Hospital Regional de Alta Especialidad de la Peninsula de Yucatan and all patients provided written informed consent. Non-critically ill patients who tested positive for SARS-CoV-2 based on real-time reverse transcriptase-polymerase chain reaction on nasal swabs were identified from hospital records and subsequently contacted to participate. COVID-19 severity was classified as mild (ambulatory without hypoxemia), moderate (ambulatory but requiring supplemental \textit{O\textsubscript{2}} of \textless 5 L/min), or severe (hospitalized with \textit{O\textsubscript{2}} \textgreater 5 L/min and in the prone position for at least 12 h per day but without invasive mechanical ventilation). Follow-up testing occurred between 30 and 90 days after the onset of acute COVID-19 symptoms. Following the administration of a standardized questionnaire to determine the presence or absence of persistent symptoms (see list in Table 1) (Carfi et al., 2020), participants completed spirometry, D\textsubscript{LCO}, and a 6-minute walk test (6MWT) according to recommended guidelines (Holland et al., 2014; MacIntyre et al., 2005; Miller et al., 2005) with data being expressed relative to predicted values (Enright and Sherrill, 1998; Hankinson et al., 1999; Stanojevic et al., 2017). Spirometry and D\textsubscript{LCO} were performed using calibrated equipment (Ultima PFT\textsuperscript{TM} Pulmonary Function System, Medical Graphics, UK or Easy One Pro\textsuperscript{®}, ndd Medical Technologies, Switzerland). Peripherial oxygen saturation via finger oximetry (Masimo RAD 5; Masimo Corporation, USA) was measured throughout the 6MWT. Independent \textit{t}-tests and Fisher’s Exact test were used where appropriate to compare groups with and without persistent dyspnoea and fatigue. A \textit{p}-value <0.05 was considered statistically significant. Data are presented as mean ± SD unless otherwise specified.

3. Results

This study included 186 COVID-19 patients with non-critical illness. There was no difference in the time of experimental testing relative to the onset of COVID-19 symptoms comparing those with and without dyspnoea (59 ± 13 vs. 60 ± 14 days, respectively). Table 1 shows anthropometric data, comorbidities, persistent symptoms, pulmonary function, and 6MWT data for the entire group and in those with and without persistent dyspnoea. Persistent dyspnoea occurred in 38 % of patients, which was the second most common persistent symptom after fatigue (67 %). The percentage of patients with mild, moderate, and severe COVID-19 (see Table 2 for descriptive characteristics of severity subgroups) was 27, 14, and 59 %, respectively, with a relatively similar distribution in the dyspnoea (21, 23, and 56 %, respectively) and non-dyspnoea groups (31, 9, and 60 %, respectively). The dyspnoea and non-dyspnoea groups had similar age, sex, height, mass, body mass index, and frequency of comorbidities. Patients with persistent dyspnoea were more likely to experience persistent fatigue, chest pain, and anosmia/ageusia compared to their non-dyspnoea counterparts (all \textit{p} < 0.05). Pulmonary function data shows that patients with persistent dyspnoea had significantly lower FVC (\textit{p} = 0.03), forced expiratory volume in 1 s (FE\textsubscript{1}, \textit{p} = 0.01), and D\textsubscript{LCO} \textit{p} = 0.01 with 47 % having a restrictive ventilatory pattern compared to 33 % in the non-dyspnoea group. Patients with persistent dyspnoea also had lower %predicted 6MWD (\textit{p} = 0.03) and end-exercise oxygen saturation during the 6MWT (\textit{p} < 0.001) compared to non-dyspnoea patients. Borg 0-10 ratings of dyspnoea and fatigue at the end of the 6MWT were significantly higher in those with persistent dyspnoea compared to those without (both \textit{p} < 0.001). A secondary analysis was performed to compare those with and without persistent fatigue given the high prevalence of this symptom (Table 3). There were no statistically significant differences in pulmonary function or 6MWD between fatigue groups, although the group with persistent fatigue had higher Borg 0-10 ratings for dyspnoea and fatigue during the 6MWT (both \textit{p} < 0.01) and were more likely to experience persistent dyspnoea (\textit{p} < 0.001), myalgias (\textit{p} < 0.001), and rhinitis (\textit{p} < 0.05) compared to the group without persistent fatigue.
19. Our results suggest that patients with persistent dyspnoea show 
future evaluation and management of people recovering from COVID-
symptoms, pulmonary function, and functional capacity in non-
persistent fatigue (Table 3), we do not see group differences in FVC, 
increased restrictive pattern may have contributed, at least in part, to 
critically ill COVID-19 survivors with and without persistent dysp 

4. Discussion

Pulmonary Function

FVC, %predicted 94 ± 13 84 ± 14 78 ± 19
FEV1, %predicted 96 ± 14 89 ± 16 84 ± 19
FEV1/FVC, % 83 ± 5 83 ± 5 86 ± 9
PEF25–75%, %predicted 104 ± 34 107 ± 35 101 ± 35
DCO2, % predicted 112 ± 23 107 ± 26 89 ± 26
VA, % predicted 99 ± 15 95 ± 11 88 ± 17

Distance, m 493 ± 74 428 ± 97 436 ± 111
Distance, % predicted 83 ± 13 82 ± 19 83 ± 21
Peak Heart Rate, bpm 110 ± 16 117 ± 17 109 ± 19
End-exercise SpO2, % 97 ± 2 94 ± 3 95 ± 3
Peak Dyspnoea, Borg 0–10 1.9 ± 1.1 2.5 ± 1.1 2.1 ± 1.6
Peak Fatigue, Borg 0–10 2.2 ± 1.5 3.4 ± 2.0 1.5 ± 1.7

Table 2

Participant Characteristics.

| Mild | Moderate | Severe |
|------|----------|--------|
| n (51) | n (26) | n (109) |
| Age, years | 42 ± 11 | 54 ± 12 | 48 ± 14 |
| Sex, %male | 53 | 50 | 68 |
| Height, cm | 161 ± 11 | 158 ± 12 | 158 ± 12 |
| Mass, kg | 77 ± 18 | 79 ± 12 | 83 ± 21 |
| BMI, kg/m² | 29 ± 6.7 | 31.7 ± 4.7 | 32.8 ± 6.9 |
| Smoking history, % | 39 | 31 | 14 |

| Comorbidities | | | |
| Obesity, % | 39 | 46 | 59 |
| Hypertension, % | 10 | 12 | 27 |
| Diabetes, % | 5 | 8 | 22 |
| Other, % | 6 | 12 | 7 |

| COVID-19 Symptoms | | | |
| Fatigue on effort, % | 59 | 73 | 70 |
| Dyspnoea, % | 29 | 62 | 36 |
| Myalgias, % | 31 | 38 | 30 |
| Cough, % | 31 | 38 | 28 |
| Chest Pain, % | 18 | 38 | 34 |
| Sore throat, % | 12 | 19 | 18 |
| Sputum Production, % | 12 | 19 | 18 |
| Diaphoresis, % | 18 | 19 | 17 |
| Headache, % | 18 | 4 | 17 |
| Rhinitis, % | 18 | 12 | 15 |
| Telogen Effluvium, % | 18 | 15 | 6 |
| Anosmia/Ageusia, % | 12 | 15 | 10 |

Table 3

Participant Characteristics.

| Mild | Moderate | Severe |
|------|----------|--------|
| n (125) | n (61) |
| Age, years | 48 ± 13 | 46 ± 13 |
| Sex, %male | 62 | 59 |
| Height, cm | 159 ± 12 | 159 ± 10 |
| Mass, kg | 80 ± 19 | 82 ± 20 |
| BMI, kg/m² | 31.7 ± 6.8 | 32.1 ± 6.3 |
| Smoking history, % | 22 | 18 |

| Disease severity, n (mild, moderate, severe) | 30, 19, 76 | 21, 7, 33 |

| Comorbidities | | | |
| Obesity, % | 51 | 52 |
| Hypertension, % | 21 | 18 |
| Diabetes, % | 22 | 2 |
| Other, % | 9 | 5 |

| COVID-19 Symptoms | | | |
| Fatigue on effort, % | 100 | 0 |
| Dyspnoea, % | 47 | 18 |
| Myalgias, % | 40 | 15 |
| Cough, % | 34 | 23 |
| Chest Pain, % | 34 | 21 |
| Sore throat, % | 20 | 10 |
| Sputum Production, % | 18 | 13 |
| Diaphoresis, % | 18 | 15 |
| Headache, % | 18 | 10 |
| Rhinitis, % | 19 | 7 |
| Telogen Effluvium, % | 11 | 10 |
| Anosmia/Ageusia, % | 14 | 7 |

| Dermatological symptoms, % | 13 | 10 |
| Wheeling, % | 7 | 7 |
| Conjunctivitis, % | 6 | 2 |
| Diarrhea, % | 3 | 3 |

| Pulmonary Function | | | |
| FVC, %predicted | 94 ± 13 | 84 ± 14 | 78 ± 19 |
| FEV1, %predicted | 96 ± 14 | 89 ± 16 | 84 ± 19 |
| FEV1/FVC, % | 83 ± 5 | 83 ± 5 | 86 ± 9 |
| PEF25–75%, %predicted | 104 ± 34 | 107 ± 35 | 110 ± 35 |
| DC02, % predicted | 112 ± 23 | 107 ± 26 | 89 ± 26 |
| VA, % predicted | 99 ± 15 | 95 ± 11 | 88 ± 17 |

| 6-Minute Walk Test | | | |
| Distance, m | 493 ± 74 | 428 ± 97 | 436 ± 111 |
| Distance, % predicted | 83 ± 13 | 82 ± 19 | 83 ± 21 |
| Peak Heart Rate, bpm | 110 ± 16 | 117 ± 17 | 109 ± 19 |
| End-exercise SpO2, % | 97 ± 2 | 94 ± 3 | 95 ± 3 |
| Peak Dyspnoea, Borg 0–10 | 1.9 ± 1.1 | 2.5 ± 1.1 | 2.1 ± 1.6 |
| Peak Fatigue, Borg 0–10 | 2.2 ± 1.5 | 3.4 ± 2.0 | 1.5 ± 1.7 |

BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory vol-
ume in 1 s; FEF25–75%, forced expiratory flow between 25–75% of FVC; DLCO, 
diffusion capacity of the lungs for carbon monoxide; VAS, alveolar volume; SpO2, 
peripheral oxygen saturation. Other comorbidities included metabolic syn-
drome, hypothyroidism, pulmonary hypertension, cancer, asthma, HIV, tuber-
culosis, and schizophrenia.

dyspnoea and fatigue are different. Based on the abnormal pulmonary function 
observed in the present study, we speculate that COVID-19 patients with persistent dyspnoea are more likely to have greater con-
straints on tidal volume expansion, exertional hypoxaemia; adoption of 
a more rapid and shallow breathing pattern; and higher levels of res-
piratory neural drive during cardiopulmonary exercise testing (CPET) 
compared to their non-dyspnoea counterparts, as shown in other 
restrictive lung diseases (Faisal et al., 2016). Employing CPET to assess 
mechanisms underpinning dyspnoea in other chronic lung diseases has 
provided important insights and may be valuable in characterizing pa-
tients recovering from COVID-19.

This study has some limitations. For example, we did not quantify the 
severity of persistent dyspnoea since patients were only asked to report 
the presence or absence of dyspnoea, nor did we have any information on 
symptoms, pulmonary function, and 6MWT prior to diagnosis with 
COVID-19. Additional studies are also needed to extrapolate these 
findings from a single centre to other ethnicities.
5. Conclusions

We have shown that dyspnoea is a common persistent symptom across varying degrees of initial COVID-19 severity. Patients with persistent dyspnoea had a number of abnormalities compared to well-matched patients without dyspnoea, including greater restriction on spirometry, lower $D_{LCO}$, reduced functional capacity, and increased desaturation and exertional symptoms during a 6MWT. This suggests that there is a true physiological mechanism that may explain persistent dyspnoea after COVID-19. Futures studies are needed to determine if the aforementioned abnormalities in resting pulmonary function translate into abnormal cardiorespiratory and sensory responses during exercise as well as the degree to which underlying physiologic abnormalities may be modified by therapeutic interventions such as rehabilitation programs.

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CRediT authorship contribution statement

Arturo Cortés-Telles: Conceptualization, Project administration, Supervision, Data curation, Formal analysis, Writing - review & editing.
Stephanie Lopez-Romero: Data curation, Formal analysis, Writing - review & editing.
Esperanza Figueroa-Hurtado: Data curation, Formal analysis, Writing - review & editing.
Yuri Noemi Pou-Aguilar: Data curation, Formal analysis, Writing - review & editing.
Alyson W. Wong: Writing - review & editing.
Jordan A. Guenette: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

References

Carfi, A., Bernabei, R., Landi, F., Gemelli Against COVID-19 Post-Acute Care Study Group, 2020. Persistent symptoms in patients after acute COVID-19. JAMA 324, 603–605.
Enright, P.L., Sherrill, D.L., 1998. Reference equations for the six-minute walk in healthy adults. Am. J. Respir. Crit. Care Med. 158, 1384–1387.
Faisal, A., Alghamdi, B.J., Ciavaglia, C.E., Elbehairy, A.F., Webb, K.A., Ora, J., Neder, J. A., O’Donnell, D.E., 2016. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. Am. J. Respir. Crit. Care Med. 193, 295–309.
Garrigues, E., Janvier, P., Kherabi, Y., Le Bot, A., Hamon, A., Guzie, H., Doucet, L., Berkani, S., Oliosi, E., Mallart, E., Corre, F., Zarrourk, V., Moyer, J.D., Galy, A., Honnel, V., Fantin, B., Nguyen, Y., 2020. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J. Infect. 81 e4-64.
Giannouchos, T.V., Susman, R.A., Mier, J.M., Poulos, K., Faralinos, K., 2020. Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory-confirmed COVID-19 cases. Eur. Respir. J. Online Ahead of Print.
Hankinson, J.L., Odencrantz, J.R., Fedan, K.B., 1999. Spirometric reference values from a sample of the general U.S. Population. Am. J. Respir. Crit. Care Med. 159, 179–187.
Holland, A.E., Spruit, M.A., Troosters, T., Puhan, M.A., Pepin, V., Saey, D., McCormack, M.C., Carlin, B.W., Scurba, F.C., Pitts, F., Wanger, J., Maclntyre, N., Kaminsky, D.A., Culver, B.H., Revill, S.M., Hernandes, N.A., Andrianopoulos, V., Camillo, C.A., Mitchell, K.E., Lee, A.L., Hill, C.J., Singh, S.J., 2014. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur. Respir. J. 44, 1428–1446.
Laviolette, L., Laveneziana, P., ERS Research Seminar Faculty, 2014. Dyspnoea: a multidimensional and multidisciplinary approach. Eur. Respir. J. 43, 1756–1762.
MacIntyre, N., Crapo, R.O., Viegi, G., Johnson, D.C., van der Grinten, C.P., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Enright, P., Gustafsson, P., Hankinson, J., Jensen, R., McKay, R., Miller, M.R., Navajas, D., Pedersen, O.F., Pellegrino, R., Wanger, J., 2005. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur. Respir. J. 26, 720–735.
Mackey, K., Ayers, C.K., Kondo, K.K., Saha, S., Advani, S.M., Young, S., Spencer, H., Rusek, M., Anderson, J., Veazie, S., Smith, M., Kangasara, D., 2020. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. Ann. Intern. Med. https://doi.org/10.7326/M20-6306 online ahead of print M20-6306.
Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P., Gustafsson, P., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J., 2005. Standardisation of spirometry. Eur. Respir. J. 26, 319–338.
Moxham, J., Jolley, C., 2009. Breathlessness, fatigue and the respiratory muscles. Clin. Med. Lond. (Lond.) 9, 448–452.
Ogedegbe, G., Ravenell, J., Adhikari, S., Butler, M., Cook, T., Francisco, F., Izurute, E., Jean-Louis, G., Jones, S.A., Onakomaiya, D., Petrilli, C.M., Pulgarin, C., Regan, S., Reynolds, H., Seixas, A., Vohplecici, F.M., Horwitz, L.I., 2020. Assessment of racial/ethnic disparities in hospitalization and mortality in patients with COVID-19 in New York City. JAMA Netw Open 3, e2026881.
Parra-Rodriguez, L., Gonzalez-Meljen, J.M., Gomez-Dantes, H., Gutierrez-Robledo, L.M., Lopez-Ortega, M., Garcia-Pena, C., Medina-Campos, R.H., 2020. The burden of disease in Mexican older adults: premature mortality challenging a limited-resource health system. J. Aging Health 32, 543–553.
Stanojevic, S., Graham, B.L., Cooper, B.G., Thompson, B.R., Carter, K.W., Francis, R.W., Hall, G.L., on behalf of the Global Lung Function Initiative TLCO working group, 2017. Official ERS technical standards: global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur. Respir. J. 50, 1700010.
Wong, A.W., Shah, A.S., Johnston, J.C., Carlsten, C., Ryerson, C.J., 2020. Patient-reported outcome measures after COVID-19: a prospective cohort study. Eur. Respir. J. 56, 2003276.