Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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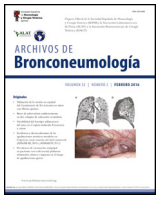

Scientific Letter

Improvement in Walking Distance Lags Raise in Lung Function in Post-COVID Patients

La distancia caminada en pacientes que padecieron COVID-19 se recupera más lentamente que otras pruebas de función respiratoria

To the Director,

Several studies agree that individuals who recover from COVID-19 often have persistent symptoms and impairment in pulmonary function tests (PFTs),[1–9] even 6 months after the presentation of COVID-19.[10] Cross-sectional evaluations have limitations in determining the course of recovery over time, and a longitudinal follow-up is more reliable, as it takes into account the initial condition, avoids difficulties with the adjustment of reference equations as well as cohort and period biases. This study aims to describe the clinical and longitudinal pulmonary function changes in subjects who have recovered from COVID-19 at ∼3 and 6 months after disease presentation.

This prospective cohort study was approved by the Ethics Committee of the institution (C16-20) and was conducted from June to December 2020 at the Department of Respiratory Physiology of the National Institute of Respiratory Diseases, located in Mexico City, at 2240 m above sea level. This study did not receive external funding.

We invited all discharged patients who were hospitalized due to COVID-19 pneumonia confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) of a respiratory tract sample to participate. Patients were excluded if they had any inability to undergo PFTs, severe respiratory distress requiring continuous oxygen, decompensated disease, or a respiratory infection within the last 14 days.

Participants signed an informed consent form and underwent a health questionnaire, anthropometric measurements, PFT-spirometry [forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC)], single-breath diffusing capacity of lung for carbon monoxide (DL_{CO}), a six-minute walking test (6-MWT), and maximal inspiratory and expiratory pressure (MIP-MEP) at approximately 3 and 6 months after presenting with the disease. Between visits, patients were prescribed strength, endurance, and flexibility exercises and pulmonary physical therapy consisting of dyspnea management with paused abdominal breathing and secretion management if present.

PFTs were performed according to American Thoracic Society and European Respiratory Society guidelines[11–15] on a Master-Screen PFT and Master-Screen Body-PFT (Vyaire; Hochberg, Germany). The 6-MWT was performed in a 30-m corridor using a pulse oximeter with a finger sensor (Massimo SET, Rad 57, Massimo, Irving, US). All PFT lab staff wore personal protective equipment; and each patient used disposable virus and bacterial filters.[16]

Comparisons of variables between visits were performed with paired Student's *t*-tests, and categorical variables were compared with McNemar's test. The changes in each variable were evaluated by a one-sample *t*-tests against a hypothesized mean of zero. Models with multilevel analysis were used to identify predictors of improvement of the main outcome variables (forced lung volumes, DL_{CO}, 6-MWT, SpO_2 nadir during the 6-MWT, MIP-MEP and clinical symptoms). The change in functional variables during follow-up was adjusted for follow-up time in months, which was not identical in all participants. Data capture was performed with RedCap®, and data analysis with the STATA v.16 program.

We invited 79 patients to participate; 70 attended the lab, 57% were men and 40 (57%) had received invasive mechanical ventilation (IMV).

The mean age was 47.2 ± 13 years, mean weight 74.6 kg ± 3 and mean height 162 cm ± 8.5; 75% of participants were overweight or obese. The mean time elapsed between the onset of symptoms and the first and second visits was 92 ± 22 days and 174 ± 37 days, respectively. At the first visit, 7 subjects did not perform the 6-MWT due to a risk of falling, alterations in gait or dizziness; at the second visit, 2 individuals could not perform any study due to anxiety or cardiovascular decompensation, and 4 additional individuals could not perform the 6-MWT.

Table 1 shows the increases in forced lung volumes, DL_{CO} and MIP-MEP at the second evaluation. The mean changes per month of follow-up were as follows: FEV_1: +23 ml (95%CI 3.2–43.2 P = .02), FVC: +45 ml (95%CI 20–70, P = .0006), and DL_{CO}: +0.7 ml/min/mmHg (units) (95%CI 0.35–1.1, P = .0002), and improvement among them was correlated. Although DL_{CO} on average, increased significantly in the participants, in two patients decreased >15%.

We observed no significant increase in the distance walked during the 6-MWT (6-MWD, +3.9 m, 95% CI −2.97 to 10.5, P = .26); moreover, 14 subjects walked 30 meters less than in the first evaluation, which is considered the minimum clinically significant difference. The change in the 6-MWD did not correlate with improvement in the other functional tests. In mixed models, the distance walked was associated with DL_{CO} (1.99 m/unit, 95% CI −0.4 to 4.4, P = .1), MIP (1.11 m/cmH_2O, 95% CI 0.4 to 1.8, P = .001), and IMV (−39.1 m, 95% CI −81 to 3.0, P = .07).

Desaturation (4% decrease from baseline or drop to <85%) during the 6-MWT was present in 65% of patients in the first evaluation

Abbreviations: 6-MWT, 6-minute walk test; 6-MWD, 6-minute walk distance; COVID-19, coronavirus disease-2019; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing lung capacity for carbon monoxide; HHR, heart rate recovery; IMV, invasive mechanical ventilation; LLN, lower limit of normal; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MERS, Middle East respiratory syndrome; FT, pulmonary function tests; SARS, severe acute respiratory syndrome; SpO2, oxygen blood saturation measured by pulse oximeter.

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Table 1
Functional Characteristics of Participants (Means ± Standard Deviation, Unless Otherwise Specified).

	Visit 1	Visit 2	Change	IC 95%
FEV_1, L	2.87 ± 0.7	2.98 ± 0.6*	0.065*	0.0214 to 0.115
FEV_1, % pred	90.8 ± 12.4	93.1 ± 13†	2.7†	1.06 to 4.4
FVC, L	3.54 ± 0.9	3.67 ± 0.86‡	0.120‡	0.054 to 0.185
FVC, % pred	90.4 ± 12.6	93.6 ± 13‡	4.2 ‡	2.3 to 6.1
DL_{CO}	29.1 ± 8.3	30.9 ± 7.8‡	1.7‡	0.82 to 2.72
DL_{CO}, % pred	92.2 ± 18.3	97.4 ± 15.5‡	6 ‡	3.13 to 8.8
VA, L	5.42 ± 1.24	5.39 ± 1.19	−0.010	−0.230 to 0.213
VA, %pred	101.3 ± 17.2	100.5 ± 17	0.4	−3.9 to 4.7
6-MWT, m	526 ± 104.5	519.8 ± 100.5	9.5	−8 to 27
6-MWT, % pred	85.2 ± 18.6	85.7 ± 18.5	2.3	−0.5 to 5
Dyspnea, initial (Borg)	0.2 ± 0.4	0.1 ± 0.5	0.06	−0.1 to 0.2
Dyspnea, final (Borg)	1.4 ± 1.4	1.1 ± 1.4	0.3	−0.04 to 0.6
Fatigue, initial (Borg)	0.5 ± 0.8	0.2 ± 0.6	−1.3	−2 to −0.6
Fatigue, final (Borg)	2.3 ± 2.3	1.8 ± 2.5	0.2	−0.01 to 0.5
Nadir SpO_2 in 6-MWT, %	86.8 (4.1)	87.9 (4.85)	0.7	−0.82 to 2.2
HRR during 6-MWT, bpm	17 (10)	13 (21.6)	−5.1	−11 to 0.8
MIP, cmH_2O	92.9 ± 25.8	101.2 ± 25.9‡	9.5‡	5.5 to 13.4
MIP, % pred	93.3 ± 23.4	102.9 ± 24.8‡	12‡	7.7 to 18
MEP, cmH_2O	108.1 ± 33.7	111.9 ± 40.2	5.7	−2.3 to 13.8
MEP, % pred	50.3 ± 15	51.6 ± 15.9	8.6*	0.21 to 17
FVC, <LLN, *n* (%)	10 (14.2)	11 (15)	–	–
DL_{CO}, <LLN, *n* (%)	20 (28)	11 (15.7) *	–	–
6MWT, <LLN, *n* (%)	19 (27)	20 (28.6)	–	–
MIP, <LLN, *n* (%)	14 (20)	9 (13)	–	–
MEP, <LLN, *n* (%)	65 (92)	63 (90)	–	–
Low HRR during 6-MWT, *n* (%)	21 (33)	30 (46)	–	–
SpO_2, <85% or Δ 4%, *n* (%)	46 (65)	32 (46)*		
Fatigue, *n* (%)	30 (43)	18 (26)	–	–
Myalgia, *n* (%)	25 (36)	17 (24)	–	–
Headache, *n* (%)	10 (14.3)	6 (8.5)	–	–
Anosmia, *n* (%)	11 (15.7)	3 (4)†	–	–
Sore throat, *n* (%)	22 (31.4)	8 (11)†	–	–
Cough, *n* (%)	15 (21.4)	7 (10)	–	–

FEV_1 = forced expiratory volume in the first second of exhalation; FVC = forced vital capacity; DL_{CO} = diffusing capacity of the lungs for carbon monoxide; VA = alveolar volume; 6-MWT = six-minute walking test; SpO_2 = oxygen saturation measured by a pulse oximeter; HRR = heart rate recovery; bpm = beats per minute; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; % pred = percentage of predicted; LLN = lower limit of normal.
Continuous variables (paired Student's *T*-test) and categorical variables (McNemar's test) were compared between the first and second visit (*$P < .05$; †$P < .01$; ‡$P < .001$).
The change of each variable between the first and second visit was evaluated by a one-sample *t*-test against a hypothesized mean of zero (*$P < .05$; †$P < .01$; ‡$P < .001$).

and in 46% of patients in the second, with a nonsignificant quantitative change (−0.01%/month, $P = .8$), even if adjusted for meters walked (2%/km/month, $P = .98$). In mixed models, desaturation during the 6-MWT was associated with higher BMI ($P = .056$), lower DL_{CO} ($P < .03$) and cough persistence ($P = .02$) but not with previous IMV ($P = .17$).

IMV during acute infection was associated with a significant decrease in DL_{CO} (2.5 ml/min/mmHg) and in the 6-MWT (41 m) ($P = .02$) but did not affect FEV_1 ($P = .98$), FVC ($P = .21$) or clinical symptoms. Surprisingly, almost half of subjects presented a slow heart rate recovery (HRR) one minute after finishing the 6-MWT, (HRR<14 beats per minute), especially in those who had IMV.

We observed that at 6 months after presentation of COVID-19, respiratory mechanics had improved slightly (<100 ml per month of follow-up), the DL_{CO} improved to a greater degree (0.7 U/month) and improvements in FEV_1, FVC and DL_{CO} were intercorrelated.

However, no improvement was observed in the distance walked, or in the oxygen desaturation after the 6MWT as a crude value or adjusted by meters walked. There were even individuals in whom the 6-MWT decreased, even though they had participated in a rehabilitation program.

This result could be due to physical deconditioning if individuals did not continue to exercise at home. Furthermore, these individuals may have important limitations that prevent increasing their exercise level, such as fatigue, weakness, mental health problems, or restriction in pulmonary circulation with or without pulmonary hypertension, which could partly explain the persistent oxygen desaturation. As shown in Table 1, 46% of participants did not exhibit proper HRR within one minute of completing the 6-MWT.

In previous studies, female sex, the presence of comorbidities, and recovering from acute respiratory distress syndrome were associated with lower 6-MWT scores. However, in our group, even individuals who did not require IMV demonstrated lack of improvement in the 6MWD with persisting oxygen desaturation, a common event at the altitude of Mexico City.[17]

After a median of 78 days, odynophagia and anosmia improved, but other symptoms persisted, regardless of whether or not patients were intubated. These findings demonstrated the long convalescence period that can accompany COVID-19, similar to other infections such as SARS-CoV and MERS.[18–20]

In conclusion, after 6 months of post-COVID follow-up, small improvements in FEV_1 and FVC and moderate improvements in DL_{CO} were observed, but the walking distance did not improve substantially. Moreover, almost half of participants manifested oxygen desaturation and delayed HR recovery after walking regardless of whether they were intubated. The impact of physical deconditioning should be eliminated as much as possible, possibly through in situ massive rehabilitation programs, whereas other pulmonary or nonpulmonary factors that may limit physical conditioning should be excluded.

Authors' Contributions

W.M-M was involved in literature search, data collection, interpretation of data for the work, and revising the content.

L.G.R contribute to the conception or design of the work; acquisition, analysis, interpretation of data, drafting the work, revising it critically for important intellectual content.

J.P-P contribute to analysis, interpretation of data, revising it critically for important intellectual content.

A.S-R was involved in literature search, data collection, data base elaboration and in the writing of the manuscript.

A.G-M was involved in data collection, interpretation of data for the work, and revising the content.

I.S-E was involved in data collection and data base elaboration.

A.D-C was involved in data collection and data base elaboration.

M.S-C was involved in data collection and data base elaboration.

C.G-V was involved in data collection, data base elaboration and design of the work.

L.L-M was involved in data collection, data base elaboration and administrative paperwork.

Conflict of Interests

L.G-R. declares fees as speaker from GSK, Astra-Zeneca, Chiesi; and as advisory board with Circassia and Vyaire Company. C G-V has competing interest with GSK.

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