Gas Exchange Impairment During COVID-19 Recovery

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BACKGROUND: Persistent impairment of pulmonary function and exercise capacity has been known to last for months or even years in the survivors who recovered from other coronavirus pneumonia. Some reports showed that subjects with coronavirus disease 2019 pneumonia after being discharged could have several sequelae, but there are few studies on gas exchange and exercise capacity complications in these subjects. AIMS: To describe residual gas exchange abnormalities during recovery from coronavirus disease 2019 pneumonia. METHODS: In an observational study, ~90 d after onset of disease, we scheduled almost 200 subjects for an outpatient visit with pulmonary function testing and computed tomography of the lungs. Lung mechanics by using body plethysmography, gas exchange with diffusing lung capacity for carbon monoxide determined by the single-breath technique (D_{LCOsb}) and diffusing lung capacity for nitric oxide determined by the single-breath technique (D_{LNOsb}), and exercise ability by using the 6-min walk test (6MWT) were measured in the subjects. The results were compared between those who required invasive mechanical ventilation and those who did not. RESULTS: A total of 171 subjects were included, the majority (96%) had signs of residual pneumonia (such as an excess of high attenuation areas) on computed tomography of the lungs. The D_{LCOSB} results were below the lower limit of the normal range in 29.2% of the subjects; during the 6MWT, 67% experienced oxygen desaturation (S_{pO_2}) > 4%; and, in 81 (47%), the dropped below 88%. Subjects who required invasive mechanical ventilation (49.7%) were more likely to have lower lung volumes, more gas exchange abnormality, less exercise capacity and more radiologic abnormality. CONCLUSIONS: Subjects who recovered from severe COVID-19 pneumonia continued to have abnormal lung function and abnormal radiologic findings. *Key words: COVID-19; pulmonary function tests; exercise and pulmonary rehabilitation; respiratory structure and function; x-rays.* [Respir Care 2021;66(10):1610–1617. © 2021 Daedalus Enterprises]

Introduction

Persistent impairment of pulmonary function and exercise capacity has been known to last for months or even years in survivors from other coronavirus pneumonia (severe acute respiratory syndrome and Middle East respiratory syndrome).[1-3] A recent report shows that subjects with coronavirus disease 2019 (COVID-19) pneumonia who were discharged still had residual abnormalities on chest computed tomography (CT), with ground-glass opacity as the most common pattern.[4] It is hypothesized that both functional and structural persistent abnormalities may be related with an incomplete lung recovery process that leads to interstitial lung fibrosis.[4-9] Lower diffusing lung capacity for carbon monoxide determined by the single-breath technique (D_{LCOsb}) have been reported in subjects with COVID-19 at 30 d after discharge.[5-9] In this study, we reported subjects in the late phase of recovery after hospitalization for COVID-19 pneumonia, confirmed the lower D_{LCOsb} of the survivors, and added the results of the diffusing lung capacity for nitric oxide by the single-breath technique (D_{LNOsb}).

Our hypothesis was that patients who required intervention with invasive mechanical ventilation would have poorer lung function and more common radiologic lung abnormalities during follow-up examinations when compared with those who were hospitalized for COVID-19 but who did not require invasive mechanical ventilation. We also hypothesized that the severity of lung function abnormality would be significantly correlated with the severity of radiologic abnormalities and with a self-reported dyspnea. The objectives of the present study were to describe the abnormalities in gas exchange measured by using D_{LCOsb}, D_{LNOsb}, and the 6-min walk test (6MWT) during the late recovery phase and reported physiologic and radiologic differences between subjects who required invasive mechanical ventilation and those who did not.

QUICK LOOK

Current knowledge

COVID-19 is a growing cause of residual respiratory impairment; however, it is incompletely understood which of the pulmonary function tests could better demonstrate those potential abnormalities.

What this paper contributes to our knowledge

In 170 subjects who recovered from severe COVID-19 pneumonia, we found that they continued to have abnormal respiratory function tests and abnormal radiologic findings on average 3 months after discharge. Based on our results, oxygen desaturation during a 6-min walk test or a low diffusing lung capacity for carbon monoxide by using the single-breath technique should trigger a follow-up every 3 months until, optimistically, full recovery.

Methods

Subjects and Ethics Concerns

For this observational study, we recruited consecutive men and women, >18 y old, hospitalized with COVID-19 pneumonia confirmed by reverse-transcriptase polymerase chain reaction, from the National Institute for Respiratory Diseases in Mexico City. Subjects who developed respiratory failure (respiratory acidosis) were intubated and given invasive mechanical ventilation. Treatment with corticosteroids and heparin were evolving during the period that these subjects were hospitalized, but most of them received corticosteroids and anticoagulation throughout their hospital stay. All these patients were admitted to an isolation ward starting in March 2020, due to severe dyspnea and hypoxemia. We avoided testing subjects with active COVID-19 infections and did not schedule pulmonary function tests (PFT) until > 6 weeks after hospitalization was completed.

Subjects were scheduled on the same day for computed tomography (CT) of the lungs and PFTs, which were completed ∼3 months after the onset of their symptoms. Patients who did not meet the inclusion criteria for this report are described in supplemental Figure 1 (see the supplemental material at http://www.rcjournal.com). In this report, we only included subjects who survived severe pneumonia (who either did or did not require invasive mechanical ventilation), and reported their lung function as out-patients during convalescence. The study respected all the ethics issues described in the Declaration of Helsinki. The institution's science and bioethics committee approved the study (C16-20), and the subjects who agreed to participate were asked to sign a letter of informed consent.

PFTs and CT Parameters

PFTs done for this report included spirometry, D_{LCOsb}, D_{LNOsb}, maximal inspiratory, and expiratory pressures (P_{Imax}- P_{Emax}) and whole-body plethysmography, all done according to contemporary guidelines from the American Thoracic Society and European Respiratory Society.[10-14] For the D_{LCOsb} and D_{LNOsb} measurements a breath-hold time of 10 s duration was performed, and values were accepted if two successive measurements of D_{LCOsb} and D_{LNOsb} were within 2.0 and 17.0 units respectively.[11,15] The results of the tests were compared with the best-fit reference equations.[16-21] For each test, the lower limit of the normal range and upper limit of the normal range were the 5th and 95th percentiles.

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Supplementary material related to this paper is available at http://www.rcjournal.com.

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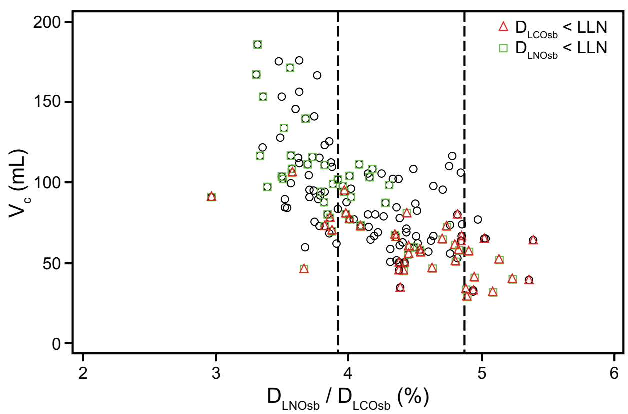

Fig. 1. A scatter plot of single-breath D_{LNO}/single-breath D_{LCO} and pulmonary capillary blood volume (V_c). Dashed lines denote lower and upper limits of normal (vertical dashed lines). D_{LNOsb} = diffusing capacity of the lung for nitric oxide determined by the single-breath technique; D_{LCOsb} = diffusing capacity of the lung for carbon monoxide determined by the single-breath technique; LLN = lower limit of normal.

Spirometry, lung volumes P_{Imax} and P_{Emax}, were measured with whole-body plethysmograph (Master-Screen Body-PFT, Vyaire, Hochberg, Germany), whereas D_{LCOsb} and D_{LNOsb} tests were conducted with a diffusor system (Master-Screen PFT, Vyaire). Volume calibration checks were done daily by using a 3-L syringe at different flows. A healthy biologic control was tested weekly to detect D_{LCOsb} instrument drift. The 6MWT was performed in a 30-m corridor by using a pulse oximeter with a finger sensor (Massimo SET, Rad 57, Masimo, Irving, California). All PFT laboratory staff wore personal protective equipment, including N-95 respirators, protective glasses, caps, gloves, and gowns. In addition, each subject used disposable virus and bacterial filters during the tests.[22]

In 159 subjects, a CT of the lungs obtained on the same day as the PFTs was available. Scans of the entire chest were routinely obtained with the subject in the supine position, during breath-hold at full inspiration, by using a multidetector row-spiral scanner (SOMATOM Definition AS 128 Dual Energy, version VA40A, Siemens AG Medical, Forchheim, Germany). A single experienced reader (APH-M), blinded to the clinical status of the subject and lung function data, independently analyzed all CTs were qualitatively and quantitative, morphologic, and functional findings were analyzed by obtaining lung volumetric and high parenchymal attenuation areas as well as healthy lung parenchyma and percentage of lung with normal density.

Statistical Analysis

Results are shown as means ± SDs or medians (interquartile ranges) according to the distribution of the variables. Associations were made by means of the Pearson or the Spearman correlation coefficient according to distribution of data. Comparisons between groups, those who required invasive mechanical ventilation versus those who did not, were analyzed by using the Student *t* test or the Mann-Whitney U test for continuous variables according to distribution and the chi-square test for percentages in dichotomic variables. Overweight was defined as a body mass index > 25 kg/m^2, and obesity was defined as body mass index > 30 kg/m^2. RedCap 10.3.1 (Vanderbilt University, 2020) and Stata v.16 (College Station, Texas) software were used to build the database and for analysis of the results. $P < .05$ was considered significant.

Results

From May 29 to October 20, 2020, 199 patients with COVID-19 who were discharged were invited to participate, and 193 reported for out-patient PFTs and CTs of the lungs ~3 months later. Some were unable to complete high-quality D_{LCOsb} and 6MWTs (see the supplementary materials at http://www.rcjournal.com). Of the 171 subjects included in the study, 64% were men, 57% were overweight, and 29% were obese. During hospitalization, 85 subjects (49.7%) required invasive mechanical ventilation, for mean ± SD 13.8 ± 7.3 d. The mean ± SD in-hospital days were 18.1 ± 12.5 d, with longer length of stay in the subjects who required invasive mechanical ventilation (mean ± SD, 26 ± 1.2 d) versus those who did not (mean ± SD, 10 ± 0.9 d) ($P < .001$).

No significant differences were found between those who required invasive mechanical ventilation versus those who had not in relation to sex, smoking status, and body mass index. Many of the subjects had comorbid conditions previously reported to cause a higher risk of COVID-19 severe disease (Table 1). Previous respiratory diseases were uncommon (see the supplementary materials at http://www.rcjournal.com). The mean ± SD duration from onset of disease to PFT was 84.3 ± 20.4 d in the subjects with pneumonia and 112.6 ± 24.7 d in those who had required invasive mechanical ventilation. Supplementary material provides the symptom rates reported by the subjects during the follow-up examination; generalized fatigue and myalgias were the most common symptoms. No differences were found between the groups (see the supplementary materials at http://www.rcjournal.com).

The subjects who had required invasive mechanical ventilation were much more likely to have abnormalities on CTs of the lungs than those who did not require invasive mechanical ventilation (Table 2). Of the 159 subjects who underwent CTs, 96% had radiologic abnormalities. More than three fourths of the subjects had ≥2 radiologic abnormalities (see the supplementary materials at http://www.rcjournal.com). For those seen < 90 d after the onset of symptoms, lung volumes by using CTs were similar in

Table 1. General Characteristics of the Subjects

Characteristic	No Invasive Ventilation (n = 85)	Invasive Ventilation (n = 86)
Age, y	46 ± 12.2	47.3 ± 11.4
Men, n (%)	55 (65)	54 (63)
Weight, kg	79.7 ± 15.1	77 ± 13.1
Height, cm	165 ± 8.4	163 ± 7.7
BMI, kg/m^2	29.3 ± 4.5	28.8 ± 4.6
Obese, n (%)	27 (31)	22 (26)
Overweight, n (%)	51 (59)	45 (53)
High blood pressure, n (%)	13 (15)	24 (28)*
Diabetes, n (%)	15 (17)	15 (18)
Gastritis or GER, n (%)	9 (10)	12 (14)

Data are expressed as mean ± SD unless otherwise stated.
*P < .05 (Student t test).
BMI = body mass index
GER = gastroesophageal reflux

Table 2. Computed Tomography of the Lungs in 159 of the Subjects

Radiologic Finding	No Invasive Ventilation (n = 77)	Invasive Ventilation (n = 82)
Pneumatocele	5 (6.5)	4 (4.9)
Reticular images	33 (42.9)	63 (76.8)†
Linear atelectasis	35 (45.5)	52 (63.4)*
Parenchymatous bands (strips)	12 (15.6)	30 (36.6)†
Ground-glass opacity	70 (90.9)	80 (97.6)
No radiologic findings	5 (6.5)	2 (2.4)
Lung volume, mean ± SD L	4.78 ± 1.21	4.44 ± 1.09*
Percentage of normal lung, mean ± SD	86.3 ± 0.95	82.7 ± 0.75†
Percentage of HAA, mean ± SD	13.7 ± 0.94	17.3 ± 0.75†

Data are n (%) unless otherwise noted.
*P < .05 (chi-square test or Fisher exact test).
† P < .01 (chi-square test or Fisher exact test).
HAA = high attenuation areas

those who required invasive mechanical ventilation when compared with those who did not require invasive mechanical ventilation. However, for those evaluated > 90 d after initial symptoms, the subjects who had required invasive mechanical ventilation had a lower percentage of normal lung (and more high parenchymal attenuation areas) than those who did not (see the supplementary materials at http://www.rcjournal.com).

The subjects with invasive mechanical ventilation had lower lung volumes (FVC, residual volume, inspiratory capacity, and total lung capacity percent of predicted) when compared with those without invasive mechanical ventilation (Table 3). FEV_1/FVC was higher for those who had required invasive mechanical ventilation because their FVC was lower; only 8 subjects (4.7%) had a FEV_1/FVC < lower limit of the normal range; and approximately one third of the subjects had inspiratory muscle weakness (< lower limit of the normal range). Abnormality rates for non–gas exchange PFTs were similar for those who had required invasive mechanical ventilation when compared with those who had not required invasive mechanical ventilation (see the supplementary materials at http://www.rcjournal.com).

The mean values of all indices of gas exchange (from the D_{LCOsb} and D_{LNOsb}) were lower (and more frequently abnormal) in the subjects with invasive mechanical ventilation when compared with those without invasive mechanical ventilation (Table 4). The D_{LCOsb} was below the LLN in 29.2% of participants, being more affected those who required invasive mechanical ventilation (P <0.001); the D_{LNOsb} was also < lower limit of range in 25% of subjects as well as the membrane diffusion (D_m) (81%). The mean ± SD D_{LNOsb}/D_{LCOsb}–was 4.32 ± 0.59 in those who had required invasive mechanical ventilation compared with 4.03 ± 0.51 in those who had not required invasive mechanical ventilation (P = .001). The memebrane diffusion (D_m)and the red cell component (V_c) of the overall diffusing conductance were also lower in those who had required invasive mechanical ventilation (P < .01), but the V_c was above of the upper limit of normal in 94 subjects (55%). D_{LNOsb}/D_{LCOsb} ratio and the V_c in all participants; 8% of the subjects had high D_{LNOsb}/D_{LCOsb} ratio while 35% had a low ratio (Fig. 1). A large proportion of the subjects who had required invasive mechanical ventilation had an abnormally low 6MWT score and walked shorter distances compared with those who did not. Two-thirds experienced oxygen desaturation (>4%); and about half had a S_{pO_2} which drop below 88%. (Table 5)

Five subjects walked < 254 m (often considered a risk factor for morbidity and mortality disability[23]): 2 had severe lesions in gait muscles and 3 were stopped during the test because the dropped below 80%. There were no differences in baseline S_{pO_2} (P = .88), the lowest S_{pO_2} during the 6MWT (P = .28), baseline dyspnea (P = .66), or the final Borg dyspnea scale (P = .17) between those who required invasive mechanical ventilation and those who did not. The subjects with lower lung volumes measured by spirometry and body plethysmography were more likely to have lower lung volumes measured by a CT of the lungs and more likely to have high parenchymal attenuation areas (ie, evidence of residual pneumonia). Worse gas exchange results were also associated with the degree of radiologic abnormality (see the supplementary materials at http://www.rcjournal.com). Oxygen desaturation during the 6MWT was associated with more high–parenchymal attenuation areas, and lower D_{LCOsb}, D_{LNOsb}, (percent of predicted).

Discussion

In this observational study, the subjects who had recovered from severe COVID-19 pneumonia continued to have

Table 3. Mechanical Pulmonary Function Tests

Test	No Invasive Ventilation ($n = 86$)	Invasive Ventilation ($n = 85$)	P
FEV_1, L	3.11 ± .68	2.97 ± .64	.032
FEV_1, % of predicted	92.9 ± 14.1	91.6 ± 13.5	.03
FVC, L	3.88 ± .86	3.58 ± .79	.03
FVC, % of predicted	94 ± 14	89 ± 14	.02
FEV_1/FVC, %	80.3 ± 5.4	83.3 ± 5.4	.005
P_{Imax}, cm H_2O	95 ± 29	92 ± 21	.27
P_{Imax}, % of predicted	91 ± 24	90 ± 18	.45
P_{Emax}, cm H_2O	114 ± 38	111 ± 27	.62
P_{Emax}, % of predicted	59 ± 16	59 ± 13	.98
TLC, L	5.65 ± .9	5.27 ± 1	.005
TLC, % of predicted	98 ± 13	92 ± 13	.004
RV, L	1.82 ± .37	1.68 ± .34	.006
RV, % of predicted	116 ± 29	103 ± 21	<.001
IC, L	2.95 ± .68	2.65 ± .66	.002
IC, % of predicted	97 ± 17	90 ± 17	.005
IC/TLC, %	52 ± 7.5	50.2 ± 8.2	.08
Alveolar volume, L	5.68 ± 1.11	5.41 ± 1.16	.14
Alveolar volume, % of predicted	103.4 ± 15.6	99.5 ± 15.6	.13

Data are expressed as mean ± SD.
Comparisons between the subjects who had required invasive mechanical ventilation and the subjects who had not required invasive mechanical ventilation were analyzed by using Student *t* tests.
P_{Imax} = maximum inspiratory pressure
P_{Emax} = maximum expiratory pressure
TLC = total lung capacity
IC = inspiratory capacity
RV = residual volume

abnormal radiologic findings and abnormal lung function. It seems logical that individuals with severe pneumonia (and perhaps thromboembolism) and required invasive mechanical ventilation would require a longer recovery time when compared with those who required hospitalization but not invasive mechanical ventilation. Our results at ~3 months after the onset of dyspnea due to COVID-19 pneumonia were similar to those of Huang et al[24] who reported results of PFTs and CTs of the lungs from 349 subjects ~6 months after hospitalization for COVID-19 pneumonia in Wuhan, China. Most of their subjects still had abnormal lung CT scan and D_{LCOsb} results; and those who required invasive mechanical ventilation (their severity scale of 5 or 6) had a higher volume of high parenchymal attenuation areas, and lower total lung capacity, D_{LCOsb}, and 6MWT scores when compared with subjects who only required oxygen therapy during their hospital stay (severity scale of 4).[24] More than half of the 88 subjects who required invasive mechanical ventilation had a $D_{LCOsb} < 80\%$ of predicted, 29% had a low 6MWT; more than half had an abnormal CT of the lungs.[24] The most frequent symptoms (fatigue and muscle pain or weakness) were the same as those reported at 6 months after a diagnosis of COVID-19.[24]

Mo et al[5] reported PFTs from 110 subjects in China at the end of a mean of 27 d of hospitalization for COVID-19 (19 who required mechanical ventilation and 67 with pneumonia who did not need invasive mechanical ventilation). The mean D_{LCOsb} for the subjects after invasive mechanical ventilation was 65% of predicted compared with 80% for those with pneumonia and who did not require invasive mechanical ventilation. These results are lower than our mean D_{LCOsb} results obtained at ~3 months after hospital discharge (85 and 96% of predicted). Previous studies of survivors of COVID-19 have not mentioned a measurement of the D_{LNOsb} as we had done. The lungs take up nitric oxide much more avidly compared with carbon monoxide, so D_{LNOsb}/D_{LCOsb} is 3.9–5.4 in healthy adults (independent of age, height, sex, altitude, and hemoglobin).[15,25] Our technique for measuring gas exchange was similar to that of Munkholm et al,[18] who tested healthy adults, so we used their D_{LNOsb}/D_{LCOsb}–lower limit of the normal range of 3.9 and upper limit of the normal range of 4.9.

Clinical studies that measured D_{LNOsb} were summarized by Hughes and Dinh-Xuan.[25] In their summary, the subjects with pulmonary vascular disease (which caused pulmonary artery hypertension) had both low D_{LCOsb} and D_{LNOsb} (means of ~65% of predicted), and their D_{LNOsb}/D_{LCOsb}–was normal to high.[25] Patients with interstitial lung disease or severe COPD also have both a low D_{LCOsb} and low D_{LNOsb} (means

Table 4. Gas Exchange Results

Gas Exchange	No Invasive Ventilation ($n = 86$)	Invasive Ventilation ($n = 85$)	P
D_{LCO}, mL/min/mm Hg	31.9 ± 8.6	27.4 ± 7.4	.001
D_{LCO}, % of predicted	95.8 ± 16.4	84.6 ± 17	<.001
K_{CO}, mL/min/mm Hg/L	5.57 ± 0.84	5 ± 0.95	<.004
K_{CO}, % of predicted	88.9 ± 11.8	81.1 ± 13.2	<.001
D_{LCOsb} mL/min/mm Hg	112.8 ± 27.5	101.1 ± 25	.007
D_{LCOsb}% of predicted	88.3 ± 16.1	82 ± 16.1	.006
K_{NO}, mL/min/mm Hg/L	19.4 ± 1.97	18.3 ± 2.2	.002
K_{NO}, % of predicted	84.4 ± 8.4	80.8 ± 8.7	.01
D_M, mL/min/mm Hg	57.2 ± 14	51.2 ± 12.8	.006
D_M, % of predicted	51.5 ± 10.1	47.7 ± 10.3	.008
V_C, mL	97.7 ± 33.6	74.8 ± 26.9	<.001
V_C, % of predicted	140.6 ± 36.7	111.3 ± 32.8	<.001
D_{LNO}/D_{LCO}, %	4.03 ± 0.51	4.32 ± 0.59	.001
D_{LCO} < LLN, n (%)	14 (17)	35 (41.2)*	.001
D_{LNO} < LLN, n (%)	16 (21.6)	26 (33.7)	.09
D_{LNO} > ULN, n (%)	2 (2.7)	2 (2.6)	.96
D_M < LLN, n (%)	68 (92)	73 (94.8)	.47
V_C < LLN, n (%)	1 (1.4)	6 (7.8)	.28
V_C > ULN, n (%)	48 (65.8)	25 (32.5)	<.001
D_{LNO}/D_{LCO} < 3.92, n (%)	38 (51.3)	21 (27.3)*	.002
D_{LNO}/D_{LCO} > 4.87, n (%)	5 (6.8)	9 (11.6)	.4

Data are expressed as mean ± SD unless otherwise noted.
Because we ran out of single-breath D_{LNO} test gas, only 74 of the subjects who had not required invasive mechanical ventilation and 77 of subjects who had required invasive mechanical ventilation had a single-breath test. Comparisons between the subjects who had required invasive mechanical ventilation vs the subjects who had not required invasive mechanical ventilation were analyzed by using Student t tests.
D_{LCO} = diffusing lung capacity of the lung determinded by the single-breath technique
K_{CO} = rate of uptake of carbon monoxide from alveolar gas
Single-breath D_{LNO} = Diffusing lung capacity of the lungs for nitric oxide determined by the single-breath technique
K_{NO} = rate of uptake of nitric oxide from alveolar gas
D_M = lung membrane diffusing capacity
V_C = pulmonary capillary blood volume
LLN = lower limit of the normal range
ULN = upper limit of the normal range

of 35 – 50% of predicted), but their D_{LNOsb} is reduced more than D_{LCOsb}, so their D_{LNOsb}/D_{LCOsb}–is often low (80 - 90% when compared with healthy individuals).[25]

Our subjects who had had COVID-19 and required invasive mechanical ventilation had a significantly lower D_{LCOsb} (41% below the lower limit of the normal range) and lower D_{LNOsb} (34% below the lower limit of the normal range) when compared with the subjects who did not require invasive mechanical ventilation (17% and 22% below the lower limit of the normal range, respectively). The mean D_{LNOsb}/D_{LCOsb}–was lower for the subjects who had not required invasive mechanical ventilation (4.0 vs 4.3). Thus, more of our subjects had a gas exchange pattern consistent with interstitial lung disease (as seen on CTs of their lungs) than persistent pulmonary vascular disease (which was seen on the pulmonary histology of most of the subjects in a large COVID-19 autopsy study[26]); it could be possible that those subjects who required invasive mechanical ventilation may have had microthrombotic phenomena that explains the lower pulmonary capillary blood volume compared with those without invasive mechanical ventilation.

Some investigators are concerned that a subset of survivors of COVID-19 will develop progressive interstitial lung disease.[27] Only long-term follow-up of a large cohort of patients who had COVID-19 and with abnormal gas exchange will answer this concern. Because many hospitals and PFT laboratories have limited resources, we suggest a parsimonious approach to follow-up with PFTs. We propose to simply measure the FVC with a spirometer to detect restriction. Measurements of total lung capacity, FRC, and residual volume, at least in the patients who recovered, does not add clinically important information. Because only 8 of the subjects had a low FEV_1/FVC (which suggested air-flow limitation), measuring slow vital capacity may be as useful as forced exhalation maneuvers.

We found the D_{LCOsb} to sensitively detect residual gas exchange abnormalities, but, in laboratories without a D_{LCOsb} machine, a 6MWT result that shows an important

Table 5. 6MWT Results

Parameter	No Invasive Ventilation ($n = 86$)	Invasive Ventilation ($n = 85$)	P
6MWD, m	567 (390–637)	503 (323–638)	<.001
6MWD, % of predicted	68.8 (53–82)	64.8 (43–83)	<.001
S_{pO_2}			
At baseline, %	93 (90–97)	93 (90–97)	.88
Lowest, %	88 (82–93)	88 (77–94)	.28
Final, %	91 (83–96)	90 (81–95)	.09
1 min after 6MWT	93 (89 –97)	93 (87–97)	.23
3 min after 6MWT	94 (91–97)	94 (91–97)	.48
5 min after 6MWT	94 (91–97)	93 (91–98)	.86
Heart rate, beats/min			
Baseline	81 (62–102)	84.5 (64–110)	.16
Highest during 6MWT	123 (101–149)	121.5 (100–145)	.54
Final	116 (87–149)	119.5 (89–143)	.92
1 min after 6MWT	97 (73–132)	101 (74–131)	.44
3min after 6MWT	91 (70–118)	92 (70–118)	.65
5 min after 6MWT	90 (62–116)	89 (71–114)	.80
Dyspnea score*			
Basal	0 (0–1)	0 (0–1)	.66
Final	1 (0–5)	.75 (0–4)	.17
Fatigue score			
Basal	0 (0–2)	0 (0–3)	.61
Final	2 (0–7)	1 (0–7)	.03
6MWT < LLN	73 (86)	79 (91.9)	.21
S_{pO_2} < 88% during the 6MWT	43 (50)	38 (44.7)	.59
Fall of S_{pO_2} > 4% during the 6MWT	58 (67)	57 (67)	.78

Data are median (5th-95th percentile). Comparisons were analyzed by using the Mann-Whitney U (continuous) and by chi-square (categorical variables) tests.
* Measured with the Borg-scale.
6MWT = 6-min-walk test
6MWD = 6-min walk distance
LLN = lower limit of the normal range

decrease in oxygen saturation during the walk (falls > 4%), and/or the 6-min walk distance result < 254 m identifies a person with clinically important lung residual sequalae; when a long indoor hallway is not available for the 6MWT, then a shorter hallway (as we had informed) gives nearly equivalent results in subjects with lung disease.[28] These patients should be prioritized for pulmonary rehabilitation and follow-up PFTs with lung CTs every 3 months to detect progression of a probable interstitial lung disease. A D_{LNOsb} measurement could be useful to differentiate greater involvement of the alveolar membrane than of the pulmonary microvasculature. The main limitation of the present study was that it did not include those individuals with mild pneumonia, which is the most common presentation of the COVID-19.

Conclusions

Based on our results, for patients who are recovering from severe COVID-19 pneumonia, we recommend a D_{LCOsb} test, which also will determine if they have low lung volumes (a low alveolar volume) or abnormal gas exchange (a low D_{LCOsb}). A 6MWT will find those who have clinically important exercise limitation, although the 6MWT results do not help with the differential diagnosis. Measurement of D_{LNOsb} (which is not widely available) at this point will probably not provide additional clinically important information.

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