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Characteristics of COVID-19 Pneumonia Survivors With Resting Normoxemia and Exercise-Induced Desaturation

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BACKGROUND: Survivors of coronavirus disease 2019 (COVID-19) associated pneumonia may show exercise-induced desaturation. We wondered whether these individuals show physiologic and symptom characteristics similar to individuals with chronic respiratory diseases with exercise-induced desaturation, namely COPD or interstitial lung diseases (ILD). We evaluated lung function, exercise capacity, and symptoms in these individuals compared with individuals with COPD or ILD and exercise-induced desaturation. METHODS: Survivors of COVID-19 associated pneumonia (study individuals), normoxemic at rest with exercise-induced desaturation, underwent assessment of dyspnea, dynamic lung volumes, carbon monoxide diffusion capacity, and the 6-min walk test. Data of individuals with COPD or with ILD and exercise-induced desaturation were also retrospectively analyzed. RESULTS: FVC was lower in individuals with COVID-19 or ILD than in those with COPD. Individuals who had COVID-19 walked < 70% of predicted and, as a whole, had a 6-min walk test performance similar to individuals with ILD but walked significantly less, showed more severe leg fatigue and dyspnea during exercise, and more exercise-induced desaturation than individuals with COPD. CONCLUSIONS: Survivors of COVID-19 associated pneumonia, who were normoxemic at rest with exercise-induced desaturation, had alterations in lung function, exercise capacity, and symptoms similar to individuals with ILD but more severe than individuals with COPD and exercise-induced desaturation. *Key words: Exercise capacity; dyspnea; exercise test; lung function.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

The severe acute respiratory syndrome coronavirus 2 coronavirus disease 2019 (COVID-19) pandemic will undoubtedly have dramatic effects throughout the world, with more than a hundred million people infected and 2 million casualties at the time of this article.[1] Approximately 80% of individuals had mild-to-moderate disease, 15% had severe disease, and 5% had critical illness.[2] The disease can cause major alveolar damage that results in hypoxemic acute respiratory failure, which requires mechanical ventilation in a high proportion of patients.[3] The long-term physical, psychologic, and cognitive impairment of survivors of COVID-19 associated pneumonia is not completely clear. [4,5] A high prevalence of muscle weakness and impairment in physical performance has been observed in hospitalized individuals recovering from COVID-19 without any previous motor limitation.

Furthermore, in individuals who required ICU admission, muscle impairment could be related, among other factors, to systemic inflammation, mechanical ventilation, sedation, and prolonged bed rest. [6] All these conditions may result in reduced exercise capacity. Furthermore, individuals recovering from COVID-19 may present a dissociation between the level of rest and exercise oxygen saturation, and subjective symptoms such as dyspnea and fatigue.[7] Also, individuals with advanced COPD or interstitial lung diseases (ILD) may have severe exertional breathlessness, reduction in exercise capacity, and daily physical activity worsening over time, with important clinical consequences, including increased mortality.[8,9] The prevalence of exercise-induced desaturation among individuals with COPD or ILD varies according to the selected study population and disease severity[10] and is an important prognostic factor for both populations. [11,12]

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We hypothesized that individuals recovering from COVID-19 associated pneumonia, who are normoxemic at rest with exercise-induced desaturation, may have physiologic and symptom characteristics similar to those of individuals with chronic respiratory diseases with exercise-induced desaturation, namely COPD and ILD. Therefore, this study aimed to evaluate lung function, exercise capacity, and symptoms in these individuals compared with those with ILD and COPD, normoxemic at rest, and with exercise-induced desaturation.

Methods

The study was approved by the Istituti Clinici Scientifici Maugeri IRCCS Ethics Committee (2440 CEC; 04/15/2020). As a retrospective study, individuals did not provide any specific written informed consent; however, at admission to affiliated institutions, they gave, in advance, their informed consent for the scientific use of their clinical data. As a retrospective cross-sectional comparative study, it was not registered.

Participants

The study was conducted by collecting data from the Automated Integrated Health Care Record Istituti Clinici Scientifici Maugeri database of in-patients who were recovering from COVID-19 and without any history of COPD or ILD who were consecutively admitted between March 15 and June 31, 2020, to 2 hospitals of the Istituti Clinici Scientifici Maugeri network (Pavia and Lumezzane) referral institutions for pulmonary rehabilitation, diagnosis, and care of individuals with post-acute and chronic disease who share the same protocols and procedures for diagnosis and management. [13,14] These individuals were transferred from the ICU and sub-ICUs, respiratory units, or general wards where they might have required oxygen therapy, with or without invasive mechanical ventilation or noninvasive mechanical ventilation. While wearing full personal protective equipment, these individuals were admitted to selected areas according to the evolution of the disease (first to a subacute treatment unit if they still had a positive swab result for COVID-19 and later to a pulmonary rehabilitation unit when they had a negative swab result), and were managed according to national and international procedures currently available.[15-18]

Data of individuals with COPD or ILD admitted to hospitals to perform a rehabilitation program between January 1, 2020 and December 31, 2020, were retrospectively analyzed in the Automated Integrated Health Care Record of Istituti Clinici Scientifici Maugeri database. Only data of individuals with $P_{aO_2}/F_{IO_2} > 250$ mm Hg, and/or $S_{pO_2} \geq 94\%$ on room air and exercise-induced desaturation were analyzed. COPD had to be confirmed by spirometry according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines.[19] The diagnosis and severity of ILD had to be reported in individuals' records according to current guidelines[20] (idiopathic pulmonary fibrosis, fibrotic nonspecific interstitial pneumonia; unclassifiable ILD, and others).

At the time of assessment, the condition of all the participants needed to be stable as assessed by the absence of worsening in symptoms, that is, no change in cough and/or sputum beyond day-to-day variability, which would have been sufficient to warrant a change in the management prescribed at discharge from acute care hospitals or prescribed at home by their general practitioner, and stability in blood gas values (eg, no respiratory acidosis). Therefore, we retrospectively selected participants with COPD or ILD and

QUICK LOOK

Current knowledge

The prevalence of exercise-induced desaturation in individuals with COPD and interstitial lung disease varies from 20% to 53%. Survivors of COVID-19 associated pneumonia may show exercise-induced desaturation similar to individuals with COPD or interstitial lung disease.

What this paper contributes to our knowledge

Individuals recovering from COVID-19 pneumonia, normoxemic at rest with exercise-induced desaturation, have exercise limitation, and, as a whole, performed similarly on walking tests to individuals with interstitial lung disease and exercise-induced desaturation.

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with measures or history assessing the stability as defined above. Individuals with previous orthopedic problems that prevented active mobilization, active malignancy, previous pulmonary surgery, unstable cardiovascular disease, and/or the need for a walking aid were excluded.

Measurements

We recorded demographics, anthropometrics, length of diseases, and percentage of comorbidities for all the subjects. We also recorded the GOLD stage for COPD,[19] and the ILD-gender age physiology (ILD-GAP) index for ILD, respectively[21]; for individuals with COVID-19, we recorded the clinical history of acute disease (acute care hospital length of stay, endotracheal intubation, use of noninvasive ventilation, oxygen therapy in the acute care setting, timing from acute onset of disease, radiologic patterns at computed tomography [CT], and oxygen use at discharge from our institutions).

The following measurements were assessed in our institutions at a mean ± SD 46.6 ± 24.4 d from the acute onset of disease in the participants with COVID-19 and within 24–48 h from admission of the participants with COPD and ILD:

- Arterial blood gases were assessed by using an automated analyzer on samples from the radial artery with the individual breathing air or oxygen while in a sitting position for at least 1 h. F_{IO_2} was calculated from the oxygen flow according to the formula $F_{IO_2} = 20\% + (O_2\ L/min \times 4)$.
- The flow-volume curve (FVC, FEV_1) and carbon monoxide diffusion capacity (D_{LCO}), were assessed according to standards[22] by using the predicted values of Quanjer [23] and Thompson et al,[24] respectively, with the Master Screen PFT and Master Screen body diffusion instruments (Carefusion, Hoechberg, Germany) in both institutions.
- Exercise tolerance was assessed by using the 6-min walk test (6MWT) according to accepted standards.[25] The walked distance was expressed as meters and as percentage of the predicted values. [26] Immediately before and immediately after the test, subjective sensations of dyspnea and leg fatigue were assessed by using the modified Borg scale. [27] S_{pO_2} and heart rate were continuously monitored (Pulse oxymeter, 8500M, Nonin), recording baseline S_{pO_2} and heart rate, nadir S_{pO_2}, peak heart rate, and mean.
- Exercise-induced desaturation was defined as: baseline S_{pO_2} - nadir S_{pO_2} (ΔS_{pO_2}) > 4% during the 6MWT.[25,28] The level of desaturation per walked meter (ΔS_{pO_2}/m) was also calculated.
- Dyspnea in activities of daily life was evaluated through the modified Medical Research Council (mMRC) scale.[29]

Statistical Analysis

Given the retrospective design of the study, the sample size was not calculated. Data were analyzed by using STATA 13.1 software (StataCorp, College Station, Texas). Continuous data are described as mean ± SD and categorical data are described as numbers and percentage. Differences among the groups were defined by the 1-way analysis of variance test and, if significant, a post hoc analysis was performed by using the unpaired *t* test with the Bonferroni correction. $P < .05$ was considered significant. The Pearson correlation was assessed to define the relationships between ΔS_{pO_2}/m and 6MWT, and anthropometric, physiologic, and clinical variables.

Results

One hundred-fifty individuals who were recovering from COVID-19 associated pneumonia were admitted during the study period for rehabilitation. Thirty-eight patients hypoxemic at rest under supplemental daytime oxygen and 72 patients normoxemic at rest and during exercise, were excluded. Forty subjects (26.6%) (22 at Pavia, 18 at Lumezzane) normoxemic at rest with exercise-induced desaturation were included. The only significant differences between the included (40) and the excluded (110) individuals with COVID-19 were found in D_{LCO} % of predicted and in P_{aO_2}/F_{IO_2} (mean ± SD D_{LCO} : 70.8 ± 36.5% of predicted vs 53.9 ± 20.8% of predicted, $P = .008$; mean ± SD P_{aO_2}/F_{IO_2} : 363.2 ± 88.3 mm Hg vs 325.1 ± 90.4 mm Hg, $P = .032$, for excluded and included individuals, respectively). The other parameters were not significantly different (mean ± SD FEV_1% of predicted: 83.7 ± 20.8% vs 77.4 ± 20.2%, $P = .12$; mean ± SD FVC % of predicted: 80.4 ± 16.7% vs 73.2 ± 21.0%, $P = .08$; mean ± SD FEV_1/FVC %: 81.6 ± 16.2% vs 85.1 ± 11.6%, $P = .24$; and mean ± SD 6MWD, 392.6 ± 173.8 m vs 350.3 ± 137.4 m, $P = .18$).

The mean ±SD length of stay in acute settings of individuals with COVID-19 was 29.3 ± 17.5 d; 35.0, 62.5, and 95.0% had undergone endotracheal intubation and mechanical ventilation, noninvasive mechanical ventilation, and oxygen therapy, respectively. They showed the following radiologic pattern on the CT: emphysema-like (7.5%), pleural effusion (22.5%), ground-glass opacities (17.5%), multiple ground-glass opacities (75.0%), nodular consolidation (30.0%), multiple consolidation (32.5%), bronchiectasis (5.0%), and lobar consolidations (5.0%).

Data of 39 of 220 individuals (17.7%) with ILD, and 41 of 450 (9.1%) with COPD were also analyzed, their characteristics are shown in Table 1. No individual was under long-term oxygen therapy. The most frequent diagnosis for ILD was idiopathic pulmonary fibrosis (12 individuals), other diagnoses included nonspecific interstitial pneumonia (5), unclassifiable ILD (8), and other diagnoses of ILD

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Table 1. Characteristics of the Individuals

Characteristic	ILD ($n = 39$)	COPD ($n = 41$)	COVID-19 ($n = 40$)	P
Age, mean ± SD y	7.3 ± 10.3	65.3 ± 8.4	65.2 ± 11.4	.043
Males, *n* (%)	24 (61.5)	28 (68.3)	26 (65.0)	.82
BMI, mean ± SD kg/m^2	27.1 ± 5.3	24.6 ± 2.8	25.9 ± 7.8	.068
Comorbidities, %				
Hypertension	66.6	60.9	55.0	.68
Cardiovascular disease	10.2	12.1	7.5	.09
Diabetes	15.3	19.5	17.5	.08
Chronic airway obstruction	0	100	17.5	.003
Obesity	2.5	26.8	20.0	.57
Renal	5.0	4.8	2.5	.93
Time of disease, mean ± SD				
Years	3.1 ± 2.2	8.3 ± 5.4	ND	.10
Days	ND	ND	35.2 ± 10.7	
ILD-GAP stage, %[*]				
1 – 2	35	NA	ND	
3 – 4	41	NA	ND	
>4	24	NA	ND	
GOLD, % ($n = 39$)				
I	NA	7	ND	
II	NA	29	ND	
III	NA	35	ND	
IV	NA	29	ND	
FEV_1, mean ± SD % of predicted	79.8 ± 19.4[*]	47.5 ± 21.9[†]	77.4 ± 20.2[*]	<.001[‡§]
FVC, mean ± SD % of predicted	77.6 ± 17.7[*]	84.5 ± 18.6[†]	73.2 ± 21.0[*]	.042[§]
FEV_1/FVC, mean ± SD %	8.9 ± 13.6[*]	42.5 ± 51.0[†]	85.1 ± 11.6[*]	<.001[‡§]
D_{LCO}, mean ± SD % predicted	53.5 ± 18.1[‖]	46.1 ± 17.9[¶]	53.9 ± 2.8[**]	.23
mMRC scale score, mean ± SD	2.1 ± 1.3	2.4 ± .8	2.5 ± .9	.33
P_{aO_2}/F_{IO_2}, mean ± SD mm Hg	353.0 ± 36.4[¶]	325.4 ± 41.4[†]	325.1 ± 9.4[††]	.09

[*] $n = 38$.
[†] $n = 39$.
[‡] Significant difference: COPD vs ILD.
[§] Significant difference: COVID vs COPD.
[‖] $n = 36$.
[¶] $n = 37$.
[**] $n = 26$.
[††] $n = 40$.
ILD = interstitial lung disease
COVID-19 = coronavirus disease 2019
BMI = body mass index
ND = no data
GAP = gender–age–physiology
NA = not applicable
GOLD = Global Initiative for Chronic Obstructive Lung Disease
D_{LCO} = carbon monoxide diffusion capacity
mMRC = modified Medical Research Council

(14). Compared with the other 2 groups, the individuals with ILD were significantly older. As expected, individuals with COPD showed an obstructive ventilatory pattern as assessed by FEV_1/FVC, whereas FVC was significantly lower in individuals with COVID-19 or ILD than in those with COPD. No significant differences among the groups were observed in level of oxygenation at rest, severity of dyspnea as assessed by mMRC, or in the number of comorbidities, with the expected exception of chronic airway obstruction. To improve dyspnea and well-being, all subjects used oxygen supplementation to maintain > 92% during exercise. Only 5 of 40 were discharged from our institutions with oxygen therapy during exercise.

The results of the 6MWT are shown in Table 2. Individuals with COVID-19 walked < 70% of predicted and had a 6MWT performance similar to those of individuals with ILD. Significantly greater differences were observed with individuals with COPD: compared with individuals with COPD, those with COVID-19 had more severe leg fatigue at rest and exercise; walked significantly less, with more severe dyspnea as assessed by the Borg scale; and showed more desaturation per walked meter. The

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Table 2. Data for the Exercise Test

Exercise Test	ILD ($n = 39$)	COPD ($n = 41$)	COVID-19 ($n = 40$)	P
6MWD, m	368.1 ± 132.0	429.1 ± 97.8	350.0 ± 137.0	.01*
6MWT, % of predicted	79.2 ± 26.6	81.9 ± 16.9	68.2 ± 24.9	.02*
Borg dypnea at rest	0.3 ± 0.9	0.3 ± 0.9	0.4 ± .8	.74
Borg dypnea at the end of the test	4.2 ± 2.8	2.6 ± 1.6	3.5 ± 2.2	.01†
Borg fatigue at rest	0.6 ± 1.2	0.1 ± 0.5	0.7 ± 1.1	.039*
Borg fatigue at the end of the test	2.9 ± 2.3	1.5 ± 1.7	2.5 ± 2.2	.01†
End test Borg dypnea/m	0.015 ± 0.017	0.007 ± 0.005	0.014 ± 0.019	.02†
End test Borg fatigue/m	0.011 ± 0.014	0.004 ± 0.005	0.011 ± 0.019	.03*
Peak heart rate				
Beats/min	12.8 ± 12.3	11.4 ± 11.0	125.2 ± 14.4	<.001*†
% of predicted	81.0 ± 9.0	71.4 ± 6.2	81.1 ± 9.8	<.001*†
S_{pO_2}				
Baseline, %	94.8 ± 1.7	93.6 ± 2.2	95.0 ± 2.2	.005*†
Mean, %	88.7 ± 2.5	88.3 ± 2.4	88.9 ± 3.4	.57
Nadir, %	85.1 ± 3.9	84.8 ± 3.2	86.2 ± 4.1	.19
ΔS_{pO_2} ‡				
Percentage	6.2 ± 2.2	5.5 ± 1.5	6.3 ± 2.1	.12
/m, %	0.021 ± 0.182	0.013 ± 0.004	0.023 ± 0.021	.02*

Data are reported as mean ± SD.
* Significant difference: COVID vs COPD
† Significant difference: COPD vs ILD;
‡ S_{pO_2} baseline – S_{pO_2} nadir.
ILD = interstitial lung disease
COVID-19 = coronavirus disease 2019
6MWD = 6-min walk distance
6MWT = 6-min walk test

Table 3. Correlations Between ΔS_{pO_2}/meter % and Physiological and Baseline Data

Independent Variable	ILD ($n = 39$)		COPD ($n = 41$)		COVID-19 ($n = 40$)	
	r	P	r	P	r	P
Age	0.1236	.45	0.0439	.79	0.0453	.78
BMI	0.2444	.14	–0.1507	.35	0.2026	.21
S_{pO_2} %	–0.3496	.03	–0.0964	.55	–0.0964	.55
P_{aO_2}/F_{IO_2}	–0.3072	.064	–0.2360	.172	–0.4317	.005
FEV_1 % of predicted	–0.2002	.23	–0.3126	.059	–0.0990	.57
FVC % of predicted	–0.2601	.12	–0.2742	.10	–0.1489	.39
FEV_1/FVC	0.0516	.76	–0.4317	.02	0.4413	.007
D_{LCO} % of predicted	–0.3019	.11	–0.5050	.005	–0.2978	.25
Borg dyspnea	0.0711	.67	0.1309	.41	–0.0736	.65
Borg fatigue	0.3571	.03	0.1007	.53	–0.1452	.37
mMRC scale	0.2558	.16	0.4484	.27	0.3958	.02

ILD = interstitial lung diseases
COVID-19 = coronavirus disease 2019
BMI = body mass index
D_{LCO} = carbon monoxide diffusion capacity
mMRC = modified Medical Research Council

correlations of levels of exercise-induced desaturation expressed as ΔS_{pO_2}/meter % with physiologic and symptom data are shown in Table 3.

The severity of exercise-induced desaturation in individuals with COVID-19 was significantly correlated with the severity of dyspnea, inversely correlated with the level of oxygenation and with the level of airway obstruction. In individuals with ILD, the depth of exercise-induced desaturation was significantly and negatively correlated with the level of oxygenation and positively correlated with leg fatigue. In the individuals with COPD, the level of exercise-induced desaturation was correlated with the severity of airway obstruction and impairment of D_{LCO}.

The correlations of exercise capacity as assessed by using 6MWT and baseline parameters are shown in Table 4. In the study, the distance walked by individuals with COVID-19 was significantly correlated with D_{LCO} and oxygenation. In individuals with ILD, the walked distance was significantly correlated with the level of hypoxemia and inversely correlated with the severity of dyspnea. In the individuals with COPD, the walked distance was inversely correlated with the severity of dyspnea and positively with FVC.

Discussion

This study showed that individuals who were recovering from COVID-19 associated pneumonia, normoxemic at rest with exercise-induced desaturation, had exercise limitation,

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Table 4. Correlations Between 6MWT and Baseline Data

Independent Variable	ILD ($n = 39$)		COPD ($n = 41$)		COVID-19 ($n = 40$)	
	r	*P*	r	*P*	r	*P*
Age	–0.3437	.032	–0.2390	.14	–0.2390	.14
BMI	–0.2269	.17	–0.0318	.85	–0.2922	.067
S_{pO_2} %	0.4590	.003	0.2701	.09	0.0248	.88
P_{aO_2}/F_{IO_2}	0.3398	.039	0.0505	.77	0.3332	.035
FEV_1 % of predicted	–0.1055	.54	0.2229	.18	0.1811	.29
FVC % of predicted	0.2638	.11	0.5450	<.001	0.1925	.26
FEV_1/FVC %	0.2890	.08	0.2127	.25	–0.3113	.064
D_{LCO} % of predicted	0.2568	.17	0.2301	.23	0.6044	.01
Borg dyspnea	–0.0018	.99	–0.2315	.15	0.1876	.25
Borg fatigue	–0.1796	.28	–0.1094	.50	0.1257	.44
mMRC scale	–0.4165	.02	–0.4091	.034	–0.1349	.45

6MWT = 6-min walk test
ILD = interstitial lung disease
COVID-19 = coronavirus disease 2019
D_{LCO} = carbon monoxide diffusion capacity
mMRC= modified Medical Research Council

and, as a whole, performed similarly on walking tests to individuals with ILD and with exercise-induced desaturation. Leg fatigue and dyspnea at the end-exercise were higher in ILD than in COPD, but the differences between COVID-19 and either COPD or ILD were not significant. Our results supported the expected similarities in the pattern of symptoms, exercise-induced desaturation, and lung function with ILD compared with COPD with exercise-induced desaturation. The physiologic similarities of individuals with COVID-19 and with exercise-induced desaturation with ILD suggest the term "fibrotic post COVID-19." It has been reported that 4 months after hospitalization for COVID-19, individuals frequently had symptoms not previously present, and lung-scan abnormalities were common, including fibrotic lesions.[30] The finding that exercise-induced desaturation correlated with the severity of dyspnea and leg fatigue may contribute to the discussion on silent hypoxemia in COVID-19 illness and the lack of a considerable effect of mild hypoxemia on exertional symptoms in many other patients with chronic lung diseases.

Results of our study suggest that exercise-induced desaturation contributes to dyspnea symptoms and exercise intolerance after having COVID-19; however, there are many other individuals recovering from COVID-19 who seem to have prolonged respiratory and exertional symptoms after recovery (so-called long COVID). The participants with COVID-19 were assessed 46.6 ± 24.4 d from the acute onset of disease. The trajectory of exercise-induced desaturation in COVID-19 induced lung disease is of utmost importance; however, answering this question was outside the scope of this article. However, it has been reported that, at 6 months after acute infection, survivors of COVID-19 were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression.[31] Shah et al [32] found that 12 weeks after COVID-19 symptom onset at least one pulmonary function variable was abnormal in 58% of their subjects and 88% had abnormal imaging on CTs of the chest. There was a strong association between the days on oxygen supplementation during the acute phase of COVID-19 and both D_{LCO} % of predicted and total CT score.

Also, our individuals recovering from COVID-19 in our study had a more severe sensation of muscle fatigue as assessed by the Borg scale, at rest and after exercise, as well as from a reduction in exercise capacity, as shown by 6MWT < 70% of predicted. These values were even worse than those of individuals with COPD and similar to ILD with exercise-induced desaturation. No significant differences among the groups were observed in, level of oxygenation at rest, or in the severity of dyspnea as assessed by mMRC. The reduction in exercise capacity in our cohort can be explained. In the survivors of COVID-19 of our study, the exercise capacity as assessed by the 6MWT was strongly correlated with D_{LCO} (Table 4). At difference, individuals with COPD or ILD did not show any correlation between 6MWT and D_{LCO} (Table 4). The study[31] also reported that survivors of COVID-19 who were more severely ill had more severe impairment of the D_{LCO} and in CT scan score.[31]

A recent systematic review on lung function after COVID-19 reports 39, 15, and 7% prevalence for altered D_{LCO}, restrictive pattern, and obstructive pattern, respectively.[33] As an original result, our individuals with COVID-19 and with exercise-induced desaturation showed D_{LCO} values approximately half of predicted, similar to individuals with ILD or with COPD and exercise-induced desaturation. What may be the cause of the low D_{LCO} reported in our and other studies, in these individuals? Our data cannot give an explanation. However, recent histopathologic studies[34-36] with lung cryobiopsies show almost pristine alveoli, enlarged and/or hyperplasic alveolar capillaries, along with dilatation of the post–capillary pulmonary venules. Besides other factors, the reported findings, therefore, could be explained by a reduction in the normal ventilation/perfusion ratio due to blood overflow around well-ventilated alveoli.[34-36]

Despite shorter walked distances with the 6MWT, the subjects with COVID-19 in our study showed higher heart rate peak % of predicted; therefore, any cardiac influence on our results cannot be excluded but need to be specifically evaluated. It was reported that subclinical myocardial dysfunction as assessed by the left-ventricular global longitudinal strain is frequent, occurring in 80% of individuals hospitalized with COVID-19, whereas prevalent left-ventricular function parameters such as reduced ejection fraction and wall motion abnormalities were less frequent findings.[37] A cardiopulmonary exercise test would have added information in this regard. Likewise, we could not

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exclude any dysfunction of peripheral muscles because, in this study, we did not assess any direct muscle function. However, in a previous study, we found a high prevalence of impairment in peripheral muscle strength (including the quadriceps) in hospitalized individuals recovering from COVID-19 pneumonia without any previous locomotor disability.[4]

When evaluating individuals with exercise-induced desaturation, a crucial point is the definition. Definitions of exercise-induced desaturation vary widely in clinical trials, including a $S_{pO_2} \leq 88\%$ and a decrease in $S_{pO_2} \geq 4\%$ with or without a nadir $S_{pO_2} < 90\%$.[11,38-40] For the purposes of this study, we defined exercise-induced desaturation as baseline S_{pO_2} – nadir $S_{pO_2} > 4\%$ during the 6MWT.[25,28] By using this definition, the prevalence of simultaneous normoxemia and exercise-induced desaturation in our individuals with COVID-19 was 26.6%. The prevalence of exercise-induced desaturation among individuals with COPD and ILD varies according to the selected study population and disease severity, which ranged from 20 to 53% for individuals with moderate-to-severe COPD,[10,11,41] whereas 49–54% of unselected individuals with ILD, experience exercise-induced desaturation. [39] However, the prevalence of exercise-induced desaturation among individuals with COPD and ILD remains unclear, in part, due to the lack of common definitions and test modalities.

Limitations of the Study

All retrospective studies have limitations. CTs of the individuals with COPD or ILD were not available and some data were missing. Neither comparisons of respiratory and peripheral muscle function nor lung volumes were reported. We used the mMRC score to assess dyspnea: in the individuals with chronic diseases such as COPD and ILD, mMRC may reflect a "steady" state, whereas COVID-19 is an evolving condition. In this case, mMRC may have assessed the status at the time of measurement, which makes a comparison among different diseases questionable.

It would have been useful to clinicians caring for such patients to know whether the addition of supplemental oxygen during exertion alleviated symptoms or improved functional ability. The beneficial effects of supplemental oxygen on exercise tolerance are well known in COPD and ILD, whereas there is still limited information with regard to COVID-19 so far.[42] The evaluation of the effects of supplemental oxygen on exercise tolerance was outside of the aims of the study. Furthermore, we believe that performing an exercise test without supplemental oxygen in individuals who are severely hypoxemic could be detrimental.[43]

Conclusions

Individuals recovering from COVID-19 associated pneumonia, normoxemic at rest with exercise-induced desaturation, have exercise limitation similar to individuals with ILD. Leg fatigue and dyspnea at the end-exercise were higher in ILD than in COPD, but the differences between COVID-19 and either COPD or ILD were not significant. Further studies should evaluate whether subjects with COVID-induced exercise-induced desaturation improve in terms of exercise capacity compared with patients with ILD and patients with COPD, who generally continue to worsen over time. Indeed, a great deal of the clinical utility of this study depends on the later trajectory of COVID-19 lung injury and exercise-induced desaturation.

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