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Symptoms, Pulmonary Function and Functional Capacity Four Months after COVID-19

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Emerging reports demonstrate persistent symptoms and lung function impairment in COVID-19 survivors discharged from hospital (1-6). However, little is known about the longer-term impact of COVID-19 in patients not requiring hospitalization. We hypothesized that both hospitalized and non-hospitalized COVID-19 survivors will have persistent symptoms, impaired pulmonary function and a diminished functional capacity three months after SARS-CoV-2 infection.

Methods

Patients were prospectively screened and recruited from The Ottawa Hospital administrative registry and from out study website (https://omc.ohri.ca/left/) in sequential order. Patients had to be ≥18 years of age and diagnosed with SARS-CoV-2 infection by RT-PCR 3-months (+6 weeks) before enrolment. The study was approved by The Ottawa Health Science Network Research Ethics Board.

Patients retrospectively reported the presence and severity of symptoms during the acute phase of illness (5-point scale; 0-absent, 4-very severe) and at the 3-month study visit (6-point scale; 0-absent, 5-much worse now). Patients underwent transthoracic echocardiography, pulmonary function testing and a symptom-limited incremental (15 watts per minute) cycle cardiopulmonary exercise test (CPET) (7).

Pulmonary function (8, 9) and CPET variables (10) were referenced to predicted normal values. Chronotropic insufficiency (CI) was defined as a heart rate reserve of <0.8 (11).

Mean differences between hospitalized and non-hospitalized patients were evaluated using Student's t-tests or Mann-Whitney U-tests. Binary variables were evaluated using Chisquare test. Analyses were performed using SPSS Version 9.0 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p<0.05$ and values are reported as mean±SD unless otherwise stated.

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Keywords: exercise, functional capacity, breathlessness, pulmonary function

Results

Between June and October 2020, 91 patients were screened for eligibility at The Ottawa Hospital. Of these, 15 refused participation and 13 did not meet the inclusion criteria. At the end, 25 hospitalized and 38 non-hospitalized patients were enrolled. Time to follow-up was 119.9±16.2 days after the first positive SARS-CoV-2 test result for hospitalized patients and 129.8±16.5 days for non-hospitalized patients. Hospitalized patients were older and had a higher prevalence of comorbid conditions (Table 1).

In both groups, fatigue (hospitalized, 92.0%; non-hospitalized, 97.4%) and exertional breathlessness (hospitalized, 76.0%; non-hospitalized, 81.6%) were frequently reported during the acute phase of COVID-19. At follow-up, fatigue (hospitalized, 72.0%; non-hospitalized, 71.1%) and exertional breathlessness (hospitalized, 68.0%; non-hospitalized,55.3%) persisted as two of the most frequently reported symptoms (Table 1).

Forced vital capacity, total lung capacity (TLC), and the diffusing lung capacity for carbon monoxide (DLCO) were lower in hospitalized patients. Subnormal TLC and DLCO were more prevalent in hospitalized patients. Left ventricular ejection fraction was similar between groups (Table 2).

Peak VO2 %predicted was lower in hospitalized vs. non-hospitalized patients (hospitalized, 64.3+19.2%; non-hospitalized, 83.5+17.9%). Indices of respiratory mechanics, including inspiratory capacity and inspiratory reserve volume were lower for a given VO2 in hospitalized patients (Table 2, Figure 1). Peak heart rate, heart rate reserve, and oxygen pulse were lower, and the ventilatory equivalent for carbon dioxide nadir was higher in hospitalized patients. CI was identified in 68.0% of hospitalized and 18.4% of non-hospitalized patients (Table 2). CI could not be explained by medication use alone, as only 35.0% and 0.0% of hospitalized and non-hospitalized patients with CI, respectively, were receiving heart rate modifying treatment. Breathlessness and leg discomfort ratings were higher for a given VO2 in hospitalized patients but were not different between groups at end-exercise (Table 2, Figure 1). Leg discomfort was the most frequently reported locus of symptom limitation to exercise in both groups, although it occurred at a lower peak VO2 in hospitalized vs. non-hospitalized patients (Table 2).

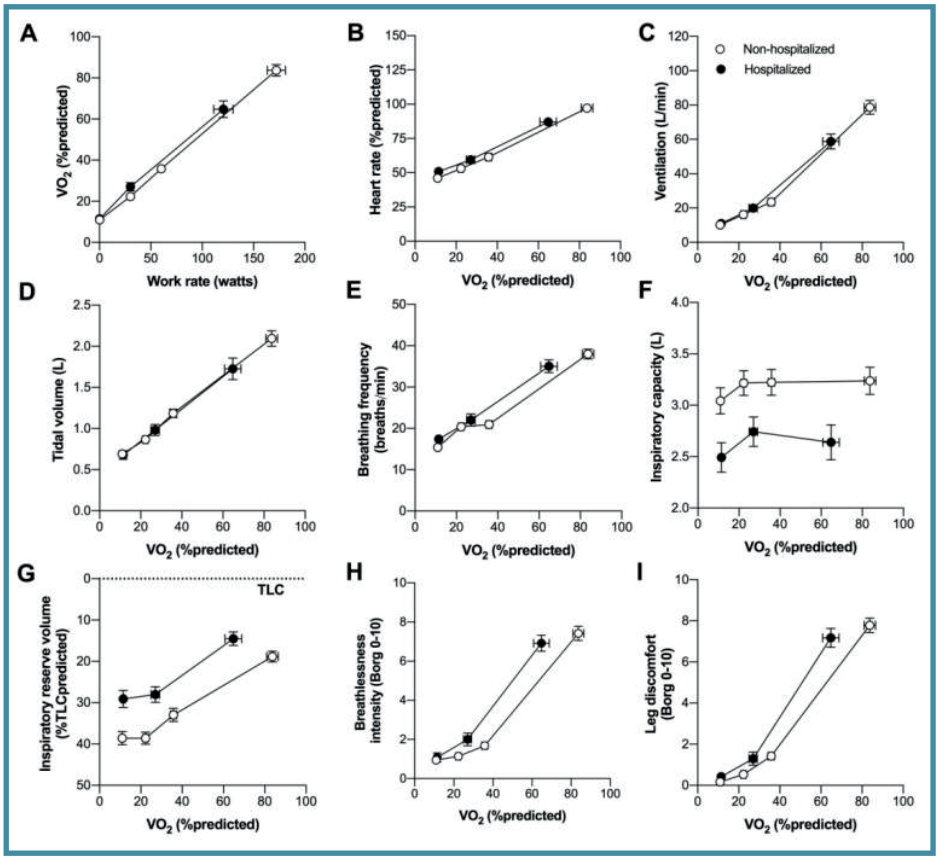

Figure 1. VO_2 during an incremental cycle exercise test (A), and heart rate (B), ventilation (C), tidal volume (D), breathing frequency (E), inspiratory capacity (F), inspiratory reserve volume (G), breathlessness intensity (H) and leg discomfort (I) for a given VO_2 %predicted in hospitalized and non-hospitalized COVID-19 patients three to four months after SARS-CoV-2 infection. Data presented at rest, iso-work rate (highest equivalent work rate completed by all patients within each group) and peak exercise. Values are mean±SEM. TLC, total lung capacity; VO_2, oxygen consumption.

Table 1. Demographics, baseline characteristics, admission details and symptoms in hospitalized and non-hospitalized COVID-19 patients.

	Hospitalized (n=25)	Non-hospitalized (n=38)
Age, years	59.1±13.5	42.4±12.9
Sex (%Male)	64.0	52.6
BMI, Kg/m²	30.07±7.50	28.17±5.62
Black, Asian and minority ethnic groups, n (%)	9 (36)	7 (18.4)
Cigarette smoking, n (%)		
Never smoker	17 (68.0)	28 (73.7)
Active smoker	0	0
Past smoker	8 (32.0)	10 (26.3)
Charlson comorbidity index	2.12±1.72	0.37±0.59
Comorbidities, n (%)		
Obesity (BMI≥30)	8 (32.0)	13 (34.2)
Hypertension	10 (40.0)	4 (10.5)
Dyslipidemia	10 (40.0)	2 (5.3)
Diabetes	10 (40.0)	1 (2.6)
Asthma (self-reported)	9 (36.0)	9 (23.7)
Chronic obstructive pulmonary disease	0	1 (2.6)
Pulmonary fibrosis	1 (4.0)	0
Obstructive sleep apnea	5 (20.0)	0
Heart failure	1 (4.0)	1 (2.6)
Atrial fibrillation	3 (12.0)	3 (7.9)
Active cancer	5 (20.0)	0
COVID-19 illness		
Symptom prevalence, n (%)		
Exertional breathlessness	19 (76.0)	31 (81.6)
Mild to moderate	4 (16.0)	22 (57.9)
Severe to very severe	15 (60.0)	9 (23.7)
Fatigue	23 (92.0)	37 (97.4)
Mild to moderate	7 (28.0)	13 (34.2)
Severe to very severe	16 (64.0)	24 (63.2)
Length of hospital stay, days	17.12±17.20	--
Required ICU admission, n (%)	10 (40.0)	--
Required oxygen, n (%)	21 (84.0)	--
Completed rehabilitation program, n (%)	5 (20.0)	0
Days to assessment, mean ±SD (days)		
Days since first positive COVID-19 test result	119.9±16.2	129.8±16.5
Days since discharge from hospital	102.3±8.4	--
Symptom persistence 3-months after COVID-19 illness, n (%)		
Exertional breathlessness	17 (68.0)	21 (55.3)
Much or somewhat better	15 (60.0)	17 (44.7)
Same as during the acute phase of infection	1 (4.0)	2 (5.3)
Worse or much worse than during the acute phase of infection	1 (4.0)	2 (5.3)
Fatigue	18 (72.0)	27 (71.1)
Much or somewhat better	15 (60.0)	19 (50.0)
Same as during the acute phase of infection	2 (8.0)	7 (18.4)
Worse or much worse than during the acute phase of infection	1 (4.0)	1 (2.6)

Values are No. (%) or mean±SD.

Table 2. Spirometry, lung volumes, diffusing lung capacity for carbon monoxide, transthoracic echocardiography and measurements at the peak of symptom-limited incremental cycle CPET in hospitalized and non-hospitalized COVID-19 patients three to four months after infection.

	Hospitalized (n=25)	Non-hospitalized (n=38)
Spirometry		
FEV_1, %predicted	90.3±13.5	95.5±14.7
FEV_1 <LLN, n (%)	4 (16.0)	4 (10.5)
FVC, % predicted	88.6±14.5	**100.7±14.3****
FVC <LLN, n (%)	6 (24.0)	**1 (2.6)***
FEV_1/FVC, %	76.0±7.0	75.5±7.8
FEV_1/FVC < LLN, n (%)	1 (4.0)	6 (15.8)
Lung volumes		
TLC, %predicted	84.7±14.5	**95.7±12.1****
TLC <LLN, n (%)	12 (48.0)	**3 (7.9)*****
RV, %predicted	76.5±21.6	79.7±17.7
RV <LLN, n (%)	8 (32.0)	4 (10.5)
RV/TLC, %predicted	30.0±6.8	**24.0±6.7*****
RV /TLC <LLN, n (%)	7 (28.0)	13 (34.2)
Diffusing capacity		
DLCO, %predicted	69.1±14.9[f]	**81.5±15.1****
DLCO < LLN, n (%)	17 (70.8)[f]	**12 (31.6)****
DLCO/VA, %predicted	90.7±14.3[f]	96.8±17.0
DLCO/VA <LLN, n (%)	2 (8.3)[f]	4 (10.5)
Transthoracic echocardiography		
LVEF, %	63.6±2.5[T]	62.7±3.7
LVEF <55%, n (%)	0[T]	1 (2.6)
Measurements at the peak of symptom-limited incremental cycle CPET		
Work rate, % predicted	80.2±24.8	**99.2±26.1****
VO_2, % predicted	64.3±19.2	**83.5±17.9*****
VO2 %predicted <85%, n (%)	20 (80.0)	**21 (55.2)***
VCO_2, L/min	1.73±0.65	**2.43±0.80*****
RQ	1.24±0.11	1.24±0.09
RQ <1.05, n (%)	1 (4.0)	1 (2.6)
HR, %predicted	86.1±15.0	**97.0±9.0****
O_2 pulse, %predicted	71.9±19.3	**81.3±12.8***
HRR, %	65.4±24.6	**87.9±18.8*****
HRR <0.8, n (%)	17 (68.0)	**7 (18.4)*****
SPO_2, %	97.0±1.5	97.0±1.7
VE, %predicted MVV	51.0±13.1	**57.8±12.2***
VE/VCO_2, nadir	32.40±5.65	**29.04±4.16****
IC, % predicted	80.6±17.9	**92.4±15.9****
IRV, L	0.92±0.50	1.13±0.48
Symptoms, Borg scale 0-10		
Breathlessness Intensity	6.8±2.1	7.4±2.2
Leg Discomfort	7.1±2.3	7.8±2.1
Reason for stopping, n (%)		
Breathing discomfort	3 (12.0)	12 (31.6)
Leg discomfort	13 (52.0)	17 (44.7)
Combination of breathing and	7 (28.0)	9 (23.7)
Other		
Anxiety	1 (4.0)	0
Knee pain	1 (4.0)	0

Values are No. (%) or mean±SD. CPET, cardiopulmonary exercise test; DLCO, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity, FEV_1, forced-expiratory volume in 1-second; HR, heart rate; HRR, heart rate reserve; IC, inspiratory capacity; IRV, inspiratory reserve volume; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MVV, maximum voluntary ventilation; RV, residual volume; RQ, respiratory quotient; SPO_2, oxygen saturation by pulse oximetry; TLC, total lung capacity; VA, alveolar volume; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption. [f]n=24, one patient was unable to perform DLCO. [T] n=24, one patient did not complete transthoracic echocardiography. *p<0.05, **p<0.01, ***p<0.001

Discussion

Consistent with previous studies, we found that hospitalized and non-hospitalized survivors of COVID-19 report persistent fatigue and exertional breathlessness and exhibit impaired lung function and diminished functional capacity three to four months after SARS-CoV-2 infection (1-6). While cardiopulmonary abnormalities were observed in both groups, they were more prevalent and severe in hospitalized patients.

Non-resolving lung parenchymal or pulmonary vascular lesions from the time of the acute infection (4) may account for the higher rate and severity of pulmonary sequelae in hospitalized patients. Persistent breathlessness in hospitalized patients may partly be explained by the residual impairments in TLC and DLCO. While these findings are consistent with studies that evaluated breathlessness in patients with similar lung function defects (12), we cannot rule out the confounding effects of age, obesity and co-morbid conditions on lung mechanics, which may explain some of the differences between groups. Furthermore, extrapulmonary factors likely also contributed to breathlessness during exercise as both groups reported severe breathlessness (Borg >6) at end-exercise despite the presence of a ventilatory reserve.

Cardiorespiratory fitness is a powerful predictor of mortality in the general population (13). It is therefore striking that >50% of our COVID-19 survivors had a peak VO_2 below 85% predicted, a rate that is comparable to patients recovered from severe acute respiratory syndrome (14). The respiratory quotient >1.05 in conjunction with a ventilatory reserve at peak exercise suggests that cardiovascular factors were the primary cause of exercise limitation in both groups. Impaired tissue perfusion and/or skeletal muscle atrophy and dysfunction may be significant mediators of a low VO_2, particularly in hospitalized patients who reported higher leg discomfort for a given VO_2. This hypothesis is supported by the observed reduction in oxygen pulse in the context of a preserved ejection fraction in hospitalized patients, increasing evidence of COVID-19 related microvascular injury in various organs, and the effects of critical illness on muscle wasting (15). Furthermore, compromised oxygen utilization at the peripheral muscles may exacerbate symptom perception, which may result in the early attainment of intolerable breathlessness and premature termination of exercise (16, 17). Physical deconditioning and concurrent comorbid conditions likely also contributed to the reduction in peak VO_2 in hospitalized patients. Finally, poor cardiorespiratory fitness in hospitalized patients may be preceded SARS-CoV-2 infection (18).

We provide the first report of CI in patients recovering from COVID-19. The lower peak VO_2 and heart rate in hospitalized vs. non-hospitalized patients in the setting of a comparable peak respiratory quotient suggests that CI contributed to exercise limitation. The source of CI is unknown but may be due to the high prevalence of comorbid conditions in hospitalized patients, or it may be secondary to patients becoming breathless and terminating exercise before achieving a maximal heart rate response.

Limitations of this study include a small samples size, lack of pre-morbid baseline information, and absence of matched control groups. Therefore, we cannot be certain if the physiologic abnormalities in our patients preceded or followed SAR-CoV-2 infection. Given the important differences in the demographic and clinical make-up of our study groups, we could not adequately assess the confounding effects of pre-existing comorbidities could have on our observations. Finally, we caution against the generalizability of our results given the small sample size and use of Canadian reference values (8-10).

In conclusion, we demonstrate mild impairments in lung volumes and gas exchange and a diminished functional capacity three to four months after discharge from hospital with SARSCoV-2 infection, which occurred in the presence of a preserved left ventricular ejection fraction. Investigations into the effects of COVID-19 on peripheral muscle structure, perfusion and function are warranted. Additional studies are required to understand the mechanisms of breathlessness after SARS-CoV-2 infection, particularly in patients not requiring hospitalization.

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