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Letter to the Editor

Cardiopulmonary exercise test with stress echocardiography in COVID-19 survivors at 6 months follow-up

To the Editor

Although many studies suggest different degrees of myocardial and pulmonary injury during the acute infection and early follow-up [1–3], there is disagreement about cardio-pulmonary injury and functional impairment due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) during mid-term follow-up [4–8]. We attempt to evaluate the cardiopulmonary function and assess the pulmonary and myocardial injury objectively in SARS-CoV-2 survivors.

We performed a monocenter, prospective, observational study, recruiting in the outpatient's post covid clinic all the consecutive patients dismissed after hospitalization from our institution's pneumology department, between 18 March to 30 June 2020, with a diagnosis of SARS-CoV-2 pneumonia. We included patients $>$ 18 and $<$ 75 years old. According to the WHO Interim Guidance we categorized severity of illness as SARS-CoV-2 mild Pneumonia, Severe Pneumonia and acute respiratory distress syndrome (ARDS) . All the patients performed a static pulmonary function test (PFT), cardiopulmonary exercise test (CPET), and exercise test combined with echocardiography on the same day, six months after the first SARS-CoV-2 positive smear. Rest and peak exercise echocardiography were carried out at the same time of cardiopulmonary exercise test. Echocardiography was performed according to the European/American Society of echocardiography guidelines, CPET was performed using a microprocessor-controlled eddy current brake ergometer . Patients wore a non-rebreathing Hans-Rudolph Mask connected to Vyntus™ CPX Metabolic Cart. All the patients completed after 3 minutes of unloaded warm-up phase a symptoms limited exercise test with a 10/W/min ramp protocol. Patients were encouraged to exercise up to the maximal effort. Oxygen saturation with pulse oximetry and heart rate with 12 lead ECG monitoring was performed during the test. Measurements of mixed expired oxygen, mixed expired carbon dioxide and expired volume were determined at rest and for each breath throughout exercise. Written informed consent was obtained from all patients, and the study was approved by the ethics committee of our institution (CHUNSC_2020_50). The normality of the data distribution was determined using the Kolmogorov-Smirnov test. Parametric unpaired t-test or Mann-Whitney U was used to evaluate the difference between two groups for continuous variables. Comparison between the three groups was performed with ANOVA test for continuous variables. Chi-squared test was used for categorical variables. All comparisons were made using two-tailed tests, and the level of significance was set at $p < 0.05$. All statistical tests were performed using the open-access statistical package the jamovi project (2021). jamovi (Version 1.6) [Computer Software].

We recruited 41 SARS-CoV-2 survivors, 16 female (39%), mean age 57,3 ± 13,7 years. 9 patients (22%) presented ARDS, 20 patients (49%) presented severe pneumonia, 12 patients (29%) presented mild pneumonia. 29 patients (70%) persisted with symptoms during follow-up; the main symptoms were dyspnoea (56,1%) and asthenia (51,2%). 46,3% of patients presented a percent predicted peak oxygen uptake (% pVO2) $<$ 80%. This impairment was mild in the majority of patients (39%). 27% of patients presented alteration of Total Lung Capacity (TLC) and/or Diffusion Capacity of CO (DLCO); the grade of alteration was mild except in one ARDS group patient. 37% of patients presented ventilatory inefficiency data. 11 symptomatic patients (27%) presented an abnormal ventilatory response without datas of cardiac or pulmonary vascular sequelae, two patients presented oxygen desaturation with exercise and pathological Dead Space to Tidal Volume Ratio (Vd/VT) increment at exercise peak.

None of the patients presented severe pulmonary hypertension at rest, only one patient presented moderate pulmonary hypertension at rest. 7% of patients presented impaired RV function. No data of LV contractility alteration and no exercise-induced arrhythmias was detected.

Comparing mild pneumonia group, severe pneumonia group and ARD's group, we found no significant trend of higher prevalence of symptoms and pulmonary sequelae according to the severity of illness. No significant trend of lower aerobic capacity between groups was detected (%pVO2: 86% Vs 82% Vs 74%; P 0,243).

We performed a complete static pulmonary test of 37 patients. 17 patients (41,5%) presented abnormal respiratory tests; 13 (76,5%) persisted with dyspnoea during follow-up.

Severe Pneumonia group and ARDS group presented a significant lower DLCO value respect to mild Pneumonia group (6,85 VS 7,72 VS 9,35 mmol/min*kPa; p 0,04, p 0,033). Abnormal DLCO and/or TLC were detected in 10 patients (27%). Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC abnormalities were detected in 8 (19,5%), 3 (7,3%), 4 (9,8%) patients, respectively.

Comparing patients with VO2 peak >80% predicted and patients with VO2< 80%, we didn't find a difference in symptoms prevalence (72% Vs 68%; NS).

There was no significant trend of reduced DLCO<80% in VO2<80% group (26,3% Vs 4,5%; p 0,063) and TLC<80% (31,6% Vs 9,1%; p 0,092) (Table 1).

Many SARS-CoV-2 survivors without cardiac or pulmonary vascular sequelae presented an abnormal ventilatory response to exercise without significant desaturation or pathological Vd/Vt increase. This subgroup of patients showed a similar ventilatory response described by Baratto et al. [5] in a CPET study at the moment of hospital discharge of SARS-CoV-2 survivors and recently by Singh et al. [6] in patients without anemia or pulmonary disease after 11 months of infection. Baratto et al., postulated an enhanced PaCO2 (arterial Co2 partial pressure) chemoreflex sensitivity in SARS-CoV-2 survivors. Because of

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Table 1
Clinical Characteristics, Static and dynamic Pulmonary function Tests results, Basal and stress test echocardiographic characteristics of COVID-19 patients at 6 months follow-up. Comparison between Severity of Illness groups and between groups with percent predicted peak oxygen uptake > and < 80%.

Illness Severity – no. (%)	Mild Pneumonia 12 (29)	Severe Pneumonia 20 (49)	ARDS 9 (22)	Total 41	P (Mild Pneumonia VS Severe Pneumonia)	P (Mild Pneumonia Vs Ards)	P(Severe Pneumonia Vs Ards)	Peak VO2<80% pred – n 19 (46%)	Peak VO2>80% pred – n 22 (54%)	P
Mean age ,years - mean (±SD)	49,2 (13,4)	60 (14)	62 (7.9)	57,3 (13,7)	0,042	0,017	0,981	57,7 (13,8)	56,9 (13,9)	0,814
Female sex – no. (%)	5 (41,7)	9 (45)	2 (22,2)	16 (39)	0,854	0,350	0,242	6 (31,6)	10 (45,5)	0,364
Mean body mass index, kg/m2-mean(±SD)	28,2 (6,4)	32,9 (7,5)	28,11 (4,3)	30,4 (6,9)	0,039	0,964	0,080	28,4 (5,0)	32,2 (7,8)	0,089
Oxygen supply – no. (%)	0	20 (100)	9 (100)	29 (71)	<0,001	<0,001	-	13(68,4)	16 (84,2)	0,763
Hemoglobin,mg/dl-mean (±SD)	14,7(0,95)	14,1(1,50)	13,9 (1,50)	14,2 (1,38)	0,239	0,193	0,817	14,2 (1,44)	14,2 (1.33)	0,953
Symptoms – no. (%)	9 (75)	13 (65)	7 (77)	29 (70)	0,555	0,882	0,491	13 (68)	16 (72)	0,763
Dyspnoea – no. (%)	5 (41,7)	12 (60)	6 (66,6)	23 (56,1)	0,314	0,256	0,732	12 (63,2)	11 (50)	0,397
Asthenia – no. (%)	7 (58,3)	9 (45)	5 (55,6)	21 (51,2)	0,552	0,899	0,686	11 (57,9)	10 (45,5)	0,516
Pulmonary Disease– no. (%)	1 (9)	2 (10)	2 (22,2)	5 (12,2)	0,876	0,368	0,368	4(21)	1(4,5)	0,226
Obesity – no. (%)	4 (33,3)	13 (65)	4 (44,4)	21 (51,2)	0,082	0,604	0,298	7 (36,8)	14 (63)	0,087
Hypertension – no. (%)	3(25)	13 (65)	4 (44,4)	20 (48,8)	0,025	0,350	0,298	10 (52,6)	10 (45,5)	0,647
Diabetes mellitus, type 2 – no. (%)	2 (16,7)	7 (35)	5 (55,6)	14 (34,1)	0,264	0,061	0,298	7 (36,8)	7 (31,8)	0,735
Ischemic Cardiomiopathy– no. (%)	0	1 (5)	1 (11,1)	2 (4,9)	0,431	0,237	0,548	0	2 (9,1)	0,178
Dyslipidemia – no. (%)	3(25)	8 (40)	4 (44,4)	15 (36,6)	0,387	0,350	0,822	6 (31,6)	9 (40,9)	0,536
Static Pulmonary Function Test										
Lung function impaired	4 (33)	8(40)	5 (55)	17 (41)	0,706	0,309	0,436	10 (53)	7 (32)	0,177
FVC <80% of predicted normal – no. (%)	2 (16,7)	4 (20)	2 (22,2)	8 (19,5)	0,815	0,748	0,891	5 (26,3)	3 (13,6)	0,307
FEV1 < 80% of predicted normal – no. (%)	0	2 (10)	1 (11,1)	3 (7,3,)	0,258	0,237	0,928	3 (15,8)	0	0,053
FEV1:FVC <70 – no. (%)	0	3 (15)	1 (11,1)	4 (9,8)	0,159	0,237	0,779	2 (10,5)	2 (9,1)	0,877
TLC <80% of predicted normal – no. (%)	2 (18,1)	4 (20)	2 (33,3)	8 (19,5)	0,902	0,482	0,497	6 (31,6)	2 (9,1)	0,092
DLCO ,mmol/min*kPa – mean (± SD)	9,35 (2,05)	7,72 (2,07)	6,85 (2,18)	8,06 (2,21)	0,044	0,033	0,378	7,54 (2,42)	8,56 (1,93)	0,169
DLCO <80% of predicted normal – no. (%)	1 (9)	2 (10)	3 (50)	6 (14,6)	0,935	0,057	0,029	5 (26,3)	1 (4,5)	0,063
TLC and/or DLCO <80%- no. (%)	2(18,1)	5(25)	3(50)	10 (27)	0,664	0,169	0,245	7 (36,8)	3 (13,6)	0,114
CPET										
Peak VO2 %pred -mean (± SD)	86,0 (16,6)	81,7 (15,2)	73,6 (15,6)	81 (16)	0,459	0,099	0,200	67,8 (8,1)	92,8 (11,0)	<0,001
Peak VO2<80%pred – no. (%)	6 (50)	8 (40)	5 (55,6)	19 (46,3)	0,581	0,801	0,436			
Breath Reserve < 20% of predicted normal – no. (%)	3 (25)	4 (20)	3 (33,3)	10 (24,4)	0,740	0,676	0,438	3 (15,8)	7 (31,8)	0,233
VO2/HR, %pred-mean (± SD)	100 (20,9)	102 (33.1)	102 (60,9)	101 (37,2)	0,857	0,413	0,409	79 (12,8)	121 (40,3)	<0,001
PetCO2@AT-mean (± SD)	38,7 (2,2)	35,8 (4,8)	36,22 (3.9)	36,7 (4,14)	0,110	0,083	0,945	36,7 (3,84)	36,7(4,47)	0,992
VE/VCO2@AT- mean (± SD)	28 (2,3)	30,8 (5,8)	32,9 (5.9)	29,4 (6,5)	0,308	0,028	0,212	30,7 (5,1)	30,3 (5,4)	0,795
VE/VCO2@AT >35 – no. (%)	0	3 (15)	2 (22,2)	5 (12,2)	0,159	0,086	0,634	3 (15,8)	2 (9,1)	0,513
Vd/Vt peak exercise – mean (± SD)	12,4 (3,6)	13,6 (3,4)	18 (5,8)	14,2 (4,5)	0,381	0,014	0,015	15.6 (4,6)	13 (4,2)	0,067

(*continued on next page*)

Table 1 (*continued*)

Illness Severity – no. (%)	Mild Pneumonia 12 (29)	Severe Pneumonia 20 (49)	ARDS 9 (22)	Total 41	P (Mild Pneumonia VS Severe Pneumonia)	P (Mild Pneumonia Vs Ards)	P(Severe Pneumonia Vs Ards)	Peak VO2<80% pred – n 19 (46%)	Peak VO2>80% pred – n 22 (54%)	P
Vd/Vt >20% – no. (%)	0	1 (5)	3 (33,3)	4 (9,8)	0,431	0,031	0,041	2 (10,5)	2 (9,1)	0,877
VCO2slope-mean (± SD)	27,8 (5)	30,5 (7,5)	29,11 (5,8)	29,4 (6,4)	0,251	0,605	0,817	28.8 (6,0)	29.9 (6,9)	0,596
VCO2slope>30 – no. (%)	2 (16,7)	10 (50)	3 (33,3)	15 (36,5)	0,059	0,375	0,404	7 (36,8)	8 (36,4)	0,975
RER-mean (± SD)	1,16 (0,05)	1,13 (0,09)	1,17 (0,06)	1,15 (0,07)	0,296	0,724	0,250	1,14(0,09)	1,16 (0,07)	0,363
HRR,beats-mean (± SD)	20 (14)	24 (16)	17 (16)	21 (15)	0,545	0,651	0,347	21(14)	21(17)	0,997
SaO2 rest,%-mean (± SD)	99,4 (0,66)	99,3 (1,17)	99,0 (1,12)	99,3 (1,03)	0,879	0,300	0,394	99,2 (0,78)	99,3 (1,21)	0,742
SaO2 peak, %-mean (± SD)	99,0 (1,13)	98,8 (1,97)	96,4 (3,78)	98,3 (2,46)	0,983	0,041	0,012	97,7 (3.26)	98,9 (1,32)	0,128
METS- mean (± SD)	6,48 (1,9)	4,85 (1,5)	5 (1,3)	5,4 (1,7)	0,015	0,066	0,750	4,92(1,7)	5,81(1,7)	0,105
Work ,% predicted-mean (± SD)	95,2 (27)	91,6 (27)	78,1 (20)	89,7 (26)	0,728	0,126	0,198	75,6 (18,5)	102,0 (25,8)	<0,001
Heart rate at rest, bpm-mean (± SD)	81,8 (16.4)	83,9 (10,1)	82,9 (23,6)	82,9 (15,3)	0,585	0,887	0,322	82,6 (16,5)	83,2 (14,5)	0,896
Heart rate at exercise peak,bpm-mean (± SD)	151,2(22,4)	136,2 (20,8)	136,6 (12.7)	141 (20,7)	0,066	0,114	0,939	141,0(18,8)	140,0 (22,2)	0,931
Basal and stress test echocardiographic characteristics										
LVEF – mean (± SD)	65,2(4,9)	65,6 (6,3)	68,8 (4,8)	66,2 (5,65)	0,843	0,113	0,117	66,7(4,2)	65,9 (6,7)	0,643
LVDd,mm– mean (± SD)	46 (4,1)	47,1 (3,2)	46,6 (3,8)	46,7 (3,5)	0,403	0,754	0,691	46,5(3,9)	46,8 (3,3)	0,827
LVDs, mm – mean (± SD)	29,4 (3,3)	28,3 (4,4)	30,1 (3,8)	29 (3,9)	0,457	0,659	0,298	29,2 (4,0)	28,9 (4,0)	0,784
LV mass,g – mean (± SD)	130 (42)	154 (30)	158 (26)	148 (34)	0,078	0,101	0,722	142 (34)	152 (35)	0,359
E Wave, cm/s– mean (± SD)	63 (17)	67 (14)	76 (29)	68 (19)	0,498	0,225	0,494	71 (19)	75 (19)	0,369
A Wave,cm/s– mean (± SD)	68 (14)	79 (29)	75 (21)	75 (24)	0,208	0,365	0,744	67 (22)	81 (24)	0,079
E/A– mean (± SD)	0,96 (0,32)	0,99 (0,53)	0,97 (0,31)	0,98 (0,43)	0,526	0,989	0,725	1,10 (0,46)	0,88 (0,39)	0,118
E/e´– mean (± SD)	6,21 (2,46)	7,68 (3,19)	8,50 (2,76)	7,43 (2,96)	0,182	0,059	0,390	7,69 (2,58)	7,20 (3,29)	0,605
E wave DT,ms-– mean (± SD)	254 (81)	262 (105)	190 (62)	244 (93)	0,836	0,063	0,069	227(98)	257(89)	0,309
RA area,cm2 – mean (± SD)	12,5 (2,9)	13,3 (2,2)	14,2 (2,7)	13,3 (2,56)	0,385	0,198	0,372	13,5(2,7)	13,1(2,5)	0,533
LA volume-index, ml/m2 – mean (± SD)	19,5 (3)	21,4 (6,9)	28,7 (11,8)	22,5 (8,09)	0,393	0,006	0,140	26,1(8,7)	19,3(6,1)	0,006
RV mean diameter, mm- mean (± SD)	23,4 (3,50)	24,9 (5,24)	29,3 (7,97)	25,4 (5,8)	0,408	0,033	0,082	26,8 (6,11)	24,1(5,40)	0,147
TAPSE rest, mm– mean (± SD)	21,8(3,5)	21,9 (3,7)	20,4 (5,0)	21,5 (3,9)	0,941	0,480	0,399	21,4 (4,9)	21,5 (2,9)	0,942
TAPSE peak, mm– mean (± SD)	32,1 (3.9)	32,1 (5,2)	28,1 (8,5)	31,2 (5,9)	0,970	0,172	0,127	30,2 (7,3)	32,1 (4,3)	0,329
S`Wave cm/s – mean (± SD)	14,0 (3,4)	13,0(2,5)	12,1 (2,6)	13,1 (2,84)	0,533	0,182	0,381	13,0 (3,6)	13,1 (2,0)	0,954
RV dysfunction no. (%)	0 (0)	1 (5)	2 (22,2)	3 (7,3)	0,451	0,086	0,122	3 (15,8)	0	0,053
RV dysfunction exercise no. (%)	0	1 (5)	1 (11,1)	2 (4,9)	0,413	0,163	0,420	2 (10,5)	0	0,119
PHT rest-no. (%)	0	0	1 (11,1)	1 (4)	-	0,146	0,063	1 (5,3)	0	0,260
Cardiac output at rest, l/min– mean (± SD)	5,52 (2,29)	5,86 (1,49)	5,43 (1,26)	5,67 (1,69)	0,255	0,464	0,463	5,58 (1,56)	5,74 (1,82)	0,769
Cardiac output at peak, l/min– mean (± SD)	12,0 (3,69)	11,6 (3,56)	9,7 (3,09)	11,3 (3,53)	0,730	0,141	0,184	10,84 (3,49)	11,7 (3,59)	0,444

ARDS=Acute Respiratory Distress Syndrome; FVC= Forced Vital Capacity; FEV1=Forced Expiratory Volume in One Second; TLC=Total Lung Capacity; DLCO: carbon monoxide diffusion capacity. CPET=Cardiopulmonary Exercise Test; Peak VO2= peak oxygen uptake, VO2/HR=Oxygen pulse; PetCO2=End-tidal CO2; VE/VCO2=Ventilatory Equivalents for Carbon Dioxide, AT= Anaerobic Threshold; Vd/VT=Dead Space to Tidal Volume Ratio;RER=Respiratory Gas Exchange Ratio VCO2/VO2;HRR= Heart Rate Reserve; SaO2= Oxygen Saturation; METs=Metabolic Equivalents;LVEF=Left Ventricle ejection Fraction; LVDd Left Ventricle Diastolic diameter; LVDs Left Ventricle Systolic diameter; LV mass=Left Ventricle mass; DT= Deceleration Time; RA area=Right Atrium Area; LA=left Atrium; RV=Right Ventricle; TAPSE=Tricuspid Annular Plane Systolic Excursion; PHT=Pulmonary Hypertension.

the absence of blood gas analysis for PaCO2 quantification during exercise, we only could hypothesize according to normal Vd/VT response of these patients that some SARS-CoV-2 survivors could persist with an enhanced chemoreflex sensitivity during follow-up. A normal or supernormal cardiac output argues against deconditioning as the main cause of impaired systemic oxygen extraction and according to Singh et al. [6] could suggest a shift in skeletal muscle fiber type and/or reduced aerobic enzyme activity.

LV function is preserved in all patients during follow-up at rest and during exercise. A central cardiac mechanism that limits oxygen delivery is excluded, excepting 3 patients (7.3%), 2 of 3 patients with previous pulmonary disease, that presented RV dilatation and dysfunction. ARDs group patients presented significant dilatation of mid-ventricular linear dimensions compared to mild pneumonia group, reinforcing the hypothesis that RV dilatation is probably related to parenchymal and/or pulmonary vascular disease [1]. Diastolic dysfunction has been described as a possible acute SARS-CoV-2 cardiac damage [1], despite in ARDs subgroup we observed a trend of shorter mitral inflow E wave deceleration time (190±62 ms VS 254±81 ms; P 0,063) and a higher LA mean volume (28,7 ml/m2 Vs. 19,5 ml/m2; P 0,006), this alteration could be secondary to higher prevalence of hypertension and older patients of this subgroup.

Patients with previous pulmonary diseases presented the most severe alteration of both DLCO and TLC. Although abnormal DLCO and TLC are the most frequent pulmonary sequelae, they don't explain aerobic capacity deterioration and dyspnoea especially in patients without diffuse pulmonary fibrosis or pulmonary vascular damage.

Differing from previous studies we cannot assert that deconditioning [7–9] or circulatory causes[8] represent the most common exercise limitation in our cohort. The main limitations of our study is a missing baseline assessment of cardiopulmonary function and PFT before SARS-CoV-2 infection and the presence of patients with previous pulmonary disease; the small number of patients in different subgroups limit the generalizability of the results.

Declaration of Competing Interest

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