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Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation

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Abstract

Rationale: This study aimed to describe cardiopulmonary function during exercise 3 months after hospital discharge for COVID-19 and compare groups according to dyspnea and intensive care unit (ICU) stay.

Methods: Participants with COVID-19 discharged from five large Norwegian hospitals were consecutively invited to a multicentre, prospective cohort study. In total, 156 participants (mean age 56.2 years, 60 females) were examined with a cardiopulmonary exercise test (CPET) 3 months after discharge and compared to a reference population. Dyspnea was assessed using the modified Medical Research Council dyspnea scale (mMRC).

Results: Peak oxygen uptake ($\dot{V}O_2$) <80% of predicted was observed in 31% (n=49). Ventilatory efficiency was reduced in 15% (n=24), while breathing reserve <15% was observed in 16% (n=25). Oxygen pulse <80% of predicted was found in 18% (n=28). Dyspnea (mMRC ≥1) was reported by 38% (n=59). These participants had similar peak $\dot{V}O_2$ (p=0.10), but lower mean peak (SD) $\dot{V}O_2$/kg % of predicted compared to participants without dyspnea (mMRC 0) (76 (16)% vs. 89 (18)%, p =0.009) due to higher body mass index (p=0.03). In participants treated at ICU vs. non-ICU, mean peak (SD) $\dot{V}O_2$ % of predicted were 82 (15)% and 90 (17)% (p=0.004), respectively. Ventilation, breathing reserve, and ventilatory efficiency were similar between the ICU and non-ICU groups.

Conclusions: One- third experienced peak $\dot{V}O_2$ <80% of predicted 3 months after hospital discharge for COVID-19. Dyspneic participants were characterised by lower exercise capacity due to obesity and lower ventilatory efficiency. Ventilation and ventilatory efficiency were similar between ICU- and non-ICU-treated participants.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic [1, 2]. COVID-19 mainly affects the respiratory system, but other organs may also be involved [3]. A recent 6-month follow-up study found the most common persistent COVID-19 symptoms to be fatigue/muscle weakness (63%) and dyspnea (26%) [4]. Several studies have reported a high prevalence of dyspnea (16% to 89%) 1.5 to 6 months after COVID-19 in hospitalised and non-hospitalised participants [5-8].

A recent report from a Norwegian cohort of hospitalised COVID-19 patients found no strong association between dyspnea at 3 months and reduced gas diffusion capacity [7], although close to one-fifth reported dyspnea >1 on the modified Medical Research Council (mMRC) dyspnea scale [7, 9]. A cardiopulmonary exercise test (CPET) might differentiate the pathophysiological mechanisms of reduced exercise capacity and dyspnea [10], as it integrates assessments of the cardiovascular, respiratory, and muscular systems during maximum exertion [11]. Two studies reporting CPET data for 81 participants after hospitalisation for moderate to severe COVID-19 found reduced peak $\dot{V}O_2$ in a large proportion of participants [3, 12]. One of the studies selectively included participants treated with mechanical ventilation, and both studies included a limited number of participants. To our knowledge, no multicentre, population-based study has yet reported extensive CPET results or compared different subgroups of hospitalised COVID-19 patients. We hypothesised that COVID-19 patients would have reduced exercise capacity. Furthermore, we hypothesised persistent cardiopulmonary exercise limitations, particularly in persons with self-reported dyspnea or intensive care unit (ICU) admission. Therefore, we aimed to determine the cardiopulmonary function during exercise 3–4 months after hospital discharge for COVID-19 compared to a reference population, and to describe characteristics of participants with exercise limitations.

Methods

Study design and sample

The current study is a substudy of Patient-reported outcomes and lung function after hospital admission for COVID-19 (PROLUN), a multicentre prospective cohort study performed at six

hospitals in Southern Norway [7]. The substudy included participants from five of the hospitals. Participants ≥18 years who had been admitted for >8 h with a discharge diagnosis of COVID-19 before June 1, 2020, were considered eligible. Exclusion criteria included prior diagnosis of chronic obstructive pulmonary disease (COPD), myocardial infarction, heart failure or peripheral arterial disease, living outside the hospitals' catchment areas, inability to provide informed consent, or participating in the World Health Organization (WHO) Solidarity trial. Further details on the study design and participants have been reported [7]. Eligible participants were invited by mail at 2–4 weeks after hospital discharge. Informed consent was obtained by returning a written signed consent form or through a secure digital consent form (Services for Sensitive Data, TSD, University of Oslo). Among the 264 participants who provided consent for the main study, 236 were invited to participate in the current substudy. The participants were examined 3 months after hospital discharge. WHO Ordinal Scale for Clinical Improvement was used to score the severity of the COVID-19 infection [13].

The study was approved by Regional Ethics Committee, South-Eastern Norway (no. 125384), and data protection officers at each participating centre. The study was registered at ClinicalTrials.gov (NCT04535154).

Pulmonary function tests

Pulmonary function tests included spirometry and diffusion capacity of the lung for carbon monoxide (*D*LCO) (Jaeger Master Screen PFT Vyaire Medical GmbH, Germany). International reference values were applied [14, 15]. The mMRC dyspnea scale was used as a self-rating tool to measure the degree of disability that breathlessness poses on activities of daily living on a scale from 0 to 4 [9]. Participants were categorised as having dyspnea (mMRC 1-4) or no dyspnea (mMRC 0).

Cardiopulmonary exercise test

CPET (Jaeger Vyntus CPX, Vyaire Medical GmbH, Germany) was performed on a treadmill with continuous measurements of ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$), expired carbon dioxide ($\dot{V}CO_2$), heart rate (HR), electrocardiogram (ECG), and oxygen saturation (SpO_2) [10, 16]. An incremental modified Bruce protocol to exhaustion was specified for each participant based on reported exercise tolerance. Concurrently perceived exertion and dyspnea were assessed using the Borg CR10 Scale [17]. $\dot{V}O_2$/kg, oxygen pulse ($\dot{V}O_2$/HR), $\dot{V}E/\dot{V}CO_2$ slope, and ventilatory equivalents were calculated. $\dot{V}O_2$/kg will be referred to as exercise

capacity. Ventilatory efficiency was assessed by the $\dot{V}E/\dot{V}CO_2$ slope up to the ventilatory compensation point and by nadir ventilatory equivalent for CO_2 ($EqCO_2$nadir). Breathing reserve was calculated as (1- $\dot{V}E$peak/maximal voluntary ventilation (MVV)) × 100%, using an estimate of forced expiratory volume in 1 s (FEV_1) × 40 for MVV [10]. The anaerobic threshold was assessed by the V-slope method [16]. A capillary blood sample was drawn from the fingertip immediately after exercise termination and analysed for lactate, pH, and carbon dioxide tension ($PcCO_2$) (ABL 800 Flex, Radiometer Medical, Denmark). All CPETs were performed at two test centres, LHL Hospital Gardermoen or St. Olav's University Hospital.

Interpretation of the cardiopulmonary exercise test

Normal values from a Norwegian reference population with similar comorbidities (hypertension and diabetes) were used to compare the participants' cardiopulmonary function during exercise [18]. Z-scores <-1.96 were defined as abnormally reduced and z-scores >1.96 as abnormally increased, corresponding to the 2.5 and 97.5 percentiles of the reference population [14, 19]. To allow comparisons with other published studies, some of the CPET variables were reported as <80% of the predicted value.

The cause of limitation to exercise was determined for all participants with $\dot{V}O_2$peak <80% of predicted. Ventilatory limitation to exercise was considered when breathing reserve was <15%. Circulatory limitation was considered when the Wassermann flowchart led to a circulatory category [16], including ECG changes consistent with ischemia or arrhythmia. Ischemia was defined as ≥1 mm horizontal or downsloping ST-segment depression in at least two adjacent leads that persisted at 80 ms after the J point. Deconditioning was considered in participants with $\dot{V}O_2$peak <80% of predicted without evidence of ventilatory or circulatory exercise limitations. For the consideration of dysfunctional breathing as a reason for high $EqCO_2$nadir and $\dot{V}E/\dot{V}CO_2$ slope, visual inspection of changes in tidal volume and respiratory frequency during exercise was made, as well as evaluation of capillary pCO_2 and pH at peak exercise.

Biochemistry

Non-fasting venous blood samples were collected to measure hemoglobin, C-reactive protein, N-terminal (NT)-pro-B-type-natriuretic-peptide (BNP) (Roche Diagnostics GmbH, Cobas 8000, e801, e601, Germany and Abbott Architect i2000SR, USA) and high-sensitive cardiac

troponin T (hs-cTnT) (Roche Diagnostics GmbH, Cobas 8000, e801, e601, Germany). The maximum values during hospital stay and after 3-months are reported.

Statistical analyses

Descriptive statistics are presented with a mean (SD), median (25th to 75th percentile), or number (%), as appropriate. Z-scores were compared with 0 using the Wilcoxon signed-rank test. Group comparisons of dyspnea vs no dyspnea and ICU vs non-ICU were performed with linear regression analysis for continuous variables, adjusting for age and sex. Because of the slight deviation from a normal distribution of the residuals in some of the linear regression models, we estimated p-values from bootstrapping with 10 000 repetitions for all models. All statistical analyses were performed using Stata version 16.1 (StataCorp., College Station, TX, USA). We chose a 5% significance level using two-sided tests.

Results

Participant characteristics and initial treatment

Of the 236 participants invited from the main study, 189 consented to participate in the present substudy, which was completed at a median of 104 (90-139) days after discharge from the hospital. Altogether 26 participants were excluded due to comorbidity (COPD, myocardial infarction, heart failure, or peripheral arterial disease), and seven had submaximal, inconclusive CPET (figure 1). Table 1 summarises the descriptives of the study. The age variation was from 18 to 88 years (table 1). Obesity (body mass index (BMI) >30 $kg \cdot m^{-2}$) was found in 46 participants (30%). Pulmonary embolus or deep vein thrombus related to the current hospitalisation were observed in 5%. The participants were hospitalised for a median of 6 (3-11) days. A total of 31 participants (20%) were treated at an intensive care unit (ICU) for median 9 (4-14) days, and 20 (13 %) were intubated and mechanically ventilated for median 9 (7-15) days. At the time of the study, 3 months after hospital discharge, results below lower limit of normal (z-score <-1.64) were observed in 13% (n=19) for FEV_1, in 5% (n=7) for FVC, in 20% (n=31) for *D*LCO, and in 6% (n=9) for *D*LCO/VA. Dyspnea, as indicated by mMRC 1–4, was reported in 59 participants (47%) (table 1).

Table 1: Descriptive statistics for 156 COVID-19 patients

		Number (%)	Mean (SD)	Median (25^{th}-75^{th} percentile)
Age at hospital discharge, years		156	56.2 (12.7)	
Female sex		60 (39)		
Body mass index, $kg \cdot m^{-2}$		152	27.9 (4.5)	
Smoking status		141		
Never smoked		83 (59)		
Formerly a daily smoker		56 (40)		
Current daily smoker		2 (1)		
Medical history		156		
CVA/TIA		2 (1)		
Hypertension		46 (31)		
Asthma		25 (16)		
Diabetes mellitus		14 (9)		
P-hsTroponin T max., hospitalisation, $ng \cdot L^{-1}$		129		8.0 (5.5-15.5)
Abnormal P-hsTroponin T max, hospitalisation		14 (9)		
P-hsTroponin T at 3 months, $ng \cdot L^{-1}$		139		7.0 (5.0-10.0)
NT proBNP max., hospitalisation, $ng \cdot L^{-1}$		132		173 (64-409)
Abnormal NT proBNP max., hospitalisation		60 (39)		
NT proBNP at 3 months, $ng \cdot L^{-1}$		148		55 (35-100)
Hemoglobin, hospitalisation, $g \cdot dL^{-1}$		154		14.2 (13.3-15.0)
Hemoglobin at 3 months, $g \cdot dL^{-1}$		148		14.5 (13.5-15.2)
C-rective protein max., hospitalisation, $mg \cdot L^{-1}$		153		110 (37-205)
Days from symptom start to PFT		150	113 (30)	
Spirometry and body plethysmography				
FVC, L		152	4.0 (1.0)	
FVC % of predicted		152	96 (14)	
FEV_1, L		152	3.1 (0.8)	
FEV_1, % of predicted		152	95 (15)	
FEV_1/FVC		152	0.78 (0.07)	
TLC, % of predicted		140	94 (16)	
Residual volume, % of predicted		140	95 (28)	
Gas diffusion				
*D*LCO, $mmol \cdot kPa^{-1} \cdot min^{-1}$		153	7.6 (2.1)	
*D*LCO % of predicted		153	84 (16)	
*D*LCO/VA, $mmol \cdot kPa^{-1} \cdot min^{-1} \cdot L^{-1}$		153	1.4 (0.3)	
*D*LCO/VA % of predicted		153	97 (18)	
modified MRC dyspnea scale		126		
	0	67 (53)		
	1	35 (28)		
	2	17 (14)		

	3	5 (4)
	4	2 (2)
WHO Ordinal Scale for Clinical Improvement		
	3	60 (39)
	4	68 (44)
	5-7	27 (17)

CVA: cerebral vascular accident; TIA: transient ischemic attack; P-hsTroponin T: plasma high sensitive Troponin T; NT proBNP: N-Terminal pro-Brain Natriuretic Peptide; PFT: pulmonary function test; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; *D*LCO: diffusion capacity of the lung for carbon monoxide; VA: alveolar volume; MRC: Medical Research Council; WHO: World Health Organization

Cardiopulmonary function

$\dot{V}O_2$peak <80% of predicted was observed in 49 participants (31%). $\dot{V}O_2$peak/kg <80% of predicted was observed in 73 participants (47%). Pathological AT, <40% of predicted $\dot{V}O_2$max, was observed in 23 participants (15%).

Ventilatory limitation was observed in 25 (16%), expressed as breathing reserve < 15% [16, 19]. Among participants with $\dot{V}O_2$peak <80% of predicted, 4 (8%) demonstrated low breathing reserve.

Mean SpO_2 at rest was 98 (1)% and at maximal load 95 (4)%. We found a desaturation of > 5% points in SpO_2 between rest and maximal load in 34 participants (23%).

Oxygen pulse <80% of predicted was observed in 28 participants (18%). Of these, four demonstrated a declining O_2-pulse curve with an increasing load. During exercise, a pathological response on ECG was observed in 12 participants (8%). Of these, ischemia and arrhythmia (mainly multifocal premature ventricular contractions) were found in seven and five participants, respectively.

Reduced ventilatory efficiency was observed in 15% (n=24), defined by high $\dot{V}E/\dot{V}CO_2$ slope and/or $EqCO_2$nadir (z-score >1.96). A high $\dot{V}E/\dot{V}CO_2$ slope was observed in 19 (12%) and high $EqCO_2$nadir in 16 (10%), respectively. Among those with reduced ventilatory efficiency, four participants (17%) had a ventilatory limitation, nine (38%) a circulatory limitation, and 11 (46%) had dysfunctional breathing patterns (hyperventilation, stress reaction). Among the nine participants with reduced ventilatory efficiency due to circulatory factors, seven demonstrated ECG pathology during exercise, and two experienced venous thromboembolism during the acute phase of COVID-19.

Exercise limiting factors were multifactorial and described in the 49 participants with $\dot{V}O_2$peak <80% of predicted. Ventilatory limitations were observed in 7 (14%), circulatory limitations in 11 (22%), and deconditioning in 31 (63%).

Table 2 summarises the differences of the CPET variables in the COVID-19 patients compared to the reference population.

Table 2: Comparison of CPET variables in COVID-19 patients with reference population

	n	Mean (SD)	Mean Z-score	P-value
Performance				
$\dot{V}O_2$ peak, mL·min^{-1}	156	2420 (754)	-0.62	<0.001
$\dot{V}O_2$ peak, % of predicted	156	89 (17)		
$\dot{V}O_2$ peak/kg, mL·kg^{-1}·min^{-1}	156	28.7 (8.4)	-0.88	<0.001
$\dot{V}O_2$ peak/kg, % of predicted	156	84 (19)		
Perceived dyspnea $Borg_{10}$ at max load	152	8.2 (2.0)		
Ventilation				
$\dot{V}E$ at max. load, L·min^{-1}	156	85.1 (28.6)	-0.65	<0.001
Breathing reserve, %	156	30 (17)	0.27	0.016
Circulation				
Heart rate at max.load, beats·min^{-1}	156	157 (20)	-1.14	<0.001
Heart rate at max. load, % of predicted	156	92 (10)		
Systolic BP at max. load, mmHg	147	193 (34)	0.20	0.048
Diastolic BP at max. load, mmHg	147	84 (19)	0.28	0.008
O_2-pulse at max. load, mL·stroke^{-1}	156	15.4 (4.2)	-0.09	0.13
O_2-pulse at max. load, % of predicted	156	98 (19)		
Gas exchange				
$\dot{V}E/\dot{V}CO_2$ slope	156	28.0 (4.5)	0.40	0.001
$EqCO_2$ nadir	156	28.5 (3.7)	0.30	0.001
RER at max. load	155	1.07 (0.10)	-1.04	<0.001
PET CO_2 at AT, kPa	155	4.7 (0.6)		
pCO_2 at max. load, kPa	143	4.6 (0.6)		
Anaerobic threshold				
$\dot{V}O_2$ at AT, mL·min^{-1} (V-slope)	152	1387 (417)		
$\dot{V}O_2$ at AT, % of predicted $\dot{V}O_2$max	152	52 (12)		
Lactate at max. load, mmol·L^{-1}	140	9.0 (3.5)	-0.1	0.22

P-values of Wilcoxon one-sample tests. $\dot{V}O_2$: oxygen uptake; $\dot{V}E$: expired ventilation; BP: blood pressure; O_2: oxygen; $\dot{V}CO_2$: carbon dioxide output; $EqCO_2$: ventilatory equivalent for carbon dioxide; RER: respiratory exchange ratio; PET: end tidal pressure; pCO_2: partial pressure of carbon dioxide; AT: anaerobic threshold

Cardiopulmonary function in subgroups

Dyspnea. The participants reporting dyspnea had significantly lower $\dot{V}O_2$peak/kg, ventilatory efficiency, heart rate, and systolic blood pressure (table 3). The low $\dot{V}O_2$peak/kg in the

dyspneic group was related to higher BMI, as $\dot{V}O_2$peak was similar between the groups (p=0.052).

ICU stay. The participants with ICU stay had significantly lower $\dot{V}O_2$peak % of predicted (90 (17)% vs 82 (15)%, p=0.004) and $\dot{V}O_2$peak/kg % of predicted (86 (19)% vs 76 (15)%, p=0.002) compared to those without ICU stay. No difference was found regarding age, BMI, ventilation, breathing reserve, oxygen desaturation, ventilatory efficiency, or O_2-pulse.

Table 3. Comparison of CPET variables according to self-reported dyspnea

	mMRC 0		**mMRC 1-4**		
	n	**Mean (SD).**	**n**	**Mean (SD)**	**P-value***
Age, years	67	54.6 (13.8)	59	55.1 (10.6)	0.81
Sex female/male	22/45	33/67%	26/33	44/56%	0.2
Body mass index, $kg \cdot m^{-2}$	66	27.2 (3.9)	58	28.9 (4.8)	0.03
Diabetes	6		7		0.77**
Performance					
$\dot{V}O_2$ peak, $mL \cdot min^{-1}$	67	2577 (825)	59	2302 (607)	0·052
$\dot{V}O_2$ peak, % of predicted	67	91 (19)	59	86 (16)	0.10
$\dot{V}O_2$ peak/kg, $mL \cdot kg^{-1} \cdot min^{-1}$	67	31.9 (9·3)	59	23.6 (7·9)	<0·001
$\dot{V}O_2$ peak/kg, % of predicted	67	89 (18)	59	76 (16)	0.009
Ventilation					
$\dot{V}E$ at max. load, $L \cdot min^{-1}$	67	86.5 (28.7)	59	83 (26.9)	0.99
Breathing reserve, %	67	29.5 (1.·0)	59	31.0 (17.0)	0.76
Circulation					
Heart rate at max. load, $beats \cdot min^{-1}$	67	162 (20)	59	152 (19)	0·001
Heart rate at max. load, % of predicted	67	94 (9)	59	89 (9)	0.001
Systolic BP at max. load, mmHg	66	197 (32)	54	186 (36)	0·12
Diastolic BP at max. load, mmHg	66	89 (20)	54	80 (15)	0·001
O_2-pulse at max. load, $mL \cdot stroke^{-1}$	67	16.0 (4.7)	59	15.1 (3.6)	0·64
O_2-pulse at max. load, % of predicted	66	99 (22)	59	99 (18)	0.81
Gas exchange					
$\dot{V}E/\dot{V}CO_2$ slope	67	26.6 (4.4)	59	28.9 (4.5)	0·004
$EqCO_2$ at nadir	67	27.4 (3.3)	59	29.2 (3.7)	0·004
RER at max. load	67	1.08 (0.10)	59	1.05 (0.09)	0.10
Anaerobic threshold					
$\dot{V}O_2$ at AT, $mL \cdot min^{-1}$ (V-slope method)	65	1436 (469)	57	1376 (348)	0.83
$\dot{V}O_2$ at AT (% of predicted $\dot{V}O_2$ max)	65	51 (13)	57	52 (11)	0.94
Lactate at max. load, $mmol \cdot L^{-1}$	64	8.9 (3.8)	55	8.1 (3.1)	0.24

* P-values for comparison of groups after adjustment for age and sex, except for $\dot{V}O_2$ peak % of predicted and BMI. **Fisher's exact test. mMRC: modified Medical Research Council scale; $\dot{V}O_2$: oxygen uptake; $\dot{V}E$: expired ventilation; BP: blood pressure; DBP: O_2: oxygen; $\dot{V}CO_2$: carbon dioxide output; $EqCO_2$: ventilatory equivalent for carbon dioxide; RER: respiratory exchange ratio; PET: end tidal pressure; pCO_2: partial pressure of carbon dioxide; AT: anaerobic threshold

Discussion

The current study demonstrated $\dot{V}O_2$peak <80% of predicted in one third of COVID-19 patients 3 months after hospital discharge. Every sixth participant had a reduced breathing reserve, ventilatory efficiency, oxygen pulse, or a combination. Deconditioning was the major cause of exercise limitation, followed by circulatory and ventilatory exercise limitation. Self-reported dyspnea was associated with lower ventilatory efficiency, and lower $\dot{V}O_2$peak/kg due to higher BMI. There was less difference in cardiorespiratory exercise response than expected between participants admitted to ICU or regular hospital ward.

Reduced exercise capacity is an independent predictor of death in men [20] and women [21]. Our finding of low $\dot{V}$O2peak compared to a reference population, therefore, emphasises the importance of regaining exercise capacity after COVID-19. Belli *et al*. reported difficulty regaining physical ability after COVID-19 [22], which has led to a recommendation of rehabilitation programs [22]. We observed that $\dot{V}O_2$peak/kg was more divergent from the reference population than $\dot{V}O_2$peak, reflecting obesity in our study population. Obesity is a well-recognized risk factor for severe COVID-19 [23].
Two studies, including COVID-19 patients, found $\dot{V}O_2$peak of 81 and 73% of predicted [3, 24], which is comparable to our results, whereas another study reported $\dot{V}O_2$peak of 57% of predicted for mechanically ventilated COVID-19 patients [12].

Exercise limiting factors can be related to ventilation, circulation, deconditioning, or peripheral mechanisms. Deconditioning was the leading cause of exercise limitation in the present study and found in every fifth participant. Immobilisation during hospitalisation for 10 days combined with further inactivity due to exertional dyspnea could be the reason for the deconditioning in our participants, where reduced cardiac output, peripheral limiting factors, and muscle waste contribute. In a recent report of 18 COVID-19 patients at the time of discharge from the hospital, peripheral limiting factors, including anemia and reduced oxygen extraction by peripheral muscles, were the major determinants of exercise limitation [25]. However, our study population did not suffer from anemia during the hospital stay or at follow-up.

The second most common cause of exercise limitation was circulatory factors. COVID-19 might affect multiple organs, including the heart and blood vessels [26]. The finding of

frequent circulatory exercise limitation could rely on other factors than post-COVID sequelae. Even though we excluded participants with known pre-existing cardiovascular disease, some might still have had undiagnosed pre-exisiting cardiovascular conditions that were revealed during CPET. Furthermore, the diagnostic accuracy of an exercise ECG is around 70% [27], and we cannot rule out deconditioning as the true exercise limitation for some of these participants. Two participants with circulatory exercise limitation experienced pulmonary embolism during the hospitalisation, but it is unlikely that this contributes to circulatory exercise limitation 3 months after discharge. A hemodynamic study of 21 mechanically ventilated COVID-19 patients, including three with pulmonary embolus, found normal pulmonary vascular resistance for all. Post-capillary pulmonary hypertension was present in 76%, but none exhibited the pre-capillary form related to pulmonary embolisation [28].

Ventilatory limitation was the third most common cause of exercise limitation. We have recently reported pulmonary parenchymal abnormalities by chest CT in 25% of a sample from the same population [7]. However, low breathing reserve was not common among our participants, showing that breathing reserve may be within normal limits, even in the presence of parenchymal abnormalities. Few participants had reduced spirometry and gas diffusion capacity, as well as reduced breathing reserve during exercise, in contrast to what was anticipated for this population in the beginning of the pandemic. The discordance in results of pulmonary function tests and the lower exercise capacity supports the finding of low occurrence of ventilatory limitation, as deconditioning represents the major limitation of the study population. Deconditioning is positive finding in the context of regaining physical function through rehabilitation.

Ventilatory efficiency was reduced in every seventh patient. There was evidence of ventilation/perfusion ($\dot{V}/Q$) mismatch due to pulmonary or circulatory factors in about half of these patients. For the other half, a dysfunctional breathing pattern seemed to contribute to the reduced ventilatory efficiency. Unfortunately, we did not have arterial blood gas analyses to prove hyperventilation. However, dysfunctional breathing pattern and hyperventilation has been reported as a frequent cause of dyspnea in a study of mild COVID-19 survivors [29]. Whether this is related to dysautonomia or other factors is unclear.

As comorbidity affects exercise capacity, we excluded participants with severe comorbidity. In contrast, we did not exclude participants with well-regulated diabetes mellitus or

hypertension, as the reference population for CPET also included such participants [18]. Asthma was common in the study population, but they did not exhibit ventilatory limitation, and well-controlled asthma should not interfere with exercise capacity.

Cardiopulmonary function in subgroups

Exertional dyspnea was frequently reported among our participants, which is in line with other studies [4-8]. Dyspnea is a complex symptom that has been defined by the American Thoracic Society as the net result of multiple physiological, psychological, social, and environmental factors [30].

When we compared participants with and without dyspnea, the dyspneic participants had significantly lower $\dot{V}O_2$peak, but there were no differences in ventilation, breathing reserve, SpO_2, and *D*LCO. This indicates that dyspnea is associated with other factors than pulmonary function.

$\dot{V}E/\dot{V}CO_2$ slope and $EqCO_2$nadir were higher in the dyspneic group. These high values mainly reflect $\dot{V}/Q$ mismatch but might also represent dysfunctional breathing.

Deconditioning alone could not explain the difference in perception of dyspnea, as $\dot{V}O_2$ at AT, both absolute and relative to predicted $\dot{V}O_2$max, were similar and low in both groups. Hence, our results indicate that dyspnea after COVID-19 is complex with several explanations.

The participants admitted to the ICU had more severe oxygenation problems in the acute phase and three times longer hospital stay than those not admitted to the ICU. At 3 months after discharge, the ICU participants had significantly lower $\dot{V}O_2$peak. Otherwise, they had similar test results. We had expected ICU participants to have more ventilatory limitations, worse O_2-desaturation, more $\dot{V}/Q$-mismatch, and earlier AT due to deconditioning. To our knowledge, there are no CPET studies on COVID-19 patients treated at ICU vs. regular ward for comparison with our findings. The ICU participants' observed results might be due to extra care after discharge, with higher attendance at inpatient rehabilitation programs than non-ICU participants. Results probably also reflect the effect of substantial lung tissue repair during the first 3 months [31, 32].

Limitations and strengths

We did not have objective measures for prior functional status and exercise capacity for the study population. We have compared the participants with a healthy reference population, although we have documented pre-existing comorbidity. Estimates of oxygen saturation during exercise using pulse oximetry should be viewed cautiously, as errors might have occurred. CPET generates numerous variables, with the risk of errors due to multiple testing. The limited number of participants in the ICU group could possibly lead to type 2 errors. The study´s strenght is its design, with an unselected hospital population and extensive medical examination of the participants. Even though less patients were treated at ICU compared to many other countries, the proportion of comorbidities and obesity is comparable to other studies, and we consider our study and the results generalisable to other countries.

Conclusions

Three months after discharge from hospital after COVID-19, $\dot{V}O_2$peak was reduced in one-third of the participants. The most common exercise limitation was deconditioning, emphasising the importance of rehabilitation programs. Circulatory limitations to exercise were more common than ventilatory limitations. Participants with self-reported dyspnea had lower $\dot{V}O_2$peak/kg and ventilatory efficiency. There were no differences in ventilation or ventilatory efficiency between those with or without ICU admission. In patients with persisting exercise limitations and dyspnea after COVID-19, cardiopulmonary exercise testing is essential for identifying the causes.

Declaration of interests

IS, OAWA, DT, EB, ØRH, TVL, KS, and AE report no conflict of interests. GE has received research grants from AstraZeneca and from Boehringer Ingelheim to perform the current study. CBI has received lecture fees from Bayer AS, unrelated to the current study.

References

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A

pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.

2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-93.

3. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, Okell T, Sheerin F, Xie C, Mahmod M, Mozes FE, Lewandowski AJ, Ohuma EO, Holdsworth D, Lamlum H, Woodman MJ, Krasopoulos C, Mills R, McConnell FAK, Wang C, Arthofer C, Lange FJ, Andersson J, Jenkinson M, Antoniades C, Channon KM, Shanmuganathan M, Ferreira VM, Piechnik SK, Klenerman P, Brightling C, Talbot NP, Petousi N, Rahman NM, Ho LP, Saunders K, Geddes JR, Harrison PJ, Pattinson K, Rowland MJ, Angus BJ, Gleeson F, Pavlides M, Koychev I, Miller KL, Mackay C, Jezzard P, Smith SM, Neubauer S. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021;31:100683.

4. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-32.

5. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-5.

6. Goertz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, Houben-Wilke S, Burtin C, Posthuma R, Franssen FME, van Loon N, Hajian B, Spies Y, Vijlbrief H, van 't Hul AJ, Janssen DJA, Spruit MA. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020; DOI: 10.1183/23120541.00542-2020.

7. Lerum TV, Aalokken TM, Bronstad E, Aarli B, Ikdahl E, Lund KMA, Durheim MT, Rodriguez JR, Meltzer C, Tonby K, Stavem K, Skjonsberg OH, Ashraf H, Einvik G. Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19. Eur Respir J. 2021 Apr 29;57(4):2003448.

8. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax. 2020 Dec 3;76(4):405-407

9. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. BMJ. 1959;2(5147):257-66.

10. Radtke T, Crook S, Kaltsakas G, Louvaris Z, Berton D, Urquhart DS, Kampouras A, Rabinovich RA, Verges S, Kontopidis D, Boyd J, Tonia T, Langer D, De Brandt J, Goertz YMJ, Burtin C, Spruit MA, Braeken DCW, Dacha S, Franssen FME, Laveneziana P, Eber E, Troosters T, Neder JA, Puhan MA, Casaburi R, Vogiatzis I, Hebestreit H. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir Rev. 2019;28(154).

11. Corra U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, Harjola VP, Hill L, Lainscak M, Lund LH, Metra M, Ponikowski P, Riley J, Seferovic PM, Piepoli MF. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(1):3-15.

12. Blokland IJ, Ilbrink S, Houdijk H, Dijkstra JW, van Bennekom CAM, Fickert R, de Lijster R, Groot FP. [Exercise capacity after mechanical ventilation because of COVID-19: Cardiopulmonary exercise tests in clinical rehabilitation]. Ned Tijdschr Geneeskd. 2020;164.

13. World Health Organization. R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. 2020. (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

14. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, Initiative ERSGLF. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

15. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, Hall GL, Global Lung Function Initiative Twg, Global Lung Function Initiative T. Official ERS

technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J. 2017;50(3).

16. Sietsema KE, Sue DY, Stringer WW, Ward SA. Wasserman & Whipp's Principles of exercise testing and interpretation. 6 ed: Wolters Kluwe; 2021.
17. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exercise. 1982;14(5):377-81.
18. Edvardsen E, Hansen BH, Holme IM, Dyrstad SM, Anderssen SA. Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. Chest. 2013;144(1):241-8.
19. Takken T, Mylius CF, Paap D, Broeders W, Hulzebos HJ, Van Brussel M, Bongers BC. Reference values for cardiopulmonary exercise testing in healthy subjects - an updated systematic review. Expert Rev Cardiovasc Ther. 2019;17(6):413-26.
20. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.
21. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CN, Lauer MS, Marwick TH, Pandey DK, Wicklund RH, Thisted RA. The prognostic value of a nomogram for exercise capacity in women. New Engl J Med. 2005;353(5):468-75.
22. Belli S, Balbi B, Prince I, Cattaneo D, Masocco F, Zaccaria S, Bertalli L, Cattini F, Lomazzo A, Dal Negro F, Giardini M, Franssen FME, Janssen DJA, Spruit MA. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived hospitalisation. Eur Respir J. 2020;56(4).
23. Sattar N, McInnes IB, McMurray JJV. Obesity Is a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms. Circulation. 2020;142(1):4-6.
24. Mohr A, Dannerbeck L, Lange TJ, Pfeifer M, Blaas S, Salzberger B, Hitzenbichler F, Koch M. Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19. Multidiscip Respir Med. 2021;16(1):732.
25. Baratto C, Caravita S, Faini A, Perego GB, Senni M, Badano LP, Parati G. Impact of COVID-19 on exercise pathophysiology. A combined cardiopulmonary and echocardiographic exercise study. J Appl Physiol. 2021;30:1470–1478.

26. Giustino G, Pinney SP, Lala A, Reddy VY, Johnston-Cox HA, Mechanick JI, Halperin JL, Fuster V. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol. 2020;76(17):2011-23.

27. Bourque JM, Beller GA. Value of Exercise ECG for Risk Stratification in Suspected or Known CAD in the Era of Advanced Imaging Technologies. JACC Cardiovasc Imaging. 2015;8(11):1309-21.

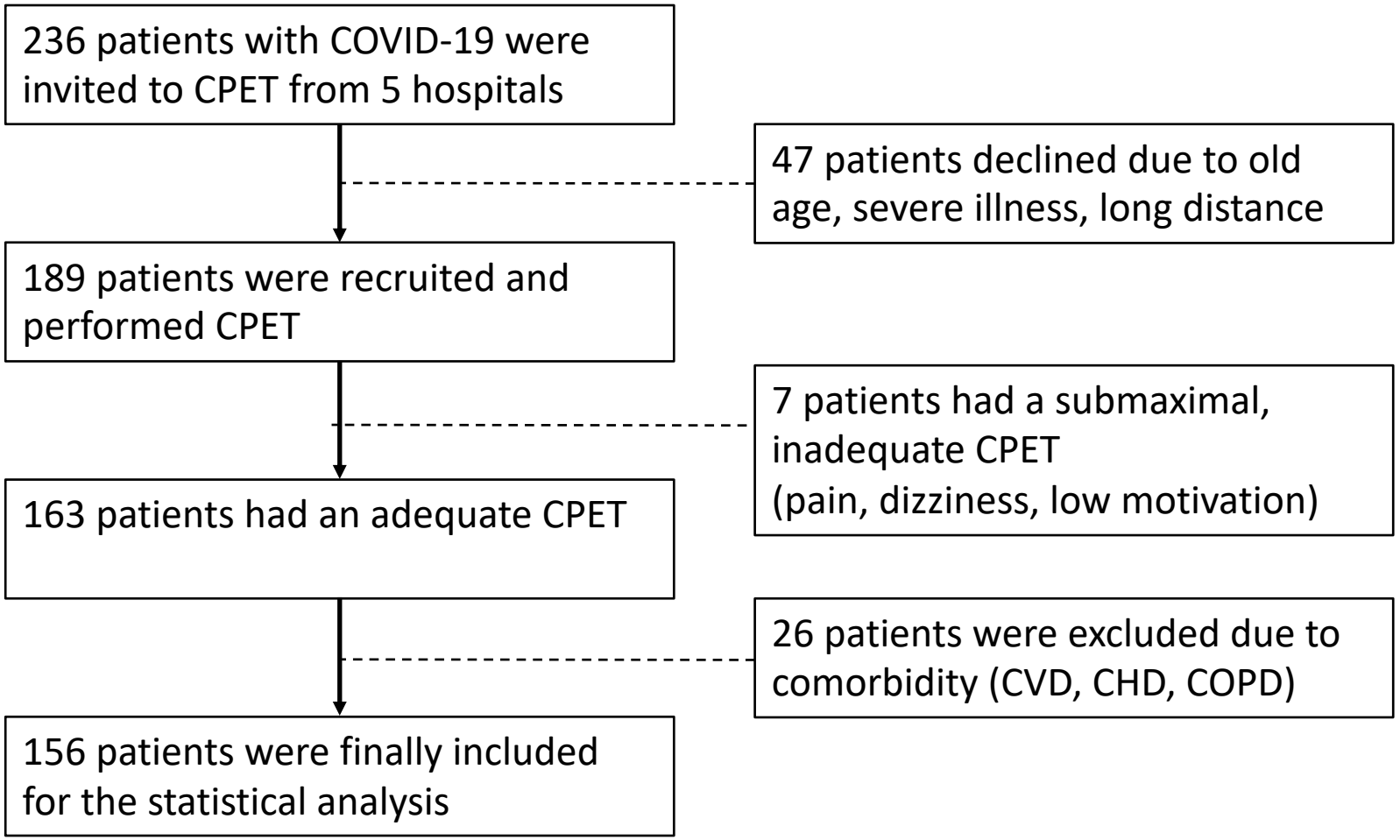
28. Caravita S, Baratto C, Di Marco F, Calabrese A, Balestrieri G, Russo F, Faini A, Soranna D, Perego GB, Badano LP, Grazioli L, Lorini FL, Parati G, Senni M. Haemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation. An invasive assessment using right heart catheterization. Eur J Heart Fail. 2020;22(12):2228-37.

29. Motiejunaite J, Balagny P, Arnoult F, Mangin L, Bancal C, d'Ortho MP, Frija-Masson J. Hyperventilation: A Possible Explanation for Long-Lasting Exercise Intolerance in Mild COVID-19 Survivors? Front Physiol. 2020;11:614590.

30. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE, American Thoracic Society Committee on D. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185(4):435-52.

31. Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, Ma WL, Wang X. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. J Korean Med Sci. 2020;35(47):e418.

32. Liu M, Lv F, Huang Y, Xiao K. Follow-Up Study of the Chest CT Characteristics of COVID-19 Survivors Seven Months After Recovery. Front Med (Lausanne). 2021;8:636298.


236 patients with COVID-19 were invited to CPET from 5 hospitals
47 patients declined due to old age, severe illness, long distance
189 patients were recruited and performed CPET
7 patients had a submaximal, inadequate CPET (pain, dizziness, low motivation)
163 patients had an adequate CPET
26 patients were excluded due to comorbidity (CVD, CHD, COPD)
156 patients were finally included for the statistical analysis