EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

Changes in cardiopulmonary exercise capacity and limitations 3 to 12 months after COVID-19

Charlotte Björk Ingul, Anne Edvardsen, Turid Follestad, Divna Trebinjac, Odd Andre Wathne Ankerstjerne, Eivind Brønstad, Øystein Rasch-Halvorsen, Bernt Aarli, Håvard Dalen, Bjarne Martens Nes, Tøri Vigeland Lerum, Gunnar Einvik, Knut Stavem, Ingunn Skjørten

Please cite this article as: Ingul CB, Edvardsen A, Follestad T, *et al*. Changes in cardiopulmonary exercise capacity and limitations 3 to 12 months after COVID-19. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.00745-2022).

Changes in cardiopulmonary exercise capacity and limitations 3 to 12 months after COVID-19

Ingul Charlotte Björk MD, PhD[1,2,3], Edvardsen Anne PhD[1,4], Follestad Turid PhD[5], Trebinjac Divna MD, PhD[1], Ankerstjerne Odd Andre Wathne MD[1], Brønstad Eivind MD, PhD[2,6], Rasch-Halvorsen Øystein MD, PhD[2,6], Aarli Bernt MD, PhD[7,8], Dalen Håvard MD, PhD[2,9,10], Nes Bjarne Martens PhD[2], Lerum Tøri Vigeland MD[11,12], Einvik Gunnar MD, PhD[4,12], Stavem Knut MD, MPH, PhD[4,12,13], Skjørten Ingunn MD, PhD[1,14]

[1]LHL Hospital Gardermoen, Jessheim, Norway

[2]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway.

[3]Faculty of Nursing and Health Sciences, Nord University, Norway

[4]Pulmonary Department, Akershus University Hospital, Lørenskog, Norway

[5]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

[6] Thoracic Department, St. Olavs Hospital, Trondheim, Norway

[7]Department of Clinical Science, University of Bergen, Bergen, Norway

[8]Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

[9]Clinic of Cardiology, St. Olavs University Hospital, Trondheim, Norway.

[10]Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway.

[11]Department of Pulmonary Medicine, Oslo University Hospital Ullevål, Oslo, Norway

[12]Institute for Clinical Medicine, University of Oslo, Oslo, Norway

[13]Health Services Research Unit, Akershus University Hospital, Lørenskog, Norway

[14]Department of Pulmonary Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway

Correspondence

Charlotte Björk Ingul, Department of Circulation and Medical Imaging, Norwegian University of Technology and Science, Trondheim, Norway. E-mail charlotte.b.ingul@ntnu.no, phone +4795805886.

Abstract

Rationale: To describe cardiopulmonary function during exercise 12 months after hospital discharge for COVID-19, assess the change from 3 to 12 months, and compare the results with matched controls without COVID-19.

Methods: In this prospective, longitudinal, multicentre cohort study, hospitalized COVID-19 patients were examined with a cardiopulmonary exercise test (CPET) 3 and 12 months after discharge. At 3 months 180 performed a successful CPET, and 177 at 12 months (mean age 59.3 years, 85 females). The COVID-19 patients were compared with controls without COVID-19 matched for age, sex, body mass index, and comorbidity. Main outcome was peak oxygen uptake (V'_{O_2peak}).

Results: Exercise intolerance (V'_{O_2peak} <80% predicted) was observed in 23% at 12 months, related to circulatory (28%), ventilatory (17%), and other limitations including deconditioning, and dysfunctional breathing (55%). Estimated mean difference between 3 and 12 months showed significant increases in V'_{O_2peak} % predicted (5.0 percent points (pp), 95% CI (3.1 to 6.9), p<0.001), $V'_{O_2peak}\cdot kg^{-1}$ % predicted (3.4 pp, (1.6 to 5.1), p<0.001), and oxygen pulse % predicted (4.6 pp, (2.5 to 6.8), p<0.001). V'_{O_2peak} was 2440 $mL\cdot min^{-1}$ in COVID-19 patients compared to 2972 $mL\cdot min^{-1}$ in matched controls

Conclusions: One year after hospital discharge for COVID-19, the majority, 77%, had normal exercise capacity. Only every fourth had exercise intolerance and in these circulatory limiting factors were more common than ventilatory. Deconditioning was common. V'_{O_2peak} and oxygen pulse improved significantly from 3 months.

Background

Severe coronavirus disease 2019 (COVID-19) may be followed by organ dysfunction and persisting symptoms (1, 2). In hospitalized patients, the lung has been the organ primarily affected by COVID-19 infection, and consequently, respiratory symptoms and exercise intolerance are prevalent (3, 4). Dyspnoea is the most frequently reported respiratory symptom after COVID-19, affecting about half of the patients 3 months after hospitalization for COVID-19 (5).

The cardiopulmonary exercise test (CPET) provides an integrated assessment of the cardiorespiratory system and is considered the gold standard for evaluating exercise capacity and dyspnoea on exertion. Hence, in patients who continue to experience dyspnoea after COVID-19, CPET is a valuable tool. Deconditioning has been considered the main limiting factor of exercise capacity 3 months after COVID-19, followed by circulatory and ventilatory limitations (5-7). However, most studies have a short time interval between COVID-19 diagnosis and follow-up, usually 3 to 6 months (6, 7), which may not be long enough for pulmonary structural changes and exercise abnormalities to resolve. Whether or not these limitations to exercise persist 1 year after COVID-19 infection, is still unknown.

In a prospective study of patients hospitalized for COVID-19, we aimed to:

1. Determine cardiopulmonary exercise capacity at 12 months, including the impact of persisting dyspnoea and treatment in intensive care unit (ICU).
2. Assess the change in cardiopulmonary exercise capacity from 3 to 12 months, and
3. Compare the results from the post-COVID-19 population with a matched control group without a history of COVID-19.

We hypothesized that exercise capacity would improve from 3 to 12 months after discharge.

Methods

Study design and variables

The present study was a substudy of all patients undergoing CPET at 3 and/or 12 months in a prospective observational study of patients hospitalized for COVID-19 in Norway, the "Patient-Reported Outcomes and Lung Function after hospitalization for COVID-19" (PROLUN). The main study included participants ≥18 years with a discharge diagnosis of COVID-19 before 1 June 2020 from six hospitals in different parts of Norway. The patients were invited to follow-up visits 3 and 12 months after discharge, with pulmonary function, dyspnoea and CT findings as primary outcomes (5, 8). Registration identifier number at Clinical Trials.gov was NCT04535154.

Among the 264 PROLUN patients providing consent, 256 attended at least one of the visits. In the present substudy, CPET was performed in 190 patients at 3 months, and 187 at 12 months (Figure 1). One of the centres performed CPET only at 12 months (n=23). All patients with valid CPET at either 3 or 12 months (n=210) were included in the analyses (Figure 1). Informed consent was obtained from all participants. Regional Ethics Committee, South-Eastern Norway (no. 125384) and data protection officers at the participating hospitals provided ethical approval.

Comorbidity was based on both medical records and self-report, and included a previous diagnosis of chronic obstructive pulmonary disease, myocardial infarction, heart failure, cerebral vascular accident, or peripheral vascular disease.

Obesity was defined as body mass index (BMI) >30 $kg \cdot m^{-2}$. The WHO Ordinal Scale for Clinical Improvement was used to score the severity of COVID-19 infection (9).

Dyspnoea and pulmonary function tests

The modified Medical Research Council (mMRC) scale (grade 0 to 4) was used to classify self-reported dyspnoea (10); mMRC 0 was defined as no dyspnoea.

Spirometry, body plethysmography and diffusing capacity of the lung for carbon monoxide (D_{LCO}) were performed (Jaeger Master Screen PFT Vyaire Medical GmbH, Germany) according to guidelines, using Global Lung Function Initiative (GLI) reference values (11-13).

CPET

Stepwise incremental treadmill exercise according to a modified Bruce protocol was applied for CPET (Vyntus CPX, Vyaire Medical), which included continuous measurement of electrocardiogram (ECG) and pulse oximetry (S_{pO_2}). Mouthpiece and nose clip were used for breath-by breath measurements of ventilation (V'_E), oxygen consumption (V'_{O_2}), and expired carbon dioxide (V'_{CO_2}). Borg CR10 scale was used for the assessment of perceived exertion and dyspnoea (14). $V'_{O_2} \cdot kg^{-1}$, oxygen pulse (V'_{O_2peak} /HR), respiratory exchange ratio (RER), V'_E/V'_{CO_2} slope, and ventilatory equivalents, were calculated. Ventilatory efficiency was assessed by the V'_E/V'_{CO_2} slope up to the ventilatory compensation point and by nadir ventilatory equivalent for CO_2 (V'_E/V'_{CO_2nadir}). Breathing reserve was calculated as (1-V'_E/maximal voluntary ventilation (MVV)) × 100%, using an estimate of forced expiratory volume in 1 s (FEV_1) × 40 for MVV (15). The anaerobic threshold (AT) was assessed by the V-slope method (16). Post-exercise capillary blood samples were collected from the fingertip within 1 minute and analyzed for lactate, pH, and carbon dioxide tension (P_{cCO_2}) (ABL 800 Flex, Radiometer Medical, Denmark). Norwegian reference values, from a healthy population, were used to calculate CPET values relative to expected for age and sex (% predicted) (17), except for V'_E/V'_{CO_2} slope and V'_E/V'_{CO_2nadir} (18). The prediction equation for

V'_{O2peak} (mL·min^{-1}) (17) was used for assessment of exercise intolerance and V'_{O2} at AT % of predicted V'_{O2max}. Exercise intolerance was defined as V'_{O_2peak} <80% predicted. Ventilatory limitation to exercise was defined when breathing reserve was <15% (15). The Wassermann flowchart was used to define circulatory limitation in participants when it led to a circulatory category (16), including ECG changes consistent with ischemia or arrhythmia.

Deconditioning was defined as V'_{O2peak} <80% predicted with normal breathing reserve and no evidence of cardiocirculatory pathology (assessed by ECG, V'_E/V'_{CO2} slope, and O_2-pulse curve) with normal or low V'_{O2peak} at AT.

Ventilatory inefficiency was defined as V'_E/V'_{CO2} and/or $V'_E/V'_{CO2nadir}$ z-score>1.645 (18).

Dysfunctional breathing was determined by random swings in ventilation due to chaotic changes in tidal volume and respiratory frequency, accompanied by hypocapnia and respiratory alkalosis. CPET was considered submaximal, and thus inconclusive and invalid, when exercise was restricted by non-cardiopulmonary factors, including back or leg pain, in patients with RER<1.0 and lactate <3.0 mmol·L^{-1}.

Matched controls* (*HUNT4 HOPE)

The matched controls were recruited from the HUNT4 HOPE, part of the large population-based Norwegian study HUNT (The Trøndelag Health study), where CPET and echocardiography were performed in 2461 participants between 2017 and 2019 (19). After matching individually for comorbidity and sex, matching on group level was done for age, BMI, and blood pressure. HUNT4 HOPE CPET treadmill protocol increased inclination and/or speed every minute until voluntary exhaustion. Continuous gas analysis was performed with the MetaLyzer II (Cortex Biophysik Gmbh, Leipzig, Germany) mixing chamber system with patients wearing an oro-nasal mask.

In total 177 patients and 207 controls were included in the analysis.

Statistical methods

Data are presented as mean (SD), median (25- and 75-percentiles), or frequency (%), as appropriate. Normality of data and residuals was checked by inspection of histograms and QQ-plots and Shapiro-Wilk's or Anderson-Darling tests.

The change in outcome variables from 3 to 12 months and potential interactions with ICU stay or dyspnoea were analyzed by linear mixed models (LMM). A subject-specific random intercept accounted for within-subject correlations. Models with and without interaction between ICU stay or dyspnoea and the categorical time variable (3 and 12 months) were fitted. Since the interaction effect was not statistically significant, results for the effect of time on ICU stay or dyspnoea from main effect models are presented. All models included sex, comorbidity (present or not present), BMI, and age, all measured at 3 months, as additional covariates, and a fixed effect for the hospitals to adjust for a potential centre effect. To explore other potential predictors of change in the outcome variables, LMMs including interactions of time with obesity, comorbidity, age, sex, in addition to ICU stay and dyspnoea, were fitted similarly. The lmer function and the models in the lme4 package were fitted in the R version 3.4.4 (20, 21).

A subset of CPET variables were compared between the patients with COVID-19 and the controls using multiple regression analysis, adjusting for age, sex, BMI, resting systolic blood pressure, COPD, diabetes, previous heart failure, and previous myocardial infarction. After matching for comorbidity and sex, matching on group level was done for age, BMI, and blood pressure. Because of the partly individual matching of controls (see Methods), LMM were first fitted to account for potential within-pair correlations. Because these correlations were very small, we used ordinary regression models. For the compared CPET variables, the normality assumption for the residuals was considered reasonable. Other assumptions for

regression analyses were checked by correlations between the variables, variance inflation factor and inspection of plots of residuals versus predicted and found to be satisfactory.
The main study, PROLUN, was an observational study with the prevalence of reduced lung function after hospitalization and interstitial lung findings after 3 and 12 months as primary outcomes. There were no a priori sample size calculations for these outcomes, and the study included all eligible patients in the six hospitals until 1 June 2020.
P-values < 0.01 were considered statistically significant to give some protection against false positive results.

Results

Study population characteristics

The 12-month visit was completed at a median (25th-75th percentile) of 376 (309-472) days after discharge from the hospital. The mean age was 58.1(13.8) years, 41% were female (n=85) and mean BMI was 28.5(4.8) $kg \cdot m^{-2}$. The patients were hospitalized for a median of 6 (3-11) days, 41 patients (20%) were treated in an intensive care unit (ICU) for a median of 10 (4-15) days, and 27 (13%) were intubated and mechanically ventilated for median 10 (7-15) days (supplementary table 1). Comorbidity at baseline was present in 26 patients (13%) and obesity in 59 patients (29%). Figure 2 summarizes the main findings of the study.
Supplementary table 1 summarizes the descriptive data of the study population.
At 12 months 41 (22%) had supervised rehabilitation. The majority attended in-patient rehabilitation (n=27), fewer attended community-based (n=8) and out-patient (n=6) rehabilitation.
The patients lost to follow-up were slightly older, had a higher degree of obesity, were female, fewer were born in Norway, and had lower V'_{O_2peak}. They had similar rates of ICU admission, comorbidity, and dyspnoea.

Descriptive results

Dyspnoea

mMRC was ≥ 1 in 86 patients (47%) at 12 months compared with 89 patients (51%) at 3 months (supplement table 1).

Pulmonary function tests at 12 months

Mean (SD) FEV_1 was 94 (15)% predicted, forced vital capacity (FVC) 97 (13)% predicted, total lung capacity (TLC) 97 (17)% predicted, and diffusion capacity of the lung for carbon monoxide (D_{LCO}) 92 (17)% predicted. Results below lower limit of normal (z-score <-1.645) were observed in 12 (7%) for FEV_1, in 14 (8%) for FVC, and in 25 (15%) for $D_{LCO.}$ V'_{O2peak} % predicted correlated with TLC % predicted (r=0.38, p< 0.001), but not with FEV_1 % predicted (r=0.01, p=0.94), or D_{LCO} % predicted (r=0.01, p=0.95).

Cardiopulmonary exercise test at 12 months

Observed CPET variables at 12 months are presented in table 1.

Exercise limiting factors

V'_{O_2peak} <80% predicted was observed in 40 patients (23%). The exercise limiting factors were circulatory limitations in 11 (28%), ventilatory limitations in 7 (17%), and other factors in 22 (55%). Among the 22 patients with other limiting factors, 3 satisfied our definition of dysfunctional breathing, and 19 satisfied the definition of deconditioning.

Ventilatory inefficiency

Ventilatory inefficiency was observed in 30 patients (17%) and was related to ventilatory factors (n=6), circulatory factors (n=10), and dysfunctional breathing (n=13). The cause of ventilatory inefficiency could not be established in one participant. Patients with ventilatory

inefficiency had lower mean (SD) V'_{O_2peak} % predicted (74 (19) vs. 97 (17) %, p<0.001), end-tidal CO_2 (P_{ETCO_2}) at maximal exercise (4.1 (0.4) vs 4.7 (0.5) kPa, p<0.001), and lactate (6.9 (3.6) vs 9.7 (3.7) $mmol \cdot L^{-1}$, p<0.001) compared to those with normal ventilatory efficiency. Among 27 patients with ventilatory inefficiency, 17 (63%) reported dyspnoea by mMRC. Among 85 patients reporting dyspnoea, 17 (20%) had ventilatory inefficiency.

Changes from 3 to 12 months and determinants of change

Exercise intolerance was observed in 23% at 12 months, compared to 34% at 3 months. V'_{O_2peak}, oxygen pulse, lactate, and P_{CO_2}, as well as V'_{O_2} at AT % of predicted V'_{O_2max}, were significantly higher at 12 months compared to 3 months after hospital discharge (table 1). Estimated mean increases in V'_{O2peak} % predicted and $V'_{O2} \cdot kg^{-1}$ % predicted were 5.0 percent points (pp) (95% CI 3.1 to 6.9) and 3.4 pp (95% CI 1.6 to 5.1), respectively. (table 1). There was little or no evidence of any interactions between time and age, sex, obesity and comorbidity (Figure 3a, supplementary table 2, supplementary table 3).

S_{pO_2} was 98 (1)% at rest and 95 (4)% at maximal load at 12 months. Desaturation (defined as S_{pO_2} desaturation >5pp) was not observed during CPET at 12 months compared to in 34 patients (23%) at 3 months.

Impact of dyspnoea or ICU treatment on cardiopulmonary function

Patients reporting dyspnoea at 3 months were more females, had a higher BMI and more comorbidity compared to patients without dyspnoea, but there were no differences in pulmonary function or number treated with non-invasive ventilation or mechanical ventilator (Supplementary table 1). Patients reporting dyspnoea had lower V'_{O_2peak} and higher V'_E/V'_{CO_2} slope at 12 months compared to those with dyspnoea (table 2, figure 3b). However, the

changes in CPET variables from 3 to 12 months were the same for patients with and without dyspnoea (table 2, figure 3b).

Patients admitted to an ICU at the index hospitalization had lower V'_{O2peak} and oxygen pulse compared to patients not treated in an ICU (table 2, figure 3b). However, the changes in CPET variables from 3 to 12 months were the same for patients with and without ICU treatment (table 2, figure 3b).

Comparison between COVID-19 patients and matched control group

At 12 months, the COVID-19 patients had lower V'_{O_2peak} and $V'_{O_2peak} \cdot kg^{-1}$ than matched controls (table 3). Maximal heart rate, breathing frequency and V'_E were lower in the COVID-19 patients compared to the matched controls (table 3).

Mean RER at maximal load was 1.10 for the controls and 1.07 for the patients, which was a significant difference in the adjusted analysis (supplementary table 4). However, there was only little evidence of differences in CPET variables between controls and patients, when RER in patients was dichotomized to greater or less than 1.10 (supplementary table 4).

Discussion

The main findings in this study were that the majority of COVID-19 patients had normal exercise capacity at 12 months, exercise intolerance was reduced, and V'_{O_2peak} and oxygen pulse improved from 3 to 12 months after hospitalization. The frequency of ventilatory limitation was low at 12 months. Patients with dyspnoea or ICU treatment had lower values of V'_{O2peak} at 12 months, but similar improvement from 3 to 12 months, compared to patients without dyspnoea or ICU-treatment. The study patients had lower V'_{O_2peak} at 12 months compared to matched controls.

Exercise capacity and limitations

Exercise capacity improved from 3 to 12 months after hospitalization, and the increase in V'_{O_2peak} was considered sufficient to have a positive impact on activities of daily living. At 12 months, the majority had regained normal exercise capacity and the prevalence of exercise intolerance was reduced to every fourth patient.

Circulatory limitations were more frequent than ventilatory limitations in patients with exercise intolerance. Mean values of pulmonary function tests were within normal limits at 12 months, few had abnormal values. Except for TLC, there were no correlations between V'_{O2peak} and pulmonary function tests, which support that exercise capacity for most patients is limited by factors other than the lungs.

The majority of patients with exercise intolerance were limited by other than circulatory and ventilatory factors. This group included patients with deconditioning and dysfunctional breathing, but other virus induced limitations may also have been present. Our study was limited to non-invasive methods, thus we cannot explain all aspects of the mechanisms interfering with exercise capacity. However, deconditioning due to inactivity seems to be the most prevalent exercise limitation. Naeije and colleagues grouped together 581 COVID-19 patients from 11 studies and found a CPET profile of deconditioning in the recovery phase of an acute inflammatory process (22).

As stated by the Fick equation, V'_{O2peak} = cardiac output x arteriovenous oxygen difference, a low V'_{O2peak} may be related to either reduced cardiac output or reduced peripheral oxygen extraction. Both these mechanisms may apply in patients with deconditioning (23, 24). Furthermore, reduced peripheral oxygen extraction has been shown in COVID-19 patients with small fibre neuropathy, complicating evaluation of exercise limitation even more (25, 26).

Dysfunctional breathing with large disharmonic variations in tidal volume and respiratory frequency, accompanied by hypocapnia and respiratory acidosis, was limiting exercise capacity in a few patients. Similar dysfunctional breathing patterns have also been observed in other studies (27, 28).

Dyspnoea

Dyspnoea was reported by half of the patients, consistent with findings in other studies (29). Among patients with dyspnoea, there were more females, more obesity, and more comorbidity compared to patients without dyspnoea. Patients with dyspnoea had lower $V'_{O_2peak} \cdot kg^{-1}$ % predicted compared to those without dyspnoea. However, in the patients reporting dyspnoea, few had circulatory or ventilatory limitations. This is similar to observations in a CPET study of COVID-19 patients with prominent dyspnoea, where only mild physiological abnormalities were found (30).

Patients with dyspnoea had reduced ventilatory efficiency, with dysfunctional breathing as the most frequent cause. Although ventilatory inefficiency and hyperventilation may account for some of the reported dyspnoea in our study, only one-fifth of the patients with dyspnoea showed ventilatory inefficiency. Perceived dyspnoea is often multifactorial (31), complicating the interpretation of this symptom. Given the magnitude of the COVID-19 pandemic, it will be essential to differentiate symptoms caused by COVID-19 from dyspnoea due to other etiologies.

ICU treatment

Patients treated in an ICU had the same improvement in V'_{O2peak} and oxygen pulse from 3 to 12 months compared to patients without ICU treatment. However, they still had lower V'_{O2peak} despite more frequent rehabilitation.

Patients and matched controls

Even though the patients in our study improved their exercise capacity from 3 to 12 months, it was still not normalized compared to the matched controls. Maximal heart rate and ventilation were lower among the COVID-19 patients compared to matched controls, indicating slightly submaximal performance. This could have influenced the comparison between patients and matched controls, but subgroup analyses show that patients with RER greater or less than 1.1 both have lower V'_{O2peak} compared to the matched controls.

Limitations

As all study patients were hospitalized in the first phase of the pandemic when vaccines were unavailable, our results may not apply to a vaccinated population. The study was performed in hospitalized patients during acute COVID-19 infection and the results may not apply to the subjects with long COVID who were not hospitalized.

Unlike the COVID-19 patients, the controls have not been hospitalized. However, the only purpose of the controls is to account for pre-existing comorbidity when evaluating if the patients have recovered their expected exercise capacity. Timely change in exercise capacity cannot be compared, as the controls only had one assessment.

CPET was performed using different equipment and protocol in the COVID-19 population and the matched HUNT control group. There have been reports of higher V'_{O_2peak} in the HUNT fitness population compared to other population cohorts and difference between patients and other controls might have been smaller (17, 19).

CPET was performed on treadmill which gives 5-10% higher V'_{O2peak} compared to cycle ergometer. Cardiac output was not measured during exercise, and muscle biopsies were not performed, thus evaluation of deconditioning is hampered with some uncertainty.
The study´s strength is the inclusion of most patients hospitalized for COVID-19 in the study's catchment areas in Norway at the beginning of the pandemic, representing an unselected, thus representative, hospital population.

Conclusions

Exercise capacity was normal in 77% of the patients one year after hospital discharge for COVID-19. In patients with exercise intolerance, circulatory limitation to exercise was more common than ventilatory limitation. Deconditioning seemed to be the most prevalent exercise limitation, but other, unknown mechanisms may have contributed to exercise intolerance. V'_{O_2peak} and oxygen pulse improved significantly from 3 to 12 months, but V'_{O_2peak} was lower compared to matched controls. Even though patients with dyspnoea or ICU treatment had lower V'_{O2peak} at one year, they still had similar improvement from 3 months, compared to patients without dyspnoea or ICU treatment.

Declaration of interests

C.B. Ingul has received lecture fees from Bayer AS, unrelated to the current study.
I. Skjørten has provided lectures for doctors' education paid by Norwegian Directorate of Health and Norwegian Medical Association. G. Einvik has received research grants from AstraZeneca to perform the current study. A. Edvardsen has received payment or honoraria for lectures, presentations or educational events from GlaxoSmithKline and Chiesi. K. Stavem has received consulting fees from UCB Pharma and MSD, unrelated to the present study.

Support statement: This work was supported by the National Association for Heart and Lung Diseases, Akershus University Hospital and Norwegian Health Association.

Acknowledgements

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Table 1: Estimated changes in CPET variables in COVID-19 patients from 3 to 12 months in estimated values from linear mixed models and observed values at 3 and 12 months.

	3 months		12 months		Change from 3 to 12 months, estimate (95%CI)	P-value
	n	Mean (SD)	n	Mean (SD)		
Performance						
V'_{O_2peak}, mL·min^{-1}	180	2306 (797)	177	2451 (776)	93 (40 to 144)	<0.001
V'_{O_2peak}, % predicted	180	87 (19)	177	92(20)	5.0 (3.1 to 6.9)	<0.001
V'_{O_2peak}·kg^{-1}, mL·kg^{-1}·min^{-1}	180	27 (9)	177	29 (8)	0.7 (0.1 to 1.3)	0.03
V'_{O_2peak}·kg^{-1}, % predicted	180	82 (19)	177	86(21)	3.4 (1.6 to 5.1)	<0.001
Perceived dyspnoea Borg CR_{10} at max load	175	8 (2)	175	9(2)	0.1 (-0.2 to 0.4)	0.39
Ventilation						
V'_E at max. load, L·min^{-1}	180	82 (30)	177	88 (29)	2.8 (-0.3 to 6.2)	0.08
Breathing reserve, %	180	20(20)	177	19(19)	-0.4 (-3.3 to 2.5)	0.80
Circulation						
Heart rate at max.load, beats·min^{-1}	180	153 (22)	177	155(22)	0.0 (-2.5 to 2.3)	0.95
Heart rate at max. load, % predicted	180	90(11)	177	92 (10)	0.5 (-1.0 to 1.8)	0.49
Systolic BP at max. load, mmHg	170	191(35)	164	190(32)	-3.8 (-10.7 to 3.2)	0.31
Diastolic BP at max. load, mmHg	170	84(18)	164	83(18)	-0.5 (-3.7 to 2.8)	0.78
Oxygen pulse at max. load, mL·stroke^{-1}	180	15(4)	177	16(4)	0.6 (0.3 to 0.9)	<0.001
Oxygen pulse at max. load, % predicted	180	98(20)	176	102(22)	4.6 (2.5 to 6.8)	<0.001
Gas exchange						
V'_E/V'_{CO_2} slope	180	29(6)	177	29 (5)	-0.1 (-0.8 to 0.7)	0.88
V'_E/V'_{CO_2nadir}	180	29 (4)	177	29(4)	-0.1 (-0.5 to 0.4)	0.77
RER at max. load	180	1.06 (0.10)	177	1.07 (0.10)	-0.01 (-0.03 to 0.01)	0.28
P_{ETCO_2} at AT, kPa	178	4.7(0.6)	173	4.8 (0.5)	0.03 (-0.04 to 0.11)	0.39
P_{CO_2} at max. load, kPa	164	4.6 (0.6)	142	4.8 (0.6)	0.2 (0.1 to 0.3)	<0.001
Anaerobic threshold						
V'_{O_2} at AT, mL·min^{-1} (V-slope)	174	1339 (423)	170	1526 (555)	53 (8 to 97)	0.02
V'_{O_2}at AT, % predicted V'_{O_2max}	174	52(12)	170	58 (18.	2.9 (1.3 to 4.6)	<0.001
Lactate at max. load, mmol·L^{-1}	160	8.2 (3.7)	162	9.2 (3.8)	0.7 (0.2 to 1.2)	0.003

Estimated change from linear mixed models. The results are adjusted for centre, ICU stay, age, sex, BMI, and comorbidity at 3 months. 95% CIs and p-values are found by bootstrapping. The results are given from models with main effects only, as the interaction effects were not significant. V'_{O_2}: oxygen uptake; V'_E: expired ventilation; BP: blood pressure; O_2: oxygen; V'_{CO_2}: carbon dioxide output; RER: respiratory exchange ratio; P_{ET}: end tidal pressure; P_{CO_2}: partial pressure of carbon dioxide; AT: anaerobic threshold

Table 2. Estimated effect of dyspnoea and ICU stay on CPET variables from linear mixed models (n=210).

	Dyspnoea vs. no dyspnoea		ICU vs. no ICU	
	Estimate (95%CI)	**P-value**	**Estimate (95%CI)**	**P-value**
Performance				
V'_{O2peak}, mL·min^{-1}	-172 (-322 to -16)	0.031	-283 (-459 to -105)	0.001
V'_{O2peak}, % of predicted	-6.6 (-11.9 to -1.0)	0.022	-10.1 (-15.9 to -4.2)	<0.001
V'_{O2peak}·kg^{-1}, mL·kg^{-1}·min^{-1}	-2.7 (-4.5 to -0.9)	0.003	-3.0 (-5.0 to -1.0)	0.004
V'_{O2peak}·kg^{-1}, % of predicted	-8.6 (-13.5 to -3.4)	0.001	-8.2 (-13.8 to -2.8)	0.003
Perceived dyspnoea BorgCR_{10} at max. load	0.4 (-0.1 to 0.9)	0.133	-0.1 (-0.6 to 0.5)	0.895
Ventilation				
V'_E at max. load, L·min^{-1}	-1.8 (-8.2 to 5.0)	0.620	-4.9 (-13.7 to 4.0)	0.280
Breathing reserve, %	1.4 (-4.3 to 7.4)	0.634	5.3 (-1.2 to 12.0)	0.109
Circulation				
Heart rate at max.load, beats·min^{-1}	-5.5 (-10.1 to -0.7)	0.020	-4.4 (-10.5 to 1.4)	0.134
Heart rate at max. load, % of predicted	-3.4 (-6.1 to -0.5)	0.016	-2.8 (-6.3 to 0.6)	0.110
Systolic BP at max. load, mmHg	-12.3 (-21.5 to -3.5)	0.008	-5.9 (-16.6 to 4.5)	0.258
Diastolic BP at max. load, mmHg	-6 (-11.0 to -1.3)	0.014	2.4 (-2.5 to 7.3)	0.335
Oxygen pulse at max. load, mL·stroke^{-1}	-0.7 (-1.5 to 0.2)	0.150	-1.4 (-2.4 to -0.5)	0.006
Oxygen pulse at max. load, % of predicted	-4.4 (-9.6 to 1.2)	0.127	-7.6 (-13.1 to -2.1)	0.009
Gas exchange				
V'_E/V'_{CO2} slope	2.1 (0.9 to 3.3)	0.001	0.9 (-0.9 to 2.9)	0.340
$V'_E/V'_{CO2nadir}$	1.0 (0.1 to 1.9)	0.029	0.7 (-0.3 to 1.7)	0.190
RER at max. load	-0.02 (-0.05 to 0.01)	0.143	0.01 (-0.02 to 0.04)	0.484
P_{ETCO2} at AT, kPa	-0.12 (-0.26 to 0.02)	0.095	0.08 (-0.06 to 0.22)	0.255
P_{CO2} at max. load, kPa	-0.1 (-0.3 to 0.1)	0.392	0.0 (-0.2 to 0.2)	0.900
Anaerobic threshold				
V'_{O2} at AT, mL·min^{-1} (V-slope)	-40 (-136 to 66)	0.513	-34 (-134 to 68)	0.502
V'_{O2} at AT, % of predicted V'_{O2max}	-1.8 (-5.0 to 1.9)	0.380	-1.4 (-4.7 to 1.9)	0.389
Lactate at max. load, mmol·L^{-1}	-0.5 (-1.5 to 0.5)	0.286	-0.1 (-1.4 to 1.2)	0.842

Estimated differences between patients with and without dyspnoea, and patients with and without ICU stay. The results are given from models with main effects only, as the interaction effects between dyspnoea or ICU stay and time were not significant (p-values ranged from 0.077 to 0.970 for dyspnoe and 0.062 to 0.997 for ICU). The results are adjusted for centre and for age, sex, BMI, and comorbidity at 3 months. 95% CIs and p-values are found by bootstrapping. V'_{CO2}: oxygen uptake; V'_E: expired ventilation; BP: blood pressure; O_2: oxygen; V'_{CO2}: carbon dioxide output; RER: respiratory exchange ratio; P_{ET}: end tidal pressure; P_{CO2}: partial pressure of carbon dioxide; AT: anaerobic threshold.

Table 3: CPET variables compared between controls and COVID-19 patients at 12 months follow-up					
	Control n=207[§]	**Patient** n=177^	**Patient vs. control** n=380#		
	Mean(SD)	Mean(SD)	Estimate	95% CI	P-value
Performance					
V'_{O2peak}, ml·min^{-1}	2952 (944)	2451 (776)	-529	(-638 to -421)	<0.001
V'_{O2peak}·kg^{-1}, mL·kg^{-1}·min^{-1}	34.9 (10.3)	28.6 (8.4)	-6.4	(-7.6 to -5.2)	<0.001
Perceived dyspnoea $Borg_{10}$ at max. load *	8.9 (1.8)	8.5 (2.0)	-0.4	(-0.8 to 0.0)	0.040
Ventilation					
V'_E at max. load, L·min^{-1}	102.7 (31.0)	87.5 (29.3)	-16.9	(-21.0 to -12.8)	<0.001
Breathing frequency at max. load, min^{-1}	43.5 (7.5)	39.0 (7.8)	-4.6	(-6.1 to -3.1)	<0.001
Circulation					
Heart rate at max.load, beats·min^{-1}	172.0 (17.0)	155.3 (21.9)	-16.7	(-19.8 to -13.5)	<0.001
Gas exchange					
RER at max. load	1.10 (0.06)	1.07 (0.10)	-0.03	(-0.05 to -0.02)	<0.001

*The Borg score from controls (HUNT4 HOPE) was a scale from 6-20, which was converted to the Borg CR10 scale used in the present study (32). Results from multiple linear regression, adjusted for age, sex, BMI, systolic blod pressure , chronic obstructive pulmonary disease diabetes, myocardial infarction, and congestive heart failure. V'_{O_2}: oxygen uptake; V'_E: expired ventilation; RER: respiratory exchange ratio

[§] Perceived dyspnoea $Borg_{10}$ at max. load n=203, heart rate at max.load=205. ^ Perceived dyspnoea $Borg_{10}$ at max. load. n=175. # Perceived dyspnoea $Borg_{10}$ at max. load n=374, Heart rate at max.load, n=378.

References

1. Nalbandian A, Sehgal K, Gupta A, *et al*. Post-acute COVID-19 syndrome. *Nature Med.* 2021;27(4):601-15.
2. https://www.ecdc.europa.eu/en/covid-19/variants-concern: European Centre for Disease Prevention and Control. SARS-CoV-2 variants of concern as of 9 June 2022. Date last assessed 29 June 2022.
3. Carfi A, Bernabei R, Landi F, *et al*. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 2020;324(6):603-5.
4. Clavario P, De Marzo V, Lotti R, *et al*. Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. *Int J Cardiol*. 2021;340:113-8.
5. Skjorten I, Ankerstjerne OAW, Trebinjac D, *et al*. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J*. 2021;58(2).
6. Jahn K, Sava M, Sommer G, *et al*. Exercise capacity impairment after COVID-19 pneumonia is mainly caused by deconditioning. *Eur Respir J*. 2022;59(1).
7. Cassar MP, Tunnicliffe EM, Petousi N, *et al*. Symptom Persistence Despite Improvement in Cardiopulmonary Health - Insights from longitudinal CMR, CPET and lung function testing post-COVID-19. *EClinicalMedicine*. 2021;41:101159.
8. Lerum TV, Aalokken TM, Bronstad E, *et al*. Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19. *Eur Respir J*. 2021; 2003448.
9. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e7.
10. Fletcher CM, Elmes PC, Fairbairn AS, *et al*. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J*. 1959;2(5147):257-66.
11. Quanjer PH, Stanojevic S, Cole TJ, *et al*. 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.
12. Stanojevic S, Graham BL, Cooper BG, *et al*. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3).
13. Hall GL, Filipow N, Ruppel G, *et al*. Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry. *Eur Respir J*. 2021;57(3).
14. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):377-81.
15. Radtke T, Crook S, Kaltsakas G, *et al*. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev*. 2019;28(154).
16. Sietsema KE, Sue DY, Stringer WW, *et al*. Wasserman & Whipp's Principles of exercise testing and interpretation. 6 Edn. Dordrecht, Wolters Kluwer 2021.

17. Edvardsen E, Hansen BH, Holme IM, *et al*. Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. *Chest*. 2013;144(1):241-8.

18. Sun XG, Hansen JE, Garatachea N, *et al*. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med.* 2002;166(11):1443-8.

19. Letnes JM, Dalen H, Aspenes ST, *et al.* Age-related change in peak oxygen uptake and change of cardiovascular risk factors. The HUNT Study. *Prog Cardiovasc Dis*. 2020;63(6):730-7.

20. Bates D, Mächler M, Bolker B, *et al*. Fitting Linear Mixed-Effects Models Using lme4. *J Stat Software*. 2015;67(1):1–48

21. Team RC. R: A language and environment for statistical computing URL https://www.R-project.org/: R Foundation for Statistical Computing, Vienna, Austria; 2018

22. Naeije R, Caravita S. Phenotyping long COVID. *Eur Respir J*. 2021;58(2).

23. Carrick-Ranson G, Hastings JL, Bhella PS, *et al*. The effect of lifelong exercise dose on cardiovascular function during exercise. *J Appl Physiol* (1985). 2014;116(7):736-45.

24. Singh I, Joseph P, Heerdt PM, *et al*. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. *Chest*. 2022;161(1):54-63.

25. Balbi P, Saltalamacchia A, Lullo F, *et al*. Peripheral Neuropathy in Patients Recovering from Severe COVID-19: A Case Series. *Medicina (Kaunas).* 2022;58(4):523.

26. Shouman K, Vanichkachorn G, Cheshire WP, *et al*. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res*. 2021;31(3):385-94.

27. Motiejunaite J, Balagny P, Arnoult F, *et al*. Hyperventilation: A Possible Explanation for Long-Lasting Exercise Intolerance in Mild COVID-19 Survivors? *Front Physiol*. 2020;11:614590.

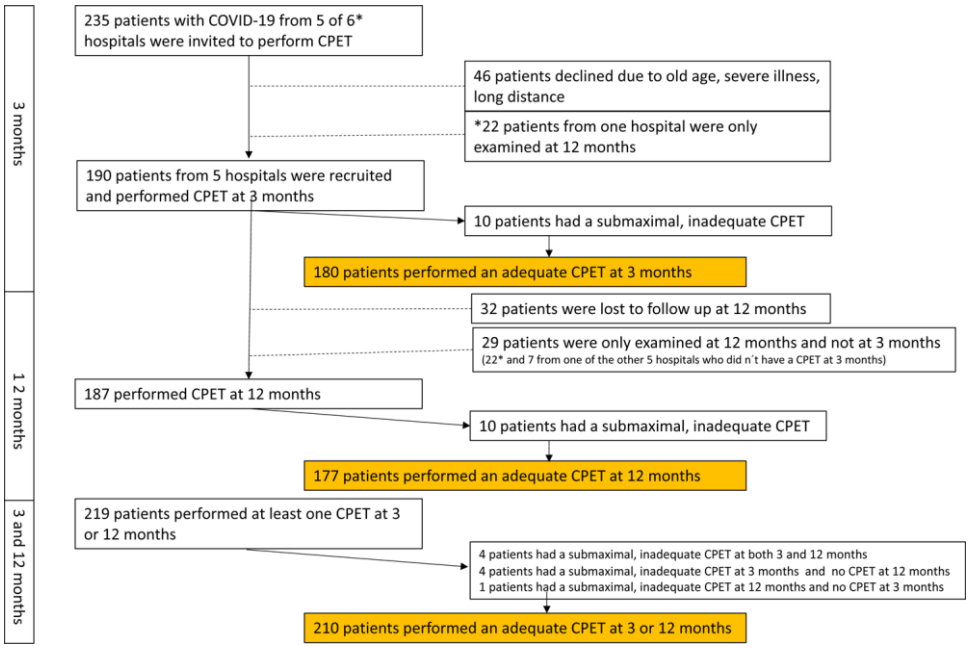
28. Taverne J, Salvator H, Leboulch C, *et al*. High incidence of hyperventilation syndrome after COVID-19. *J Thorac Dis*. 2021;13(6):3918-22.

29. Eberst G, Claude F, Laurent L, *et al*. Result of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia. *Ann Intensive Care*. 2022;12(1):23.

30. Alba GA, Ziehr DR, Rouvina JN, *et al*. Exercise performance in patients with post-acute sequelae of SARS-CoV-2 infection compared to patients with unexplained dyspnea. *EClinicalMedicine*. 2021;39:101066.

31. Parshall MB, Schwartzstein RM, Adams L, *et al*. 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.

32. Borg G, Borg E. The Borg CR Scales Folder. http://www.borgperception.se. Borg Perception AB. Date last accessed: 29 June 2022.


3 months
1 2 months
3 and 12 months
235 patients with COVID-19 from 5 of 6* hospitals were invited to perform CPET
46 patients declined due to old age, severe illness, long distance
*22 patients from one hospital were only examined at 12 months
190 patients from 5 hospitals were recruited and performed CPET at 3 months
10 patients had a submaximal, inadequate CPET
180 patients performed an adequate CPET at 3 months
32 patients were lost to follow up at 12 months
29 patients were only examined at 12 months and not at 3 months
(22* and 7 from one of the other 5 hospitals who did n´t have a CPET at 3 months)
187 performed CPET at 12 months
10 patients had a submaximal, inadequate CPET
177 patients performed an adequate CPET at 12 months
219 patients performed at least one CPET at 3 or 12 months
4 patients had a submaximal, inadequate CPET at both 3 and 12 months
4 patients had a submaximal, inadequate CPET at 3 months and no CPET at 12 months
1 patients had a submaximal, inadequate CPET at 12 months and no CPET at 3 months
210 patients performed an adequate CPET at 3 or 12 months

Cardiopulmonary exercise capacity and limitations one year after COVID-19

6 hospitals

Number of participants in the PROLUN study

3 months → **180** people
12 months → **177** people

ICU treatment

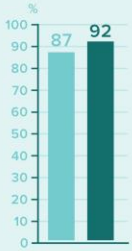
20% treated in ICU
65% on ventilator

Dyspnoea

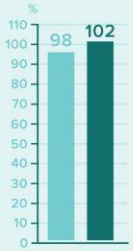
51% dyspnoea
49% no dyspnoea

Cardiopulmonary exercise test results

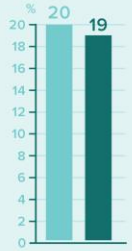
V'O₂peak % of predicted



Oxygen pulse % of predicted



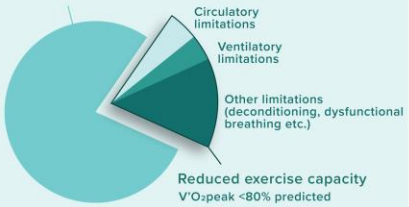
Breathing reserve



3 months 12 months

Exercise capacity at one year

Normal exercise capacity
V'O₂peak >80% predicted



Reduced exercise capacity
V'O₂peak <80% predicted

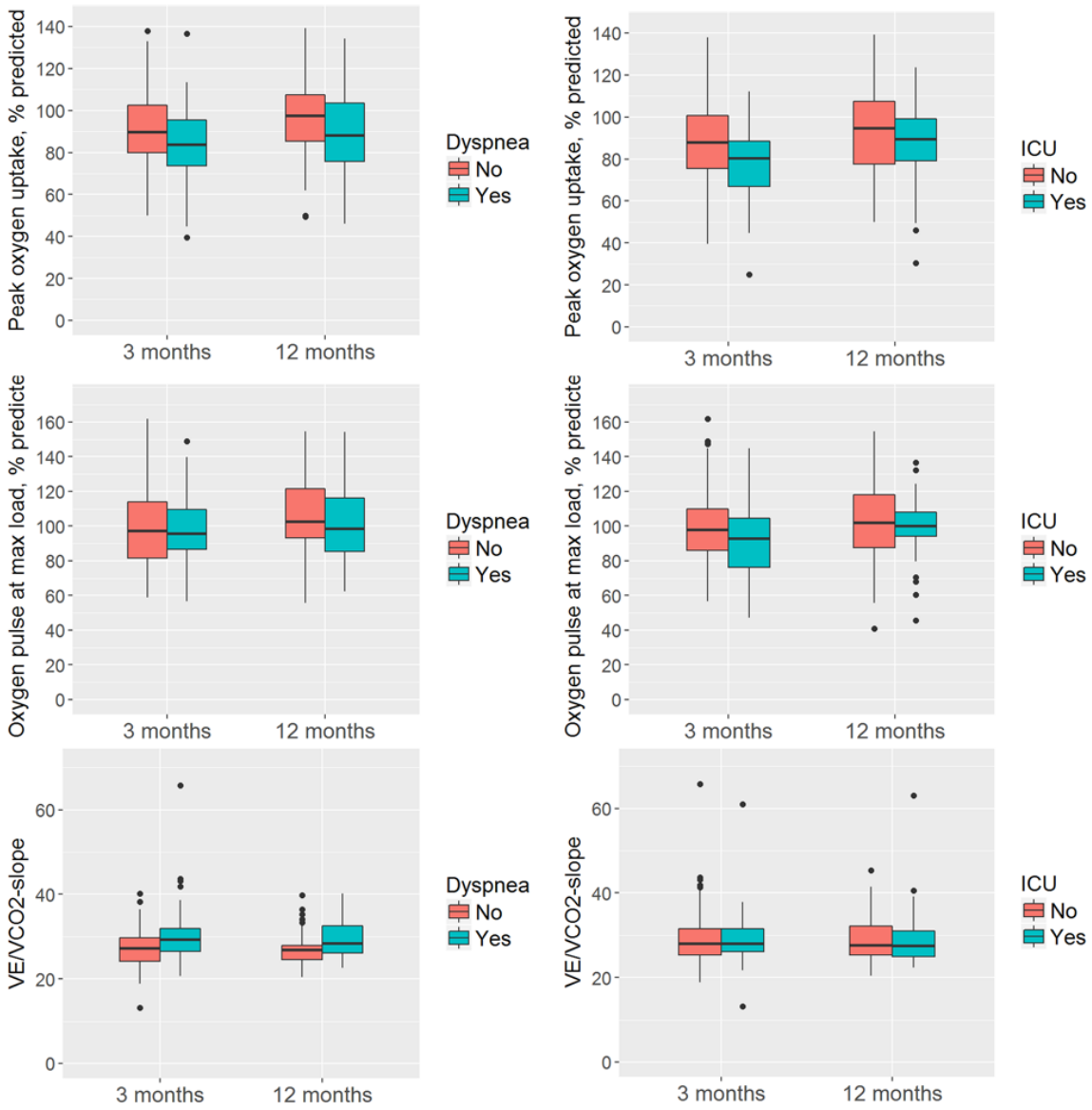


Figure 3a. V'O2peak % predicted and oxygen pulse % predicted, and V'E/V'CO2 slope according to dyspnoea and ICU status at three and 12 months.

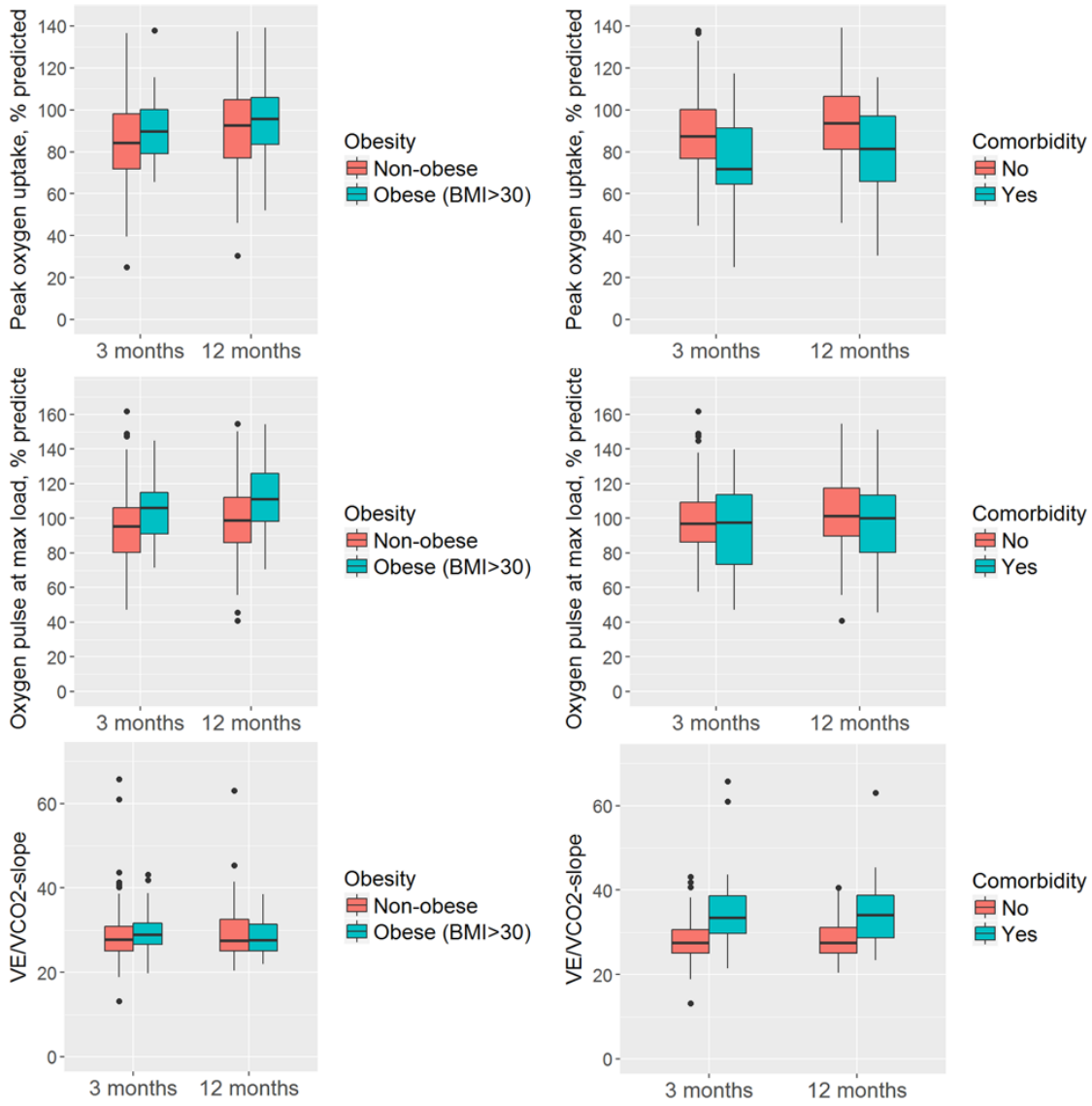


Figure 3b. V'O2peak % predicted and oxygen pulse % predicted, and V'E/V'CO2 slope according to obesity and comorbidity status at three and 12 months.

Supplementary Table S1: Descriptive statistics for all COVID-19 patients at 12 months with a valid CPET at either 3 or 12 months after hospitalization (n=210) and subgroups of the patients with and without dyspnoea at 3 months.

	All patients (n=210)	**Dyspnoea (n=85)**	**No dyspnoea (n=87)**
	Number (%)/Mean (SD)	**Number (%)/Mean (SD)**	**Number (%)/Mean (SD)**
Age at hospital discharge, years	210 / 58.1 (13.8)	57.7(13.3)	56.8(14.0)
Female sex	85 (41%)	42(49)	
Body mass index, $kg \cdot m^2$, 3 months/12 months	28.0 (4.4)%/28.5 (4.8)	29.1(4.6)/30.2(5.5)	27.2(3.9)/27.6(3.9)
Smoking status (n=176)			
Never smoked	113 (64)	45(54)	55(64)
Formerly a daily smoker	78 (44)	35(42)	31(36)
Current daily smoker	5 (3)	4(5)	0(0)
Medical history (n=208)			
Myocardial infarction	14 (7)	8(10)	4(5)
Heart failure	8 (4)	6(7)	2(2)
CVA/TIA	3 (1	2(2)	1(1)
Hypertension (n=203)	66 (32)	27(33)	25(29)
COPD	7 (3)	3(4)	1(1)
Asthma	39 (18)	19(23)	9(10)
Diabetes mellitus	16 (8)	8(10)	7(8)
Spirometry and body plethysmography			
FEV_1 % predicted, 12 months (n=189)	94 (15)	94(13)	95(14)
FVC % predicted, 12 months (n=187)	97 (13)	96(13)	96(16)
TLC, % predicted, 12 months (n=156)	97 (17)	97(15)	96(15)
Gas diffusion			
D_{LCO} % predicted, 12 months (n=184)	92 (17)	92(15)	96(16)
modified MRC dyspnoea scale 3 months/12 months (	176/183		
0	87 (49.4%)/97 (53.0)		
1-4	89 (50.6)%/86(47.0)		
Advanced oxygen treatment	58	28	25
High flow nasal oxygen	3(2)	3(4)	0(0)
CPAP	15(8)	7(8)	7(8)
BiPAP	14(7)	7(9)	7(8)
Mechanical ventilation with intubation	26(13)	11(13)	11(13)
WHO Ordinal Scale for Clinical Improvement	208		
3	75 (36)	25(29)	34(40)
4	96 (46)	43(51)	39(45)
5-7	37 (18)	17(20)	13(15)

The number of patients represents all patients that had at least one valid CPET at either 3 or 12 months. * Maximum values during hospitalization.CVA: cerebral vascular accident; TIA: transient ischemic attack; 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; V_A: alveolar volume; MRC: Medical Research Council; CPAP: Continuous Positive Airway Pressure, BiPAP: Bi-level Positive Airway Pressure, WHO: World Health Organization

Supplementary Table S2. Estimated effect of the interaction between the categorical time variable (3 or 12 months) and obesity or comorbidity on the outcome variables, given as the difference in change from 3 to 12 months between obese and non-obese (n=204), and between comorbidity and no-comorbidity (n=208).

	Time by obesity (BMI>30)		Time by comorbidity	
	Estimate (95% CI)	p	Estimate (95% CI)	p
Performance				
V'_{O_2peak}, mL·min^{-1}	-110 (-270 to 42)	0.150	-110 (-237 to 12)	0.076
V'_{O_2peak} % of predicted	-3.4 (-9.0 to 1.8)	0.202	-4.2 (-9.3 to 0.9)	0.098
V'_{O_2peak}·kg^{-1}, mL·kg^{-1}·min^{-1}	-1.5 (-3.2 to 0.2)	0.077	-0.7 (-2.5 to 1.0)	0.372
V'_{O_2peak}·kg^{-1}, % of predicted	-4.3 (-9.2 to 0.5)	0.083	-2 (-7.7 to 3.5)	0.452
Perceived dyspnoea $Borg_{10}$ at max load	0.7 (-0.1 to 1.6)	0.110	0.8 (-0.6 to 2.0)	0.230
Ventilation				
V'_E at max. load, L·min^{-1}	-2.4 (-9.5 to 4.7)	0.482	2.2 (-7.7 to 12.0)	0.672
Breathing reserve, %	0.3 (-6.5 to 7.5)	0.894	-0.7 (-12.6 to 11.7)	0.910
Circulation				
Heart rate at max.load, beats·min^{-1}	-5.3 (-11.3 to 0.5)	0.074	-0.2 (-8.0 to 7.8)	0.927
Heart rate at max. load, % of predicted	-3.1 (-6.6 to 0.3)	0.070	0.0 (-4.9 to 5.1)	0.976
Systolic BP at max. load, mmHg	-10.7 (-26.7 to 6.0)	0.215	-9.4 (-35.2 to 15.0)	0.430
Diastolic BP at max. load, mmHg	-10.8 (-18.4 to -2.9)	0.006	-4.7 (-16.0 to 6.2)	0.382
Oxygen pulse at max. load, mL·stroke^{-1}	-0.3 (-1.0 to 0.5)	0.446	-0.8 (-1.9 to 0.2)	0.112
Oxygen pulse at max. load, % of predicted	-0.3 (-5.1 to 4.4)	0.864	-3.3 (-11.0 to 3.9)	0.357
Gas exchange				
V'_E/V'_{CO_2} slope	-0.5 (-2.2 to 1.3)	0.550	-2.6 (-6.5 to 0.8)	0.145
V'_E/V'_{CO_2nadir}	0.2 (-0.8 to 1.3)	0.717	0.8 (-0.9 to 2.6)	0.365
RER at max. load	0.01 (-0.02 to 0.05)	0.474	0.03 (-0.01 to 0.09)	0.180
P_{ETCO_2} at AT, kPa	0.11 (-0.11 to 0.36)	0.368	-0.24 (-0.58 to 0.08)	0.152
P_{CO_2} at max. load, kPa	0.1 (-0.2 to 0.3)	0.522	0.1 (-0.3 to 0.5)	0.662
Anaerobic threshold				
V'_{O_2}at AT, mL·min^{-1} (V-slope)	28 (-76 to 137)	0.596	40 (-110 to 201)	0.616
V'_{O_2peak} at AT, % of predicted V'_{O_2max}	1.0 (-3.0 to 5.4)	0.636	1.4 (-5.7 to 9.0)	0.713
Lactate at max. load, mmol·L^{-1}	0.1 (-1.0 to 1.2)	0.824	0.1 (-1.4 to 1.6)	0.900

Estimates are from linear mixed models including main effects and interactions with time for ICU stay and dyspnoea, age, sex, obesity and comorbidity at 3 months. 95% CIs and p-values are found by bootstrapping.

Supplementary Table S3. Estimated effect of the interaction between the categorical time variable (3 or 12 months) and obesity or comorbidity on the outcome variables, given as the difference slope for age at 12 months vs 3 months (n=210), and in change from 3 to 12 between males and females (n=210).

	Time by age		Time by sex	
	Estimate (95% CI)	p	Estimate (95% CI)	p
Performance				
V'_{O_2peak}, mL·min^{-1}	11 (-27 to 52)	0.525	-70 (-183 to 31)	0.190
V'_{O_2peak}, % of predicted	0.6 (-0.9 to 2.1)	0.387	-3.7 (-8 to 0.1)	0.058
$V'_{O_2peak}\cdot kg^{-1}$, mL·kg^{-1}·min^{-1}	0.1 (-0.3 to 0.6)	0.516	-1.4 (-2.9 to -0.1)	0.029
$V'_{O_2peak}\cdot kg^{-1}$, % of predicted	0.6 (-0.9 to 2.0)	0.390	-4.1 (-8.5 to -0.3)	0.038
Perceived dyspnoea $Borg_{10}$ at max load	-0.1 (-0.4 to 0.2)	0.411	-0.3 (-1.0 to 0.3)	0.300
Ventilation				
V'_E at max. load, L·min^{-1}	-2.2 (-5.3 to 0.7)	0.148	2.1 (-4.5 to 8.9)	0.521
Breathing reserve, %	0.2 (-2.6 to 3.1)	0.939	-2.6 (-9.3 to 4.4)	0.461
Circulation				
Heart rate at max.load, beats·min^{-1}	-1.1 (-3.4 to 1.1)	0.321	-3.0 (-8.7 to 2.4)	0.294
Heart rate at max. load, % of predicted	-0.6 (-2.0 to 0.6)	0.319	-1.8 (-5.2 to 1.4)	0.273
Systolic BP at max. load, mmHg	0.0 (-5.9 to 6.3)	0.970	-15.5 (-31.3 to 0.5)	0.054
Diastolic BP at max. load, mmHg	0.5 (-2.3 to 3.5)	0.683	-4.1 (-11.0 to 3.1)	0.244
Oxygen pulse at max. load, mL·stroke^{-1}	0.3 (0.0 to 0.5)	0.049	-0.2 (-0.9 to 0.5)	0.512
Oxygen pulse at max. load, % of predicted	1.2 (-0.5 to 3.1)	0.173	-2.9 (-7.5 to 1.8)	0.214
Gas exchange				
V'_E/V'_{CO_2} slope	-0.5 (-1.1 to 0.0)	0.075	1.5 (0.1 to 3.0)	0.040
V'_E/V'_{CO_2nadir}	-0.1 (-0.5 to 0.2)	0.393	0.8 (-0.1 to 1.7)	0.071
RER at max. load	-0.01 (-0.03 to 0.00)	0.088	-0.02 (-0.06 to 0.02)	0.289
P_{ETCO_2} at AT, kPa	-0.01 (-0.07 to 0.07)	0.828	-0.12 (-0.29 to 0.06)	0.171
P_{CO_2} at max. load, kPa	-0.1 (-0.2 to 0.0)	0.163	0.0 (-0.2 to 0.2)	0.900
Anaerobic threshold				
V'_{O_2} at AT, mL·min^{-1} (V-slope)	-9 (-50 to 33)	0.674	-32 (-134 to 70)	0.544
V'_{O_2peak} at AT, % of predicted V'_{O_2max}	0.0 (-1.5 to 1.5)	0.986	-2.5 (-6.6 to 1.9)	0.238
Lactate at max. load, mmol·L^{-1}	0.0 (-0.4 to 0.3)	0.828	1.4 (0.4 to 2.3)	0.002

Estimates are from linear mixed models including main effects and interactions with time for ICU stay and dyspnoea, age, sex, obesity, and comorbidity at 3 months. 95% CIs and p-values are found by bootstrapping.

Supplementary Table 4. RER at max. load greater or less than 1.1 with the estimate of difference between patients and controls at 12 months

		RER < 1.1		RER ≥ 1.1		Interaction	
	n	**Estimate 95% CI**	**p-value**	**Estimate 95 % CI**	**p-value**	**Estimate 95 % CI**	**p-value**
Performance							
V'_{O2peak}, $mL \cdot min^{-1}$	380	-488 (-642 to -335)	<0.001	-553 (-695 to -371)	<0.001	-45 (-269 to 179)	0.693
$V'_{O2peak} \cdot kg^{-1}$, $mL \cdot kg^{-1} \cdot min^{-1}$	380	-6.1 (-7.7 to -4.4)	<0.001	-6.4 (-8.2 to -4.7)	<0.001	-0.4 (-2.8 to 2.1)	0.764
Perceived dyspnoea $Borg_{10}$ at max. load *	374	0 (-0.5 to 0.5)	0.944	-0.7 (-1.2 to -0.1)	0.017	-0.7 (-1.5 to 0.1)	0.075
Ventilation							
V'_E at max. load, $L \cdot min^{-1}$	380	-15.8 (-21.2 to -10.3)	<0.001	-13.0 (-18.7 to -7.2)	<0.001	2.8 (-5.2 to 10.8)	0.489
Breathing frequency at max. load, min^{-1}	380	-4.6 (-6.7 to -2.6)	<0.001	-4.0 (-6.2 to -1.8)	<0.001	0.7 (-2.4 to 3.7)	0.667
Circulation							
Heart rate at max.load, $beats \cdot in^{-1}$	378	-19.4 (-23.8 to -15.0)	<0.001	-11.3 (-15.9 to -6.6)	<0.001	8.1 (1.7 to 14.5)	0.013

Estimated difference between patients and controls in each of the subgroups RER <1.1 and RER ≥ 1.1, and :
Interaction: the difference in differences (Interaction; difference RER ≥ 1.1 - difference RER <1.1), adjusted for age, sex, BMI, systolic blood pressure , chronic obstructive pulmonary disease, diabetes, myocardial infarction, and congestive heart failure. CI: Confidence interval. V'_{O2}: oxygen uptake; V'_E: expired ventilation; RER: respiratory exchange ratio