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Effect of a home-based inspiratory muscular training programme on functional capacity in patients with chronic COVID-19 after a hospital discharge: protocol for a randomised control trial (InsCOVID trial)

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ABSTRACT

Introduction Exercise intolerance and fatigue are the most common symptoms in patients with chronic COVID-19 after hospital discharge. Supervised exercise training programmes improve symptoms, but scarce research has been done on home-based exercise programmes on the maximal functional capacity for discharged symptomatic COVID-19 patients. This study evaluates whether a home-based inspiratory muscle training (IMT) programme improves maximal functional capacity in chronic COVID-19 after hospital admission.

Methods and analysis This single-centre, assessor-blinded randomised controlled trial, powered for superiority, seeks to evaluate maximal functional capacity as the primary endpoint. A total of 26 eligible patients with a previous admission for acute respiratory syndrome coronavirus 2 pneumonia (>3 months after hospital discharge) will be randomised (1:1) to receive a 12-week programme of IMT versus usual care alone. A blinded assessor will measure outcomes at baseline and after the intervention (12 weeks). An analysis of variance will be used to compare continuous outcomes among the two-intervention groups. As of 21 March 2022, eight patients have been enrolled.

Ethics and dissemination The research ethics committee (Comité Ético de Investigación con Medicamentos de l'Hospital Clínic Universitari de València) approved the protocol following the principles of the Declaration of Helsinki and national regulations (Approval Number: 021/226). Findings will be published in peer-reviewed journals and conference publications.

Trial registration number NCT05279430.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Home-based programmes' feasibility and clinical utility on maximal functional capacity and quality of life in chronic COVID-19 are small or even absent, particularly in more symptomatic postdischarged patients.

WHAT THIS STUDY ADDS

⇒ This study will add information about the effects of a home-based inspiratory training programme on maximal functional capacity in symptomatic patients with a previous admission due to SARS-CoV-2 pneumonia beyond 3 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If this study demonstrates that home-based inspiratory muscle training programmes effectively improve exercise tolerance and symptoms of chronic COVID-19, it will offer an accessible physical therapy model, requiring minimal resources.

INTRODUCTION

Chronic COVID-19 is a common heterogeneous syndrome characterised by persistent symptoms beyond 3 months of COVID-19 infection that predominantly affects women and postdischarged patients.[1] The most common reported symptoms among chronic COVID-19 patients are fatigue and dyspnoea.[1–5] Compared with control individuals matched for age, sex and comorbidities, patients with chronic COVID-19 have significantly impaired exercise capacity.[6] One of the most common findings in pulmonary function tests at long-term follow-up was a reduced diffusing capacity of the lungs for carbon monoxide (DLCO) in patients with chronic COVID-19 who recover from an acute infection requiring hospitalisation.[7]

Along this line, current evidence from supervised exercise training programmes[8 9] and unsupervised training programmes[10] supports the beneficial effect of physical therapies on chronic COVID-19. Nevertheless, the

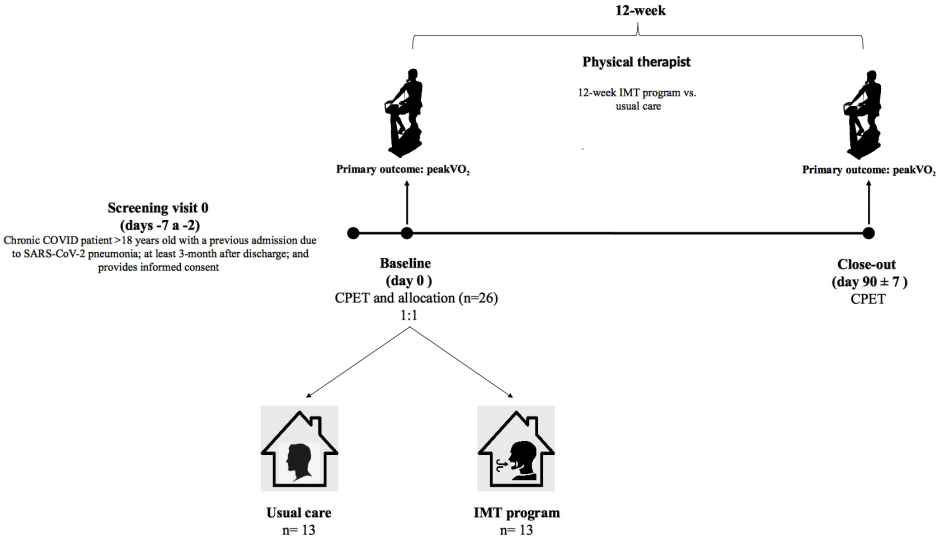

Figure 1 Flow chart for patient inclusion and follow-up. CPET, cardiopulmonary exercise testing; IMT, inspiratory muscle training; peakVO_2, peak oxygen consumption at maximal exercise.

feasibility and clinical utility of home-based programmes on maximal functional capacity in chronic COVID-19 are small or even absent, particularly in more symptomatic postdischarged patients. Therefore, this randomised controlled study aims to evaluate the effect of a 12-week home-based inspiratory muscle training programme (IMT) on maximal functional capacity and quality of life (QoL) in patients with chronic COVID-19 recovering from an acute respiratory syndrome coronavirus 2 pneumonia requiring hospitalisation.

METHODS

Study design

This study is designed as a prospective, controlled, randomised, two-armed, efficacy trial of symptomatic patients with a previous admission due to SARS-CoV-2 pneumonia beyond 3 months. The study will be conducted in a single centre in Spain. A summary of the study design is described in figure 1. Discounting the time due to staggered entry, the total duration of a patient's follow-up will be 3 months. In addition, this protocol follows Standard Protocol Items: Recommendations for Interventional Trials guidelines.[11] The study registration was in March 2022.

Study population sampling

Candidate patients will be selected from the post-COVID Pneumology outpatient clinics of the Hospital Clínico Universitario of Valencia. The eligibility of candidate patients will be based on the following inclusion criteria: (1) symptomatic adult >18 years old with a previous admission due to SARS-CoV-2 pneumonia; (2) at least 3 months after discharge and (3) provide informed consent.

Exclusion criteria will be: (1) inability to perform a maximal baseline exercise test; (2) structural heart disease, valve heart disease or diastolic dysfunction estimated by two-dimensional echocardiography; (3) previous ischaemic heart disease, heart failure, myocardiopathy or myocarditis; (4) effort angina or signs of ischaemia during cardiopulmonary exercise testing (CPET); (5) significant primary pulmonary disease, including a history of pulmonary arterial hypertension, chronic thromboembolic pulmonary disease or chronic obstructive pulmonary disease; (6) treatment with digitalis, calcium channel blockers, β-blocker or ivabradine; (7) chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2); (8) patients with pacemakers or previous history of atrial fibrillation; (9) autoimmune, inflammatory or active neoplastic disease; (10) anaemia and (11) pregnancy.

Enrolment, allocation and concealment

A schedule of enrolment, interventions, and procedures along the visits is summarised in table 1. After reviewing the inclusion/exclusion criteria, signing the informed consent form, and finishing the baseline assessment, patients will be randomly allocated (in a 1:1 ratio) to receive: (1) a home-based 12-week programme of IMT or (2) usual care (UC) by a computer-generated randomisation scheme. Due to the nature of the intervention (physical therapy programme), it will not be possible for blind participants and respiratory physiotherapists to the intervention. Therefore, all the evaluators of the primary and secondary outcomes (two pulmonologists, three cardiologists and one nurse) will be blinded to group allocation.

Table 1 Schedule of enrolment, interventions and assessments

	Study period					
Visits	**Screening**	**Baseline**	Physical therapist **(first visit)**	Physical therapist **(training)**	Physical therapist **(last visit)**	**Close-out**
Timepoint	**−7 to −2 days**	**Day 0**	**Day 1 (±3)**	**Days 1–90 (weekly)**	**Day 90 (±5)**	**Day 90 (±7)**
Enrolment						
Eligibility screen	x					
Informed consent	x					
Medical history		x				
Physical examination		x				
Pulmonary function test	x					
CPET		x				
Echocardiography		x				
Health-related QoL		x				
Blood sample		x				
Allocation		x				
Interventions						
Usual care			x		x	
IMT programme			x	x	x	
Assessments						
PeakVO2		x				x
VE/VCO2 slope		x				x
Chronotropic response		x				x
Health-related QoL		x				x
Inspiratory Muscle Strength test			x	x	x	

CPET, cardiopulmonary exercise testing; IMT, inspiratory muscle training; QoL, quality of life; VE/VCO2 slope, ventilatory efficiency.

Visits and interventions

Screening and baseline visit

After reviewing the inclusion/exclusion criteria and signing the informed consent form (Screening visit), a comprehensive medical history, physical examination, anthropometry and examination tests will be performed by two blinded cardiologists to patients' allocation groups (baseline visit). The examination tests will include an ECG, two-dimensional transthoracic echocardiography, a CPET, QoL assessment by EQ-5D-3L (EuroQol Five-Dimensional Questionnaire, Three-Level Version) instrument, pulmonary function tests and blood samples for a panel of baseline biomarkers.

Finally, if the patient rules out all the exclusion criteria (including a valid CPET without signs of ischaemia) will be randomised in a 1:1 ratio to one of the following interventions: (1) a home-based 12-week programme of IMT or (2) UC.

Intervention

UC group

Patients allocated to this arm will not receive any physical therapy. Patients allocated to this arm will be checked at the physical therapist's first visit (at day 1±3) and last visit (at day 90±5) by a physiotherapist who will measure their maximal inspiratory pressure (MIP).

IMT group

Patients allocated to the IMT arm will be instructed to train at home twice daily, for 20 min each session, and for 12 weeks using a threshold inspiratory muscle trainer (Threshold IMT, Respironics). At the physical therapist's first visit (at day 1±3), a respiratory physiotherapist will instruct and educate patients to maintain diaphragmatic breathing during the training period. MIP will be measured during each physical therapist visit (first visit—day 1±3, training sessions—weekly—and last visit—day 90±5). After the first visit, the subjects will start home-based inspiratory training at a resistance equal to 25%–30% of MIP for 1 week. Then, the respiratory therapist will

examine the patients at weekly intervals by checking the diary card and measuring their MIP. The resistance will be modified each session according to 25%–30% of their MIP measured.

Close-out visit

Two blinded cardiologists will evaluate all patients at 12 weeks after randomisation. Additional visits based on the clinical status will be permitted. Evaluation will include medical history, physical examination, anthropometry, CPET and QoL (EQ-5D-3L). The flow chart is summarised in figure 1.

Additional visits will be permitted according to the patient's clinical status and will be registered.

Study procedures

Cardiopulmonary exercise testing

Maximal functional capacity will be evaluated using incremental and symptom-limited CPET (Vyntux, Jaeger) on a bicycle ergometer, beginning with a workload of 10 W and gradually increasing in a ramp protocol of 10 W increments every 1 min. We will define maximal functional capacity as the point when the patient stops pedalling because of symptoms and the respiratory exchange ratio is ≥1.05. Patients will be monitored with 12-lead ECG and blood pressure measurements every 2 min during exercise. Gas exchange data and cardiopulmonary variables will be averages of values taken every 10 s. Peak oxygen consumption (peakVO_2) will be defined as the highest value 30 s average of oxygen consumption (VO_2). Once peakVO_2 is obtained, we will calculate its percent of predicted peakVO_2 (peakVO_2%), defined as the percentage of predicted peakVO_2 adjusted for sex, age, exercise protocol, weight and height according to the Wasserman/Hansen standard prediction equation. The anaerobic or ventilatory threshold will be defined as the point at which the ventilatory equivalent for oxygen (VE/VO_2) is lower, followed by a progressive increase.

The ventilatory efficiency will be determined by measuring the slope of the linear relationship between minute ventilation (VE) and carbon dioxide production (VCO_2) across the entire course of the exercise (VE/VCO_2 slope). It will be considered normal if the VE/VCO_2 slope is <30. In addition, the oxygen uptake efficiency slope will be analysed. Hypocapnia will be defined as a resting end-tidal CO_2 ($PetCO_2$) below the lower limit of normal (<35 mm Hg).

We will review all data about VE versus time, respiratory rate (RR) and tidal volume versus VE (mL/min).

Blunted heart rate (HR) response during a maximal CPET will be defined as a chronotropic index <0.8 (chronotropic index=[HRpeak exercise – HRrest)] / [(220 – age – HRrest)]).

Each subject will undergo two CPET (at baseline and 12 weeks).

Pulmonary function test

Pulmonary function tests will be performed, including forced vital capacity, forced expiratory volume at the first second of exhalation and DLCO.

Each subject will undergo one examination (at baseline).

Echocardiography

A two-dimensional Doppler echocardiogram will be performed under resting conditions. Each subject will undergo one examination (at baseline). All parameters, including tissue Doppler parameters, are measured according to the European Society of Echocardiography.[12]

Inspiratory muscle strength test

MIP will be obtained using a hand-held respiratory mouth pressure metre (electronic manometer-ELKA, PM15). With a nose clip, patients will be instructed to breathe through a mouthpiece only during inspiration. The MIP values will be obtained in a standing position by inspiration from residual volume. At each visit, the MIP will be repeated within a 1 min interval until three technically satisfactory and reproducible measurements are obtained (variation of −10%).

Health-related QOL

EQ-5D-3L instrument will be used to assess the impact of the intervention on QoL.[13] Each subject will undergo two tests (at baseline and 12 weeks).

Blood sample

One blood sample (at baseline) will be collected under standardised conditions. We will evaluate baseline haemoglobin, renal function, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and C reactive protein levels.

Outcomes

The primary endpoint of the study is the 3-month change in peak VO_2.

The secondary endpoints are (1) 3-month changes in QoL assessed by EQ-5D-3L), (2) 3-month changes in VE/VCO_2 slope and (3) 3-month changes in chronotropic response during CPET.

Sample size calculation

The study's null hypothesis is that there are no differences between all study-group means for the primary endpoint. This study's sample size determination assumes two-sided testing at the 0.05 significance alpha level. The effect size for the primary endpoint is based on data from two randomised control studies that evaluated the effects of 12 week IMT programmes on (1) middle-aged diabetic patients with peripheral neuropathy with obstructive sleep apnoea[14] and (2) patients with heart failure and preserved ejection fraction.[15] Based on these previous

Table 2 Baseline characteristics of the included patients

Demographic and clinical variables at admission		
Age, years	54 (43–55)	
Women, %	62.5	
Length of stay, days	12 (6–16)	
Abnormal X-rays or CT, n (%)	8 (100)	
Received steroids, n (%)	8 (100)	
Received antibiotics, n (%)	8 (100)	
Received oxygen therapy, n (%)	8 (100)	
Received remdesivir, n (%)	6 (75)	
Received tocilizumab, n (%)	4 (50)	
Required intubation, n (%)	1 (12.5)	
Clinical, echocardiographic, laboratory and pulmonary parameters		
Time to tests after discharge, days	336 (315–394)	
BMI, kg/m^2	29 (26.5–30.5)	
FEV1, %	61.2±4	
Structural heart disease, n (%)	0 (0)	
Valvular heart disease, n (%)	0 (0)	
DLCO, %	65.5 (62.5–68.5)	
Haemoglobin,g/L	138 (138–150)	
NT-pro-BNP, pg/mL	25.5 (15–35)	
CRP, mg/L	3.2 (1.1–6.5)	
CPET Variables	Rest	Peak exercise
Workload, W		95.5 (83–124)
Exercise time, min		9 (8.4–12)
HR, bpm	76±12.9	146±16.7
Chronotropic index*		0,76±0.17
SBP, mm Hg	118.1±9.2	155.8±20.2
RR, breaths/min	16±3.3	28±5.5
Breathing reserve >30%, n (%)		8 (100)
VE, L/min	11.5 (10–13)	45.5 (42–73)
O_2 desaturation during CPET, n (%)		8 (100)
RER		1.13±0.34
Reached VT, n (%)		8 (100)
PeakVO_2, mL/kg/min		17.2±3.8
PeakVO_2%, %		74.2±12.2
VO_2AT, mL/kg/min		10.6±2.4
$PetCO_2$, mmHg	33.5 (30.5–35.5)	38.6 (36.5–40.5)
VO_2 pulse, mL/beat		10.1 (8.4–10.4)
VE/VCO_2 slope		31.2±5.3
OUES, mL/min		1670 (1290–1995)
Predicted OUES		2219 (1920–2637)
Mild reduction of peakVO_2% (80%–90%), n (%)	3 (37.5)	
Moderate reduction of peakVO_2% (60-<80%), n (%)	5 (62.5)	
Abnormal flow-volume curve at spirometry, n (%)	0 (0)	
CPET Limiting symptoms		
Muscular fatigue	5	

Continued

Table 2 Continued

Dyspnoea	2
Muscular fatigue and dyspnoea	1
Chest pain	0
Dizziness	0
Arrhythmias	0

Continuous variables are expressed as means (±1 SD) or medians (IQR), and discrete variables as frequencies and percentages.
*Chronotropic index= [$HR_{peak\ exercise}$ – HR_{rest})] / [(220 – age – HR_{rest})]).
BMI, body mass index; CPET, cardiopulmonary exercise testing; CRP, C reactive protein; DLCO, diffusing capacity of lungs for carbon monoxide; FEV1, forced expiratory volume 1 s; HR, heart rate; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; OUES, oxygen uptake efficiency slope; PeakVO_2, peak oxygen uptake; PeakVO_2%, percent of predicted peak oxygen uptake; PetCO_2, end-tidal CO2; RER, respiratory exchange ratio; RR, respiratory rate; SBP, systolic blood pressure; VE, minute ventilation; VE/VCO2 slope, ventilatory efficiency; VO_2AT, oxygen consumption at anaerobic threshold; VT, ventilatory threshold.

studies, IMT was associated with a significant increase of at least a mean of peakVO_2 of 3 mL/kg/min, with an SD of ±2.5.

Assuming an allocation ratio of 1:1, 26 patients (13 patients per group) would provide 80% of power at a significance alpha level <0.05. In addition, we assume 15% of withdrawals or lost to follow-up. Thus, 13 patients per arm (26 patients) will be enrolled. The software used for sample size calculation was GRANMO.

Data analysis plan

Continuous variables will be presented as mean±SD or median (IQR) as appropriately; categorical variables as percentages. All statistical comparisons will be made under the intention-to-treat principle. An analysis of variance will be used to compare continuous outcomes among the two-intervention groups. A two-sided p<0.05 will be considered to be statistically significant for all analyses. All analyses will be performed with Stata V.15.1.

Data management

The base data used for this project's development will be treated by the Regulation 2016/679 of the European Parliament and of the Council of April 27th, 2016 and Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights.

Future access to the base data for other researchers who may be legitimately interested in them will be subject to the approval of an ethics commission. In this way, the Open Access data requirements are fulfilled, which must be met by projects that have public funding, at the same time that they are kept in a restricted environment in accordance with their character of personal data.

Safety and monitoring of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to IMT, whether or not considered causally related to the IMT. An undesirable medical condition can be symptoms (eg, fatigue, dyspnoea), signs (eg, tachycardia, oedema) or the abnormal results of an investigation (eg, laboratory findings, ECG). An AE will include an undesirable medical condition occurring at any time.

Any AE will be monitored and registered during the study.

Patient and public involvement

Patients or the public were not involved in this study design, but they will be informed of our research plans, including the protocol's development, recruitment timing and assessments. Maximal functional capacity was selected as the trial's primary outcome as it is an outcome of crucial importance to people with chronic COVID-19.

Current status

Patients started enrolling on 30 January 2022. On 20 March, a total of eight patients were enrolled. The baseline characteristics of the included patients are summarised in table 2.

The inclusion rate is appropriate, and we expect to finish the recruitment at the end of October 2022.

DISCUSSION

An important amount of patients discharged from the hospital after COVID-19 pneumonia reported symptoms of breathlessness, exercise intolerance and reduced QoL.[6] Despite being a contemporary challenge, these patients' pathophysiological mechanisms of impaired exercise capacity and poor QoL are not entirely clarified.[6 16 17] Data from previous more extensive CPET studies in Long-COVID at 3 months after discharge[18–20] showed that deconditioning was the leading cause of exercise limitation in those patients, followed by elevated breathing rate or increased VE/VCO_2[19 20] during exercise. Among cardiac mechanisms, poor HR variability or blunted HR associated with autonomic dysfunction have been proposed as pathophysiological mechanisms.[21 22]

From an epidemiological perspective, most chronic COVID-19 included in previous studies are young to middle-aged individuals.[23] Along this line, persistent symptoms in a significant proportion of chronic COVID-19 patients are a burden on individuals and their caregivers as well as on outpatient care, public health and the economy.[23] Although supervised exercise programmes have beneficial effects on persistent symptoms,[8 9] further cost-effective initiatives are needed to overcome this public health burden. In this regard, the home-based IMT programme seems to be a safe and feasible approach demonstrating significant improvement in peakVO_2 in other clinical scenarios (14,15). Worth noting is that IMT does not require particular logistics or human resources to be implemented, and the patient could follow a home-based training after short and simple instructions.

Biological plausibility

Currently, a previous randomised study evaluated the effect of a home-based IMT programme on reported QoL (primary endpoint), perceived dyspnoea (secondary endpoint) and an indirect evaluation of fitness (secondary endpoint) in a non-selected population of outpatients patients recovering from self-reported COVID-19 disease.[10] The authors reported improved perceived dyspnoea with no differences in the primary endpoint. Although the authors did not directly measure the maximal functional capacity, they reported a significant improvement in the trained group's indirect measurement of peakVO_2 (using a step test). Despite the lack of evidence of an unsupervised IMT programme in post-discharged chronic COVID-19 patients, in the light of the principal CPET findings, we speculate that a home-based IMT programme could improve maximal functional capacity in those patients. Along this line, several potential beneficial effects underlying the effects of an IMT programme stand out: (1) decreases the rating of perceived exertion and improves respiratory muscle economy,[24 25] improving exercise tolerance; (2) improves ventilatory efficiency and improves breathing patterns during exercise hyperpnea[24 26] and (3) attenuates the respiratory muscle metaboreflex,[24 27] which leads to sympathetic attenuation and autonomic regulation.

Feasibility and future implications

The results of this trial will provide valuable information for daily clinical practice. First, if this study demonstrates that home-based IMT programmes are effective for improving exercise tolerance and symptoms, it will offer an accessible physical therapy model, requiring minimal resources. Second, this low-cost home-based programme could rapidly be uptake into clinical practice globally. Finally, it will provide clinicians and physical therapists with information regarding the effects of an IMT programme on CPET variables and symptoms in patients with chronic COVID-19.

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Contributors Conceptualisation and design: PP, ED, CG and LL. Acquisition, analysis or interpretation of data for the work: PP, ED, CS, MLM, CG, EB, CA, JN and LL. Drafting protocol manuscript: PP, ED, CS, MLM, CG, EB, CA, JN and LL. Critical review of protocol manuscript: PP, ED, CS, MLM, CG, EB, CA, JN and LL.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by 021/226. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The base data used for this project's development will be treated by the Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 and Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights. Future access to the base data for other researchers who may be legitimately interested in them will be subject to the approval of an ethics commission. In this way, the Open Access data requirements are fulfilled, which must be met by projects that have public funding, at the same time that they are kept in a restricted environment in accordance with their character of personal data.

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