ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of the coordinating center. Informed consent was not deemed necessary due to the observational, retrospective nature of the study. As a limitation, the SAGER (Sex and Gender Equity in Research) guidelines were not applied.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in this study.

AUTHORS' CONTRIBUTIONS

D. Cordero Pereda and C. de Rueda Panadero contributed equally to this work as first authors and prepared the initial draft of the manuscript. D. Cordero Pereda and J. Álvarez-García conceived and designed the study and analyzed the data. C. de Rueda Panadero, J. de Juan Bagudá, M. Gómez Bueno, and A. Robles-Mezcua collected and interpreted the data and participated in the critical review and discussion. All authors approved the final version of the manuscript for publication.

CONFLICTS OF INTEREST

The authors do not have conflicts of interest in relation to this article.

APPENDIX. PRINCIPAL INVESTIGATORS AND PARTICIPATING CENTERS

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Baseline resting heart rate and responsiveness to a home-based inspiratory muscle training program in long COVID

Frecuencia cardiaca basal en reposo y respuesta a un programa domiciliario de entrenamiento de la musculatura inspiratoria en COVID persistente

To the Editor,

Individuals with long COVID may exhibit alterations in heart rate (HR), including an elevated resting HR (rest-HR) or diminished HR variability, among other abnormalities. These perturbations in HR dynamics are believed to be linked to underlying autonomic dysfunction and are associated with higher self-reported symptoms.[1,2]

Under normal physiological conditions, the diaphragm plays a pivotal role in modulating HR variability and regulating sympathetic tone.[3] Previous evidence has suggested that improved muscle function may have a beneficial effect on cardiovascular function and the re-establishment of sympathovagal balance facilitated by ergoreflex modulation.[4] Given these considerations, we hypothesized that, in long COVID individuals with higher baseline sympathetic tone surrogates, improved respiratory muscle function through inspiratory muscle training (IMT) may further enhance tolerance to physical activity by regulating sympathetic activation and cardiovascular stress. In this post

Table 1
Baseline characteristics of patients who receive d IMT stratified by median baseline heart rate.

Variables	All patients	Baseline HR ≥ 77 bpm	Baseline HR < 77 bpm	*P*
No. (%)	**13 (100)**	**7 (53.8)**	**6 (46.2)**	
Demographic and medical history				
Age, y	55 [43-56]	55 [41-65]	49 [43-56]	.617
Women, %	7 (53.8)	2 (28.6)	5 (83.3)	.048
BMI, kg/m^2	29 [26-32]	29 [26-30]	30 [22-38]	.047
Hypertension	1 (7.7)	1 (14.3)	0 (0)	.335
Current smoker	1 (7.7)	0 (0)	1 (16.7)	.250
Prior smoker	4 (30.8)	2 (28.6)	2 (33.3)	.853
Length of hospital stay, d	6 [5-15]	15 [6-18]	5 [5-6]	.074
Received steroids	12 (92.3)	6 (85.7)	6 (100)	.253
Vital signs, laboratory values, echocardiography parameters and maximal inspiratory pressure				
Systolic blood pressure, mmHg	120 (110-122)	110 (110-126)	120 (110-122)	.520
Diastolic blood pressure, mmHg	60 [60-66]	60 [60-70]	60 [60-65]	.317
Hemoglobin, g/dL	14.6 ± 1.4	15.1 ± 1.6	14.1 ± 0.9	.210
CRP, mg/L	1.8 [0.8-3]	2.4 [0.8-3.9]	1.3 [0.7-])	.865
NT-proBNP, pg/mL	30 [18-36]	18 [11-42]	33 [30-36]	.224
LVEF, %	63.6 [61.3-69.3]	64 [62.6-71]	62.5 [60.6-68.5]	.284
PAPS, mmHg[a]	25 [22.5-31.5]	30 [25-33]	22 [20-25]	.074
MIP, cmH_2O	80 [65.7-101]	95 [66.4-105]	70.9 [61.5-92]	.198
CPET variables				
Exercise time, sec	615 [515-751]	640 [514-756]	574 [515-720]	.082
Peak heart rate, bpm	148 [127-163]	148 [130-169]	138 [124-163]	.432
Chronotropic index[b]	0.72 [0.58-0.89]	0.87 [0.59-0.91]	0.65 [0.55-0.75]	.475
Peak systolic blood pressure, mmHg	160 [146-170]	160 [140-190]	148 [146-170]	.758
RER	1.12 [1.1-1.16]	1.13 [1.1-1.16]	1.1 [1.1-1.13]	.520
Peak VO_2, mL/kg/min	16.9 [15.5-21.1]	17.6 [15.5-21.1]	15.7 [13.8-27.5]	.522
pp-peak VO_2, %	76.8 [64-87.6]	67 [61-90]	84 [77-87]	.317
VE/VCO_2 slope	28.3 [24.5-29.1]	28.5 [22.3-34.4]	27.9 [25.7-29]	.886

BMI, body mass index; bpm, beats-per-minute; CPET, cardiopulmonary exercise testing; CRP, C-reactive protein; HR, heart rate; LVEF, left ventricle ejection fraction; MIP, maximal inspiratory pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; peak VO2, peak oxygen consumption; pp-peak VO2, percent of predicted peak oxygen consumption; RER, respiratory exchange ratio; VE/VCO2, ventilatory efficiency.
The data are expressed as No. (%), mean ± standard deviation, or median [interquartile range]. Baseline variables were compared among treatment groups with unpaired Student *t* test, Mann-Whitney *U* test, or chi-square test as appropriate.
[a] Data available in 8 patients (5 in baseline HR ≥ 77 bpm group and 3 in baseline HR < 77 bpm group).
[b] Chronotropic index formula = peak HR-rest HR/[(220-age)-rest HR)].

hoc substudy of the InsCOVID trial, we aimed to assess the influence of rest-HR on responsiveness to a 12-week IMT program in terms of peak oxygen consumption (peak VO_2) among patients with long COVID.

The InsCOVID trial was a randomized clinical trial conducted at a single center with blinded assessors and 26 patients with long COVID. The trial investigated the impact of a 12-week home-based IMT vs usual care (UC) on peak VO_2 in individuals with prolonged symptoms postsevere acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia hospitalization. The design and primary outcomes of the trial were registered at Clinical Trials (NCT05279430) and have been previously published.[5,6] Informed consent was obtained from all participants, and the trial was approved by the local research ethics committee following the Declaration of Helsinki and national regulations.

The inclusion criteria for participant enrollment were: *a)* symptomatic adults previously admitted due to SARS-CoV-2 pneumonia; *b)* a minimum of 3 months since discharge; and *c)* provision of informed consent. The main exclusion criteria encompassed: *a)* the inability to undergo maximal baseline cardiopulmonary exercise testing (CPET); *b)* structural heart disease, valve heart disease or diastolic dysfunction estimated by 2-dimensional echocardiography; *c)* significant pulmonary disease; *d)* the presence of angina or ischemia during CPET; *e)* chronic kidney disease (glomerular filtration rate < 60 mL/min/1.73 m^2); *f)* anemia (hemoglobin level of < 12 g/dL in women and < 13 g/dL in men); and *g)* treatment with negative chronotropic drugs or individuals with a pacemaker.

The IMT intervention commenced with an initial diaphragmatic breathing instruction using a threshold inspiratory muscle trainer. Subsequently, patients participated in a home-based training regimen involving 2 daily 20-minute sessions over 12 weeks at a resistance level set at 25% to 30% of their maximal inspiratory pressure. Weekly assessments by a physiotherapist allowed adjustments to be made to resistance settings.

Maximal functional capacity was evaluated using incremental and symptom-limited CPET on a bicycle ergometer. HR was assessed at rest and peak effort (peak-HR). The HR response during

CPET was evaluated following the chronotropic index (CIx) formula = peak-HR-rest-HR/ [(220-age)-rest-HR)].

We used a linear mixed regression model to analyze between-treatment changes in peak VO_2. Baseline age, sex, hemoglobin, body mass index (BMI), baseline maximal inspiratory pressure, and the baseline values of peak VO_2 were included as covariates. All analyses were performed with STATA 17.0 (StataCorp LP, College Station, United States).

There were no significant differences across treatment arms at baseline in the InsCOVID trial.[6] Baseline characteristics across median baseline rest-HR among patients assigned to the IMT arm are presented in table 1. The median age was 55 (43-56) years, with 46.2% of the participants being women. Overall, patients with a higher rest-HR were predominantly men and showed lower BMI, with no other significant differences.

Compared with patients in the UC group, those assigned to the IMT group exhibited an enhanced increment in peak VO_2 at 12 weeks if they had a higher rest-HR at baseline (*P* value for between-treatment comparison = .011), as illustrated in figure 1.

Regarding HR response to treatment, a statistically significant increase was observed in both peak-HR and CIx (Δ + 11.42; 95% confidence interval [95%CI], 0.33-22.5; *P* = .044 and Δ + 0.13, 95%CI, 0.01-0.26; *P* = .046, respectively) in the IMT group compared with the UC group. No significant differences in treatment were observed at 12 weeks for rest-HR in the IMT group compared with the UC group (Δ – 3.85; 95%CI, – 15.8 to 8.06; *P* = .509).

The main finding of this substudy is that baseline rest-HR was related to maximal aerobic capacity response to IMT. Furthermore, we found significant improvement in HR response to exercise. Overall, our results highlight the role of IMT as a simple and valuable treatment for improving aerobic capacity in long COVID patients, especially in those with higher rest-HR. Notably, patients showing higher rest-HR and greater functional capacity improvement were mostly men with lower BMI. The current findings contribute important insights to previous work[6] as they clarify which patients stand to benefit most from IMT.

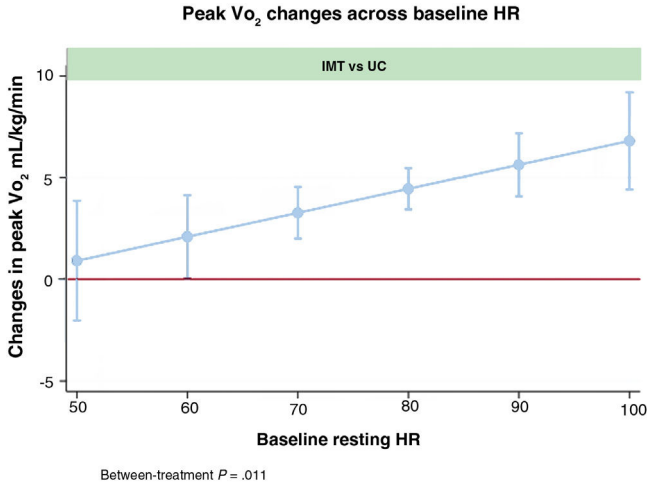

Figure 1. Peak VO_2 changes across baseline rest-HR. HR, heart rate; IMT, inspiratory muscle training; peak VO_2, peak oxygen consumption; UC, usual care.

Despite the lack of clear understanding regarding the precise mechanisms through which IMT enhances exercise capacity in individuals with long COVID, we postulate that IMT, facilitated by cardiac and peripheral autonomic modulation, may enhance HR response to exercise as well as the muscle ergoreflex,[3,4] thus improving short-term exercise tolerance.

The main limitation of this post hoc substudy is its small sample size, which increases the risk of type II error and reduces statistical power for detecting significant effects. Nevertheless, the findings of the study provide valuable insights and warrant further investigation into the underlying pathophysiological mechanisms through which IMT enhances exercise tolerance in patients with long COVID and its potential application in other cardiovascular disorders.

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ETHICAL CONSIDERATIONS

Informed consent was obtained from all participants, and the local research ethics committee approved the trial in accordance with the principles outlined in the Declaration of Helsinki and national regulations. Possible sex/gender biases have been considered in the preparation of this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used.

AUTHORS' CONTRIBUTIONS

All authors have read and approved the manuscript.

CONFLICTS OF INTEREST

None.

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Diagnosis of transthyretin amyloidosis in patients with established cardiomyopathy

Diagnóstico de amiloidosis por transtirretina en pacientes con una miocardiopatía previa

To the Editor,

Cardiac amyloidosis (CA) is a serious, progressive disease that is more common than previously thought. Early diagnosis is crucial, as treatment can alter prognosis.[1–3] CA can coexist with more common cardiomyopathies and remain unnoticed for years, affecting overall prognosis.[4] Familiarity with the typical signs and symptoms of CA (red flags) can lead to an earlier diagnosis.[1,2] We present 3 cases of CA that were not initially suspected.

The first case involved a 73-year-old man with triple-vessel coronary artery disease treated with surgical revascularization. Following an echocardiogram showing left ventricular hypertrophy (20 mm), the patient was referred for cardiac magnetic resonance imaging (MRI), which confirmed the hypertrophy and showed anteroseptal mesocardial late gadolinium enhancement (LGE). There was no family history of hypertrophic cardiomyopathy (HCM). Next-generation sequencing (NGS) of sarcomeric genes and phenocopies detected a pathogenic variant in *TNNC1* (p.Ala8Val), confirming the diagnosis of HCM. Family members underwent genetic testing, but no other cases of HCM were detected. During follow-up, the patient developed signs of heart failure with a typical CA strain pattern and the Popeye sign. He had recently undergone surgery for lumbar spinal stenosis. A diagnosis of wild-type transthyretin (ATTRwt) CA was confirmed by

Table 1
Patient characteristics

	Initial cardiomyopathy, age at diagnosis	Genetic variant identified	Pathogenicity of variant according to ACMG	Relatives studied/ variant carriers, No.	Amyloidosis red flags	99mTc-DPD scintigraphy	EMB	Age at diagnosis of amyloidosis, y
Patient 1	Nonobstructive HCM (73 y)	*TNNC1* (p.Ala8Val)	Pathogenic	3/0	• Popeye sign • Lumbar spinal stenosis • Reduced LGS with apical conservation	Grade 3	Yes	77
Patient 2	Obstructive HCM (74 y)	*MYL3* (p.Met173Val)	Likely pathogenic	1/0	• Popeye sign • First-degree atrioventricular block • Diffuse LGE (MRI) • Abnormal gadolinium kinetics (MRI) • High native T_1 (1123 ms; Philips Ingenia 1.50 T) (MRI) • Increased ECF volume (66%) (MRI)	Grade 3	No	78
Patient 3	Titin cardiomyopathy (76 y)	*TTN* (p.Trp19433*)	Pathogenic	16/9	• Carpal tunnel syndrome • Lumbar spinal stenosis • Hypotension in previously hypertensive patient • Pseudoinfarct pattern and low voltages on ECG • Aortic stenosis • Mild pericardial effusion • Diffuse LGE (MRI) • Abnormal gadolinium kinetics (MRI) • High native T_1 (1103 ms; Philips Ingenia 1.50 T) (MRI) • Increased ECF volume (45%) (MRI)	Grade 1	No	78

^{99m}Tc-DPD, technetium-99m with 3,3-diphosphono-1,2-propanedicarboxylic acid; ACMG, American College of Medical Genetics; ECG, electrocardiogram; ECV, extracellular volume; EMB, endomyocardial biopsy; HCM, hypertrophic cardiomyopathy; LGS, global longitudinal strain; LTR, late gadolinium enhancement; MRI, magnetic resonance imaging.