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Scientific letter

[[en]]Ventilatory efficiency in response to maximal exercise in persistent COVID-19 syndrome patients: a cross-sectional study

Eficiencia ventilatoria en respuesta al ejercicio máximo en pacientes con diagnóstico de COVID-19 persistente: un estudio transversal

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To the Editor,
Currently, the clinical course of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains uncertain, particularly given the variety of chronic symptoms in the subsequent weeks and months.[1] Parameters such as ventilatory efficiency and exercise capacity allow objective assessment of an individual's ventilatory and functional response, and also provide prognostic information on their clinical status, with important implications for treatment.[2]

The aim of the present study was to examine the—as yet unassessed—effect of persistent coronavirus disease 19 (COVID-19) on parameters of ventilatory efficiency and exercise capacity, in comparison with a group of patients with no history of COVID-19. The sample for this exploratory observational study included 95 individuals (77% were women) with a diagnosis of COVID-19 and mild or moderate symptoms, who had not previously been hospitalized, and had no structural heart disease or lung disease. Patients were considered to have persistent COVID-19 on the basis of compatible signs or symptoms and a positive polymerase chain reaction test for SARS-CoV-2. In addition, they were required to have symptoms persisting for 3 months after the infection, as assessed with a semistructured questionnaire previously used and validated by international expert consensus, which included self-diagnosis of 21 relevant symptoms 3 months after infection (yes/no answers).[3]

The group of patients with no history of COVID-19 ($n = 95$; 54% women) had not had SARS-CoV-2 infection and were recruited from the exercise capacity and cardiometabolic risk assessment clinic in our hospital. They underwent clinical assessment and functional testing of resting calorimetry, ergospirometry, vascular function, and body composition. Patients were also asked about their physical activity level. The study was approved by the ethics committee of Hospital Universitario de Navarra, and the participants gave signed informed consent (PI_2020/140).

The most prevalent persistent symptom was chronic fatigue (96.1%), followed by headache (81.4%), memory loss (80.4%), and difficulty concentrating (79.4%), the same symptoms as observed in previous studies.[4,5] The results of the univariate general linear model (ANCOVA), adjusted for age, sex, and body mass index, showed that, during exercise, the group with persistent COVID-19 had lower oxygen uptake and metabolic equivalents (METs), as well as significantly higher oxygen pulse, the ratio between oxygen uptake and heart rate (VO_2/HR), at the first ventilatory threshold (VT_1) and at maximum load ($P < .01$). Significant between-group differences were also observed at peak VO_2, as well as in the pulmonary ventilation (VE)/CO_2 output (VCO_2) slope ($d = 0.708$), the VE/VO_2 slope ($d = 0.531$), watts ($d = 0.436$), VE ($d = 0.257$), VO_2/HR ($d = 0.424$), METs ($d = 0.836$), and heart rate (HR) as percentage of predicted ($d = 0.314$) (Table 1). Approximately 85% of the patients with COVID-19 had a moderate/severe ventilatory limitation score (Table 2).

In previous studies,[1] patients with COVID-19 showed peak VO_2 values that were 35% lower (~15 $mL/kg^{-1} \cdot min^{-1}$) than the control group (～23 $mL/kg^{-1} \cdot min^{-1}$) at 30 days after hospital discharge. Debeaumont et al.[4] reported on parameters of VO_2 and maximum power of, respectively, ～80% and ～90% of predicted values for age at 6 months after discharge. Similarly, patients with persistent COVID-19 symptoms had a significant reduction in 6-minute walk test at 6 months after onset of symptoms.[5] In our series, the COVID-19 group showed peak VO_2 values ～18% lower than the control group. There was also a mixed pattern of abnormalities in parameters of ventilatory efficiency including VO_2 at VT_1 (70% vs 54%), abnormal VE/VCO_2 (46% vs 36%), and a very low VE/VCO_2 ratio (COP) (11% vs 0%), indicating a higher risk of functional deterioration.

To date, the mechanisms to explain the reduced exercise capacity in patients with persistent COVID-19 are unknown, but it has been hypothesized that excess adiposity (as seen in this series) and low levels of physical activity could partly explain the findings of this study.[1] The myopathic effect of SARS-CoV-2 has also not been excluded as a cause of functional deterioration in patients after COVID-19.[2] However, experimental studies are needed to corroborate these hypotheses.[2,4] The main limitations of our study are the number of patients included, the inclusion of a majority of women (a characteristic of persistent COVID-19 syndrome) and the lack of previous measures of exercise capacity, a limitation that is difficult to solve given the emergent nature of the pandemic.

More research is needed to better understand the long-term consequences of COVID-19 on functional capacity over the whole spectrum of the disease, especially the underlying biological mechanisms that characterize its pathophysiology. Considering the central role of exercise capacity in patients with persistent COVID-19, exercise rehabilitation could be fundamental in this new and little-known situation. Therefore, it is essential to establish strategies with multicomponent programs, to optimize recovery in these patients.

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AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the concept and design, data acquisition, analysis, and interpretation, as well as the writing, review, and intellectual content of the manuscript.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

References

<BIBL>
<BIB>
1
S Pleguezuelos F E.
S Del Carmen F A.
S Llorensi F G.<ET-AL>
AT Severe loss of mechanical efficiency in COVID-19 patients
JT J Cachexia Sarcopenia Muscle.
V 12
D 2021
P 1056-L 1063
</BIB>

<BIB>
2
S Berenguel Senen F A.
S Borrego-Rodríguez F J.
S de Cabo-Porras F C.
S Gigante-Miravalles F E.
S Arias MÁ
S Rodríguez-Padial F L.

AT Ergoespirometría en pacientes con disnea persistente tras la COVID-19
JT REC CardioClinics.
DOI 10.1016/j.rccl.2021.07.002
D 2021
</BIB>

<BIB>
3
S Whitaker F M.
S Elliott F J.
S Chadeau-Hyam F M.<ET-AL>
AT Persistent COVID-19 symptoms in a community study of 606,434 people in England
JT Nat Commun.
V 13
D 2022
P 1957
</BIB>

<BIB>
4
S Debeaumont F D.
S Boujibar F F.
S Ferrand-Devouge F E.<ET-AL>
AT Cardiopulmonary exercise testing to assess persistent symptoms at 6 months in people with covid-19 who survived hospitalization: a pilot study
JT Phys Ther.
V 101
D 2021
P pzab099
</BIB>

<BIB>
5
S Delbressine F J.M.
S Machado F F.V.C.
S Goërtz F Y.M.J.<ET-AL>
AT The impact of post-COVID-19 syndrome on self-reported physical activity
JT Int J Environ Res Public Health.
V 18
D 2021
P 6017
</BIB>
</BIBL>

Table 1 Clinical characteristics and ergospirometry parameters of the study population by group

	COVID-19 (n░=░95)	Control (n░=░95)	Cohen's *d*	*P*
[0,1-5]*Characteristics* [a]				
▓Sex (male/female), No.	73/22	51/44	–	–
Age, y	47.37 (45.45-	52.21 (49.84-	0.441	<░.001

	49.31)	54.60)		
Height, m	1.66 (1.64-1.68)	1.66 (1.63-1.68)	0.026	.303
Weight, kg	74.52 (71.30-78.42)	71.27 (69.30-75.13)	0.159	.185
Body mass index	27.12 (25.99-28.26)	26.03 (24.85-26.65)	0.262	.063
Total fat, %	38.93 (37.35-40.51)	33.01 (31.13-34.88)	0.686	< .001
Lean mass, %	58.9 (57.44-60.36)	64.55 (62.80-66.31)	0.707	< .001
PA, MET-min/week	983.59 (754.73-1212.47)	1732.77 (1395.45-2070.11)	0.517	< .001
Physical activity levels (low/medium/high), %[b]	56/42/4	37/40/23	–	< .001
[0,1-5]*Calorimetry at rest*[c]				
Caloric expenditure at rest, kcal/d	1511.13 (1450.75-1571.52)	1544 (1484.87-1605.01)	0.150	.434
Caloric expenditure per kg, kcal/d/m	20.37 (19.78-20.96)	21.52 (20.99-22.04)	0.349	.005
VO_2, mL/min	222.97 (207.87-238.07)	223.74 (214.99-232.50)	0.014	.932
VCO_2, mL/min	177.80 (170.65-184.95)	180.73 (173.21-188.26)	0.054	.575
Respiratory quotient	0.82 (0.80-0.83)	0.81(0.80-0.82)	0.175	.396
[0,1-5]*Risk factors*[c], %				
Overweight[b]	33	47	-	.006
Obesity[b]	29	10	-	.006
Systolic blood pressure, mmHg	128.35 (125.26-131.44)	133.18 (130.04-136.32)	0.321	.031
Diastolic blood pressure, mmHg	83.83 (81.89-85.77)	90.90 (77.68-104.13)	0.138	.280
Blood pressure > 135/85 mmHg, %[b]	60	63	-	.721
Coronary score	-	214.68 (105.30-324.05)	-	-
Cardio-ankle vascular index	6.86 (6.60-7.12)	6.81 (6.38-7.24)	0.340	.848
Ankle-brachial index	1.11 (1.09-1.13)	1.06 (1-1.13)	0.123	.248
[0,1-5]*Cardiovascular response*[c]				
VO_2 at VT1, $mL/kg^{-1}\cdot min^{-1}$	9.55 (8.96 –10.14)	11.02 (10.37 –11.68)	0.488	.002
VO_2 at maximum load $mL/kg^{-1}\cdot min^{-1}$	21.30 (20.17–22.43)	26.24 (25.01–27.48)	0.825	< .001
O_2 pulse at VT1, mL/beat	6.83 (6.34-7.32)	8.42 (7.71-9.14)	0.601	< .001
O_2 pulse at maximum load, mL/beat	10.92 (10.17-11.67)	12.76 (11.56-13.97)	0.505	.007
Watts at VT1	42.73	46.16	0.199	.203

	(39.24−46.22)	(42.33−49.98)		
▓Watts at maximum load	125.31 (118.12−132.50)	140.81 (132.94−148.69)	0.436	.006
▓HR at VT1, bpm	105.83 (102.82−108.84)	98.90 (95.36−102.25)	0.472	.004
▓HR at maximum load, bpm	148.15 (143.76−152.53)	155.26 (150.21−160.30)	0.257	.042
▓METs at VT1	2.73 (2.56−2.90)	3.15 (2.97-3.34)	0.504	.001
▓METs at maximum load	6.08 (5.76−6.40)	7.71 (7.36−8.06)	0.836	<░.001
[0,1-5]*Ventilatory efficiency*[c]				
▓VE/VCO_2 slope	34.37(33.18-35.56)	31.44 (30.58-32.30)	0.737	<░.001
▓Baseline $PECO_2$, mmHg	21.65 (20.72-22.58)	23.11 (22.33-23.88)	0.463	.021
▓$PECO_2$ at VT1, mmHg	25.18 (24.26-26.10)	26.79 (25.84-27.73)	0.432	.017
▓$PECO_2$ at maximum load, mmHg	25.23 (24.37-26.09)	27.48 (26.57-28.38)	0.663	<░.001
▓$VEVCO_2$ at VT1	33.24 (31.89-33.59)	30.89 (30.04-31.74)	0.491	<░.001
▓$VEVCO_2$ at maximum load	34.64 (33.64−35.64)	31.12 (30.02−32.22)	0.708	<░0.001
▓$VEVO_2$ at VT1	36.59 (35.50−37.67)	33.73 (32.54−34.92)	0.531	.001
▓$VEVO_2$ at maximum load	36.59 (35.50−37.67)	33.73 (32.54−34.92)	0.531	.001
▓VE at VT1, L/min	21.72 (20.41−23.03)	20.94 (19.50−22.37)	0.121	.439
▓VE at maximum load, L/min	60.93 (57.33−64.52)	65.50 (61.56−69.44)	0.330	.101
▓OUES at maximum load	2097.36 (1933.54-2261.18)	2301.02 (2081.40-2520.63)	0.244	.134
[0,1-5]*Effort exerted*[a]				
▓Exercise time, min	13.05 (11.99-14.11)	16.11 (14.69-17.53)	0.594	.001
VO_2 (≥ 85% predicted)[b]	68.13 (64.92-71.35)	85.02 (80.33-89.72)	0.869	<░.001
HR (≥ 85% predicted)[b]	86.29 (84.11-88.47)	91.92 (89.54-94.33)	0.314	.005
Respiratory quotient at maximum load	1.05 (1.04-1.07)	1.08 (1.07-1.10)	0.329	.010

HR, heart rate; METs, metabolic equivalents; OUES, oxygen uptake efficiency slope; PA, physical activity; $PECO_2$, expired CO_2 pressure; VE/VCO_2, slope of the pulmonary ventilation and VCO_2 ratio; $VEVCO_2$, ventilatory equivalent for CO_2, $VEVO_2$, ventilatory equivalent for O_2; VO_2, oxygen uptake; VT1, first ventilatory threshold.

[a]Data are presented as mean and 95% confidence intervals (95% CI) without adjustment or percentage as appropriate.

[b]Data presented as percentage (%).

[c]Data presented as marginal mean and 95% CI. General linear univariate model (ANCOVA), adjusted for age, sex, and body mass index. The ergospirometry test on cycle ergometer (Lode Excalibur Sport, Germany) consisted of incremental ramp increases in load, starting with 25 W with 25-W increments every 2 min (pedaling cadence, 50-60 revolutions/min). The variables VO_2 ($mL/kg^{-1}\cdot min^{-1}$), oxygen pulse (VO_2/HR), parameters VE and VT (L/min^{-1}), ventilatory equivalents of O_2 and CO_2 ($VEVO_2$, $VEVCO_2$), and expiratory CO_2 pressure ($PECO_2$) were recorded at the first ventilatory threshold (VT1) and at maximum load using flow analysis and concentrations of inhaled and exhaled respiratory gases in the mixing chamber (QUARK CPET, Cosmed, Italy).

Table 2 Comparison of ergospirometry criteria and ventilatory performance score by study group

Criteria	Categories	[0,3-4]COVID-19 (n = 95)*	[0,5-6]Control (n = 95)*	χ^2	*P*
[1,0]VO_2 inflection at VT_1[a]	Normal > 11, mL/kg/min	29 (30)	44 (46)	[1,0]4.587	[1,0].006
	Abnormal < 11, mL/kg/min	67 (70)	51 (54)		
[1,0]VE/VCO_2[b]	Normal < 34, slope in degrees	51 (54)	74 (77)	[1,0]11.318	[1,0].001
	Abnormal > 34, slope in degrees	44 (46)	21 (23)		
[1,0]OUES[c]	Normal > 1550 mL	65 (68)	72 (76)	[1,0]0.942	[1,0].331
	Abnormal < 1550 mL	30 (32)	23 (24)		
[1,0]COP[d]	Normal < 30 L	85 (89)	95 (100)	[1,0]8.550	[1,0].003
	Abnormal > 30 L	10 (11)	0 0		
[1,0]ΔVO_2/HR VT_2 vs VT_1[e]	Normal > 0	92 (97)	89 (94)	[1,0]0.467	[1,0].494
	Abnormal < 0	3 (3)	6 (6)		
[2,0]Ventilatory performance score[f]	No limitation	14 (15)	29 (31)	[2,0]9.847	[2,0].007
	Moderate limitation	62 (65)	58 (61)		
	Severe limitation	19 (20)	8 (8)		

COP, cardiorespiratory optimal point; HR, heart rate; OUES, oxygen uptake efficiency slope; VCO_2, carbon dioxide produced; VE, pulmonary ventilation; VO_2, oxygen uptake; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold.

[a]Point of inflection of VO_2 expressed in mL/kg/min and estimated manually on the graph of VO_2 at VT_1.

[b]Ventilatory efficiency or class derived from the VE/VCO_2 slope.
[c]OUES VO_2 efficiency slope.
[d]COP estimated based on the minimum VE/VCO_2 ratio.
[e]Difference in oxygen pulse between VT_2 and VT_1, derived from VO_2/HR ratio.
[f]Ventilatory performance criteria score was derived from the sum of the abnormal criteria in a-e, then classified as: no ventilatory limitation (no abnormal criteria), moderate limitation (1-2 abnormal criteria), and severe limitation (more than 3 abnormal criteria).
Values are expressed as No. (%).