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Cardiopulmonary Exercise Testing in Post-Covid-19 Patients

Prueba de ejercicio cardio-pulmonar en pacientes pos-COVID-19

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ABSTRACT

Introduction: Recently, it has been documented that a significant number of recovered patients experience persistent symptoms after the infection period. This clinical condition, known as "post-COVID-19 syndrome" has a prevalence ranging from 40% to 90% among individuals who have been discharged from the hospital.
Objectives: The objective of the study was to compare the results of the cardiopulmonary exercise test in patients with and without post-COVID-19 syndrome.
Materials and methods: A cross-sectional, analytical study was conducted on post-COVID patients. Patients were classified in two groups: those who met the criteria for post-COVID-19 syndrome and those who did not. The T-Student and Mann-Whitney U test were used as appropriate. A p-value of <0.05 was considered statistically significant, and SPSS 23 software was used. A total of 47 post-COVID patients were included; 53.2% (25/47) were in the post-COVID-19 syndrome group, while 46.8% (22/47) formed the other group.
Results: The mean age, weight, and percentage of females were: 44.52 years (SD 14.52), 80.06 kg (SD 20.19), and 52% in the post-COVID-19 syndrome group, and 41.86 years (SD 11.76), 64.04 kg (SD 17.72), and 90.9% in the other group, respectively. The respiratory reserve showed an average difference of 8.4% (95% CI 1.8% - 15%) with a p-value of 0.013.
Conclusions: The parameters measuring ventilatory efficiency (VE/VCO2 and PETCO2) showed clear, significant differences between the groups evaluated, which could be secondary to a ventilation-perfusion mismatch as a manifestation of post-COVID sequelae.

Key words: COVID-19; post-acute COVID-19 syndrome; exercise test

RESUMEN

Introducción: Recientemente se ha documentado que un notable número de pacientes recuperados presenta una persistencia de síntomas tras el período de infección. Esta entidad clínica se denomina «síndrome pos-COVID-19» y su prevalencia se sitúa en un rango del 40 % al 90 % entre aquellos individuos que han recibido el alta hospitalaria.
Objetivos: El objetivo del estudio fue comparar los resultados de la prueba de ejercicio cardiopulmonar en pacientes con y sin síndrome pos-COVID-19.

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Material y métodos: Se realizó un estudio de corte transversal, analítico, realizado en pacientes pos-COVID. Se clasificaron los pacientes en dos grupos, aquellos con o sin criterio positivos para síndrome pos-COVID-19. Se utilizó la prueba de T-Student y la prueba U de Mann-Whitney según fuera necesario. Se consideró estadísticamente significativo un valor $p < 0,05$ y se utilizó el *software* SPSS 23. Se incluyeron 47 pacientes pos-COVID; el 53,2 % (25/47) era parte del grupo con síndrome pos-COVID-19, mientras que el 46,8 % (22/47) conformó el otro grupo.
Resultados: La media de edad y peso y porcentaje de sexo femenino fue de 44,52 (DS 14,52), 80,06 (DS 20,19), el 52 % para el grupo con el síndrome y 41,86 (DS 11,76), 64,04 (DS 17.72), el 90,9 % para el otro grupo. La reserva respiratoria obtuvo un promedio para la diferencia de 8,4 % (IC 95 % 1,8 %-15 %) con un valor *p* de 0,013.
Conclusiones: Los parámetros que miden la eficiencia ventilatoria (VE/VCO_2 y $PET-CO_2$) evidenciaron claras diferencias significativas entre los grupos evaluados, lo cual podría ser secundario a un trastorno ventilación-perfusión como manifestación de secuela pos-COVID.

Palabras clave: COVID-19; Síndrome pos-agudo COVID-19; Prueba de ejercicio

INTRODUCTION

In late December 2019, a series of cases of unknown pneumonia were reported, later named Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Finally, in March 2020, the World Health Organization (WHO) issued an official declaration on the COVID-19 pandemic. The rapid global spread of SARS-CoV-2 posed an unprecedented public health challenge worldwide.

In this context, it is noteworthy how medical practice faced intense demand due to the symptoms associated with this disease, given that, in many cases, these symptoms did not correlate with abnormalities that are evident in commonly conducted diagnostic tests.

While the preference for lung damage, particularly at the parenchymal level, associated with SARS-CoV-2 infection is well known, the presence of possible pulmonary vascular injuries should not be underestimated. This includes phenomena such as endothelial injury, dysregulation of pulmonary vascular tone, and in situ microthrombosis, which represent entities worthy of consideration.[2,3]

Recently, it has been documented that a significant number of recovered patients experience persistent symptoms after the infection period. This clinical condition, known as "post-COVID-19 syndrome" has a prevalence ranging from 40% to 90% among individuals who have been discharged from the hospital.[1-3]

The cardiopulmonary exercise testing (CPET) is recognized as the gold standard for assessing aerobic exercise, as it can differentiate cardiovascular, ventilatory, and musculoskeletal limitations during exercise by monitoring changes in oxygen levels, carbon dioxide, minute ventilation, and heart rate.[4] For this reason, the CPET stands out as one of the most effective non-invasive methods for comprehensive evaluation in post-COVID-19 individuals. Authors such as Dorelli and Clavario have shown that more than half of non-severe COVID-19 survivors exhibit limitations in functional capacity.[5,6]

The objective of the study was to compare the results of the cardiopulmonary exercise test in patients with and without post-COVID-19 syndrome.

MATERIALS AND METHODS

A cross-sectional, analytical study was conducted with patients treated at the Instituto Neumonológico del Sur (INeuS) in Bahía Blanca over a six-month period in 2022. The patients were classified in two groups: those who met the criteria for post-COVID-19 syndrome and those who did not (without dyspnea). Patients over 16 years old with a positive COVID-19 diagnosis documented by PCR/antigen were included, and they underwent the CPET between 60 and 120 days after the infectious diagnosis. Patients with a positive COVID-19 diagnosis based only on epidemiological criteria were excluded. With regard to elimination criteria, patients unable to complete the CPET would be excluded.

The following variables were considered for this study:

Post-COVID-19 syndrome: Defined as dyspnea or fatigue persisting for at least 60 days from symptom onset, up to 120 days, based on WHO criteria.

Cardiopulmonary exercise testing: A treadmill exercise test was conducted using cardiopulmonary equipment with continuous analysis of gas exchange during respiration on a breath-by-breath basis (MedGraphic Ultima CPX, Breeze suite software). The modified Bruce protocol was used for the treadmill tests. Measurements included heart rate (HR), oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE) and the ratio between VE and VCO_2. The quality of the exercise effort was evaluated using the Respiratory Exchange Ratio (RER) [RER (VCO_2/VO_2)]. A RER greater than 1.1 was considered indicative of maximum effort. The functional capacity was defined as normal when the predicted maximum VO_2 was ≥85%. The VO_2 at the anaerobic threshold (AT) was identified using the V-Slope method. Other variables analyzed included sex, age, weight, and height.

Statistical analysis: Continuous variables are summarized as mean ± standard deviation (SD) or median (interquartile range of 25 to 75) depending on their distribution, while categorical variables are expressed as percentages. The Student's T-test was used, after verifying the assumptions, to compare the mean values of continuous variables in each group; if the assumptions were not met, the Mann-Whitney U test was used. A p-value of <0.05 was considered statistically significant, and IBM SPSS 23 software was used (Windows version).

Ethical considerations: The researchers fully adhered to the National Personal Data Protection Act (No. 25326) and the Declaration of Helsinki of the World Medical Association.

RESULTS

A total of 47 patients diagnosed with COVID-19 were included in the study. From those 47 patients, 53.2% (25/47) were in the post-COVID-19 syndrome group, while 46.8% (22/47) formed the group without post-COVID-19 syndrome.

Regarding the baseline characteristics of the total sample, it was found that the percentage of female participants in the post-COVID-19 syndrome group was 52% (13/25), whereas in the other group, 90.9% (20/22) were female.

The mean age was 44.52 years (SD 14.52) for the post-COVID-19 group, while the mean age for the other group was 41.86 years (SD 11.76). In terms of weight, height, and body mass index (BMI), the average values obtained for the post-COVID-19 group were 64.04 kg (SD 20.19), 1.72 m (SD 64.29), and 26.19 kg/m^2 (SD 5.01), respectively. In contrast, the group without post-COVID-19 syndrome had mean values of 80.06 kg (SD 20.19), 1.70 m (SD 9.82), and 27.33 kg/m^2 (SD 5.91), respectively.

Regarding the analysis conducted with the CPET for both groups, a mean difference of 8.4% (95% CI 1.8%-15%) was obtained for respiratory reserve, with a p-value of 0.013. The results for the other variables are displayed in the table below (Table 1).

DISCUSSION

This study represents one of the few local investigations comparing CPET findings in subjects based on the presence or absence of post-COVID-19 syndrome. This fact deserves to be highlighted, as the persistence of exercise intolerance following COVID-19 infection is widely recognized but still poorly understood. There is heterogeneous evidence regarding the time elapsed since the disease until evaluation, the severity of the illness, the diversity of post-COVID-19 sequelae, the average age of patients, and sample sizes.[7-9]

Patients in our study with post-COVID-19 syndrome predominantly reported dyspnea and chest pain as persistent symptoms. The prevalence of these symptoms is consistent with other studies,[10] where dyspnea is identified as one of the most common respiratory symptoms after recovery from the infection. The presence of chest pain, along with the ventilatory inefficiency identified in the CPET, suggests the need for a comprehensive diagnostic approach that considers not only direct pulmonary sequelae but also the possibility of thromboembolic complications. The parameters measuring ventilatory efficiency (VE/VCO_2 and $PETCO_2$) showed clear, significant differences between the groups evaluated, which could be secondary to a ventilation-perfusion mismatch as a manifestation of post-COVID sequelae. Previously, a study revealed that approximately half of the survivors of mild COVID-19 experience a reduction in functional capacity (predicted VO2 MAX), attributing the results primarily to muscular deterioration.[9] However, this study did not compare the characteristics of cardiopulmonary exercise testing between patients who developed post-COVID-19 syndrome and those who did not. Additionally, our specific approach on ventilatory efficiency in those who developed post-COVID-19 syndrome reveals an additional dimension that may be linked to processes of microthrombosis or persistent endothelial dysfunction. In this regard, CPET has been particularly useful in identifying patterns of ventilatory inefficiency that could warrant further investigation to rule out pulmonary thromboembolism (PTE), a

TABLE 1. Comparison of cardiopulmonary exercise test variables according to the presence or absence of post-COVID-19 syndrome

		Pos-COVID-19	*n*	Mean	SD	Difference of mean values	Difference of standard error	95% CI of the difference		*p* value
VENTILATION	RR (br/min) in AT	NO	25	20.12	5.77	–8.09	1.79	–11.69	–4.48	<0.001£
		YES	22	28.21	6.51					
	RR (br/min) (VO_2Max)	NO	25	31.41*	9.63**					0.003§
		YES	22	35.89*	9.45**					
	VE BTPS (L/min) (VO_2Max)	NO	25	66.28	19.40	5.11	4.99	–4.95	15.18	0.312
		YES	22	61.16	14.02					
	VE BTPS (L/min) (VO_2Max/PredAT)	NO	25	45*	16**					0.310§
		YES	22	51*	20**					
	Vd/Vt-est at rest	NO	25	0.14*	0.07**					0.088§
		YES	22	0.17*	0.05**					
	Vd/Vt-est in AT	NO	25	0.11	0.030	–0.041	0.009	–0.058	–0.023	<0.001£
		YES	22	0.15	0.030					
	Vd/Vt-est (VO_2Max)	NO	25	0.09	0.025	–0.033	0.007	–0.048	0.018	<0.001£
		YES	22	0.12	0.026					
	RR in AT	NO	25	120*	19**					0.681§
		YES	17	126*	31**					
CONSUMPT ?? O_2	VO_2 in AT (mL/kg/min)	NO	25	18.2*	8**					0.044§
		YES	22	17.3*	4**					
	VO_2 (mL/kg/min) (VO_2Max)	NO	25	26.5*	11**					0.075§
		YES	22	24.6*	7**					
	VO_2 (mL/kg/min) (Pred)	NO	25	27.6*	10**					0.301§
		YES	22	25.7*	6**					
	VO_2 (mL/kg/min) (VO_2Max/)	NO	25	104.36	19.933	6.224	5.609	–5.074	17.521	0.273
		YES	22	98.14	18.3					
	VO_2 (mL/kg/min) (AT/Pred)	NO	25	68.39	23.65	1.017	6.246	–11.57	13.61	0.871
		YES	21	67.37	17.56					
V/Q	VE/VO_2 in AT	NO	25	23.68	2.78	–5.047	0.871	–6.802	–3.292	<0.001£
		YES	22	28.73	3.195					
	VE/VCO_2 in AT	NO	25	26.8	3.175	–6.882	0.894	–8.682	–5.081	<0.001£
		YES	22	33.68	2.918					
	$PETO_2$ (mmHg) in AT	NO	25	99.44	5.075	–6.969	1.424	–9.837	–4.101	<0.001£
		YES	22	106.41	4.626					
	$PETCO_2$ (mmHg) in AT	NO	25	42.28	4.326	7.189	1.14	4.892	9.486	<0.001£
			22	35.09	3.351					

*Median/**Interquartile range§/Mann-Whitney U test£

complication with increased prevalence in post-COVID-19 patients.

In our study, there were no significant differences in functional capacity. On the other hand, another study showed that more than 25% of patients who recovered from hospitalization due to COVID-19 experienced ventilatory inefficiency during exercise.[8]

Ventilatory inefficiency was the most evident factor in our patients with post-COVID syndrome. The presence of ventilatory inefficiency in the post-COVID-19 context suggests that these patients could benefit from pulmonary rehabilitation intervention specifically aimed at improving ventilation and gas exchange efficiency. Rehabilitation programs could focus on aerobic and respiratory exercises designed to optimize the ventilatory function and correct potential abnormalities in the ventilation-perfusion ratio. Moreover, regular follow-up through CPET in these patients could be useful for monitoring the evolution of ventilatory inefficiency and adjusting therapeutic strategies in a personalized manner, addressing both ventilatory efficiency and overall muscular strengthening.

This study has some limitations. Due to the design and setting of the study, there is a possibility of selection bias that could affect the results. This bias may reinforce the findings, as more subjects with non-post-COVID-19 comorbidities might have exhibited lower performance on CPET. Additionally, retrospective information on pulmonary function estimated through spirometry could not be obtained in a reliable manner, so this data was not included in the analysis.

On the other hand, the sample size is a significant limitation, considering the prevalence values of the event reported in the literature.[11] The higher proportion of female participants in the group without post-COVID-19 syndrome could also introduce a bias into the study. Moreover, the gender composition, with a predominance of females in the group without post-COVID-19 syndrome, could introduce a bias that affects the findings regarding ventilatory efficiency. Future research with a larger number of participants and a balanced gender composition would be useful to validate these results and minimize potential bias. Despite these limitations, this study provides valuable evidence by exploring physical fitness in patients with post-COVID-19 syndrome. Further studies are needed to determine whether the abnormalities identified in the CPET can have prognostic value and, ultimately, can be modified through therapeutic intervention such as rehabilitation programs. Our study also highlights the potential of the CPET to identify patients who may benefit from additional evaluations to rule out PTE and from targeted management of ventilatory inefficiency.

CONCLUSIONS

The results of this cardiopulmonary exercise testing study reveal significant differences in the variables of interest between the evaluated groups. These findings suggest a clear dissociation in the capacity to adapt to cardiovascular exertion, with ventilatory inefficiency being the fundamental element differentiating the two examined groups.

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Conflict of interest

Authors have no conflicts of interest to declare.

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