ORIGINAL ARTICLE

Cardiopulmonary Rehabilitation in Pulmonary Hypertension: Experience in a Referral Center

Rehabilitación cardiorrespiratoria en hipertensión pulmonar: experiencia en un centro de referencia

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ABSTRACT

Background: Pulmonary hypertension (PH) comprises a heterogeneous group of diseases resulting in disability and increased morbidity and mortality. Cardiopulmonary rehabilitation (CR) is a therapeutic resource not widely used in this condition.
Objective: The aim of this study was to evaluate the effects of a CR program on a walking test and on the quality of life in patients with group 1 and group 4 PH
Methods: Patients were evaluated before and after the intervention with the six-minute walk test (6MWT) and Saint George's Respiratory Questionnaire (SGRQ). The program consisted of 8 weeks of supervised exercises within the institution.
Results: Nineteen patients with precapillary PH diagnosed by right heart catheterization were included; 18 were women (94.7%) with a mean age of 45.5 ± 14.3 years. Thirteen (68.4%) patients had group 1 PH and 6 (31.6%) had group 4 PH. There were statistically significant changes in the 6MWT [mean difference (MD) 31 ±27.3 m; p<0.001], and in the SGRQ (MD 8.2 ± 10.2; p<0.01). No adverse events were reported during the program.
Conclusions: Our study suggests that a supervised CR program in patients with PH could improve the distance walked and the quality of life.

Keywords: Pulmonary hypertension - Cardiac rehabilitation - Six-minute walk test - Quality of life

RESUMEN

Introducción: La hipertensión pulmonar (HP) abarca un grupo heterogéneo de enfermedades que genera discapacidad y aumento de la morbimortalidad. La rehabilitación cardiorrespiratoria (RC) es un recurso terapéutico subutilizado en esta condición.
Objetivo: Estimar los efectos de un programa de RC en una prueba de caminata de campo y en la calidad de vida de pacientes con diagnóstico de HP de los grupos I y IV.
Materiales y Métodos: Los pacientes fueron evaluados antes y después de la intervención mediante la prueba de caminata de 6 minutos (PC6M) y el Saint George's Respiratory Questionnaire (SGRQ). El programa de RC consistió en 8 semanas de ejercicios supervisados con modalidad institucional.
Resultados: Se incluyeron 19 pacientes con diagnóstico de HP precapilar por cateterismo cardíaco derecho, 18 mujeres (94,7%) con una media de edad de 45,5 ± 14,3 años. Trece (68,4%) presentaron HP del grupo I, y 6 (31,6%) HP del grupo IV. Se observaron cambios estadísticamente significativos en la PC6M (diferencia de medias -DM- 31 ± 27,3 metros; p <0,001), y en el SGRQ (DM 8,2 ± 10,2; p<0,01). No se reportaron eventos adversos graves durante el programa.
Conclusiones: Nuestro estudio sugiere que un programa de RC supervisado en pacientes con HP podría mejorar la distancia caminada y la calidad de vida.

Palabras clave: Hipertensión pulmonar - Rehabilitación cardíaca - Prueba de caminata de seis minutos - Calidad de vida

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INTRODUCTION

Pulmonary hypertension (PH) is a rare, chronic and disabling disease that severely affects exercise tolerance and quality of life (QoL). (1,2) There is currently no cure for PH, and specific pharmacological therapies focus on the three main pathways of pulmonary vascular remodeling: endothelin, nitric oxide and prostacyclin. (1) Studies with these drugs have shown increased survival, but symptoms, functional capacity, exercise tolerance and QoL do not always seem to improve. (2) Considering this context, it is essential to use other therapeutic interventions, such as rehabilitation. (2)

Cardiopulmonary rehabilitation (CR) is a comprehensive and multidisciplinary intervention based on a thorough assessment with patient-tailored therapies including exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory and heart diseases and to promote changes favoring long-term lifestyle behaviors. (3,4) Cardiopulmonary rehabilitation in PH improves exercise capacity, functional class (FC), peak oxygen consumption and resting heart rate (HR). (5) It can also improve QoL, depression, fatigue, muscle function and possibly right ventricular function. (6-10) Besides the clinical effects, CR can also reduce inflammation and cell proliferation, producing a beneficial effect on pulmonary vessels. (6) The results of CR studies in PH have been favorable, but they have either included few patients or were developed under strict supervision, and some were performed in inpatient settings, which is quite different from the usual clinical practice. (1)

The primary objective of this study was to evaluate the effects of a CR program on a field walking test and on the QoL in patients with group I and IV PH at a referral center. The secondary objectives included changes in FC, intensity of workload for aerobic endurance, perception of dyspnea and laboratory tests parameters, and development of complications during the intervention.

METHODS

We conducted a retrospective and observational case series study. Selected patients were > 18 years, with a diagnosis group 1 and group 4 PH according to the criteria of the 6th World Symposium on PH (Nice, 2018) (11), i.e., with mean pulmonary artery pressure (mPAP) > 20 mm Hg, pulmonary capillary wedge pressure < 15 mm Hg and a pulmonary vascular resistance (PVR) > 3 Wood Units measured by right heart catheterization. (1,11)

To be included in the program, subjects should be physically deconditioned, i.e., unable to comply with the physical activity recommendations for adults between 18 and 64 years. These recommendations include moderate-intensity aerobic physical activity for at least 150 to 300 minutes a week; or high-intensity aerobic physical activity for at least 75 to 150 minutes a week; or an equivalent combination of moderate/vigorous-intensity activities throughout the week; plus moderate- to high-intensity muscle-strengthening activity of major muscle groups for at least two days a week. (12) Patients should be in functional class (FC) I to III. (1,13) Subjects with any of the following were excluded: history of smoking, restrictive ventilatory defect, other unstable or severe pulmonary or heart diseases, active infections, history of hospitalization within the previous three months, and those with orthopedic, neurological or psychiatric disorders or with myopathies limiting the performance of the CR program. Patients not receiving specific pharmacologic treatment were excluded from the analysis (14,15), as patients who attended < 50% of the sessions (three or less). (16) The study was approved by the Institutional Review Board.

The baseline data included demographic and clinical data, laboratory tests, and results of the right heart catheterization and echocardiogram. The distance achieved in the 6-minute walk test (6MWT) and the QoL measured by the Saint George's Respiratory Questionnaire (SGRQ) were analyzed after and before the CR program. The 6MWT is a submaximal field assessment evaluating the ability to perform daily life physical activities. Minimum oxygen saturation (SpO2), resting heart rate (HR), peak exercise HR, HR recovery 1 minute after peak exercise, and perceived exertion were recorded. (17) The SGRQ is a self-administered questionnaire made up of 50 questions comprising three domains: symptoms, activity, and impact, with a score ranging from 0 to 100, zero indicating the best function. A difference of 4 points was considered clinically relevant. (18) Functional class, intensity of workload for aerobic endurance, perception of dyspnea, performance of biomarkers and inflammatory markers [N-terminal pro-B-type natriuretic peptide (NT-proBNP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], white blood cell count and neutrophils, hemoglobin and hematocrit values, and the development of complications during the intervention were also measured at the beginning and at the end of the CR program. The intensity of workload for aerobic endurance achieved during incremental exercise tests was evaluated. The peak load achieved in kilogrameters (kgm) on a bicycle ergometer FM500 (Zuccolo, CABA, Argentina) and the maximum speed achieved in kilometers per hour (km/h) on a KIPRUN KR 320/5 treadmill (Kip Machines, Rosario, Argentina) were recorded. Both tests were stopped when the patient reached 60% of peak HR, a HR of 120 beats per minute or SpO2 of 85-90%. (6) Dyspnea was measured with the modified Medical Research Council (mMRC) scale and through the visual analog scale (VAS), with a score from 0 to 10, perceived on a usual day (average value reported in the previous week). (19) The presence of complications (cardiac arrest, fatal arrhythmias and myocardial infarction), and signs and symptoms during the intervention were recorded. (20)

The CR program lasted eight weeks. The individuals attended the rehabilitation facility once a week for two hours, and those with an indication of oxygen therapy used it during the intervention. The session consisted of a warm-up phase, training, and a cool-down phase. During training, aerobic endurance exercises were performed on bicycle ergometer and on treadmill, and muscular strength was developed by exercise of the main muscle groups using the own body weight. Variable and constant continuous methods were used to aerobic endurance training, with workload set to percentages of the workload achieved during incremental exercise tests. Flexibility, relaxation and breathing exercises were performed for cooling down. The program was monitored and supervised by a specialized kinesiologist; vital signs (SpO2, HR, respiratory rate, blood pressure) and effort perception with the modified Borg scale were recorded at rest, training, and recovery. The rehabilitation facility counted with an emergency care protocol.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), according to their distribution. Categorical variables were reported as absolute numbers and percentages. The results of the continuous variables after and before CR were compared using the paired-samples t test or the Wilcoxon rank sum test, as applicable. To correlate the SGRQ and the 6MWT changes, Pearson's correlation coefficient or Spearman's correlation coefficient were used, depending on the distribution of the variable. Correlation coefficients of > 0.50, 0.35–0.50, and < 0.35 were considered strong, moderate, and weak, respectively. A p value < 0.05 was considered statistically significant. Data were analyzed using IBM SPSS 22.0 software package for Macintosh (IBM Corp, Armonk, NY, USA).

Ethical considerations

The study was approved by the institutional review board of Hospital Juan A. Fernández (CEIHF).

RESULTS

Of the 29 eligible subjects, 10 were excluded due to lack of adherence because of difficult transportation to the rehabilitation facility (n = 4), medical reasons (n = 3), work-related reasons (n = 1), and personal reasons (n = 2). Figure 1 shows the flowchart for patient selection. The characteristics of the population included are reported in Table 1. The population was made up of 18 (94.7%) women with mean age of 45.5 ± 14.3 years. Thirteen (68.4%) patients were in group 1 PH and 6 (31.6%) were in group 4 PH.

The results of the differences before and after CR are shown in Table 2. Mean baseline distance walked in the 6MWT was 430 ± 94.1 m for a predicted mean distance of 574 ± 113 m. The walked distance significantly increased by the end of the program [mean difference (MD) 31 ± 27.3; p < 0.001). There were no differences in resting HR, minimum SpO2, peak HR during the 6MWT and HR recovery 1 minute after peak exercise (p = 0.38, p = 0.26, p = 0.4 and p = 0.08, respectively). The SGRQ total score exhibited a significant decrease after CR (MD 8.2 ± 10.2; p < 0.01), significant in all its domains as shown in Figure 2. There was no correlation between the 6MWT and the SGRQ (r: 0.38; p = 0.11). The FC did not show significant differences before and after CR (p = 0.32). The performance on bicycle ergometer (p < 0.001) and on treadmill (p < 0.001) improved. Dyspnea measured with the mMRC scale was not modified (p = 0.65), but there were favorable changes after CR in the VAS (p < 0.01). The ESR was the only laboratory test with a statistically significant difference (p = 0.02). The program was well tolerated by all the patients. Lower limb fatigue (n = 16), exercise-induced dyspnea (n = 11), chest pain (n = 8), dizziness (n = 8), desaturation (n = 9) and headache (n = 1) were reported. There were no complications during the CR program.

DISCUSSION

The CR program proposed produced changes in the 6MWT and SGRQ. At the end of the program, the distance walked in the 6MWT increased by 31 m. The effects of training on the distance walked on the 6MWT have been verified in recent years by four meta-analyses demonstrating improvement between 53 and 72 m. (21-24) Grünig and Mereles showed higher values on average, varying between 78 and 96 m, respectively. (5, 25) However, the CR plan was longer in these studies, 15 weeks, including three weeks in which the patients were hospitalized, and the number of sessions was the same or greater. The study by Grünig included all PH groups. Chan et al. reported an improvement by 56 meters with a 10-week outpatient program, but only 10 female patients with group 1 PH were included. (7) In 2012, Mathai published that

Fig. 1. Flowchart for selection of patients with groups 1 and 4 pulmonary hypertension.

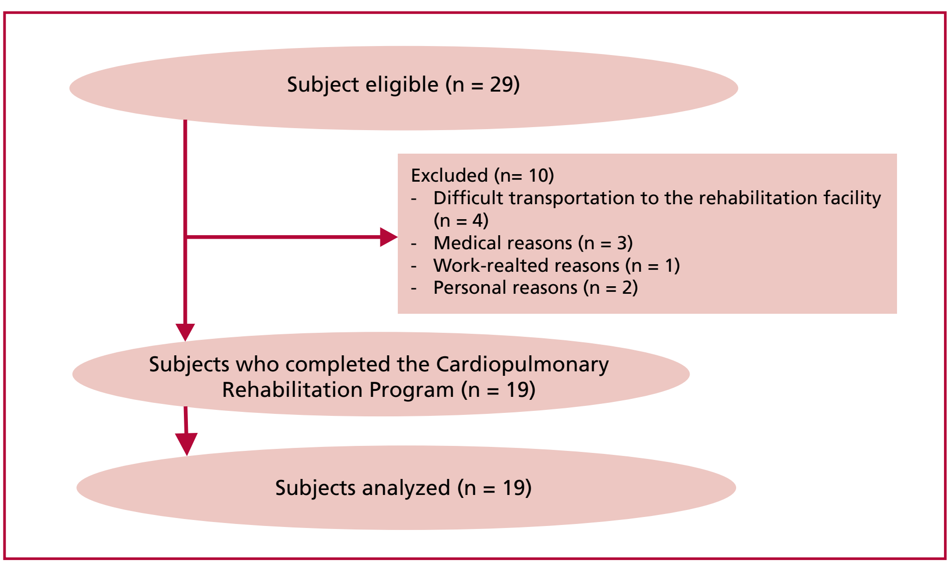

Table 1. Demographic characteristics of the individuals (n = 19)

Characteristics	Number of patients
Age in years, mean (SD)	45.5 (14.3)
Female sex, n (%)	18 (94.7)
Height in cm, median (IQR)	1.64 (1.52-1.67)
Weight in kg, mean (SD)	75.3 (21.9)
BMI, mean (SD)	29 (8.2)
Classification of PH (Nice, 2018)	
Group 1 PH, n (%)	13 (68.4)
Idiopathic, n (%)	3 (15.8)
Associated with:	
HIV infection, n (%)	1 (5,2)
Congenital heart defects, n (%)	3 (15.8)
Connective tissue diseases, n (%)	6 (31.6)
Group 4 CTEPH, n (%)	6 (31.6)
Comorbidities	
Diabetes, n (%)	2 (10.5)
Hypertension, n (%)	6 (31.6)
Dyslipidemia, n (%)	2 (10.5)
Obesity, n (%)	9 (47.4)
Postmenopause, n (%)	7 (36.8)
Time from diagnosis to CR in years, median (IQR)	4 (1 - 9)
Medication	
Endothelin receptor antagonists, n (%)	7 (36.8)
PDE5 inhibitors, n (%)	15 (78.9)
GMP-c stimulators, n (%)	1 (5.3)
Prostanoids and prostacyclin receptor agonists, n (%)	1 (5.3)
Anticoagulants, n (%)	8 (42.1)
Oxygen therapy, n (%)	4 (21.1)
Right cardiac catheterization	
SPAP in mm Hg, mean (SD)	73.7 (20.1)
MPAP in mm Hg, mean (SD)	47.4 (12)
DPAP in mm Hg, mean (SD)	32.9 (10.7)
Echocardiography	
SPAP in mm Hg, mean (SD)	65.6 (24.7)
Right ventricular dilation, n (%)	15 (78.9)
TAPSE in mm, mean (SD)	19.5 (4.4)
RA area in cm^2, mean, (SD)	24.5 (8.2)

SD: standard deviation; n: number; IQR: interquartile range; BMI: body mass index; CR: cardiopulmonary rehabilitation; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; HIV: human immunodeficiency virus; CTEPH: chronic thromboembolic pulmonary hypertension; PDE5: phosphodiesterase 5; GMP-c: guanylate cyclase; SPAP: systolic pulmonary artery pressure; MPAP: mean pulmonary artery pressure; DPAP: diastolic pulmonary artery pressure; TAPSE: tricuspid annulus plane systolic excursion; RA: right atrial.

the minimal important difference in the 6MWT was 33 m, and in the systematic review by Morris et al. published in the Cochrane database in 2017, a value of 30 m was reported for the same parameter. (24,26) Clinical trials of approved medications for PH have achieved very similar results in the 6MWT to those found in our study, 36.4 m with iloprost and 36 m with bosentan. (27-29) Furthermore, the mean distance walked in absolute values in the 6MWT in our study was > 440 meters after CR, a desirable value for this test, that is associated with favorable outcome. (13) The SGRQ scale showed a statistically significant improvement in all domains and in the total score of the questionnaire, exceeding the minimal clinically important difference. (30) We emphasize the importance of symptoms improvement in this incurable disease. Several studies show that, in patients with PH, training improved different aspects of QoL, as assessed with the SGRQ scale and other tools. (6) Raskin et al. included 23 patients who attended an outpatient CR program and showed a significant improvement in the impact domain of the SGRQ, but not in the total score or in the symptoms domain. There was even a clinically significant decrease in the activity domain . (31) Some possible explanations for these differences are that, in this series, the population had a more serious baseline status, was older, more patients required oxygen therapy, and the average baseline walked dis-

Table 2. Results before and after cardiopulmonary rehabilitation (CR) (n = 19)

Variables	Before CR	After CR	p
Field walking test			
6MWT in meters, mean (SD)	430.4 (94.1)	461.4 (91.9)	< 0.001
Resting HR, bpm, mean (SD)	75.8 (7.6)	79.2 (15.2)	0.38
Minimum SpO2, mean (SD)	82.7 (7.8)	85 (7.7)	0.26
Peak HR, bpm, (SD)	119.2 (30.4)	111.2 (35.1)	0.4
HR recovery, bpm, median (IQR)	96 (78.5 - 119)	110 (95 - 118)	0.08
Quality of life			
Total SGRQ, mean (SD)	42.8 (25.0)	34.6 (21.8)	< 0.01
SGRQ symptoms, mean (SD)	37.6 (25.2)	24.4 (20.8)	< 0.01
SGRQ activity, mean (SD)	56.1 (31.0)	50.8 (31.1)	0.018
SGRQ impact, mean (SD)	36.8 (25.6)	28.6 (22.0)	0.03
Functional class, median (IQR)			0.32
FC I, n (%)	9 (47.4)	10 (52.6)	-
FC II, n (%)	8 (42.1)	8 (42.1)	-
FC III, n (%)	2 (10.5)	1 (5.3)	-
Intensity of training load			
Bicycle ergometer, kgm, median (IQR)	450 (300 - 600)	600 (450 - 750)	< 0.001
Treadmill, km/h, mean (SD)	4.7 (1.2)	5.4 (1.1)	< 0.001
Dyspnea			
mMRC, median (IQR)			0.65
mMRC0, n (%)	5 (26.3)	6 (31.6)	-
mMRC1, n (%)	4 (21.05)	4 (21.05)	-
mMRC2, n (%)	7 (36.8)	5 (26.3)	-
mMRC3, n (%)	2 (10.5)	3 (15.8)	-
mMRC4, n (%)	1 (5.3)	1 (5.3)	-
VAS, median (IQR)	4 (1-6)	1 (0-4)	< 0.01
Laboratory tests			
NT-proBNP, pg/mL, median (IQR)	163.5 (89.2-805)	185 (88.7-788.7)	0.86
ESR, mm, median (IQR)	10 (3.5-19)	10 (6-24)	0.02
CRP, mg/dL, median (IQR)	0.9 (0.7-2.3)	0.75 (0.6-1.15)	0.34
White blood cells, n x 103, median (IQR)	6.3 (5.7-7.6)	6.0 (5.6-8.7)	0.86
% neutrophils, mean (SD)	57.7 (8.3)	56.3 (10.2)	0.41
Hematocrit, median (IQR)	39.5 (37.6-44.9)	38.6 (36.4-1.6)	0.03
Hemoglobin, g/dL, mean (SD)	13.4 (2.0)	12.9 (2.1)	0.04

SD: standard deviation; n: number; IQR: interquartile range; 6MWT: six-minute walk test; HR: heart rate; SpO2: oxygen saturation; SGRQ, Saint George´s Respiratory Questionnaire; FC: functional class; mMRC: modified Medical Research Council; VAS: visual analogous scale; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

tance in the 6MWT was lower at the beginning of the program. Inagaki found improvement in QoL in eight patients who completed a home-based CR program in the SGRQ activity domain, but not in the impact or symptoms domains, or total score. (15) This may be because they did not complement the exercises with an institutional intervention.

The FC did not show statistically significant differences before and after CR. The results of FC in the bibliography are dissimilar. Some controlled studies showed significant improvement, but their CR programs were conducted in hospitalized patients. (6) Only one publication showed a significant improvement in FC in outpatients, but the sample consisted of only four patients with PH associated with congenital heart diseases. (32) The effects of training on workload have been verified in recent years. Such studies showed that the workload was 14.9 watts higher. (21-24) Our reports showed a significant improvement of 150 kgm (25 watts) in the achieved workload on bicycle ergometer. In our study, the maximum speed achieved on treadmill was like the single study that

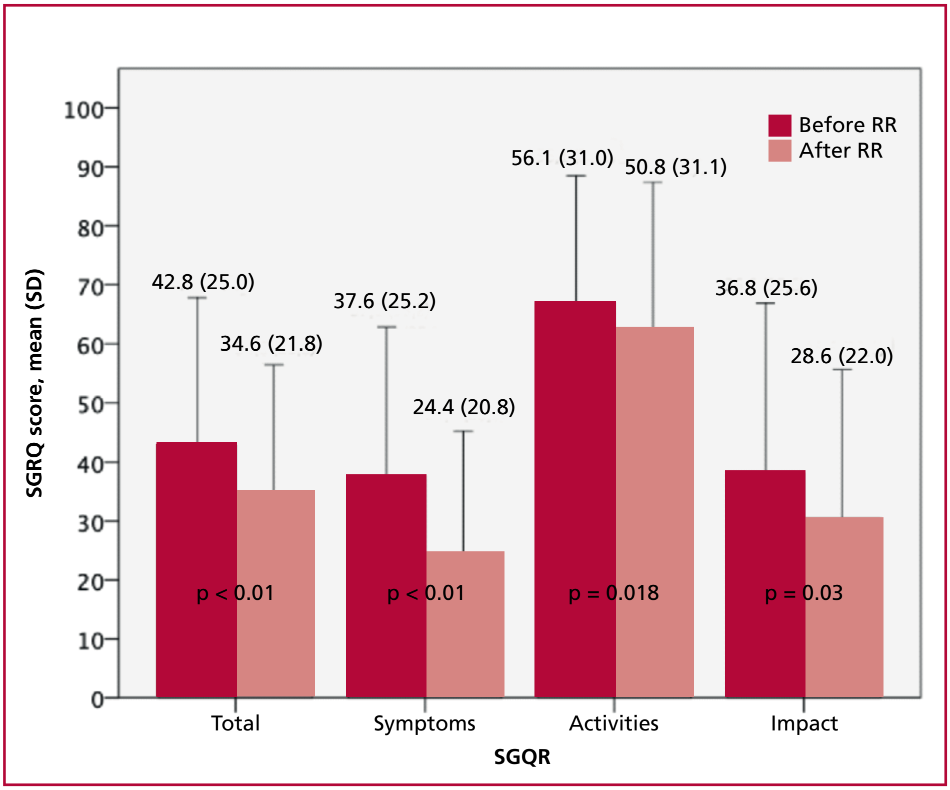

Fig. 2. Saint George's Respiratory Questionnaire (SGRQ) values before and after cardiopulmonary rehabilitation.

evaluated this parameter, which reported an increase of 0.9 mph (1.45 km/h). (33) As for dyspnea, we found statistically significant differences in the VAS, but not in the mMRC scale. As far as we know, there are no published data on these scales, and our study is the only one reporting this estimation. We believe that the role of these scales should be investigated, since they could provide a more objective approach to these patients. Measurement of biomarkers after CR showed similar effects to those reported in other publications. Six studies performed in patients with PH attending CR programs on outpatient basis have found no significant improvement in NT-proBNP values, as was the case in our results. (32, 34-38) With regard to indicators of inflammation, only ESR demonstrated a statistically (but unlikely clinically relevant) significant difference. Its value is still unknown, and we are not aware of any other publications mentioning this parameter.

Among the limitations of our study, we are aware of the small sample size, and of the design, which, although does not allow us to establish causality, based on the results obtained, let us prudently infer the benefits of CR on the 6MWT and QoL in patients with PH. (39,40) The present study showed the short-term effects of a CR program, but did not evaluate the long-term effects. Pulmonary hypertension groups 2, 3 and 5 were not evaluated.

Using the correct dosage, physical training has proved to be a safe and effective treatment. The evidence recommends careful selection of individuals, specific medical therapy, appropriate environment, multidisciplinary and specialized rehabilitation teams, patient-tailored training protocols, and close monitoring. (6) Our findings are consistent with these statements and the reports of this study may open the door to further research on CR in PH.

Based on our observations, and like the findings of other studies, we can conclude that the implementation of an 8-week CR program in individuals with group 1 and group 4 PH in a referral center and with professionals specialized in the area, resulted in an improvement in the walked distance in the 6MWT, and QoL.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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