EDITORIAL

Physical Exercise, an Inexcusable Part of the Treatment of Patients with Pulmonary Hypertension

El ejercicio físico, una parte inexcusable del tratamiento de pacientes con hipertensión pulmonar

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Pulmonary hypertension (PH) is a pathophysiological alteration present in multiple clinical situations, frequently associated with heart disease with left heart failure (PH group 2 of the clinical classification) and also with lung disease and other causes of hypoxemia (group 3). (1) In general, the treatment of these forms of PH is that of the underlying cardiac or pulmonary disease.

In contrast, PH in groups 1 (pulmonary arterial hypertension -PAH-) and 4 (associated with pulmonary thromboembolic disease) has a low prevalence. These forms of PH usually have a progressive course, with severe functional limitation and high mortality. For several decades we have witnessed notable advances in the pharmacological therapy of these patients, while the role of rehabilitation treatment through physical exercise (supervised by a multidisciplinary team) has received less attention. In 2006, Mereles et al (2) published a first prospective and randomized study in this field, which showed a significant improvement in exercise capacity and quality of life, which prompted a growing interest in knowing the impact on functional capacity and prognosis provided by this important therapeutic pillar. Table 1 shows the main publications (2-7) that have contributed to generating evidence of the benefit of physical exercise in patients with PH in groups 1 and 4, which has been reflected in the highest-ranking recommendations in recent clinical practice guidelines.

In this context, the work of Lardiés et al. (7) published in this issue of Rev Argent Cardiol is of great interest, and its authors should be congratulated for providing original results on a topic of enormous relevance for the comprehensive management of this pathology. This is a retrospective study that describes the effect of a cardiorespiratory rehabilitation program in a small group of patients with PH in groups 1 and 4. The authors conclude that the treated patients showed improvement in their functional capacity and quality of life. However, the characteristics of the study make a critical analysis necessary to properly qualify these conclusions.

In the first place, we must point out that the group of 19 patients finally included in this study, far from being a typical "real life" population in a PH unit, presents quite unusual characteristics: despite 4 years of follow-up, these are young patients (5-10 years younger than the rest of the series) in whom the functional class (FC) I-II predominates, with low levels of NT-proBNP, who walk an average of 430 meters in the 6-minute walk test (6MWT), and most of them receive PH medication as monotherapy. All of this reflects a population with milder forms of PH than usual. In addition, the fact that people who habitually performed some degree of physical exercise were excluded from the study, and that more than one third of the eligible population was excluded due to poor adherence to the rehabilitation program, suggests a selection bias that greatly limits the applicability of the results to other populations of patients with PH.

Another question that arises when considering the methods of the study refers to the applied intervention. The physical exercise controlled by the multidisciplinary team was performed in a single weekly session of 2 hours, and the duration of the program was only 8 weeks. Table 1 shows how the rest of studies implemented exercise programs of longer duration (10 to 15 weeks), with several weekly sessions, typically 3 to 7 sessions/week. Thus, the patients in the rest of the studies had performed between 30 and 100 exercise sessions (of probably shorter duration, typically 45-60 minutes) before assessing the effect of the program, compared to the 8 sessions applied by the group de Lardies et al. We understand that the local peculiarities of each hospital and social environment may have conditioned the program logistics.

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Table 1.

Author, year, reference	n	Design	HP Group	Age (m±de) / % women	Intervention Time/sessions	Main results
Mereles D et al, 2006 2	30	Prospective, randomized: intervention vs control	1 and 4	50 ± 13 70%	Physical + respiratory exercise 15 weeks	↑↑ distance PC6M ↑ C of V (SF-36) ↑ $VO2_{max}$ and $_{Wload}$
From Man FS et al, 2009 3	19	Prospective series	1 (only HAP idiop .)	67.7 ± 11.6 72%	Physical exercise 12 weeks	↑ exercise time ↑ Anaerobic threshold ↑ strength, metab . and muscle capillarization Does not improve 6MWC/ $VO2_{max}$
Chan L et al, 2013 4	23	Prospective, randomized: education+exercise vs education	1	54 ± 11 100%	Physical exercise 10 weeks 3 sessions/week	↑ PC6M distance ↑ exercise time ↑ C of V (SF-36 and CAMPHOR) ↑ $VO2_{max}$ and $_{Wload}$
Ehlken N et al, 2016 5	87	Prospective, multicenter, randomized: exercise vs control	1 and 4	56 ± 15 54%	Physical exercise 15 weeks 4-7 sessions/week	↑↑ $VO2_{max}$ ↑ spending and card index . ↑ PC6M distance ↑ C of V (SF-36)
Grünig E et al, 2021 6	116	Prospective, multicenter, randomized: exercise vs control	1 and 4	53.6 ± 12.5 73%	Physical exercise 15 weeks 3-7 sessions/week	↑ PC6M distance ↑ C of V (SF-36) ↑ $VO2_{max}$ –
Lardies J et al, 2022 7	19	Retrospective series	1 and 4	45.5 ± 14.3 95%	cardiorespiratory rehabilitation 8 weeks 1 session/week	↑ PC6M distance ↑ C of V (SGRQ)

6MWT: 6-minute walk test QoL : Quality of life PAH: Pulmonary arterial hypertension
W Load: work load VO2 max : Maximum oxygen

Finally, we must make some considerations about the results obtained. Regarding the prolongation of the distance in the 6MWT, it is necessary to remember the limitations of this test: it is a submaximal test, dependent on the motivation of the individual, not validated in the less severe FCs. It has a "ceiling effect" that limits its ability to demonstrate worsening or improvement in less severe patients, who are those capable of walking more than 450 meters. (8) In this article, almost 90% of the patients were in FC I-II and walked a mean of 430±90 m at baseline. Evaluation by ergospirometry (considered the gold-standard in this field) would have provided greater sensitivity and specificity to detect changes in follow-up, along with more pathophysiological information. In addition, 6MWT a "learning effect" is present, due to familiarization and the development of skills for its execution after multiple repetitions, which can explain up to 15-30% of the differences found. (9) Studies aimed at discovering the clinical significance of the increase in the distance walked in 6MWT (in general, as a result of pharmacological interventions) with a 12-week interval, have shown that the minimum threshold for a significant reduction in clinical events to occur in follow-up was 41.8 meters. (10) Other authors, reflected in the discussion of Lardiés et al. paper, set the threshold at 30 and 33 meters. In any case, the increase of 31 m obtained in this study, despite being statistically significant, might not be so relevant from the clinical point of view.

Regarding the use of the Quality of Life scale "Saint George's Respiratory Questionnaire" (SGRQ), we must point out that its application in the population with PAH is not adequately validated in the literature. This questionnaire was specifically designed to quantify the impact of obstructive respiratory pathologies (such as COPD and asthma) on health-related quality of life (HRQoL) and well-being perceived by the patient. (11) In fact, many of its questions assess symptoms not typical of PAH (for example, productive cough and wheezing), and yet the clinical manifestations attributable to *cor pulmonale*, which are commonly developed by patients with advanced PAH, are not addressed in the SGRQ. As an alternative, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (12) could have been used, a specific questionnaire widely validated to assess HRQoL in PAH, which has demonstrated its superiority over

other non-specific instruments classically used in PH, such as the SF-36. (13)

It is noteworthy that the authors do not describe in Methods section aspects such as health education talks and psychological support, which can be of great importance for the success of these multidisciplinary programs. This could explain the improvement in all the explored areas of quality of life (symptoms, activities and impact), not observed in studies whose intervention is based only on physical exercise. (2,3,5,6)

Beyond the indicated limitations, the work of Lardiés et al. shows benefits of exercise in patients with PH that are consistent with those of previous randomized trials, and has the virtue of reminding us of the need to provide this therapeutic resource to our patients with PH in group 1. In fact, the clinical practice guidelines of the European Society of Cardiology recently published gave this recommendation the highest level of agreement and scientific evidence, which in practice makes its application inexcusable in our setting .

Future studies with an appropriate design will contribute to understanding the mechanisms responsible for the benefit of exercise in patients with PH, as well as other aspects of great practical importance, including the most convenient content, intensity, frequency and duration of the sessions to achieve the maximum benefit. of the rehabilitation programs in our patients with PH.

Conflicts of interest

None declared.

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

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