



## Editorial

## [Translated article] Exercise Tolerance in Pulmonary Hypertension

### Tolerancia al esfuerzo en la hipertensión pulmonar



Exercise intolerance is common in patients with chronic respiratory diseases and impacts on quality of life and activities of daily living.<sup>1</sup> This limitation is caused by the dysfunction of certain physiological systems involved in exercise and is associated with a greater intensity of symptoms such as dyspnea.<sup>2</sup> From the physiological point of view, the mechanisms involved in exercise intolerance include impaired ventilation and gas exchange, systemic and/or pulmonary hemodynamic limitations, and skeletal muscle abnormalities.<sup>1</sup>

Pulmonary hypertension (PH) is a hemodynamic disorder characterized by an abnormal increase in mean pulmonary arterial pressure greater than 20 mmHg and pulmonary vascular resistance greater than 3 Wood units at rest.<sup>3</sup> Exercise capacity assessment can provide valuable information for the diagnosis, treatment, and prognosis of PH.<sup>4</sup> Although PH has different causes, they all share a cardiovascular component, so tests that evaluate aerobic capacity are an important factor in both diagnosis and follow-up.

Exercise limitation is a common characteristic of PH, and is therefore a crucial component in the clinical evaluation of the disease.<sup>5</sup> The most common way to assess exercise capacity in PH is with the 6-minute walk test (6MWT), a submaximal test that is easy to perform, inexpensive, and widely used in clinical practice. This test can be used to evaluate the effect of an intervention and provides prognostic information,<sup>6</sup> but it does not explain the origin of the aerobic limitation. In the past, the 6MWT was used to evaluate the efficacy of PH treatments,<sup>7</sup> and it is now used as one of the essential elements in the multi-parameter assessment of the mortality risk.<sup>8,9</sup>

Another way to assess maximum exercise capacity is with cardiopulmonary exercise testing (CPET), which provides information on cardiovascular response to maximum exercise.<sup>10</sup> This test provides diagnostic and prognostic information complementary to that provided by the 6MWT. Some CPET parameters, such as peak oxygen consumption, oxygen pulse, and the ventilatory equivalent for CO<sub>2</sub> at the anaerobic threshold (VE/VCO<sub>2</sub>) have been shown to be predictors of survival in pulmonary arterial hypertension.<sup>11</sup>

In patients with chronic lung diseases, such as chronic obstructive pulmonary disease or diffuse interstitial lung disease, CPET helps clarify the nature of exercise limitation. Various studies have shown that in these chronic lung diseases, the presence of

PH significantly reduces peak oxygen consumption by more than 4 ml/min/kg and the oxygen pulse by about 2 ml/beat,<sup>12</sup> confirming that the ventilatory limitation typical of the underlying respiratory disease is compounded by a significant cardiovascular limitation.<sup>13</sup>

In operable chronic thromboembolic PH, the 6MWT is routinely performed before and after pulmonary endarterectomy as a means of assessing disease severity, functional capacity, and prognosis.<sup>14</sup> Distance walked on the 6MWT and the VO<sub>2</sub> obtained on CPET have been associated with residual post-operative PH.<sup>15,16</sup>

Conscious of this situation, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) now include in their risk assessment distance walked on 6MWT, peak oxygen consumption on CPET, and the New York Heart Association (NYHA) functional class, which also contributes to assessing the functional status of patients with PH.<sup>4</sup>

Exercise tolerance testing is not only used in the evaluation of patients with PH. Because clinical guidelines recommend its use, studies of therapeutic interventions have also adopted exercise tolerance as one of the most important parameters for assessing the effectiveness of their treatments. Thus, exercise tolerance appears regularly in studies evaluating not only the effectiveness and safety of new drugs, but also surgical procedures and pulmonary rehabilitation.<sup>16–18</sup>

In short, the assessment of exercise tolerance should be included in the evaluation of patients with PH, irrespective of the cause. There is little question that its utility in diagnosis and prognosis will offer a greater understanding of ventilatory and circulatory changes, substantially improving the management of this disease.

#### Funding

This study has received funding from the Health Research Fund, Instituto de Salud Carlos III (PI21/0555), the European Regional Development Fund (ERDF) and the European Union “A Way to Make Europe”, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Catalan Society of Pulmonology (SOCAP). The work of Rodrigo Torres-Castro was funded by a grant from the National Agency for Research and Development (ANID)/DOCTORATE SCHOLARSHIPS CHILE/2018 – 72190117.

#### Conflict of interests

The authors state that they have no conflict of interests.

DOI of original article: <https://doi.org/10.1016/j.arbres.2021.11.012>

<https://doi.org/10.1016/j.arbres.2021.11.018>

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## References

- Vogiatzis I, Zakyntinos S. Factors limiting exercise tolerance in chronic lung diseases. *Compr Physiol*. 2012;2:1779–817.
- Armstrong M, Vogiatzis I. Personalized exercise training in chronic lung diseases. *Respirology*. 2019;24:854–62.
- Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53.
- Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorse. *Eur Heart J*. 2016;37:67–119.
- Babu AS, Arena R, Morris NR. Evidence on exercise training in pulmonary hypertension. *Adv Exp Med Biol*. 2017;1000:153–72.
- Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1428–46.
- Zheng YG, Ma H, Hu EC, Liu G, Chen G, Xiong CM. Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials. *Pulm Pharmacol Ther*. 2014;29:241–9.
- Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50:1700889. Available from: <https://erj.ersjournals.com/content/50/2/1700889> [cited 15.11.21].
- Kylhammar D, Kjellström B, Hjalmarsson C, Jansson K, Nisell M, Söderberg S, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2018;39:4175–81. Available from: <https://academic.oup.com/eurheartj/article/39/47/4175/3860046> [cited 15.11.21].
- Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary exercise testing: what is its value? *J Am Coll Cardiol*. 2017;70:1618–36.
- Grünig E, Tiede H, Enyimayew EO, Ehlken N, Seyfarth H-J, Bossone E, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation*. 2013;128:2005–15.
- Torres-Castro R, Gimeno-Santos E, Vilaró J, Roqué-Figuls M, Moisés J, Vasconcello-Castillo L, et al. Effect of pulmonary hypertension on exercise tolerance in patients with COPD: a prognostic systematic review and meta-analysis. *Eur Respir Rev*. 2021;30:200321.
- Blanco I, Valeiro B, Torres-Castro R, Barberán-García A, Torralba Y, Moisés J, et al. Effects of pulmonary hypertension on exercise capacity in patients with chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2020;56:499–505.
- Richter MJ, Milger K, Tello K, Stille P, Seeger W, Mayer E, et al. Heart rate response during 6-minute walking predicts outcome in operable chronic thromboembolic pulmonary hypertension. *BMC Pulm Med*. 2016:16.
- van der Plas MN, Surie S, Reesink HJ, van Steenwijk RP, Kloek JJ, Bresser P. Longitudinal follow-up of six-minute walk distance after pulmonary endarterectomy. *Ann Thorac Surg*. 2011;91:1094–9.
- Ruigrok D, Meijboom LJ, Nossent EJ, Boonstra A, Braams NJ, van Wezenbeek J, et al. Persistent exercise intolerance after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2020:55.
- Hoepfer MM, Sanchez M-AG, Humbert M, Pittrow D, Simonneau G, Gall H, et al. Riociguat treatment in patients with pulmonary arterial hypertension: final safety data from the EXPERT registry. *Respir Med*. 2021;177:106241.
- Grünig E, MacKenzie A, Peacock AJ, Eichstaedt CA, Benjamin N, Nechwatal R, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. *Eur Heart J*. 2021;42:2284–95.

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