

Editorial

Pulmonary Hypertension Associated With Lung Disease: Is a Jar Half Full or Half Empty?



Hipertensión pulmonar asociada a enfermedad pulmonar: ¿el vaso está medio lleno o medio vacío?

"A problem well put is half solved." John Dewey, *How We Think* (1910)

After decades of limited acknowledgement, pulmonary hypertension (PH) associated with chronic lung diseases has emerged as a highly relevant public health problem.¹ This under-recognition can be mainly attributed to the invasive nature of right heart catheterization required for definitive diagnosis, the predominant notion that PH merely reflects end-stage pulmonary pathology, and the lack of sensitive tools for early detection.² As a result, scientific evidence has been scarce for many years. However, in the past five years, both international clinical practice guidelines³ and expert consensus statements⁴ have increasingly emphasized the clinical relevance and high prevalence of PH in the context of respiratory diseases. These developments highlight the imperative to enhance diagnostic tools, promote earlier identification, and implement individualized therapeutic strategies tailored to the underlying pathophysiological mechanisms.

In the last years, there has been a remarkable revived interest in the study of Group 3 PH. The previous decades of research into the molecular and pathophysiological alterations of this complex and heterogeneous disease group allowed to unravel its pathogenesis. Common pathways, but also crucial differences, were uncovered between Group 3 PH and both the underlying parenchymal lung disease and the paradigmatic form of PH, pulmonary arterial hypertension. Building up on this knowledge, renewed efforts have been undertaken to increase diagnostic accuracy and therapeutic options, with some incremental advances (Fig. 1).

The successful INCREASE trial,⁵ which demonstrated a beneficial effect of inhaled treprostinil in patients with interstitial lung disease (ILD)-PH, provided great impulse to clinical trials in an area of PH where previous efforts had been rather disappointing. The focus on hemodynamically confirmed PH, as well as the inhaled route of administration, might have proved decisive and a clue for future study designs, although this success has not been repeated with the same molecule in chronic obstructive pulmonary disease (COPD) patients.⁶ The possibility of pharmacologic treatment, badly needed in patients with the worst mortality rate of all PH groups,⁷ thus revived the difficult balancing act of diagnosing common forms of PH through a multi-dimensional process, requiring invasive haemodynamics and great expertise. In parallel, the

advent of major international collaborations,⁸ registry data⁹ and claim-based analyses¹⁰ allowed research on big cohorts of patients, affording to distinguish previously unknown crucial differences between subgroups.¹¹ However, much is still unknown about the different phenotypes and what characterizes them. Indeed, similarities have been drawn between patients diagnosed with different PH groups, notably blurring the lines between Group 1 and Group 3 patients⁸ and partially putting into question the structure of the current classification.

In COPD-PH, the focus on severe PH with moderate COPD has attracted great attention, given the severe prognosis and high morbidity burden. Despite ongoing clinical trials both with old and new compounds, there is still no approved treatment except lung transplant and the use of off-label pulmonary vasodilators on a case-to-case basis. In ILD-PH, the approval of the use inhaled treprostinil in some countries, potential use of phosphodiesterase-5 inhibitors in severe PH and several ongoing trials for new compounds have all bolstered efforts to understand the best tool for early diagnosis. In obesity-hypoventilation syndrome (OHS)-PH, data are still limited to small cohorts from specialist centres and very little is known about the condition. In all three cases, a clear stepwise approach to screening and diagnosis is badly needed to reduce the unacceptably long time to detection of PH from the moment symptoms arise, and needs to be put at the centre of future investigations in Group 3 PH.

From a clinical perspective, PH remains a highly undesirable complication in the natural history of chronic respiratory diseases, adversely impacting symptom progression, oxygenation and survival outcomes. Significant challenges still exist in the detection and therapeutic management of this condition due to its inherent pathophysiological complexity.¹² The technical limitations, high patient volumes, and variable availability of echocardiography underscore the need for standardized protocols in monitoring these patients, particularly those with ILD, COPD, and OHS. The proper execution and interpretation of invasive haemodynamic assessment in this population demands a comprehensive approach that extends beyond isolated evaluation of right heart catheterization parameters. Clinicians must avoid confirmatory testing during respiratory exacerbations, while ensuring expert interpretation integrating multimodal data, including imaging findings, labora-

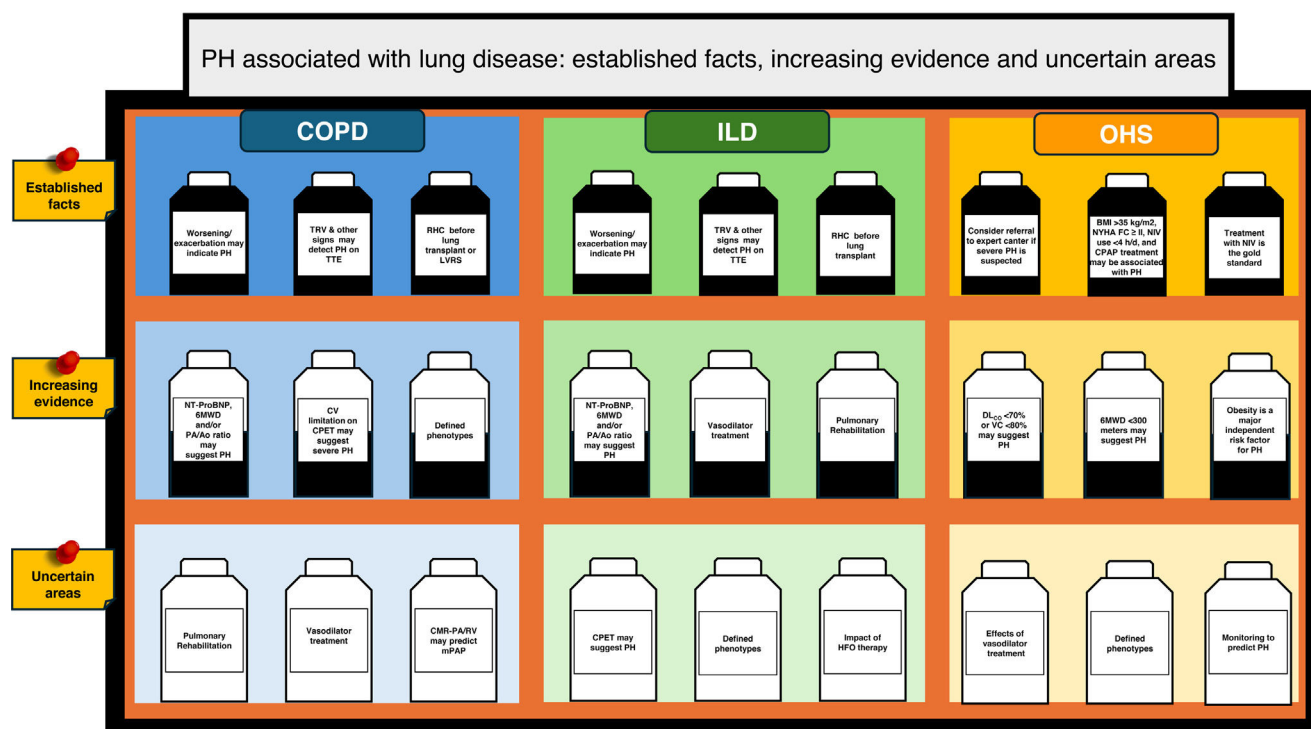


Fig. 1. Current evidence on pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and obesity-hypoventilation syndrome (OHS): The jars symbolize knowledge: full (established facts), half-full (increasing evidence), or empty (uncertain areas). *Abbreviations:* BMI: body mass index; CMR-PA/RV: cardiac magnetic resonance of the pulmonary artery/right ventricle; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CPET: cardiopulmonary exercise testing; CV: cardiovascular; DLCO: diffusing capacity of the lung for carbon monoxide; FC: functional class; HFO: high flow oxygen; ILD: interstitial lung disease; LVRS: lung volume reduction surgery; mPAP: mean pulmonary arterial pressure; NIV: noninvasive ventilation; OHS: obesity-hypoventilation syndrome; PA/Ao: pulmonary artery to aorta ratio; PH: pulmonary hypertension; RHC: right heart catheter; TRV: tricuspid regurgitation velocity; TTE: transthoracic echocardiogram, VC: vital capacity; 6MWD: six-minute walking distance.

tory results, pulmonary function testing, and careful consideration of comorbidities and potential alternative PH etiologies.⁴ Notably, the field still lacks robust evidence to establish clear severity stratification for Group 3 PH.¹³

While emerging data have renewed optimism about targeted PH therapies for select Group 3 patients, a tailored approach must carefully balance potential therapeutic benefits on an individual basis with rigorous attention to the treatment-related adverse effects, the limitations of current evidence, and the fundamental imperative to optimize the treatment of the underlying respiratory disorder and symptomatic measures.¹⁴ This is particularly true for OHS-PH, where weight reduction and non-invasive ventilation remain the only interventions with demonstrated ability to ameliorate, and in select cases reverse, the underlying haemodynamic derangements.¹⁵ In addition, for eligible patients, timely referral for lung transplantation assessment remains an essential component of comprehensive care.

In conclusion, there is a growing clinical and scientific interest in expanding our understanding of PH associated with respiratory diseases. Researchers and clinicians managing PH in respiratory diseases must collaborate closely to bridge current knowledge gaps. Although this has led to the emergence of additional evidence and potentially some modifications in clinical practice, a critical question remains: should we be satisfied with these advances? Or are we merely choosing to view the jar as half full?

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Authors' contributions

DAR, LP and AGO: designed contents, wrote the manuscript draft and approved the final manuscript.

Conflicts of interest

DAR in the last five years received honoraria for speaking at sponsored meetings from Ferrer, MSD and Janssen. Received assistance to meeting travel from MSD and Janssen. Act as a consultant for Ferrer. Unrestricted research grants from Ferrer and MSD.

LP in the last five years has provided paid consultancy services in an advisory capacity to Ferrer, Gossamer, Liquidia, MSD Spain and United Therapeutics, has served as speaker and provided educational material to Ferrer, Janssen, Medscape, and United Therapeutics, received research grants from Ferrer and travel support to attend conferences from Ferrer, Janssen and MSD Spain, all of which not related to this work.

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