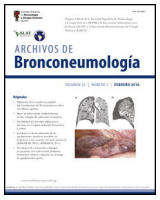
Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
Bronconeumología

www.archbronconeumol.org



Editorial

New Phenotypes of Pulmonary Hypertension Associated With Respiratory Diseases: Towards Traits to Treat

When pulmonary arterial hypertension (PAH) or group 1 pulmonary hypertension (PH) was defined in the last third of the 20th century, it was described as a rare and severe disease that, in its more prevalent form, was thought to be idiopathic and affect mainly young women.[1] It was also considered that, when PH and any pulmonary disease – mainly emphysema and fibrosis – coincided in the same patient, PH could be explained by those conditions and its approach as a separate clinical entity was not recommended.

PAH in-depth study began in the 80s. At that time, considering that PAH was a rare and severe disease, clinicians took a pragmatic approach based on the description of carefully selected patients with well-defined etiologies and clearly pathologic hemodynamic diagnostic criteria in order to provide a precise picture of the disease.[2] In addition, the decision to use highly selective criteria to define PAH patients led to the approval of the first PAH effective drugs. So, looking back, we can say that this initial approach was effective.

Since then, knowledge on PH has evolved dramatically. Focusing specifically on PAH, and based on the evidence provided by several national registries created on the early 2000s, now we know that PAH also presents in the elder and in patients with comorbidities as an independent condition that adversely affects prognosis. Indeed, a specific and more conservative, therapeutic approach has been proposed for this group of PAH patients presenting with comorbidities, as it has been demonstrated that they benefit from pulmonary vasodilators too, but might not tolerate the intensive approach proposed for patients without comorbidities, better represented in clinical trials.[3–5]

With this background, and focusing on PH associated with respiratory diseases (group 3 PH), clinical classification clearly distinguishes it from PAH (group 1PH). Nonetheless, this distinction is becoming increasingly blurred as knowledge about PH increases and its epidemiology is redefined. For instance, a new PAH phenotype, the *pulmonary phenotype*, has been described. The characteristic patient would be a man over 65 years old, with smoking history and diffusing capacity for carbon monoxide <45%, who has normal spirometry and no relevant abnormalities in the lung on chest computed tomography.[6] This PAH phenotype has specific prognostic features and different response to vasodilator therapy, which are similar to those expected in group 3 PH rather than PAH. Although these patients are strictly classified as group 1 PH, they may benefit from a more conservative approach, similar to that used in the management of group 3 PH, where most attempts to demonstrate the effectiveness of pulmonary vasodilators have failed and only inhaled vasodilators currently show some benefit in patients with interstitial lung diseases (ILD).[7] Thus, PH guidelines propose treating patients with severe group 3 PH defined as pulmonary vascular resistances >5 Wood Units (WU), and this may be a reasonable approach for this other group of patients too.[4,8,9] At the same time, we also have the other side of the story: patients who present with mild parenchymal lung disease and disproportionately significant PH. These shared clinical aspects between different PH groups challenges the clinical classification and, subsequently, the management of these patients.[4] To add more confusion regarding the management of these patients, the recent update of the PH hemodynamic definition lowers the thresholds for diagnosis, forcing us to contemplate PH at earlier stages, when clinical presentation might even be absent.[10] This “grey area” we find ourselves in, highlights that we are only beginning to understand how PH behaves when it coexists with lung disease. This increasingly challenging clinical scenario is reinforced by recent findings from novel imaging and multi-omic techniques, which support the complexity of PH pathophysiology and suggest that we are moving along a continuum where PH and respiratory comorbidities coexist, resulting in different PH behaviors in patients who, *a priori*, share the same underlying lung disease.[10,11]

In conclusion, PH is a relevant, prevalent and serious complication of the main respiratory diseases. Although this scenario shares some clinical features with PAH, at the same time, carries a wide range of variability that is not possible to fit in the current clinical classification and also hampers the understanding of how relevant vascular involvement is in most cases. The beneficial effects of pulmonary vasodilators in patients with ILD associated PH have only recently been identified, opening the door to changing the behavior of the disease. In this scenario, we need new tools to better understand the different traits of PH associated with respiratory diseases and be able to predict its subsequent clinical behavior.[12] While basic research is focused on the understanding of the molecular mechanisms of arterial remodeling at the most sophisticated level (-omics, big data, machine learning, network medicine, and functional genetics),[10] at the clinical level we are exploring the different faces of the disease improving the tools we already have (cardiopulmonary exercise test, hemodynamics, echocardiography and magnetic resonance) and combining them with interesting results.[13]

Pulmonologists must feel compelled to protocol and systematize the study of PH associated with respiratory diseases, in close

https://doi.org/10.1016/j.arbres.2024.10.008

Please cite this article as: M. López Meseguer and B. Sáez Giménez, New Phenotypes of Pulmonary Hypertension Associated With Respiratory Diseases: Towards Traits to Treat, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2024.10.008

collaboration with other PH related specialists. We must be aware of our patients' risk of developing PH, and trigger a complete evaluation when suspected with the aim of phenotyping our patients or, in the absence of this possibility at present, at least study this complication in depth and increase our knowledge. Clinical protocols are needed to guide us in the screening of PH in our respiratory patients and how to implement a stepwise investigation of this complication.

If we focus on thoroughly studying these patients and collect our data in cohort registries, this could provide valuable insights to identify traits with potential for treatment that could alter disease behavior.

Conflict of Interests

The authors state that they have no conflict of interests.

References

1. Rich S, Dantzker D, Ayres S, Bergofsky E, Brundage B, Detre K, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987;107(2):216–23.
2. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30(20):2493–537.
3. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. Eur Respir J. 2015;46(4):1113–30.
4. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.
5. Nathan SD, Barnett SD, King CS, Provencher S, Barbera JA, Pastre J, et al. Impact of the new definition for pulmonary hypertension in patients with lung disease: an analysis of the United Network for Organ Sharing database. Pulm Circ. 2021;11(2):1–7.
6. Hoeper MM, Dwivedi K, Pausch C, Lewis RA, Olsson KM, Huscher D, et al. Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. Lancet Respir Med. 2022;10(10):937–48.
7. Waxman A, Restrepo-Jaramillo R, Thenappan T, Engel P, Bajwa A, Ravichandran A, et al. Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study. Eur Respir J. 2023;61(6):2202414.
8. Waxman AB, Elia D, Adir Y, Humbert M, Harari S. Recent advances in the management of pulmonary hypertension with interstitial lung disease. Eur Respir Rev. 2022;31(165):210220.
9. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384(4):325–34.
10. Rhodes CJ, Sweatt AJ, Maron BA. Harnessing big data to advance treatment and understanding of pulmonary hypertension. Circ Res. 2022;130(9):1423–44.
11. Boucly A, Tu L, Guignabert C, Rhodes C, De Groote P, Prévot G, et al. Cytokines as prognostic biomarkers in pulmonary arterial hypertension. Eur Respir J. 2023;61(3):2201232.
12. Weatherald J, Hemnes AR, Maron BA, Mielniczuk LM, Gerges C, Price LC, et al. Phenotypes in pulmonary hypertension. Eur Respir J. 2024;64(3):2301633.
13. Badagliacca R, Rischard F, Papa S, Kubba S, Vanderpool R, Yuan J, et al. Clinical implications of idiopathic pulmonary arterial hypertension phenotypes defined by cluster analysis. J Heart Lung Transplant. 2019;38(4):S488.

Manuel López Meseguer[a,b,*], Berta Sáez Giménez[a,b,c]
[a] *Unidad de Trasplante Pulmonar y Patología Vascular Pulmonar, Hospital Vall d'Hebron, Barcelona, Spain*
[b] *CIBER de Enfermedades Respiratorias (CIBRES), Spain*
[c] *Departament de Immunologia, Biologia Cel·lular i Fisiología Mèdica, Universitat Autònoma de Barcelona, Barcelona, Spain*

*Corresponding author.
E-mail address: manuel.lopez@vallhebron.cat (M. López Meseguer).