Pulmonary arterial hypertension and pulmonary hypertension due to left heart disease: so near and yet so far

To the editor  Pulmonary arterial hypertension (PAH) is a heterogeneous clinical condition. Due to its hemodynamic features and pathophysiological mechanisms, it is categorized as a form of precapillary pulmonary hypertension (PH). However, progressive epidemiological changes in the demographic characteristics of individuals with PAH are still providing new nosological insights in clinical practice. The article by Jonas and Kopeč1 referred to a challenging phenotype of PAH, which still presents a hemodynamic profile compatible with precapillary PH, together with an increased prevalence of risk factors predisposing to left heart disease, particularly to left ventricular diastolic dysfunction. In the analysis involving patients enrolled in the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry between May 2007 and April 2015, Optiz et al2 first coined the term “atypical PAH,” while “PAH with comorbidities” was subsequently provided in the recommendations from the 2nd Cologne Consensus Conference 2018 to alternatively identify this hybrid PH phenotype.3 Although efforts were made to indicate peculiar features defining such a new PH entity, data from the literature suggested possible overlaps between the pathobiological mechanisms of PAH and PH regarding heart failure with preserved ejection fraction (HFpEF). These 2 PH phenotypes have been shown to share a neurohormonal basis predisposing to right ventricular (RV) failure and pulmonary vascular disease. Endothelin-1 (ET-1) has been reported to play a pivotal role in the development of vascular abnormalities in PAH, including pulmonary vasoconstriction, smooth cell proliferation, and vascular remodeling. In contrast, the counterregulatory peptide adrenomedullin is known for its cardioprotective effect on pulmonary circulation, including vasodilatation and inhibition of vascular disruption. The co-upregulation of both these pathobiological pathways has been described in animal models of PAH. Furthermore, their activation has also been proposed as an early noninvasive marker of pulmonary vascular disease and RV dysfunction in patients with HFpEF. In their analysis, Obokata et al4 found higher plasma levels of both C-terminal proET-1 and midregion proadrenomedullin in patients with HFpEF, both at baseline and on exertion. Apart from that, they reported a significant direct correlation with mean pulmonary arterial pressure and pulmonary artery wedge pressure, as well as an inverse relationship with pulmonary arterial compliance.

Another aspect suggesting a potential disease continuum between PAH and PH in HFpEF is a weaker response to targeted PAH-therapy in patients with PAH and concomitant risk factors for left heart disease, which raises suspicion that these factors may potentially contribute to such low therapeutic efficacy. A plausible explanation of the weaker response to treatment takes into account the potential impact of cardiovascular risk factors and comorbidities on developing systemic inflammation and coronary microvascular disease, with subsequent RV impairment, lower exercise tolerance, and nonresponsiveness to PAH-specific drugs, which act mainly on pulmonary circulation. Finally, in patients with atypical PAH, a trend toward higher pulmonary artery wedge pressure and left ventricular end-diastolic pressure was observed, which raise RV afterload and impair RV function.5,5

In conclusion, research on atypical PAH provides new insights suggesting a closer interplay between PAH and PH in HFpEF and offers a hypothesis on a potential disease continuum between these 2 PH phenotypes. Further studies are needed to elucidate a plausible etiological link between PAH and coexisting cardiovascular risk factors in order to stratify the therapeutic response to targeted PAH-treatment in this population.

ARTICLE INFORMATION

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As recently shown, the observed shift in the epidemiology of PAH and the higher number of cardiovascular comorbidities in patients with PAH can be associated with an increasing age of diagnosed patients. What is more, some of the main cardiovascular risk factors, including alterations in glucose and lipoprotein metabolism, can serve as prognostic factors and affect patients’ survival. As shown recently, the observed shift in the epidemiology of PAH and the higher number of cardiovascular comorbidities in patients with PAH can be associated with an increasing age of diagnosed patients. What is more, some of the main cardiovascular risk factors, including alterations in glucose and lipoprotein metabolism, can serve as prognostic factors and affect patients’ survival. As shown recently, the observed shift in the epidemiology of PAH and the higher number of cardiovascular comorbidities in patients with PAH can be associated with an increasing age of diagnosed patients. What is more, some of the main cardiovascular risk factors, including alterations in glucose and lipoprotein metabolism, can serve as prognostic factors and affect patients’ survival. As recently shown, the observed shift in the epidemiology of PAH and the higher number of cardiovascular comorbidities in patients with PAH can be associated with an increasing age of diagnosed patients. What is more, some of the main cardiovascular risk factors, including alterations in glucose and lipoprotein metabolism, can serve as prognostic factors and affect patients’ survival.
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