A challenging phenotype of pulmonary arterial hypertension

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To the editor Pulmonary arterial hypertension (PAH) is a rare disease in which the progressive narrowing of the lumen of pulmonary arteries leads to a rise in pulmonary arterial pressure and pulmonary vascular resistance (PVR). It results in progressive right heart failure, functional decline, and, ultimately, death. The hemodynamic classification of pulmonary hypertension (PH) places PAH within a group of precapillary PH, assuming that it results entirely from the arteriolar narrowing and excluding the role of a passive backward transmission of left ventricular filling pressure in its pathogenesis.[1-3] Recently, the experts of the 6th World Symposium on Pulmonary Hypertension proposed to define PAH as a mean pulmonary artery pressure (mPAP) higher than 20 mm Hg, accompanied by elevated PVR higher than 3 Wood units, and a pulmonary artery wedge pressure lower than or equal to 15 mm Hg.[4]

In the first PAH registry initiated in the 1980s by the US National Institutes of Health (NIH), the mean (SD) age of enrolled patients with primary PH (currently referred to as idiopathic PAH [IPAH]) was 36 (15) years. Consequently, for many years, PAH was considered a disease that affects mainly young people. However, more recent epidemiological studies from the United States and Western European countries indicate that the mean age of patients diagnosed with PAH has increased.[5] For example, in the REVEAL study (Registry to Evaluate Early and Long-term PAH Disease Management) that recruited patients 30 years after the NIH registry had been compiled, the mean age in the IPAH group was 53 years, while in the European COMPERA registry (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), patients with incident IPAH were in their 70s at the time of diagnosis.[6,7] Furthermore, the aging of the PAH population influences its phenotype. The comparison of patients with IPAH diagnosed in the United Kingdom and Ireland in the years 2001–2003 and 2007–2009 showed a significant increase in the age at the time of diagnosis (45 years vs 52 years) accompanied by an increased prevalence of obesity (31% vs 43%), ischemic heart disease (5.8% vs 16.3%), and diabetes (5.7% vs 18.3%), which are important risk factors for left ventricular diastolic dysfunction and, consequently, postcapillary PH.[8,9] Therefore, it has been postulated that some older patients diagnosed with PAH who still meet the hemodynamic criteria of precapillary PH may still have some degree of left ventricular diastolic dysfunction and constitute a unique phenotype of "mixed" PH.

Currently, it remains unclear whether the changing demographics of the PAH population influences the course and outcome of this severe disease. The recent analysis of the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial, which was one of the landmark studies in PAH, is of interest in this context. This trial showed that the upfront combination of tadalafil and ambrisentan in the group of treatment-naive patients with PAH resulted in a significantly lower risk of clinical failure than observed in monotherapy with either ambrisentan or tadalafil. McLaughlin[10] made use of the fact that the inclusion criteria were revised in the course of the trial to minimize the risk of enrolling patients in whom left ventricular diastolic dysfunction may have been a factor contributing to PH. Accordingly, the cutoff for PVR was increased from 3 WU to 3.75 WU, and the cutoff for pulmonary artery wedge pressure was reduced from ≤15 mm Hg to ≤12 mm Hg if PVR was less than 6.25 WU. Additionally, patients with 3 or more risk factors for heart failure with reduced diastolic function were excluded from the study. These risk factors included: body mass index ≥30 kg/m^2, history of essential hypertension, diabetes mellitus, and history of severe coronary artery disease. Patients who met the amended eligibility criteria (the primary analysis group) as compared

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with those who did not (the ex-primary analysis group) were younger, had greater 6-minute walk distance, and fewer comorbidities. What is more, the primary analysis group had fewer events of clinical failure, higher rates of satisfactory clinical response, and lower rates of permanent study drug withdrawal due to adverse effects than the ex-primary analysis group. Although the beneficial effects of the initial combination therapy versus pooled monotherapy were found in both populations, they were of a lower magnitude in the ex-primary analysis group.

Although left ventricular dysfunction and the so called "mixed" phenotype of PAH could have contributed to the worse response to treatment in the group with multiple risk factors, it should be acknowledged that some of them may directly affect pulmonary vasculature. Recently, several reports[11-15] have documented the clinical impact of diabetes, insulin resistance, and impaired lipid metabolism, including a low level of high-density lipoprotein cholesterol, on disease severity and outcome of patients with PAH. These risk factors have also been shown to be more prevalent in patients with PAH than in age-matched controls. As the exact mechanism of these associations is still poorly understood, further research is needed to elucidate this challenging new phenotype of PAH.

ARTICLE INFORMATION

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