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How to select the appropriate candidate of pulmonary arterial hypertension: specific therapy in elderly patients with pulmonary hypertension

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Recent reports from pulmonary arterial hypertension (PAH) registries suggest that the mean age at diagnosis is increasing in a growing proportion of elderly patients.[1–6] The combination of several reasons such as aging population, increase in life expectancy, growing PAH awareness of physicians and patients, and availability of more treatment options could explain the changing picture of PAH. PAH should be considered as an emerging entity in the elderly. Elderly PAH patients suffer from severe pulmonary vascular disease with a poor survival rate.[7] This population has an increased likelihood of comorbidities or physiological age-related changes that could make PAH diagnosis challenging. Diagnostic workup of severe pulmonary hypertension (PH) in the elderly should be performed in such a way as to discriminate between the expected consequences of aging, pulmonary vascular disease, and other frequent causes of secondary PH (left heart disease or lung disease). Careful evaluation by right heart catheterization (RHC) is mandatory. The progressive decline in lung function with normal aging has been demonstrated.[8] A decrease in left heart compliance is also observed.[9] Systolic pulmonary artery pressure (sPAP) estimated by Doppler echocardiography shows a significant age-related increase of approximately 1 mmHg per decade.[10] Age-related physiological changes of the cardiovascular and respiratory systems should be kept in mind when PH is suspected in the elderly. PAH could be suspected in the elderly who present hemodynamic and clinical alterations "out of proportion to age" with very unusually elevated pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP).

Chronic obstructive pulmonary disease (COPD) can lead to PH. Severe PH rarely occurs in stable COPD patients.[11] When disproportionate PH is suspected in COPD, confirmation by RHC should be performed. Potential associated conditions should be considered because they could be easily treatable.[11] Further studies evaluating the pathobiology of PH in COPD and characterizing the phenotype of the combination of a rare disease (PAH or PAH-like) and a very frequent one (COPD) are needed.

Left heart disease is the most frequent cause of PH. Heart failure with preserved ejection fraction (HFpEF) PH may be more difficult to assess, may be associated with dyspnea or considered as related to aging. HFpEF PH is a major differential diagnosis of PAH. Some patients with HFpEF could be missed. In this condition, the transpulmonary gradient (TPG) is low (≤ 12 mmHg) and PH is considered as passive. TPG validity has been recently challenged.[12] In the elderly, the increased stiffness of the pulmonary vessels may indeed lead to a disproportionate increase in sPAP. Elevated left ventricle (LV) filling pressure and diminished pulmonary vascular recruitment may lead to elevated TPG, erroneously suggesting a precapillary component. Supplementary parameters such as elevated PVR or diastolic pulmonary gradient should be considered to better assess the real precapillary component of Group 2 PH.[13] HFpEF could be unmasked by fluid challenge in patients with normal pulmonary capillary wedge pressure and suspected diastolic dysfunction.[14] The so-called precapillary component might not be that clear-cut in this subset of patients. PAH and HFpEF-PH could be more accurately differentiated by using predictive modeling. Advanced age, the presence of hypertension and coronary heart disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output best differentiated one from another. It is plausible to adequately evaluate and hemodynamically investigate elderly patients with severe unexplained PH in detail in expert center. Data from the French registry showed that the delay between first exposure and PAH diagnosis ranged between

5 and 12 years, suggesting that new incident cases can be expected in the next years and that one should identify whether a toxic exposure may have acted as a trigger for PAH when taking PH history, particularly in the elderly. With regard to the evaluation of elderly patients and the mandatory elements that have to be fulfilled to confirm PAH, hemodynamic parameters assessed by RHC should be examined carefully. Consistent with some of the age-related physiological changes, mPAP may be expected ≥ 25 mmHg in 1 in 250 healthy subjects aged ≥ 50 years, whereas it can be seen in only 1 in 5000 younger ones.[7]

Discrimination between precapillary and postcapillary might not be that simple. Reliance on pulmonary artery wedge pressure (PAWP) rather than left ventricular end diastolic pressure (LVEDP) in patients with suspected elevated left filling pressure may result in misdiagnosis of PAH. When left heart catheterization (LHC) measurement is not available, discrepancies with LVEDP could be reduced by careful analysis of the RHC acquisition curves and PAWP values determined at the end of the respiratory cycle instead of a digitized calculated mean.[15] This is an important issue, especially regarding PAH evaluation in the elderly. It is reasonable and probably mandatory to consider LVEDP measurement by LHC in patients where HFpEF-PH must be ruled out. One should also remember that mild diastolic dysfunction is a common condition in older patients that could lead to unduly rule out PAH. Thus, elderly patients with suspicion of PAH should be referred to an expert PH center for a precise hemodynamic evaluation and an appropriate diagnosis.

PAH-specific therapy is widely accepted for many patients with group 1 PAH, who have World Health Organization (WHO) functional class II, III, or IV. In contrast, it should only be administered on a case-by-case basis for patients with group 3 PH, group 4 PH, or group 5 PH. PAH-specific therapy should not be administered to most patients with group 2 PH.[16,17] The evidence supporting PAH-specific therapy comes primarily from studies that included patients with idiopathic PAH or scleroderma-related PAH. It could be hypothesized that targeting precapillary HFpEF-PH patients with PAH-specific therapy may be rational. However, there is currently a lack of evidence supporting the role of drugs that could even be deleterious to patients with other forms of PH. However, there are a few situations in which PAH-specific therapy may be considered for group 2 PH (e.g., patients with persistent PH due to mitral valve disease who have undergone mitral valve replacement with normalization of left atrial pressure).[18] Shujaat, *et al*.[19] performed a retrospective chart review of consecutive patients with non-WHO group 1 PH treated with PAH-specific therapy. The 6-minute walk distance (6-MWD) improved significantly only in patients with obstructive sleep apnea (OSA) or patients with severe PH.[19] Therefore, the use of PAH-specific therapy in selected patients with non-WHO group I PH may result in significant improvement in 6-MWD, particularly in patients with OSA or severe PH.

There is no single best approach to selecting an agent for PAH-specific therapy. Initial monotherapy or combination therapy, and sequential combination therapy could be considered based on multiple factors including WHO functional class, right ventricular function, hemodynamics, vasoreactivity test, patient characteristics and preferences, and country and regional variations.[16,17,20] Whether sequential combination therapy results in similar long-term benefits compared with initial combination therapy is not known. Clinicians with expertise in the treatment of patients with PAH may also individualize therapy based on their clinical experience. For patients in class II and III with a new diagnosis of PAH, many experts initially administer oral agents that target the endothelin and nitric oxide-cyclic guanosine monophosphate pathways in combination. The combination of ambrisentan and tadalafil is preferred because it is associated with a significant reduction in the rate of clinical failure compared to monotherapy with either drug alone. For those who have a contraindication to either agent, substitution with another oral agent in the same class is preferred, although such combinations are less well proven and drug interactions can potentially limit the outcome.

The elderly candidate for PAH-specific therapy should be selected by experienced clinicians and must be based upon an appropriately established diagnosis and evaluation of the patient's disease severity. The options for pharmacotherapy in such patients include several drug classes and delivery routes.

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