Pulmonary hypertension (PH) is present in a broad spectrum of systemic diseases (1). Despite an established World Health Organization (WHO) classification system (1) and an expanding armamentarium of available pharmacotherapies (2), the prevalence of PH in the general population remains unknown. Pulmonary hypertension has been reported in specific patient populations with variable frequency (i.e., portal hypertension: 0.6% to 2% [3], systemic sclerosis: 12% to 33% [4,5], obstructive sleep apnea: 15% to 20% [6]), but is particularly common in heart failure with reduced left ventricular ejection fraction (68% to 76% [7,8]) and mitral stenosis (9).

In this issue of the Journal, Lam et al. (10) provide the first population-based report of the prevalence, severity, and prognostic implications of PH in heart failure (HF) with preserved left ventricular ejection fraction (HFpEF). The investigators are to be commended for including consecutive patients with HFpEF (n = 222) and appropriate hypertensive control subjects (n = 719) from the same community, with complete follow-up for a median of 2.8 years. Pulmonary hypertension, as defined by echocardiogram-derived pulmonary artery systolic pressure (PASP) >35 mm Hg (11), was present in 83% of patients with HFpEF and only 8% of controls. In addition to the excellent discriminatory power of PH for the diagnosis of HFpEF, PASP was the only echocardiogram-derived parameter in HFpEF that predicted mortality in this cohort.

Requisite fulfillment of Framingham Heart Study criteria for HF (12) within 1 day of study (13) and frequent hospitalization at the time of echocardiogram likely led to overestimation of HFpEF patients’ average ambulatory PASP, and therefore may have resulted in a higher discriminatory capacity of PASP than if it were measured in stable outpatients. In fact, the median PASP of 48 mm Hg in this study was highly consistent with the median PASP of 47 mm Hg reported in a case series of similar patients hospitalized for decompensated HFpEF (14).

However, the extent to which PASP increases with HF exacerbations may in fact be modest. Recently reported experience with permanent implantable hemodynamic monitoring devices in patients with HFpEF enrolled in the COMPASS (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study indicated that median daily right ventricular systolic pressure increased by only 8% (from 50 ± 10 mm Hg to 54 ± 12 mm Hg, p < 0.001) between baseline evaluation, 7 weeks before HF exacerbation, and 1 day before urgent presentation for hypervolemia (15). Further investigation is needed to establish the temporal stability of repeated echocardiographic PASP measurements in HFpEF. If low biologic variance in resting PASP is confirmed, it will add to the utility of this measurement in the diagnosis and treatment of HFpEF.

The way in which HFpEF is defined may also influence the reported burden of PH in this patient population. The use of Framingham Heart Study criteria to define HFpEF can lend itself to inclusion of patients with WHO classes 1, 3, 4, and 5 PH, who may manifest Framingham Heart Study criteria (i.e., jugular venous distention, hepatojugular reflux, lower-extremity edema, or radiographic cardiomegaly) because of symptomatic right HF, on account of pulmonary arterial hypertension, instead of PH secondary to left ventricular diastolic dysfunction (LVSD). The investigators appropriately conducted subgroup analysis to exclude chronic obstructive pulmonary disease and definitive cases in which alternative causes of PH were likely, which did not alter their conclusions. However, in further mechanistic studies to characterize PH in HFpEF, it will be important to narrowly define HFpEF and to consider independent processes influencing pulmonary arterial and right ventricular function.

The use of echocardiography to assess PASP and pulmonary capillary wedge pressure (PCWP) limits precision (16,17) and relies on a discernable tricuspid regurgitant jet that was absent in 13% of patients with HFpEF in this study. Nonetheless, one of the most important findings of this article was the significant pre-capillary, pulmonary arterial contribution to PH in HFpEF. After adjusting for PCWP, PASP remained significantly higher in HFpEF than in hypertensive controls. The investigators point out a significant relationship between PCWP and PASP (r = 0.21, p < 0.007), consistent with a passive contribution of pulmonary venous hypertension to increased PASP in HFpEF. However, the weakness of this relationship is striking and indicates marked variability in PASP at a given left-sided...
filling pressure in HFpEF (see Fig. 2 in Lam et al. [10]). This finding, coupled with the evident prognostic importance of PH in HFpEF, opens the door to investigation of genetic, environmental, and biochemical factors mediating such heterogeneity in pre-capillary PH in HFpEF.

Disproportionate increases in pulmonary arterial pressure (PAP) relative to left-sided filling pressures in HFpEF are not unexpected based on our knowledge of other left-sided conditions such as LVSD. Butler et al. (8) showed that elevated pulmonary vascular resistance (PVR, as defined by [mean PAP – PCWP]/cardiac output), reflecting pulmonary arterial hypertension superimposed on pulmonary venous hypertension, was present in 72% of patients with New York Heart Association functional class II to IV with chronic LVSD (8). Pre-capillary PH in LVSD is mediated by hypertension characterized by insensitivity to vasodilators acting through nitric oxide, endothelin, or prostaglandin signaling pathways (18), and vascular remodeling consisting of abnormal thickening of arterial neointima and medial hypertrophy with notable absence of plexiform lesions (19). Variable success in reducing fixed pulmonary hypertension has been reported with strategies to improve left ventricular performance with inotropes such as milrinone and dobutamine (20), vasodilators such as nesiritide (21), and left ventricular assist devices (22).

Clinical consequences of developing pre-capillary PH are significant. In LVSD, as in other World Health Organization classes of pulmonary arterial hypertension, elevated PAP and PVR potently predict morbidity and mortality (7). In addition, there is a strong inverse relationship between PVR and exercise capacity as measured by peak $\dot{V}O_2$ (8,23). Finally, pre-capillary PH is closely associated with inefficient ventilation (high VE/VCO2 slope) (24), which contributes to hyperpnea and dyspnea on exertion and portends a poor prognosis (25).

Hence, it is intriguing to postulate that in HFpEF, the propensity for individuals to develop pre-capillary PH in response to elevated filling pressures may contribute to the development of signs and symptoms of HF before left ventricular remodeling results in diminution of left ventricular ejection fraction. At the very least, the discriminatory power of elevated PASP in HFpEF reflects the fact that PASP is an integrative barometer of both left-sided filling pressures and pulmonary vascular tone.

Invasive studies are needed to precisely quantify transpulmonary gradients in HFpEF and to elucidate mediators of pre-capillary PH in HFpEF. Unanswered questions include whether there is differential expression of genes or biochemical profiles shown to mediate pulmonary arterial hypertension (26) in HFpEF and whether subclassification of secondary PH in HFpEF based on responsiveness of the pulmonary vasculature to exercise or vasodilator treatments predicts responsiveness to pulmonary vasodilator therapies in HFpEF.

In light of the findings of Lam et al. (10) coupled with disappointing results from recent pharmacotherapy trials in HFpEF (27,28), it is attractive to consider pharmacotherapy directed at pre-capillary PH in HFpEF. Pulmonary vasodilation poses the risk of increasing transit of blood to the left atrium and thereby dangerously elevating left-sided filling pressures in left heart disease. However, the phosphodiesterase 5 inhibitor sildenafil has recently been shown to improve exercise capacity and ventilatory efficiency in LVSD (29–31). The magnitude of improvement in peak $\dot{V}O_2$ with sildenafil treatment was proportionate to reduction in exercise PVR, and no increase in rest or exercise PCWP was observed compared with placebo (30). The recently initiated RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure) trial will test the hypothesis that phosphodiesterase 5 inhibition improves exercise capacity and quality of life in patients with HFpEF.

In summary, Lam et al. (10) provide strong evidence that PH is common in HFpEF and that noninvasive measurement of PASP may prove useful in diagnosing HFpEF and in selecting patients at increased risks for adverse events. Further studies are needed to determine mediators of secondary PH in HFpEF and to test the hypothesis that PH is a potential target for therapeutic intervention.

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