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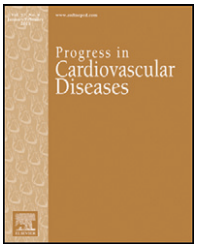

Development of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Pulmonary hypertension (PH) is common in patients with heart failure with preserved ejection fraction (HFpEF). While PH-HFpEF may affect more than a million patients in the United States alone, it has been difficult to study its epidemiology and response to treatment due to difficulty in properly defining the illness. While chronic remodeling of the pulmonary vasculature is related to chronic passive congestion of the pulmonary circulation from the pulmonary veins, there are likely other contributors to the development of PH-HFpEF. We explore the potential direct contributions of obesity, diabetes mellitus, genetics, and sleep apnea on the pulmonary circulation in those with PH-HFpEF, and we discuss the potential role of exercise testing or fluid challenge during diagnostic testing.

Pulmonary hypertension (PH) related to left heart disease (PH-LHD) is the most common form of PH in clinical practice and results from heart failure (HF) with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF)/diastolic dysfunction (DD).[1,2] HFpEF is affecting an increasing proportion of patients admitted with HF exacerbations. Estimates report that a large portion of patients with HFpEF will go on to develop PH (PH-HFpEF).[3–6] While there have been advances in treating certain subsets of PH, PH-LHD (designated Group II by the World Health Organization's classification) and the subgroup of PH-HFpEF remain without specific treatment modalities despite a decade of attempts.[7] This lack of proven therapy is attributable to a complex underlying pathophysiology and difficulty in accurately defining the parameters of these diseases. This review will attempt to summarize the definitions of HFpEF and PH-HFpEF, their epidemiology and pathophysiology, and to focus on why patients with HFpEF may develop PH-HFpEF.

Definitions

HFpEF remains primarily a diagnosis of exclusion for patients undergoing evaluation for exercise intolerance or admitted with the syndrome of HF and found to have a normal ejection fraction (EF) on transthoracic echocardiography (TTE). Current definitions of HFpEF rely on a clinical diagnosis of HF and the findings supported by echocardiographic data of chronically impaired active relaxation or ventricular compliance.[8,9] The ability to differentiate between pre and post-capillary PH-HFpEF requires right heart catheterization, which can help to determine if

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Abbreviations and Acronyms

BMPR2 = bone morphogenetic peptide receptor 2

CO = cardiac output

CPET = cardiopulmonary exercise test

DD = diastolic dysfunction

DM = diabetes mellitus

dPAP = diastolic pulmonary arterial pressure

DPG = diastolic pulmonary gradient

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricle

mPAP = mean pulmonary arterial pressure

NO = nitric oxide

OSA = obstructive sleep apnea

PAH = pulmonary arterial hypertension

PASP = pulmonary artery systolic pressure

PCWP = pulmonary capillary wedge pressure

PH = pulmonary hypertension

PH-HFpEF = pulmonary hypertension and heart failure with preserved ejection fraction

PH-LHD = pulmonary hypertension and left heart disease

PVR = pulmonary vascular resistance

RHC = right heart catheterization

RV = right ventricle

sPAP = systolic pulmonary arterial pressure

TPG = transpulmonary gradient

TTE = transthoracic echocardiogram

V_{CO2} = carbon dioxide output

VE = minute ventilation

VO_2 = peak oxygen consumption

medications will help or harm patients.[2] Thus, it is common for PH-HFpEF to be diagnosed by a right heart catheterization (RHC) performed in the workup of the dyspneic or otherwise minimally improving HFpEF patient. A pulmonary capillary wedge pressure (PCWP) over 15 mmHg and a mean pulmonary artery pressure (mPAP) over 25 mmHg are typically used to diagnose PH-HFpEF in this setting; however, this definition does not account for differences in chronic remodeling of pulmonary vasculature between patients with HFpEF. Thus, there have been recent proposals to broaden the definition to include within PH-LHD a "mixed" or pre/post-capillary definition of PH-LHD that would highlight a subgroup in which pulmonary vasculature is no longer a passive circuit, but has remodeled to the point of having increased resistance.[7] Three calculated criteria obtained during RHC are proposed to identify this subgroup; pulmonary vasculature resistance (PVR) over 3 Woods units, transpulmonary gradient (TPG) over 12 mmHg, and/or diastolic pulmonary gradient (DPG) over 7 mmHg.[2,7]

Epidemiology

PH-LHD is the most common form of PH, with roughly half of patients with either systolic or DD having evidence of chronically elevated pulmonary afterload.[2] The true prevalence of PH-HFpEF is difficult to know due to differences in study design (mostly retrospective or single center data) and differing methods for diagnosing the condition (with or without RHC).[2] It has been well established that the prevalence of PH-HFpEF increases in patients who are female, older, have one or more features of the metabolic syndrome, and have more cardiac co-morbid conditions compared to other groups of PH-LHD.[10] PH-HFpEF appears so common that it skewed a recent trial of combination therapy intended for patients with pulmonary arterial hypertension (which included only patients with PCWP under 15), so that the exclusion criterion was amended to remove patients at risk for having HFpEF.[11] A retrospective cohort analysis of 244 patients with HFpEF found a prevalence of 80% using a pulmonary arterial systolic pressure (PASP) over 35 mmHg on TTE as their definition of PH-HFpEF.[4] Another single center retrospective cohort study found PH-HFpEF (PASP over 35 mmHg on TTE) in 44% among patients admitted with HFpEF.[3] In TOPCAT, PASP greater than 35 mm Hg was noted in 36% of those with HFpEF.[12] As this study was prospective and multicenter, it is likely more reliable than the previously stated single center studies. Other registry studies used RHC to define PH-HFpEF and still found that roughly 50% of patients with HFpEF had PH-HFpEF.[12] All of the above studies had methodological weaknesses: the definitions of both HFpEF and PH-HFpEF varied, invasive hemodynamics were rarely used, and they could only detect prevalence, not incidence. However, if there are 5.1 million patients in the US with HF,[13] and 50% have HFpEF, and 50% of those will go on to develop some form of PH-HFpEF, then roughly 1.3 million patients in the US will suffer from PH-HFpEF. This common disease also has an unpredictable disease course, with an expected 5-year mortality that appears to be about 50%.[13,14] This underscores the importance of understanding the pathophysiology of this disease.

Pathophysiology

It is important to consider the development of PH-HFpEF in those with HFpEF. As the above prevalence data do not discern when a person with HFpEF develops PH-HFpEF, only that it is a common occurrence, we do not know how long it takes to