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Recognizing Pulmonary Hypertension and Right Ventricular Dysfunction in Heart Failure

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ARTICLE INFO

Keywords:
Pulmonary hypertension
Right ventricular dysfunction
Heart failure

ABSTRACT

Pulmonary hypertension (PH) in the setting of left heart disease (LHD) or heart failure (HF) is the most common form of PH, yet its prevalence is underappreciated. Varying terminology possibly leads to misconceptions in pathophysiology, diagnosis and management. The accurate diagnosis of PH due to LHD is contingent upon hemodynamic assessment via right heart catheterization, however due to limitations in access, comprehensive echocardiography and integrative scoring systems are frequently used. When present in the setting of PH due to LHD, right ventricular dysfunction (RVD) confers a poor clinical prognosis. The management of RVD is directed towards treating underlying HF and/or valvular disease. Implantable hemodynamic monitors may offer opportunity to obtain longitudinal information to increase diagnostic accuracy as well as monitor the effect of treatment of PH in the setting of HF with and without the presence of RVD.

Pulmonary hypertension (PH) in the setting of heart failure (HF) with reduced (HFrEF) or preserved ejection fraction (HFpEF) develops as a result of a chronically elevated left atrial pressure (LAP; a post capillary phenomenon). In the face of persistently elevated pulmonary arterial (PA) pressures (PAPs), and the failure to adapt to chronically elevated afterload, right ventricular (RV) dysfunction (RVD) may develop with adverse consequences to patient functional capacity and survival. The World Health Organization has categorized PH in the setting of left heart disease (LHD) or HF as Group 2 PH, and its presence is frequently under recognized. Despite being the most common form of PH, its true incidence is not well known.[1]

The following review will broadly cover the pathophysiology of PH in the setting of HF, but will primarily focus on its recognition, accurate diagnosis and associated clinical outcomes in the context of RVD. Epidemiology and in depth discussion of the pathobiology of PH in the setting of LHD as well as treatment options are the subject of other reviews.[2,3]

Pathophysiology of PH–LHD

PH in the presence of LHD occurs in a variety of conditions, including left ventricular (LV) systolic dysfunction, diastolic dysfunction and valvular heart disease (VHD). What these conditions share in common is an elevated LAP that is transmitted backwards towards the pulmonary veins and capillaries. In response to chronically elevated pulmonary venous pressures, the pulmonary arteries vasoconstrict thereby increasing pulmonary vascular resistance (PVR). A subset of PH in LHD patients will experience pulmonary vascular remodeling similar to that seen in Pulmonary Artery Hypertesion patients (PAH; Fig 1).[4] It is unclear what drives

Statement of Conflict of Interest: see page 422.

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http://dx.doi.org/10.1016/j.pcad.2016.01.005
0033-0620/

Abbreviations and Acronyms

6MWT = six minute walk test

2DSTE = two-dimensional speckle tracking echocardiography

BNP = B-type natriuretic peptide

CMRI = cardiac magnetic resonance imaging

CO = cardiac outputCVP, central venous pressure

DPG = diastolic pressure gradient

EF = ejection fraction

FAC = fractional area change

HF = Heart Failure

HFpEF = Heart Failure with preserved ejection fraction

HFrEF = Heart failure with reduced ejection fraction

HT = heart transplantation

LAP = left atrial pressure

LHD = left heart disease

LV = left ventricle or ventricular

LVAD = left ventricular assist device

LVEDP = left ventricular end diastolic pressure

LVEF = left ventricular ejection fraction

mPAP = mean pulmonary arterial pressure

MRI = magnetic resonance imaging

NO = nitric oxide

NYHA = New York Heart Association

PA = pulmonary artery or arterial

PAH = pulmonary arterial hypertension

PAP = pulmonary arterial pressure

PASP = pulmonary artery systolic pressure

PCWP = pulmonary capillary wedge pressure

PH = pulmonary hypertension

this vascular remodeling, but heightened responses of the pulmonary endothelium,[5] varying functionality of nitric oxide (NO) pathways leading to a loss of NO,[6] and altered levels of circulating endothelin have all been proposed as mechanisms.[7]

Pulmonary venous hypertension (PVH) or **PH due to LHD** is most accurately measured by invasive hemodynamic monitoring during right heart catheterization (RHC). It is defined as a mean PAP (mPAP) greater than 25 mm Hg in the presence of a pulmonary capillary wedge pressure (PCWP) greater than 15 mm Hg or LV end diastolic pressure (LVEDP) greater than 18 mm Hg at rest, irrespective of cardiac output (CO). Hemodynamic assessment allows for the differentiation of PVH (WHO II), from other forms of PH (WHO Class I, III, IV and V), which are due to PAH, lung disease and/or hypoxemia, chronic thromboembolic disease, or multifactorial mechanisms, respectively. In these forms of PAH, the PCWP must be by definition less than 16 mm Hg. Other hemodynamic parameters which are assessed during RHC, include the following: **transpulmonary gradient** (**TPG**) which is defined as the mPAP minus the PCWP, and is normally less than 10 mm Hg; **PVR** which is equal to the TPG/CO and is less vulnerable to changes in CO; and the **diastolic pressure gradient** (**DPG**) which is the difference between the PA diastolic pressure and the PCWP (normal <7 mm Hg). The DPG is the least flow-dependent measurement, and has been proposed as the main classifier of PH due to LHD.[8] In typical cases of PH due to LHD, the PVR is less than 3 Woods units and the DPG is less than 7 mm Hg. Normal values as well as those encountered in other PH scenarios are outlined in Table 1.

Shortcomings of terminology in PH due to LHD

Multiple terms have been coined to describe PH in LHD. These include: 1) reactive PH; 2) fixed or irreversible PH; 3) PH "out of proportion" of LHD; and 4) mixed or combined precapillary and post capillary PH.[4] Since there is no accepted definition of what "out of proportion" truly means, its presence may be subjectively interpreted leading to variable clinical management. The lack of a clear definition may preclude some patients from receiving advanced therapies, such as heart transplantation (HT) and left ventricular assist device (LVAD) therapy, which are often contingent upon strict PVR criteria for eligibility. Furthermore, corrective left heart valve surgery may be withheld in the assumed presence of irreversible or fixed PH. Finally, some may be compelled to prescribe pulmonary vasodilators which are indicated for PAH, but not established for use in PH due to LHD due to mixed study results.[5–8] Of the four terms mentioned here, "combined precapillary and post capillary PH" best reflects underlying pathophysiology, and PVR and RV performance have been proposed as the central unifying themes by which PH patients are classified.[9]

LHD: HFrEF and HFpEF

PH frequently develops in the setting of clinical HF, and its prevalence is similar across the full range of LV ejection fraction (LVEF).[9,10] In the case of HFrEF, the remodeled LV fills with a higher volume and pressure leading to elevations in LV end-diastolic pressure (LVEDP) and PCWP by way of passive congestion. There exists a direct, linear correlation between PCWP and PAP, but one cannot estimate the extent of PH based on a given PCWP alone.[11,12] In addition to increases in pulmonary vascular tone, a key determinant of PH in the setting of LV systolic dysfunction is the extent of functional mitral regurgitation rather than EF alone.[13] In the case of HFpEF, LV hypertrophy, fibrosis or infiltration leads to an upward and leftward displacement of the LV EDP–volume relationship, whereby the LV fills at a higher pressure for a similar volume as compared to normal hearts. The clinical syndrome of HFpEF may be under recognized due to its heterogeneous clinical phenotypes, but is frequently seen in elderly women with systemic hypertension, coronary artery disease and obesity.[14]]

Definitions and pathophysiology of RVD

Evaluating RV function independent of LV function has remained challenging due to the limitations encountered in imaging the RV's complex geometric shape and the performance of proper, dynamic hemodynamic assessment.[15] Even