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iREVIEW

STATE-OF-THE-ART PAPER

Pulmonary Hypertension in Valvular Disease

A Comprehensive Review on Pathophysiology to Therapy From the HAVEC Group

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ABSTRACT

Pulmonary hypertension (PH) is a classic pathophysiological consequence of left-sided valvular heart disease (VHD). However, as opposed to other forms of PH, there are relatively few published data on the prevalence, impact on outcome, and management of PH with VHD. The objective of this paper is to present a systematic review of PH in patients with VHD. PH is found in 15% to 60% of patients with VHD and is more frequent among symptomatic patients. PH is associated with higher risk of cardiac events under conservative management, during valve replacement or repair procedures, and even following successful corrective procedures. In addition to its usefulness in assessing the presence and severity of VHD, Doppler echocardiography is a key tool in diagnosis of PH and assessment of its repercussion on right ventricular function. Assessment of pulmonary arterial pressure during exercise stress echocardiography may provide additional prognostic information beyond resting evaluation. Cardiac magnetic resonance is also useful for assessing right ventricular geometry and function, which provide additional prognostic information in patients with VHD and PH.
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Pulmonary hypertension (PH) related to left heart disease represents group 2 of the new clinical classification of PH (1), and subgroup 2.3 is specifically dedicated to valvular heart disease (VHD). VHD is a frequent etiology of PH, which may result from multiple mechanisms such as an increase in pulmonary vascular resistance, pulmonary blood flow, or pulmonary venous pressure. The chronic rise in pulmonary arterial pressure (PAP) often leads to right ventricular (RV) pressure overload and subsequent RV failure. When present, PH is a marker of poor outcome in VHD. Assessment of the presence and severity of PH thus has an important role in the risk stratification and therapeutic management of VHD.

In this paper, we review all relevant studies reporting mechanism, prevalence, and impact on outcomes of PH in patients with left-sided VHD. The final selection of discussed studies was based on the authors' consensus regarding robustness of data, sample size, and quality of methodology.

DEFINITION

Definitive diagnosis of PH related to VHD is based on the following criteria: mean PAP ≥25 mm Hg (2)

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

AVR = aortic valve replacement

LA = left atrial/atrium

LV = left ventricular/ventricle

MR = mitral regurgitation

MS = mitral stenosis

PAP = pulmonary arterial pressure

PCWP = pulmonary capillary wedge pressure

PH = pulmonary hypertension

RA = right atrial

RV = right ventricular/ventricle

TR = tricuspid regurgitation

VHD = valvular heart disease

together with an abnormally high pulmonary capillary wedge pressure (PCWP) >15 mm Hg or left ventricular (LV) end-diastolic pressure >18 mm Hg in the context of significant VHD. When pulmonary venous congestion is the main determinant of PH, PH is named isolated post-capillary PH or pulmonary venous hypertension. In this case, the transpulmonary pressure gradient is <7 to 10 mm Hg and the pulmonary vascular resistance is <1.5 Wood Units. In the more advanced stage of the disease, combined post-capillary and pre-capillary PH can be observed (PCWP >15 mm Hg and transpulmonary pressure gradient ≥7 to 10 mm Hg or pulmonary vascular resistance >1.5 Wood Units) (3). This form of PH is considered "out of proportion" to the LV filling pressure and results from a mixed pathophysiology (passive venous transmission, reversible pulmonary arterial vasoconstriction, fixed pulmonary vascular remodeling).

PATHOPHYSIOLOGY

An increase in LV filling pressure and left atrial (LA) pressure leads to a passive rise in backward pressure of the pulmonary vein (**Figure 1**). Persistently elevated pulmonary venous pressure can favor fragmentation of the structure and result in "alveolar-capillary stress failure," accompanied by capillary leakage and acute alveolar edema. This acute phase is completely reversible, but long-term persistence of high pulmonary venous pressure may induce some degree of irreversible remodeling of the alveolar-capillary membrane, with excessive deposition of type IV collagen. In addition, chronic elevated pulmonary venous pressure progressively and passively increases PAP and concomitantly produces pathological changes in pulmonary veins (**Figure 1**) and arteries, leading to increased pulmonary vascular resistance (3). The pathophysiology of PH in VHD thus involves progressive structural alteration of the pulmonary vascular bed mediated by the potent vasoconstrictor endothelin-1 (4). An increase in pulmonary-arterial vasoconstriction and systolic PAP results into RV dilation and hypertrophy. The RV failure is associated with tricuspid annulus dilation and an increase in tricuspid regurgitation severity, which further acerbates RV dysfunction. At the decompensated phase, systolic PAP can decrease despite the increase in pulmonary vascular resistance, due to the fall in RV stroke volume related to advanced RV failure.

After treatment, the reversibility of PH depends on the type, severity, and chronicity of VHD, as well as the underlying pathophysiological adaptations. For instance, in mitral stenosis (MS), a rapid decrease in PAP is observed after relief of the stenosis, whereas a longer time could be required in other VHDs, especially when PH is linked to volume overload, as in mitral regurgitation (MR).

DIAGNOSTIC WORK-UP

Distinctive clinical signs and symptoms of left-sided VHD PH are orthopnea and paroxysmal nocturnal dyspnea, which are generally not features of other types of PH (5). However, patients can remain asymptomatic for a long time, which often delays the diagnosis. Signs of RV failure, such as peripheral edema, ascites, and syncope, are frequently observed at an advanced stage of the disease. Clinical tests frequently reveal findings suggestive of left-sided VHD PH: presence of significant VHD; pulmonary vascular congestion, pleural effusion, or pulmonary edema on chest x-ray or computed tomography; and LV/LA hypertrophy on electrocardiogram.

Although current European guidelines state that Doppler echocardiography does not measure PAP but gives only an estimate of it and that right heart catheterization is mandatory for the confirmation of a PH diagnosis, echocardiography remains key for the differential diagnosis and evaluation of consequences of PH and has a central role in the assessment of VHD. Furthermore, in this specific clinical setting and in the likely diagnosis of PH using echocardiography (**Table 1**), the requirement of invasive measurement of PAP could be debated. Nuclear imaging has little use in this setting except to rule out ischemic heart disease, detect viable myocardium, and evaluate ventricular function. Similar information can be obtained with cardiac magnetic resonance, the main role of which is to evaluate the consequences/causes of VHD. In some cases, invasive hemodynamic evaluation with right heart catheterization is required to confirm the diagnosis because echocardiography often underestimates the systolic PAP and does not provide an accurate assessment of PCWP (or mean PAP).

RESTING ECHOCARDIOGRAPHY. In patients with confirmed or suspected PH, echocardiography is helpful for: 1) detection of increased right chamber pressure; 2) evaluation of RV changes as a consequence of increased afterload; 3) assessment of LV size and function; and 4) measurement of systolic PAP.

PH can be reasonably excluded when the following parameters are within the normal range or absent (**Table 1**, **Figure 2**) (6–8): LV and RV size and function