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Pulmonary Hypertension Associated With Left Heart Disease: Characteristics, Emerging Concepts, and Treatment Strategies

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Abstract Left heart disease (LHD) represents the most common causes of pulmonary hypertension (PH). Whether caused by systolic or diastolic dysfunction or valvular heart disease, a hallmark of PH associated with LHD is elevated left atrial pressure. In all cases, the increase in left atrial pressure causes a passive increase in pulmonary pressure. In some patients, a superimposed active component caused by pulmonary arterial vasoconstriction and vascular remodeling may lead to a further increase in pulmonary arterial pressure. When present, PH is associated with a worse prognosis in patients with LHD. In addition to local abnormalities in nitric oxide and endothelin production, gene modifiers such as serotonin polymorphisms may be associated with the pathogenesis of PH in LHD. Optimizing heart failure regimens and corrective valve surgery represent the cornerstone of the treatment of PH in LHD. Recent studies suggest that sildenafil, a phosphodiesterase-5 inhibitor, is a promising agent in the treatment of PH in LHD. Unloading the left ventricle with circulatory support may also reverse severe PH in patients with end-stage heart failure allowing candidacy to heart transplantation. (Prog Cardiovasc Dis 2011;54:154-167)

Keywords: Pulmonary hypertension; Left heart disease; Heart failure; Hemodynamics; Imaging; Diastolic heart failure and exercise

Left heart disease (LHD) represents the most common cause of pulmonary hypertension (PH).[1-4] Whether caused by systolic or diastolic dysfunction or valvular heart disease, a hallmark of PH associated with LHD is elevated left atrial pressure. When present, PH is usually associated with poor prognosis in patients with LHD. In this review, we will discuss the characteristics, emerging concepts, and treatment strategies in patients with PH in LHD. We will also review novel genetic insights on the pathogenesis of PH in LHD.

Methodology

A search was performed in MEDLINE and PubMed for original articles published between 1950 and 2011 that focused on left-sided PH and heart failure (HF). The search term used included "secondary pulmonary hypertension," "pulmonary hypertension," "heart failure," "post capillary pulmonary hypertension," "pulmonary remodeling," and "valvular heart disease." The search was limited to articles in English and French. For this review, we chose selected articles that reflect recent development in the field of PH in LHD.

Statement of Conflicts of Interest: see page 164.

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Abbreviations and Acronyms

BMPR = bone morphogenic protein receptor

ET = endothelin

HF = heart failure

HFpEF = heart failure preserved ejection fraction

HT = hydroxytryptamine

LHD = left heart disease

LVAD = left ventricular assist device

(M)PAP = (mean) pulmonary artery pressure

NO = nitric oxide

PAH = pulmonary arterial hypertension

PAP = pulmonary artery pressure

PCWP = pulmonary capillary wedge pressure

Definition and classification of PH in LHD

The classification of PH has gone through a series of changes since the first classification was proposed in 1973 at an international conference on primary PH endorsed by the World Health Organization (WHO).[3,4] Pulmonary hypertension is classified into 5 groups according to the pathophysiology and hemodynamic characteristics of PH (Table 1). Pulmonary hypertension associated with LHD represents group II PH in the Dana Point classification (2008).[3,4] Decades ago, mitral valve disease was the most common cause of PH in LHD.[5-8] Currently, HF with preserved ejection (HFpEF) and HF associated with systolic dysfunction are the most common causes of PH in LHD.[9-23]

Hemodynamically, left-sided PH is defined by a mean pulmonary artery pressure (MPAP) greater than 25 mm Hg in the presence of pulmonary capillary wedge pressure (PCWP) greater than 15 mm Hg (Table 2).[3,4] In most patients with HF, the increase in MPAP is proportional, and patients maintain a normal transpulmonary gradient (TPG; TPG <12 mm Hg).[3,4] However, in an estimated quarter to third of cases, the TPG is greater than 12 to 15 mm Hg, and pulmonary vascular resistance (PVR) is greater than 2.5 to 3 Wood units (Fig 1).[3,10,12] This is often referred to as "reactive" or "disproportionate" PH. In patients with elevated PVR, assessment of vasoreactivity may be especially useful when stratifying patients for heart transplantation.[12,24,25] Different agents have been used to assess vasoreactivity in HF including sodium nitroprusside, inhaled nitric oxide (NO), prostaglandin E_1, sildenafil, milrinone (intravenous or inhaled), and dobutamine.[2,12,26-31] Pulmonary hypertension is considered vasoreactive in patients with left HF if PVR can be lowered to less than 2.5 Wood units in the absence of systemic hypotension. This definition of vasoreactivity is different than the one used in pulmonary arterial hypertension (PAH; WHO group I PH); in WHO group I PAH, vasoreactivity is defined by consensus as a decrease in MPAP of at least 10 mm Hg to a level of 40 mm Hg or less, with either no change or an increase in cardiac output.[4,32] As can be seen, the terminology used in patients with left-sided PH may lead to some confusion because "reactive" PH refers to PH with elevation in PVR and not to the vasoreactive nature of PH in patients with LHD (Table 2).

Although PCWP is central to the diagnosis of left-sided PH, 2 caveats need to be emphasized. First, the actual pressure measurement of PCWP may vary within patients over time as a result of aggressive diuresis, leading to low PCWP at the time of right heart catheterization potentially missing a diagnosis of dynamic PH.[2,3,33] Second, some patients with PAH may have PCWP greater than 15 mm Hg due to ventricular interdependence (usually in the presence of marked right ventricular [RV] enlargement) and not necessarily secondary to an intrinsic left-sided process.[2,3,33]

Also, in recent years, much attention has been focused on exercise-induced PH with the underlying thought that exercise may unmask early diastolic dysfunction as well as

Table 1
Updated clinical classification of PH (Dana Point, 2008). Reprinted with permission from Simonneau et al.[3]

1. PAH
 1.1. Idiopathic PAH
 1.2. Heritable
  1.2.1. BMPRII
  1.2.2. Activin receptor-like kinase1 (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia)
  1.2.3. Unknown
 1.3. Drug- and toxin-induced
 1.4. Associated with:
  1.4.1. Connective tissue diseases
  1.4.2. HIV infection
  1.4.3. Portal hypertension
  1.4.4. Congenital heart diseases
  1.4.5. Schistosomiasis
  1.4.6. Chronic hemolytic anemia
 1.5. Persistent PH of the newborn
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. PH owing to LHD
 2.1. Systolic dysfunction
 2.2. Diastolic dysfunction
 2.3. Valvular disease
3. PH owing to lung diseases and/or hypoxia
 3.1. Chronic obstructive pulmonary disease
 3.2. Interstitial lung disease
 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
 3.4. Sleep-disordered breathing
 3.5. Alveolar hypoventilation disorders
 3.6. Chronic exposure to high altitude
 3.7. Developmental abnormalities
4. Chronic thromboembolic PH
5. PH with unclear multifactorial mechanisms
 5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis