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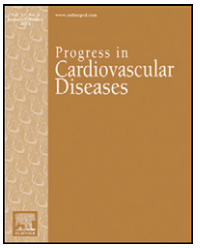

The Diagnostic Challenge of Group 2 Pulmonary Hypertension

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ABSTRACT

Pulmonary hypertension (PH) secondary to left heart diseases associated with an increased pulmonary venous pressure is the second of a total of five groups recognized in the classification of PH. Group 2 PH is the commonest form of PH, and is associated with high morbidity and mortality. The diagnosis of group 2 PH relies on a clinical probability assessment in which echocardiography plays a major role, eventually followed by the invasive measurements of a mean pulmonary artery pressure (mPAP) ≥25 mmHg and a wedged PAP (PAWP) >15 mmHg. This combination of mPAP and PAWP defines "post-capillary PH" (pcPH). Post-capillary PH is most often associated with a diastolic pressure gradient (DPG) or gradient between diastolic PAP and PAWP <7 mmHg and/or a pulmonary vascular resistance (PVR) ≤3 Wood units (WU), and is called isolated pcPH (IpcPH). Postcapillary PH with a DPG ≥7 mmHg and/or a PVR >3 WU is then combined pre- and postcapillary PH (CpcPH). Post-capillary PH is associated with a decreased survival in proportion to increased PAP and decreased right ventricular (RV) ejection fraction. CpcPH occurs in 12–13% of patients with pcPH. CpcPH is associated with pulmonary vascular remodeling and altered RV-arterial coupling. The prognosis of CpcPH is poor.

Clinical relevance of pulmonary hypertension (PH) on left heart disease (LHD)

A series of world symposiums on PH held every 5 years since the late 1990s have led to an internationally accepted classification in 5 groups: pulmonary arterial hypertension (PAH), PH on LHD with increased pulmonary venous pressure (PH-LHD), PH on lung diseases and/or hypoxia, chronic thromboembolic PH (CTEPH) and a PH on miscellaneous causes including glycogen storage diseases, hemolytic anemias, sarcoidosis and histiocytosis X.[1]

PH-LHD is by far the most common PH diagnosed in catheterization laboratories. The cause of PH-LHD is upstream transmission of increased pulmonary venous pressure on heart failure (HF) with either decreased left ventricular (LV) ejection fraction (EF) (HFrEF) or preserved LVEF (HFpEF) or mitral or aortic valvular diseases. There may be an addition factor of increased pulmonary arteriolar resistance. PH-LHD is a cause of decreased exercise capacity and systemic congestion, and is associated with a poor prognosis.[2,3]

The prevalence of PH-LHD has been reported to range from 20 to close to 100%, depending on whether the studies were

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Abbreviations and Acronyms

Ca = pulmonary arterial compliance

CpcPH = combined pre- and post-capillary PH

CO = cardiac output

CTEPH = chronic thrombo-embolic PH

dPAP = diastolic PAP

DPG = diastolic pulmonary pressure gradient

Ea = arterial elastance

Ees = end-systolic elastance

EF = ejection fraction

HF = heart failure

HFpEF = HF with preserved EF

HFrEF = HF with reduced EF

IpcPH = isolated post-capillary PH

IVC = inferior vena cava

LHD = left heart disease

LV = left ventricle

mPAP = mean PAP

PAP = pulmonary artery pressure

PAWP = wedged PAP

PH = pulmonary hypertension

PP = pulse pressure

PVR = pulmonary vascular resistance

RVOT = right ventricular outflow tract

sPAP = systolic PAP

SV = stroke volume

TPG = transpulmonary pressure gradient

community- or tertiary center-based, echocardiography or cardiac catheterization and cut-off values.[2,3] Most studies rely on systolic PAP (sPAP), which is easily obtained by echocardiography, increases in proportion to PAWP, and belongs to the definition of PH when recalculated as mPAP. There is a continuum of events or mortality as a function of increased sPAP in HFpEF, HFrEF as well as in HF on valvulopathies.[4–8] The common denominator to PH-LHD is thus a high PAWP.

What causes PH in HF?

Steady-flow hemodynamics

The pulmonary vascular resistance (PVR) equation states that mPAP is proportional to PAWP and cardiac output (CO) at any given functional state of the pulmonary resistive vessels:

$$PVR = (mPAP–PAWP)/CO$$

$$mPAP = PVR \times CO + PAWP$$

The inherent assumption is that at an unchanged CO and resistive vessel diameter, mPAP increases with any increase in PAWP in a one for one proportion.

However, pulmonary resistive vessels are known to be distensible, so that their size increases with trans-mural pressure. The diameter of in vitro-mounted pulmonary vessels increases by 2% per mmHg trans-mural pressure, and this natural compliance is remarkably constant over a wide range of animal species.[9] Linehan et al. modeled the pulmonary circulation taking into account the compliance of resistive vessels, and conceived an improved PVR equation incorporating a resistive vessel distensibility coefficient α[10]

$$PVR = \left[(1+\alpha.mPAP)^5 – (1+\alpha.PAWP)^5\right]/5.\alpha.CO$$

The equation rewritten as:

$$mPAP = \left[\left((1+\alpha PAWP)^5 + 5\alpha PVR.CO\right)^{1/5} – 1\right]/\alpha$$

shows that PAWP transmission upstream to mPAP in less than 1/1 and decreases with increasing flow. An interesting application of this equation is that α can be calculated from a set of PAP, PAWP and CO measurements.[9,11] Invasive and noninvasive studies have shown that α is normally between 1 and 2%/mmHg, higher in young healthy women compared to men, and decreased with aging or chronic hypoxic exposure.[11] The same improved PVR equation was used to show a decreased resistive vessel distensibility in early or latent pulmonary vascular disease.[12]

There has been no report yet on α calculations in HF. However, even if one assumes a decreased resistive vessel compliance because of increased distending pressure-induced stiffening, the upstream transmission of PCWP to mPAP may theoretically approach a one for one ratio.[13]

However, the above considerations are based on a simplification of the pulmonary circulation as a steady flow system, which cannot explain "out of proportion" PH commonly observed in HF[2,3] including patients with no persistent PH after successful cardiac transplantation.[14] An "out of proportion" HF-PH is defined by a >1/1 upstream transmission of increased PAWP to mPAP, and thus also the transpulmonary gradient (TPG), or the difference between mPAP and PAWP.

$$TPG = mPAP–PAWP$$

The limits of normal of the TPG are not exactly known. The upper limit of normal of the TPG was thought to be of 10 mmHg until the 1970s,[15] but later drifted upwards to 12 mmHg and, most recently, to 15 mmHg.[3] Higher than normal TPG in heart failure suggests pulmonary vascular remodeling and/or pulmonary vasoconstriction. This has been shown to be related to endothelial dysfunction with increased release of endothelin-1 and decreased release of nitric oxide (NO) and prostacyclin (PGI_2), causing a progressively less reversible increase in PVR.[2,16]

Pulsatile-flow hemodynamics

Another yet even more common cause of increased TPG is related to the natural pulsatility of the pulmonary circulation. An increase in PAWP decreases pulmonary arterial compliance (Ca) calculated as stroke volume (SV) divided by pulse pressure (PP), ie., the difference between sPAP and diastolic PAP (dPAP).

$$Ca = SV/PP$$

A decrease in Ca increases the TPG, and this effect is increased at larger SV. This was initially modeled by Harvey et