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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Pulmonary Hypertension in Heart Failure

Pathophysiology, Pathobiology, and Emerging Clinical Perspectives

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ABSTRACT

Pulmonary hypertension is a common hemodynamic complication of heart failure. Interest in left-sided pulmonary hypertension has increased remarkably in recent years because its development and consequences for the right heart are now seen as mainstay abnormalities that begin in the early stages of the disease and bear unfavorable prognostic insights. However, some knowledge gaps limit our ability to influence this complex condition. Accordingly, attention is now focused on: 1) establishing a definitive consensus for a hemodynamic definition, perhaps incorporating exercise and fluid challenge; 2) implementing the limited data available on the pathobiology of lung capillaries and small arteries; 3) developing standard methods for assessing right ventricular function and, hopefully, its coupling to pulmonary circulation; and 4) searching for effective therapies that may benefit lung vessels and the remodeled right ventricle. The authors review the pathophysiology, pathobiology, and emerging clinical perspectives on pulmonary hypertension across the broad spectrum of heart failure stages. (J Am Coll Cardiol 2017;69:1718–34) © 2017 by the American College of Cardiology Foundation.

These studies have revealed that it is the disturbance of the pulmonary circulation that is the center of the problem of congestive failure.
—Parker and Weiss (1)

Pulmonary hypertension (PH) in heart failure (HF) is common, pathophysiologically relevant, and highly prognostic (2). It is now clear that abnormalities in pulmonary hemodynamic status occur beginning in the early stages of HF and may be detected even in patients who are optimally treated. There are, however, gaps in knowledge and limitations in treatment that represent the background content for the present State-of-the-Art paper.

HISTORICAL NOTES

HF has long been known to affect the pulmonary circulation (PC). Early studies performed in the 1930s focused on mitral stenosis (1). A histological profile of the effects of PH on the long-standing increase in pulmonary venous pressure was defined and consisted of arteriolar remodeling with various combinations of medial hypertrophy, intimal proliferation, adventitial thickening, microthrombi, rarely with fibrinoid necrosis and never with plexiform lesions, venular remodeling, mainly with increased muscularization, dilated and muscularized lymphatics, thickened alveolocapillary membranes, and hemosiderosis (3,4). Typical arteriolar and alveolocapillary changes are illustrated in **Figure 1** (left). In 1945, Cournand et al. (5) performed the first right heart catheterization in a patient with severe mitral stenosis. As shown in the upper right of **Figure 1**, pulmonary artery (PA) and right ventricular (RV) pressure curves looked similar because of a wide pulmonary pulse, and both presented with late

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systolic peaking of pressure. "Ventricularization" and late systolic peaking of the PA pressure (PAP) curve have since been recognized as features of advanced pulmonary vascular disease and marked increase in RV afterload (5). Since the 1950s, invasive measurements of the PC have become part of catheterization laboratories' routines, documenting that PAP increases either as an effect of high pulmonary blood flow, such as in left-to-right cardiac shunts or hyperkinetic states, or as an increase in left atrial pressure (LAP), as in mitral stenosis and left ventricular (LV) failure. In 1958, Wood (6) proposed a hemodynamic classification of PH in which a pathological increase in mean PAP (mPAP) was "passive" (rise in LAP), "hyperkinetic" (increase in cardiac output [CO]), or caused by an excessive pulmonary vascular resistance (PVR) due to obstruction (thrombosis), obliteration (decreased pulmonary vascular capacity), or constriction. The frame of this classification corresponded to the PVR equation: $PVR = (mPAP - LAP)/CO$, which can be rewritten as $mPAP = PVR \times CO + LAP$.

Wood catheterized 60 healthy volunteers to determine the limits of normal and found that mPAP never exceeded 20 mm Hg, which has been repeatedly confirmed since then (7).

With the validation of LAP measurements by a PA wedge pressure (PAWP) in the early 1950s (8), it became possible to generate a complete set of pulmonary hemodynamic measurements only by right heart catheterization. Exercise stress measurements were implemented to disclose latent PH at rest, as illustrated in **Figure 1** (lower right), showing brisk increases in mPAP and PAWP with exercise from near normal measurements at rest (6). For many years since then, knowledge of PH in HF has been anecdotal and limited to a few studies, primarily involving patients with valvular heart disease and candidates for heart transplantation (stage D). Most recently, PH has become an upfront topic of interest, with its pathophysiology a key target of therapy from earlier HF stages (B to C), which are categorized into 2 phenotypes according to whether LV ejection fraction (EF) is preserved (HF with preserved EF [HFpEF]) or reduced (HF with reduced EF [HFrEF]), and related comorbid disorders (**Figure 2**).

PC: HEMODYNAMIC DETERMINANTS AND IMPLICATIONS IN HF

At variance with the systemic circulation, which combines a resistive and capacitive load that can vary (at least in part) independently of each other, the PC shows a more equally distributed resistance and compliance over the whole arterial small vessel system. This peculiar distribution is unaltered by PH and results in PVR and pulmonary artery compliance (PAC) (i.e., CO/pulse pressure) usually evolving together, but in opposite directions, and thus PVR and PAC are inversely related. Thus, the product of PVR and PAC (resistance [R] and compliance [C] time) is nearly constant (2).

Reduced PAC occurs early as a consequence of the PAWP increase and mediates increased mPAP at any given level of PAWP, as initially modeled by Harvey et al. (9) in the early 1970s and recently revisited with focus on HF by Tedford et al. (10). This is illustrated in **Figure 3** for patients with chronic increase in PAWP versus normal (**Figure 3A**) or patients with acutely increased exercise PAWP (**Figure 3B**). A reduction in PAC due to increased PAWP would enhance RV afterload by elevating the pulsatile load relative to the resistive load, thereby contributing to RV dysfunction.

Changes in PVR occur later than PAC in the natural history of the disease, and reasons for abnormal PVR at the small-vessel level include not only remodeling but also vasoconstriction and endothelial dysfunction, which affect vessel distensibility and PVR calculation.

Indeed, the PVR equation rests on the assumptions that the pulmonary vascular pressure-flow relationship is linear and crosses the origin and that LAP is transmitted upstream to mPAP in a 1:1 manner (11). However, the pulmonary "resistive" vessels, which are distal in the pulmonary arterial tree, are distensible in physiological conditions (11,12). The diameter of in vitro mounted pulmonary vessels increases by 2%/mm Hg transmural pressure, which is remarkably constant over a wide range of animal species (12). Linehan et al. (13) modeled the PC, taking into account the distensibility of the resistive vessels, and conceived an improved PVR equation incorporating a resistive vessel distensibility coefficient α: $TPVR = [(1 + \alpha \times mPAP)^5 - (1 + \alpha \times LAP)^5]/^5 \times \alpha \times CO$, where TPVR is total PVR, or mPAP/CO. This equation rewritten as $mPAP = \{[(1 + \alpha LAP)^5 + 5\alpha TPVR \times CO]^{1/5} - 1\}/\alpha$ shows that LAP transmission upstream to mPAP is <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

ABBREVIATIONS AND ACRONYMS

ATPase = adenosine triphosphatase
CO = cardiac output
CpcPH = combined pre- and post-capillary pulmonary hypertension
DPG = diastolic pressure gradient
Ea = arterial elastance
EDV = end-diastolic volume
Ees = end-systolic elastance
EF = ejection fraction
ESP = end-systolic pressure
ESV = end-systolic volume
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
IpcPH = isolated post-capillary pulmonary hypertension
LAP = left atrial pressure
LV = left ventricular
mPAP = mean pulmonary artery pressure
NO = nitric oxide
PA = pulmonary artery
PAC = pulmonary artery compliance
PAH = pulmonary arterial hypertension
PAP = pulmonary artery pressure
PAWP = pulmonary artery wedge pressure
PC = pulmonary circulation
PH = pulmonary hypertension
Pmax = maximum pressure
PVR = pulmonary vascular resistance
RV = right ventricular
sPAP = systolic pulmonary artery pressure
SV = stroke volume
TAPSE = tricuspid annular plane systolic excursion
TPG = transpulmonary gradient
TPVR = total pulmonary vascular resistance