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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.

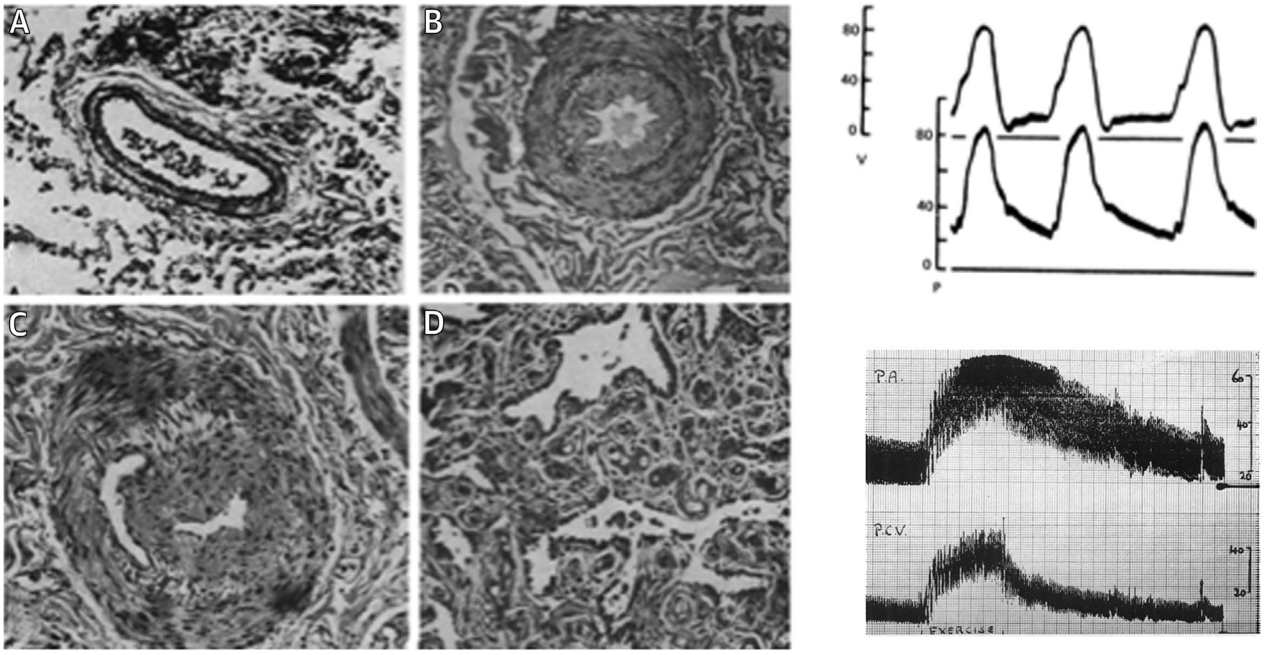
Changes in PVR occur later than PAC in the natural history of the disease, and reasons for abnormal PVR at the small-vessel level include not only remodeling but also vasoconstriction and endothelial dysfunction, which affect vessel distensibility and PVR calculation.

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

FIGURE 1 Pulmonary Hypertension in Heart Failure: Historical Findings on Histopathology and Hemodynamic Status



(Left) Lung histopathology from patients with mitral stenosis and pulmonary hypertension (PH). **(A)** Normal arteriole. **(B)** Medial hypertrophy with intimal and adventitial proliferation. **(C)** Recanalized fibrotic thrombus. **(D)** Thickened alveolar-capillary membrane with fibrosis and epithelial alveolar and endothelial capillary proliferation. Reprinted with permission from Tandon and Kasturi (4). **(Top right)** Right ventricular **(top)** and pulmonary arterial **(bottom)** pressure tracings in a patient with PH and mitral stenosis. The right ventricular pressure wave shows a sharp initial upstroke, followed by a short plateau and a late systolic rise. The pulmonary artery pressure (PAP) curve shows a wide pulse pressure and late systolic peaking. Reprinted with permission from Cournand et al. (5). **(Bottom right)** PAP and pulmonary artery wedge pressure (PAWP) in a patient with mitral stenosis at rest and at exercise. Exercise induces an increase in cardiac output (not shown) and parallel increases in PAP and PAWP. Reprinted with permission from Wood (6).

measurements (12). Invasive and noninvasive studies have shown that α calculated in this way is normally between 1% and 2%/mm Hg, higher in young, healthy women compared with men, and is decreased with aging or chronic hypoxic exposure (14). The same improved PVR equation was recently used to show reduced resistive vessel distensibility in early or latent pulmonary vascular disease (15). There has been just 1 report on α calculations in HF and in pulmonary arterial hypertension (PAH). On average, α moderately decreased to 0.8% to 0.9%/mm Hg in patients with HFpEF or HFrEF and 1.4%/mm Hg in control subjects (16). Interestingly, α was positively correlated with RV EF, independently of predicted peak oxygen uptake and cardiovascular mortality, and improved with sildenafil therapy (16).

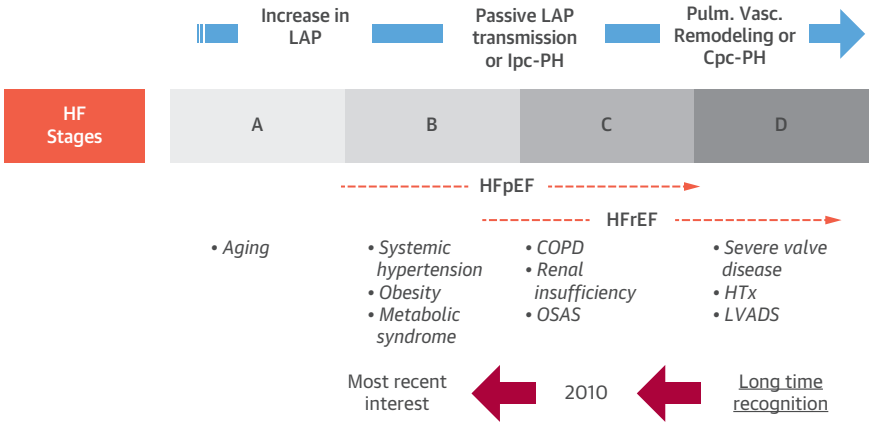
Assuming an even more decreased resistive vessel distensibility in HF caused by the extensive arteriolar and alveolocapillary remodeling, the upstream transmission of PAWP to mPAP may eventually approach a 1:1 ratio (11).

These considerations are on the basis of a simplification of the PC as a steady flow system. Indeed, this model cannot explain a disproportionate (>1:1) increase in mPAP with respect to PAWP in patients with HF with no evidence of pulmonary vascular remodeling. Accordingly, the pulsatility of the PC and vasoconstriction play a major role in changes in the transpulmonary gradient (TPG; mPAP – PAWP) and its normalization after cardiac transplantation (17). TPG normal limits are not yet exactly defined. Until the 1970s, the identified upper cutoff was 10 mm Hg (18), which has more recently drifted to 15 mm Hg.

As PVR is actually normalized for blood flow, its use may appear more advantageous compared with TPG. Nonetheless, any error in the determination of CO will affect the derived value of PVR. This can become quite significant in low-output states, as often observed in HF.

When vessel distensibility significantly decreases, it also becomes a mediator of changes in the diastolic pressure gradient (DPG) (diastolic pulmonary

FIGURE 2 Pulmonary Hypertension and its Clinical "Inducers" According to Heart Failure Stages



For many years, pulmonary hypertension (PH) has been considered to have clinical meaning in advanced heart failure (HF) stages, whereas more recently, interest is focused on earlier stages and corresponding comorbid precipitating factors. COPD = chronic obstructive pulmonary disease; Cpc = combined pre- and post-capillary; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTx = heart transplantation; Ipc = isolated post-capillary; LAP = left atrial pressure; LVADS = left ventricular assist devices; OSAS = obstructive sleep apnea syndrome.

pressure – PAWP). Indeed, although a preserved resistive vessel distensibility results in a decreased DPG, its loss results in an unchanged DPG at increased PAWP, as shown in **Figure 4** (11).

It is easy to predict that resistive vessel distensibility similarly affects the TPG at increased PAWP, which explains the variability of the TPG in HF, even when PAC is markedly reduced.

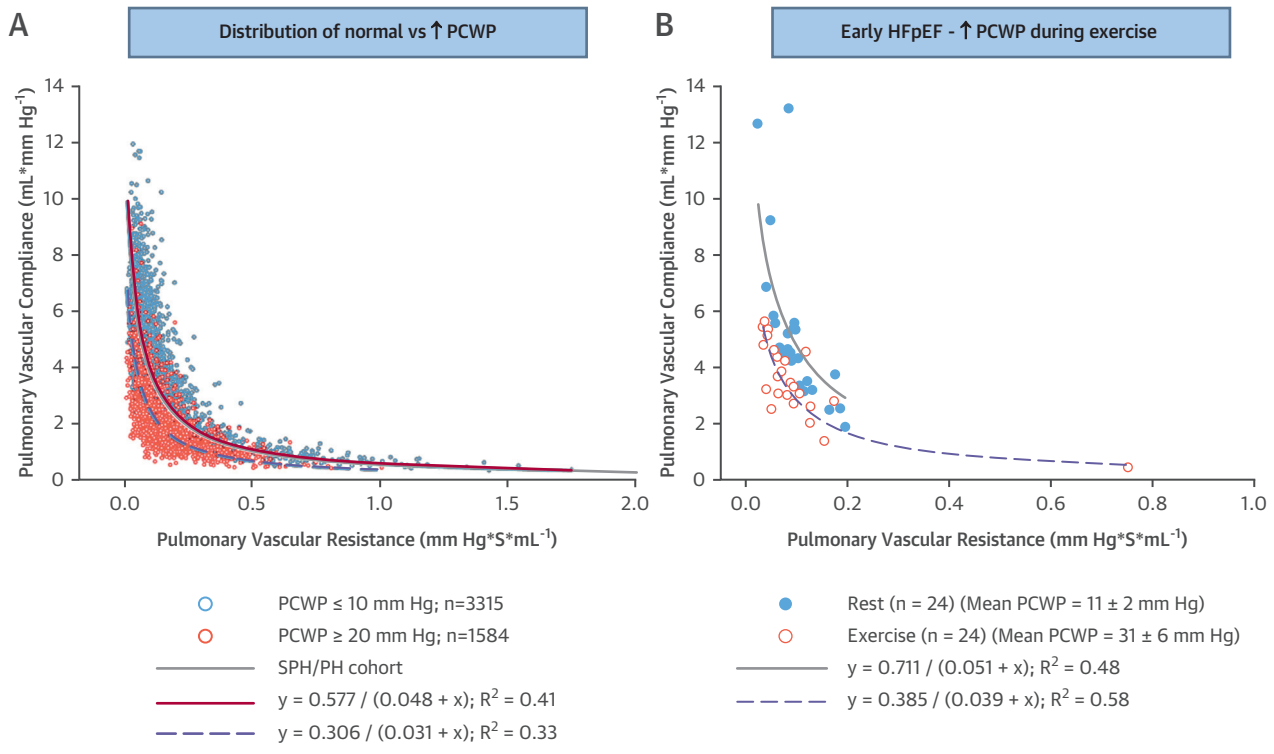
Of note, coexistence of mitral regurgitation becomes a further source of increased pulsatile loading and PH (19). Data on the true prevalence of PH in the presence of mitral regurgitation range from 23% to 73% in HFrEF (20), with a significantly lower rate in HFpEF (21). Exercise is the typical physiological condition that triggers dynamic mitral regurgitation and further increases in PH, which portends an unfavorable outcome, especially when RV failure coexists (22).

PATHOBIOLOGICAL CHANGES IN LUNG CAPILLARIES, ARTERIOLES, AND VEINS

At variance with noncardiac forms of PH, the typical manifestation of group 2 PH is pulmonary congestion due to pressure injury of the capillary wall, otherwise called stress failure, a process initially described by West and Mathieu-Costello (23) in a series of laboratory preparations. Stress failure disrupts the anatomic integrity of the alveolar-capillary unit and alters endothelial permeability, fluid filtration, and reabsorption. Alveolar flooding is the most impressive consequence of stress failure (23). When LAP elevation is less striking and long-lasting, true capillary remodeling occurs with associated alteration in gas exchange (24). The typical fluid overload of HF reproduced in experimental models by saline infusion 0.5 ml/min/kg for 180 min in the rabbit PA led to 44% fluid accumulation in the interstitial space, ultrastructural changes, and impairment of gas transfer (25). Edema induces activation of metalloproteinases that degrade matrix proteoglycan and alter the composition of the plasma membrane, causing increased endothelial membrane fluidity. The weakened tensile strength of the membrane potentiates endothelial stress failure (25). The pathophysiological correlates of alveolar-capillary stress failure in patients with cardiac disease have been poorly investigated. In a study of 53 patients with acute cardiogenic pulmonary edema, injury of the alveolar-capillary barrier was associated with increased levels of plasma pulmonary surfactant-associated proteins A and B, and tumor necrosis factor-α (26). Persistence of elevated levels of tumor necrosis factor-α after pulmonary edema resolution may reflect pulmonary inflammation and explains why fluid accumulation can persist despite resolution of hydrostatic stress failure.

Reversibility in the impaired biology of lung capillaries is uncertain. Experimental models of PH due to cardiac dysfunction have brought important insights. In a mouse model of PH and HFpEF with LV

FIGURE 3 Pulmonary Vascular Resistance-Compliance Relationships Obtained in a Large Dataset of Patients With Pulmonary Artery Hypertension of Different Etiologies

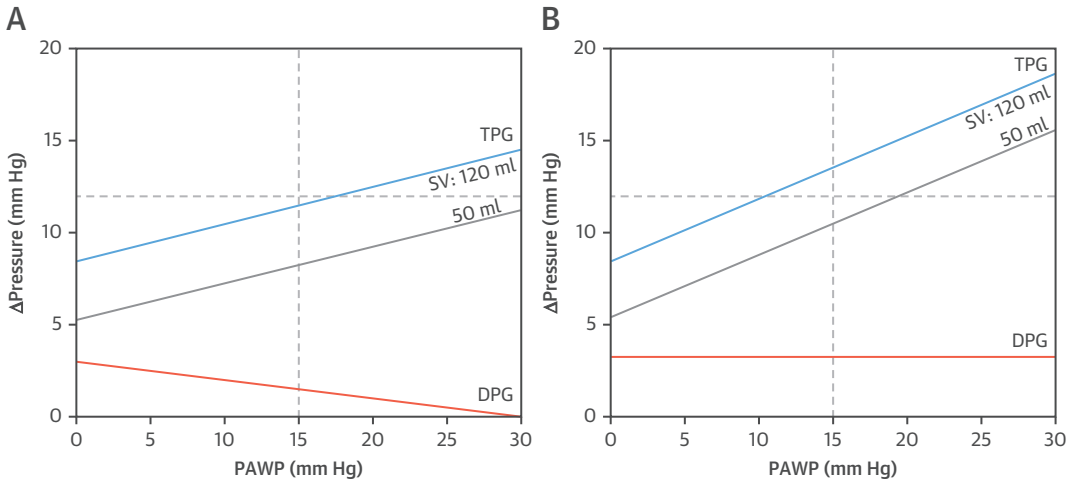


(A) The leftward shift relationship in patients with high pulmonary artery wedge pressure (PAWP) due to decreased pulmonary artery compliance. Interestingly, this leftward shift is also induced by an acute PAWP increase during exercise, even in the early stages of heart failure with preserved ejection fraction (HFpEF) **(B)**. Reprinted with permission from Tedford et al. (10). PCWP = pulmonary capillary wedge pressure; SPH = secondary pulmonary hypertension.

hypertrophy, the rise in LAP promoted impressive arteriolar remodeling and increased vascular oxidative stress, leukocyte infiltration, and lung fibrosis after 4 weeks (27). In addition, lung weight changes were due to tissue and vascular changes rather than extravascular lung water (27). These features are reminiscent of the extracellular matrix thickening and proliferation reported in patients with mitral stenosis and pulmonary venous pressure elevation (28,29), a process that might be protective against excessive fluid accumulation. Specifically, the increase in lung interstitial connective tissue associated with chronic capillary hydrostatic overload results in increased extravascular fluid storage attributable to increased production of an extracellular matrix component (mainly glycosaminoglycans) that has the potential to absorb and accommodate fluid in the interstitium. At least in cases of a subcritical persistent rise in LAP, this compensatory mechanism could prove beneficial by constraining fluid in the perivascular space without limiting gas diffusion (30).

An increase in collagen content typically occurs in post-capillary PH and is mediated by proliferation of myofibroblasts, termed interstitial contractile cells (31). Growth factors that can trigger proliferation are classical local growth factors, such as angiotensin II, endothelin-1, tumor necrosis factor-α, and especially transforming growth factor, which is a major inducer of epithelial-mesenchymal transition in the fibrotic lung (32). The caveolin family of proteins (Cav-1, Cav-2, and Cav-3), which are the main structural component of caveolar membranes surrounding the vesicular invaginations arising from plasma membranes, is seemingly involved in the remodeling process through hyperactivation of the Janus kinase/signal transducer and activator of transcription signaling cascade (33). In a mouse knockout of Cav-2, there is a significant thickening of alveolar septa, and in a post-myocardial infarction model, Cav-1 and Cav-2 expression is reduced to undetectable levels (34). Along with modifications in extracellular matrix composition and function, abnormalities in

FIGURE 4 Modeled Effects of Pulmonary Artery Wedge Pressure on the Transpulmonary Pressure Gradient or the Diastolic Pressure Gradient at 2 Extremes of Stroke Volume



Plots show that the diastolic pressure gradient (DPG) decreases **(A)** or not **(B)** depending on resistive vessel distensibility. At a high-normal stroke volume (SV) of 120 ml, the transpulmonary pressure gradient (TPG) reaches 12 mm Hg at a pulmonary artery wedge pressure (PAWP) of 15 mm Hg, and higher PAWPs are necessarily associated with higher TPGs **(B)**. With lower SV and persistent resistive vessel distensibility, the TPG may remain at 12 mm Hg at PAWPs up to 30 mm Hg **(A)**. Reprinted with permission from Naeije et al. (11).

endothelial function (35) and alveolar fluid reabsorption participate in the pathobiological derangement (36). Park et al. (37) found that lung microvascular endothelial cells exposed to cyclic mechanical strain in vitro released proinflammatory and profibrotic mediators, identifying a specific putative role for monocyte chemoattractant protein 1.

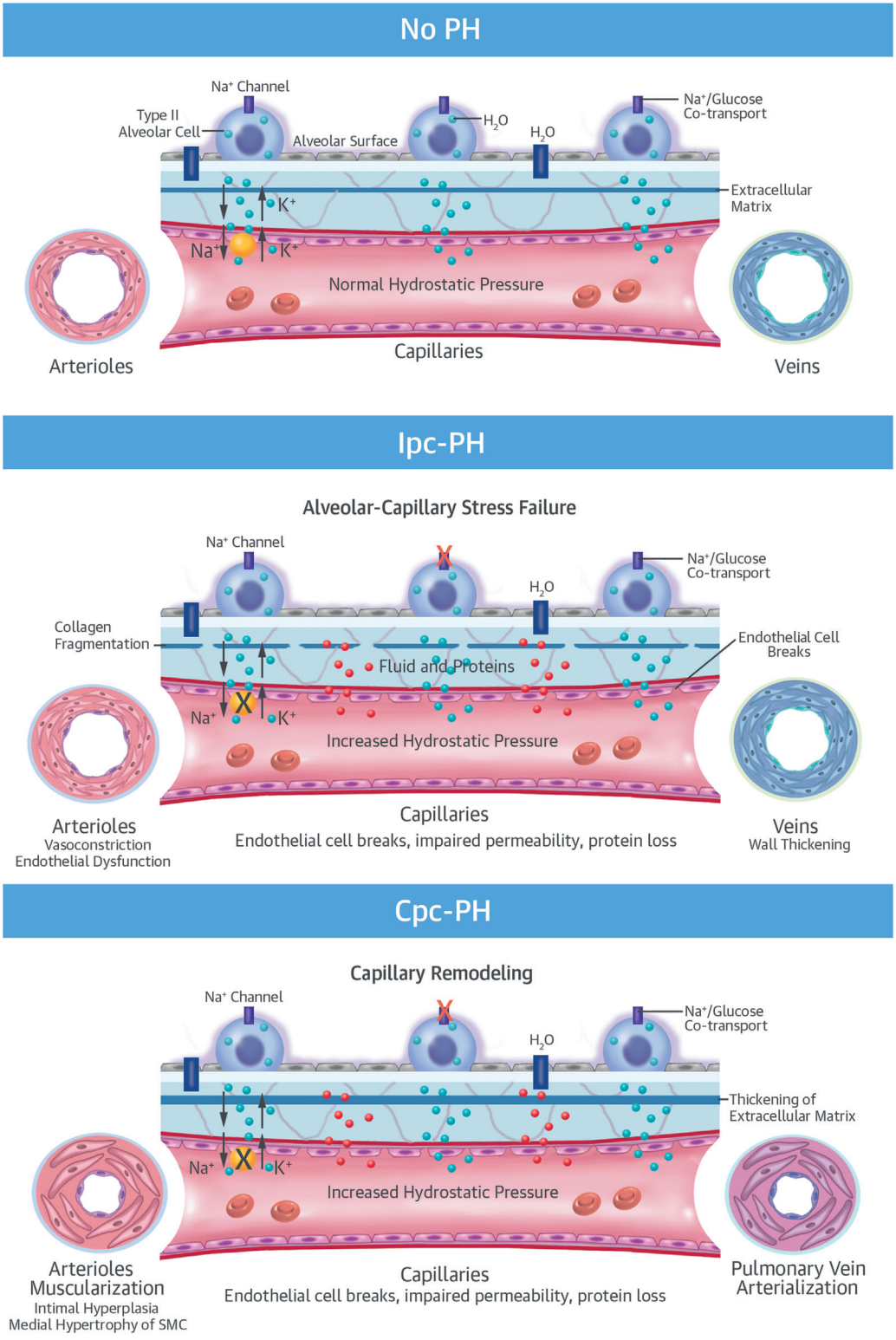
A recent gene ontology analysis performed in a sample of 165 patients with HF with PH revealed enrichment in genes related to cytoskeleton structure and immune function, with significant pathways including extracellular matrix, basement membrane, transferase activity, pre-ribosome structure, and major histocompatibility complex class II protein (38).

In the PC, the endothelium-mediated local control of vasomotility is primarily challenged by an imbalance between nitric oxide (NO) and endothelin-1 (39,40). Studies with blockade of NO synthesis have confirmed that endothelium-derived NO is a basic determinant of the baseline pulmonary vascular tone and a mediator of the dilating response to endothelium activation (41). In normal subjects, systemic infusion of NG-monomethyl-L-arginine, an analog of L-arginine that inhibits NO synthase, raises PAP, enhances pulmonary vasoconstriction (39), and inhibits the lung diffusion of carbon monoxide by lowering the alveolar-capillary membrane conductance (42). In patients with HF, infusion of NG-monomethyl-L-arginine in the pulmonary circuit causes dose-dependent vasoconstriction, which is partially reversed by acetylcholine (43). However, vessel dilation is refractory when the baseline pressure is elevated.

Despite the importance of pulmonary veins in normal lung vascular physiology, few data are available on venous pathobiological changes possibly associated with left-sided PH. In an elegant parallel study performed in rats and humans with HF, undergoing selected lung biopsies during LV assist device implantation and removal, Hunt et al. (44) detected overexpression of urokinase plasminogen activator in remodeled pulmonary veins and some degrees of so-called arterialization of the veins in patients with advanced PH, which could reverse after device removal.

ALVEOLAR FLUID CLEARANCE. Fluid clearance from alveoli to capillaries is a process of vital importance, especially in PH and HF. Sodium (Na^+) transport across the alveolar epithelium helps reabsorb fetal fluid (36), ensures proper thinness of the adult alveolar fluid (the so-called film), and keeps the alveolar space free of fluid, especially in pathological states, when alveolar permeability to plasma proteins is increased (24). The alveolar type II cell transport of Na^+ provides the major driving force for water removal from the alveolar space. After uptake, Na^+ is

CENTRAL ILLUSTRATION **Main Pathobiological and Functional Abnormalities in Alveoli, Capillaries, Small Arteries and Veins**



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Continued on the next page

pumped actively into the lung interstitium by the sodium-potassium (Na^+, K^+)-adenosine triphosphatase (ATPase). For optimal gas exchange, the fine mechanisms that control alveolar Na^+ and water metabolism are fundamentally involved. Although disorders in lung diffusion in cardiac patients have generally been referred to as alterations of endothelial and alveolar epithelial cells, experimental observations are also consistent with involvement of alveolar water metabolism (45). Interestingly, overexpression of the Na^+, K^+-ATPase α_1 subunit in rats by adenovirus gene transfer promotes increased fluid clearance. In the same model, Na^+ transport and alveolar water clearance in the presence of elevated LAP was not different from that in rats studied at normal LAP (46). Hypoxia, another common association with chronic HF, is also capable of inhibiting the alveolar Na^+, K^+-ATPase function and transalveolar fluid transport (47). These findings support the intriguing hypothesis that impaired Na^+, K^+-ATPase gene expression occurs during acute lung injury and provide evidence that the result of a pressure and/or a volume overload on the lung circulation is an increase in capillary permeability to water and ions and disruption of local mechanisms for gas exchange.

Overall, these structural and functional modifications of the alveolar-capillary membrane trigger an increased impedance to gas transfer (47). In HF, assessment of lung diffusion capacity by measuring the alveolar membrane conductance component enables quantification of the anatomic and functional integrity of the alveolar-capillary unit, which provides prognostic insights (48), and should likely receive more attention in the complex pathophysiological context of group 2 PH development (49) (**Central Illustration**).

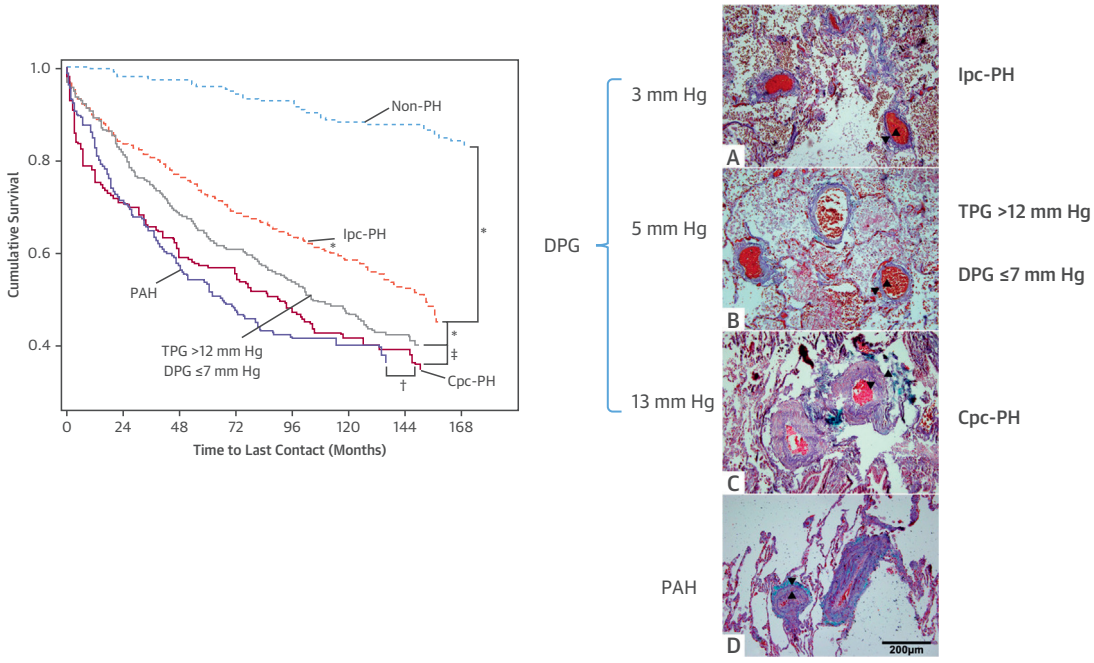
PULMONARY VASCULAR PRESSURE GRADIENTS

As discussed in part previously, there are 3 commonly used measures of out-of-proportion PH: TPG, DPG, and PVR, each of which increases definitively in the presence of pulmonary vascular remodeling (2,6,11,50). Nonetheless, although increases in TPG and PVR may also occur without true vascular remodeling, DPG might be a more sensitive and specific reflection of the condition. Despite the fact that PVR remains a cornerstone reference variable, some recent insights deserve consideration. The DPG was used in the 1970s in combination with PAWP, CO (or arteriovenous oxygen content difference), and blood pressure measurements in decision trees for the differential diagnosis of cardiac and pulmonary causes of acute respiratory failure (51). The normal upper limit of DPG was assumed to be 5 mm Hg (9), as derived from athletic young adults. The DPG was recently revisited by Gerges et al. (52) in a study of 2,056 patients with HF. PH, defined by mPAP >25 mm Hg, was diagnosed in 1,094 of these patients, a TPG >12 mm Hg was diagnosed in 490, and a combination of TPG >12 mm Hg and a DPG >7 mm Hg in 179 (16%). The survival of the patients with high TPG and DPG was very poor, comparable with that of untreated PAH. Some histopathologic examinations of the pulmonary small vessels in patients with both increased TPG and DPG have shown pulmonary vascular remodeling with medial hypertrophy, intimal thickening, and adventitial proliferation (**Figure 5**). From multivariate analysis, the DPG emerged as an independent predictor of survival, with a cutoff value of 7 mm Hg (52). These data, and refreshed pathophysiological reasoning, inspired a revision of definitions and terminology of PH on HF at

CENTRAL ILLUSTRATION Continued

No pulmonary hypertension (PH): Configuration of the 3-layer structure of the alveolar-capillary membrane. Fluid is continuously cleared from the alveolar surface by the Na^+ channels and Na^+-glucose co-transport system passively. Then the adenosine triphosphate (ATP) dependent Na^+-K^+ pumps "drain" fluid through the interstitium and the vascular bed. In between the alveolar surface and capillary there is the extracellular matrix with cellular attachments composed primarily by collagen type IV. Isolated post-capillary PH (IpcPH): This hemodynamic condition leads to a pathological increase in left atrial pressure (LAP), pulmonary artery wedge pressure (PAWP) and mean pulmonary artery pressure (mPAP) with pulmonary vascular resistance (PVR) and diastolic pressure gradient (DPG) still in the normal range. The increase in capillary hydrostatic pressure promotes some anatomic breaks in the endothelium and vascular wall and fluid swelling in the interstitium and in the alveoli. Along with fluid a certain amount of proteins may overcome the vascular barrier and carry in additional fluid clearance. In addition, some initial impairment in the alveolar surface continuous fluid reabsorption (by Na^+ Channels) and capillary Na^+-K^+ pumps may occur. Overall, these disruptive processes are resembled under the "alveolar capillary stress failure" definition and consists in a series of cellular and molecular changes described in the text. Small arteries exhibit endothelial dysfunction and vasoconstriction but no defined changes in the composition of small pulmonary arteries are detectable, the pulmonary veins already show some thickness and trend to arteriolarization. Molecular mechanisms involved in these processes are reported in the text. CpcPH: This hemodynamic stage is characterized by a further mechanical injury and progressive increase in PVR, DPG and mPAP. As protection toward the excessive fluid swelling from capillaries, a progressive thickening and collagen proliferation of the lamina densa occurs. This phenomenon protects against fluid swelling but compromise gas exchange diffusion for lengthening the path between air and red blood cell. The alveolar surface continuous fluid reabsorption and capillary Na^+-K^+ pumps activity become fully impaired. The venous system becomes fully arteriolarized and the small arteries exhibit a clear muscularization process and remodeling. Molecular mechanisms involved in these processes are reported in the text.

FIGURE 5 Survival Analysis and Capillary Histological Characterization in Group 2 Pulmonary Hypertension and Its Evolving Stages Compared With Nonpulmonary Hypertension and Pulmonary Arterial Hypertension



Kaplan-Meier survival curves **(A)** and related pathobiological changes in lung arterioles and capillaries **(B)** in group 2 pulmonary hypertension (PH) on the basis of diastolic pressure gradient (DPG) stages versus idiopathic precapillary pulmonary arterial hypertension (PAH) and non-PH subjects **(A)**. Data show that the greatest drop in mortality rate is observed between non-PH and isolated post-capillary PH (Ipc-PH). Combined pre- and post-capillary PH (CpC-PH) confers a mortality profile similar to pre-capillary PAH. Interestingly, anatomic changes in microvessels are observed since the earlier stages of Ipc-PH, with DPG <3 mm Hg. Adapted with permission from Gerges et al. (52). TPG = transpulmonary pressure gradient.

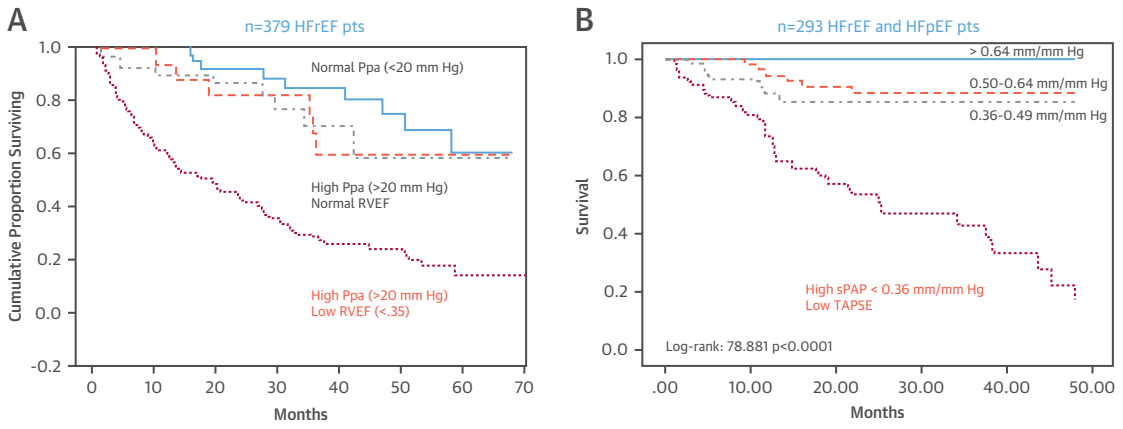
the Fifth World Pulmonary Hypertension Symposium, held in Nice, France, in 2013 (53). PH, defined by mPAP ≥25 mm Hg, was qualified as pre-capillary with PAWP ≤15 mm Hg and post-capillary with mean PAWP >15 mm Hg. Post-capillary PH was further divided into isolated post-capillary PH (IpcPH) with a normal DPG and combined pre- and post-capillary (CpcPH) with a DPG ≥7 mm Hg. Thus, the acronym CpcPH was proposed to replace the terms *out-of-proportion* PH and *reactive*.

Revisiting the DPG in clinical trials has stirred some controversy. Tampakakis et al. (54) recently reported that poor outcome in PH and HF is related to a low DPG. However, this is not entirely in contradiction with the study by Gerges et al. (52), who actually reported on flexible hazard ratio survival functions corrected for sex, age, ischemia, and creatinine clearance, which were bow shaped, with predictive power for either very low or high DPG (55). Thus, survival would be decreased in the case of either very low or higher than normal DPG. Very low DPG may occur in the case of a rapid rise in PAWP and a slower rise in diastolic PAP and mPAP related to preserved resistive vessel distensibility in acute or subacute HF. However, the lack of prediction of a high DPG in the study by Tampakakis et al. might be explained by a small proportion of patients with "true" pulmonary vascular disease in their database. Furthermore, RV function adaptation to afterload may matter more to prognosis than pulmonary pressure alone (56,57).

According to the debate generated, the 2015 European Society of Cardiology guidelines redefined CpcPH as a combination of DPG ≥7 mm Hg and/or PVR >3 Wood units (50). Although adding a PVR criterion makes sense, as the DPG is much smaller than PAP or the TPG (57), an isolated increase in PVR in HF with a normal DPG may erroneously double the prevalence of Cp-PH in HF (58). Defining CpcPH by a combination of a DPG ≥7 mm Hg and PVR >3 Wood units is probably the best option.

How common is CpcPH in HF? This was explored in a retrospective and prospective database of nearly 4,000 cardiac catheterizations for suspected PH or for valve replacements, percutaneous interventions, and

FIGURE 6 Heart Failure Patient Survival by Systolic Pulmonary Artery Pressure and Right Ventricular Function Categorization



Survival rates are grouped according to the coupling between mean pulmonary artery pressure (PAP) and right ventricular ejection fraction (RVEF) **(A)** and tricuspid annular plane systolic excursion (TAPSE) and systolic PAP (sPAP) **(B)**. Patients with a decreased RVEF and high sPAP and those with low TAPSE and high sPAP had the worst prognosis. Of note, invasive and echocardiography-derived measures provided the same prognostic profile definition over time. Reprinted with permission from Ghio et al. (56) **(A)** and Guazzi et al. (60) **(B)**. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; Ppa = pulmonary arterial pressure.

surgical procedures (59). HF was diagnosed in 30% to 50% of cases and PH in 50% to 80% of them. Approximately 20% of patients with PH met the CpcPH hemodynamic definition. The prevalence of CpcPH did not appear specific to HFpEF or HFrEF, which were almost equally distributed. Predictors of CpcPH were younger age and coexistent chronic obstructive pulmonary disease or valvular heart disease. The only echocardiographic variable discriminating between IpcPH and CpcPH was the ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic PAP (sPAP), an indicator of RV-to-PC coupling (60).

EXERCISE AND FLUID CHALLENGES

Assessing pulmonary hemodynamic status during exercise (61) or fluid loading (62) appear remarkable tools for the reproduction of symptoms, in-depth understanding of the pathophysiology, and detection of initial abnormal adaptations in hemodynamic status, typical of early stages of the disease (61). In this respect, an additional opportunity is the ability to uncover group 2 PH in patients with HFpEF with normal PAWP at rest (63,64). Despite this background, experts remain utterly cautious. European Society of Cardiology guidelines recommend against the use of exercise stress testing or volume loading because of insufficient evidence about the limits of normal and prognostic or therapeutic implications (50). However, the practice has been around since the early times of cardiac catheterization (6), and significant progress and information have been gained in recent years (61).

It is now well established that the upper limit of normal of mPAP during an incremental dynamic exercise challenge is 30 mm Hg at a CO <10 l/min, which corresponds to a TPVR (mPAP/CO) of 3 Wood units (65). The cause of higher than normal mPAP during exercise, or "exercise-induced PH," is either an upstream transmission of increased PAWP, as in HF, or an increase in PVR, as in pulmonary vascular disease, disturbed lung mechanics, or hypoxia (5,65). The differential diagnosis is most often clinically straightforward but must be established by precise measurement and interpretation of PAWP or LV end-diastolic pressure. The upper limit of normal of PAWP during exercise is generally thought to be between 15 and 20 mm Hg, but higher values can be recorded in older subjects (66). Some consider 20 mm Hg a reasonable upper limit of normal (67). However, a cutoff value of 25 mm Hg has been proposed for the diagnosis of HFpEF (61). Likewise, for mPAP, a flow-corrected measure may be more appropriate, but there has been no study specifically addressing this issue. As TPVR decreases during exercise by up to 25% (68), PAWP-CO slopes should not exceed 2 mm Hg/l/min, as observed in control groups of studies on exercise testing in HF (61).

Measurements of PAP and PAWP during exercise are technically challenging because of respiratory pressure swings. Although it would then seem preferable to average the reading of pulmonary vascular

pressure curves over several respiratory cycles (69), this is not the general practice (61,67). Guidelines recommend measurements at end-expiration at rest, but allow averaging over several respiratory cycles during exercise when respirophasic changes become excessive (50). This recommendation is ambiguous, because switching from one mode to the other remains undefined.

There has been also an ongoing debate about how to standardize a fluid challenge and what cutoff values for PAWP to consider. Fluid loading increases PAWP in healthy volunteers as a function of age, sex, amount infused, and infusion rate (62). Although there is some consensus to infuse 500 ml of saline in 5 to 10 min, some groups consider a PAWP of 15 mm Hg as a reasonable cutoff for a pathological response (64). However, a reanalysis of existing data in healthy subjects and accumulating clinical experience are drifting this cutoff value to 20 mm Hg or, more precisely, 18 mm Hg, as recently demonstrated in 212 patients referred for PH, challenged with 7 ml/kg of saline given in <5 min (70). Both exercise and fluid loading increase systemic venous return, but the net hemodynamic result may differ (71). Indeed, exercise promotes sympathetic nervous system activation, intrathoracic pressure changes, and mixed venous or even arterial hypoxemia. Fluid challenge may precipitate interstitial fluid accumulation, impaired gas diffusion, and irritation of J receptors (72). This will need further clarification.

RV DYSFUNCTION AND FAILURE

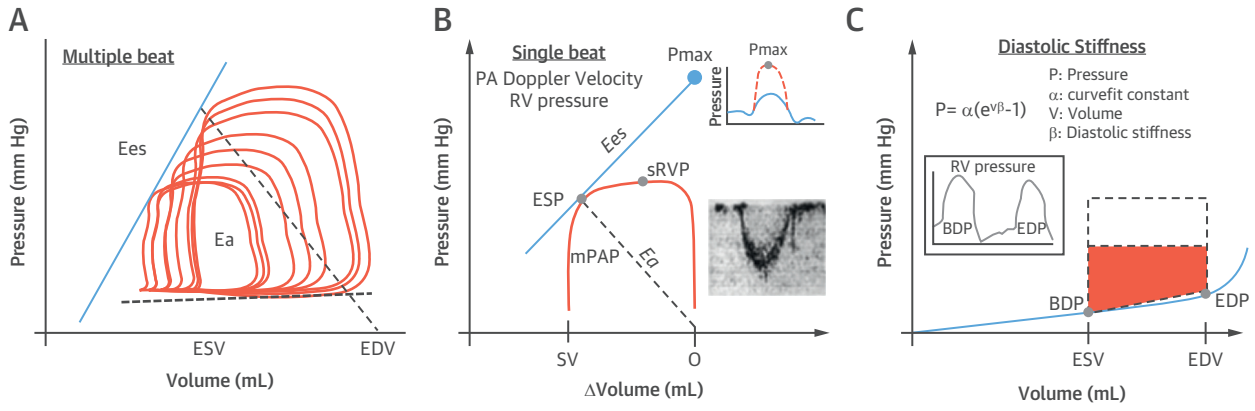
RV EF predicts exercise tolerance and survival in advanced HF (73). However, RV EF is inversely proportional to PAP; thus, this result could simply reflect the impact of increased PAP. PH has been repeatedly shown to be associated with decreased exercise capacity and shorter life expectancy in HF (22,73). The first study combining pulmonary hemodynamic status with RV EF and CO measurements was reported in 2001 in 377 consecutive patients with HF (56). Mean PAP and RV EF were inversely related; they independently predicted death or urgent heart transplantation at multivariate analysis. The prognosis of patients with PH and preserved RV EF was similar to that of patients without PH (**Figure 6A**). Similar prognostic curves were obtained in a more recent analysis when using TAPSE instead of RVEF and echocardiography-estimated sPAP (**Figure 6B**) (60).

Why is RV function a major determinant of outcome in HF? A main reason is ventricular interdependence, defined as the forces directly transmitted from one ventricle to the other through the myocardium and pericardium. As early as in 1910, Bernheim (74) had postulated that LV hypertrophy and dilation could compress the right ventricle and diminish its function. Only a few years later, Henderson and Prince (75) showed that the "Bernheim effect" could be reversed, as in an isolated cat heart preparation, pressure and volume loading of one ventricle decreased the output and function of the contralateral ventricle.

These pioneering studies mainly demonstrated a diastolic interaction (i.e., ventricular competition for filling space within an acutely indistensible pericardium). More recent studies pointed also to the importance of systolic interaction, by which contraction of one ventricle supports the contraction of the other. Measurements of ventricular pressure changes caused by sudden release of aortic or pulmonary constriction showed greater pressure coupling in right-to-left than LV-to-RV interaction (76,77). It is estimated that 20% to 40% of RV systolic pressure results from LV contraction and that 4% to 10% of LV systolic pressure results from RV contraction (78).

In addition to ventricular interdependence, the thin-walled flow-generator right ventricle is not designed to cope with brisk increases in PAP, as may occur because of upstream transmission of increased PAWP. However, a progressive increase in PAP allows the right ventricle to adapt by an increased contractility to match the increase in afterload and to maintain systemic oxygen transport adapted to metabolic demand. Failure to do so results in larger dimensions, systemic congestion, and decreased survival (79). Thus, the adaptation of the right ventricle to increased loading conditions is (very much as for the left ventricle) basically homeometric or systolic and becomes heterometric through dimension increase when systolic function fails (80,81). This has been demonstrated in various animal models of PH (81) and in patients with PAH or chronic thromboembolic PH (82). The gold standard of in vivo measured contractility is end-systolic elastance (Ees), or end-systolic pressure (ESP) divided by end-systolic volume (ESV). An acceptable measure of afterload is arterial elastance (Ea), calculated as ESP divided by stroke volume (SV). The optimal mechanical coupling of RV function to afterload corresponds to an Ees/Ea ratio of 1. RV-arterial coupling allowing RV flow output at a minimal energy cost is at an Ees/Ea ratio of 1.5 to 2. Kuehne et al. (81) showed that Ees increases in PAH but may be insufficient to preserve Ees/Ea, indicating RV-arterial uncoupling. Subsequent studies have shown that the Ees/Ea ratio may be maintained or decreased in PAH and in chronic thromboembolic PH (83,84). No such study has yet been reported in PH on HF.

FIGURE 7 Methods Used to Measure Right Ventricular-Arterial Coupling and Diastolic Stiffness (β)



(A) Multiple-beat method. End-systolic elastance (Ees) is determined by a tangent fitted on the end-systolic portions of a family of pressure-volume (PV) loops at decreasing venous return; arterial elastance (Ea) is the slope of a straight line drawn from end-systolic to end-diastolic PV relationship, or more simply to end-diastolic volume (EDV) at P = 0. **(B)** Single-beat method. Ees is determined by the slope of a straight line drawn from a maximum pressure (Pmax) calculated by nonlinear extrapolation of early and late portions of the right ventricular (RV) pressure (RVP) curve, tangent to a systolic PV relationship (with V determined either directly or by integration of pulmonary RV outflow tract flow), and Ea determined as in **(A)**. Pmax corresponds to the systolic RVP (sRVP) of a nonejecting beat at EDV. Using an alternative pressure method, Ees is calculated as Pmax minus either mean pulmonary artery (PA) pressure (mPAP) or sRVP as estimates of end-systolic pressure (ESP), divided by stroke volume (SV), and Ea is calculated as mPAP or sRVP divided by SV. The Ees/Ea ratio then becomes Pmax/mPAP (or sRVP) − 1. The volume method to calculate Ees/Ea relies on omission of pressure as a common term, resulting in Ees/Ea = SV/ESV. **(C)** Diastolic stiffness is calculated by fitting the nonlinear exponential, $P = \alpha(e^{V\beta} - 1)$, to pressure and volume measured at the beginning (beginning diastolic pressure [BDP] and ESV) and the end of diastole (end-diastolic pressure [EDP] and EDV). Beta is a stiffness coefficient; α is a curve fit constant. Adapted with permission from Naeije (87).

The Ees/Ea ratio below which the adaptation of the right ventricle becomes heterometric with increased dimensions, ESV and end-diastolic volume (EDV), filling pressures, and with systemic congestion is not presently known. The Ees/Ea may be preserved at rest but decreases during exercise in patients with severe PH, suggesting a reduced contractile reserve preceding the onset of RV-arterial uncoupling at rest. Thus, exercise stress testing may help identify a phenotype of "pending" right HF in severe PH (84).

Determinations of Ees and Ea require instantaneous measurements of RV pressure and volume to generate a pressure-volume loop, obtained by a decrease of venous return by stepwise inflations of an inferior vena cava balloon or a Valsalva maneuver, are quite demanding and difficult to implement at the bedside. Accordingly, a single-beat approach has been validated for the right ventricle (85). The method relies on a maximum pressure (Pmax), corresponding to the Pmax of a nonejecting beat calculated from the nonlinear extrapolations of the early and late systolic portions of the RV pressure curve, and Ees determined by a straight-line tangent to the end-systolic portion of the pressure-volume relationship. Further simplifications have been relatively well validated, including pressure measurements with a fluid-filled Swan-Ganz catheter and volume measurements by magnetic resonance imaging or computed tomographic angiography, eventually limited to EDV and ESV measurements.

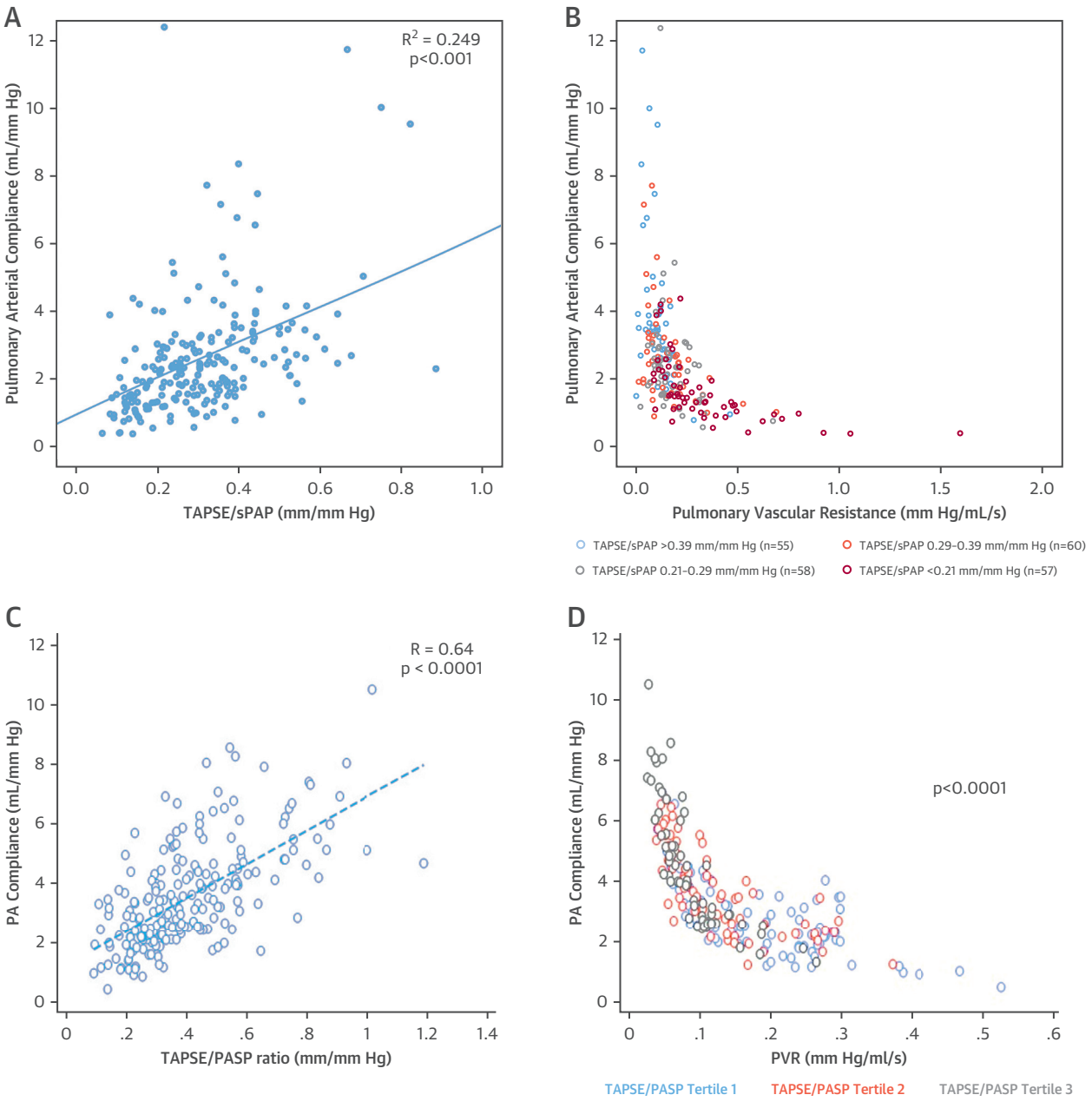
The pressure-volume loop also offers a diastolic elastance curve as a gold-standard measure of diastolic function. A diastolic elastance curve has a curvilinearity that increases with increased EDV and can be described by an equation that contains a diastolic stiffness coefficient, β. The diastolic stiffness of the right ventricle correlates with disease severity in PAH (86). This is a relevant aspect that has not yet been explored in PH due to HF. These methodological aspects are illustrated in **Figure 7** (87).

Studies on experimental animal models of PH suggest that failure of Ees to increase and RV uncoupling occur at lower PAP in the presence of systemic inflammation, sepsis, or left HF (88). Specifically, reduction of Ees/Ea from 1.81 to 0.77, which was restored by milrinone infusion, was observed in a model of HF with borderline PH (88).

SIMPLIFIED BEDSIDE MEASUREMENTS OF RV FUNCTION

A simple imaging "volume method" was proposed by Sanz et al. (89), using the reasoning that

FIGURE 8 Relationship Between PA Compliance and TAPSE/sPAP and Distribution of TAPSE/sPAP in the PVR/PAC Exponential Relationship



(A, C) Correlations between pulmonary artery (PA) compliance (PAC) and tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP). **(B, D)** Scatter distribution of TAPSE/sPAP along the PAC versus pulmonary vascular resistance (PVR) relationship. Tertile 1, <0.35; tertile 2, 0.35 to 0.57; tertile 3, >0.57. TAPSE/sPAP was the only echocardiography-derived measure that correlated with PAC. The distribution for the progressively worse TAPSE/sPAP ratio, along with a worse PAC versus PVR relationship, is suggestive of a quite good reflection by the TAPSE/sPAP definition of the load imposed on the right ventricle. Reprinted with permission from Gerges et al. (59) **(A, B)** and Guazzi et al. (92) **(C, D)**.

Ees and Ea have a common pressure term and that, accordingly, the Ees/Ea ratio can be simplified as a ratio of volumes: Ees/Ea = ESP/ESV/ESP/SV = SV/ESV.

An alternative "pressure method" using right heart catheterization only assumes mPAP equal to ESP and simplifies the Ees/Ea ratio by the slope of Pmax − mPAP on SV divided by mPAP/SV (90): Ees/Ea = (Pmax − mPAP)/SV/mPAP/SV = Pmax/mPAP − 1.

In a recent, larger study of 140 patients with PAH, both EF and SV/ESV independently predicted survival, with rigorous receiver-operating characteristic-defined cutoff values of 32.5 and 53.4, respectively (91). The relationship between SV/ESV and EF is hyperbolic, such that SV/ESV is more sensitive to changes in RV function in less severe disease.

The difference between SV/ESV and EF or SV/EDV resides in the relatively greater pre-load sensitivity of EF. It is conceivable that optimal volume control by diuretic agents and cautious use of vasodilators in selected patient populations result in the same information content of both ratios of volumes. It is also possible that EF becomes even more sensitive to deterioration in RV systolic function with increase in volumes. The SV/ESV ratio is probably more informative in earlier PH stages.

In their study of patients with PH secondary to HF, Gerges et al. (59) calculated Pmax values on stored RV pressure curves and estimated Ees/Ea by the pressure method, Pmax/mPAP − 1. This ratio deteriorated in CpcPH but was preserved in IpcPH. Thus, worse prognosis of CpcPH may be attributable to associated RV failure.

Guazzi et al. (60) recently proposed the use of the TAPSE/sPAP ratio, which determines RV-arterial coupling, as TAPSE is a surrogate of contractile function and sPAP largely reflects afterload. The TAPSE/sPAP ratio emerged as a potent prognostic marker in HF (60). A decreased TAPSE/sPAP correlates with depressed Ees/Ea (59) but is probably more afterload-dependent.

Nonetheless, in 2 studies (59,92), TAPSE/sPAP emerged as the echocardiography-derived independent predictor of CpcPH correlating with PAC (**Figures 8A and 8C**) and was scattered in the hyperbolic relationship of PAC versus PVR according to group categorization (**Figures 8B and 8D**). Interestingly, this ratio accurately stratifies prognosis across the spectrum of HF, also including moderately reduced EF, in agreement with the recent classification in the European Society of Cardiology guidelines (93).

Certainly, it should be remembered that these numbers may not reflect coupling in advanced stages, when sPAP decreases because of loss in RV contractility, and although TAPSE may be severely depressed, the "normalized" sPAP keeps the ratio similar to that observed in a subject with elevation of sPAP and a mild to moderate reduction in TAPSE.

It is interesting that depressed RV-arterial coupling, however measured, predicts CpcPH or, alternatively, that CpcPH is a cause of RV failure. Exquisite sensitivity of the right ventricle to afterload in HF is explained by the fact that cardiac diseases generally do not spare the right heart, decreased LV contractility negatively affects RV contractility, and also RV afterload in these patients increased more than estimated from PVR because of a disproportionate reduction in PAC (10). A marked decrease in PAC by long-standing elevation in PAWP increases pulmonary arterial pulse pressure, and thereby RV afterload, by a proportional rise in systolic pressure, as illustrated in **Figure 1**. Thus, PVR underestimates afterload, and the right ventricle uncouples from the PC at lower PAP.

RV-TO-PC COUPLING DURING EXERCISE

Because the right ventricle is functionally coupled to the PC, their integrated response is of relevance in different physiological settings (65). Indeed, exercise provides the most physiological setting for studying the functional RV reserve in HF (22,94). Interestingly, Borlaug et al. (94) recently found that even early stages of HFpEF may be paralleled by the same degree of impaired RV reserve and uncoupling because of a concurrent increase in LV filling pressures.

In a study of 97 patients with advanced HFrEF, RV exercise contractile reserve and RV-to-PC coupling response to maximal exercise were analyzed through the relationships of sPAP to TAPSE and sPAP to CO using stress echocardiography and cardiopulmonary exercise testing (22). Patients were categorized into 3 groups according to TAPSE at rest ≥16 mm (group A, n = 60) and those with TAPSE at rest <16 mm, who were further divided into 2 subgroups (group B, n = 19; group C, TAPSE <15.5 mm, n = 18) according to whether their respective median TAPSE was higher or lower than 15.5 mm at peak exercise. Group B, at variance with group C, showed an upward shift of the TAPSE-versus-sPAP relationship and some degree of favorable coupling adaptation during exercise. Thus, severely impaired RV function at rest may still be associated with the capacity to improve RV-to-PC coupling in a proportion of patients with HFrEF (22). Interestingly, the worst RV-to-PC coupling pattern was associated with the highest rate of exercise ventilation inefficiency.

THERAPEUTIC PERSPECTIVES AND CONCLUSIONS

Because preservation of RV function is of basic relevance for good outcomes in HF, it seems reasonable to identify the abnormalities in LV filling and PC as therapeutic targets, in order to minimize RV afterload. The first target should be to maintain low LAP, with the 2-fold aim of reducing congestion and RV pulsatile loading. These aims, however, may be insufficient once remodeling of pulmonary arterioles has occurred, considering that the hypothesis that good control of LAP will prevent development of precapillary PH is yet to be proven. The second goal is an ambitious one, because it implies the possibility of reversing the pathobiology and epigenetics of pulmonary microvessel disease (38,95).

Overall, hemodynamic phenotyping is still the method that should drive effective treatment of PH. From a therapeutic point of view, both IpcPH and CpcPH benefit from the recommended therapeutic regimen of HFrEF using beta-blockers, angiotensin-converting enzyme inhibitors, and spironolactone, with diuretic agents as needed for the relief of congestion. It is unknown whether therapies targeting the PC and proved efficacious in PAH, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, guanylate cyclase activators, or even prostanoids may be beneficial in CpcPH. In most trials performed in the past, these drugs were used in unselected populations of HF, which may explain the lack of positive results. However, more effort has recently been undertaken to figure out what patients are "responders" to interventions potentiating the NO pathway.

Contrasting results were obtained from 2 single-center studies investigating the effects of phosphodiesterase-5 inhibition by sildenafil on hemodynamic status and RV-to-PC coupling (96,97). The patients included in the positive study had high PVR, right atrial pressure, and pericardial-mediated and RV-to-LV interactions suggestive of the CpcPH phenotype.

Neutral findings have been reported for cyclic guanosine monophosphate stimulation with riociguat in HFpEF (98) and HFrEF (99). Recently, the effects of inhaled inorganic nitrite were tested in patients with PH and HFpEF, showing a positive effect on PAWP (100) and, especially, on the PAC-PVR relationship (101). In a recent substudy of a European registry including 5,935 patients with PH receiving pulmonary vasodilators, idiopathic PAH (n = 421), atypical idiopathic PAH (>3 risk factors for HF; n = 139), and PH and HFpEF (n = 226) all showed improvement in functional class, exercise capacity, and natriuretic peptides (102). The patients with PH and HFpEF had very high TPGs (on average 26 mm Hg) and PVR (on average 7 Wood units), suggestive of CpcPH and supporting the notion that the CpcPH phenotype may benefit from therapies targeting the PC, especially sildenafil because it was the drug administered in a higher rate.

If future trials of targeted therapies are to be considered in PH due to HF, it will be essential to primarily target the less common patients with CpcPH, who most likely present with pulmonary vascular disease, relatively higher PVR, and altered RV function.

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