

# Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure

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**ABSTRACT:** Increased pulmonary venous pressure secondary to left heart disease is the most common cause of pulmonary hypertension (PH). The diagnosis of PH due to left heart disease relies on a clinical probability assessment followed by the invasive measurements of a mean pulmonary artery pressure (PAP)  $\geq 25$  mm Hg and mean wedged PAP (PAWP)  $> 15$  mm Hg. A combination of mean PAP and mean PAWP defines postcapillary PH. Postcapillary PH is generally associated with a diastolic pulmonary pressure gradient (diastolic PAP minus mean PAWP)  $< 7$  mm Hg, a transpulmonary pressure gradient (mean PAP minus mean PAWP)  $< 12$  mm Hg, and pulmonary vascular resistance  $\leq 3$  Wood units (WU). This combination of criteria defines isolated postcapillary PH. Postcapillary PH with elevated vascular gradients and pulmonary vascular resistance defines combined post- and precapillary PH (Cpc-PH). Postcapillary PH is associated with a decreased survival in proportion to increased pulmonary vascular gradients, decreased pulmonary arterial compliance, and reduced right ventricular function. The Cpc-PH subcategory occurs in 12% to 13% of patients with PH due to left heart disease. Patients with Cpc-PH have severe PH, with higher diastolic pulmonary pressure gradient, transpulmonary pressure gradient, and pulmonary vascular resistance and more pronounced ventilatory responses to exercise, lower pulmonary arterial compliance, depressed right ventricular ejection fraction, and shorter life expectancy than isolated postcapillary PH. Cpc-PH bears similarities to pulmonary arterial hypertension. Whether Cpc-PH is amenable to therapies targeting the pulmonary circulation remains to be tested by properly designed randomized controlled trials.

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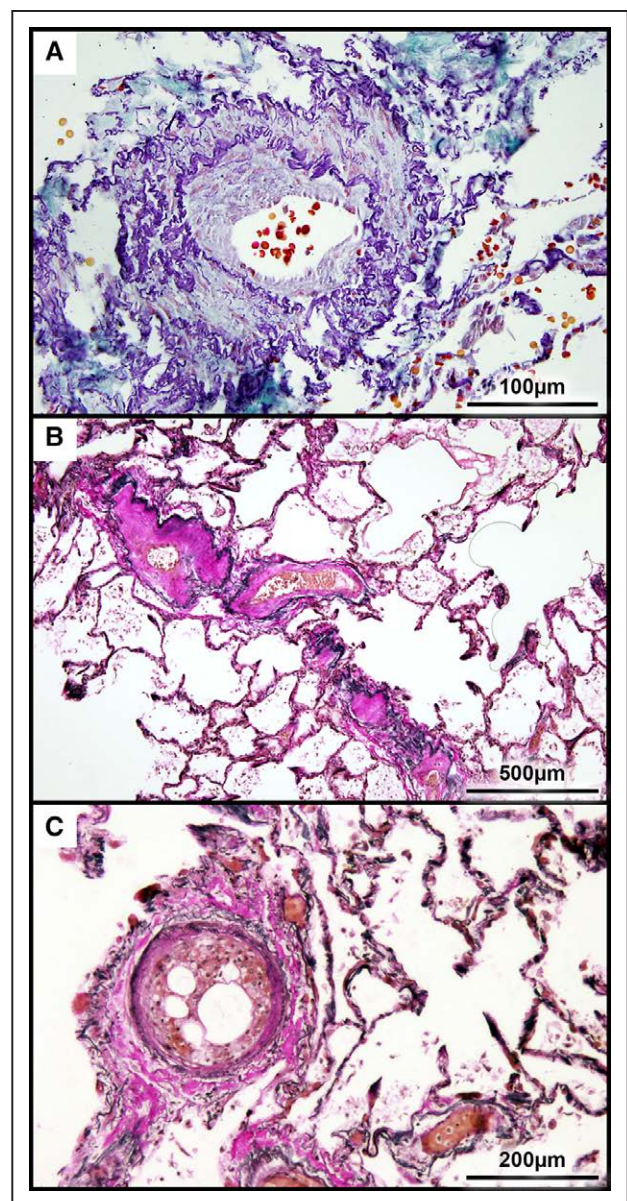
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**H**eat failure (HF) has long been known to affect the pulmonary circulation by upstream transmission of increased pulmonary venous pressures as a cause of pulmonary congestion and pulmonary vascular remodeling. The histopathologic profile of pulmonary vascular disease was established before the introduction of cardiac catheterization in clinical practice,<sup>1</sup> and hemodynamic correlates of high pulmonary vascular gradients and increased pulmonary vascular resistance (PVR) soon followed.<sup>2,3</sup> Thus, pulmonary hypertension due to left heart disease (PH-LHD) was characterized by various combinations of arteriolar medial hypertrophy, intimal proliferation, adventitial thickening and microthrombi, rarely fibrinoid necrosis (identified in exceptionally severe mitral stenosis), capillary congestion with hemosiderosis, thickened alveolo-capillary membranes and sometimes interstitial fibrotic changes, venules undergoing medial hypertrophy and intimal fibrosis, dilated/muscularized lymphatics, but no plexiform lesions.<sup>1,3</sup> Some of these aspects are illustrated in Figure 1.

PH-LHD is currently defined by a mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg with a wedged PAP (PAWP)  $>15$  mmHg<sup>4-6</sup> and is also called postcapillary PH. A passive increase in mPAP in proportion to increased PAWP defines isolated postcapillary PH (Ipc-PH). An out-of-proportion increase in mPAP with respect to increased PAWP suggestive of pulmonary vascular remodeling and constriction defines combined post- and precapillary PH (Cpc-PH).<sup>2,4-6</sup>

## PULMONARY ARTERIAL COMPLIANCE

The PVR equation rests on the assumptions that the pulmonary vascular pressure difference–flow relationship is linear and crosses the origin and that left atrial pressure is transmitted upstream to mPAP in a 1:1 ratio.<sup>7</sup> While PAWP is a reasonable estimate of left atrial pressure,<sup>8</sup> the assumption of a linear proportional upstream transmission of left atrial pressure to mPAP is not correct because of the natural compliance of pulmonary vessels. Furthermore, PVR calculations do not take into account the pulsatility of the pulmonary circulation, that is, the difference between systolic PAP (sPAP) and diastolic PAP (dPAP) or pulse pressure (PP), which increases with pulmonary arterial stiffening. Thus, there is interest in estimating pulmonary arterial compliance ( $C_{PA}$ ). For this purpose, several methods have been proposed. The most accurate is the PP method, which uses a 2-element Windkessel model with flow waveform and resistance as inputs to estimate the compliance value that best predicts systolic and diastolic pressures.<sup>9</sup> However, most clinical studies use the ratio of stroke volume (SV) to pulmonary artery PP, or difference between sPAP and dPAP, which is simpler to calculate from standard right heart catheter-



**Figure 1. Histopathology of pulmonary vessels in pulmonary hypertension due to left heart disease (PH-LHD).**

**A**, Medial hypertrophy with intimal and adventitial proliferation of a small pulmonary artery. **B**, Medial hypertrophy with intimal and adventitial proliferation of a small pulmonary vein. **C**, Recanalized fibrotic thrombus in arterioles. Scale bars are shown for individual panels.

ization measurements. The SV/PP ratio assumes that the complete SV is buffered in the large elastic arteries in systole, without any peripheral outflow. In such a hypothetical closed system, SV is the volume increase and PP is the associated pressure increase. However, there is a continuous flow toward the periphery, and the volume increase during ejection is only a fraction of SV. Therefore, SV/PP is a theoretical maximum possible pulmonary vascular compliance and overestimates the true  $C_{PA}$  by 60% to 80%.<sup>10</sup> However, whether this is

clinically relevant has not been tested in patients with PH. Right ventricular (RV) afterload is determined by a dynamic interplay between PVR,  $C_{PA}$ , and wave reflections.<sup>11</sup> An increase in PAWP decreases  $C_{PA}$ <sup>12,13</sup> and may, therefore, be an important cause of RV dysfunction. On the other hand, the product of PVR and  $C_{PA}$  is fairly constant over a wide range of severities of PH in HF<sup>13</sup> and other types of PH,<sup>14</sup> suggesting a negligible contribution of wave reflection on RV afterload.

$C_{PA}$  integrates the volume change per pressure change in the entire arterial segment of the pulmonary circulation. Large artery compliance by magnetic resonance imaging of instantaneous volume changes per pressure changes amounts to no more than 20% of  $C_{PA}$ .<sup>14</sup> Therefore, proximal pulmonary arterial stiffness is then an only minor component of RV afterload.

A decrease in  $C_{PA}$  has been shown to be an independent predictor of outcome in HF over a wide range of PVR.<sup>15–18</sup> This may be explained by the fact that decreased  $C_{PA}$  increases RV afterload and may, thus, determine a predominantly right HF phenotype of poor prognosis. The exquisite sensitivity of  $C_{PA}$  to increased PAWP<sup>12,13</sup> makes it also a marker of the severity of left ventricular (LV) failure, which in itself is an additional risk factor of decreased survival.

## THE TRANSPULMONARY PRESSURE GRADIENT

Chronically increased pulmonary venous pressure is a cause of endothelial dysfunction related to perturbation of a series of signaling pathways with increased endothelin-1 and decreased nitric oxide and prostacyclin.<sup>6,19–21</sup> This is associated with pulmonary vasoconstriction and remodeling identified at hemodynamic measurements by a >1:1 upstream transmission of PAWP and, thus, an increased PVR.<sup>4–7,20,22</sup> When cardiac output (CO) is normal or low-normal, the difference between mPAP and PAWP, or transpulmonary pressure gradient (TPG), becomes a major determinant of increased PVR. The limits of normal TPG are not exactly known. The upper limit of normal of TPG was thought to be 10 mmHg until the 1970s,<sup>23</sup> but has since drifted upwards to 12 mmHg<sup>24</sup> or even most recently to 15 mmHg.<sup>25</sup> The differential diagnosis between pulmonary vascular tone versus remodeling versus decreased  $C_{PA}$  as causes of disproportional increase of mPAP may be difficult. The definitive test is repetition of measurements after a therapeutic decrease in PAWP, such as with diuretics, acute vasodilator testing in pretransplantation evaluation of HF,<sup>26–29</sup> mechanical left ventricular assist,<sup>29</sup> and of course cardiac transplantation.<sup>28</sup> A persistently high PVR in spite of normalized PAWP can only but be explained by irreversible pulmonary vascular remodeling.

## THE DIASTOLIC PULMONARY PRESSURE GRADIENT

Another more straightforward approach for the diagnosis of pulmonary vascular disease in PH-LHD relies on the measurement of the gradient between dPAP and mean PAWP (mPAWP) or diastolic pulmonary pressure gradient (DPG). A progressive increase in PAWP in lpc-PH or in healthy subjects inevitably increases sPAP, mPAP, and dPAP.<sup>12,13</sup> The increase in dPAP is proportionally less than the increase in mPAP. With increased PAWP, the TPG increases, but DPG on average does not change.<sup>7,12</sup>

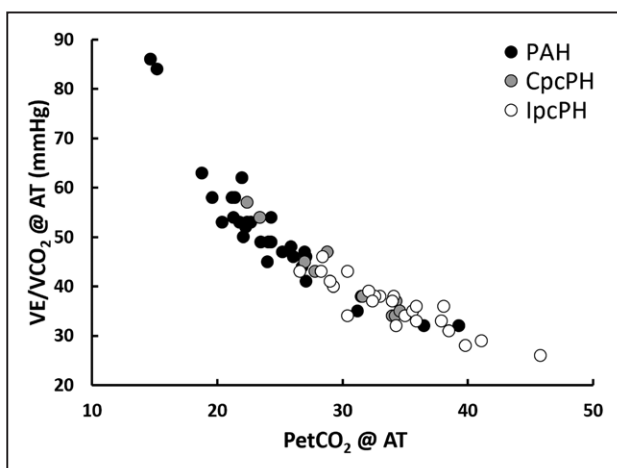
The DPG was used in the 1970s in combination with PAWP, CO (or arteriovenous oxygen content difference), and systemic blood pressure measurements for the differential diagnosis of cardiac and pulmonary causes of acute respiratory failure.<sup>30</sup> The upper limit of normal of DPG was assumed to be 5 mmHg,<sup>12</sup> derived from measurements in healthy athletic young adults. The true upper limit of normal over the entire age range and levels of fitness and ages is probably a few mmHg higher.

Soon after its revival,<sup>7</sup> DPG was evaluated for the differential diagnosis of PH-LHD in a large patient database.<sup>31</sup> Pulmonary vascular gradients were assessed in 3107 patients referred to the catheterization laboratory of the General Hospital of Vienna (AKH-Wien), Medical University of Vienna. PH-LHD defined by mPAP  $\geq 25$  mmHg and mPAWP  $> 15$  mmHg was diagnosed in 1094 of these patients, TPG  $> 12$  mmHg in 490 of them, and DPG was in addition increased  $\geq 7$  mmHg in 179, accounting for 16% of PH-LHD patients. Survival of patients with both high TPG and DPG was poor, like untreated pulmonary arterial hypertension (PAH). In multivariate analysis, DPG emerged as an independent predictor of survival with a cutoff value of 7 mmHg rigorously derived from the best combination of sensitivity and specificity.

This data inspired a revision of definitions and terminology of PH-LHD at the 5<sup>th</sup> World PH Symposium held in Nice in 2013, with introduction of the new acronyms lpc-PH and Cpc-PH.<sup>4</sup> It is of interest that Cpc-PH was initially defined solely by a DPG  $\geq 7$  mmHg,<sup>4</sup> but an element of increased PVR was added in the European guidelines definitions of the European Society of Cardiology/European Respiratory Society.<sup>5</sup> Adding a PVR makes sense, as the DPG is much smaller than PAP but exposed to the same magnitude of errors on the measurement. Therefore, a combination of increased DPG and PVR (or TPG) may indeed be preferable for more robust Cpc-PH phenotyping. However, increased DPG with or instead of and increased PVR as written in the guidelines<sup>5</sup> doubles the prevalence of Cpc-PH from some 12%–14% to 24% in patients with PH-LHD.<sup>32</sup> Accordingly, defining Cpc-PH by the combination of increased DPG and PVR seems preferable.<sup>32,33</sup>

Histopathologic correlates of DPG are scarce. Some sections of pulmonary vessels of patients with both increased TPG and DPG showed pulmonary vascular remodeling with medial hypertrophy, intimal thickening, and adventitial proliferation,<sup>31</sup> as previously reported in severe PH secondary to HF.<sup>1,3</sup>

Support for the clinical relevance of DPG for the definition of Cpc-PH was given by a small study in which the ventilatory equivalents for carbon dioxide ( $V_E/V_{CO_2}$ ) slope during a cardiopulmonary exercise test was found to be high in PAH, intermediate in Cpc-PH, and mild in lpc-PH, while exercise oscillatory ventilation occurred in 40% of lpc-PH and 17% of Cpc-PH and was absent in PAH patients<sup>34</sup> (Figure 2). Patients with PAH present with markedly increased ventilation but no oscillatory ventilation during exercise, while patients with advanced lpc-PH may present with exercise oscillatory ventilation known as a marker of poor prognosis.<sup>35</sup> In another larger scale study, fluid challenge did not affect the time constant of the pulmonary circulation, or  $PVR \times C_{PA}$ , in Cpc-PH or in PAH, while it decreased it significantly in lpc-PH, suggesting fixed pulmonary vascular remodeling in Cpc-PH.<sup>36</sup> Biological support for a Cpc-PH phenotype was recently provided by an analysis of a large database of 2817 PH patients from Vanderbilt University in Nashville.<sup>37</sup> In that study, patients with Cpc-PH were younger but with more severe pulmonary vascular disease than patients with lpc-PH, despite similar comorbidities and prevalence, severity, and chronicity of LHD, and presented with 75 exonic single-nucleotide polymorphisms enriched in pathways involving cell structure, extracel-



**Figure 2.** Ventilatory equivalents for CO<sub>2</sub> ( $V_E/V_{CO_2}$ ) as a function of end-tidal partial pressure of CO<sub>2</sub> ( $PetCO_2$ ) in patients with pulmonary arterial hypertension (PAH), combined pre- and postcapillary pulmonary hypertension (Cpc-PH), and isolated postcapillary pulmonary hypertension (lpc-PH) showing ventilatory responses to exercise measured at the anaerobic threshold (AT) of Cpc-PH being intermediate to those of PAH and lpc-PH.

Data derived from Caravita et al.<sup>34</sup>

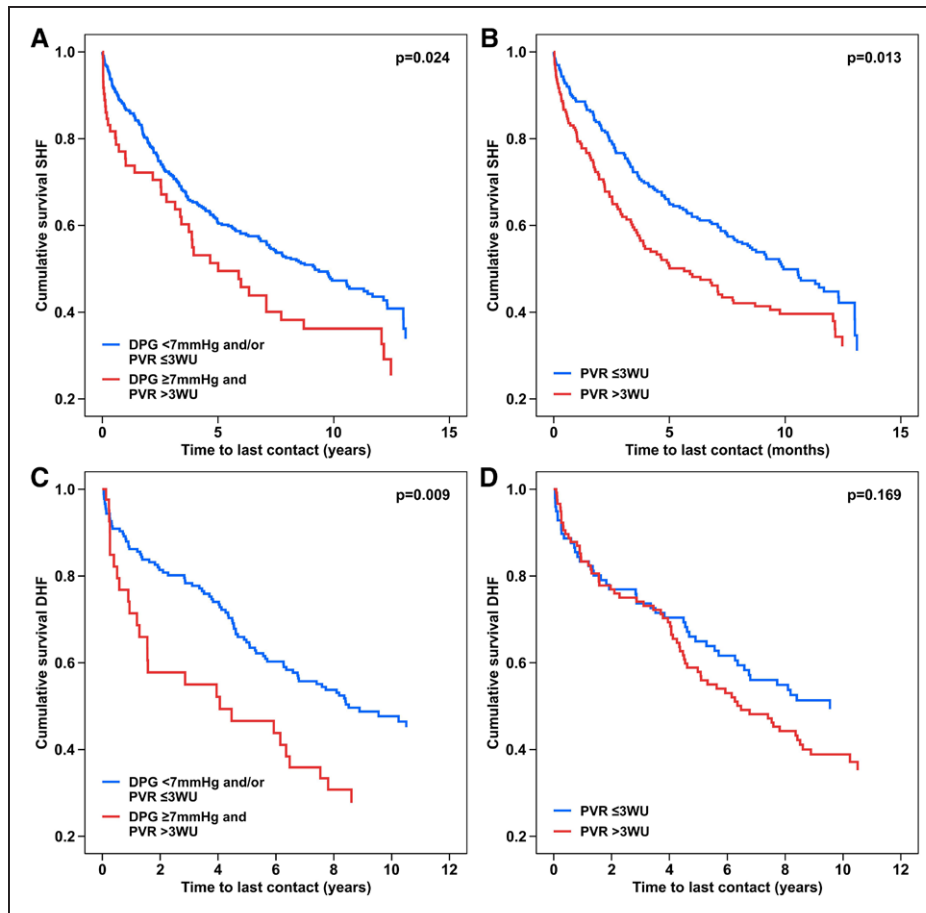
lular matrix, and immune function that were shared with PAH and not with lpc-PH patients.

The prevalence of Cpc-PH in PH-LHD is not exactly known, but may be around 12% to 14% in patients with HF referred to the catheterization laboratory.<sup>37,38</sup> In the database of the Medical University of Vienna, independent predictive capability of DPG by multivariate analysis was significant in both diastolic HF (DHF)/HF with preserved ejection fraction (EF) and systolic HF (SHF)/HF with reduced EF, even when the definition included a PVR >3 WU. However, PVR alone was a predictor of outcome in HF with reduced EF but not in HF with preserved EF (Figure 3). By contrast, in the database of the Vanderbilt University, DPG did not predict outcome, while PVR only predicted outcome in patients with Cpc-PH. Furthermore, prognosis of Cpc-PH and lpc-PH was not found to be different.

Previous studies have generally found PVR to be a strong predictor of outcome in PH-LHD,<sup>39,40</sup> raising discussion about the added predictive value of DPG in PH-LHD. At present, an almost equal number of studies have confirmed<sup>41–43</sup> or refuted<sup>44–46</sup> the prognostic relevance of DPG. These discrepancies are explained by the fact that the DPG represents a small number, is exposed to instability, as shown in studies where high DPGs were sometimes found in patients with a normal PVR<sup>44</sup> or where DPG was reported as negative in a proportion of patients,<sup>47</sup> conditions which are both physiologically impossible. TPG or PVR have to increase in proportion of the DPG,<sup>7</sup> while reported negative DPG values may be because of improper incorporation of V waves in the reading of PAWP tracings or simply because of a lack of precision of the measurement.<sup>48</sup> On the other hand, the severity of PH and degree of RV dysfunction may be predominant in the impact on outcome.<sup>49</sup>

## THE RIGHT VENTRICLE IN LEFT HEART FAILURE

PH is associated with decreased exercise capacity and shorter life expectancy in HF.<sup>4–6,25</sup> This could be explained by more advanced HF causing more upstream transmission of increased PAWP to PAP and, thus, by afterload-induced RV failure. Preserved RV EF as measured with radionuclide technology had been shown to predict exercise capacity and survival in advanced HF.<sup>50</sup> The first study combining pulmonary vascular function and RV function measurements was reported in 2001.<sup>51</sup> The authors measured pulmonary vascular pressures, CO, and thermodilution-derived RVEF in 377 consecutive patients with HF. Mean PAP and RVEF were inversely correlated, but were shown to be independent predictors of death or urgent transplantation in multivariate analysis. The prognosis of patients with PH but a preserved RVEF was similar to that of patients without PH.



**Figure 3.** Survival curves illustrating a population of 636 patients with heart failure with reduced ejection fraction/systolic heart failure (SHF) pulmonary hypertension (A and B) and 286 patients with heart failure with preserved ejection fraction/diastolic heart failure (DHF) pulmonary hypertension (C and D) with diastolic pulmonary pressure gradient (DPG) <7 mm Hg and pulmonary vascular resistance (PVR) ≤3 WU, versus DPG of ≥7 mm Hg and PVR >3 WU (A and C) and PVR ≤3 WU alone versus PVR >3 WU alone (B and D).

Data derived from Gerges et al.<sup>38</sup>

These results have been confirmed,<sup>52</sup> and emphasize that RV function is a major determinant of outcome in severe PH.<sup>53</sup>

The RV in PH-LHD is exquisitely sensitive to afterload. As already discussed, increased PAWP increases RV afterload out of proportion to increased PVR because of associated decrease in  $C_{PA}$ . Furthermore, cardiomyopathies of course involve the RV, which may fail to adapt to minimally increased PAP. This has been demonstrated by rigorously defined coupling of RV function to the pulmonary circulation by the measurement of the ratio of end-systolic to arterial elastances in an animal model of overpacing-induced HF with reduced EF and "borderline PH."<sup>54</sup> On the other hand, 20% to 40% of RV systolic pressure results from LV contraction<sup>55</sup>; thus, decreased LV contractility and associated systemic hypotension alters ventricular systolic interdependence and, thereby, impairs coupling of RV function to the pulmonary circulation. As patients with Cpc-PH have higher pulmonary vascular pressure gradients and PVR than Ipc-PH, they are more likely to have RV failure

and shorter life expectancy, even though this may vary depending on the underlying cause of HF.

In the large PH-LHD database of the Medical University of Vienna,<sup>38</sup> standard echocardiography was not able to discriminate between Ipc-PH and Cpc-PH, except when tricuspid annular plane systolic excursion to sPAP ratio was calculated. The tricuspid annular plane systolic excursion/sPAP ratio was initially introduced as an estimate of RV length-tension relationship,<sup>56</sup> but also considered as an indirect estimate of RV-arterial coupling.<sup>57-60</sup> The tricuspid annular plane systolic excursion/sPAP ratio has been shown to be a potent predictor of survival in HF, alone,<sup>56</sup> combined with cardiopulmonary exercise testing,<sup>57</sup> or measured at rest and during exercise to assess RV contractile reserve.<sup>58</sup> However, the exact functional significance of tricuspid annular plane systolic excursion/sPAP is not yet entirely understood.<sup>59</sup>

Accordingly, RV pressure curves of the large cohort of patients with PH-LHD of the Medical University of Vienna were analyzed to derive end-systolic and arterial elastances<sup>38</sup> as gold standard measures of contractility

and afterload.<sup>53</sup> End-systolic elastance increased from lpc-PH to idiopathic PAH, with Cpc-PH in between, but the ratio of end-systolic to arterial elastance was decreased in Cpc-PH only as a function of increased DPG.<sup>38</sup> RV contractility increases in the presence of increased afterload to preserve RV–arterial coupling.<sup>53</sup> This is observed in PAH at rest,<sup>60–62</sup> if not during exercise.<sup>61,62</sup> Altered RV–arterial coupling in severe PH results in increased RV dimensions, systemic congestion, and decreased survival.<sup>53</sup>

The observation that Cpc-PH is more likely associated with worse RV function is further underscored by the DPG-dependent clustering of PAH, Cpc-PH, and lpc-PH in relation to RV and LV volumes and a filling pressures-dependent prediction score for precapillary PH developed from invasive and noninvasive measurements in 240 patients referred with PH<sup>63,64</sup> (Figure 4).

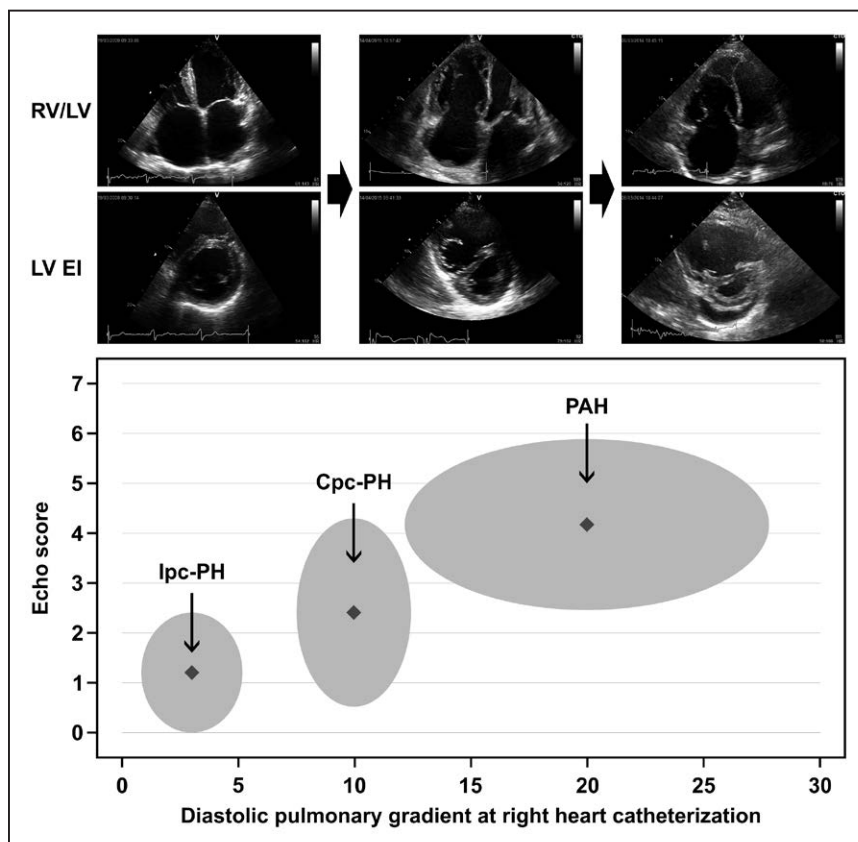
### PROVOCATIVE TESTING

Provocative testing of the pulmonary circulation relies mainly on exercise test or fluid challenge. Both approaches have been part of standard clinical practice for decades, but have only been recently standardized.

The upper limit of normal of mPAP during an incremental dynamic exercise challenge is now well established at 30 mmHg at a CO <10 L/min, which corresponds to a total pulmonary vascular resistance (TPR, or mPAP/CO).

of 3 WU.<sup>65–67</sup> Meaningful accurate but less precise noninvasive measurements of PAP and CO during exercise are being reported by dedicated groups.<sup>65,66</sup> The cause of higher than normal mPAP during “exercise or exercise-induced PH” is either an upstream transmission of increased PAWP, such as in HF, or an increase of PVR, such as in pulmonary vascular disease, disturbed lung mechanics, or hypoxia.<sup>65,66</sup> This differential diagnosis is most often clinically straightforward but has to 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 mmHg, but higher values can be recorded in athletes and in elderly subjects.<sup>68</sup> A cutoff value of 25 mmHg has been proposed for the diagnosis of HF.<sup>69,70</sup> Likewise, for mPAP, a flow-corrected measure may be more appropriate for PAWP, but there has been no study specifically addressing this.

A fluid challenge is probably easier to standardize than an exercise stress test. Any condition associated with altered LV diastolic compliance or valvular heart disease will be associated with a rapid increase in PAWP when challenged with an increased systemic venous return.<sup>2,71</sup> There is an emerging consensus to infuse 500 mL or 7 mL/kg of saline in 5 to 10 minutes as best compromise between safety and stress efficacy, and 18 mmHg seems to be the optimal cutoff to separate abnormal from normal.<sup>71–76</sup>



**Figure 4.** Clustering of isolated postcapillary pulmonary hypertension (lpc-PH), combined pre- and postcapillary pulmonary hypertension (Cpc-PH), and pulmonary arterial hypertension (PAH) as a function of diastolic pulmonary pressure gradient (DPG).

A high DPG is closely associated with an increased ratio of right ventricular (RV) to left ventricular (LV) surface areas (RV/LV) and decreased LV eccentricity index (EI). A scoring system from 1 to 6 facilitates the diagnosis of precapillary pulmonary hypertension (PH) in patients referred for PH. Adapted from D’Alto et al<sup>64</sup> with permission. Copyright ©2017, Wolters Kluwer Health, Inc.

## CONCLUSIONS

PH as a complication of left heart conditions with increased pulmonary venous pressure can be differentiated in Cpc-PH and lpc-PH phenotypes based on clinical features, pulmonary vascular pressure gradients, and RV function. The prognosis of Cpc-PH is poor. Whether therapies targeting the pulmonary circulation and efficacious in PAH improve the outcome of Cpc-PH remains to be tested in properly designed multicenter randomized controlled trials.

## DISCLOSURES

Dr Naeije has relationships with drug companies, including AOPOrphan Pharmaceuticals, Actelion, Bayer, Reata, Lung Biotechnology Corporation, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Drs M. Gerges and C. Gerges have received compensation for scientific symposia from AOPOrphan Pharmaceuticals AG, Actelion, and GlaxoSmithKline. Dr M. Gerges received in the past an educational grant from United Therapeutics Corporation (Grant No. REG-NC-002). Dr C. Gerges received in the past an educational grant from Bayer (Grant No. 15662). Dr Vachieri has relationships with drug companies, including Actelion, Bayer, Glaxo, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Dr Caravita has received an ERS PAH Short-Term Research Training Fellowship (STRTF 2014–5264), was supported by an unrestricted grant from GSK, and received payment of expenses related to congress participations by Bayer, Actelion, and Pfizer. Dr Lang has relationships with drug companies, including AOPOrphan Pharmaceuticals, Actelion, Bayer-Schering, Astra-Zeneca, Servier, Cordis, Medtronic, GSK, Novartis, Pfizer, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

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## FOOTNOTES

*Circ Heart Fail* is available at <http://circheartfailure.ahajournals.org>.

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### Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure

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