

Clinical update

# Left ventricular heart failure and pulmonary hypertension†

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In patients with left ventricular heart failure (HF), the development of pulmonary hypertension (PH) and right ventricular (RV) dysfunction are frequent and have important impact on disease progression, morbidity, and mortality, and therefore warrant clinical attention. Pulmonary hypertension related to left heart disease (LHD) by far represents the most common form of PH, accounting for 65–80% of cases. The proper distinction between pulmonary arterial hypertension and PH-LHD may be challenging, yet it has direct therapeutic consequences. Despite recent advances in the pathophysiological understanding and clinical assessment, and adjustments in the haemodynamic definitions and classification of PH-LHD, the haemodynamic interrelations in combined post- and pre-capillary PH are complex, definitions and prognostic significance of haemodynamic variables characterizing the degree of pre-capillary PH in LHD remain suboptimal, and there are currently no evidence-based recommendations for the management of PH-LHD. Here, we highlight the prevalence and significance of PH and RV dysfunction in patients with both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), and provide insights into the complex pathophysiology of cardiopulmonary interaction in LHD, which may lead to the evolution from a ‘left ventricular phenotype’ to a ‘right ventricular phenotype’ across the natural history of HF. Furthermore, we propose to better define the individual phenotype of PH by integrating the clinical context, non-invasive assessment, and invasive haemodynamic variables in a structured diagnostic work-up. Finally, we challenge current definitions and diagnostic short falls, and discuss gaps in evidence, therapeutic options and the necessity for future developments in this context.

**Keywords** Pulmonary hypertension • Heart failure • Pre-capillary • Post-capillary

## Introduction

Pulmonary hypertension (PH) is a frequent condition, which may occur as a consequence of pulmonary vascular disease, chronic left heart or lung disease, pulmonary embolism, or other aetiologies.<sup>1–3</sup> Among the various PH groups, PH associated with left heart failure (HF) represents by far the most common form of PH. In fact, left heart diseases (LHD) account for 65–80% of PH cases. Whereas targeted therapies are available for pulmonary arterial hypertension (PAH),<sup>3,4</sup> these treatments have not been adequately evaluated or are not indicated and may even be harmful in patients with PH

related to LHD. It is therefore of key importance to establish a precise diagnosis and classification of PH before treatment decisions are made. However, in clinical practice, there are significant inconsistencies, which are a matter of concern: on one hand, patients with PH and occult LHD are frequently misclassified as PAH and treated with PAH-specific drugs, or patients with PH of unclear origin receive targeted therapy without proper classification. On the other hand, HF is often associated with PH and RV dysfunction, which have an important impact on disease progression, morbidity, and mortality, and this tends to be underestimated in the field of HF.<sup>5</sup> Nevertheless, the haemodynamic interrelations when a pre-capillary

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component is present in post-capillary PH are complex, and the efficacy and safety of targeted PH therapies remain unproven. Here, we aim to highlight the prevalence and significance of PH and RV dysfunction in patients with left ventricular (LV) HF, provide insights into the complex pathophysiology of cardiopulmonary interaction in LHD, challenge current definitions and diagnostic short falls, and to discuss therapeutic options and the necessity for future developments in this context.

## Haemodynamic definitions and classification of pulmonary hypertension related to left heart disease

Regardless of the origin, PH is defined by a mean pulmonary artery pressure (PAP)  $\geq 25$  mmHg.<sup>1,6</sup> Based on the left-sided filling pressure [determined either as LV end-diastolic pressure (LVEDP), left atrial pressure (LAP), or pulmonary arterial wedge pressure (PAWP)], the haemodynamic definition further distinguishes pre- ( $\leq 15$  mmHg) and post-capillary PH ( $> 15$  mmHg). In post-capillary PH, the elevation of PAWP leads to a proportionate increase of the mean PAP, maintaining a normal transpulmonary pressure gradient (TPG = mPAP – PAWP)  $< 12$  mmHg, and low pulmonary vascular resistance (PVR)  $< 3$  Wood units (WU) or  $< 240$  dynes  $\text{s cm}^{-5}$ . However, chronic elevation of the left-sided filling pressure associated with neurohormonal and other mediator activation as well as neurogenic effects may cause excess vasoconstriction with or without vascular remodelling leading to a ‘disproportionate’ increase of the PAP, and thus resulting in an elevated TPG and PVR, which has been described as ‘reactive’, ‘out-of-proportion’, or ‘mixed’ PH.<sup>1,7</sup> While the TPG is influenced by volume load and cardiac function, and does not prognosticate outcome in PH-LHD,<sup>8</sup> the diastolic pressure gradient (DPG)—defined by the difference between diastolic PAP and PAWP—is assumed to be less dependent of stroke volume and loading conditions,<sup>9</sup> and was shown to correlate with pulmonary vascular remodelling in PH-LHD.<sup>10</sup> These findings led to the current terminology and classification of post-capillary PH as either isolated post-capillary PH (Ipc-PH), if the DPG is  $< 7$  mmHg and/or PVR  $\leq 3$  WU, or combined post- and pre-capillary PH (Cpc-PH), if the DPG is  $\geq 7$  mmHg and/or PVR  $> 3$  WU.<sup>11,12</sup>

## Prevalence and significance of pulmonary hypertension in left ventricular heart failure

The presence and extent of PH and RV dysfunction—which are both common in LV HF—are associated with disease progression, decreased exercise tolerance, and an unfavourable outcome. Data on the prevalence of PH in patients with HF yield variable numbers and depend on the method of PAP measurement, the definition of PH, and the populations studied. Although both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) belong to the clinical syndrome of ‘heart failure’, they

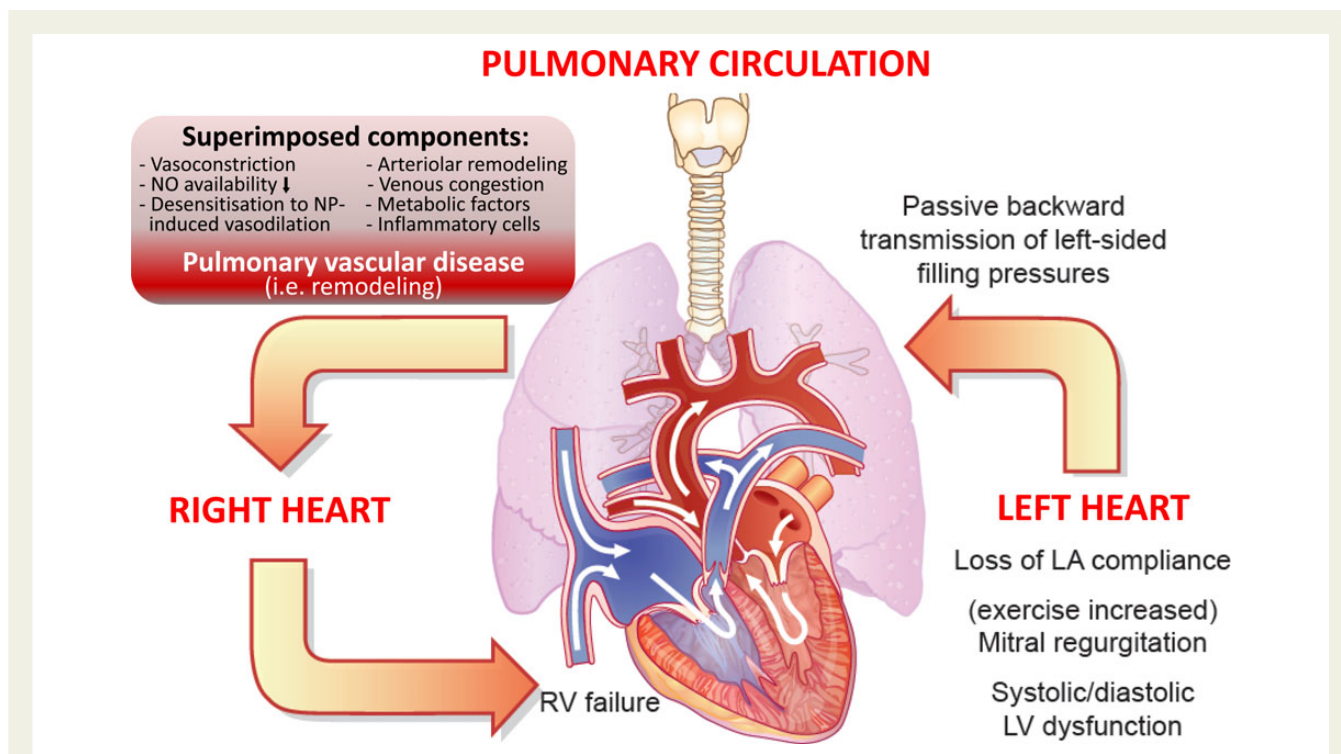
constitute distinct entities with regard to pathophysiology, clinical characteristics, haemodynamics, cardiopulmonary interaction, and response to therapy, and should thus be viewed separately. In HFrEF, the prevalence of PH as assessed by RHC was reported to be between 40 and 75%.<sup>8,13,14</sup> In patients with HFpEF, recent studies utilizing either echocardiography or RHC indicated a PH prevalence in a range between 36 and 83%.<sup>15–17</sup>

A community-based study in patients with HF demonstrated that pulmonary artery systolic pressure (PASP) estimated by echocardiography strongly predicted all-cause and cardiovascular mortality independently of known predictors of outcome.<sup>18</sup> While numerous studies have consistently shown an inverse correlation between PH and survival, a combination of elevated PAP and reduced RV systolic function was particularly associated with an unfavourable outcome in HFrEF.<sup>13</sup> In HFpEF, studies demonstrated that the presence of PH was also strongly associated with mortality.<sup>15–17</sup> Furthermore, HFpEF patients commonly display RV dysfunction, which is associated with elevated PAP, occurs at more advanced stages, and represents a strong predictor of death.<sup>19,20</sup>

Haemodynamic parameters that are predictive of poor survival in HF include an increased PAWP, mean PAP, and PVR, and a reduced PA compliance/capacitance.<sup>8,14,21–23</sup> Significant efforts were made to better define PH-LHD and harmonize definitions. However, there is still a debate on the best haemodynamic predictor of outcome. Recent studies on the prognostic value of the DPG in PH-LHD have yielded conflicting results.<sup>10,14,22–24</sup> This may be explained, at least in part, by the populations studied and by methodological limitations including inconsistencies in data due to the presence of negative DPG and elevated DPG in patients without PH. The nature of the controversial value of the DPG in HF patients needs to be further addressed in future studies. Recent data indicate that—depending on the consideration of the DPG and/or PVR—the prevalence of Cpc-PH in patients with HF is 12–38%.<sup>10,14</sup> The above data collectively indicate that PH and RV dysfunction are frequent and associated with a poor outcome in patients with LV HF.

## Pathobiology of pulmonary hypertension related to left heart disease

The pathobiology of PH in left HF is complex and highly heterogeneous, and remains incompletely understood. Pulmonary hypertension primarily results from the passive backward transmission of elevated left-sided filling pressures, which occur as a consequence of systolic or diastolic LV dysfunction (*Figure 1*).<sup>11</sup> Furthermore, functional mitral regurgitation (MR) will result in elevations of LAP and PAP, which usually worsen during exercise. In addition to LV remodelling and dysfunction, an increase in LA size (which is relatively load-independent and serves as a marker of morbidity and mortality in HF), interstitial fibrosis causing LA stiffness, and reduced LA compliance, as well as impaired LA contractility, contribute to pathogenic alterations in the pulmonary circuit and right heart (*Figure 2*). These alterations of LA diastolic and systolic properties affect cardiac filling and output, and the backward transmission of elevated left-sided filling pressures leads to an increase of pulmonary pressures, particularly during exercise.<sup>25,26</sup> Consistently, LA dysfunction



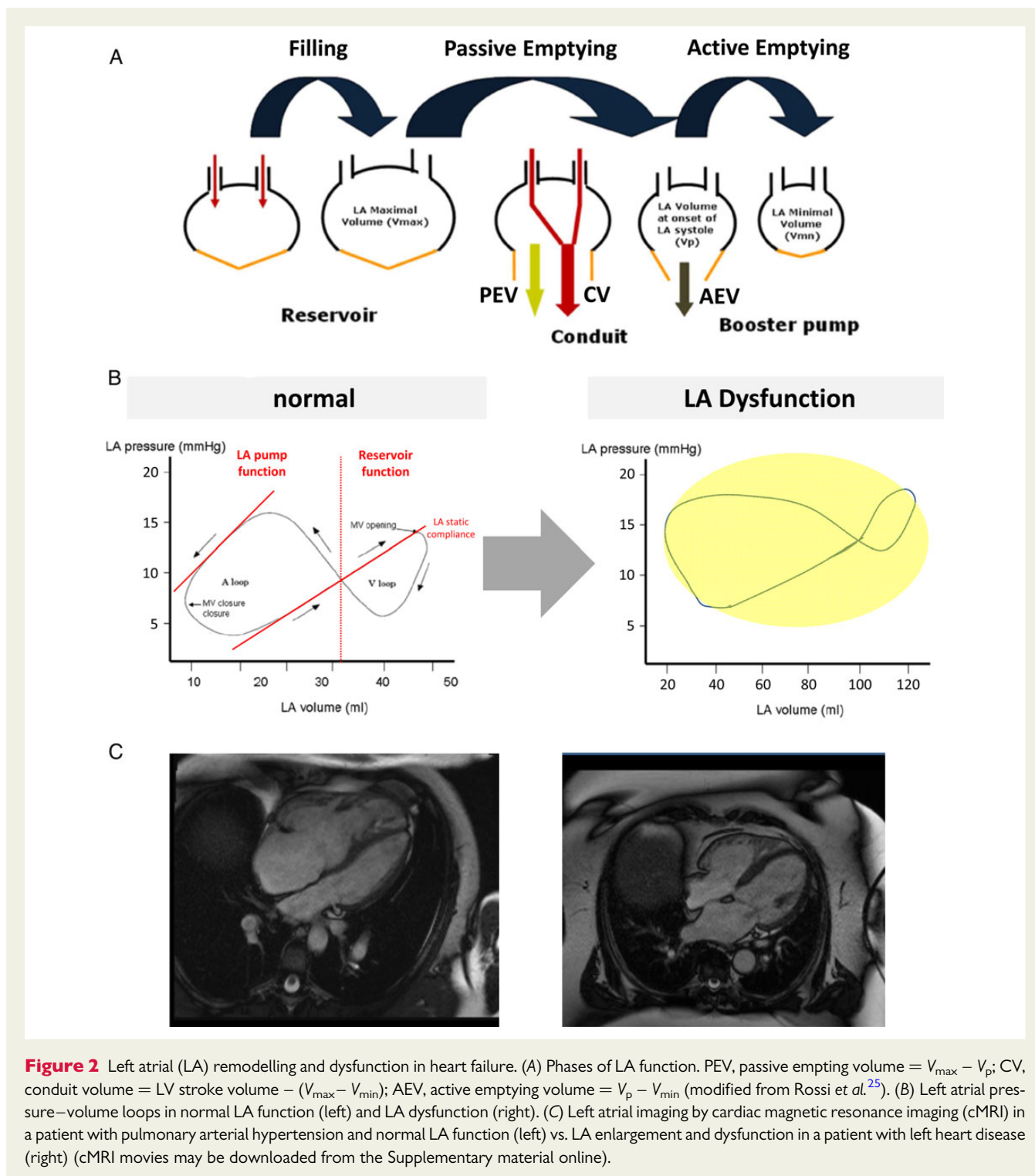
**Figure 1** Cardiopulmonary interaction and pathobiology of pulmonary hypertension (PH) in left ventricular heart failure. Shown is (i) the backward transmission of elevated left ventricular filling pressures into the pulmonary circulation (*post-capillary haemodynamic profile*), (ii) potential superimposed components contributing to the extent of PH (leading to a *pre-capillary component*),<sup>11</sup> which may be associated with (iii) pulmonary vascular remodelling in some patients, thus leading to (iv) right ventricular strain and dysfunction over time. Right ventricular (RV) dilation and increase in wall stress/tension (internal RV afterload) result in elevated myocardial oxygen consumption, which with concomitant reduction in coronary perfusion gradient leads to RV ischaemia and progressive RV failure.

relates to symptom onset in patients with HFpEF.<sup>27</sup> In addition to its pathophysiological significance, LA dysfunction may also determine treatment responses to targeted PH therapies in patients with LHD, since lowering of PVR and increased pulmonary blood flow may lead to increased PAWP and pulmonary oedema in patients with reduced LA compliance.

In the pulmonary circulation, sudden increases of LAP may cause 'alveolar-capillary stress failure', a reversible barotrauma altering endothelial permeability and allowing leakage of erythrocytes, proteins, and fluid into the alveolar lumen, thus causing interstitial and alveolar oedema. Sustained elevation of left-sided filling pressure and pulmonary venous pressure may be accompanied by superimposed components in the pulmonary circuit, which include decreased NO availability, increased expression of endothelin-1, desensitization to natriuretic peptide-induced vasodilatation, infiltration of inflammatory cells, and neurogenic or metabolic factors.<sup>11</sup> Furthermore, hypoxia promotes vasoconstriction and growth responses in the pulmonary circuit,<sup>28</sup> and tachyarrhythmias, particularly atrial fibrillation, may precipitate PH in patients with LV HF. These additional components may trigger pulmonary arterial vasoconstriction, and—over time—structural remodelling of small pulmonary resistance arteries, indicative of a pre-capillary component of PH where PAP further increases in excess of PAWP elevation (Figure 1). Indeed, pulmonary arteriolar remodelling similar to PAH has been described in severe PH-LHD, particularly in patients with

Cpc-PH ( $DPG \geq 7$  mmHg).<sup>10</sup> Histopathological changes include thickening of the alveolar-capillary membrane, medial hypertrophy, intimal and adventitial fibrosis, and luminal occlusion in small pulmonary arterioles, whereas 'plexiform lesions' pathognomonic of PAH are not usually found.<sup>10,29,30</sup> The fact that unloading of the LV by implantation of a LV assist device (LVAD) in patients with HFpEF and severe 'fixed' PH may substantially lower or even normalize PAP over time indicates that the alterations in the pulmonary circulation are partly reversible at least in some patients.<sup>31,32</sup> In contrast to the systemic circulation, where vascular compliance is mainly determined by the aorta, arterial compliance in the lung is distributed over the entire pulmonary vascular bed, so that resistance (R) and compliance (C) are predominantly determined by the small resistance vessels. Hence, pulmonary arteriolar remodelling mainly contributes to the increase in PVR and reduced PA compliance in Cpc-PH.

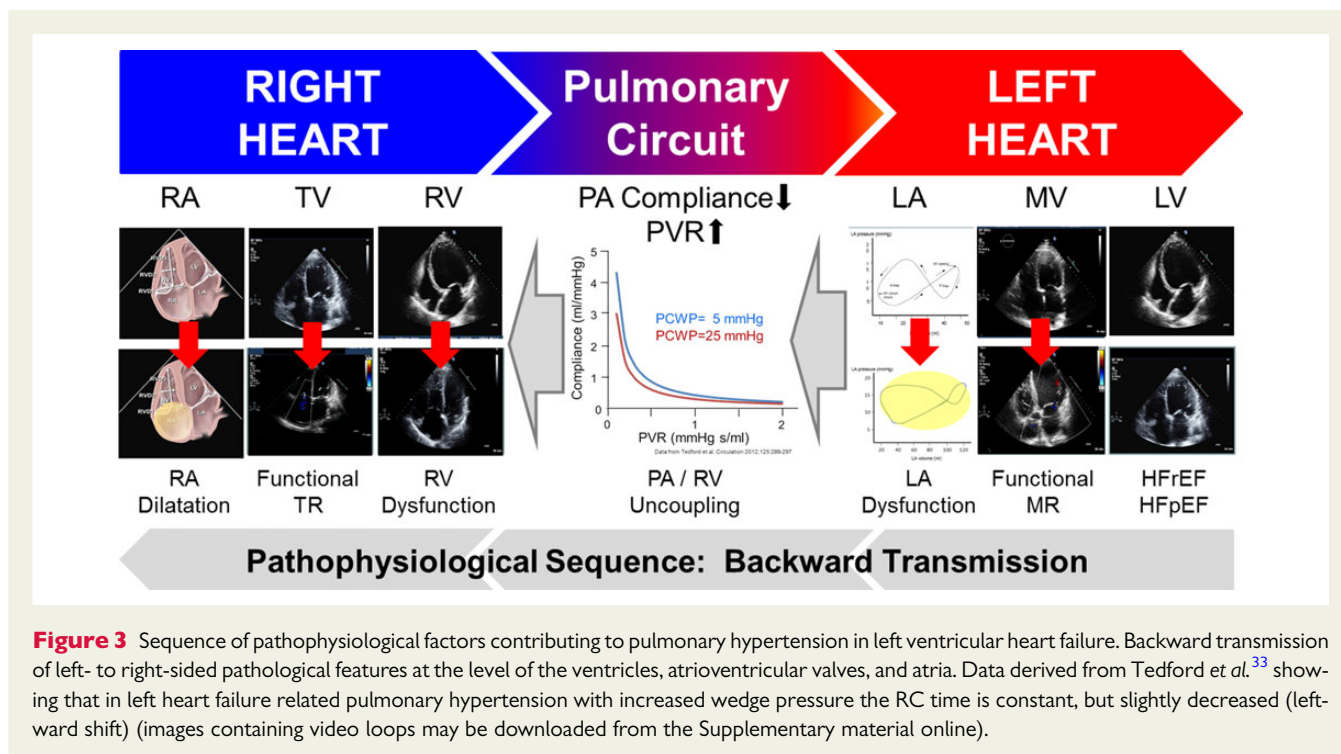
Of interest, there is an inverse relation between R and C in the pulmonary circulation, and this holds true in PH-LHD.<sup>22,33</sup> The product of R and C (RC time) determines the drop in PAP after pulmonary valve closure. It was found that in left HF with increased PAWP, the RC time under the influence of the increased PAWP is slightly decreased in comparison with PAH (Figure 3). Whether this is due to abnormal pulmonary venous remodelling, increased pulmonary vascular tone in left HF or just the consequence of the increased wedge pressure on the RC time calculations remains unknown. It has been suggested that the pressure gradient between



**Figure 2** Left atrial (LA) remodelling and dysfunction in heart failure. (A) Phases of LA function. PEV, passive emptying volume =  $V_{max} - V_p$ ; CV, conduit volume = LV stroke volume - ( $V_{max} - V_{min}$ ); AEV, active emptying volume =  $V_p - V_{min}$  (modified from Rossi *et al.*<sup>25</sup>). (B) Left atrial pressure–volume loops in normal LA function (left) and LA dysfunction (right). (C) Left atrial imaging by cardiac magnetic resonance imaging (cMRI) in a patient with pulmonary arterial hypertension and normal LA function (left) vs. LA enlargement and dysfunction in a patient with left heart disease (right) (cMRI movies may be downloaded from the Supplementary material online).

the diastolic PAP and PAWP (DPG) is less dependent on volume load and stroke volume than the TPG, and that an elevated DPG may therefore be a better indicator of a pre-capillary component of PH.<sup>9</sup> However, the DPG may not be an ideal parameter, as it is subject to inaccuracies related to heart rate, hypoxia, catheter whip, utilizing computer-generated measurements, and the presence of negative values or elevated DGP without PH. While in two retrospective studies, the DPG was shown to be a predictor

of survival in PH-LHD,<sup>10,22</sup> two other studies failed to demonstrate a prognostic impact of the DPG in patients with cardiomyopathy or heart transplantation and PH.<sup>14,24</sup> Thus, its role for prognostication of survival and/or response to PH therapies must be further explored. Another implication of the constant RC is that based on the inverse relationship between compliance and resistance, PA compliance is a more sensitive marker for early disease than PVR. Indeed, a reduced PA compliance and abnormal RV/PA coupling



are found even in early stages of HFpEF, and PA compliance appears to be prognostically relevant even with normal PVR.<sup>21–23,34,35</sup>

The elevations of pulmonary pressures and PVR represent an increase of both resistive and pulsatile RV afterload, which results in dilatation and maladaptive remodelling of right heart chambers, functional tricuspid regurgitation, and ultimately RV dysfunction and failure. Pathological changes of the RV include hypertrophy, fibrosis, dilatation, and a change in RV shape from a crescent to a more spherical shape, which is associated with functional tricuspid regurgitation and elevated right atrial pressure (RAP). Right ventricular dysfunction resulting in low cardiac output is a key determinant of outcome in PH-LHD. In fact, the prognostic significance of an elevated PAP in HF increases with the degree of RV dysfunction irrespective of LVEF.<sup>13,19</sup> However, the relationship between the severity of PH and RV dysfunction is not 'linear', as some patients with severe PH display normal RV function. In summary, a dysfunctional RV and clinical signs of right HF in patients with LHD occur as a consequence of pathological changes at the level of the ventricles, atrioventricular valves, and atria in both the left and right heart, and complex pathomechanisms of cardiopulmonary interaction affecting PVR and PA compliance determine the impact of LHD on the right heart (Figure 3).

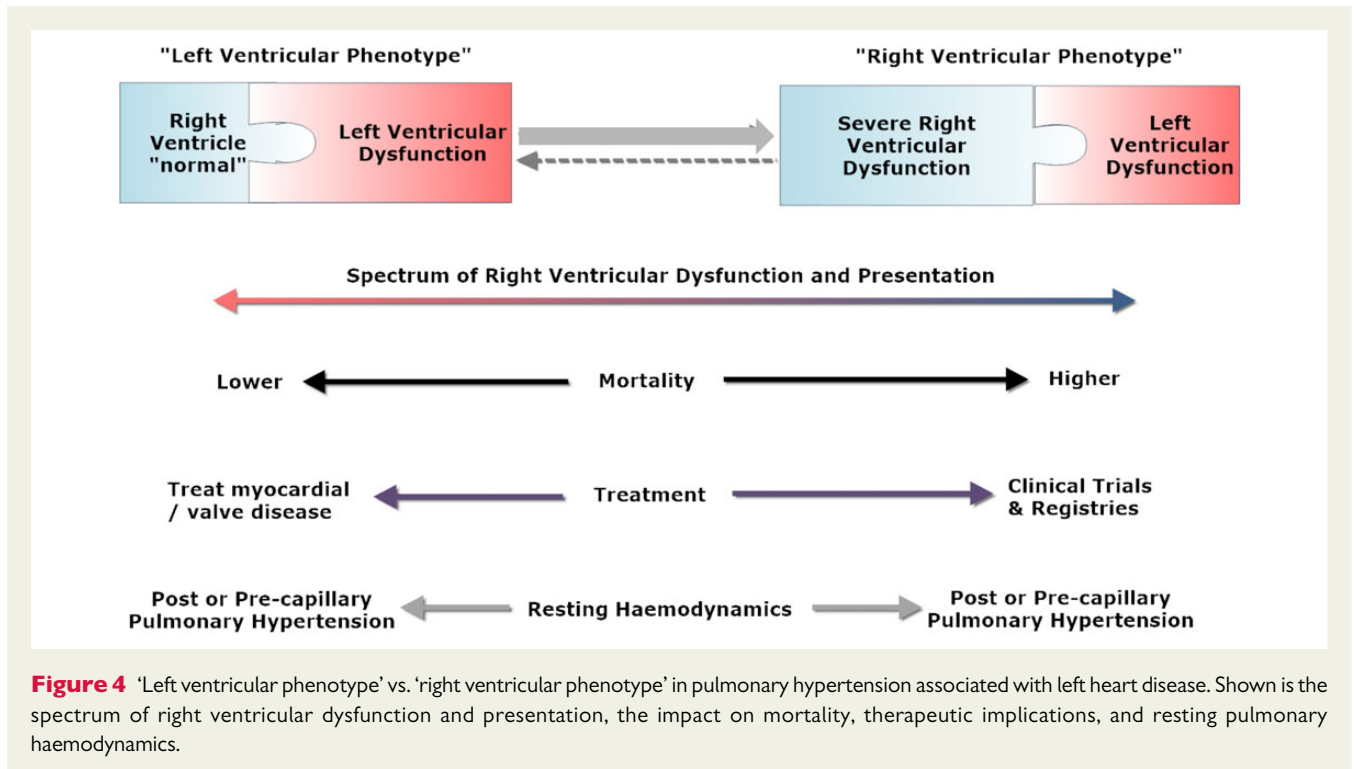
### Left vs. right ventricular phenotype

The current knowledge about the heterogeneity of PH in LV HF and the reasons, why some patients develop severe PH and RV dysfunction whereas others do not, remains limited. Two factors may be key: (i) the susceptibility for pulmonary vascular disease (due to genetic factors and/or environmental stressors and/or comorbidities) and (ii) the factor 'time'. In many cases, only a 'snapshot' of a patient is considered during the course of HF development and

progression. However, in HF patients who are susceptible for pulmonary vasculopathy, a potential evolution of LV disease to right ventricular (RV) dilatation and functional impairment as a result of PH may be observed. During this evolution, the heart alters progressively across a spectrum from a picture of an abnormal LV with an otherwise normal RV ('left ventricular phenotype') into a picture of a dilated and functionally impaired RV which may even dominate over the LV abnormality ('right ventricular phenotype') (Figure 4). The appearance of LV or RV phenotype depends on the point in this evolution that cardiac imaging is undertaken. This is supported by the fact that RV dysfunction in HFpEF is associated with more advanced stages of the disease.<sup>20</sup> Examples of PH and RV phenotype developing over time—depending on patient's susceptibility—are depicted in Supplementary material online, Figure S1. Mortality increases as the RV phenotype develops. It must be emphasized that invasive haemodynamics are not always reliable in differentiating between different phenotypes across the spectrum because the use of diuretics and alterations in fluid status may influence ventricular filling pressures. While post-capillary haemodynamics indicate that LV disease is driving PH, pre-capillary haemodynamics do not exclude LV disease with certainty.

### The dilemma of pulmonary arterial wedge pressure measurements to discriminate pre- and post-capillary pulmonary hypertension

Pulmonary arterial wedge pressure measurements are prone to significant errors which have direct implications on PH classification



and treatment decisions. Limitations and uncertainties include the threshold level of PAWP that discriminates between pre- and post-capillary PH, technical difficulties to obtain correct recording of pressure tracings, as well as lack of proper standardizations of calibration (zero level), and particularly the method of PAWP reading in relation to the respiratory cycle (Table 1).

Although physicians use the same threshold level of 15 mmHg to discriminate between pre- and post-capillary PH worldwide,<sup>1,6,36</sup> 'expert centres' utilize different methods of measurement, which may produce a mean difference of 4–6 mmHg.<sup>37–39</sup> These differences are due to respirophasic variations of intrathoracic pressures, resulting in lower values during inspiration, and higher values during expiration (Figure 5A). Additional sources of error include uncertainties about the threshold level and the impact of volume load (Figure 5B). Directly opposing studies have recently been published regarding the method of PAWP measurement and potential misclassifications between PAH and PH due to LHD (particularly HFpEF). Whereas one study indicated that the use of a digital mean value averaged across the respiratory cycle instead of the end-expiratory mean value frequently leads to misclassifications of PH-HFpEF as PAH,<sup>37</sup> the other study revealed that reliance on end-expiratory PAWP instead of the digital mean value may lead to misclassifications of pre- as post-capillary PH<sup>38</sup> (see Figure 5A). This dilemma highlights the high degree of variability, and the differences may in part be explained by the patient populations studied: while the end-expiratory method appears to be appropriate to distinguish between PAH and HFpEF, the digital mean value may be more appropriate in patients with COPD in whom respiratory swings are usually more pronounced.<sup>37,38,41</sup>

In clinical practice, misclassifications of PH-HFpEF as PAH and inappropriate treatment of such patients with targeted PAH drugs appears much more common than vice versa. Furthermore, the end-expiratory method of PAWP reading was recently shown to correlate well with direct measurement of LVEDP, and to a pre-capillary pattern.<sup>37,42</sup> In order to minimize the risk of misclassifying PH-LHD as PAH, at least in elderly patients and those with signs or risk factors of LHD, and in accordance with the recommendations of the 5th World Symposium on Pulmonary Hypertension 2013 in Nice,<sup>6,11</sup> the following standardization of PAWP measurement appears most appropriate, particularly to discriminate between PAH and PH due to LHD:

- **Zero level:** the zero reference level should be set at the mid-thoracic position, which represents the level of the left atrium.<sup>39</sup>
- **Pulmonary arterial wedge pressure threshold:** the threshold level to discriminate between pre- and post-capillary PH should be 15 mmHg, but suspicion for PH-HFpEF should be raised at values between 12 and 15 mmHg particularly in diuretic patients and/or risk factors for LHD.<sup>6,11</sup>
- **Reading of PAWP:** PAWP should be measured at end-expiration, where the effects of intra-thoracic pressure swings are minimal.<sup>6</sup> Patients should not hold their breath, and must not erroneously perform a Valsalva manoeuvre.
- **Direct measurement of LVEDP:** should be considered if PAWP is not reliably measurable or uncertain, or if significant LHD is suspected.

Nevertheless, physicians have to be aware of the limitations of PAWP measurement in general (Table 1), and of potential misclassifications

**Table 1** Potential confounders and criteria of valid measurement, reading and interpretation of pulmonary arterial wedge pressure tracings

<i>Measurement and reading of pressure tracings</i>	
Measurement	may be challenging not possible in every patient (dilated arteries)
Zero point	should be mid-thoracic
Point of reading	end of normal expiration (during free respiration)
<i>Factors preventing correct interpretation of pressure tracings</i>	
Diuretic use	may artificially lower PAWP/LVEDP in patients with LHD
COPD	prominent respiratory swings, digital mean method may be preferred
Atrial fibrillation	variable/unreliable values due to interbeat variation mean of five measurements should be calculated
High v-wave	consider mitral regurgitation (diastolic LV dysfunction)
Thorax deformities	referencing may be difficult
Abdominal obesity	raised intra-abdominal and intra-thoracic pressure
<i>Criteria for valid PAWP measurement</i>	
PAWP value	PAWP equal or lower than diastolic PAP
Pressure tracing	similar to atrial pressure tracing (a- and v-wave)
Respirophasic variations	respiratory swings visible
Catheter position	stationary catheter position (fluoroscopy)
Aspiration	free flow within the catheter (aspiration possible)
O <sub>2</sub> saturation	in occluding position, aspiration of oxygen-rich blood (SO <sub>2</sub> >94%) from the distal lumen

when using either the digitized mean value or the end-expiratory method of PAWP reading. In patients with COPD and pronounced respiratory swings, utilization of the digitized mean value may be appropriate.

## Distinction between pulmonary arterial hypertension and pulmonary hypertension associated with left heart disease

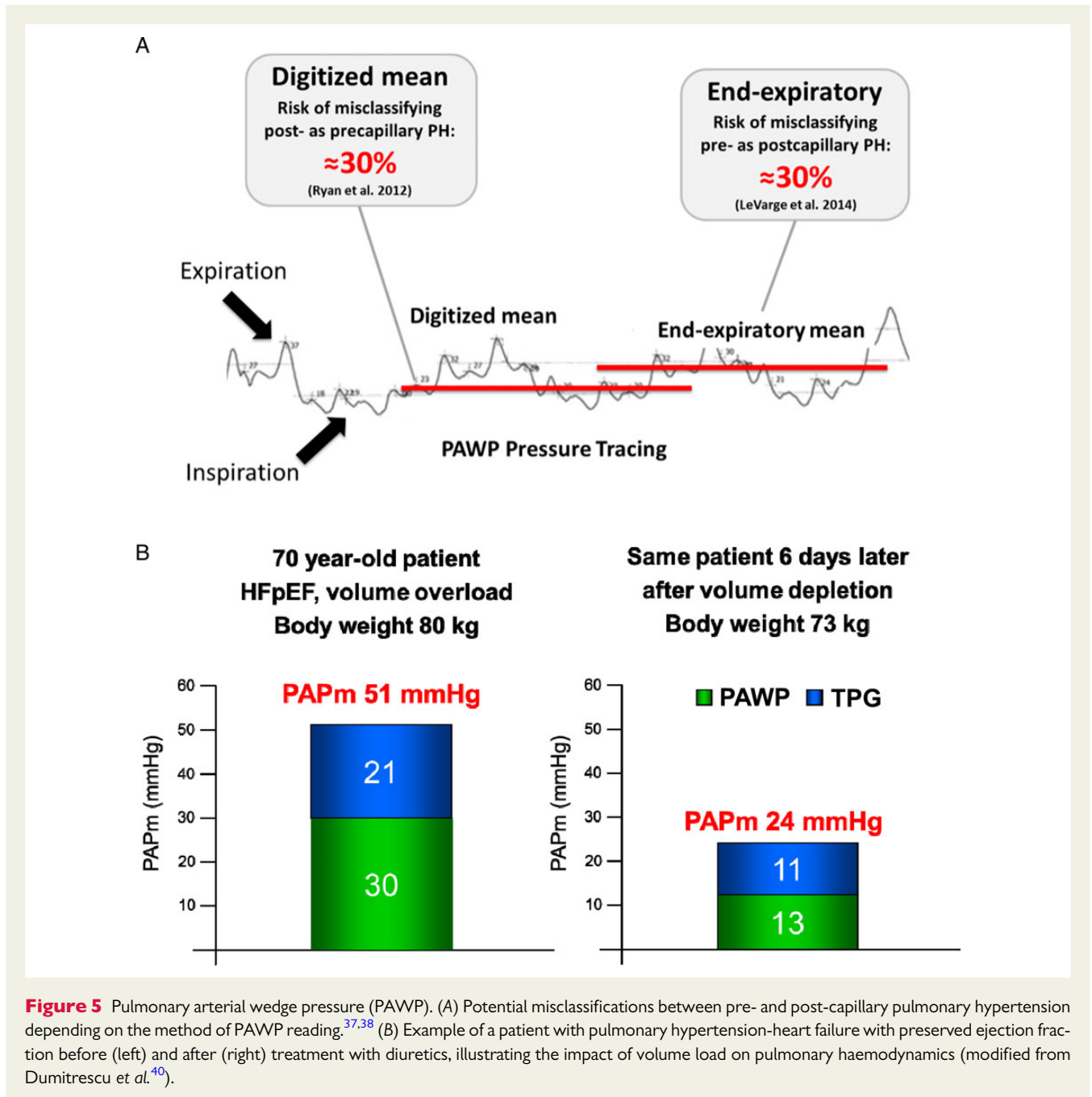
Current guidelines indicate that RHC is mandatory to confirm the diagnosis of PH, and—based on the PAWP—to allow for a precise haemodynamic classification as pre- or post-capillary PH.<sup>12</sup> However, due to the above mentioned limitations of PAWP measurement and interpretation, and to the high degree of variability, this is not always applicable in clinical practice. While RHC is indeed required for proper diagnostic work-up in PH, invasively measured haemodynamics alone are in many cases not sufficient to establish a precise diagnosis. Instead, an integrated interpretation of invasive and non-invasive evaluations is required. *Figure 6* provides a diagnostic algorithm/decision-making tree, which may help to integrate RHC and non-invasive findings, and to better elucidate the underlying cause and pathophysiology of PH in the context of LHD. Patients suspected to have PH should undergo clinical evaluation and basic non-invasive testing, and—if indicated—additional tests should be performed. A predictive model incorporating medical history, ECG, and echocardiography data helps to

discriminate PAH from PH-LHD.<sup>43</sup> Based on the results of a comprehensive non-invasive work-up, a 'suspected diagnosis' should be formulated. Clinical features, specific findings, and test results that may be suggestive of either PAH or PH-LHD are listed in *Table 2*.

Since here we focus on the differentiation between PAH and PH-LHD, we do not specify other forms of PH (Nice Groups 3–5) which should certainly be diagnosed or ruled out accordingly.<sup>2,6,12</sup> In cases of mild PH and dominant LHD, further testing for PH is usually not required. Instead, left heart catheterization may be indicated, and LHD treated. If PAH is suspected, or severe PH is present in addition to (mild) LHD, invasive assessment of pulmonary haemodynamics by RHC is usually indicated.

When performing RHC, there are three main tasks (three C's) (*Figure 6*):

- (1) *Confirm*: the presence of PH should be confirmed by a mean PAP  $\geq 25$  mmHg.
- (2) *Complete*: it is crucial to obtain the complete set of pulmonary haemodynamics; this includes measurement of PAP (systolic, diastolic, and mean), RAP, cardiac output/cardiac index, mixed venous oxygen saturation, and calculation of the TPG (mean PAP – PAWP), DPG (diast PAP – PAWP), and PVR (mean PAP – PAWP/CO). Furthermore, pulmonary haemodynamics must always be interpreted in relation to systemic vascular resistance (PVR/SVR ratio).
- (3) *Characterize*: PH should be characterized as pre-, isolated post-capillary, or combined post- and pre-capillary, based on the

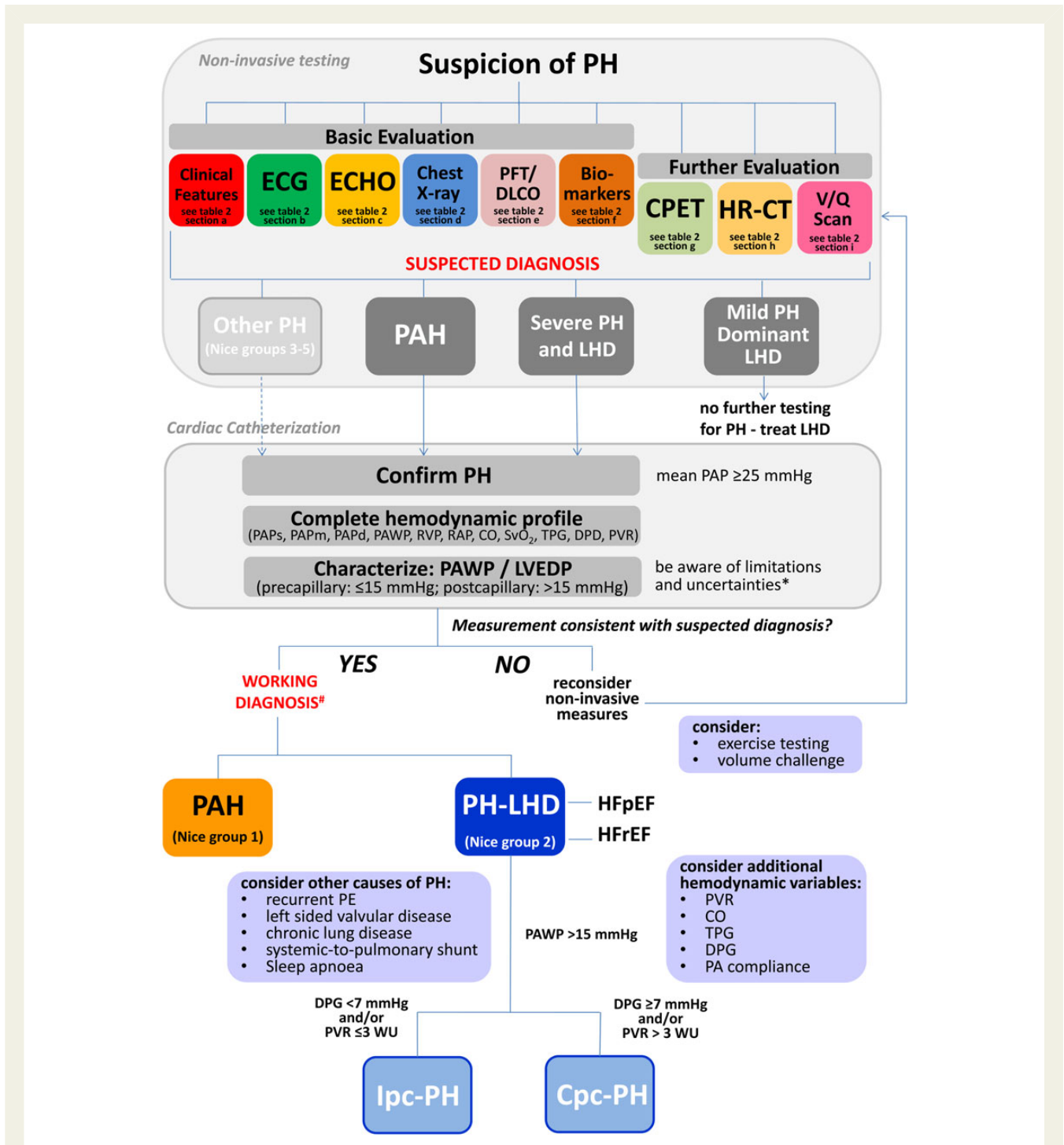


assessment of LV filling pressure either measured as PAWP or LVEDP. When interpreting the pressure tracings, it is critical to be aware of the limitations and sources of error with regard to PAWP measurement (Table 1).

It is of key importance to ask whether the results obtained by invasive measurement of haemodynamics are consistent with the 'suspected diagnosis' based on the results of non-invasive testing. If the answer is 'yes', then a 'working diagnosis' is established, and patients should be treated accordingly. If the answer is 'no', then non-invasive measures—particularly echocardiographic parameters—

should be reconsidered, and invasive haemodynamics must be interpreted in the clinical context. Of note, as the LVEDP depends on the loading condition of the LV, unloading (e.g. by forced diuresis) can decrease LVEDP (and consecutively PAWP) to values <15 mmHg, even in patients with LHD. In cases of doubt, invasive assessment of LV filling at rest and during a stress test (either exercise or fluid challenge) may be performed. As HFpEF patients have a steep end-diastolic pressure/volume relationship, even small changes in volume are associated with a significant increase in filling pressures, and a 'volume challenge' (e.g. infusion of 500 mL of saline within 5–10 min) may be feasible to unmask occult pulmonary





**Figure 6** Differential diagnosis between pulmonary arterial hypertension (PAH, Nice Group 1) and pulmonary hypertension associated with left heart disease (PH-LHD Nice Group 2). Shown is a diagnostic algorithm, integrating non-invasive tests, and haemodynamic variables assessed by cardiac catheterization. For interpretation of non-invasive tests, see corresponding Table 2. \*Limitations and uncertainties of pulmonary arterial wedge pressure/left ventricular end-diastolic pressure measurement are depicted in Table 1. Ipc-PH, isolated post-capillary PH; Cpc-PH, combined post- and pre-capillary PH.

venous hypertension.<sup>46</sup> Based on current data, a PAWP >18 mmHg may be considered as an abnormal response to fluid challenge.<sup>47</sup> An alternative may be the integration of exercise testing

into the diagnostic work-up.<sup>48</sup> However, such tests lack proper standardization and are awaiting further evaluation and validation before their use in clinical practice can be recommended.

**Table 2** Results of non-invasive diagnostic tests may be suggestive of either pulmonary arterial hypertension or pulmonary hypertension associated with left heart disease

	Suggestive of PAH (Nice group 1)	Suggestive of PH-LHD (Nice group 2)
a. Clinical features	Younger age, familial cases, bendopnea <sup>a</sup> , risk factors for PAH: CTD, CHD, severe liver disease, portal hypertension, HIV	Older age, hypertension, diabetes, CAD, BMI >30, pulmonary congestion, history of pulmonary oedema, orthopnoea
b. ECG	RV hypertrophy, right axis, RV strain	LV hypertrophy (Sokolow–Lyon index: S in V1 + R in V6), left axis, atrial fibrillation
c. ECHO <sup>b</sup>	No signs of LHD, PASP elevated, RV > LV, RV hypertrophy/dysfunction (TAPSE), RVOT notching <sup>c</sup> , small LA, dilated IVC	Enlarged LA, LV hypertrophy, signs of systolic (EF) and/or diastolic (E/A, DT, E/E') LV dysfunction, valvular disease
d. Chest X-ray	Enlarged right heart chambers, dilated PA, peripheral PA pruning	Pulmonary congestion, Kerley B lines, pleural effusions, enlargement of left heart chambers
e. PFT/DLCO	Normal/mild obstructive spirometry, normal or moderately decreased DLCO <sup>d</sup> , low p <sub>c</sub> CO <sub>2</sub> (≤36 mmHg) <sup>e</sup>	Normal/obstructive spirometry, normal DLCO (may be decreased due to comorbid COPD), high p <sub>c</sub> CO <sub>2</sub> (>36 mmHg) <sup>e</sup>
f. Biomarkers	BNP/NTproBNP elevated (not discriminate between Groups 1 and 2)	BNP/NTproBNP elevated (not discriminate between group 1 and 2)
g. CPET	Low P <sub>ET</sub> CO <sub>2</sub> at AT, decreasing during exercise; high VE/VCO <sub>2</sub> , increasing during exercise	P <sub>ET</sub> CO <sub>2</sub> at AT normal or slightly lowered, not decreasing during exercise, VE/VCO <sub>2</sub> not increasing during exercise
h. HR-CT	To diagnose or rule out parenchymal lung disease (not discriminate between Groups 1 and 2)	To diagnose or rule out parenchymal lung disease (not discriminate between Groups 1 and 2)
i. V/Q scan	To diagnose or rule out CTEPH (not discriminate between Groups 1 and 2)	To diagnose or rule out CTEPH (not discriminate between Groups 1 and 2)

<sup>a</sup>Bendopnea is typical in PAH, but may be found in HFREF, particularly when associated with RV dysfunction and elevated RAP as described in Ref. 44.

<sup>b</sup>A score of five echocardiographic variables may be utilized to discriminate between pre-capillary PH (RV/LV ratio ≥1.0, LVEI >1.2, E/E' ≤10, RV forming apex, IVC >20 mm without inspiratory collapse) and post-capillary PH (RV/LV ratio <1.0, LVEI ≤1.1, E/E' >10, RV not forming apex, IVC ≤20 mm and collapsible).<sup>53</sup>

<sup>c</sup>RVOT notching.<sup>54</sup>

<sup>d</sup>Marked hypoxemia and low DLCO may suggest pulmonary veno-occlusive disease (PVOD).

<sup>e</sup>Role of the capillary pCO<sub>2</sub> (p<sub>c</sub>CO<sub>2</sub>) described in Ref. 45. CTEPH, chronic thromboembolic pulmonary hypertension; CAD, coronary artery disease

## Non-invasive tools to differentiate between pulmonary arterial hypertension and pulmonary hypertension-heart failure with preserved ejection fraction

While systolic dysfunction in patients with PH-HFrEF is usually easy to detect, the proper distinction between PAH and PH associated with HFpEF is much more challenging. Regardless of the presence of PH, there are reliable non-invasive tools that indicate the presence of diastolic LV dysfunction (Table 2).<sup>11,49</sup> The gold standard for the assessment of LV diastolic function is the invasive assessment of the pressure–volume relationship which usually requires an estimation of LV volume by the conductance method. It has been shown that LV stiffness is a reliable characteristic in patients with HFpEF.<sup>50,51</sup> An alternative to the assessment of invasive haemodynamics can be comprehensive echocardiography, which—in combination with natriuretic peptides—is feasible to diagnose HFpEF as proposed by a consensus statement.<sup>49</sup> Echocardiographic assessment for HFpEF includes estimation of LVEDP by E/E', assessment of left atrial size, E/A ratio, and deceleration time.<sup>52</sup> It should be noted, however, that echocardiographic parameters such as E/E' also have their limitations in accurately diagnosing HFpEF. An integrative score of five echocardiographic variables (RV/LV ratio, left ventricular eccentricity index (LVEI), E/E', RV forming apex, width

and inspiratory collapse of IVC) as well as additional parameters such as the shape of the RV outflow tract Doppler envelope ('RVOT notching') may be utilized to discriminate between pre- and post-capillary PH.<sup>53,54</sup> The presence of one or more of the above findings should prompt one to suspect PH-HFrEF instead of PAH, even if the left-sided filling pressure as assessed by PAWP or LVEDP measurement during cardiac catheterization may be <15 mmHg.

## Treatment of pulmonary hypertension in left ventricular heart failure

The prognostic impact of PH and RV dysfunction in LV HF provides the rationale for targeting PH as a potential additional treatment option in both HFrEF and HFpEF. However, it is critical to precisely determine the cause and severity of PH, before any treatment decisions are made. Therefore, a comprehensive diagnostic work-up is necessary, and targeted HF treatments (medical/interventional) remain the only established therapies. Nevertheless, the treatment options in HF—particularly HFpEF—remain limited, and the classification of PH may be challenging in individual patients. In selected cases presenting with a 'right ventricular phenotype' in whom PH and RV dysfunction are prominent, targeted judicious PH therapy may be considered despite the presence of LHD.<sup>55</sup>

## Treatment of left heart disease and lowering of left-sided filling pressure

The clinical impact of elevated PAWP/LVEDP and PAP in patients with LV HF warrants attention. Optimized treatment of the underlying LHD including medical treatments (reaching the target dosages) and interventional therapies (e.g. CRT, ICD, LVAD, MitraClip) usually helps to lower left-sided filling pressure and is always the primary aim in HF patients. Nevertheless, the consideration of pulmonary haemodynamics may be helpful, and volume depletion is usually associated with a substantial reduction of left-sided filling pressure (PAWP/LVEDP), PAP, and TPG (see *Figure 5C*). In this context, the CHAMPION trial has shown that consideration of the PAP (assessed by an implantable device) as an additional treatment target profoundly reduced the rate of HF-associated hospitalizations in both HFpEF and HFrEF.<sup>56,57</sup> Of note, reductions of PAP were not achieved by targeted PAH drugs in this trial, but by optimized HF treatment including adjustment of diuretics.

## Repair of mitral regurgitation in heart failure

Particularly in patients with HFrEF and dilated left-sided heart chambers, functional MR is common, may represent the main cause of PH, and leads to increased mortality.<sup>58</sup> Even exercise-induced PH and RV dysfunction were recently shown to be associated with adverse outcome in patients with asymptomatic MR.<sup>59,60</sup> There is good evidence in patients with LV HF and functional MR, that proper treatment of the mitral valve including catheter-based approaches such as Mitral Clipping or Cardio-Band lead to substantial improvement of pulmonary haemodynamics, including reductions of the mean PAP and PAWP (mainly via reduction of the v-wave), and a profound improvement of cardiac index.<sup>61</sup> While the evidence remains limited and outcome trials are still lacking, percutaneous mitral valve repair was shown to improve clinical symptoms, exercise capacity, quality of life, and HF-associated hospitalizations in HF patients.<sup>62</sup> Hence, MR has to be considered as the potential cause of PH in LV HF, and appropriate valve repair should be initiated in patients who are on optimized medical treatment.

## Targeted treatment of pulmonary hypertension in patients with left ventricular heart failure

Based on the prognostic impact of PH and RV dysfunction in both HFrEF and HFpEF, treatment of PH in addition to established HF therapies may appear to be a promising approach. Targeted therapies approved for the treatment of PAH include endothelin receptor antagonists (ERAs), prostanoids, phosphodiesterase type 5 inhibitors (PDE5i), and stimulators of soluble guanylate cyclase (sGC).<sup>3,4</sup> It should be emphasized that none of these compounds are approved for the treatment of PH-LHD. A concern with the use of targeted PAH drugs in patients with LHD is that pulmonary vasodilation and increasing pulmonary blood flow in the presence of elevated left-sided filling pressures may potentially lead to pulmonary oedema and cardiac decompensation. Despite these concerns, such compounds have been investigated in patients with HF.

Randomized controlled trials (RCTs) investigating the efficacy and safety of ERAs and prostanoids have shown no benefit, or PH therapies have even proved harmful (summarized in Refs 11,55). For instance, the FIRST trial, which investigated intravenous epoprostenol in patients with PH-HFrEF, was prematurely terminated due to a trend for increased mortality in the treatment group when compared with placebo. Notably, ERAs have only been investigated in patients with HF in general without considering the presence of PH, so their impact on PH-LHD remains unknown. Few data are currently available in PH-HFpEF, and the use of ERAs may be associated with an increased risk of peripheral oedema in such patients. An ongoing Phase II trial (MELODY) currently investigates the safety and potential efficacy of the novel ERA macitentan in patients with HFpEF and Cpc-PH (*Table 3*).

More recent studies have focused on targeting the NO pathway in patients with PH-LHD (*Table 3*). The randomized controlled RELAX trial has shown that the PDE5i sildenafil did not improve peak oxygen consumption (primary endpoint) and exercise capacity in patients with HFpEF in the absence of PH.<sup>63</sup> In a recent single-centre RCT, sildenafil also failed to improve haemodynamics or exercise capacity in 53 patients with HFpEF and Ipc-PH.<sup>64</sup> On the other hand, small single-centre studies have consistently shown that sildenafil improved haemodynamic parameters and exercise capacity in patients with severe PH that was associated with either HFrEF or HFpEF.<sup>65–67</sup> A meta-analysis of six RCTs investigating the efficacy and safety of PDE5i in patients with HFrEF—each performed in small numbers of patients—revealed that additional use of a PDE5i improved haemodynamics and exercise capacity, and reduced clinical symptoms and hospitalizations when compared with placebo.<sup>68</sup> However, such data should be interpreted with great caution, as they were obtained in highly selected patients, and data from larger RCTs are yet lacking.

An alternative way to modulate the NO pathway is the stimulation of sGC. The sGC stimulator riociguat (which is approved for PAH and inoperable CTEPH) was recently investigated in two RCTs in PH-LHD. In patients with PH-HFrEF, the LEPHT trial failed to reach the primary endpoint of lowering PAP vs. placebo, but led to a substantial increase in cardiac index, resulting in lowering of PVR.<sup>69</sup> Likewise, a proof-of-concept trial testing the acute effects of riociguat in patients with PH-HFpEF (DILATE) obtained similar results.<sup>70</sup> These findings may suggest a systemic and/or cardiac effect of riociguat rather than pulmonary vasodilation. Targeting this pathway in HF awaits further investigation.

Based on the current evidence, the use of targeted PAH therapies in patients with PH related to left HF is discouraged, and selected patients with Cpc-PH and/or RV phenotype should be referred to centres with expertise in both HF and PH, and should—whenever possible—be included into clinical trials.

## Clinical relevance and future considerations

In patients with LV HF, PH is a common and life-threatening complication that remains underestimated in clinical cardiology. Given the relentlessly increasing incidence and prevalence of HF, particularly HFpEF, and the poor prognosis of patients who develop PH and

**Table 3** Summary of recently completed and ongoing clinical trials in pulmonary hypertension associated with left heart disease

Drug	n	Start	End	Duration	Primary endpoint	Secondary endpoints
HF with reduced EF <b>Riociguat</b> LEPHT <sup>69</sup>	201	Results available		16 weeks	Change in mPAP from baseline	Haemodynamic and echocardiographic variables, biomarker levels, safety, pharmacokinetics
<b>Sildenafil</b> Sil-HF (NCT01616381)	210	9/2012	6/2014	24 weeks	Patient Global assessment 6MWD	QoL, Kansas city questionnaire, safety
<b>Tadalafil</b> PITCH-HF (NCT01910389)	2102	Study terminated February 2014 <sup>a</sup>		Up to 54 months	Time to CV death or 1st HF hospitalization	Biomarkers levels, exercise capacity, QoL, safety
HF with preserved EF <b>Sildenafil</b> RELAX <sup>63</sup>	216	Results available		24 weeks	Change in peak VO <sub>2</sub> from baseline	Exercise capacity, clinical status, QoL, safety
<b>Sildenafil</b> Hoendermis et al. <sup>64</sup>	52	Results available		12 weeks	Change in mPAP from baseline	Change in PAWP, cardiac output, peak VO <sub>2</sub>
<b>Riociguat</b> DILATE <sup>70</sup>	48	Results available		16 weeks	Change in mPAP from baseline	Haemodynamic and echocardiographic variables, biomarker levels, safety, pharmacokinetics
HF with EF >35% <b>Macitentan</b> MELODY-1 (NCT02070991)	60	5/2014	10/2015	12 weeks	Safety and tolerability (fluid retention)	PVR, haemodynamics, changes in TPG and DPG, echocardiographic variables (RV function)

All studies were performed in heart failure patients with and/or without preserved ejection fraction.

mPAP, mean pulmonary artery pressure; DPG, diastolic pressure gradient; HF, heart failure; PVR, pulmonary vascular resistance; QoL, quality of life; RV, right ventricle; 6MWD, six minute walking distance; TPG, transpulmonary pressure gradient.

<sup>a</sup>The study has been terminated by the funding agency.

RV dysfunction secondary to LV HF, it is imperative to further improve our understanding of the pathophysiology of PH-LHD, and to establish an evidence-based approach for the management of HF patients developing PH. Harmonized terminology and a new classification of PH-LHD (Ipc-PH vs. Cpc-PH) have improved the clinical assessment and should help prevent the inappropriate off-label use of PAH drugs in PH-LHD. In addition, they provide better tools to identify a subset of patients with HF and PH who deserve special attention. Despite significant achievements that were made recently, important evidence gaps remain that need to be addressed in future studies.

## Specific propositions

- Since cardiopulmonary interaction in HF is complex and variable, the definitions and prognostic significance of haemodynamic variables characterizing the degree of pre-capillary PH in LHD need to be further improved. This may be achieved by integrated measures of pulmonary vascular and RV function.
- As the differential diagnosis between pre- and post-capillary PH remains challenging, an integrative approach considering the clinical context, non-invasive assessment, and invasive haemodynamic variables is critical. The role of volume challenge and exercise stress testing to unmask occult LHD needs to be established and requires standardization and validation.
- The evolution from an LV phenotype to an RV phenotype over time as a result of PH requires further investigation. We need to better understand the susceptibility for pulmonary vascular disease in HF in a subset of patients (genetic predisposition, contributing factors), and to collect data on the prevalence and timing of such an evolution, which will ideally help to predict which patients with LHD will develop significant PH and RV dysfunction.
- Specifically, longitudinal studies should be performed that investigate the development of RV dysfunction in patients with LV HF over time.
- Thus far, targeted PH therapies have never been investigated properly in PH-LHD. Carefully controlled randomized trials in larger populations of well characterized patients (PH-HFrEF and PH-HFpEF separately), with longer observation times, and definitive endpoints are needed. In such trials, it must be assured that patients are on optimized regimens of HF therapy and fluid balance before randomization, which may be achieved by a 'run-in' phase.
- Proof-of-concept studies in limited numbers of haemodynamically well characterized patients, focusing on patients with Cpc-PH, together with the improvement of non-invasive variables that better characterize the degree of pre-capillary PH in PH-LHD, may better inform larger RCTs.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Authors' contributions

All authors contributed to literature search, figure design, and writing/reviewing the manuscript; drafted the manuscript; and made critical revision of the manuscript for key intellectual content.

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