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REVIEW

Pulmonary hypertension in left heart disease

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ABSTRACT: Pulmonary hypertension (PH) is a frequent complication of left heart disease arising from a wide range of cardiac disorders. In the clinical classification, PH associated with left heart disease is classified as Group 2, which includes left heart systolic dysfunction, left heart diastolic dysfunction and left heart valvular disease. In the past, rheumatic mitral valve disease was the most common cause of PH in left heart disease; however, today it is more likely to be associated with hypertensive and/or ischaemic heart disease.

As the incidence of these conditions is increasing, the number of patients presenting with PH is also increasing and, today, left heart disease represents the most frequent cause of PH. The development of PH in patients with left heart disease is associated with poor prognosis. However, despite the increasingly large number of patients affected and the impact of PH on outcome, there are currently no specific treatment options for these patients.

This review gives an overview of the pathophysiology and epidemiology of PH associated with left heart disease, and discusses the challenges associated with its management and treatment.

KEYWORDS: Left heart disease, preserved ejection fraction, pulmonary hypertension

Left heart disease (LHD) is the most frequent cause of pulmonary hypertension (PH), arising in response to increased left ventricular (LV) or left atrial filling pressure in a wide range of cardiac disorders [1]. PH is defined by a mean pulmonary arterial pressure (P_{pa}) $\geqslant$25 mmHg; in the case of PH associated with LHD, otherwise defined as Group 2 [2], this is associated with a pulmonary capillary wedge pressure (P_{pcw}) >15 mmHg [3]. In the classification of PH, Group 2 is divided into three distinct subcategories based on aetiology: left heart systolic dysfunction, left heart diastolic dysfunction and left heart valvular disease [2]. More recently, a different nomenclature has been proposed by using the terms heart failure with reduced LV ejection fraction (HFREF), corresponding to systolic heart failure, and heart failure with preserved LV ejection fraction (HFPEF), corresponding to diastolic heart failure (table 1) [4]. PH in HFREF is primarily associated with ischaemic and dilatative cardiomyopathy, whereas a wide range of underlying conditions may lead to HFPEF (table 1). While in the past, mitral valve disease was the most common cause of Group 2 PH, HFPEF has become recognised more and more in clinical practice and its incidence is increasing. HFPEF is predominantly associated with hypertensive and coronary artery disease [5] and has a reported prevalence of ~30–50% in patients with overt heart failure [6, 7]. Whatever the underlying cardiac disease, the presence of PH in patients with heart failure is associated with poor prognosis [8, 9]. However, despite the relatively large number of affected patients, and the link with poor outcome, there is not a definitive appreciation as to whether PH is a ''marker'' of severity or pulmonary vascular involvement becomes an important component of heart failure syndrome. In addition, there are currently no specific therapeutic options for these patients. This article discusses the epidemiology and pathogenesis of Group 2 PH, and reviews diagnostic and treatment strategies in this increasingly important patient population.

PATHOPHYSIOLOGY OF PH-LHD

The underlying pathogenesis of PH in LHD is not fully understood and is likely to be multifactorial. Patients with LHD have abnormalities that result in increased LV or left atrial filling pressures. The initial cascade of events starts with the increase in filling pressures in the left heart (either in the left atrium, left ventricle or both), which causes a passive increase in backwards pressure on the pulmonary veins. Persistently elevated pulmonary venous pressure may result in fragmentation

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TABLE 1 Classification of pulmonary hypertension (PH) owing to left heart diseases

Heart failure with reduced left ventricle ejection fraction (ejection fraction ⩽50%[#]; systolic dysfunction[¶])
Ischaemic cardiomyopathy
Dilated cardiomyopathy
Heart failure with preserved left ventricle ejection fraction (ejection fraction >50%[#]; diastolic dysfunction[¶])
Hypertensive heart disease
Coronary heart disease
Diabetic cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Constrictive pericarditis
Valvular diseases
Aortic valve stenosis
Aortic valve regurgitation
Mitral valve stenosis
Mitral valve regurgitation
Persistent/residual PH after effective valvular defect correction
Other causes
Cor triatriatum
Myxoma or left atrial thrombus

[#]: the cut-off value for preserved *versus* reduced ejection fraction varies between studies; [¶]: definition from SIMONNEAU *et al.* [2]. Modified from [4].

of the delicate structure of the alveolar–capillary walls, referred to as ''alveolar capillary stress failure'', which is characterised by capillary leakage and acute alveolar oedema [10, 11]. In this acute setting, alveolar–capillary stress failure is a reversible phenomenon [12]. However, if the increase in venous pressure persists, the alveolar–capillary membrane may undergo potentially irreversible remodelling, characterised by excessive deposition of type IV collagen, which is mainly observed in animal models [13]. These structural changes generally increase the impedance to gas transfer, resulting in a decrease in lung diffusion capacity [14]. In addition, persistently increased pulmonary venous pressure (and consequent passive increase of P_{pa}) may lead to pathological changes in the pulmonary veins and arteries, including muscularisation of the arterioles, medial hypertrophy and neointima formation of distal pulmonary arteries [15], leading to the increase of pulmonary vascular resistance (PVR). In addition to structural changes in the pulmonary vessels, endothelial damage may lead to dysfunction and an imbalance in the production of vasoactive mediators such as nitric oxide (NO) and endothelin (ET)-1 resulting in impaired vascular smooth muscle relaxation [16, 17]. The importance of NO in pulmonary vascular tone in patients with heart failure has been shown using infusions of NG-mono-methyl-L-arginine, an inhibitor of NO production, which results in a lower degree of dose–dependent vasoconstriction in heart failure patients with elevated PVR index (PVRI) compared with those with normal PVRI or healthy individuals [16]. High levels of ET-1, a powerful vasoconstrictor, have been found in the pulmonary endothelium and plasma of patients with heart failure, and have been shown to be strongly predictive of mortality [18–20]. Both pathological and functional changes in the distal pulmonary arteries and arterioles are responsible for the increase of PVR, and may be considered a type of ''pre-capillary component'' that, in conjunction with the ''passive component'' due to the backward transfer of the increased pulmonary venous pressure, determines the final extent of PH. For the sake of clarity, it should be outlined that the pathological changes observed in the arterioles and in the distal pulmonary arteries of patients with PH-LHD are definitely different from those of the other clinical groups of PH, in particular when compared with Group 1 pulmonary arterial hypertension (PAH) [3, 21].

The progressive functional and structural changes in the pulmonary vasculature are reflected in the pattern of pulmonary haemodynamics seen in patients with PH-LHD. In the early ''passive'' stage, increases in systolic P_{pa} arise solely from increased LV filling pressure and/or left atrial pressure; P_{pcw}, which is an indirect measure of left atrial pressure, is >15 mmHg, but transpulmonary pressure gradient (mean P_{pa} - P_{pcw}) and PVR are within the normal limits [3]. This stage is generally considered to be reversible. However, as discussed previously, chronically elevated P_{pcw} leading to pathological changes in the distal pulmonary arteries and arterioles may induce an increase in transpulmonary pressure gradient of >15 mmHg and an increase in PVR. At this stage, termed ''reactive'' or ''out of proportion'' PH (due to the disproportionate increase of mean P_{pa} as compared to the elevation of P_{pcw}), changes may still be reversible, for example, in the case of normalisation of the P_{pcw} (*i.e.* after successful mitral valve disease correction). In the majority of the cases in which no regression of PH is observed after mitral valve surgery, a persistent increase in P_{pcw} is detected (due to persistent mitral valve malfunction or concomitant LV disease). In rare cases, a persistent PH may be observed despite a normalisation of the P_{pcw} and it is conceivable that in this setting the regression of the obstructive pathological changes has been incomplete. The time course and extent of both development and regression of the obstructive pathological changes observed in PH-LHD may be variable according to individual patients and are likely to be linked to constitutional factors.

An association between the severity of LV diastolic dysfunction and increasing P_{pa} has been shown previously [22]; however, there would not appear to be a simple relationship between the severity of heart failure and the development of PH, as marked elevations in P_{pa} can arise in patients with mild or moderate LV dysfunction. In the study by LAM *et al.* [23], patients with systemic hypertension and HFPEF had a higher systolic P_{pa} than patients with systemic hypertension but without heart failure, despite similar P_{pcw} values, providing the suggestion that the presence of heart failure may influence the elevation of P_{pa}. Further data come from a recent large community study by BURSI *et al.* [9], who found that systolic P_{pa} remained a strong predictor of all-cause and cardiovascular-related mortality in patients with heart failure even after adjusting for diastolic function. Therefore, the independence between LV function and systolic P_{pa} seen in these patients supports the existence of a constitutional component in the development of PH-LHD.

Once reactive/out-of-proportion PH is established, the obstructive effects on the pulmonary arteries and increase in P_{pa} leads to an increase of the right ventricle (RV) afterload. The RV adapts to maintain output in the face of this, primarily by the development of muscle wall hypertrophy and eventually, if the

overload persists to dilatation, tricuspid regurgitation, loss of contractility (by muscle mass unit) and an irreversible decrease in RV function [1]. RV dysfunction and tricuspid regurgitation further complicate heart failure syndrome as they lead to an increase in right atrial pressure, which facilitates oedema, affects the release of natriuretic peptides and results in renal venous congestion and, eventually, in the impairment of renal function [1, 24, 25]. Together with PH, the development of RV dysfunction is known to be among the most significant modifiers of both the natural history and prognosis of heart failure resulting from LV disease, with an ominous impact on functional capacity and prognosis [26].

EPIDEMIOLOGY AND NATURAL HISTORY OF PH-LHD

The true prevalence of PH-LHD, and particularly PH-HFPEF, is unclear but available data suggest it arises in a large proportion of heart failure patents. In the community-based study of BURSI *et al.* [9] including >1,000 patients with heart failure, systolic P_{pa} >35 mmHg (prospectively assessed by echocardiography) was present in 79% of patients. PH is highly prevalent in patients with HFPEF; depending on the diagnostic criteria used, studies quote rates of between 50% and >80% [23, 27]. In another community-based study, 83% of patients with systemic hypertension and HFPEF had PH (defined as systolic P_{pa} >35 mmHg estimated by echocardiography) compared with only 8% of patients with systemic hypertension, but no heart failure [23]. It has to be noted that the definition of PH by a systolic P_{pa} >35 mmHg (estimated by echocardiography) is prone to overestimation due to false positive cases. In fact, in the study by LEUNG *et al.* [27], PH (defined as mean P_{pa} >25 mmHg) was present in 53% of patients with HFPEF. The reported prevalence of PH in patients with HFREF (LV ejection fraction <50%) varies between ~16% and 63% depending on the patient population investigated and the criteria used [28–31]. PH is a common complication of mitral valve disease and may affect as many as 73% of patients depending on disease severity [32, 33]. The prevalence of PH in patients with aortic stenosis is lower than in those with mitral stenosis but is still considerable at ~30–50% [34–36].

DIAGNOSIS OF PH-LHD

The development of PH in patients with LHD is associated with poor prognosis. PH has been shown to be an independent predictor of mortality in patients with a range of cardiac dysfunctions, including those with heart failure [23, 31], dilated cardiomyopathy [28], stable coronary artery disease [37] and following acute myocardial infarction [38]. In the community-based study of patients with heart failure by BURSI *et al.* [9], there was a strong positive association between systolic P_{pa} and overall and cardiac mortality that was independent of age, sex, comorbidities, LV ejection fraction and diastolic function (fig. 1). Similarly, LAM *et al.* [23] demonstrated that systolic P_{pa} was the only echocardiographic parameter independently associated with decreased survival even after adjustment for age. The degree of PH in patients with HFPEF in this study was often severe, and systolic P_{pa} above the study median (48 mmHg) was associated with significantly shorter survival rates, confirming findings of earlier studies demonstrating that PH is an important determinant of mortality and morbidity in patients with heart failure [28, 31, 39]. P_{pa}, systolic P_{pa} and diastolic P_{pa} have also been shown to be predictive of a need for heart transplantation in patients with severe LV dysfunction [40]. In patients with valvular disease, PH increases the likelihood of poor surgical outcome, although surgery is associated with better outcome overall compared with conservative management [8]. A significant proportion of patients with severe systolic LV dysfunction and PH have RV dysfunction [30], which has been shown to be predictive of survival and clinical events in patients with PH and chronic heart failure [41–46].

Interestingly, recent observations obtained in acute decompensated heart failure after initial diuretic and vasodilator therapy suggest increased mortality rates in the subgroup of patients with reactive PH [47].

In patients with suspected PH, a number of characteristics favour the likelihood of Group 2 PH-LHD. These include older age (>65 yrs), elevated blood pressure, elevated pulse pressure, obesity, coronary artery disease, diabetes mellitus and atrial fibrillation [3, 48]. Clinically, patients may present with signs and symptoms that are generally not found in other forms of PH such as orthopnoea and paroxysmal nocturnal dyspnoea [1]. Chest radiographs may show pulmonary vascular congestion, pleural effusion or pulmonary oedema, and LV hypertrophy may be evident on electrocardiogram. Doppler echocardiography is recommended as the optimal screening tool for PH-LHD [1] and cardiopulmonary exercise testing has been used increasingly for diagnosing and managing patients with systolic and diastolic LV dysfunction [5]. Echocardiographic signs of LV dysfunction include left atrial enlargement, LV hypertrophy and indicators of elevated LV filling pressure [49]. LV diastolic

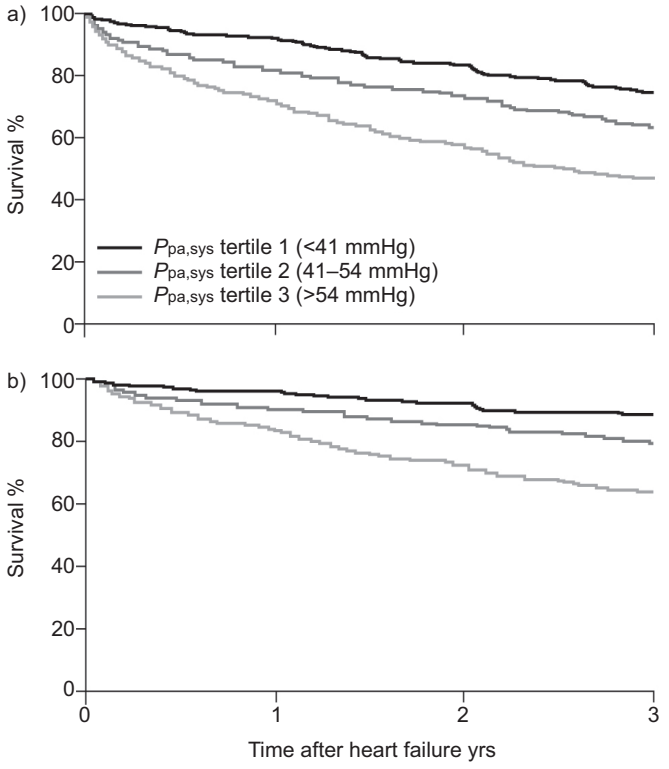

FIGURE 1. a) Overall survival by systolic pulmonary artery pressure ($P_{pa,sys}$) tertiles in 1,049 heart failure patients ($p<0.001$). b) Survival from cardiovascular death by $P_{pa,sys}$ tertiles in 975 heart failure patients ($p<0.001$). Reproduced from [9] with permission from the publisher.

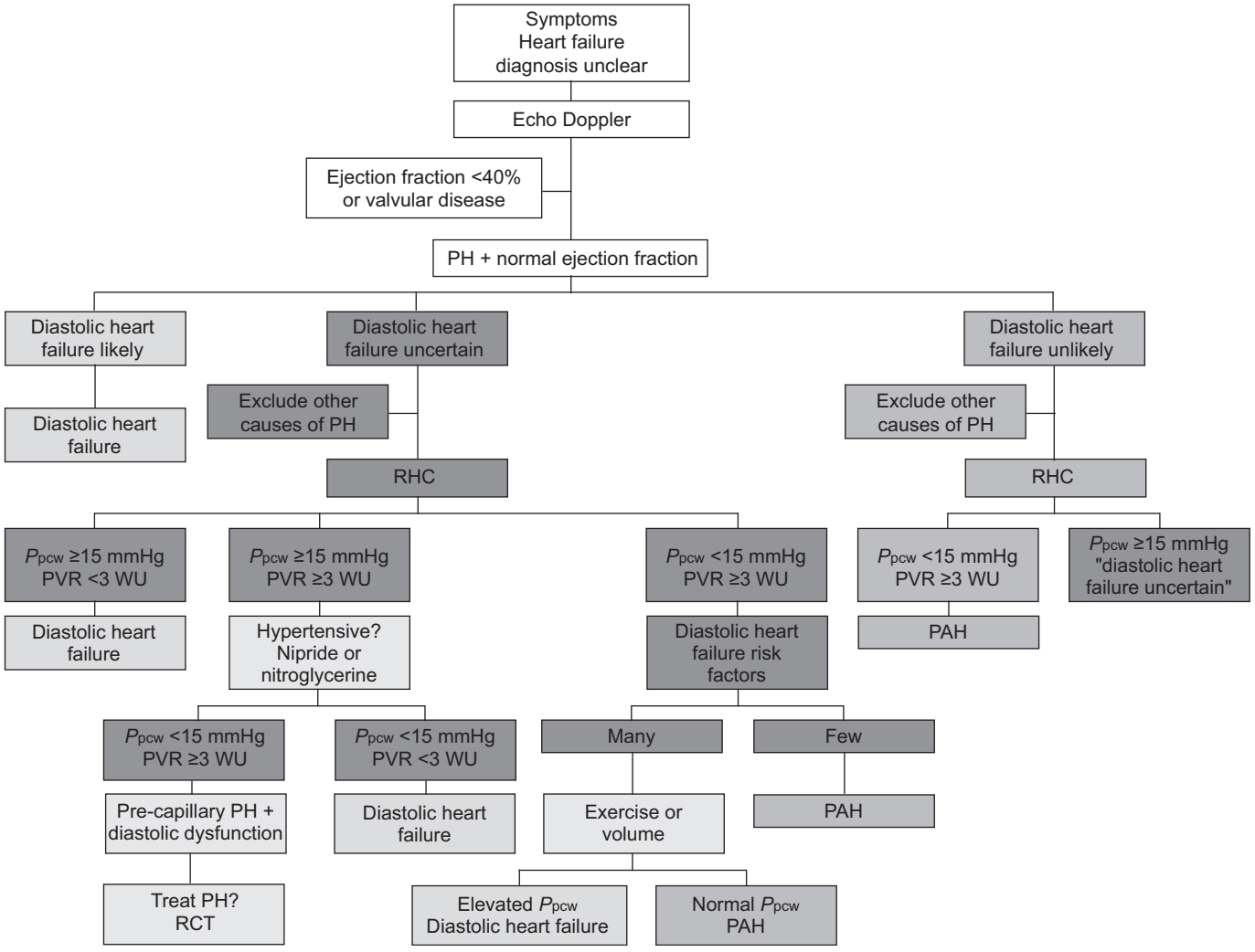

FIGURE 2. Diagnostic approach to distinguishing between pulmonary arterial hypertension (PAH) and pulmonary hypertension (PH) caused by diastolic left heart disease. RHC: right heart catheterisation; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RCT: randomised controlled trial; WU: Wood units. Reproduced from [50] with permission from the publisher.

dysfunction should be suspected in the presence of a combination of the following signs: dilated left atrium, atrial fibrillation, characteristic changes in mitral flow profile, pulmonary venous flow profile, mitral annulus tissue Doppler signals and LV hypertrophy. Based on patient characteristics, clinical findings and noninvasive testing, diagnostic guidelines divide patients with a suspicion of PH without clear evidence of heart failure into three groups: 1) those who are unlikely to have PH-HFPEF *versus* PAH (younger patients without hypertension, coronary artery disease *etc.*, with normal LV on echocardiography, *etc.*); 2) those who are likely to have PH-HFPEF (older patients, hypertensive patients, obese patients, patients with coronary heart disease, atrial enlargement, LV hypertrophy *etc.*); and 3) those in which PH-HFPEF is uncertain (no signs of heart failure, normal brain natriuretic peptide levels) (fig. 2) [50]. In this latter group of patients right heart catheterisation (RHC) is suggested and in patients presenting with P_{pcw} <15 mmHg a volume challenge is proposed even though specific directions on the amount of fluid overload are lacking.

LV filling pressures can be estimated by echocardiography, and the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) (E/E′ ratio) has been originally shown to give a reliable estimate of left atrial pressure [51, 52]. However, data have questioned this assumption. In a recent study performed in patients with HFPEF there is the suggestion that E/E′ may not reflect changes in P_{pcw} reliably, especially during variable loading conditions elicited by fluid challenge and mechanical preload reduction by lower body negative pressure [53]. In addition, echocardiographic parameters may not be easily measurable in all patients. Therefore, although echocardiography may be a useful screening method, invasive measures of P_{pcw} or LV end-diastolic pressure (LVEDP) by RHC (or left heart catheterisation) may be needed in order to confirm a diagnosis of PH-LHD [3].

According to guidelines, PH-LHD is distinguished from PAH by the presence of a P_{pcw} >15 mmHg [3]. While P_{pcw} is widely assumed to be a surrogate marker for LVEDP, there are few

data supporting this in patients with PH. In a large study including >4,000 patients with PH, around half of those diagnosed with PAH based on P_{pcw} were found to have PH-LHD when assessed by LVEDP [54]. Reliance on P_{pcw} rather than LVEDP in patients with PH-LHD may, therefore, result in misdiagnosis. However, routine measurement of LVEDP by left heart catheterisation carries increased risks and inconvenience for patients, and would also increase costs and resource utilisation. Measurement of LVEDP in those patients with a high suspicion of PH-LHD, but an apparently ''borderline'' normal P_{pcw} at RHC might be a viable compromise. A recent study suggests that it may also be possible to improve the correlation between P_{pcw} and LVEDP by using different parameters. RYAN *et al*. [55] evaluated digitised mean P_{pcw} ($P_{pcw,digital}$) compared with end-expiratory P_{pcw}, and assessed their correlations with LVEDP. Their data showed that the common practice of using $P_{pcw,digital}$ significantly underestimated LVEDP and that end-expiratory P_{pcw} gave a more reliable reflection of LVEDP (fig. 3). Using LVEDP <15 mmHg as the reference standard for diagnosis, $P_{pcw,digital}$ had 100% sensitivity but only 12.5% specificity, while end-expiratory P_{pcw} had a sensitivity of 86% and a specificity of 100%. Extrapolated to their cohort of patients with suspected PH, this translated to nearly 30% being misclassified as having PAH, rather than PH with HFPEF. However this study presents an important limitation due to the absence of evaluation of end-expiratory LVEDP. In fact, end-expiratory LVEDP may be higher when compared with ''average'' LVEDP (the reduction of lung volumes may increase LV filling) and then the observed difference with the end-expiratory P_{pcw} could be present in this condition (and justified by the intrinsic characteristics of the two methods of measurement).

In any case, reliance on P_{pcw} as opposed to LVEDP may be inappropriate in some cases and further research into appropriate cut-off values or identification of factors which might improve diagnostic sensitivity and specificity, particularly in those patients who fall into diagnostic ''grey areas'', is required. The picture seems a little more complex when considering differential diagnosis in patients with concurrent chronic obstructive pulmonary disease or restrictive lung disease. In these cases confirming the haemodynamic concordance between P_{pcw} and end-diastolic pressure at end-expiration seems of special importance.

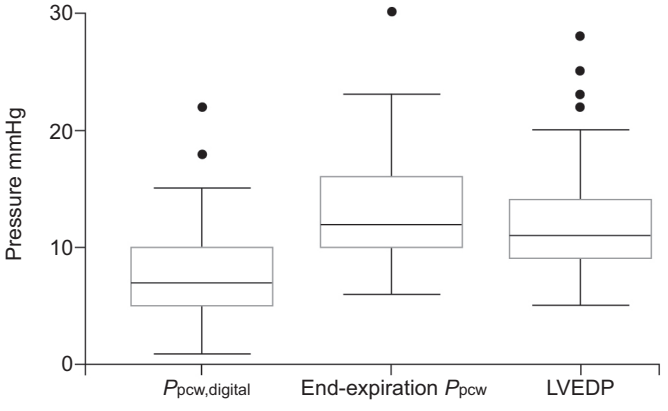

FIGURE 3. Comparison between digitised pulmonary capillary wedge pressure ($P_{pcw,digital}$) and end-expiration P_{pcw}, and their relationship to directly measured left ventricular end-diastolic pressure (LVEDP). Box plots show the median values and interquartile range. Error bars represent values within two standard deviations of the mean. Dots represent outliers. $P_{pcw,digital}$ was significantly lower ($p<0.05$) than end-expiration P_{pcw} and LVEDP. Reproduced from [55] with permission from the publisher.

Exercise haemodynamics and volume challenge have been proposed as methods to help identify patients with PH-LHD, and particularly those patients with resting P_{pcw} in the range of 13–18 mmHg [56]. In a study of 406 patients with exercise limitation but normal P_{pa} at rest, a substantial proportion of patients who had RHC-defined PH during maximal exercise (mean $P_{pa} \geqslant 30$ mmHg) were identified as potentially having Group 2 PH ($P_{pcw} \geqslant 20$ mmHg) [57]. Exercise haemodynamics during supine exercise has also been utilised to distinguish PH-HFPEF (P_{pcw} >25 mmHg at peak exercise) in a study of euvolaemic patients with exertional dyspnoea, normal brain natriuretic peptide and normal cardiac filling pressures at rest [58]. Patients with exercise-induced increases in P_{pcw} also showed corresponding increases in LVEDP and P_{pa} during exercise; these increases were considered to be exclusively related to pulmonary venous hypertension as PVRI decreased similarly both in patients with and without increased P_{pcw} on exercise. However, the interpretation of these studies is complicated by the lack of a control group of age- and sex-matched normal individuals. In fact it is well known that normal individuals may also reach similar values of P_{pcw} ($\geqslant 20$ mmHg) on supine exercise [59].

Although interesting, maximal exercise testing in patients with potential heart failure or PH may be difficult, and the use of RHC during exercise is challenging so use of this technique as a routine test may be limited. Identification of noninvasive ways of assessing PH-LHD during submaximal exercise may help address these limitations.

A number of potential echocardiographic markers of PH may be of interest, including mean P_{pa}, estimated from the maximum velocity of tricuspid regurgitation, and cardiac output, calculated from the aortic velocity–time integral [60], mitral effective regurgitant orifice [61, 62], tricuspid annular plane systolic excursion [63] and mid-systolic ''notching'' of the RV outflow tract Doppler flow velocity envelope [64]. However, to date, there is no accepted protocol for the determination of exercise-induced PH in patients with LHD and further evaluation is required. Also, in this case, it would be relevant to compare results with a matched control group.

MANAGEMENT OF PH-LHD

In contrast with the advances in treatment which have occurred in recent years for PAH, virtually no progress has been made for PH-LHD. Guidelines give little advice, other than to manage systemic hypertension and volume status [65] and to optimise underlying conditions [3]. In addition, the European Society of Cardiology/European Respiratory Society guidelines clearly discourage the use of drugs approved for PAH in PH-LHD due to the lack of evidence for a favourable risk-to-benefit ratio. Cardiovascular medications (*e.g*. diuretics, angiotensin converting enzyme inhibitors, β-adrenoceptor blockers and inotropic agents) and specific interventions (*e.g*. LV assist device

implantation and valvular surgery) may reduce PH through a drop in left-sided filling pressures [3], but in those patients with residual elevated P_{pa}, despite P_{pcw} normalisation, there is little evidence on which to base recommendations.

In particular, the value of targeting PH directly by medical therapy remains to be established. It can be hypothesised that targeting pulmonary vascular remodelling may be helpful in patients with reactive PH-LHD, particularly where PH dominates the clinical picture [8]. However, the removal of the ''precapillary component'' may increase the P_{pcw} leading to lung oedema [66, 67]. This may explain why the guidelines suggest that patients with PH-LHD should be enrolled in suitable randomised and multicentre clinical trials with such agents to finally clarify the risk-to-benefit ratio [3].

The lack of recommendations concerning the use of PAH-specific therapies in patients with PH-LHD reflects the current lack of favourable data. Studies are few and results generally disappointing. Inhaled NO selectively targets the pulmonary arterial circulation and has been tested for the treatment of advanced left-sided PH in post-LV assist device placement and post-transplant. In patients with an LV assist device, inhaled NO reduces P_{pa} and increases LV assist device flow [68]. In post-transplant PH management only inhaled NO, and not intravenous prostacyclin, prostaglandin E1 and sodium nitroprusside, induced a selective decrease in PVR with no change in systemic resistance [69]. At variance with these favourable results, other investigators reported no significant changes in P_{pa} and an increase in P_{pcw}, possibly due to an increased preload of a poorly compliant LV [70], which may lead to the development of acute alveolar oedema in some cases [67].

Prostanoids have shown favourable acute and long-term haemodynamic effects in patients with PH-LHD included in small studies. They lead to a decrease in P_{pa}, P_{pcw} and PVR, and increase in cardiac output, but also to a drop in systemic arterial pressure and resistance [71–73]. In a multicentre international randomised study including 471 patients (FIRST study), treatment of patients with severe LV failure (reduced ejection fraction; mean P_{pcw} 25 mmHg) with intravenous epoprostenol failed to improve exercise capacity or quality of life, or to reduce morbidity compared with the standard of care (*e.g.* angiotensin converting enzyme inhibitors, β-agonist, diuretics *etc.*) [74]. This study was prematurely terminated because epoprostenol treatment (which is the most powerful treatment for PAH and the only agent with demonstrated improvement in survival in this condition) was associated with a strong trend towards decreased survival [74, 75]. A subsequent *post hoc* evaluation showed that patients with a marked reduction of the P_{pcw} (>9 mmHg) treated with epoprostenol had an outcome similar to ''standard-of-care-patients'', confirming that surrogate endpoints are not predictive of the drug effects in heart failure trials.

In animal models of heart failure, long-term treatment with ET-1 receptor antagonists led to improvements in haemodynamics, cardiac remodelling and survival [76]. Encouraging results were also seen following acute treatment using the ETA/B antagonist bosentan in patients with symptomatic heart failure. P_{pa}, right atrial pressure, P_{pcw}, systemic pulmonary resistance and PVR were reduced while cardiac output and stoke volume were increased [77]. Despite such positive initial findings, results from large-scale trials of bosentan in patients with chronic heart failure have been disappointing, with an overall lack of measurable treatment benefit and an apparent increase in the risk of heart failure and adverse events during treatment that led to early termination of studies [78–80]. However, PACKER *et al.* [79] found that, in patients treated with a full 26 weeks of therapy, while there was an increased risk of heart failure during the first month of treatment with bosentan compared with placebo, there was a decreased risk over the subsequent 5 months of therapy [79]. In addition, patients in the bosentan group who remained on therapy were more likely to improve and less likely to deteriorate than the placebo group. However, any interpretation of these *post hoc* evaluations are limited and possibly influenced by selection and regression to the mean biases. Whether it might be possible to identify a subset of patients who may respond to bosentan in this setting is unclear. Other ET-1 antagonists, including darusentan [81] and tezosentan [82], have also failed to demonstrate any long-term benefit of treatment in patients with HFREF.

There has been increasing interest in the use of phosphodiesterase type-5 inhibitors in PH-LHD. In patients with HFREF and PH, there is evidence of both acute (single dose of 50 mg) efficacy and safety of sildenafil in the evaluation of PH in severe heart failure [83, 84] and is effective and well tolerated in longer term trials [85–87]. 12 weeks of treatment with sildenafil significantly reduced PVR and increased cardiac output with exercise compared with placebo, without altering P_{pcw} or mean P_{pa}, heart rate or systemic vascular resistance [86]. Exercise capacity, ventilation efficiency and quality of life also improved. There is also evidence that sildenafil may help to modulate and reverse the abnormal oscillatory ventilator pattern seen in patients with PH-LHD at higher risk [88]. More recently, a 1-yr study of 44 patients with HFPEF demonstrated significant improvements in: mean P_{pcw}, RV function and geometry; increased tricuspid annular plane systolic excursion and ejection rate; and reduced right atrial pressure with sildenafil *versus* placebo at 6 months [89]. This response was maintained up to 12 months. However, for this class of drugs a formal multicentre, international randomised controlled study evaluating the real risk-to-benefit ratio in PH-LHD is lacking. In particular because concerns have been raised about the possible induction of sudden death in PH-LHD patients by phosphodiesterase type-5 inhibitors [90]. Small, single-centre studies can be considered as proof-of-concept experiences (favourable preliminary single-centre studies were also published with prostanoids [73] and endothelin receptor antagonists [77]) and cannot be considered as a substitute for formal registration large studies or encourage the clinical use of these compounds.

In patients with PH-LHD due to valvular disease, correction of the underlying valve problem usually leads to resolution, or near resolution, of PH. In mitral valve patients treated with mitral balloon valulvoplasty, younger patients with shorter disease duration improve to the greatest degree, although in all cases improvement takes time [91, 92]. Additionally, pre-operative severity of PH does not appear to affect long-term outcome following successful mitral balloon valvuloplasty, with systolic P_{pa} falling to normal levels after 6–12 months, even in patients with high pre-mitral balloon valvuloplasty levels (≥80 mmHg) [90]. Similarly, mitral valve replacement has been shown to be safe in patients with high pre-operative

P_{pa} (>50 mmHg), with resultant marked post-operative declines in P_{pa} and PVR, and long-term improvements in functional class, as long as P_{pa} did not exceed systemic pressure [93]. Where P_{pa} exceeded systemic pressure, mitral valve replacement carried a higher risk of mortality and individual patients may have some degree of persistent post-operative PH despite normalisation of P_{pcw}. This may not represent a contraindication to surgery because the survival would be worse without it.

A number of factors that should be taken into account outside of therapy should be evaluated, and addressing modifiable risk factors may result in marked improvements in patient's condition. For example, morbidly obese patients have increased pulmonary venous pressure even in the absence of overt pulmonary disease symptoms, such as daytime hypoxia or uncontrolled systemic hypertension [94]. Although there are no clinical trials of the effects of weight loss in obese patients with PH-LHD, such data, taken together with the multiple positive effects of weight loss in terms of hypertension, diabetes, sleep apnoea, exercise capacity *etc.*, should encourage weight management in obese patients with PH-LHD. Obstructive sleep apnoea is known to be associated with increased risk of cardiovascular morbidity and mortality, and is being implicated increasingly in a range of cardiovascular diseases, including PH [95]. Management of obstructive sleep apnoea by continuous positive airway pressure administration may, therefore, be of benefit, although clinical data are currently lacking.

CONCLUSION

PH associated with LHD arises from impaired LV systolic and diastolic function and from mitral valve disease, which leads to increased filling pressures in the left heart. This initiates a series of adverse pathological and functional changes in the pulmonary vasculature and eventually in the right heart. PH is a common complication of LHD. The increasing prevalence of LHD, and in particular of HFPEF, means that a significant proportion of patients with heart failure will present with PH [7]. Currently, treatment guidelines are limited, reflecting a general lack of data in this patient population. Diagnosis and therapy of PH-LHD are challenging. To date, most therapeutic strategies aimed at PH have not shown positive results, although initial experiences with phosphodiesterase type-5 inhibitors appear encouraging, but not definitive. A formal registration study with these compounds is required before any recommendation can be made. There is a clear need for more research into the underlying mechanisms of PH in LHD and new therapeutic options to help drive the development of treatment guidelines for this increasingly important patient group.

STATEMENT OF INTEREST

M. Guazzi has served as a consultant for medical meetings from Merck and received payment for lecture fees from Actelion Pharmaceuticals Ltd. N. Galiè has served as a consultant and received payment for lecture fees from Actelion Pharmaceuticals Ltd, Pfizer, GSK, Eli Lilly and Bayer Schering Pharma.

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