Pulmonary hypertension in left heart disease

Marco Guazzi* and Nazzareno Galié*

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 affected patients, 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 (Ppa) >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 (PCWP) >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 dilative 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
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 systolic 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 Burri 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

---

**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].
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 patients. In the community-based study of Burri et al. [9] including >1,000 patients with heart failure, systolic \( P_{\text{pa}} \geq 35 \text{ mmHg} \) (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 \( P_{\text{pa}} > 35 \text{ mmHg} \) 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 \( P_{\text{pa}} > 35 \text{ mmHg} \) (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 \( P_{\text{pa}} > 25 \text{ mmHg} \)) 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 [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 Burri et al. [9], there was a strong positive association between systolic \( P_{\text{pa}} \) 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 \( P_{\text{pa}} \) 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 \( P_{\text{pa}} \) 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]. \( P_{\text{pa}} \), systolic \( P_{\text{pa}} \) and diastolic \( P_{\text{pa}} \) 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 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].

**FIGURE 1.** a) Overall survival by systolic pulmonary artery pressure (\( P_{\text{pa,sys}} \)) tertiles in 1,049 heart failure patients (\( p<0.001 \)). b) Survival from cardiovascular death by \( P_{\text{pa,sys}} \) tertiles in 975 heart failure patients (\( p<0.001 \)). Reproduced from [9] 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 \( P_{pcw} <15 \text{ mmHg} \) 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 \( P_{pcw} >15 \text{ mmHg} \) [3]. While \( P_{pcw} \) is widely assumed to be a surrogate marker for LVEDP, there are few

---

**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.
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 Ppcw were found to have PH-LHD when assessed by LVEDP [54]. Reliance on Ppcw 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 Ppcw at RHC might be a viable compromise. A recent study suggests that it may also be possible to improve the correlation between Ppcw and LVEDP by using different parameters. Ryan et al. [55] evaluated digitised mean Ppcw (Ppcw,digital) compared with end-expiratory Ppcw, and assessed their correlations with LVEDP. Their data showed that the common practice of using Ppcw,digital significantly underestimated LVEDP and that end-expiratory Ppcw gave a more reliable reflection of LVEDP (fig. 3). Using LVEDP <15 mmHg as the reference standard for diagnosis, Ppcw,digital had 100% sensitivity but only 12.5% specificity, while end-expiratory Ppcw 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 Ppcw could be present in this condition (and justified by the intrinsic characteristics of the two methods of measurement).

In any case, reliance on Ppcw 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 Ppcw and end-diastolic pressure at end-expiration seems of special importance.

Exercise haemodynamics and volume challenge have been proposed as methods to help identify patients with PH-LHD, and particularly those patients with resting Ppcw in the range of 13–18 mmHg [56]. In a study of 406 patients with exercise limitation but normal Ppa at rest, a substantial proportion of patients who had RHC-defined PH during maximal exercise (mean Ppa >30 mmHg) were identified as potentially having Group 2 PH (Ppcw >20 mmHg) [57]. Exercise haemodynamics during supine exercise has also been utilised to distinguish PH-HFPEF (Ppcw >25 mmHg at peak exercise) in a study of euvoalamic patients with exertional dyspnoea, normal brain natriuretic peptide and normal cardiac filling pressures at rest [58]. Patients with exercise-induced increases in Ppcw also showed corresponding increases in LVEDP and Ppa 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 Ppcw 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 Ppcw (>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 Ppa, 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 PH-LHD. Studies are few and results generally disappointing. Inhaled NO selectively targets the pulmonary vascular remodelling may be helpful 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 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/\(\beta\) antagonist bosentan in patients with symptomatic heart failure. $P_{pa}$, right atrial pressure, $P_{pcw}$, systemic pulmonary resistance and $P_{VR}$ were reduced while cardiac output and stroke 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 $P_{VR}$ 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 valvuloplasty, 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 ($\geq$80 mmHg) [90]. Similarly, mitral valve replacement has been shown to be safe in patients with high pre-operative
individual patients may have some degree of persistent post-
valve replacement carried a higher risk of mortality and
and individual patients may have some degree of persistent post-
operative PH despite normalisation of Ppcw. 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 out-
side of therapy should be evaluated, and addressing modifi-
able 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. Obstruc-
tive 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, there-
fore, 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 increas-
ingly 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 Aetion Pharmaceuticals
Ltd. N. Galié has served as a consultant and received payment for
lecture fees from Aetion Pharmaceuticals Ltd, Pfizer, GSK, Eli Lilly
and Bayer Schering Pharma.
ACKNOWLEDGEMENTS
We received editorial support from L. Quine (Elements Communi-
cations Ltd, Westerham, UK) supported by Aetion Pharmaceuticals
Ltd (Allschwil, Switzerland).

REFERENCES
1 Guazzi M, Arena R. Pulmonary hypertension with left-sided heart
disease. Nat Rev Cardiol 2010; 7: 648–659.
2 Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical
classification of pulmonary hypertension. J Am Coll Cardiol 2009;
54: Suppl. 1, S43–S54.
3 Galié N, Hoeper MM, Humbert M, et al. Guidelines for the
diagnosis and treatment of pulmonary hypertension: the Task Force
for the Diagnosis and Treatment of Pulmonary Hypertension of the
European Society of Cardiology (ESC) and the European
Respiratory Society (ERS), endorsed by the International Society
of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30:
2493–2537.
4 Rosenkranz S, Bonderman D, Buerke M, et al. Pulmonary
hypertension due to left heart disease: updated recommendations
of the Cologne Consensus Conference 2011. Int J Cardiol 2011;
154: Suppl. 1, S34–S44.
5 Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart
disease. Circulation 2012; 126: 975–990.
6 Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with
preserved ejection fraction in a population-based study. N Engl J
Med 2006; 355: 260–269.
7 Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and
outcome of heart failure with preserved ejection fraction. N Engl J
Med 2006; 355: 251–259.
8 Haddad F, Kudelho K, Mercier O, et al. Pulmonary hypertension
associated with left heart disease: characteristics, emerging
concepts, and treatment strategies. Prog Cardiovasc Dis 2011; 54:
154–167.
9 Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures
and death in heart failure: a community study. J Am Coll Cardiol
2012; 59: 222–231.
10 West JB, Mathieu-Costello O. Vulnerability of pulmonary capillaries
in heart disease. Circulation 1995; 92: 622–631.
11 Kurlak SS, Namba Y, Fu Z, et al. Effect of increased duration of
high perfusion pressure on stress failure of pulmonary capillaries.
Microvasc Res 1995; 50: 235–248.
12 Tsukimoto K, Mathieu-Costello O, Prediletto R, et al. Ultrastructural
appearances of pulmonary capillaries at high transmural pressures.
J Appl Physiol 1991; 71: 573–582.
13 Townsley MI, Fu Z, Mathieu-Costello O, et al. Pulmonary microvascular
permeability. Responses to high vascular pressure after induction of pacing-induced heart failure in dogs. Circ Res
1995; 77: 317–325.
14 Guazzi M. Alveolar gas diffusion abnormalities in heart failure.
J Card Fail 2008; 14: 695–702.
15 Rich S, Rabinovitch M. Diagnosis and treatment of secondary
(non-category 1) pulmonary hypertension. Circulation 2008; 118:
2190–2199.
16 Cooper CJ, Jevnikar FW, Walsh T, et al. The influence of basal
nitric oxide activity on pulmonary vascular resistance in patients
with congestive heart failure. Am J Cardiol 1998; 82: 609–614.
17 Ooi H, Colucci WS, Givertz MM. Endothelin mediates increased
pulmonary vascular tone in patients with heart failure: demon-
stration by direct intrapulmonary infusion of sitaxsentan. Circulation
2002; 106: 1618–1621.
18 Cody RJ, Haas GJ, Binkley PF, et al. Plasma endothelin correlates
with the extent of pulmonary hypertension in patients with
chronic congestive heart failure. Circulation 1992; 85: 504–509.
19 Rodeheffer RJ, Lerman A, Heublein DM, et al. Increased plasma
concentrations of endothelin in congestive heart failure in humans.
 Mayo Clin Proc 1992; 67: 719–724.
20 Gaid A, Yanagisawa M, Langleben D, et al. Expression of
endothelin-1 in the lungs of patients with pulmonary hyper-
tension. N Engl J Med 1993; 328: 1732–1739.
21 Wagenvoort CA, Wagenvoort N, eds. The Pathology of Pulmonary
Circulation. New York, John Wiley, 1977.
J. Heart Lung Transplant 2011; 4: 257–265.
49. Paulus WJ, Tschoep C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28: 2539–2550.
50. Hoepner MM, Barberà JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009; 54: Suppl. 1, S85–S96.
51. Nagaeuf SE, Bhatt R, Vivo RF, et al. Echocardiographic evaluation of hemodynamics in patients with decompenated systolic heart failure. Circ Cardiovasc Imaging 2011; 4: 220–227.
52. Nagaeuf SE, Middleton KJ, Kopefen HA, et al. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997; 30: 1527–1533.
53. Bhella PS, Pacini EL, Prasad A, et al. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. Circ Cardiovasc Imaging 2011; 4: 482–489.
54. Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest 2009; 136: 37–43.
55. Ryan JJ, Rich JD, Thiruvooipati T, et al. Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension. Am Heart J 2012; 163: 589–594.
56. Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. Circulation 2009; 120: 992–1007.
57. Tolle J, Waxman AB, Van Horn TL, et al. Exercise-induced pulmonary arterial hypertension. Circulation 2008; 118: 2183–2189.
58. Borlaug BA, Nishimura RA, Soraia P, et al. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010; 3: 588–595.
59. Naeije R, Mélot C, Niset G, et al. Mechanisms of improved arterial oxygenation after peripheral chemoreceptor stimulation during hypoxic exercise. J Appl Physiol 1993; 74: 1666–1671.
REVIEW: PH IN LEFT HEART DISEASE

ARGENTIO P, CHESTERS N, MULÈ M, ET AL. Exercise stress echocardiography for the study of the pulmonary circulation. *Eur Respir J* 2010; 35: 1273–1278.

TUMMINIELLO G, LANCELLOTTI P, LEMPEREUR M, ET AL. Determinants of pulmonary artery hypertension at rest and during exercise in patients with heart failure. *Eur Heart J* 2007; 28: 569–574.

MILLER WL, MAHONEY DW, MICHELENA HI, ET AL. Contribution of ventricular diastolic dysfunction to pulmonary hypertension complicating chronic systolic heart failure. *JACC Cardiovasc Imaging* 2011; 4: 946–954.

GIO S, RECUSANI F, KLERSY C, ET AL. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 2000; 85: 837–842.

ARKLES JS, OPORTOWSKY AR, OJEDA J, ET AL. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. *Am J Respir Crit Care Med* 2011; 183: 268–276.

MAUCLAIR H, ARVICH SL, BADESCH DB, ET AL. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *Circulation* 2009; 119: 2250–2294.

LOH E, STMALER JS, HARE JM, ET AL. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. *Circulation* 1994; 90: 2780–2785.

BOCCIA EA, BACAL F, AULER JÚNIOR JO, ET AL. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol* 1994; 74: 70–72.

COGENZIANO M, CHOUDHRI AF, MOAZAMI N, ET AL. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac Surg* 1998; 65: 340–345.

KIELER-JENSEN N, LUNDIN S, RICKSTEN SE. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. *J Heart Lung Transplant* 1995; 14: 436–443.

HARE JM, SHERNAN SK, BODY SC, ET AL. Influence of inhaled nitric oxide on systemic flow and ventricular filling pressure in patients receiving mechanical circulatory assistance. *Circulation* 1997; 95: 2250–2253.

YUI Y, NAKAJIMA H, KAWAI C, ET AL. Prostacyclin therapy in patients with congestive heart failure. *Am J Cardiol* 1982; 50: 320–324.

HARALDSSON A, KIELER-JENSEN N, NATHORST-WESTFELT U, ET AL. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *Chest* 1998; 114: 780–786.

SUETA CA, GHEORGHIADE M, ADAMS KF JR, ET AL. Safety and efficacy of epoprostenol in patients with severe congestive heart failure. *Epoprostenol Multicenter Research Group. Am J Cardiol* 1995; 75: 34A–43A.

CALIFF RM, ADAMS KF, MCKENNA WJ, ET AL. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997; 134: 44–54.

SHAH MR, STINNETT SS, MCNULTY SE, ET AL. Hemodynamics as surrogate end points for survival in advanced heart failure: an analysis from FIRST. *Am Heart J* 2001; 141: 908–914.

MULDER P, RICHARD V, DERMUEUX G, ET AL. Role of endogenous endothelin in chronic heart failure: effect of long-term treatment with an endothelin antagonist on survival, hemodynamics, and cardiac remodeling. *Circulation* 1997; 96: 1976–1982.

SÜTSCH G, KOWSKI W, YAN XW, ET AL. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation* 1998; 98: 2262–2268.

KALRA PR, MOON JC, COATS AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? *Int J Cardiol* 2002; 85: 195–197.

PACKER M, McMURRAY J, MASSIE BM, ET AL. Clinical effects of endothelin receptor antagonist with bosentan in patients with severe chronic heart failure: results of a pilot study. *J Card Fail* 2005; 11: 12–20.

KALUSKI E, COTTER G, LEITMAN M, ET AL. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systemic dysfunction, associated with secondary pulmonary hypertension – a multi-center randomized study. *Cardiology* 2008; 109: 273–280.

ANAND I, McMURRAY J, COHN JN, ET AL. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364: 347–354.

MCMURRAY JJ, TEERLINK JR, COTTER G, ET AL. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007; 298: 2009–2019.

ALAEDDINI J, UBER PA, PARK MH, ET AL. Efficacy and safety of sildenafil in the evaluation of pulmonary hypertension in severe heart failure. *Am J Cardiol* 2004; 94: 1475–1477.

GUAZZI M, TUMMINIELLO G, DI MARCO F, ET AL. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. *J Am Coll Cardiol* 2004; 44: 2339–2348.

GUAZZI M, SAMAJA M, ARENA R, ET AL. Long-term use of sildenafil in the therapeutic management of heart failure. *J Am Coll Cardiol* 2007; 50: 2136–2144.

LEWIS GD, SHAH R, SHAHZAD K, ET AL. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation* 2007; 116: 1555–1562.

BEHLING A, RODHE LE, COMOLBO FC, ET AL. Effects of 5′-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. *J Card Fail* 2008; 14: 189–197.

GUAZZI M, VICENZI M, ARENA R. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. *Eur J Heart Fail* 2012; 14: 82–90.

GUAZZI M, VICENZI M, ARENA R, ET AL. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation* 2011; 124: 164–174.

VARMA A, SHAH KB, HESS ML. Phosphodiesterase inhibitors, congestive heart failure, and sudden death: time for re-evaluation. *Congest Heart Fail* 2012; 18: 229–233.

FAWZY ME, HEGAZY H, SHOUKRI M, ET AL. Long-term clinical and echocardiographic results after successful mitral balloon valvotony and predictors of long-term outcome. *Eur Heart J* 2005; 26: 1647–1652.

FAWZY ME, HASSAN W, STEFADOUROS M, ET AL. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotony. *J Heart Valve Dis* 2004; 13: 942–947.

MUBEEN M, SINGH AK, AGARWAL SK, ET AL. Mitral valve replacement in severe pulmonary arterial hypertension. *Asian Cardiovasc Thorac Ann* 2008; 16: 37–42.

HER C, CERABONA T, BAEK SH, ET AL. Increased pulmonary venous resistance in morbidly obese patients without daytime hypoxia: clinical utility of the pulmonary artery catheter. *Anesthesiology* 2010; 113: 552–559.

LURIE A. Cardiovascular disorders associated with obstructive sleep apnea. *Adv Cardiol* 2011; 46: 197–266.