

Chapter 10

Pulmonary hypertension associated with left heart disease



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SUMMARY: Left heart disease (LHD) is probably the most frequent cause of pulmonary hypertension (PH). Although in the past, rheumatic mitral valve stenosis has been the most common cause of this condition, PH-LHD mainly results from heart failure related to systolic and/or diastolic dysfunction of the left ventricle (LV) and is associated with elevated left-sided cardiac filling pressures. Most patients have a passive increase in pulmonary arterial pressure (P_{pa}) due to backward transmission of the elevated left atrial pressure, while a small subset develop severe PH with elevated transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR). When present, PH is usually associated with a poor prognosis and increased mortality. Optimising heart failure regimens and corrective valve surgery are the cornerstones of the treatment of PH in LHD. Although PH-LHD may evolve to right ventricular (RV) failure and is associated with some changes in the pulmonary vascular bed similar to pulmonary arterial hypertension (PAH), there are no data to support the use of PAH-specific therapies in the setting of PH-LHD. However, recent studies have suggested the usefulness of sildenafil, a phosphodiesterase type-5 inhibitor (PDE-5 I). This chapter addresses the epidemiology, pathophysiology, risk factors and treatment controversies of PH-LHD.

KEYWORDS: Heart failure, left heart disease, pulmonary hypertension, valvular disease

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Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (P_{pa}) ≥ 25 mmHg at rest as assessed by right heart catheterisation (RHC) [1, 2]. The clinical classification of PH includes heterogeneous conditions with different clinical presentations, pathophysiology and management [1, 2]. The first category, termed pulmonary arterial hypertension (PAH), is characterised by the presence of pre-capillary PH in the absence of other causes of the pre-capillary PH. PAH includes a group of rare diseases characterised by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular (RV) failure and premature death [1, 2]. With

minimal prevalence and incidence of 15 cases per million and 2.4 cases per million per year, respectively, PAH is clearly a rare disease. The second clinical classification includes patients with PH secondary to elevated left-sided cardiac filling pressures due to left heart disease (LHD), as assessed by pulmonary capillary wedge pressure (P_{pcw}) or left ventricular (LV) end-diastolic pressure. These patients are classified according to the Dana Point classification as World Health Organization (WHO) group 2, PH due to PH-LHD, which is the most common form of PH (table 1) [1, 2]. Furthermore, pulmonary complications of acute and/or chronic increases in LV filling pressure are a primary cause of increased morbidity and mortality in patients with a failing heart [3, 4]. PH-LHD can result from any of a number of left-sided valvular or myocardial diseases [5–7]. Although in the past, rheumatic mitral valve stenosis has been the most common cause of this condition, PH-LHD most commonly results from heart failure related to systolic and/or diastolic dysfunction of the LV [5–7]. The prevalence of PH-LHD reported in the literature varies greatly, depending on the severity of LV dysfunction and the definition of PH. Heart failure with preserved ejection fraction (HFPEF) is increasingly recognised as the predominant cause of PH-LHD [7, 8], and was recently reported by the Dana Point updates to be the most frequent cause of PH-LHD [9].

The pathophysiology, haemodynamic characteristics, clinical presentation and treatment options of PH-LHD are reviewed in this chapter.

Pathophysiology

Pathological changes

Increased pulmonary venous pressure may lead to functional and structural changes in the pulmonary circulation. The earlier changes are seen in the alveolocapillary membrane. Previous studies reported increased capillary endothelial basement membrane thickness due to excessive deposition of type IV collagen in lung biopsies from patients with pulmonary venous hypertension secondary to heart failure or mitral stenosis [10–12].

Increased lung interstitial connective tissue in conjunction with increased production of extracellular matrix components raise extravascular fluid storage capacity and serve as a compensatory mechanism to eliminate alveolar oedema [13].

Increased venous pressure with disruption of the endothelium may cause activation of vascular serine elastase and matrix metalloproteinases; these, together with release of growth factors, lead to smooth muscle growth and migration and elastin synthesis, which promote hypertrophy with fibrous changes. Lung biopsies in these patients exhibit enlarged and thickened pulmonary veins, pulmonary capillary dilatation, alveolar haemorrhage, and lymphatic vessel and lymph node enlargement [14]. Distal pulmonary arteries may be affected by medial hypertrophy and intimal fibrosis, explaining the so-called “reactive” component of the elevated pulmonary pressures [14, 15]. Importantly, plexiform lesions are not seen in patients with PH-LHD.

Interestingly, these changes are not uniform in all patients with increased pulmonary venous pressure, accounting for the different haemodynamic patterns and suggesting a genetic predisposition in patients with prominent morphological changes [6, 16].

Endothelial dysfunction

In the pulmonary vasculature, as in the systemic circulation, the endothelium plays a central role in the local

Table 1. Haemodynamic definition of pulmonary hypertension (PH) secondary to left heart disease (LHD)

Definition	Characteristics
PH	Mean $P_{ba} \geq 25$ mmHg
Post-capillary PH[#]	Mean $P_{ba} \geq 25$ mmHg $P_{pcw} > 15$ mmHg
Passive	TPG ≤ 12 mmHg
Out-of-proportion (reactive)	TPG > 12 mmHg

P_{ba} : pulmonary artery pressure; P_{pcw} : pulmonary capillary wedge pressure; TPG: transpulmonary gradient. #: PH-LHD group 2.

control of tone through the regulated release of nitric oxide (NO) and endothelin [17]. Indeed, the importance of endothelium-derived NO in determining the basal pulmonary vascular tone was reported in previous studies [17]. Both animal and human studies suggested that NO-dependent pulmonary vasodilatation is impaired in heart failure. PORTER *et al.* [18], using intravascular ultrasound, found that intrapulmonary infusion of acetylcholine caused vasoconstriction, which was accentuated by inhibition of guanylate cyclase in patients with heart failure and normal P_{pa} , but failed to cause vasodilatation in patients with heart failure and PH. COOPER *et al.* [19] demonstrated that the vasoconstriction response to N^G -mono-methyl-L-arginine (L-NMMA), an analogue of L-arginine that inhibits NO synthase, was attenuated in patients with heart failure and PH. These and other findings suggest that the loss of NO-dependent vasodilatation may contribute to the development of PH.

Endothelin is a potent arterial and venous vasoconstrictor peptide that is stored in the pulmonary epithelium and both produced and cleared by the lungs [20]. Endothelin might also induce proliferation and hypertrophy of smooth muscle, and increase collagen synthesis, contributing to pulmonary vascular remodelling [21]. Elevated plasma endothelin (ET)-1 levels were found in patients with heart failure, and a direct correlation between P_{pa} and circulating ET-1 levels was reported [22, 23]. Plasma ET-1 levels increased significantly in heart failure patients from the pulmonary artery to the capillary wedge region, with a consequent net pulmonary ET-1 production that is also proportional to PVR [24]. ET-1 mediates its effects through two types of receptors: ETA, which promotes vasoconstriction and cellular growth; and ETB, which mediates ET-1 clearance. ETB receptors were reduced in patients with heart failure, while ETA was upregulated, explaining the elevated ET-1 blood levels and the enhanced vasoconstriction [25, 26].

Haemodynamics

It is well known that elevated left-sided filling pressures can generate PH by passive or reactive mechanisms; however, the risk factors for this mechanism are not known, and it is not possible to predict which patients will develop PH and to what degree.

Passive PH

Most patients will have a passive increase in P_{pa} due to the backward transmission of the elevated left atrial pressure necessary to overcome the increased downstream resistance. The necessity for the RV to generate high systolic pressures to ensure adequate cardiac output results in moderate degrees of PH. In such a case, RHC will disclose elevated P_{pcw} and mean P_{pa} , with minimal increase in transpulmonary gradient (TPG; defined as mean P_{pa} minus P_{pcw} , normal values ≤ 12 mmHg), and, usually, normal PVR [1, 2]. Interventions that normalise the P_{pcw} , such as diuretic therapy, would also be expected to normalise the P_{pa} . This is generally referred to as reversible PH and it is presumed that there are no demonstrable abnormalities in the pulmonary arterial bed [1, 2, 6, 7]. Indeed, a study that evaluated 1,000 patients with advanced heart failure for heart transplantation found that the systolic P_{pa} (sP_{pa}) was closely correlated with P_{pcw} , and the reduction in sP_{pa} during therapy was strongly determined by P_{pcw} reduction [27]. The same authors also reported that in patients with HFPEF, right-sided filling pressures often reflect left-sided filling pressures [28]. Other studies in patients with mitral stenosis and PH have shown that removing the mitral valve gradient, either surgically or with percutaneous balloon valvuloplasty, results in normalisation of the P_{pa} [29–31].

Reactive PH

In a second, smaller group of patients, the PH is the result of functional and/or structural abnormalities of the pulmonary vascular bed, caused by the chronically elevated P_{pcw} , as discussed earlier in the Pathological changes section [15, 17]. These patients will have increased mean P_{pa} , TPG (>12 mmHg) and PVR; and, in contrast to the passive form, lowering the P_{pcw} to normal may not

normalise the P_{pa} [1, 2, 32]. These patients can develop severe PH, also termed reactive or out-of-proportion PH [1, 2, 6, 7]. Interestingly, several studies of the haemodynamic characteristics of patients with heart failure and out-of-proportion PH reported a severe increase in sP_{pa} and only a mild increase in diastolic P_{pa} , and a low diastolic $P_{pa}-P_{pcw}$ gradient (≤ 5 mmHg) [33, 34]. It seems that the diastolic $P_{pa}-P_{pcw}$ gradient (≥ 10 mmHg) can differentiate between passive and reactive increases in P_{pa} , an approach proposed in the past that should be considered part of the definition of out-of-proportion PH in order to avoid the marked flow and pressure dependency of the TPG [35, 36]. It is important to emphasise that the development of out-of-proportion PH is probably not closely related to the severity of heart failure, since severe PH was reported in patients with mild LV dysfunction and only mildly elevated P_{pcw} .

Challenge and vasoreactivity testing

Interestingly, borderline P_{pcw} at rest may be found on RHC in patients with heart failure, in particular if diuretics are used. In this scenario, an exercise test, or fluid or inotropic challenge at the time of RHC may induce an increase of P_{pcw} , helping to differentiate between idiopathic pulmonary arterial hypertension (IPAH) and HFPEF with out-of-proportion PH (HFPEF-PH) [37–40]. However, there is no consensus on specific protocols for either exercise or fluid challenge, and normal age-related P_{pcw} values are not available in these settings.

Acute vasoreactivity test during RHC is recommended in patients with out-of-proportion PH, particularly in candidates for heart transplantation [32, 41]. Various drugs have been used to assess acute vasoreactivity in PH-LHD, including intravenous sodium nitroprusside, prostacyclin and inhaled NO (table 2). The objective is to see whether the PH is reversible, as evidenced by reduction of the TPG and PVR during drug administration, without raising P_{pcw} or lowering cardiac output, or causing systemic hypotension. However, there is no standard definition of a responder in patients with PH-LHD. Inhaled NO testing in heart failure leads to a reduction of PVR that is attributable to an increase in P_{pcw} with no change in cardiac output, whereas the use of nitroprusside is limited by systemic hypotension (table 2) [41].

Exercise-induced PH

Exercise-induced PH is common in patients with both reduced as well as preserved LV ejection fraction (LVEF) [42]. It is considered an important cause of exertional dyspnoea and exercise intolerance. In patients with heart failure and normal P_{pa} at rest, P_{pcw} elevation in response to mild exercise, in concert with an abnormal pulmonary vascular response, failing to appropriately decrease PVR relative to the increase of cardiac output leads to increased P_{pa} [42–45]. HA *et al.* [42] reported that exercise-induced PH is common in subjects with HFPEF and that it is strongly associated with tricuspid regurgitant jet velocity (TRJV), age and increase in LV filling pressure, estimated by the ratio between early and later ventricular filling ratio (E/Ea). SHIM *et al.* [43] found that patients with HFPEF who had exercise-induced PH in the presence of elevated the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e') had a higher rate of hospitalisation or mortality. These studies suggest that exercise-induced PH is an early, mild and clinically relevant phase of PH, and screening and early intervention for exercise-induced PH may be indicated

Table 2. The haemodynamic effects of the most commonly used agents for pulmonary vasoreactivity tests in patients with heart failure

Drug	Dose	PVR	TPG	P_{pcw}	SBP
Intravenous nitroprusside	250–750 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	↓	↓	-	↓
Intravenous epoprostenol	2–10 $\text{ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	↓	↓	-	↓
Inhaled NO	10–40 ppm	↓	↓	-/↑	-

PVR: pulmonary vascular resistance; TPG: transpulmonary gradient; P_{pcw} : pulmonary capillary wedge pressure; SBP: systemic blood pressure; NO: nitric oxide. ↓: reduction; -: no effect; ↑: increase.

[42–45]. Exercise-induced PH is not specific to heart failure. Elite athletes show a higher increase in P_{pa} in response to exercise because of a larger increase in stroke volume, and patients with PAH may also have exaggerated responses to exercise with marked increases in P_{pa} . Therefore, the assessment of pulmonary pressures under conditions of exercise remains an area of controversy, mainly because of the lack of standardised data and the lack of a concept by which to categorise an abnormal response. One consensus appears to be that mean P_{pa} during submaximal exercise should be measured in the context of flow.

Epidemiology and risk factors

Heart failure is largely a disease of old age and represents the leading hospital diagnosis in older adults [46, 47]. It has been estimated that there are currently over 6.5 million heart failure patients in Europe and over 5 million in the USA; more than 550,000 new cases are diagnosed annually in the USA [46, 47]. Approximately two-thirds of cases are secondary to systolic dysfunction and about one-third are secondary to diastolic dysfunction [46, 47]. However, the prevalence of HFPEF is increasing with age, approaching 50% in patients over 70 years old [48].

PH is present in about two-thirds of patients with severe heart failure and reduced LVEF, which is commonly associated with RV dysfunction [32, 39, 49].

The prevalence of PH in HFPEF has not been established. KLAPHOLZ *et al.* [50] reported a mean \pm SD sP_{pa} of 47 ± 17 mmHg in 44% of 272 patients hospitalised for exacerbation of HFPEF diagnosed by echocardiography. A community-based study of 244 patients with HFPEF (age 76 ± 13 years; 45% males) reported that PH was highly prevalent (83%), often severe (median sP_{pa} of 48 mmHg, measured by echocardiography) and strongly predicted mortality [51]. The development of PH in this study was related to the extent of pulmonary venous hypertension as estimated by Doppler indexes. However, after accounting for this passive component of PH, the severity of PH suggests that some cases may have been affected by out-of-proportion PH [51]. A retrospective analysis of 477 consecutive echocardiographic studies in subjects with HFPEF demonstrated an association between the severity and grade of diastolic dysfunction and estimated P_{pa} [52].

Compared with patients with HF and reduced LVEF, where coronary artery disease and primary cardiomyopathy are the most common causes, those with HFPEF are typically older and more likely to be female, and have a higher likelihood of having hypertension (prevalence up to 88%), obesity (prevalence of body mass index (BMI) >30 $\text{kg}\cdot\text{m}^{-2}$, approximately 40%) and atrial fibrillation [53–55]. In conjunction, the prevalence of diabetes (about 30%) and coronary artery disease (40–50% of patients with HFPEF) is substantial, being similar to that in patients with heart failure and reduced LVEF [54]. Individuals with metabolic syndrome and normal LV systolic function frequently show abnormalities in LV diastolic function (*i.e.* impaired relaxation). These findings are also evident in subjects with only one or two metabolic syndrome criteria (or pre-metabolic syndrome), and components of the metabolic syndrome such as hypertension and obesity are independent predictors of the development of HFPEF [56–58]. Whether the presence of metabolic syndrome also confers increased risk for PH is unknown, although it is plausible. ROBBINS *et al.* [58] described 17 patients (77% female) with HFPEF-PH who had two or more components of metabolic syndrome. According to recent studies, patients with HFPEF-PH are older, mostly females, and have a higher prevalence of cardiovascular features of metabolic syndrome (obesity, diabetes, hypertension and ischaemic heart disease) and atrial arrhythmia [33, 34]. THENAPPAN *et al.* [34] compared the clinical, echocardiographic and haemodynamic features of patients with HFPEF-PH ($n=100$), PAH ($n=522$) and HFPEF without pulmonary vascular disease ($n=45$). Compared with patients with PAH, those with HFPEF-PH were older, had a higher prevalence of cardiovascular comorbidities, worse exercise capacity and renal function, more frequent left atrial enlargement and less frequent right atrial enlargement. PH was less severe in HFPEF-PH patients than in PAH patients. Compared with HFPEF patients without PH, HFPEF-PH patients were often female and more symptomatic, more often had RV hypertrophy and right atrial enlargement, and had higher right atrial pressure (P_{ra}).

Systemic hypertension and peripheral vascular stiffness are known independent risk factors for the development of HFPEF [48, 59]. Furthermore, recent studies have demonstrated that metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness [59]. Vascular stiffness, in turn, may contribute to the development of HFPEF and may also directly involve the pulmonary vasculature, leading to increased PVR and P_{pa} . A recent study demonstrated that unlike the systemic circulation, pulmonary vascular resistance and compliance display a highly predictable, inverse correlation [60]. The consistent relationship between PVR and pulmonary vascular compliance allows the prediction of the decline of PVR required by a given treatment to adequately lower pulmonary vascular compliance and, thus, reduce pulsatile and net RV afterload. The PVR–pulmonary vascular compliance relationship was found to be sensitive to changes in pulmonary venous pressure (mean P_{pcw}) because elevation of this pressure lowers pulmonary vascular compliance for any given PVR, augmenting RV pulsatile afterload. Furthermore, in patients with HFPEF with a marked rise in P_{pcw} during exercise, a disproportionate decline in pulmonary vascular compliance and increased pulsatile load was found. This identifies a novel mechanism whereby left-side diastolic dysfunction contributes to RV load [60].

Development of PH in association with valvular dysfunction has been shown to be a marker of severity. PH frequently complicates mitral stenosis and may significantly influence long-term prognosis [29–31, 36]. The increase in P_{pa} may be out of proportion with the degree of left atrial pressure increase, reflecting an increase in PVR. Elevation of PVR is an important pathophysiological event in mitral stenosis, and the level of P_{pa} is an indicator of surgical risk. Interestingly, there is a subset of mildly symptomatic patients with severe mitral stenosis and severe PH who are usually young, with preserved sinus rhythm [61, 62].

PH can also occur in patients with mitral regurgitation. The evolution of PH in these patients is not necessarily related to the LV dysfunction that complicates advanced stages of mitral regurgitation, and may occur in patients with chronic, isolated mitral regurgitation with normal LV function [63].

PH in the setting of aortic valve stenosis and/or regurgitation is less common than in mitral valve disease. SILVER *et al.* [64] performed RHC in 45 patients with aortic stenosis and found PH, defined as $sP_{pa} > 50$ mmHg, in 13 (29%) of them. Patients with aortic stenosis and PH had a higher incidence of congestive heart failure, a lower LVEF and cardiac index, and more mitral regurgitation compared with patients with aortic stenosis and normal P_{pa} . Eight of the 13 patients had a TPG ≥ 10 mmHg, suggesting a “fixed” component of the elevated pulmonary pressures. In another study, the incidence of PH ($sP_{pa} \geq 60$ mmHg) in 139 patients with severe aortic regurgitation was reported to be 24% [65]; all had high left-sided filling pressures, suggesting that PH was a consequence of severe, long-standing regurgitation with ventricular dysfunction.

Diagnosis

The clinical manifestations of PH-LHD do not differ significantly from those of PAH; both exhibit dyspnoea on exercise and, eventually, overt RV failure and peripheral oedema. Important and distinctive symptoms of PH-LHD not shared by PAH are orthopnoea and paroxysmal nocturnal dyspnoea [66, 67].

Effort dyspnoea is the most common symptom of PH-LHD. In patients with chronic LV failure, LV function at rest is poorly correlated with exercise capacity. During exercise, systemic vascular resistance (SVR) falls while PVR remains elevated, leading eventually to overt RV failure and peripheral oedema; in addition, there is an inverse relationship between peak oxygen uptake ($V'O_2$) and resting P_{pa} or PVR, as opposed to a positive correlation between RV ejection fraction at rest and exercise to peak $V'O_2$. These findings suggest that increasing RV afterload during exercise is responsible for the reduced exercise capacity [39, 41, 68, 69].

Patients with HFPEF and normal P_{pa} at rest often exhibit P_{pcw} elevation in response to mild exercise, which may result in increased P_{pa} . This may be due to failure of an associated abnormal pulmonary vascular response to appropriately decrease PVR relative to the increase of cardiac

output. These patients probably have worse outcomes and a higher rate of hospitalisation and mortality than those without exercise-induced PH [43, 45].

An ECG in these patients may show evidence of old myocardial infarction, left atrial enlargement and LV hypertrophy. Chest radiography may show signs of pulmonary congestion with redistribution of pulmonary vessels, cardiomegaly, Kerley B lines and pleural effusion. Computed tomography (CT) of the chest may reveal a mosaic perfusion pattern with diffuse ground-glass opacities.

Echocardiography plays a critical diagnostic role in patients with heart failure, in part because the physical examination, ECG and chest radiograph do not provide information that distinguishes diastolic from systolic heart failure [70]. Furthermore, echocardiography identifies valvular dysfunction and assesses its severity [70]. In patients with preserved ejection fraction, the presence of a dilated left atrium, abnormal Doppler estimates of mitral and pulmonary venous flow velocity, and abnormal mitral tissue Doppler velocities suggest HFPEF [33, 51]. The ratio of early mitral flow velocity (E) to early mitral tissue Doppler velocity (E1) was found to correlate with left atrial pressure, and an E/E1 ratio >15 was almost invariably associated with a mean left atrial pressure >15 mmHg [71]. Despite the evidence documented by echocardiography, RHC with measurement of P_{pcw} and/or LV end-diastolic pressure remains the gold standard for diagnosis of heart failure and assessment of PH [72].

Prognosis

When present, PH is usually associated with a poor prognosis in patients with LHD.

Elevated P_{pa} and abnormal RV function are important determinants of exercise capacity and prognosis in patients with heart failure and reduced LVEF, and the mortality associated with biventricular failure is more than two-fold higher compared with isolated LV failure [40, 68, 69, 73–78]. In the advanced stages, when RV failure complicates the course of heart failure and reduced LVEF, patients have severe tricuspid regurgitation secondary to annular dilatation, with increased jugular venous pulse, chronic liver congestion, ascites and peripheral oedema. GHIO *et al.* [49] followed 377 patients with moderate-to-severe heart failure (ejection fraction $<35\%$) for a median of 17 months following RHC and found that those with PH and reduced RV function had the worst prognosis and survival among patients with advanced heart failure and reduced LVEF. The prognosis in patients with normal RV function and PH was similar to that in patients with normal P_{pa} . In contrast, when P_{pa} was normal, reduced RV function did not carry an additional risk. However, another study found that RV dysfunction is more common in patients with dilated cardiomyopathy compared with patients with ischaemic cardiomyopathy (65% versus 16%), although the mean P_{pa} was the same in both groups, suggesting that the impact of PH *per se* on the prognosis is difficult to assess [73].

Severe PH is a contraindication for orthotopic cardiac transplantation since the RV of the implanted organ will fail acutely due to the high PVR, resulting in allograft failure and death. The risk was shown to be directly proportional to both PVR and TPG [79–82].

BUTLER *et al.* [39] studied 182 patients with baseline normal pulmonary pressures or reversible PH, defined as a decrease in PVR to ≤ 2.5 Wood units, who underwent heart transplantation. Those with systolic $P_{pa} > 50$ mmHg and TPG ≥ 16 mmHg had a higher risk of mortality, suggesting that pre-transplant PH, even when reversible to a PVR of ≤ 2.5 Wood units, is associated with a higher mortality post-transplant. Specific values of PVR and TPG have been proposed as risk predictors. Heart failure patients with a TPG < 12 mmHg or PVR < 3 Wood units are considered suitable with an acceptable risk in most transplant centres, whereas patients with a TPG ≥ 15 mmHg or PVR ≥ 5 Wood units, despite acute reversibility testing, are considered unsuitable candidates [83–88]. Following a successful transplantation in patients with mild-to-moderate PH, P_{pa} values tend to normalise over a 6–12-month period. The greater the PH level prior to surgery, the longer the time to resolution. In some patients, an incomplete resolution may be observed, with residual elevations in P_{pa} and PVR [89, 90].

The prognosis for patients with HFPEF-PH is not well defined. However, recent studies suggested that PH, evaluated by echocardiography, has a negative impact on mortality. LAM *et al.* [51] reported that $sP_{pa} > 35$ mmHg was strongly associated with mortality, and KJAERGAARD *et al.* [91] found that the presence of PH increased short- and long-term mortality in patients with HFPEF.

In patients with valvular heart disease, PH increased the likelihood of poor surgical outcomes. However, surgery in these patients is still associated with better outcomes compared with conservative management [62–65, 92].

Treatment

In patients with HF, reduced LVEF and PH, the traditional therapies for heart failure of diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and β -blockers may result in reduction of the P_{pa} [93–95]. However, if the patient remains significantly symptomatic despite these measures and moderate-to-severe PH persists, RHC may be indicated to clarify the haemodynamic details. A search for other causes of PH should also be undertaken, such as ventilation/perfusion scanning and polysomnography.

There is no evidence-based treatment for patients with HFPEF and there are no data on the therapeutic approach to patients complicated by PH. Treatment of HFPEF is linked primarily to the underlying aetiology [48, 96–98]. Aggressive management of systemic hypertension should be instituted, especially in patients with LV hypertrophy and diabetes mellitus [96–98]. The cornerstones of therapy include sodium restriction and judicious use of diuretics and nitrates to relieve symptoms of congestion, together with drugs that slow the heart rate and improve diastolic filling time, such as β -blockers and calcium channel blockers (CCBs) [96–98]. Several recent studies demonstrated that angiotensin receptor antagonists improve exercise tolerance in this setting [99, 100]. The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Preserved trial suggested that treatment with candesartan reduces hospitalisation related to diastolic heart failure, although there was no effect on mortality [100].

Even when the left atrial pressures are normalised, a proportion of these patients are left with significant PH. Whether modification of the features of the metabolic syndrome, such as dietary control, weight reduction and blood pressure control, will result in an improvement of symptoms and P_{pa} in patients with HFPEF remains an open question and worth investigation.

There are no clear indications for additional therapeutic measures in patients with out-of-proportion PH other than optimising traditional therapy for heart failure. In fact, there is no evidence that the drugs approved for PAH are effective and safe in this setting. The main concern is that by decreasing the PVR, the consequent increase in venous return to the LV may further increase the already elevated left heart filling pressure, resulting in deterioration rather than improvement. Early experiences with PAH-specific treatments in the setting of LV failure were disappointing. The major clinical studies assessing vasodilators in the treatment of PAH in patients with heart failure are summarised in table 3.

Prostacyclins

SUETA *et al.* [101] studied the acute and prolonged effects (12 weeks) of continuous *i.v.* epoprostenol on 33 patients with severe heart failure: the drug resulted in significant reductions in mean P_{pa} , PVR and P_{pcw} , and a marked increase in cardiac output. These beneficial haemodynamic effects persisted with long-term infusions. Based on this and other studies that suggested clinical benefit of *i.v.* epoprostenol [101, 113], a large randomised controlled study (Flolan International Randomized Survival Trial; FIRST) was initiated [102]. The FIRST study randomised 471 patients with advanced heart failure to receive continuous epoprostenol infusion plus standard care or standard care alone. Although a haemodynamic improvement was seen acutely among patients receiving epoprostenol, evidenced by an increase in cardiac index and a decrease in P_{pcw} and PVR, the study was terminated

early due to a strong trend toward increased mortality rates in patients on the drug. Based on the findings of this study, chronic use of epoprostenol in patients with systolic heart failure is considered contraindicated. Explanations for the increase in mortality include sympathetic stimulation due to systemic vasodilatory effects and/or unknown detrimental effects of prostanoids in this setting [114]. The more recent data on the inhaled prostacyclin analogue iloprost indicate short-term beneficial effects in patients undergoing assessment for heart transplantation, with improvements recorded in mean P_{pa} , PVR and P_{pcw} during vasoreactivity testing, but these findings must be considered with caution [115].

Endothelin receptors antagonist

Plasma levels of endothelin have been shown to be elevated in heart failure, to correlate with the severity of heart failure and may contribute to the excessive systemic and pulmonary vasoconstriction that exists in the disease [116–118]. In animal models of heart failure, treatment with both selective and nonselective endothelin receptor antagonists (ERAs) prevented LV remodelling and improved exercise capacity [119, 120].

Studies on the short-term haemodynamic effect of ERAs in patients with chronic heart failure were initially encouraging [103, 121, 122]. A randomised, placebo-controlled study evaluating the haemodynamic effects of 6-hour infusions of tezosentan compared with placebo in 61 patients with New York Heart Association (NYHA) functional class III–IV heart failure demonstrated increased cardiac index with reduction in P_{pcw} PVR and SVR [121]. Similar results were reported in a larger study of patients admitted to hospital and in need of *i.v.* treatment for acute heart failure [103]. A short-term study evaluating 2 weeks of the nonselective ERA bosentan in 36 patients with symptomatic heart failure, despite treatment with standard regimen, resulted in a reduction of both systemic and pulmonary pressures, and an increase in cardiac output [122]. These encouraging results prompted long-term randomised trials. In the REACH-1 (Research on Endothelin Antagonists in Chronic Heart Failure) study, 370 patients with advanced heart failure (NYHA functional class IIIB–IV) received bosentan or placebo and were followed for up to 26 weeks [104]. The target dose of bosentan was 500 mg twice a day, which is much higher than the current recommended dose for PAH. The trial was stopped prematurely due to safety issues, namely elevated liver transaminases; the question of the possible long-term benefit of using lower doses was also raised based on a trend towards reduction in morbidity and mortality. A larger study, ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure), evaluated the effects of low-dose bosentan in patients with severe heart failure (LVEF <35%, NYHA functional class IIIB–IV) [105]. A total of 1,613 patients were randomised to receive either bosentan (125 mg twice a day) or placebo [105]. No improvement in outcome was demonstrated in either group. There was an increased risk of early heart failure exacerbations due to fluid retention in patients treated with bosentan. Other studies using selective ETA antagonists also failed to improve outcome, and showed a trend towards increased mortality and early exacerbation of heart failure [106, 107].

The reasons for the lack of efficacy of ERAs in heart failure are unclear; the small relevance of endothelin system activation in patients already treated with US Food and Drug Administration (FDA)-approved drugs for heart failure has been suggested [123].

Phosphodiesterase type-5 inhibitors

Previous studies in animal models and in humans suggest that endothelial dysfunction is present in heart failure, with a relative deficiency in NO production [124, 125]. Inhaled NO administered to patients with heart failure lowers PVR, increases cardiac index and improves exercise capacity, without altering systemic arterial pressure, suggesting that phosphodiesterase type-5 (PDE-5) inhibition may reduce PVR and improve cardiac performance [126]. Recent studies reported that PDE-5 is also present in cardiac myocytes and PDE-5 inhibition resulted in antihypertrophic, anti-apoptotic and ischaemic pre-conditioning effects [127–132]. Acute administration of sildenafil in

Table 3. Major trials with pulmonary vasodilators in patients with heart failure

First author [ref.]	Patient population	Treatment	Primary end-point	Findings and outcome
SUETA [101]	Advanced systolic heart failure, NYHA FC III–IV, n=33	Continuous <i>i.v.</i> epoprostenol infusion for 12 weeks	6MWD	Significantly improved 6MWD
CALIFF [102]	Advanced systolic heart failure, NYHA FC IIIB–IV, n=471	Continuous <i>i.v.</i> epoprostenol	Survival	Improved haemodynamics Early termination because of strong trend toward decreased survival in the patients treated with epoprostenol
TORRE-AMIONE [103]	Advanced systolic heart failure, NYHA FC III–IV, n=61	6-hour infusions of tezosentan at 5, 20, 50 and 100 mg·h ⁻¹	Safety and haemodynamic parameters	Tezosentan significantly decreased PVR and P_{bcw} , and significantly increased cardiac index
PACKER [104]	Advanced systolic heart failure, NYHA FC III–IV, n=371	Bosentan 500 mg twice daily for 26 weeks		Safety concerns led to early termination of the trial (liver toxicity) when only 174 patients completed 26 weeks of therapy Bosentan-treated patients had an increased risk of heart failure during the first month of treatment but a decreased risk of heart failure during the fourth, fifth and sixth months of therapy
The ENABLE study [105]	Advanced systolic heart failure, NYHA FC IIIB–IV, n=1613	Bosentan 125 mg twice daily for 1.5 years	All-cause mortality or hospitalisation for heart failure	Treatment with bosentan appeared to confer an early risk of worsening heart failure, necessitating hospitalisation as a consequence of fluid retention
LÜSCHER [106]	Advanced systolic heart failure NYHA FC III, n=157	Darusentan 30, 100 or 300 mg daily for 3 weeks	Haemodynamic and neurohumoural effects	Cardiac index significantly increased but P_{bcw} , P_{pa} , PVR and P_{ta} did not change Heart rate, mean arterial pressure and plasma catecholamine levels remained unaltered, but SVR decreased significantly Higher dosages were related to more adverse events (including death), particularly early exacerbation of congestive heart failure
ANAND [107]	Advanced systolic heart failure, NYHA FC II–IV, n=642	Darusentan at 10, 25, 50, 100 or 300 mg daily for 24 weeks	Change in LVESV at 24 weeks from baseline, measured by MRI	Darusentan did not improve cardiac remodelling, clinical symptoms or outcomes

Table 3. Continued

First author [ref.]	Patient population	Treatment	Primary end-point	Findings and outcome
GUAZZI [108]	Advanced systolic heart failure, NYHA FC II–III, n=46	Sildenafil 50 mg three times daily for 6 months	Assessments of endothelial function by brachial artery flow-mediated dilatation, cardiopulmonary exercise testing and ergoreflex response	Sildenafil improved exercise ventilation and aerobic efficiency
LEWIS [109]	Advanced systolic heart failure, NYHA FC II–IV with secondary PH, mean P_{pa} >25 mmHg, n=13	Sildenafil 25–75 mg three times daily for 3 months	Change in peak $\dot{V}O_2$ from baseline	The change in peak $\dot{V}O_2$ from baseline was greater in the sildenafil group Sildenafil significantly reduced PVR and increased cardiac output with exercise without altering P_{pcw}
TEDFORD [110]	Advanced heart failure, treatment with LV assist device implantation and persistent PH (defined as PVR >3 Wood units), n=58	Sildenafil 25–75 mg orally three times daily for 3 months	Change in PVR	Sildenafil significantly reduced PVR and mean P_{pa}
BEHLING [111]	Stable heart failure with moderate PH, n=22	Sildenafil 50 mg three times daily for 4 weeks	Peak $\dot{V}O_2$ and systolic P_{pa} assessed by echocardiography	Sildenafil improved function capacity and $\dot{V}O_2$ kinetics, and significantly reduced systolic P_{pa}
GUAZZI [112]	HFPEF and systolic P_{pa} >40 mmHg, n=44	Sildenafil 50 mg three times daily for 1 year	Pulmonary haemodynamics and RV performance	Sildenafil improved pulmonary haemodynamics, RV function and dimension, LV relaxation and distensibility, and lung interstitial water metabolism

NYHA: New York Heart Association; FC: functional class; *i.v.*: intravenous; 6MWD: 6-minute walking distance; PVR: pulmonary vascular resistance; P_{pcw} : pulmonary capillary wedge pressure; P_{pa} : pulmonary artery pressure; P_{ra} : right atrial pressure; SVR: systemic vascular resistance; LVESV: left ventricular end-systolic volume; MRI: magnetic resonance imaging; $\dot{V}O_2$: oxygen uptake; RV: right ventricular; LV: left ventricular; PH: pulmonary hypertension; HFPEF: heart failure with preserved ejection fraction.

patients with PH secondary to heart failure and reduced LVEF improved exercise capacity, gas exchange and pulmonary haemodynamics in a dose-dependent manner [132–134]. The haemodynamic benefits were specific to the pulmonary circulation and most dramatic in patients with severe PH. The effects observed in the acute setting may also persist during longer-term treatment [108, 109]. LEWIS *et al.* [109] studied 34 patients with symptomatic heart failure, reduced LVEF and associated PH before and after randomisation to either sildenafil or placebo for 12 weeks. Sildenafil improved peak $\dot{V}O_2$, PVR and cardiac output with exercise, and there was also improvement in exercise capacity and quality of life. The dose of sildenafil was 50 mg three times a day at completion of the study, which is higher than the FDA-approved dose for PAH (20 mg three times a day). It can be speculated that higher doses may offer additional benefits, particularly over longer durations of treatment. A recent study reported on six patients excluded from heart

transplantation due to severe PH; after 1 month of sildenafil (50 mg *b.i.d.*), five patients had significant reductions in PVR and TPG [135]. However, since no patient had undergone transplantation at the time of publication, the significance of the haemodynamic improvement is still unclear. Although the results observed in small, single-centre experience are encouraging, they should be treated with extreme caution, as similar results were also observed after epoprostenol and ERAs, and were contradicted by large clinical trials.

Sildenafil was investigated in 26 patients with advanced heart failure, candidates for heart transplantation in whom PH persisted after adequate LV unloading *via* recent LV assist device therapy [110]. The addition of sildenafil (50 mg three times a day for 3 months) together with continued LV assist device support substantially and rapidly lowered mean P_{pa} and PVR to levels <3 Wood units without elevating P_{pcw} , and RV function also improved [133]. BEHLING *et al.* [111] found that sildenafil (50 mg three times a day for 4 weeks) in patients with advanced systolic heart failure substantially improved exercise capacity, ventilatory efficiency and $V'O_2$ kinetics, with concomitant sustained reductions in P_{pa} .

Long-term use of PDE-5 inhibitors (PDE-5 I) in patients with heart failure and reduced LVEF has not been investigated to date, and there are concerns that long-term PDE-5 inhibition might produce adverse events, such as the increase in mortality seen with the PDE-3 inhibitor milrinone [136].

GUAZZI *et al.* [112] assessed the effectiveness of sildenafil in a 1-year, placebo-controlled, randomised study of 44 patients with HFPEF-PH. Sildenafil (50 mg *t.i.d.*) improved pulmonary haemodynamics, RV function and dimension, LV relaxation and distensibility, and lung interstitial water metabolism. The evolving data on the possible advantages of PDE-5 inhibition prompted the initiation of the RELAX (Phosphodiesterase-5 Inhibition to Improve Quality of Life and Exercise Capacity in Diastolic Heart Failure) trial, which is examining the effectiveness of sildenafil in patients with a clinical diagnosis of HFPEF, focusing on exercise capacity as the primary end-point.

In patients with PH secondary to valvular dysfunction, surgical correction of the failing valve is usually indicated. Several clinical studies have shown that removing the mitral valve gradient, either surgically or with percutaneous balloon valvuloplasty, will result in an immediate fall in the P_{pa} [29–31]. The degree of the fall, however, can vary considerably, with some patients achieving normal haemodynamics immediately following an intervention and others taking many months to improve. FAWZY *et al.* [31] reported that in patients with mitral stenosis and severe PH, the pulmonary pressure regressed to normal levels over 6–12 months after successful mitral balloon valvuloplasty. The magnitude and rate of regression may be related to the severity of the vascular disease, which in turn may be related to the duration of PH and to constitutional factors. These may either induce more severe vascular disease or slow the reverse remodelling of the obstructive changes in the distal pulmonary arteries.

ROSENHEK *et al.* [137] evaluated the outcome of a watchful waiting strategy in patients with asymptomatic severe mitral stenosis until they were referred for surgery when symptoms occurred or when asymptomatic patients developed LV enlargement, LV dysfunction, PH or recurrent atrial fibrillation. Only five out of 132 patients followed for a median of 62 months developed new onset of atrial fibrillation or PH. These findings are in agreement with the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with valvular heart disease [61], which recommend mitral valve surgery for asymptomatic patients with chronic severe mitral stenosis, preserved LV function and PH ($sP_{pa} >50$ mmHg at rest or >60 mmHg with exercise).

PH frequently complicates the perioperative management of patients undergoing mitral valve surgery and may be aggravated by endothelial dysfunction due to cardiopulmonary bypass procedure [138, 139]. Exacerbation of PH may result in acute RV failure, which is associated with high morbidity and mortality [140]. A recent study randomised 20 patients with chronic PH undergoing mitral valve repair to receive inhaled iloprost or *i.v.* nitroglycerine [141]. Iloprost, which was administered during weaning from cardiopulmonary bypass, selectively decreased PVR index and TPG with an associated improvement in indices of RV function, and was apparently more pulmonary selective than *i.v.* nitroglycerine. However, the real clinical benefit of these effects is not clear.

MALOUF *et al.* [142] analysed the clinical characteristics and outcomes of 47 patients (mean age 78 years) with severe PH and severe aortic stenosis. Aortic valve replacement (AVR) was performed in 37 (79%) patients and 10 (21%) patients were treated conservatively. 15 (32%) of the group that underwent AVR died, compared with 80% of the conservatively treated group. In contrast with the severity of LV systolic dysfunction or concomitant coronary artery bypass grafting, severe PH was an independent predictor of perioperative mortality. However, it seems that the prognosis for patients with aortic stenosis and severe PH treated conservatively without AVR is dismal. Although AVR is associated with higher than usual mortality, the potential benefits outweigh the risk of surgery [64]. An interesting recent study reported that a single dose of a PDE-5 I is safe in patients with severe symptomatic aortic stenosis and is associated with acute improvements in pulmonary and systemic haemodynamics, resulting in biventricular unloading [143]. However, longer-term studies to evaluate the role of PDE-5 inhibition as an adjunctive medical therapy in patients with aortic stenosis are needed.

AVR in patients with severe aortic regurgitation and PH resulted in decreased PVR and normalisation of P_{pa} in most patients, with no increased mortality compared with patients with no PH [64].

Future directions

PH is common in patients with LHD, and an increasing number of patients with severely increased P_{pa} are referred to PH centres for evaluation, even when PH is moderate. In addition, PH complicating HFPEF is often misdiagnosed as PAH, resulting in inadequate use of PAH-specific therapies. The term “out-of-proportion PH” adds to the confusion, since some physicians believe it is similar to PAH. It is therefore critical to better identify the phenotype of the subgroup of patients presenting an exaggerated increase in mean P_{pa} in response to the initial insult of a passive increase in left heart filling pressures. That identification is complicated by the lack of knowledge about the natural history of passive PH and the factors that contribute to the development of severe and out-of-proportion PH. It is possible that genetic predisposition and changes in cell phenotype play a role in the course of PH owing to LHD. There is also a need to better define the haemodynamic classification of post-capillary PH. Because most patients with PH-LHD essentially have an increase in sP_{pa} with high pulse pressure, it might be more accurate to rely on the diastolic $P_{pa}-P_{pcw}$ difference rather than the TPG. The potential for reversibility and the role of vasoreactivity tests in this population need to be addressed. Because the current literature lacks consistency, there is no clear recommendation as to what should be considered reversible, or which agent should be used in the setting of PH-LHD. It has also been shown that simply unloading the left heart by implanting a LV assist device may normalise pulmonary haemodynamics.

Therapy for PH-LHD remains an unmet medical need. Randomised controlled trials have been conducted on heart failure with reduced ejection fraction using PAH-specific therapies: all of them failed to demonstrate a clinical benefit and, in some cases, even led to clinical deterioration. No large trial has been performed on the limited population of patients presenting heart failure and PH. Small trials using the PDE-5 I sildenafil in this setting have been encouraging, both in patients with preserved EF [122] and those with decreased ejection fraction [71, 72]. However, such initial positive experience needs to be confirmed in large-scale clinical trials. A phase II trial is underway with the guanylate cyclase stimulator riociguat in PH-LHD with reduced ejection fraction. Until more data are available, the use of specific PAH therapy in patients presenting PH in the context of LHD is not recommended [2].

Conclusion

LHD is the most common cause of PH and, in most cases, complicates heart failure with or without impaired LVEF. When present, PH owing to LHD is associated with increased symptoms, impaired quality of life and poor outcome. In a sizeable subgroup of patients, the increase in mean P_{pa} by factors other than the passive elevation of left-sided filling pressures leads to pulmonary vascular remodelling and significant PH. More data are needed to establish the risk factors for

developing PH in LHDs, and to better characterise this population. A first important step would be to reconsider the current definition of post-capillary PH in its “reactive” component. Such efforts are urgently needed as they are the first step to exploring potential therapies. In this setting, only appropriately sized and long-term randomised controlled studies can define the safety and efficacy of approved PAH drugs.

Statement of Interest

None declared.

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