Pulmonary hypertension with left-sided heart disease

Marco Guazzi and Ross Arena

Abstract | Pulmonary hypertension (PH) with left-sided heart disease is defined, according to the latest Venice classification, as a Group 2 PH, which includes left-sided ventricular or atrial disease, and left-sided valvular diseases. These conditions are all associated with increased left ventricular filling pressure. Although PH with left-sided heart disease is a common entity, and long-term follow-up trials have provided firm recognition that development of left-sided PH carries a poor outcome, available data on incidence, pathophysiology, and therapy are sparse. Mitral stenosis was reported as the most frequent cause of PH several decades ago, but PH with left-sided heart disease is now usually caused by systemic hypertension and ischemic heart disease. In patients with these conditions, PH develops as a consequence of impaired left ventricular relaxation and distensibility. Chronic sustained elevation of cardiogenic blood pressure in pulmonary capillaries leads to a cascade of untoward retrograde anatomical and functional effects that represent specific targets for therapeutic intervention. The pathophysiological and clinical importance of the hemodynamic consequences of left-sided heart disease, starting with lung capillary injury and leading to right ventricular overload and failure, are discussed in this Review, focusing on PH as an evolving contributor to heart failure that may be amenable to novel interventions.

Guazzi, M. & Arena, R. *Nat. Rev. Cardiol.* advance online publication XX Month 2010; doi:10.1038/nrcardio.2010.144

Introduction

In 1998[1] and 2003[2] the WHO convened a panel of experts to develop a classification of pulmonary hypertension (PH) in order to provide guidelines for diagnosis and treatment. PH, identified as any condition with a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest, was classified into five major categories. The category of patients with chronic elevated pulmonary capillary wedge pressure (PCWP) secondary to left-sided valvular or myocardial diseases, who require treatment for improving left ventricular (LV) pump function or diastolic compliance, or for correcting valvular mechanical defects, was indicated as having 'pulmonary venous hypertension' in the former classification, and 'non-pulmonary arterial hypertension with left heart disease', or Group 2 PH, in the latter classification. In the original nomenclature from 1998,[1] this form of PH had been classified as 'passive pulmonary arterial hypertension' because it originates from raised pulmonary vein and capillary pressures that are associated with a concomitant increase in pulmonary artery perfusion pressure.[3] The category of disease with elevated left-sided cardiac filling pressure is perhaps the most common PH scenario, and 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.[4,5] The prevalence of PH as a consequence of LV failure is undefined, however, with a wide range of estimates reported in the literature depending on the severity of LV dysfunction and the cut-off used to define PH.

Decades ago, mitral valve disease was the primary cause of PH with left-sided heart disease. Currently, common cardiac-related causes of increased LV filling pressure in referral clinical practice are systemic hypertension and ischemic heart disease, in which PH develops as a direct consequence of impaired LV relaxation and distensibility. Heart failure with preserved LV ejection fraction (HFpEF) is increasingly recognized as the predominant cause of left-sided PH in both acute[6] and chronic forms[7–11] associated with left-sided heart disease. Accordingly, the 2009 Dana Point updates of PH recognize HFpEF as the most frequent cause of left-sided PH.[12] In this Review, we focus on the pathophysiology and clinical correlates of the retrograde pulmonary hemodynamic consequences of PH in left-sided heart disease, from lung capillary injury to right ventricular overload and failure.

Pathophysiology of left-sided PH

Pressure-induced injury of lung capillaries

Excessive pressure elevation in the pulmonary capillaries has an adverse effect on the alveolar–capillary unit. When pressure elevation in the pulmonary venous circulation is sustained, the arterioles and pulmonary arteries are subjected to both structural and functional changes. This type of change occurs at an even earlier stage in the capillaries. Injury to the alveolar–capillary barrier as a result

Competing interests
The authors declare no competing interests.

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Key points

- Pulmonary hypertension (PH) with left-sided heart disease is a common clinical entity that usually develops as a consequence of impaired relaxation and distensibility of the left ventricle
- Although left-sided PH has a poor outcome, and patients with this condition have a high risk of developing right ventricular failure, available data on PH incidence, pathophysiology, and therapy are limited
- Chronic sustained cardiogenic pressure elevation in pulmonary capillaries leads to a cascade of adverse retrograde anatomical and functional events that represent potential targets for intervention
- Therapy of left-sided PH is challenging and most therapeutic strategies tested for this condition have had negative results
- Although precise guidelines on the most beneficial and cost-effective strategies for managing left-sided PH are lacking, promising results have been observed with the use of PDE5 inhibitors

of hydrostatic pressure elevation is of pathophysiological importance, mainly in view of its acute clinical correlates, such as alveolar edema. However, the multistep adaptive process that is triggered by excessive pressure elevation and involves the microcirculation and the alveolar wall, together with its clinical manifestations, is mostly overlooked.[13] The resistance of capillaries to a rise in hydrostatic pressure is partly challenged by the thin walls of the alveolar–capillary unit, which are a basic requirement for gas diffusion. The alveolar–capillary unit consists of an alveolar epithelial layer made up of cells that provide both mechanical (type I) and metabolic (type II) support, the interstitial space, and the capillary endothelium. The capillary endothelium is permeable to ions and small molecules, but is almost impermeable to proteins,[14] whereas the alveolar epithelium is resistant to the transition of small ions and allows passage of water and solutes from the alveolar lumen to the interstitium.[15] Owing to differences in interstitial composition, one side of the alveolar–capillary membrane is thinner than the other by a direct fusion of the basement membrane of the alveolar epithelium and the vascular endothelium, whereas the thicker portion of the membrane has a greater collagen content. As a result of this configuration, gas diffusion is facilitated through the thinnest part of the membrane, and the interstitium is shielded from electrolyte and fluid overflow.

West *et al.* investigated the structural changes induced by a progressive rise in the pulmonary capillary pressure, and coined the term 'alveolar capillary stress failure' to describe the fragmentation of the alveolar–capillary membrane components during mechanical injury.[16] Tsukimoto *et al.* studied the sequential disruption of the capillary endothelial and alveolar epithelial layers during a stepwise increase in hydrostatic pressure, reproducing the transition from interstitial leakage of protein (low-permeability stage) to alveolar lumen leakage of protein and erythrocytes (high-permeability stage of pulmonary edema).[17] A number of animal studies that have focused on the biological features of alveolar stress failure provide evidence that mechanisms other than mechanical injury may determine capillary stress.[18–20] Remarkably, vascular perfusion of 0.5 ml/min^{-1}/kg^{-1} saline solution for 180 min in the rabbit pulmonary artery was associated with a 44% portion of fluid accumulating in the interstitial space, ultrastructural changes, and impairment of gas transfer.[18] Development of hydraulic edema leads to activation of metalloproteinases,[19] which degrade matrix proteoglycan and alter the composition of the plasma membrane, causing increased endothelial membrane fluidity. The weakened tensile strength of the membrane potentiates endothelial stress failure.[20]

These findings might explain the acute rise in pulmonary hydrostatic pressure and pulmonary edema seen in humans, even if the pathophysiological correlates of alveolar–capillary stress failure in patients with cardiac disease have not been extensively investigated. In a study of 53 patients with acute cardiogenic pulmonary edema, injury of the alveolar–capillary barrier was associated with increased levels of plasma pulmonary surfactant-associated proteins A and B and tumor necrosis factor.[21] Persistence of elevated levels of tumor necrosis factor after pulmonary edema resolution may reflect pulmonary inflammation and explains why fluid accumulation can persist despite resolution of hydrostatic stress failure.

Pressure elevation and capillary remodeling

Stress failure is an acute reversible phenomenon,[17] whereas the alveolar–capillary membrane can undergo a remodeling process during chronic capillary pressure elevation that might not be reversible. Animal models of pacing-induced cardiomyopathy have shown alveolar–capillary membrane thickening as a result of excessive deposition of type IV collagen (the main component of the membrane lamina densa).[22] This feature is reminiscent of the extracellular matrix thickening reported in patients with mitral stenosis and pulmonary venous pressure elevation,[23,24] in whom this feature accounts for the structural changes observed. An increase in collagen content can be triggered by local growth factors, such as angiotensin II, and might be a safety mechanism against excessive fluid leakage from the alveolar–capillary membrane.[25] The increase in lung interstitial connective tissue associated with chronic capillary hydrostatic overload results in increased extravascular fluid storage owing to increased production of an extracellular matrix component (mainly glycosaminoglycans) that has the potential to absorb and accommodate fluid in the interstitium. At least in cases of a subcritical rise in persistent left atrial pressure, this compensatory mechanism could prove beneficial by constraining fluid in the perivascular space without limiting gas diffusion.[26] Alveolar hypoxia may substantially affect the composition of the extracellular matrix by increasing the expression of genes that encode extracellular matrix proteins.[13]

These structural modifications generally increase the impedance to gas transfer.[13] In patients with heart failure, assessment of lung diffusion capacity by measuring the alveolar membrane conductance component enables quantification of the anatomical and functional integrity of the alveolar–capillary unit, which provides prognostic insights.[27] Transition from stress failure to remodeling is an essential step in the development of PH, and the true reversibility of this process is unknown. The pathophysio-

logical transition from capillary injury to alveolar stress failure, capillary remodeling, and impairment of gas diffusion have been consistently demonstrated in animal models, but they are still to be definitively confirmed in humans. A proposed sequence of events is illustrated in Figure 1.

Vessel response to chronic pressure elevation

Increased intraluminal pressure promotes hypertrophy and fibrous changes in the pulmonary arteries and veins. The main changes are medial hypertrophy of the muscular branches with peripheral extension of the smooth muscle coat into the smaller intra-acinar branches, which results in a 'muscularization' of arterioles. Pressure-induced disruption of the endothelium can be viewed as a trigger step that makes it possible for serum proteins to enter the vessel wall and activate endogenous vascular serine elastase and matrix metalloproteinases. The induction of endogenous vascular serine elastase is a basic mechanism of the hypertrophic process[28] and, together with the release of growth factors and glycoproteins (tenascin-C and fibronectin), stimulates smooth muscle growth and migration. The activation of endogenous vascular serine elastase and matrix metalloproteinases disrupt the elastic lamina and elicit elastin synthesis.

Pulmonary vein 'arterialization' takes place when medial hypertrophy becomes prominent. Pulmonary vascular structural changes elicited by elevated venous pressure can be quite variable across individuals, which indicates a role for individual variability of genetic factors.[29] Regression of structural remodeling after venous pressure lowering as, for example, after cardiac transplantation, is generally not complete; however, in patients evaluated for cardiac transplantation, improvement in pulmonary hemodynamics following provocative vasodilator therapy carries a good prognosis.[30]

Plexiform lesions are generally not observed in patients with pulmonary pressure elevation owing to left-sided heart disease. Nonetheless, in the subset of patients who develop reactive pulmonary vasoconstriction with marked elevation in pulmonary arterial diastolic pressure (beyond that which is necessary to maintain cardiac output), more severe arterial changes have been reported, including neointima formation.[29] This change has been studied extensively in patients with mitral stenosis, but is less well characterized in patients with LV failure. These patients are likely to have a permissive genotype that becomes dominant when they are exposed to high pulmonary vascular resistance.[31]

Impaired pulmonary vascular smooth muscle relaxation as a retrograde effect of left-sided heart disease is predominantly due to endothelial dysfunction. The endothelium seems to have an integral part in mediating the functional alterations of the pulmonary vasculature. In the pulmonary circulation, the endothelium-mediated local control of vasomotility is primarily based on a balanced release of nitric oxide (NO) and endothelin-1 (ET_1); evidence suggests that raised pulmonary pressure owing to left-sided heart disease is critically sensitive to imbalance of these two opposing systems.[32,33]

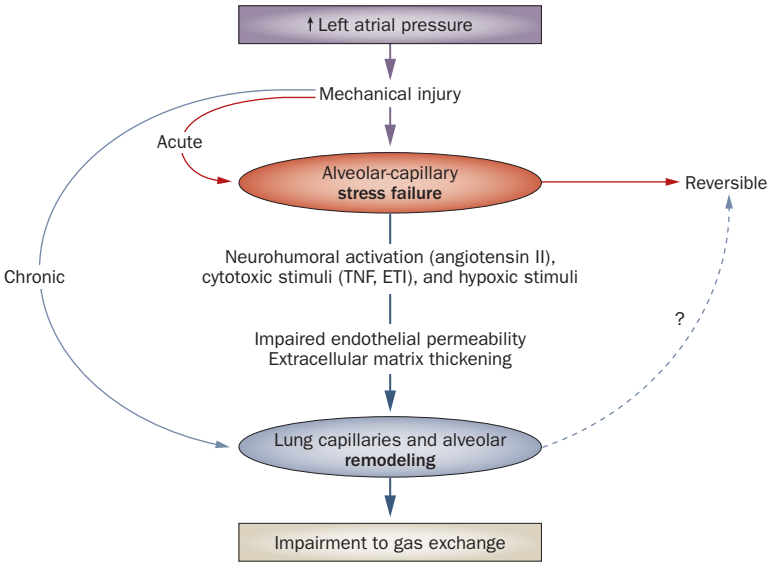

Figure 1 | Elevation in left atrial pressure and proposed sequence of events that lead to capillary stress failure and alveolar membrane remodeling. Development of acute PH as a result of an increase in left atrial pressure leads to alveolar stress failure, a process that disrupts the functional properties of the alveolar–capillary unit, but is reversible. In chronic PH, a superimposition of additional factors other than mechanical stress, such as neurohumoral, cytotoxic, hypoxic, and genetic factors, injure lung capillaries and alveolar spaces further, which triggers a process of alveolar remodeling that ultimately leads to gas exchange impairment. Abbreviations: ET_1, endothelin-1; PH, pulmonary hypertension; TNF, tumor necrosis factor.

Studies with blockade of NO synthesis suggest that endothelium-derived NO is a basic determinant of the baseline pulmonary vascular tone, and a mediator of the dilating response to endothelium activation. In healthy individuals, systemic infusion of NG-monomethyl-L-arginine (L-NMMA), an analog of L-arginine that inhibits NO synthase, raises pulmonary artery pressure,[34] enhances hypoxia-induced pulmonary vasoconstriction,[35] and inhibits the lung diffusion of carbon monoxide by lowering the alveolar–capillary membrane conductance.[36] In patients with HF, infusion of L-NMMA in the pulmonary circuit causes a dose-dependent vasoconstriction, which is partially attenuated by acetylcholine.[33] Human and animal studies suggest that NO-mediated pulmonary vasodilatation is impaired in left-sided heart disease. Pother *et al.* assessed pulmonary artery diameter with intravascular ultrasonography and reported vessel dilatation when acetylcholine was infused in patients with LV dysfunction and normal pulmonary artery pressure, but dilatation was refractory when the baseline pressure was elevated.[37] Data that support attenuation or loss of NO-dependent vasodilatation as a basic contributor to pressure elevation have also been provided by recording pulmonary blood flow velocity during intrapulmonary infusion of L-NMMA.[33] In healthy individuals and in patients with LV dysfunction with normal pulmonary vascular resistance, L-NMMA elicited a conspicuous vasoconstrictor response. This effect was attenuated when L-NMMA was infused in patients with HF and PH. Notably, vasoconstriction was similar in the three groups in response to phenylephrine.

ET_1, a potent vasoconstrictor and platelet-aggregating peptide, is stored in pulmonary endothelium and is active on two types of receptors: ET_A, which promotes vasoconstriction and cellular growth, and ET_B whose vascular effects may be either constricting (smooth muscle activity) or dilating (endothelial cell activity).[38] However, the net effect of ET_1 on pulmonary vessels is constriction,[39] with the ratio of ET_A to ET_B receptors in human resistance and conduit pulmonary vessels being approximately 9:1. ET_1 might also induce pulmonary vascular remodeling by promoting proliferation and hypertrophy of vascular smooth muscle cells and collagen synthesis. Pulmonary vascular endothelial cells obtained from patients with HF and elevated pulmonary pressure show high ET_1 expression.[40] Increased plasma ET_1 expression has been repeatedly shown in experimental models[41] and human patients with HF,[42] and is a powerful predictor of mortality.[43] Despite this evidence, when ET_1 receptor antagonists have been assessed in clinical trials of patients with LV dysfunction, they have repeatedly failed to demonstrate a sustained clinical benefit.[44]

Pulmonary hemodynamics

Passive PH

Left-sided PH is described as passive in the early stages, to indicate that the elevation of pulmonary arterial systolic pressure (PASP) is solely the consequence of increased LV filling pressure (PCWP ≥15 mmHg) and of a transpulmonary gradient (difference between mPAP and PCWP) within normal range (5–9 mmHg), and that no component of the PH is derived from abnormalities intrinsic to the pulmonary arterial bed. This stage is generally referred to as reversible. Studies by Drazner *et al.* investigating a large number of heart transplant candidates found a good correlation between PASP and PCWP.[45] A reduction in PASP was strongly dependent on a PCWP reduction, which implies that left-sided filling pressures largely determine pulmonary artery pressure in HF. Notably, the same group of investigators reported a similar behavior in patients with HFpEF,[46] suggesting that PH is not invariably related to the degree of LV systolic dysfunction. Evidence also exists for a relationship between PASP and indices of LV diastolic function and degree of functional mitral regurgitation as derived from Doppler echocardiography.[47]

Reactive PH

As the pulmonary venous pressure continues to increase, a large number of patients with HF develop pulmonary vascular disease with vasoconstriction and remodeling of the pulmonary arterial bed caused by the chronically elevated PCWP. In terms of hemodynamics, these changes include elevated PCWP and mPAP, with an augmented transpulmonary gradient (>15 mmHg) and usually elevated pulmonary vascular resistance. This 'intrinsic' form of PH may be either reversible or permanent. In the latter case, mPAP does not normalize following alleviation of the high downstream pressure, which is a fixed arterial component of PH. At this stage, both functional and structural abnormalities of the pulmonary vascular bed are presumed to exist, and histological changes in the vasculature of affected patients may not be distinguishable from those of patients with precapillary PH. An approach proposed in the past to differentiate between a passive transmission of the left-sided filling pressures and remodeling of the pulmonary venules is the incorporation of the diastolic PAP–PCWP gradient into the diagnostic work-up of affected patients.[48] Use of this gradient would avoid the marked flow-dependency and pressure-dependency of the mPAP–PCWP gradient, which can result in a misleading diagnosis of PH.[49] Notably, PCWP might not reflect the true downstream pressure in the presence of increased pulmonary venous resistance. In this case, the pulmonary arterial occluding pressure provides a more accurate estimate of left atrial pressure.[50]

The degree of change in vessel structure and vascular resistance in response to venous hypertension varies widely, which means that the natural evolution of PH is very different across the spectrum of patients with HF. Specifically, uncertainty exists on the exact time frame of the transition from pulmonary hemodynamic reversibility to irreversibility. The assumption that development of a fixed component is closely related to the severity of HF has been challenged by the observation that marked elevation in mPAP may develop in mild or moderate LV dysfunction. In this setting, regardless of whether the PH is reversible or fixed, the elevation in PASP would be considered out of proportion to the underlying causes of HF. Although a precise pathophysiological and clinical characterization of this stage is missing because of a lack of specifically designed large studies, pharmacological and hemodynamic tests of vasoreactivity may help to distinguish reversible and irreversible structural obstructive remodeling of the pulmonary resistance vessels.

An important example of 'out of proportion' PH has been reported by Lam *et al.* in a population-based study of PH in patients with HF with preserved LVEF and systemic hypertension.[11] In most hypertensive patients symptomatic for HF, an upward shift of the relationship between PASP and PCWP was observed, with a higher PASP for a similar PCWP than among hypertensive asymptomatic individuals, which provides the first evidence of the considerable precapillary pulmonary arterial contribution to PH in HFpEF. These findings, although intriguing, might be weakened by the use of echocardiography to assess PASP and PCWP, which relies on a discernible tricuspid regurgitant jet that was not detectable in 13% of patients with HFpEF in this study.[11]

Right ventricular overload and failure

The right ventricle empties its volume into a very low-impedance circulation. In the absence of cardiac or pulmonary disease, it has an almost passive role in the maintenance of stroke output according to venous return and preload. Whereas the normal left ventricle can accommodate an acute increase in afterload with little or no change in stroke output, the right ventricle is quite sensitive to changes in afterload, and responds to acute increases in pressure or impedance to ejection

Table 1 | Predictive value of RV dysfunction and failure in CHF patients with left-sided pulmonary hypertension

Study	Number of patients	NYHA class	RV dysfunction measures	Main findings
Polak *et al.*[58]	34	II–IV	RVEF ≤35	23% event-free survival in CHF patients with depressed RV function vs 71% event-free survival in CHF patients without RV dysfunction at 2 years
Di Salvo *et al.*[59]	67	II–IV	RVEF ≤35	RV dysfunction predictor of survival at 2 years
Sun *et al.*[60]	100	III–IV	RV area/LV area >0.5	RV dilatation predictor of survival at 2 years
Gavazzi *et al.*[61]	142	II–IV	RVEF ≤20	RV dysfunction predictor of survival at 2 years
Gorcsan *et al.*[62]	16	IV	RV pressure–volume loop and RV contractile reserve assessment	RV contractile reserve predictor of short-term adverse events
De Groote *et al.*[63]	205	II–III	RVEF ≤35	RV dysfunction independent predictor of survival
Ghio *et al.*[57]	377	III–IV	RVEF ≤35	Incremental value of RV dysfunction and PAP in survival prediction
Meluzin *et al.*[64]	140	II–IV	RVMPI >120	RVMPI predictor of survival
Field *et al.*[65]	77	III–IV	RVMPI	RVMPI predictor of survival and increased risk for every 0.1 unit increase
Meyer *et al.*[66]	2,708	II–III	RVEF	RVEF <20% predictor of survival and hospitalization

Abbreviations: CHF, chronic heart failure; LV, left ventricular; PAP, pulmonary artery pressure; RV, right ventricular; RVEF, right ventricular ejection fraction; RVMPI, right ventricular myocardial performance index.

with a considerable fall in stroke volume.[51] However, the right ventricle can activate mechanisms of adaptation to a sustained increase in stroke work that enable it to maintain a constant output against excessive ejection impedance. The main adaptive mechanism is the development of hypertrophy. In patients with severe mitral stenosis, massive right ventricular hypertrophy is able to maintain a pulmonary artery systolic pressure similar to or higher than the systemic pressure. When the excess of afterload is long-standing, the right ventricle dilatates, with progressive transformation of the normal crescent shape into a more spherical structure, which leads to tricuspid incompetence. The dilated right ventricle increases output through the Frank-Starling mechanism. Once all mechanisms of contractile reserve are exhausted, systemic pressure begins to fall, with a sudden and irreversible decrease in right ventricular contractile function. This sequence of events was first described in 1954 by Guyton *et al.* who proposed a model of progressive constriction of the pulmonary artery until right ventricular contractile reserve became exhausted.[52] Hypertrophy usually decreases right ventricular subendocardial perfusion; dilatation results in increased wall stress, which enhances the myocardial oxygen need, and, if the pericardium is intact, in compromised LV filling. This effect is due to leftward shift of the septum, increase or further increase (in the case of LV dilatation) in intrapericardial pressure, reducing the transmural filling pressure, which represents the true preload of the ventricle.[53]

When the left ventricle is failing, pulmonary vein and capillary pressures are raised and generally lead to the pulmonary artery perfusion pressure to rise correspondingly. Alveolar and microvascular injury, remodeling of the pulmonary arteries and veins, changes in their reactivity to vasoconstrictor stimuli, and alteration in endothelial function are considered to be additional and principal causes of PH in patients with HF. The 'restrictive' pattern of pulmonary function and the impeded alveolar–capillary gas exchange can affect the pulmonary circulation by alveolar hypoxia.[4] Finally, the rise in PAP may further worsen structural damage to the smaller branches of the pulmonary circulation and serve as a stimulus for the development of medial hypertrophy.

Occurrence of right-sided ventricular dysfunction and tricuspid regurgitation are undesirable in HF, as they compromise the ventricular forward output and facilitate edema formation by raising the right atrial pressure. Other often underestimated but no less important consequences of right atrial pressure elevation include an effect against lung lymphatic drainage and interstitial fluid accumulation, which can further increase the resistance to right ventricular ejection and the cardiac extramural pressure. This effect potentially impairs atrial distention and release of atrial natriuretic peptides, and increases renal venous pressure, with a consequent reduction in the pressure driving filtration through the kidney, which impairs renal Na^+ excretion.[54] A progressive right ventricular overload can trigger positive feedback loops that might hasten HF evolution towards refractoriness.[55,56]

More than two-thirds of patients with deterioration of LV systolic function have secondary pulmonary pressure elevation and impaired right ventricular performance.[57] Development of right ventricular failure is an important hallmark of worse prognosis, increasing mortality risk more than twofold compared with that in patients with similar LV function and preserved right ventricular performance.[57] Table 1 reports studies assessing the usefulness of right ventricular dysfunction and failure in patients with left-sided PH in prediction of clinical events.[57–66] For all these considerations, right ventricular unloading deserves specific attention as an important therapeutic option in left-sided PH.

Clinical features of left-sided PH

Diagnosis and assessment

Distinctive clinical signs and symptoms of left-sided PH are orthopnea and paroxysmal nocturnal dyspnea, which are generally not features of other types of PH.[30] Clinical tests often reveal findings suggestive of left-sided PH. A chest X-ray can show pulmonary vascular congestion, pleural effusion and, eventually, pulmonary edema. An electrocardiogram may show LV hypertrophy rather than right ventricular hypertrophy. High-resolution chest CT can be helpful because it can reveal a mosaic perfusion pattern and ground-glass opacities consistent with chronic pulmonary edema. Invasive measures of LV end-diastolic pressure, left atrial pressure, and PCWP are required to definitively secure the diagnosis of elevated LV filling pressure and pulmonary venous hypertension.

Although the burden of HFpEF has been increasingly appreciated as one of the main causes of left-sided PH,[7–9] the natural evolution and clinical impact of PH manifestations in this condition have not been systematically investigated in randomized clinical trials. The HFpEF population includes predominantly elderly patients with systemic hypertension and LV hypertrophy, coronary artery disease, or diabetes and obesity. Given the current epidemic increase of this population, readily available noninvasive variables suggestive of increased LV filling pressure, abnormal LV relaxation, or preserved ejection fraction have become extremely important, especially in the presence of clinical suspicion of PH of cardiac origin.[67] Essential in the evaluation of these patients are physical examination, chest radiography, and echocardiography. Biomarkers are not always sensitive enough to differentiate between systolic and diastolic HF. Several ultrasonography findings might be suggestive of HFpEF, such as the presence of a dilated left atrium, abnormal Doppler estimates of mitral and pulmonary venous flow velocity, and mitral tissue Doppler velocities. Standard Doppler flow indices are determined both by left atrial pressure and by LV relaxation, and might overestimate LV filling pressure, since they cannot separate the effects of LV relaxation from those of preload. Tissue Doppler velocities are highly related to LV relaxation and may be combined with standard Doppler flow indices in order to separate these confounding factors. Accordingly, the most reliable correlate of LV end-diastolic pressure and left atrial pressure is the combination of early mitral flow velocity (E) with early mitral tissue Doppler velocity (E1).[68] The use of the E/E1 ratio as a reliable estimate of left atrial pressure has been validated in heterogeneous groups of patients with cardiac disease undergoing right heart catheterization.[68] In patients with impaired relaxation and elevated left atrial pressure, E is elevated, but E1 is reduced and an E/E1 ratio >15 is almost invariably associated with a mean left atrial pressure >15 mmHg.[68] Although echocardiography provides important and quite often definitive information to ascertain the diagnosis of HFpEF, invasive hemodynamic assessment with LV pressure–volume loop analysis might still be required.[69] Studies assessing pulmonary hemodynamics in patients with HFpEF are primarily limited to echocardiography. A report on the combined assessment of echocardiography-derived and invasive pulmonary hemodynamics has provided evidence for a precise and comprehensive clinical evaluation when these approaches are used together.[70]

Interesting evidence shows that, in addition to diastolic impairment, an important determinant of PH in patients with LV dysfunction is the extent of functional mitral regurgitation, namely the size of the mitral valve regurgitant orifice.[47] An increased regurgitant mitral area is also a strong predictor of increased pulmonary pressure and development of acute pulmonary edema in patients with functional mitral regurgitation due to ischemic heart disease.[71] A role of mitral insufficiency as a contributory factor for the development of PH is also suspected in patients with HFpEF, although this relationship has not yet been addressed in properly designed trials.[72]

Volume or exercise challenges can unmask cases of left-sided PH that are not detectable at rest due to unloading and diuretic therapies. A vasodilator[73] or inotropic[74] challenge during diagnostic cardiac catheterization is useful for evaluating changes in PCWP during cardiac output increase. A classic clinical example of exercise-induced increase in PCWP in patients with HFpEF was reported by Kitzman *et al.* in a group of selected patients with severe clinical HF, but with normal systolic function and LV concentric hypertrophy.[75] Compared with age-matched and gender-matched controls, patients with HFpEF showed no increase in their LV end-diastolic volumes and had a marked PCWP increase to hydrostatic capillary pressures >25 mmHg. In another report, 406 unselected consecutive patients referred for unexplained dyspnea due to various causes of PH underwent invasive hemodynamic assessment.[76] Interestingly, 48% of patients developed exercise-induced PH owing to LV failure, and LV diastolic dysfunction represented one of the largest categories of unexplained exertional dyspnea. Assessment of functional mitral regurgitation might also be appropriate during exercise testing, given the very likely possibility that patients with no or minimal mitral regurgitation at rest develop severe insufficiency during exercise, which is another important clinical determinant of left-sided PH.[47,77]

Clinical correlates of left-sided PH

Exertional dyspnea is the most common symptom of left-sided PH as a result of several pathophysiological impairments that can be revealed by the analysis of gas exchange during exercise with cardiopulmonary testing.[78] The pulmonary vasculature considerably influences exercise capacity in HF patients with secondary PH. Pulmonary vascular resistance can remain elevated throughout a maximal exercise test, which imposes an increased load to the right ventricle; a positive correlation between right ventricular ejection fraction and peak VO_2 (maximal oxygen uptake) is present in patients referred for cardiac transplantation.[78] Of note, patients with HF display a number of ventilatory abnormalities that are, at least in part, related to the development of left-sided PH.

In patients with stable HF, an impaired exercise ventilation efficiency, as assessed by the steepness of the relationship between ventilation and CO_2 production rate (VE/VCO_2 slope), is related to pulmonary vasoconstriction, elevated PASP,[79] pulmonary vascular tone, and RV function.[80] This observation has important implications, considering the established strong predictive value of the VE/VCO_2 slope for adverse clinical events in both systolic and diastolic HF.[81,82] Remarkably, some patients with LV dysfunction exhibit an oscillatory ventilatory pattern during exercise. This phenomenon is characterized by a cyclic increase and decrease of expired gases, and carries an unfavorable prognosis[83] that correlates with pulmonary hemodynamics, especially PCWP, which may disappear after correction of pulmonary vasoconstriction with nitroprusside infusion.[84]

The relationship between sleep-disordered breathing and pulmonary hemodynamics in HF is being increasingly recognized. In HF patients with elevated PCWP, the incidence of central sleep apnea is frequent, and a strong relationship exists between PCWP, hypocapnia, and central apnea severity.[85]

Morbidity and mortality

The extent of left-sided PH is an important determinant of morbidity and mortality in patients with HF. An increased mortality and hospitalization rate is reported in HF patients with PH determined by echocardiography,[86] and PASP is an independent predictor of the need for cardiac transplantation.[87] At least two-thirds of patients with severe systolic LV dysfunction have PH with associated right ventricular failure, and mortality associated with biventricular failure is twofold higher than isolated LV failure.[57] Observations obtained from 2,008 patients enrolled in the BEST trial have highlighted a right ventricular ejection fraction <20% as an independent predictor of mortality and hospitalization for HF.[66] Development of right ventricular failure might also be an important concern for patients who received a heart transplant, and data from the International Society of Heart Transplantation registry indicate that right ventricular dysfunction accounts for 50% of all cardiac complications and 19% of early deaths in this patient population.[88]

Therapeutic approaches

Pharmacological agents

Early experience with drugs currently used for patients with other categories of pulmonary arterial hypertension that target the pulmonary vasculature and right ventricular ejection impedance has been quite disappointing. These poor results might be caused by the use of selective pulmonary vasodilators in patients with elevated PCWP, which substantially raises the likelihood of rapid clinical deterioration, possibly owing to an abrupt increase in right ventricular output in the setting of a lowered pulmonary capillary and venous pressure. Clinical studies assessing drugs used in the long-term treatment of pulmonary arterial hypertension in patients with HF are summarized in Table 2.

Prostaglandins

Prostaglandins are powerful vasodilators and a cornerstone therapy for the treatment of precapillary pulmonary arterial hypertension. Initial observations obtained in left-sided PH with acute administration of intravenous prostacyclin documented a decrease in PCWP and pulmonary vascular resistance, and an increase in cardiac index; however, these effects were paralleled by a drop in systemic arterial pressure and resistance, with a consequent rise in plasma concentrations of epinephrine, norepinephrine, renin, and aldosterone.[89] A small number of nonrandomized trials have shown a trend towards improved outcomes through intermittent infusion of prostaglandin E1.[90] Epoprostenol added to conventional therapy improved performance of the 6 min walk test distance.[91] In patients undergoing assessment for cardiac transplantation, inhaled iloprost—a prostacyclin analog—improved arterial pressure, PCWP, and vascular resistance.[92] In the Flolan International Randomized Trial (FIRST), however, in which patients with advanced HF were treated with intravenous epoprostenol, a strong trend towards decreased survival was reported in treated patients despite improvement in PCWP and cardiac index. These results led to the trial being prematurely terminated.[93] A positive inotropic effect of epoprostenol was postulated as a potential cause of increased mortality. Importantly, PH with left-sided heart disease was not a prespecified inclusion criterium in this trial.

ET_1 receptor blockers

ET_1 is one of the most potent natural vasoconstrictors, with a crucial role in the regulation of vascular tone. Benefits of ET_1 receptor antagonists, however, seem to be confined to experimental models. In animals, nonselective and selective ET_1 antagonists improved cardiac remodeling and survival.[94] Blockade of the ET_1 receptor subtype ET_A in a dog model, in which HF was induced by rapid ventricular pacing, decreased pulmonary vascular resistance whereas an ET_B antagonist produced the opposite effect.[95]

Acute and short-term effects of intravenous nonselective ET_1 blockade with bosentan in humans included a reduction in mPAP, right atrial pressure, PCWP, and pulmonary vascular resistance, as well as an increased cardiac and stroke volume index without changes in heart rate.[96] Nonetheless, a series of large-scale trials assessing the effects of bosentan in patients with chronic HF had discouraging results.[97–102] In the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) study,[97] treatment with bosentan increased the risk of worsening HF. Packer *et al.* found that use of bosentan caused an increased risk of HF during the first month of treatment, but a decreased risk of HF during the fourth, fifth, and sixth months of therapy compared with placebo.[98] The major noncardiac adverse effects of bosentan included an increase in serum transaminases (in 15.6% of patients), and a decrease in hemoglobin.[98] In the only long-term trial in which left-sided PH was a prespecified end point, patients receiving bosentan experienced more serious adverse events than controls.[99]

Table 2 | Studies assessing treatment in CHF patients with left-sided pulmonary hypertension

Study and number of patients	Study design	Therapy	Population	Findings and outcome
Serra *et al.*[90] (*n*=22)	Prospective, controlled, nonrandomized study	PGE1 10 ng/kg/min IV infusion for a total of 24 h over 3 consecutive days every 3 months	Advanced HF, NYHA class III–IV	PASP decrease from 57.7 mmHg to 48.8 mmHg (*P*<0.01) Significant improvement in LVEF and in NYHA class 36-month survival: 72.7% in the PGE1 group and 56% in the control group (NS)
Sueta *et al.*[91] (*n*=33)	Prospective, controlled, nonrandomized study	Prostacyclin continuous IV infusion for 12 weeks	Advanced HF, NYHA class III–IV	Increase in 6 min walk test distance
Califf *et al.*[93] FIRST (*n*=471)	Prospective, controlled, nonrandomized study	Epoprostenol 4 ng/kg/min IV infusion for 2 years	Advanced HF, NYHA class III–IV	No improvement in quality of life and increased mortality
ENABLE[97] (*n*=1,600)	Prospective, placebo-controlled, randomized study	Bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily for 1.5 years	Advanced HF, NYHA class III–IV	Early risk of worsening HF necessitating hospitalization as a consequence of fluid retention
Packer *et al.*[98] REACH-1 (*n*=370)	Double-blind, placebo-controlled, randomized study	Bosentan 500 mg twice a week	Advanced HF, NYHA class III–IV	Terminated early owing to detection of liver function test abnormalities in the treated group
Lüscher *et al.*[100] HEAT (*n*=157)	Double-blind, placebo-controlled, randomized study	Randomization to either 30, 100, or 300 mg darusentan or placebo for 3 weeks	Advanced HF, NYHA class III	Increase in cardiac index (*P*<0.0001 versus placebo) PCWP, PAP, PVR, and right atrial pressure unchanged Heart rate, MAP, and plasma catecholamine levels unaltered, but SVR decreased significantly (*P*=0.0001) Higher doses were associated with a higher incidence of adverse events (including death), particularly early exacerbation of CHF without further benefit as compared with moderate doses
Kaluski *et al.*[99] (*n*=84)	Multicenter, double-blind, placebo-controlled, randomized study	Bosentan 8–125 mg twice daily for 20 weeks	Advanced HF, NYHA class III–IV Systolic PAP >40 mmHg	No differences in systolic PAP changes Patients in the bosentan arm experienced a higher incidence of serious adverse events
Anand *et al.*[101] EARTH (*n*=642)	Parallel, placebo-controlled, randomized study	Randomization to either 10, 25, 50, 100, or 300 mg darusentan or placebo	Advanced HF, NYHA class II–IV	No changes on LV remodeling
Givertz *et al.*[103] (*n*=48)	Multicenter, double-blind, placebo-controlled, randomized trial	Randomization to either 1.5, 3, or 6 mg/kg sitaxsentan or placebo as IV infusion over 15 min	Advanced HF, NYHA class III–IV	Significant decrease in PASP, PVR, mPAP, and right atrial pressure No effect on heart rate, MAP, PCWP, cardiac index, or SVR
Guazzi *et al.*[118] (*n*=16)	Double-blind, placebo-controlled, randomized study	Oral sildenafil 50 mg three times a day for 6 months	Stable CHF with moderate PH	Significant decrease in PASP (*P*<0.01)
Lewis *et al.*[119] (*n*=13)	Double-blind, placebo-controlled, randomized study	Oral sildenafil 25 mg to 50 mg three times a day for 3 months	Stable CHF with moderate PH	Significant decrease in resting and exercise PVR without changes in PCWP (*P*=0.008)
Behling *et al.*[120] (*n*=19)	Double-blind, placebo-controlled, randomized study	Oral sildenafil 50 mg three times a day for 3 months	Stable CHF with moderate PH	Significant decrease in PASP (*P*=0.003)
Tedford *et al.*[121] (*n*=57)	Placebo-controlled, randomized study	Oral sildenafil 75 mg three times a day for 3 months	Advanced HF with moderate to severe PH	Significant decrease in mPAP and PVR (*P*<0.05)

Abbreviations: CHF, chronic heart failure; HF, heart failure; IV, intravenous; LV, left ventricular; LVEF, LV ejection fraction; MAP, mean arterial pressure; mPAP, mean PAP; NS, nonsignificant; PAP, pulmonary arterial pressure; PASP, pulmonary arterial systolic pressure; PCWP, pulmonary capillary wedge pressure; PGE1, prostaglandin E1; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Short-term administration of darusentan improved cardiac index in the Heart Failure ET(A) Receptor Blockade Trial (HEAT),[100] but did not change PCWP, pulmonary vascular resistance, or right atrial pressure. Of note, a trend towards increased mortality and early exacerbation of HF was observed. In the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH),[101] blockade of ET_1 with darusentan did not improve outcomes in patients with chronic HF. Tezosentan, a short-acting intravenous ET_1 receptor antagonist, did not reduce the incidence of death or worsening of HF.[102] Initial results with the selective ET_A antagonist sitaxentan were promising concerning pulmonary hemodynamics.[103] According to the present evidence, therefore, no clinical support exists for the use of non-selective and selective ET_1 antagonists in the treatment of LV failure and left-sided PH.

Inhaled nitric oxide

Owing to the involvement of NO in the regulation of pulmonary vessel tone and motility, strategies for manipulating NO activity in the lung circulation are of considerable interest. Inhaled NO diffuses rapidly across the alveolar–capillary membrane into the smooth muscle

of pulmonary vessels, and concentrations from 5–80 ppm have been tested for the treatment of advanced left-sided PH, especially after LV assist device (LVAD) placement and after transplantation. In patients with a LVAD, inhaled NO reduces PAP and increases LVAD flow.[104] In post-transplant PH management, inhaled NO induced a selective decrease in pulmonary vascular resistance, whereas intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside did not; no changes in systemic resistance were observed with NO treatment.[105] In contrast to these favorable results, other investigators reported that NO treatment did not significantly change PAP and led to a rise in PCWP, which was possibly due to an increased preload of a poorly compliant left ventricle.[106,107] This condition has been observed to lead to development of acute alveolar edema in some cases.[108] Because of its short half-life, NO has to be administered continuously, and even short interruptions might cause a sudden rebound of PH, leading to a decrease in cardiac output and systemic hypotension.[109]

PDE5 inhibitors

Interest in the use of phosphodiesterase-5 (PDE5) inhibitors as a means to improve the NO pathway in the lung has been increasing. PDE5 is the predominant isoenzyme that metabolizes cyclic 3'-5'-guanosine monophosphate (cGMP)—the second messenger of the NO pathway—which is highly expressed in the smooth muscle cells of pulmonary arteries and veins of the normal lung. PDE5 activity is increased in several experimental models of PH.[110] Interestingly, inhibition of PDE5 with sildenafil restores a normal cGMP transpulmonary gradient in patients with HF and high pulmonary vascular resistance.[111]

Sildenafil is effective in various forms of human PH, such as idiopathic PH, PH associated with repaired congenital systemic-to-pulmonary shunts, and PH secondary to diseases of the connective tissue; sildenafil is also an approved treatment for Group 1 pulmonary arterial hypertension.[112] In contrast to other pulmonary vasodilators, evidence is accumulating that PDE5 inhibitors have a valuable role as right ventricular unloading agents in HF.[113] Indeed, in patients with left-sided PH of varying severity, both acute (25 mg or 50 mg)[111,114–117] and chronic (75 mg or 150 mg per day)[118–121] oral sildenafil therapy is well tolerated. In these patients, sildenafil showed a specific pulmonary vascular selectivity (decrease in PASP and pulmonary vascular resistance) without substantial changes in systemic arterial pressure and resistance. No cases of pulmonary edema have been reported in these studies. The improvement in alveolar–capillary membrane conductance achieved with sildenafil in this category of patients is noteworthy, as it indicates an important role for NO in the facilitation of alveolar gas conductance.[116] Sildenafil might also eliminate or attenuate a component of alveolar hypoxia and improve functional capacity in HF. Three studies have specifically addressed the hemodynamic and functional effects of chronic sildenafil therapy in patients with stable HF already receiving an optimal drug treatment.[112-116] A sustained lowering effect on PAP and pulmonary vascular resistance was observed, as well as an improvement in peak aerobic capacity and ventilation efficiency, as documented by a reduced VE/VCO_2 slope.[112–116] Sildenafil has also been investigated in patients with severe HF with persistent PAP elevation, despite LV unloading with implantation of LVADs.[121] After 2–4 weeks of PDE5 inhibition with sildenafil, a ~50% reduction in pulmonary vascular resistance and a ~30% decrease in mPAP were observed. According to one report, nitrate combined with sildenafil exerted synergistic pulmonary vasodilating activity without adverse systemic hemodynamic consequences in patients with advanced HF, high PAP, and low systemic arterial pressure.[122] Finally, in patients with severe PH unresponsive to the acute vasoreactivity test with prostaglandin E1, sildenafil promoted reversibility,[111] indicating that PDE5 inhibition would be of help in the assessment of true irreversible pulmonary hypertensive states.

The clinical experience on inhibition of PDE5 with sildenafil in left-sided PH has been gained in patients with systolic HF who had primarily mild to moderate PH. No studies have been performed in patients with HFpEF or in other relevant clinical conditions, such as valvular heart diseases and acute HF. Nonetheless, the use of PDE5 inhibitors as right ventricular unloading agents in HF is currently an open and promising field of investigation. A better appreciation of the potential benefits derived from the use of this class of compounds will be likely to enable advancements in the control of HF with respect to the retrograde effects of left-sided PH.

Nonpharmacological agents

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is a class IIa level of evidence B therapy in systolic HF.[123] Most of the studies investigating the benefits of CRT in patients with HF have focused on the systemic hemodynamic and LV reverse remodeling effects of this approach.[124] Substantial improvement in pulmonary hemodynamics has been noted in some studies.[125,126] In a single case report of a patient with advanced HF and pulmonary vasoreactivity tests documenting fixed PH and unchanged pulmonary vascular resistance, CRT therapy modulated pulmonary hemodynamics to the point in which the patient became eligible for cardiac transplantation.[125] In 56 patients with end-stage HF, Blecker *et al.* reported a reversal of right ventricular remodeling and a decrease in PAP in patients receiving CRT therapy.[126] This finding was partially reproduced by Shalaby *et al.*, who documented the utility of noninvasive PASP monitoring for the clinical and prognostic follow-up of HF patients with left-sided PH and CRT device implantation.[127]

LV assist devices

LVADs are an important therapeutic resource as a 'bridge' to heart transplantation. When pharmacological interventions fail to decrease pulmonary vascular resistance sufficiently to allow for heart transplantation, LVAD implantation may definitively promote reverse

remodeling of the left ventricle with some recovery of LV hemodynamics. Convincing evidence on the effectiveness of LVADs to modulate permanent PH also exists, regardless of the type of LVAD employed (pulsatile or nonpulsatile flow devices); the effectiveness of this approach makes most patients with advanced PH who received a LVAD eligible for cardiac transplantation.[128,129]

Conclusions

PH with left-sided heart disease is a common clinical entity that usually develops as a consequence of impaired LV relaxation and distensibility. Elevated pressure leads to a cascade of adverse anatomical and functional effects on the pulmonary capillaries, arterial and venous circulation, and right ventricular function. The extent of PH with left-sided heart disease is an important determinant of morbidity and mortality, and patients with this condition have an increased risk of developing right ventricular failure. Developing novel therapeutic interventions aimed at targeting left-sided PH is an important challenge for the clinician. Promising results have been seen with the use of PDE5 inhibitors owing to their strong selectivity for targeting the NO pathway in the pulmonary circulation. At present, however, precise guidelines on the most beneficial and cost-effective strategies for the treatment of PH with left-sided heart disease are still to be provided.

Review criteria

A search was performed in MEDLINE and PubMed for original articles published between 1950 and 2009 that focused on left-sided pulmonary hypertension and heart failure. The search terms used were "pulmonary hypertension", "secondary pulmonary hypertension", "post-capillary pulmonary hypertension", "systolic heart failure", and "diastolic heart failure". The literature search was limited to full-text articles in the English language. We also searched the reference lists of identified articles for further papers, as well as published abstracts from international scientific conferences.

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Acknowledgments
This work was supported by a grant from the Monzino Foundation.

Author contributions
M. Guazzi and R. Arena contributed to discussion of content for the article, researched data to include in the manuscript, reviewed and edited the manuscript before submission, and revised the manuscript in response to the peer-reviewers' comments.