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Pulmonary Hypertension Secondary to Left Ventricular Systolic Dysfunction: Contemporary Diagnosis and Management

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Abstract

Pulmonary hypertension secondary to left ventricular systolic dysfunction is often a poor prognostic marker in chronic heart failure. In this article, we review evidence supporting modern strategies addressing pulmonary hypertension in patients with left ventricular systolic dysfunction, including right-sided heart catheterization with vasoreactivity testing and subsequent parenteral, oral, and inhaled therapy. We delineate a diagnostic approach to secondary pulmonary hypertension and outline evidence-based therapeutic strategies for management in acute and chronic heart failure.

Introduction

Pulmonary hypertension (PH) secondary to left ventricular systolic dysfunction (LVSD) is present in approximately 68% to 78% of patients with advanced heart failure (HF) and concomitant right ventricular (RV) dysfunction [1–3]. Increased pulmonary vascular resistance (PVR) and poor RV performance are potent prognostic indicators of reduced exercise capacity [1,4] and poor clinical outcomes [3,5,6]. The hemodynamic definition of PH includes a resting mean pulmonary arterial (PA) pressure of more than 25 mm Hg, a mean PA pressure of more than 30 mm Hg on exercise, and/or a resting PVR of more than 3 Wood units [7]. Secondary PH is further divided by the presence (postcapillary) or absence (precapillary) of pulmonary venous pressure elevation. PH secondary to LVSD is almost always accompanied by pulmonary venous hypertension that is related to an elevation in left ventricular (LV) diastolic pressure. It was designated as category 2 PH at the World Health Organization (WHO) World Symposium on PH in Venice, Italy in 2003.

The pathophysiologic hallmarks of PH include vasoconstriction, local thrombosis, and arterial remodeling, which are all pathologic hallmarks of PH [7], and the endothelial cell is critical in the pathogenesis of PH [7,8]. Therapies targeting endothelial and smooth muscle cell function have been extensively investigated in the treatment of PH. In this review, we focus on the diagnosis and treatment of PH secondary to LVSD.

Epidemiology of Secondary PH in LVSD

Pulmonary vasoconstriction is a frequent occurrence in patients with LVSD. Costard-Jackle and Fowler [2] identified PH (defined as a PVR > 4.0 Wood units) in 79% of patients with advanced HF who were referred for consideration of cardiac transplantation. The vasoconstriction observed was transiently reversible in the majority of patients with the administration of sodium nitroprusside. Butler et al. [1] identified PH in a similar number

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(72%) of patients referred to an academic program. Of interest was the identification of PH in the majority of patients with mild to moderate HF symptoms, as 52% of patients with a peak oxygen consumption of more than 16 mL/kg/min during exercise had abnormal PVR. It was also observed that the occurrence of an elevation of pulmonary resistance was not related to LV ejection fraction.

Initial Evaluation of Secondary PH

Initial clinical evaluation of patients with LVSD and PH focuses on assessment of RV function and potentially reversible factors that exacerbate PH. Given the prevalence of sleep-disordered breathing in HF and its effect on PH [9], physical or historic clues, suggestive of obstructive sleep apnea, should be sought. Evidence of valvular heart disease, specifically mitral regurgitation as a cause or contributor to LVSD and PH, should be elicited. A history of ablation for atrial fibrillation may point towards pulmonary venous stenosis (as opposed to LVSD) as a potential cause of HF. A history of repaired congenital heart disease, pulmonary thromboembolic disease, or (most commonly) intrinsic pulmonary disease should also be obtained. As cigarette smoking can lead to both chronic pulmonary disease and LVSD secondary to ischemic heart disease, patients with this history should be carefully reviewed for the possibility that the loss of pulmonary vasculature related to emphysematous changes can lead to PH.

Physical evidence of RV dysfunction may manifest as right-sided volume overload (jugular venous distension with Kussmaul sign, peripheral edema), an increased pulmonic component of the second heart sound (S_2), an RV heave or right-sided S_3 or S_4 , or tricuspid regurgitation. Peripheral systemic arterial oxygen desaturation may indicate pulmonary venous hypertension, right-to-left shunt, or restrictive or obstructive pulmonary disease. Although patients with LVSD and PH do not need to be in decompensated HF, evidence of volume overload should be elicited. Initial radiographic and laboratory investigation would include chest radiography (to assess HF, pulmonary disease, and PA dimensions), transthoracic echocardiography (for PA pressures and RV function), and delineation of contributing noncardiac etiologies of PH, including pulmonary function testing, with testing for diffusion capacity, high resolution chest CT for pulmonary embolism and interstitial lung disease, and ventilation-perfusion scans.

The gold standard for the assessment of PH in patients with LVSD remains right-sided heart catheterization. The general aim of right-sided heart catheterization includes 1) assessing the degree of PH (ie, PVR and PA pressure), 2) determining the contribution of elevated LV filling pressures (ie, pulmonary capillary wedge pressure and transpulmonary gradient), 3) measuring cardiac output, and 4) assessing for pulmonary vasomotor reactivity. In patients with significant tricuspid regurgitation, the determination of cardiac output by way of the Fick method (with directly measured oxygen consumption) is preferred over thermodilution measurements for the calculation of PVR. Furthermore, given the dependence of PVR on cardiac output, some authors have suggested the transpulmonary gradient (the difference between the mean PA and pulmonary capillary wedge pressure) is a more optimal index of secondary PH [10]. A normal value for transpulmonary gradient is 5 to 7 mm Hg, with more than 15 mm Hg related to higher post-transplant mortality [10].

Aside from defining the severity of PH, right-sided heart catheterization allows characterization of the response of pulmonary pressures to vasodilator therapy. This is a particularly useful assessment in patients for whom cardiac transplantation is being considered, as postoperative RV dysfunction related to fixed pulmonary vasoconstriction can be a significant cause of morbidity and mortality in the transplant recipient. Supine measurements of PA pressure, pulmonary capillary wedge pressure, cardiac output, and

superior vena cava and PA oxygen saturation (to screen for intracardiac left-to-right shunt) are recorded at baseline and during administration of 100% oxygen. Thereafter, parenteral nitroprusside, nitroglycerin, or inhaled nitric oxide (NO), which is a more direct and locally acting pulmonary vasodilator, may be administered with close titration to achieve a “positive” vasodilator response, defined as a reduction in PVR to less than 2.5 Wood units [2]. Other agents, including adenosine, prostacyclin, milrinone, or nesiritide may also be used.

Other important diagnostic information can be obtained during right-sided heart catheterization in the patient with suspected PH and LVSD. The presence of a left-to-right shunt can be assessed by oximetry. Although this is more commonly present at the atrial level, a postinfarct ventricular septal defect that has not previously led to acute hemodynamic instability can be identified. Occasionally, measurements of pulmonary capillary wedge pressure may vary among the different pulmonary artery branches. This may be a diagnostic clue to the presence of pulmonary venoocclusive disease [11] or pulmonary venous stenosis. The latter can be a consequence of scarring after the thermal injury that is induced during atrial fibrillation ablation procedures and is becoming a more common diagnosis. Imaging with CT or magnetic resonance angiography can confirm these diagnoses.

Chronic administration of oral vasodilators to patients with idiopathic PH who have a positive vasodilator response during catheterization has demonstrated hemodynamic and survival benefits [12]. This benefit has not been replicated in patients with PH and LVSD. Currently, there are no approved therapies for secondary PH in HF, and the primary clinical application of vasodilator testing is in the pretransplant management of elevated PVR [10]. However, there is evidence linking elevated PA pressures, RV dysfunction, and increased mortality and poorer functional capacity in chronic HF [3,5]. Furthermore, there is evidence in small cohorts suggesting therapies aimed at pulmonary vasodilatation may be fruitful in patients with advanced HF [13,14•]. The remainder of this review will focus on evidence supporting different vasodilator agents in patients with PH and LVSD.

Endothelin-1 Receptor Antagonists

Endothelin-1 (ET-1) is an endothelial-derived peptide that controls vascular tone by binding two distinct receptors, ET_A and ET_B [15]. ET_A stimulation causes vasoconstriction, whereas ET_B stimulation promotes vasodilatation and allows clearance of ET-1 [15]. ET_A receptors are more abundant in the pulmonary vasculature, suggesting a mechanistic link between ET-1 and PH [15]. In patients with HF, elevated levels of ET-1 correlate with higher clinical severity, higher PVR, worsening pulmonary hemodynamics, decreased exercise capacity, and greater LV dilatation [16,17].

Acute administration of ET_A receptor antagonists decreases PA pressure and PVR with a neutral or beneficial effect on cardiac index and systemic vascular resistance [18]. This effect is not seen in patients with normal LV function [19], implicating higher levels of ET-1 in the pathogenesis of PH in LVSD. These acute effects on pulmonary hemodynamics have been replicated with bosentan, a nonselective ET-1 receptor blocker [20]. Unfortunately, the ENABLE study found an early trend towards increased HF hospitalization and liver function abnormalities in HF patients treated with bosentan [21]. Although ET-1 receptor nonselectivity was thought to be responsible for nonresponse [21], subsequent studies of specific ET_A blockade demonstrated no difference in clinical outcomes at 24 weeks [22]. Further investigation into possible direct myocardial effects of ET-1 antagonism may reveal additional causes for the limited benefit of this therapy.

Epoprostenol

Epoprostenol (prostacyclin) is a potent pulmonary vasodilator, with demonstrated sustained hemodynamic and survival benefits in idiopathic PH [23]. In patients with PH and LVSD, epoprostenol causes acute reduction in LV filling pressures and pulmonary and systemic vascular resistance, an increase in cardiac index [24], and may have positive inotropic effects [25]. Inhaled iloprost (an analogue of epoprostenol) improves PVR by augmenting cardiac index [26], but its short duration of action (2–4 hours) and frequent administration render it impractical for most patients. In the FIRST trial, epoprostenol dramatically improved pulmonary hemodynamics in patients with advanced HF, but led to increased mortality [27]. Given its impact on hemodynamics, debate remains on whether epoprostenol might be used to bridge patients to hemodynamic recovery [25]. However, between its potential effects on inotropy and excessive systemic vasodilatation, an application for epoprostenol in patients with LVSD and secondary PH remains limited.

Milrinone

Milrinone is a type 3 phosphodiesterase (PDE) inhibitor that potentiates the cAMP-mediated rise in intracellular calcium, resulting in positive inotropy and systemic and pulmonary vasodilatation. In patients with PH and LVSD, milrinone reduces PH in proportion to improvements in cardiac output [28] and the degree of underlying PH [29]. Furthermore, milrinone has been shown to augment RV function by reducing PVR in patients with RV failure post-LV assist device implantation [30]. In patients with HF and secondary PH awaiting transplantation, milrinone successfully supports hemodynamics in a safe manner [31]. Although inotrope use in advanced HF has been shown to increase mortality, milrinone has a role in our institution in the management of patients with advanced HF and secondary PH awaiting cardiac transplantation.

Nesiritide

Nesiritide, a human recombinant B-type natriuretic peptide, is a potent pulmonary and systemic arterial vasodilator. In patients with HF and secondary PH, nesiritide improves LV filling pressures, PA pressures, and cardiac output [32]. Infusion of nesiritide may increase NO bioavailability in pulmonary arterial blood [33]. Furthermore, nesiritide may affect PVR in situations in which milrinone and nitroprusside have failed [34].

A major concern with nesiritide therapy has been the potential for increased short-term mortality and worsening renal function in patients with acute decompensated HF [35,36]. Recent large-scale prospective data from the FUSION II study suggest that nesiritide does not have adverse effects on mortality, renal function, or subsequent HF hospitalization [37]. Furthermore, unlike milrinone and nitroprusside, nesiritide does not exhibit inotropic or toxic properties on chronic infusion. Although this strategy has not been formally tested in a randomized trial, we consider nesiritide as an inotrope-sparing mode of lowering pulmonary and LV filling pressures in patients with LVSD and secondary PH unresponsive to oral vasodilator therapy.

Inhaled NO

Endothelial-derived NO increases intracellular cGMP by activation of soluble guanylate cyclase, prompting smooth muscle relaxation and vasodilatation [8]. Patients with HF and secondary PH may be NO deficient [38]. Unlike parenteral pulmonary vasodilators, inhaled NO may reduce PVR without incurring a risk of systemic hypotension [39,40]. Inhaled NO increases exercise capacity in patients with HF in proportion to the degree of RV dysfunction or PH [41]. Furthermore, inhaled NO has short-acting, pulmonary-specific

effects, including improvement in ventilation-perfusion matching [42]. Inhaled NO has found broad applications in PVR reduction in the pretransplant setting [43], cardiogenic shock due to RV myocardial infarction [44], and optimization of hemodynamics during LV assist device placement [45].

In some patients, increased pulmonary venous return during NO inhalation leads to higher pulmonary capillary wedge pressures and risk of worsening HF [40,42,46]. Additionally, the small but present risk of methemoglobinemia with continuous inhalation [42] and the lack of data supporting chronic NO in secondary PH have limited its wide utilization in LVSD with PH. At our institution, we use inhaled NO as a vasodilator during right-sided heart catheterization and therapeutically in patients with LVSD with severe PH complicated by RV dysfunction, with careful monitoring of PA and LV filling pressure.

PDE5 Inhibitors

cGMP PDEs are involved in the conversion of cGMP to GMP, limiting the downstream vasodilatory effect of cGMP signaling [42]. PDE5 is the major PDE isoform in the lung [47]. Accordingly, sildenafil, a selective PDE5 inhibitor, has been shown to improve PA pressure, exercise capacity, and functional status in patients with idiopathic PH [48]. In LVSD and secondary PH, sildenafil improves exercise capacity, gas exchange, and pulmonary hemodynamics [49] in a dose-dependent manner. In addition, hemodynamic benefits are specific to the pulmonary vasculature [14•] and most dramatic in patients with severe PH [49]. In a recent randomized blinded study of 34 patients with New York Heart Association (NYHA) class II and III HF due to LVSD, exercise capacity was shown to be improved with chronic sildenafil administration (Fig. 1) [14•], and the improvement in exercise capacity was proportionate to the PVR and the degree of RV dysfunction prior to therapy. These acute benefits of PDE5 inhibition on hemodynamics and quality of life may be sustained during long-term follow-up [13,14•,50]. Moreover, sildenafil may safely facilitate transplantation by reduction in PVR [51] and promote a weaning of inotropes and inhaled NO in patients who are post-LV assist device placement [52•]. In contrast to inhaled NO, sildenafil causes a small reduction in systemic vascular resistance, but has no effect on LV filling pressures [49]. PDE5 inhibition may also be synergistic with other pulmonary vasodilators, including inhaled NO [53] and ET-1 antagonists.

At present, sildenafil is only approved for use in patients with idiopathic PH. Although the initial studies suggest the safety of sildenafil administration in chronic HF [14•], there is currently no evidence on the safety of long-term sildenafil use in HF. Given the data generated from our laboratory and others [13,14•,50], we use sildenafil in patients with HF and PH with RV dysfunction in patients who are responsive to acute vasodilator testing with an aim to improve RV hemodynamics, exercise capacity, and quality of life.

Management

Although several medications used in the management of idiopathic PH have proven unsuccessful or even harmful in secondary PH, the goals of managing PH in patients with HF are similar to those in idiopathic PH: aggressive reduction in PA pressure to optimize RV afterload, careful management of volume status, and vigilance for the development of fixed (nonvasoreactive) PH.

Acute HF Syndromes

A pathophysiologic distinction of acute HF syndromes in patients with LVSD and PH is RV function. Although management of patients with LVSD and PH relies on the reduction of LV filling pressures with diuretic therapy, similar to patients without PH, decreased RV

compliance and systolic function in patients with PH may lead to a relatively preload-dependent RV. In this setting, aggressive diuresis or systemic afterload reduction may lead to hypotension, renal dysfunction, and worsening HF. This condition is often uncovered empirically during therapy, although echocardiographic clues of RV dysfunction may be useful. Additionally, in patients with LV failure and cardiogenic shock with concomitant RV dysfunction, optimization of RV preload with invasive goals (central venous pressure 12–15 mm Hg) may be advised to support RV output.

Despite recent results questioning the effectiveness of routine use of right-sided heart catheterization in decompensated HF, patients who remain in HF after initial diuretic therapy and judicious LV afterload reduction may benefit from invasive hemodynamic profiling to balance the degree of LV versus RV dysfunction and to quantify PH. Patients with a predominant LVSD phenotype manifest elevations in pulmonary capillary wedge pressure and/or depressed cardiac index out of proportion to chronic PH and RV dysfunction. These patients may benefit from a trial of a mixed pulmonary and systemic vasodilator (eg, nitroprusside, milrinone, or nesiritide) in combination with diuretic therapy to optimize preload, with a move towards inotropic or mechanical support and more advanced therapies if attempts at decongestion fail. Given its more potent effect as a pulmonary vasodilator, we prefer milrinone to dobutamine in these cases.

In patients in disproportionate RV failure secondary to PH and concomitant LVSD, initial therapies aimed at pulmonary vasodilatation and improved RV afterload during decongestion are crucial. In this scenario, options include the addition of intravenous nesiritide, milrinone, nitroprusside, nitroglycerin, or inhaled NO to concomitant diuretic therapy, with careful monitoring for hypotension. Given the difficulties with increased LV filling pressures after the initiation of high-dose inhaled NO [40,42,46], we prefer to withhold this therapy in patients with pulmonary capillary wedge pressure of more than 25 mm Hg [44]. In some cases, we have successfully used sildenafil in the management of these patients [53], although its use precludes nitrate-based vasodilator therapy. In patients who fail this initial approach, more advanced therapies aimed at RV afterload reduction, including inhaled NO, RV or LV assist device, and cardiac transplantation should be considered.

Chronic HF

The aim of managing the patient with advanced HF with secondary PH focuses on attention to volume status and reduction in PH to forestall development of fixed elevation in PVR, which may limit transplantation. In our experience, optimal volume status in patients with LVSD and PH seems to be largely dependent on RV function, such that patients with more RV dysfunction may require higher filling pressures to avoid symptomatic or orthostatic hypotension.

Although increased PA pressures are a poor prognostic marker in chronic HF, there are few data suggesting that aggressive reduction of PH in the setting of chronic HF improves mortality. However, many patients with advanced HF and PH are awaiting cardiac transplantation, and assessment of PVR and vasoreactivity are performed to lower PVR to forestall development of fixed PH. In these patients, we advocate right-sided heart catheterization to ensure full decongestion prior to pulmonary vasoreactivity testing. If patients have a positive response to intravenous pulmonary vasodilators, we attempt to transition these patients from intravenous to oral vasodilator therapy (predominantly sildenafil or combination nitrate-hydralazine therapy) with an aim to maintain reduction in PA pressures. If this is unsuccessful, chronic intravenous pulmonary vasodilator therapy with intravenous nesiritide or inotropic therapy with milrinone is considered a bridge to

future transplantation. In addition to medical therapy, cardiac resynchronization therapy [54] or LV assist device placement [55] in patients with postcapillary reversible PH and LVSD may be useful.

Conclusions

Secondary PH is common in patients with advanced HF and portends a poor prognosis. However, there currently remains a need for data endorsing a mortality benefit to reducing PH in chronic HF. Of the therapies addressing secondary PH, PDE5 inhibition is the only therapy to have shown a sustained functional and hemodynamic benefit with potentially limited risk in small cohorts, and larger studies are forthcoming to address safety and mortality reduction. In addition, mechanistic insights into the demonstrated functional benefit of PH reduction in patients with advanced HF receiving PDE5 inhibitors (eg, by improvement in gas exchange efficiency and vascular function) are currently under investigation. Expanding these insights in patients with poor LV function to patients with diastolic HF and PH is currently ongoing in the RELAX trial. With a better understanding of the physiology of secondary PH and an arsenal of medications to safely address secondary PH, we may afford patients with PH and advanced HF not only an improved survival to transplantation, but perhaps a longer transplant-free survival.

Clinical Trial Acronyms

ENABLE	Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure
FIRST	Flolan International Randomized Survival Trial
FUSION II	Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure
REACH-I	Rehabilitation Among Women with Coronary Heart Disease Research on Endothelin Antagonism in Chronic Heart Failure
RELAX	Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure

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Papers of particular interest, published recently, have been highlighted as:

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•• Of major importance

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Figure 1.

In a randomized double-blind study of chronic oral phosphodiesterase 5 inhibitor administration to patients with New York Heart Association class II and III heart failure due to left ventricular systolic dysfunction, exercise capacity (as assessed by peak oxygen consumption) increased by 18% in subjects receiving sildenafil and was unchanged in those receiving placebo. Individual and mean ($\pm$ SEM) values for peak exercise at baseline and after 12 weeks of placebo (*left*) or sildenafil (*right*) are shown [14].