## **Pulmonary Hypertension in Heart Failure Patients Who Are Referred for Cardiac Transplantation**



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### Epidemiology

Left-sided heart failure is an important and common cause of pulmonary hypertension (PH). In the United States, >5 million people are affected by heart failure, and approximately 550,000 new cases are diagnosed annually.<sup>1,2</sup> It affects 10% of the population over 65 years of age, and is the leading cause of hospitalization among adults. Approximately two-thirds of heart failure is secondary to diminished left ventricular contractility or systolic dysfunction, and the remaining are due to impaired left ventricular filling / diastolic dysfunction. Coronary artery disease and primary cardiomyopathy are the most common causes of systolic left ventricular failure, while hypertension is the leading cause of diastolic heart failure (**Table 1**).

Advanced heart failure accounts for at least 10% of all heart failure (approximately 500,000 patients), and its prevalence is increasing, particularly because of increased emphasis upon evidence-based medical therapies, and because of reduction in sudden cardiac death due to prophylactic defibrillator implantation. Severe heart failure is frequently associated with PH, perhaps in 25-50% of patients, but unfortunately there is little epidemiologic information available on its prevalence. Pulmonary hypertension in association with left-sided heart failure may be either mild or moderate, though it can be severe in up to a third of patients. The speculation is that significant PH may be present in up to 250,000 heart failure patients in the United States, which is far greater than the reported prevalence of PH associated with other conditions. It is therefore critical that every heart failure patient with advanced symptoms undergo a thorough evaluation to ascertain the presence and severity of PH.<sup>3</sup> The focus of this discussion will be PH that is associated with systolic heart failure.

## Hemodynamic Characterization

The human pulmonary circulation, unlike the systemic circulation, is a low resistance vascular bed.<sup>4</sup> According to the hydrodynamic equation which draws an analogy from Ohm's

# Table 1. Leading Causes of Systolic and DiastolicHeart Failure in the US

#### Systolic

- Coronary artery disease
- Primary cardiomyopathy
- Hypertension
- Valvular heart disease
- Myocarditis
- Drug-induced
- Toxin-induced

#### Diastolic

- Hypertension
- Coronary artery disease
- Aging
- Restrictive heart disease
- Hypertrophic cardiomyopathy
- Valvular heart disease

law, the resistance to flow (R) varies directly with the pressure drop ( $\Delta P$ ) and inversely with the rate of flow(Q) across the pulmonary vascular bed such that  $R = \Delta P/Q$ . The pressure drop in the pulmonary vascular bed is also known as the trans-pulmonary pressure gradient (TPG), which is the difference between the measured mean pulmonary artery pressure and pulmonary capillary wedge pressure (PCWP). Pulmonary vascular resistance (PVR) is calculated by dividing TPG by flow or cardiac output. It is important to remember that TPG is a measured variable, whereas PVR is calculated. PH in heart failure patients is usually "post-capillary," characterized by an elevated PCWP (>15 mm Hg) and PVR. Initially, in PH associated with left-sided heart failure, the TPG is normal, though over time it increases (>10 mm Hg). The hemodynamic progression of PH is typically characterized by a progressive rise in TPG and PVR over time (Table 2). In the later stages, pulmonary artery pressures and cardiac output fall as right ventricular failure sets in, with marked elevations in right atrial pressure. Occasionally, the pulmonary artery pressure and TPG may be very high. Many clinicians consider this to be a form of PH "out of proportion" to left-sided heart failure. Whether or not this is an

## Table 2. Hemodynamic Progression of PH inLeft Heart Failure

		Vasoreactive		Nonvasoreactive		
	Normal	Early Stage	Mid Stage	Late Stage	End Stage	
PCWP	Ν	ſ	111	氜	€	
PA	Ν	↑↑	111	1111	↑↑	
TPG	Ν	Ν	€	$\Uparrow \Uparrow$	111	
CO	Ν	Ν	N or ↓	$\Downarrow$	$\Downarrow \Downarrow$	
PVR	Ν	Ν	↑↑	们们	1111	
RAP	Ν	Ν	N or ∬	氜	们们	
		Increased morbidity and mortality				

extreme manifestation of PH in the spectrum of left-sided heart failure or a combination of heart failure and intrinsic pulmonary vascular disease is unknown. This topic is addressed in the 2 separate articles elsewhere in this issue.

PH can be hemodynamically classified as mild, moderate or severe, based upon measured values of mean pulmonary artery pressures, TPG and calculated PVR (**Table 3**). Initially, PH in heart failure is "reactive" and readily reversed acutely with vasodilator challenge. Over time, PH becomes "non-vasoreactive" or "fixed," with reduced or no responsiveness to pharmacologic treatments.<sup>5</sup> Histologically, PH associated with left-sided heart failure is characterized by intimal thickening and fibrosis, medial hypertrophy and adventitial fibrosis of the pulmonary vasculature. Hemodynamic progression from "reactive" to "fixed" disease is accompanied by progressive structural pulmonary vascular remodeling. Plexiform lesions, which are the histologic signature of idiopathic PH, are not typically seen in heart failure patients with PH.<sup>6,7</sup>

## Pathogenesis

Left ventricular injury leading to structural remodeling and dysfunction is the seminal event in the progression of heart failure (Figure 1). The translation of injury to remodeling is dependent on the up-regulation and down-regulation of several neuro-hormone and cytokine pathways that results in neurohormonal imbalance. The renin-angiotensin-aldosterone system, the sympathetic nervous system and endothelin are the vasoconstrictor systems that are activated whereas endogenous vasodilator systems, such as nitric oxide and kinins are deactivated. All of these systems extensively interact with each other resulting in pulmonary vascular endothelial cell dysfunction. This triggers pulmonary vasoconstriction and vascular remodeling through multiple mechanisms, leading to the development of pulmonary hypertension. The translation from endothelial cell dysfunction to intimal thickening and medial hypertrophy is not well understood, but involves endothelin-1 and nitric oxide, both of which play a critical role in the maintenance of vascular tone in health.<sup>8</sup> Left ventricular remodeling also results in

## Table 3. Hemodynamic Classification of PHin Left Heart Failure

	Mean pulmonary artery pressure (mmHg)	TPG (mm Hg)	PVR (Wood units)
Mild	25-34	10-12	2.5-3.4
Moderate	35-44	13-15	3.5-4.9
Severe	>45	>15	>5

mitral regurgitation which causes left atrial hypertension and further triggers pulmonary vascular endothelial dysfunction.<sup>9</sup>

Plasma endothelin-1 levels vary directly with pulmonary artery pressure and PVR, and vary inversely with stroke volume in heart failure patients with PH.<sup>10</sup> Plasma endothelin-1 level is a direct correlate of mortality in heart failure patients.<sup>11-13</sup> The increased pulmonary artery pressure and vascular resistance increases the afterload of the right ventricle leading to right ventricular dysfunction, remodeling and failure. Thus, left ventricular dysfunction always results in right ventricular failure by way of pulmonary hypertension. However, when the initial insult affects both ventricles simultaneously, such as in acute myocarditis or myocardial infarction involving the right and left ventricles, pulmonary hypertension rarely develops as the failing right ventricle is unable to generate high pulmonary pressures to overcome the downstream resistance to flow.

## Diagnosis

Every patient with PH associated with left-sided heart failure must have a detailed diagnostic work-up to help characterize the etiology of the heart failure and to identify if the heart failure is from systolic or diastolic left ventricular dysfunction<sup>14</sup> (**Figure 2**). A transthoracic echocardiogram can frequently recognize the presence of PH and right ventricular dysfunction, in addition to providing evaluation of the left ventricle and the valves. Pulmonary artery pressure can be estimated from the Doppler measurement of the regurgitation velocity across the tricuspid valve. Right heart catheterization must however be performed to accurately measure pulmonary artery pressures, PCWP, TPG and cardiac output. Other potential causes or contributors to PH should be considered and appropriate testing done as indicated. In particular, thromboembolic pulmonary disease, coexistent pulmonary parenchymal disease such as chronic obstructive pulmonary disease, and sleep apnea should be ruled out.

If the TPG and PVR are elevated, acute vasoreactivity testing should be done at the time of right heart catheterization, particularly if the patient is to be considered for cardiac transplantation.<sup>15-19</sup> Intravenous sodium nitroprusside, milrinone, prostacyclin or inhaled nitric oxide are generally used to assess acute vasoreactivity in PH associated with left-sided heart failure (**Table 4**). Though there is no standard definition to identify a responder, the goal is to see if the TPG and PVR can be decreased appreciably, without



Figure 1—Proposed mechanism of pathogenesis of PH in left heart failure. LVEDP=left ventricular end-diastolic pressure, EC=endothelial cell, MR=mitral regurgitation, ET=endothelin-1, NO=nitric oxide. Adapted from Moraes et al. *Circulation.* 2000; 102:1718-23.

raising PCWP or lowering cardiac output or causing systemic hypotension. Patients who are acutely vasoreactive and listed for transplantation will require serial testing every 6-8 weeks to ensure that they remain vasoresponsive.

#### **Clinical Course and Prognosis**

When PH complicates heart failure, both morbidity and mortality are increased.<sup>20</sup> Patients complain of worsening fatigue and dyspnea, and declining exercise tolerance. The peak exercise oxygen consumption (peak VO<sub>2</sub>) inversely correlates with mean pulmonary pressure and PVR, and correlates directly with resting right ventricular ejection fraction.<sup>21,22</sup> Atrial arrhythmias are more frequent, which further compromises cardiac output. As right ventricular failure sets in, cardio-renal syndrome with progressive renal insufficiency, hyponatremia, and diuretic resistance develop. In the advanced stages, patients have anasarca, severe tricuspid regurgitation secondary to annular dilatation, and chronic hepatic congestion that can lead to cardiac cirrhosis. Rarely, patients develop hypoxemia either at rest or with activity because of a right to left shunt through a patent foramen ovale. Heart failure patients with PH have increased frequency of hospitalizations, increased risk of cardiovascular events, and a higher mortality, compared to patients without PH. The risk of death is directly proportional to the pulmonary vascular resistance.23

#### **PH in Transplant Candidates**

In heart failure patients, the presence of significant PH is a contraindication to orthotopic cardiac transplantation.<sup>24,25</sup>



Figure 2—Proposed diagnostic work-up if PH is detected in a patient with left heart failure. Once the diagnosis is suspected by echocardiography and confirmed by catheterization, other contributing factors such as pulmonary emboli, parenchymal lung disease and sleep apnea has to be ruled out. RHC=right heart catheterization, V/Q scan=ventilation-perfusion scan, CT=computed tomography, CTEPH=chronic thrombo-embolic PH, PFT=pulmonary function test, ABG=arterial blood gases, COPD=chronic obstructive pulmonary disease.

## Table 4. Vasoreactivity Testing in PHAssociated With Left Heart Failure

#### Drugs used to assess vasoreactivity

- 1. IV Nitroprusside 250-750 mcg/kg/min q 10 min
- 2. IV Epoprostenol 2-10 ng/kg/min q min
- 3. Inhaled nitric oxide 10-40 ppm q 2 min
- 4. IV Milrinone 25-50 mcg/kg bolus over 5 mins
- 5. IV Neseritide 2mcg/kg bolus, 0.01 mcg/kg/min over 30 mins

## Definition of "response"

No "standard" definition

- Fall in TPG to  $\leq 12 \text{ mmHg}$ , OR
- Fall in PVR to  $\leq$ 3 Wood units, OR
- Fall in PVR by 20%, AND
- Unchanged or increased CO from baseline, AND
- No increase in PCWP from baseline, AND
- Systolic arterial pressure >80 mmHg

The donor right ventricle will fail acutely, resulting in allograft failure and death if it is required to pump into a high resistance pulmonary circulation. A normal right ventricle cannot acutely generate a pressure in excess of 50 mm Hg. The risk posed by PH in transplant candidates is a continuous risk that is directly proportional to both PVR and TPG; in other words, the greater the TPG and PVR, the higher the risk of acute right ventricular failure following transplantation.<sup>26-28</sup>

Nonetheless, for clinical reasons, thresholds have been defined for PVR and TPG beyond which the risk is considered excessive, and orthotopic transplantation contraindicated.<sup>29</sup> These thresholds vary among transplant programs,



Figure 3—Proposed algorithm for management of PH in left heart failure. In patients who are acutely vasoreactive, the testing should be repeated every 6-8 weeks as they await transplantation.

and are higher in experienced, high volume transplant centers. Heart failure patients with a TPG <12mm Hg or PVR <3 Wood Units are considered suitable with an acceptable risk in most transplant centers, whereas patients with a TPG  $\geq$ 15 mm Hg or PVR  $\geq$ 5 Wood Units, despite acute vasoreactive testing, are clearly not appropriate candidates. The early post-transplant mortality is 3-fold higher in the latter high risk group, and even higher if the gender is female.<sup>30-</sup> <sup>34</sup> In these patients, heterotopic transplantation, where a donor heart is implanted without explantation of the recipient heart or heart-lung transplantation may be considered. Long-term outcomes with heterotopic heart transplantation are inferior to orthotopic transplantation, and therefore not performed in most transplant centers.<sup>35</sup> Heart-lung transplantation is limited by the lack of availability of donors. A Domino procedure where the cardiac allograft from a donor with idiopathic pulmonary hypertension who is to receive a heart-lung transplantation is used has been advocated for severe PH patients. The remodeled, hypertrophied right ventricle in these allografts can adequately sustain function in the early post-operative period.<sup>36</sup> Data from the International Society for Heart and Lung Transplantation (ISHLT) registry demonstrate that pre-transplantation PH is an independent risk factor for poor outcome following transplantation.<sup>37</sup> This risk exists even with oversizing the donor allograft.

Left-sided heart failure patients with PH who undergo transplantation will have gradual, complete resolution of their PH during the first 6-12 months.<sup>38-40</sup> However, even those with only a mild to moderate degree of PH pre-transplantation have residual PH during the first few months.<sup>41</sup> The greater the severity of PH prior to surgery, the longer the time to resolution. In some patients with severe PH, there is incomplete resolution, with residual elevations in pulmonary pressures and PVR. Even those patients who undergo heterotopic heart transplantation have some resolution of PH over time.<sup>35</sup> Remodeling of the allograft right ventricle and development of tricuspid insufficiency accompany the resolution of PH after transplantation.

Drug	РАН	PH associated with LHF
Nitrates (oral or intra- venous or sublingual)	No	Acute hemodynamic; chronic symptomatic benefit
Calcium channel blockers	Chronic benefit (in vaso- reactive patients only)	No (except amlodipine that causes chronic symptomatic benefit)
Endothelin receptor antag- onists (Bosentan)	Acute hemodynamic and chronic clinical benefit*	Acute hemodynamic; but no chronic clinical benefit
Prostanoids (Epoprostenol)	Acute hemodynamic and chronic clinical benefit*	Acute hemodynamic; but no chronic clinical benefit
PDE-III inhibitors (Milrinone)	No	Acute hemodynamic benefit; ↑ mortality during chronic therapy
PDE-V inhibitors (Sildenafil)	Acute hemodynamic and chronic clinical benefit*	Acute hemodynamic; chronic benefit unknown
Digoxin	No	Chronic clinical benefit*
ACE inhibitors	No	Chronic clinical benefit*
β-blockers (Carvedilol, Metoprolol succinate)	No	Chronic clinical benefit*
Aldosterone antagonists	No	Chronic clinical benefit*
Hydralazine + Isosorbide Dinitrate	No	Chronic clinical benefit*
VAD	No	Acute hemodynamic; chronic clinical benefit*

Figure 4—The list of treatments available for pulmonary arterial hypertension (PAH) and PH associated with left heart failure (LHF). \*FDA approved, PDE=phosphodiesterase, ACE=angiotensin converting enzyme, VAD=ventricular assist device

#### Management

The managment paradigm for PH associated with left-sided heart failure is outlined in Figure 3. All left-sided heart failure patients whether they have associated PH or not, should be treated with evidence-based therapies which include digoxin, diuretics, angiotensin converting inhibitors, β-adrenergic blockers and aldosterone antagonists.<sup>42</sup> Any contributing condition should also be treated appropriately. If PH is present and acutely vasoreactive, the patient may be considered for transplantation, provided there are no other contraindications. Every effort must be made to prevent the progression of PH until transplantation and frequent monitoring (every 6-8 weeks) with right heart catheterization may be necessary. If PH is not acutely vasoreactive, then chronic infusions of intravenous Neseritide (48-72 hrs) or intravenous milrinone (up to 2 weeks) or aerosolized inhalation of milrinone should be considered in order to decrease pulmonary pressures, TPG and PVR.43-46 Chronic left ventricular unloading with a left ventricular assist device (either continuous flow or pulsatile) may also be considered in select patients to reverse PH.<sup>47,48</sup> If there is significant improvement in pulmonary hemodynamics with any of these strategies, cardiac transplantation may be feasible.

None of the therapies that are approved for the treatment of pulmonary arterial hypertension have shown benefit in chronic heart failure patients<sup>49</sup> (**Figure 4**). Except for amlodipine, calcium channel blockers worsen outcomes in patients with left heart failure due to systolic dysfunction. Though acute administration of endothelin antagonists induces pulmonary vasodilation in left-sided heart failure patients, chronic therapy has no proven survival benefit in randomized, controlled trials.<sup>50,51</sup> Likewise, intravenous epoprostenol infusions failed to show survival benefit in patients with chronic heart failure.<sup>52</sup> Incidently, several patients in this study experienced reductions in pulmonary pressures, PCWP and PVR.<sup>53</sup> Unfortunately, none of the aforementioned clinical trials carefully evaluated the long-term clinical and survival benefits in patients with PH associated with chronic left heart failure. Oral sildenafil, a phosphodiesrterase-5 inhibitor, which is approved for the treatment of pulmonary pressures and PVR in PH associated with heart failure.<sup>54</sup> This hemodynamic effect is augmented when the drug is co-administered with inhaled nitric oxide.<sup>55, 56</sup> Whether chronic treatment with sildenafil can cause sustained benefit in PH associated with heart failure.

#### **Summary**

Left heart failure is an important, and perhaps common cause of PH. The morbidity and mortality in left heart failure is independently determined by the presence of associated PH which also directly contributes to the progressive decline in symptoms and functional status in these patients. Though, advances in medical and surgical therapy have significantly improved the outlook of chronic left heart failure patients, to date, there is no FDA approved therapy for PH associated with left heart failure. Cardiac transplantation is risky in general, but can be offered for vasoreactive patients, who have no other contraindications. Parenteral continuous therapy with neseritide or milrinone and chronic left ventricular unloading with a left ventricular assist device may improve pulmonary hemodynamics and allow successful transplantation in certain select patients, who are not responsive to acute vasoreactivity challenge. Clearly, further research to identify targeted therapy for PH associated with left heart failure is sorely needed.

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