Published in final edited form as:

ASAIO J. 2016 ; 62(5): 505–512. doi:10.1097/MAT.0000000000000408.

Pulmonary Hypertension in the Era of Mechanical Circulatory Support

Yamini Krishnamurthy, BA*, Lauren B. Cooper, MD*, Kishan S. Parikh, MD*, G. Michael Felker, MD, MHS*, Carmelo A. Milano, MD*, Joseph G. Rogers, MD*, Adrian F. Hernandez, MD, MHS*, and Chetan B. Patel, MD*

*Duke Clinical Research Institute and the Department of Medicine, Duke University Medical Center, Durham, NC

Abstract

Left heart disease (LHD) represents the most common cause of pulmonary hypertension (PH), and is associated with worse prognosis compared to LHD without PH. In addition, PH due to LHD may prevent patients from receiving heart transplantation, due to risk of perioperative right ventricular failure. Current literature lacks comprehensive descriptions and management strategies of PH due to LHD. In this review, we summarize the literature that is available to highlight the definition, pathogenesis, and prognosis of PH due to LHD. Furthermore, we discuss the use of mechanical circulatory support in this population. Finally, we provide recommendations regarding the management and reassessment of PH due to LHD in the specific context of mechanical circulatory support.

Keywords

heart failure; pulmonary hypertension due to left heart disease; mechanical circulatory support

Pulmonary hypertension (PH) due left heart disease (LHD) represents the most common cause of PH, and is associated with higher morbidity and mortality compared to LHD without PH.¹ PH due to LHD is subcategorized into four distinct groups: 1) PH due to heart failure with reduced ejection fraction (HFrEF); 2) PH due to heart failure with preserved ejection fraction (HFpEF); 3) PH secondary to valvular heart disease; or 4) PH due to left heart inflow or outflow tract obstruction and congenital cardiomyopathies. The presence of

Address for correspondence: hetan B. Patel, MD; DUMC 3034, Durham, NC 27710; Tel: (919) 681-3398; Fax: (919) 668-7078; chetan.patel@duke.edu.

Conflict of Interest Disclosures

Y Krishnamurthy: Ms. Krishnamurthy has no relevant disclosures to report.

LB Cooper: Dr. Cooper has no relevant disclosures to report.

KS Parikh: Dr. Parikh has no relevant disclosures to report.

GM Felker: Dr. Felker has no relevant disclosures to report.

CA Milano: Dr. Milano reports consulting or other services from Thoratec Corp. and Heartware Inc.

JG Rogers: Dr. Rogers reports consulting or other services (including CME) from Bayer AG, Boston Scientific Corporation, Medtronic, Inc., and Thoratec Corporation (all modest)

AF Hernandez: Dr. Hernandez reports research funding from AstraZeneca, GlaxoSmithKline, Merck and Novartis; consulting for AstraZeneca, Merck and Novartis.

CB Patel: Dr. Patel reports consulting for Thoratec Corp. and Heartware Inc.

PH secondary to LHD influences the medical and surgical management of advanced systolic heart failure, particularly in patients who develop refractory disease.² PH is an important consideration when assessing candidacy for orthotopic heart transplantation (OHT). Severe PH (defined as pulmonary vascular resistance [PVR] >5 wood units [WU] or transpulmonary pressure gradient [TPG] >16–20 mmHg) is considered a contraindication for transplantation.^{3,4} More recently, the increased use of mechanical circulatory support (MCS) has impacted clinical decision making with regard to the treatment of patients with refractory PH due to LHD. Many questions remain, including whether treatment of PH prior to MCS implantation is beneficial, when to reassess hemodynamics after implantation, and whether adjunctive therapy should be used in patients whose pulmonary pressures fail to normalize. While patients with LHD may have other contributing factors such as chronic pulmonary embolism, or hypoxia due to sleep apnea, chronic obstructive lung disease, or interstitial lung disease that could worsen PH, for the purposes of this review we focused solely on PH due to LHD. Furthermore, since advanced therapies for HF (i.e., MCS and OHT) are usually reserved for patients with HFrEF, our review highlights the characteristics of PH due to HFrEF, and addresses important clinical issues surrounding the treatment of these patients.¹

Pulmonary Hypertension in Left Heart Disease

Definition

The hemodynamic parameters that define PH due to LHD are not uniform in practice or in the published literature.⁵ Generally, a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg associated with left ventricular dysfunction or other forms LHD has been used to define PH due to LHD (Figure 1).^{6,7} Terms such as post-capillary PH (pulmonary venous hypertension, pulmonary capillary wedge pressure [PCWP] >15 mmHg), pre-capillary PH (pulmonary arterial hypertension, PCWP ≤15 mmHg), or “out-of-proportion” PH have been used to better characterize and describe the pathophysiology of PH due to LHD.⁸ Historically, there were no clear hemodynamic parameters that defined out-of-proportion PH, though it is assumed that PH develops out-of-proportion to the elevated PCWP due to vascular remodeling.^{7,9,10}

Viachery et al. suggest a simple way to reconsider PH due to LHD: 1) an elevated PCWP, but no significant change in pulmonary circulation (i.e.: no vascular remodeling); 2) an elevated PCWP with vascular remodeling; 3) a previously elevated but currently normal PCWP, with persistence of vascular remodeling.⁹ A key issue is therefore the degree of vascular remodeling that occurs due to this passive congestion which secondarily results in a compensatory increase in right ventricular and systolic PA pressure. Thus, a challenge for Viachery et al.’s approach to PH due to LHD is how to best describe pulmonary vascular remodeling without biopsy or imaging. They posited that an elevated diastolic pressure gradient (DPG)—diastolic PAP minus PCWP—may capture the passive nature of this remodeling process. Recent European Society of Cardiology/European Respiratory Society guidelines defined “out-of proportion” PH as DPG >7 mmHg.⁸

Pathophysiology

Despite attempts to quantify the degree of remodeling using hemodynamic variables, the actual pathophysiologic processes leading to PH is not well-understood. The early stage of PH due to LHD is thought to be characterized by venous remodeling from pulmonary venous hypertension. An increase in pulmonary venous pressure results in reactive mechanical changes, which can trigger additional remodeling such as decreased nitric oxide availability, increased endothelin-1 expression, desensitization to natriuretic peptide-induced vasodilation, and arterial remodeling (Figure 2).^{11–13} Therefore, as the disease state progresses, pathophysiologic features of pulmonary arterial hypertension develop. While data validating this process in humans is limited, preclinical models have demonstrated that such remodeling may be reversible.^{14,15}

Medical Management of LHD-Associated PH

While there are no Food and Drug Administration approved medications to treat PH due to LHD, pharmacotherapy for the treatment of PH has targeted two pathophysiologic mechanisms: 1) vasodilators for reversal of pulmonary arterial hypertension in the presence of a significant pre-capillary component; and 2) decongestion and left-ventricular unloading for reduction of pulmonary venous hypertension. One limitation of pulmonary artery vasodilation in patients with elevated left-sided filling pressures is the risk of increasing blood flow into a high-pressure vascular bed resulting in pulmonary edema and increased ventilation-perfusion mismatch.¹⁶ Vasodilators—nitroprusside and inhaled nitric oxide—may maintain benefit by reducing pulmonary pressures. However, other direct pulmonary vasodilators (e.g., prostaglandins and ET antagonists) have shown to be detrimental in patients with HF (Table 1).^{17–20} The Safety and Tolerability of Macitentan in Subjects with Combined Pre- and Post-Capillary Pulmonary Hypertension due to Left Ventricular Dysfunction (MELODY-1) trial aims to assess the affect of macitentan—an endothelin receptor antagonist (ERA) indicated for pulmonary arterial hypertension—on PH due to HFrEF and HFpEF; this Phase 2 trial will further elucidate the role of ERAs in PH due to LHD.²¹

Targeting the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway is a potential therapeutic target for worsening HFrEF and PH. The Left Ventricular Systolic Dysfunction Associated with Pulmonary Hypertension Riociguat Trial (LEPHT) assessed the effect of riociguat on hemodynamics in patients with PH caused by systolic left ventricular dysfunction (defined as ejection fraction < 40%). Riociguat is a novel soluble guanylate cyclase stimulator with a dual mechanism of action: 1) it sensitizes guanylate cyclase to endogenous nitric oxide and 2) it directly stimulates guanylate cyclase independent of nitric oxide. In this randomized, double-blind, placebo-controlled study, mPAP did not significantly vary between the placebo and treatment arms; however, riociguat was well-tolerated, and improved cardiac index and pulmonary and systemic vascular resistance.²² Other soluble guanylate cyclase stimulators, such as Vericiguat, are also being studied in patients with worsening HFrEF.²³ Further clinical trials of novel soluble guanylate cycle stimulators are needed to determine the potential role of these drugs in patients with HFrEF.

Phosphodiesterase type 5 inhibitors that modulate endogenous nitric oxide production have shown promise in patients with HFrEF. An observational study of sildenafil in HFrEF patients with PH showed improvement in exercise capacity, quality of life, and re-hospitalization. Clinical status and hemodynamic parameters, including PVR and cardiac output, improved as well.²⁴ A long-term randomized placebo-controlled study of 46 patients supported these findings, showing an improvement in peak oxygen consumption from 14.8 ± 1.5 to 18.7 ± 1.7 ml min⁻¹kg⁻¹ ($p < 0.01$) over 6 months in the treatment group, while the placebo group showed no improvement.²⁵ Of note, sildenafil therapy in the HFpEF population did not result in significant improvement of exercise capacity or clinical status.²⁶ The Food and Drug Administration has approved sildenafil for the treatment of pulmonary arterial hypertension, but not for the treatment of PH due to LHD; thus, larger, event-driven studies in a carefully selected patient population are needed to further understand the role of sildenafil in treating PH due to LHD.

Pulmonary Hypertension and Heart Transplantation

PH is a contraindication to OHT due to increased risk of early graft dysfunction from RV failure and all-cause mortality.⁴ An assessment of PH reversibility is an important component when evaluating the HFrEF patient who is being considered for OHT. A study from Stanford University demonstrated how two essential aspects of reversibility should be assessed. First, PVR must decrease to < 2.5 WU with the use of intravenous nitroprusside. Second, systolic blood pressure should remain > 85 mmHg in response to nitroprusside therapy. This study showed that in 293 OHT candidates who were tolerant of nitroprusside, those with a PVR > 2.5 WU had a 3-month post-transplant mortality rate of 17.9% versus 6.9% ($p < 0.02$) in patients with a PVR ≤ 2.5 WU. The 3-month mortality after transplant in patients tolerant of nitroprusside was only 3.8%, compared to 40.6% in those who did not respond to nitroprusside, and 27.5% in those who responded, but experienced a drop in systolic blood pressure < 85 mmHg.²⁷ Of note, most studies consider nitroprusside to be the standard to test for PH reversibility in OHT candidates; however, vasodilators such as inhaled nitric oxide and inhaled prostacyclins have also been shown to be effective for demonstrating vascular reactivity in OHT candidates, but with minimal systemic hypotension given their selectivity for pulmonary vasculature.^{28–30}

Inotropic therapy is an additional strategy to reducing pulmonary pressures prior to transplant or MCS. Pulmonary pressure monitoring and tailored medical therapy can be important for reducing PVR prior to transplant, particularly if pulmonary pressure monitoring allows for optimization of diuresis and inotropic therapy to meet hemodynamic goals.^{31–33} Short-term studies with milrinone have suggested that the decrease in PVR is due primarily to the acute increase in cardiac output.³⁴ However, in patients with prohibitively high pulmonary pressures, longer-term milrinone therapy may provide gradual normalization of PVR. Older studies that predate the use of modern heart failure therapies (such as implantable cardioverter defibrillator, cardiac resynchronization therapy, or aldosterone antagonist) suggest that this strategy is limited by the typically steep decline in survival among patients who are initiated on chronic inotropic support.³⁵ A recent study evaluated outcomes of long-term inotropes in patients with HFrEF, and found that of the 60 patients who were placed on inotropes as a bridge to transplant or left ventricular assist

device (LVAD), 55 were successfully maintained on inotropes until transplant or LVAD. Survival on inotropes for patients who were not candidates for transplant or LVAD was found to be better than previously reported, but remained poor.³⁶

Pulmonary Hypertension and Left Ventricular Assist Devices

If PH due to LHD is refractory to medical intervention, then treatment with LVAD therapy may provide an alternative strategy. For patients who meet LVAD implantation criteria, several studies have demonstrated that LVAD therapy can effectively reduce left-sided filling pressures and lead to PH improvement.^{37–41} The goals of lowering PA pressure with LVAD are two-fold: 1) to prevent late RV dysfunction; and 2) to optimize PA pressures and permit successful OHT in patients who initially have preclusive PH. The reversal of pulmonary hypertension with LVAD therapy was first demonstrated with pulsatile-flow LVADs.^{35,37,40} However, continuous-flow LVADs are now considered standard of care, and recent studies have demonstrated that continuous-flow LVADs are as effective as pulsatile devices for reversing PH (Table 2).^{37–9,41–5}

More specifically, in a prospective 6-week study, 35 patients with severe HF and a PVR >3.5 (despite pharmacotherapy challenge with inhaled nitric oxide, nitroglycerin, and prostaglandin I₂) underwent support with Novacor, Micromed DeBakey and DuraHeart LVADs. The average mPAP was 44 ± 6.2 mmHg prior to LVAD implantation with a PVR of 5.1 ± 2.6 WU. Within 3 days of LVAD implantation, the PVR fell significantly to 2.9 ± 1.3 WU ($p < 0.0001$). After 6 weeks of support, the mPAP was reduced to 18.4 ± 4.3 mmHg and PVR to 3.0 ± 0.8 WU.⁴⁰ In a study of 43 patients who received the Heartmate XVE (pulsatile flow) and 34 patients who received the HeartMate II (continuous flow), there were significant reductions in mPAP as early as 1 month after implantation in the HeartMate II group.⁴⁴

An observational study of 21 patients supported with HeartMate II LVAD therapy reviewed echocardiograms prior to LVAD implantation, as well as at 1 month and 6 months post-LVAD implantation.⁴⁶ Here, PVR was derived from maximum tricuspid regurgitation velocity and right ventricular outflow tract velocity-time integral. At 1-month post-LVAD implantation, tricuspid regurgitation velocity decreased from 3.07 ± 0.44 m/s to 2.45 ± 0.34 m/s ($p < 0.001$) and PVR decreased from 3.51 ± 0.9 WU to 2.0 ± 0.5 WU ($p < 0.001$). Furthermore, a retrospective study identified 27 patients with fixed PH (defined as mPAP >25 mmHg, PVR >2.5 WU, TPG >12 mmHg despite pharmacologic therapy) who received a continuous-flow LVAD. These 27 patients were divided into three groups on the basis of examination time during LVAD support. After LVAD implantation, mPAP fell from 37.26 ± 6.35 mmHg to 21.00 ± 7.51 mmHg ($p = 0.007$), PVR fell from 3.49 ± 1.47 WU to 1.53 ± 0.66 WU ($p = 0.000$), and TPG fell from 15.04 ± 5.22 mmHg to 7.78 ± 3.21 mmHg. This study also suggested that improvement in hemodynamic parameters occurred in the first 6 months post-LVAD implantation, with minimal improvement in pulmonary pressures after that time period.⁴⁷ Similarly, a study of 29 patients with HFrEF and PH who were implanted with a continuous-flow LVAD observed significant reductions in mPAP, TPG, and PVR within 1 month post-LVAD implantation, reaching a nadir by 3 months.⁴⁸

The ability of LVAD therapy to improve PH has proven useful in patients who are bridged to successful OHT. In a case series of six patients with end-stage heart failure and irreversible PH, all patients were successfully bridged to transplantation after LVAD implantation due to a reduction in pulmonary pressures. After LVAD implantation, PVR had fallen from 5.7 ± 0.7 WU to 2.0 ± 1.2 WU.⁴⁹ In another study of 17 patients who received LVAD, six patients with PH were initially not considered suitable OHT candidates. With LVAD support, mPAP and PVR decreased, and four patients were successfully transplanted without major post-operative difficulties.⁴³ A larger study of 54 patients who received an LVAD as bridge-to-transplant, compared post-transplant outcomes between 22 patients with fixed PH before LVAD implantation (defined as PVR >3 WU and resistant to vasodilators) and 32 patients who did not have fixed PH before LVAD implantation. Findings from this study demonstrated that pulmonary pressures were comparable between the two groups immediately pre-transplant and during the first year post-transplant. The incidence of post-transplant RV failure and post-transplant survival was similar between groups.⁵⁰

While LVAD support is associated with a reduction in mPAP and PVR over weeks to months, and thus plays a crucial role as a bridge-to-transplant, a subset of patients may not respond to device therapy alone. In this patient population, additional pharmacotherapy may be needed for PH that persists after LVAD implantation. Tedford et al. studied 138 consecutive patients undergoing LVAD therapy with a PVR >3 WU, and found that 58 patients had persistent elevation of PVR 1–2 weeks after LVAD implantation. Sixteen patients received sildenafil and 32 patients served as non-randomized controls. At 12–15 weeks after LVAD placement, the sildenafil-treated patients exhibited a reduction in mPAP from 36.5 ± 8.6 mmHg to 24.3 ± 3.6 mmHg ($p < 0.001$) and experienced improvement in RV function.⁵¹ In contrast, the LVAD control patients did not have a statistically significant reduction in pulmonary pressures during the same time period, although there was a trend toward improvement. Thus, in patients that do not respond to LVAD therapy alone or do not respond rapidly, there could benefit from adjuvant sildenafil therapy. The ability to lower pulmonary pressures in a shorter time frame allows for the potential of earlier transplantation.

The International Society of Heart and Lung Transplantation (ISHLT) guidelines for MCS recommend considering phosphodiesterase type 5 inhibitors for patients with persistent PH and RV dysfunction after LVAD implantation.⁵² ISHLT guidelines for heart transplant listing criteria suggest that adjuvant therapy post-LVAD implantation with phosphodiesterase type 5 inhibitors may be utilized.³ However, for the subset of patients that do not respond to LVAD therapy, there is no established hemodynamic definition or length of time after which one can describe persistent PH after LVAD implantation; therefore, each patient's hemodynamic status post-LVAD implantation must be assessed on an individual basis. Concomitant use of phosphodiesterase type 5 inhibitors to help RV function in the setting of LVAD is increasingly being used in some centers. Further investigation of phosphodiesterase type 5 inhibitors for patients with persistent PH after LVAD implantation is necessary in the form of randomized controlled trials.

Risk Assessment and Re-evaluation

Efforts to refine patient risk assessment and selection for LVAD therapy continue to be of interest. Preoperative hemodynamic variables, when combined with other variables into multivariable risk models can assess predictors of death after LVAD implantation. Preoperative risk stratification includes previously available scores, as well as novel scoring systems, to describe post-operative risk of RV failure, yet no model has specifically assessed the response of PH to chronic MCS or defined non-responders. Such data would be informative with regard to decision making for transplantation or risk of late RV failure from elevated RV afterload.

Further investigation is also required to determine the frequency and best method for reassessing PH after MCS. Current ISHLT guidelines recommend reevaluation of hemodynamics should be done 3 to 6 months after LVAD implantation to determine reversibility of PH.³ Furthermore, right heart catheterization is considered definitive for reassessment of PH; however, the Wireless Pulmonary Artery Hemodynamic Monitoring in Chronic Heart Failure (CHAMPION) trial demonstrated that in patients with HFrEF and HFpEF incorporating data from a wireless implantable hemodynamic monitor allowed for further optimization of patients' medical management leading to fewer heart failure hospitalizations, decreased PAP, and improved quality of life.⁵³ Thus, implantable hemodynamic monitoring may play a role in monitoring PH after LVAD implantation.

In addition, there may be an emerging role for non-invasive monitoring. The primary imaging modality to monitor patients with LVADs is echocardiography, which can determine ventricular size, function, and intracardiac hemodynamics.⁴⁶ However, right ventricular assessment by echocardiography is subjective and can be limited by poor ultrasound windows in LVAD patients leading to inaccuracies and imprecision. As a result, additional studies will be required to determine the role of echocardiography in following PH and influencing clinical decisions after LVAD implantation.

Conclusions and Looking Forward

PH due to LHD is the most common form of PH. In many patients, the degree of PH is out of proportion to elevated left-sided filling pressures, as a result of both pulmonary venous hypertension and pulmonary arterial hypertension pathophysiology. An important step to the future study of this clinical problem will be to standardize definitions across disciplines to facilitate an evidence base that is interpretable across all clinical practice settings.

Pulmonary hypertension precludes heart transplantation in those with end-stage heart failure; thus LVADs will come to play a greater role as a strategy to improve pulmonary pressures prior to transplantation. Studies have demonstrated that LVADs can improve pulmonary pressures as early as 1 month. However, it may take up to 3 to 6 months to achieve maximum reversibility. While recent guidelines suggest that re-evaluation of hemodynamics with right heart catheterization should be done 3 to 6 months after LVAD implantation, current indications for LVADs, and the frequency and modality of monitoring PH after LVAD require ongoing investigation. Further discussion should also include

utilizing pharmacologic therapy to target PH after LVAD implantation, as phosphodiesterase type 5 inhibitors may come to play an important role for expediting PH reversal for those who require transplantation sooner or for those who do not respond to device therapy alone. This will require a commitment to innovative clinical trial design incorporating active controls and registry data, as well as carefully selected outcomes that incorporate hemodynamics, functional status, and adverse events. Finally, improvements in device technology will certainly play an important role.

Acknowledgments

Sources of Funding

Dr. Cooper was supported by grant T32HL069749-11A1 from National Institute of Health.

Dr. Parikh was supported by grant 5T32GM086330-05 from National Institute of Health.

Dr. Hernandez was supported, in part, by funding by grant number U19HS021092 from Agency for Healthcare Research and Quality.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Agency for Healthcare Research and Quality.

References

1. Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Kober L, Torp-Pedersen C, Hassager C. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol*. 2007; 99:1146–1150. [PubMed: 17437745]
2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology*. 2013; 62(25 Suppl):D34–41. [PubMed: 24355639]
3. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplantation*. 2016; 35:1–23.
4. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International society for heart and lung transplantation guidelines for the care of cardiac transplant candidates--2006. *J Heart Lung Transplant*. 2006; 25:1024–1042. [PubMed: 16962464]
5. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *Journal of the American College of Cardiology*. 2009; 54:S55–665. [PubMed: 19555859]
6. Galie N, Hoeper MM, Humbert M, Torbicki A, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (esc) and the European respiratory society (ers), endorsed by the international society of heart and lung transplantation (ishlt). *Eur Heart J*. 2009; 30:2493–2537. [PubMed: 19713419]
7. Flores ED, Lange RA, Hillis LD. Relation of mean pulmonary arterial wedge pressure and left ventricular end-diastolic pressure. *Am J Cardiol*. 1990; 66:1532–1533. [PubMed: 2252011]
8. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016; 37(1):67–119. [PubMed: 26320113]
9. Vachiery JL, Adir Y, Barbera JA, et al. Pulmonary hypertension due to left heart diseases. *Journal of the American College of Cardiology*. 2013; 62:D100–108. [PubMed: 24355634]

10. Rapp AH, Lange RA, Cigarroa JE, Keeley EC, Hillis LD. Relation of pulmonary arterial diastolic and mean pulmonary arterial wedge pressures in patients with and without pulmonary hypertension. *Am J Cardiol.* 2001; 88:823–824. [PubMed: 11589862]
11. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: The role of the endothelium in pathophysiology and management. *Circulation.* 2000; 102:1718–1723. [PubMed: 11015353]
12. Cooper CJ, Jevnikar FW, Walsh T, Dickinson J, Mouhaffel A, Selwyn AP. The influence of basal nitric oxide activity on pulmonary vascular resistance in patients with congestive heart failure. *Am J Cardiol.* 1998; 82:609–614. [PubMed: 9732889]
13. Melenovsky V, Al-Hiti H, Kazdova L, et al. Transpulmonary b-type natriuretic peptide uptake and cyclic guanosine monophosphate release in heart failure and pulmonary hypertension: The effects of sildenafil. *Journal of the American College of Cardiology.* 2009; 54:595–600. [PubMed: 19660688]
14. Chou SH, Chai CY, Wu JR, et al. The effects of debanding on the lung expression of et-1, enos, and cgmp in rats with left ventricular pressure overload. *Experimental biology and medicine.* 2006; 231:954–959. [PubMed: 16741030]
15. Stewart DJ, Levy RD, Cernacek P, Langleben D. Increased plasma endothelin-1 in pulmonary hypertension: Marker or mediator of disease? *Ann Intern Med.* 1991; 114:464–469. [PubMed: 1994793]
16. Bocchi EA, Bacal F, Auler JO Junior, Carmone MJ, Bellotti G, Pileggi F. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol.* 1994; 74:70–72. [PubMed: 8017311]
17. Anand I, McMurray J, Cohn JN, et al. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the endothelina receptor antagonist trial in heart failure (earth): Randomised, double-blind, placebo-controlled trial. *Lancet.* 2004; 364:347–354. [PubMed: 15276394]
18. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The flolan international randomized survival trial (first). *Am Heart J.* 1997; 134:44–54. [PubMed: 9266782]
19. Kalra PR, Moon JC, Coats AJ. Do results of the enable (endothelin antagonist bosentan for lowering cardiac events in heart failure) study spell the end for non-selective endothelin antagonism in heart failure? *Int J Cardiol.* 2002; 85:195–197. [PubMed: 12208583]
20. Kaluski E, Cotter G, Leitman M, et al. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systolic dysfunction, associated with secondary pulmonary hypertension—a multi-center randomized study. *Cardiology.* 2008; 109:273–280. [PubMed: 17873492]
21. Actelion. Safety and tolerability of macitentan in subjects with combined pre- and post-capillary pulmonary hypertension due to left ventricular dysfunction (melody-1). 2014 2015.
22. Bonderman D, Ghio S, Felix SB, et al. Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial Study G. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: A phase iib double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation.* 2013; 128:502–511. [PubMed: 23775260]
23. Gheorghiadu M, Greene SJ, Butler J, et al. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. *JAMA.* 2015; 314(21):2251–62. [PubMed: 26547357]
24. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation.* 2007; 116:1555–1562. [PubMed: 17785618]
25. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. *Journal of the American College of Cardiology.* 2007; 50:2136–2144. [PubMed: 18036451]

26. Redfield MM, Chen HH, Bolaug BA, et al. RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: A randomized clinical trial. *JAMA*. 2013; 309:1268–1277. [PubMed: 23478662]
27. Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: Testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *Journal of the American College of Cardiology*. 1992; 19:48–54. [PubMed: 1729345]
28. Pasero D, Rana NK, Bonato R, et al. Inhaled nitric oxide versus sodium nitroprusside for preoperative evaluation of pulmonary hypertension in heart transplant candidates. *Transplantation proceedings*. 2013; 45(7):2746–9. [PubMed: 24034038]
29. Torres Macho J, Delgado Jimenez JF, Sanz Salvo J, et al. Effect of different pharmacologic agents to reverse severe pulmonary hypertension among end-stage heart failure patients. *Transplantation proceedings*. 2009; 41(6):2477–9. [PubMed: 19715956]
30. Sablotzki A, Hentschel T, Hofmann S, Simm A, Muhling J, Czeslick E. Inhaled aerosolized iloprost in the evaluation of heart transplant candidates--experiences with 45 cases. *Journal of clinical anesthesia*. 2006; 18(2):108–13. [PubMed: 16563327]
31. Stevenson LW. Tailored therapy before transplantation for treatment of advanced heart failure: Effective use of vasodilators and diuretics. *J Heart Lung Transplant*. 1991; 10:468–476. [PubMed: 1854776]
32. Stevenson LW. Are hemodynamic goals viable in tailoring heart failure therapy? Hemodynamic goals are relevant. *Circulation*. 2006; 113:1020–1027. discussion 1033. [PubMed: 16490837]
33. Campana C, Alessandrino G, Striuli L, et al. The tailored medical therapy in patients with advanced heart failure referred for cardiac transplantation. *Transplant Proc*. 2008; 40:1999–2000. [PubMed: 18675112]
34. Gracin N, Johnson MR, Spokas D, et al. The use of apache ii scores to select candidates for left ventricular assist device placement. *Acute physiology and chronic health evaluation*. *J Heart Lung Transplant*. 1998; 17:1017–1023. [PubMed: 9811411]
35. Bayram M, De Luca L, Massie MB, Gheorghiadu M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am J Cardiol*. 2005; 96:47G–58G.
36. Hashim T, Sanam K, Revilla-Martinez M, et al. Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. *Circulation Heart Failure*. 2015; 8(5): 880–6. [PubMed: 26179184]
37. Gallagher RC, Kormos RL, Gasior T, Murali S, Griffith BP, Hardesty RL. Univentricular support results in reduction of pulmonary resistance and improved right ventricular function. *ASAIO J*. 1991; 37:M287–288.
38. John R, Liao K, Kamdar F, Eckman P, Boyle A, Colvin-Adams M. Effects on pre- and posttransplant pulmonary hemodynamics in patients with continuous-flow left ventricular assist devices. *J Thoracic Cardiovasc Surg*. 2010; 140:447–452.
39. Smedira NG, Massad MG, Navia J, et al. Pulmonary hypertension is not a risk factor for rvad use and death after left ventricular assist system support. *ASAIO J*. 1996; 42:M733–735. [PubMed: 8944978]
40. Zimpfer D, Zrunek P, Roethy W, et al. Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. *J Thoracic Cardiovasc Surg*. 2007; 133:689–695.
41. Miller LW, Guglin M. Patient selection for ventricular assist devices: a moving target. *Journal of the American College of Cardiology*. 2013; 61(12):1209–21. [PubMed: 23290542]
42. Nair PK, Kormos RL, Teuteberg JJ, et al. Pulsatile left ventricular assist device support as a bridge to decision in patients with end-stage heart failure complicated by pulmonary hypertension. *J Heart Lung Transplant*. 2010; 29:201–208. [PubMed: 20113910]
43. Salzberg SP, Lachat ML, von Harbou K, Zund G, Turina MI. Normalization of high pulmonary vascular resistance with lvad support in heart transplantation candidates. *Eur J Cardiothorac Surg*. 2005; 27:222–225. [PubMed: 15691674]
44. Haft J, Armstrong W, Dyke DB, et al. Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. *Circulation*. 2007; 116:18–15. [PubMed: 17846330]

45. Ozturk P, Engin AY, Nalbantgil S, et al. Comparison of continuous-flow and pulsatile-flow blood pumps on reducing pulmonary artery pressure in patients with fixed pulmonary hypertension. *Artificial organs*. 2013; 37(9):763–7. [PubMed: 24033601]
46. Lam KM, Ennis S, O'Driscoll G, Solis JM, Macgillivray T, Picard MH. Observations from non-invasive measures of right heart hemodynamics in left ventricular assist device patients. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*. 2009; 22:1055–1062. [PubMed: 19647406]
47. Mikus E, Stepanenko A, Krabatsch T, et al. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. *Eur J Cardiothorac Surg*. 2011; 40(4):971–7. [PubMed: 21354812]
48. Kutty RS, Parameshwar J, Lewis C, et al. Use of centrifugal left ventricular assist device as a bridge to candidacy in severe heart failure with secondary pulmonary hypertension. *Eur J Cardiothorac Surg*. 2013; 43(6):1237–42. [PubMed: 23345184]
49. Martin J, Siegenthaler MP, Friesewinkel O, et al. Implantable left ventricular assist device for treatment of pulmonary hypertension in candidates for orthotopic heart transplantation-a preliminary study. *Eur J Cardiothorac Surg*. 2004; 25:971–977. [PubMed: 15144997]
50. Alba AC, Rao V, Ross HJ, et al. Impact of fixed pulmonary hypertension on post-heart transplant outcomes in bridge-to-transplant patients. *J Heart Lung Transplant*. 2010; 29:1253–1258. [PubMed: 20620083]
51. Tedford RJ, Hemnes AR, Russell SD, Champion HC, et al. Pde5a inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. *Circulation: Heart failure*. 2008; 1:213–219. [PubMed: 19808294]
52. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant*. 2013; 32(2):157–87. [PubMed: 23352391]
53. Benza RL, Raina A, Abraham WT, et al. Pulmonary hypertension related to left heart disease: Insight from a wireless implantable hemodynamic monitor. *J Heart Lung Transplant*. 2015; 34:329–337. [PubMed: 24999252]

Figure 1. Hemodynamic Profile in PH Due to LHD

This figure displays the hemodynamic profile in PH due to LHD as: a) normal pulmonary pressures; b) post-capillary PH; and c) "out-of-proportion" PH (all values in mmHg).

Adapted with permission from Egton Medical Information Systems Limited.

Abbreviations: LA, left atrium; LHD, left heart disease; LV, left ventricle; PA, pulmonary artery; PH, pulmonary hypertension; PV, pulmonary vein; RA, right atrium; RV, right ventricle

Figure 2. Pathophysiology of PH Due to LHD

This figure demonstrates the pathophysiology of PH due to LHD, including aspects that are reversible with certain treatments.

Abbreviations: EF ejection fraction; ET-1, endothelin-1; HF, heart failure; LV, left ventricular; LVAD, left ventricular assist device; NO, nitric oxide; RV, right ventricular

Selected studies of Pharmacotherapy for PH

Table 1

Trial	Subjects	Drug	Inclusion Criteria	Primary Endpoint	Study Outcome	Comments
FIRST ¹⁸	471	Epoprostenol: 4.0 ng/kg/min	EF <25%, NYHA III–IV	Survival	Negative	Acute improvements in mPAP, mPCWP, and PVR chronic no improvement in 6MWT, QOL or morbidity
ENABLE ¹⁹	1613	Bosentan: 125 mg bid, 9 mos	EF <35%, NYHA IIIB–IV	All-cause mortality + HF hospitalizations	Negative	Worsening HF on bosentan
EARTH-2 ¹⁷	642	Darusentan: dose range, 24 weeks: 10, 25, 50, 100, 300 mg	EF <35%, NYHA III–IV	Change in left ventricular end-systolic volume measured by MRI	Negative	No significant effect on remodeling of the heart or clinical symptoms
Sildenafil/placebo in HF ²⁴	46	Sildenafil: 6 months, 50 mg tid	<65 years, NYHA II–III, cardiomyopathy, EF <45%	Change in exercise capacity, ventilation efficiency, symptoms	Positive	Improved exercise ventilation and aerobic efficiency
Sildenafil/placebo in HF ²⁵	34	Sildenafil: 12 weeks, 25–75 mg tid	>18 yrs; NYHA II–IV on conventional therapy, EF <40%, mPAP >25 mmHg	Peak VO ₂	Positive	Improved peak VO ₂ , 6MWT, and QOL; decreased HF hospitalizations
LEPHT ²⁰	201	Riociguat: 16 weeks, 0.5–2 mg tid	18–80 yrs; EF <40%, mPAP 25 mmHg	Change in mPAP from baseline to week 16	Negative	Improved cardiac index and pulmonary and systemic vascular resistance

Abbreviations: 6MWT, 6-minute walk time; bid, twice daily; EF, ejection fraction; HF, heart failure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; QOL, quality of life; tid, three times daily; VO₂, volume of oxygen consumption; yrs, years

Table 2

Selected Studies Demonstrating LVAD Effect on PH

Study	Year	Subjects	Devices	PVR (WU)		Mean PAP (mmHg)		TPG (mmHg)	
				Before	After	Before	After	Before	After
Gallagher, et al. ³⁷	1991	16	Novacor (P ¹ / _J)	3.8	1.5	NA	NA	23	12
Smedira, et al. ³⁹	1996	63	HeartMate XVE (P)	5.0	3.7	41	30	24	10
Salzberg, et al. ⁴³	2005	6	Micromed Debakey (C ² / ₂)	5.0	2.1	NA	NA	NA	NA
Haft, et al. ⁴⁴	2007	34	HeartMate XVE (P) HeartMate II (C)	NA	NA	37	20	NA	NA
Zimpfer, et al. ⁴⁰	2007	35	Novacor (P) Micromed Debakey (C) Duraheart (C)	5.1	2.0	46	21	NA	NA
John, et al. ³⁸	2010	50	HeartMate II (C)	3.6	2.1	36.7	22.5	12.6	9.43
Nair, et al. ⁴²	2010	58	Novacor (P) Thoratec LVAD (P) HeartMate XVE (P) Thoratec VAD (P)	2.8	1.6	34.6	21.9	11.7	8.4
Mikus, et al. ⁴⁷	2011	27	Incor (C) HeartMate II (C)	3.5	1.5	37.3	21.0	15.0	5.2
Kutty, et al. ⁴⁸	2013	29	HeartWare HVAD (C) VentrAssist (C)	5	2.1	42	18	14	9

¹P indicates pulsatile-flow left ventricular assist device

²C indicates continuous-flow left ventricular assist device

LVAD, left ventricular assist device; NA, not applicable; VAD, ventricular assist device