Intersection of Pulmonary Hypertension and Right Ventricular Dysfunction in Patients on Left Ventricular Assist Device Support

Is There a Role for Pulmonary Vasodilators?

ABSTRACT: Left ventricular assist devices (LVADs) improve survival and quality of life in patients with advanced heart failure. Despite these benefits, combined post- and precapillary pulmonary hypertension can be particularly problematic in patients on LVAD support, often exacerbating right ventricular (RV) dysfunction. Both persistently elevated pulmonary vascular resistance and RV dysfunction are associated with adverse outcomes, including death after LVAD. These observations have led to significant interest in the use of pulmonary vasodilators to treat pulmonary hypertension and preserve RV function among LVAD-supported patients. Although pulmonary vasodilators are commonly used for the treatment of pulmonary hypertension and RV dysfunction in LVADs, the benefits of this practice remain unclear. The purpose of this review is to highlight the current challenges in managing pulmonary vascular disease and RV dysfunction in patients with heart failure on LVAD support.

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Left ventricular assist devices (LVADs) are increasingly being used for the management of select patients with advanced heart failure (HF). Although survival and quality of life are generally improved with this therapy, elevated pulmonary vascular resistance (PVR) and right ventricular (RV) dysfunction can limit these benefits. Up to 25% of patients with HF and reduced ejection fraction (HFrEF) will have combined post- and precapillary pulmonary hypertension (CPC-PH) or mixed PH, which can be particularly problematic in patients considered for left-sided mechanical support or heart transplant.[1–4] Despite the importance of CPC-PH in advanced HF, controversy remains regarding the best treatment approach.

Although limited data support the medical treatment of PH in advanced HF, several case series suggest that pharmacological or LVAD therapy can improve PVR and facilitate heart transplantation in patients with CPC-PH.[5–17] Although LVADs may improve secondary PH through sustained lowering of left-sided cardiac filling pressures, a subset of patients are left with persistent PH and RV dysfunction, both of which are associated with adverse outcomes.[18–24] These observations have led to significant interest in the use of pulmonary vasodilators to treat PH and preserve RV function among patients supported with LVADs.

To date, several small studies have suggested the benefit of phosphodiesterase type 5 (PDE-5) inhibitors on hemodynamic and echocardiographic measures of RV function in LVAD-supported patients.[20,25–30] Although these observations have fueled the use of pulmonary vasodilators for the treatment of PH and RV dysfunction in LVADs, the benefits of this practice remain unclear. The purpose of this review is to highlight the current challenges in managing the dangerous dyad of

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CPC-PH and RV dysfunction in patients with HF on LVAD support. To facilitate this discussion, we will review the pathogenesis of CPC-PH and the clinical data addressing the role of pulmonary vasodilators in patients with HF, with a focus on patients receiving LVAD support. The relevant outstanding questions and controversies surrounding the management of CPC-PH in patients with LVAD will be highlighted, and future clinical trials of pulmonary vasodilator therapy will be discussed.

PH AND LEFT HEART DISEASE

Left heart disease is the most common cause of PH worldwide. Secondary PH because of left heart disease (World Health Organization Group 2 PH) is defined as the presence of mean pulmonary arterial pressure (mPAP) ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg in the presence of left heart disease. PH occurs in as many as 80% of patients with advanced HF and is associated with adverse clinical outcomes, including diminished exercise capacity, decreased quality of life, and increased mortality.[31–37] Efforts have been made to distinguish CPC-PH from isolated postcapillary PH, or passive PH, on the grounds that the former identifies a high-risk subpopulation in which pulmonary vascular remodeling has occurred.[36,38] Unlike those with isolated postcapillary PH, patients with CPC-PH often are left with persistent PH, despite therapeutic lowering of left-sided filling pressures, which has implications for clinical outcomes after LVAD or heart transplant. This paradigm implies distinct pathophysiologic mechanisms underlying CPC-PH and suggests novel therapeutic targets.

Although the pathogenesis of CPC-PH is not well understood, it has been suggested that high PVR in these patients results from either structural or functional vascular remodeling. Chronic elevation of left-sided filling pressures is thought to trigger pulmonary vascular pathology through mechanical stress in the pulmonary venous system, leading to enhanced endothelin-1 expression, decreased NO availability, and subsequent arterial remodeling.[39–46] Unfortunately, biomarkers, genetic analysis, and imaging studies that specifically identify vascular remodeling have not been adapted in practice, leaving clinical determination of CPC-PH to less-specific hemodynamic surrogates.

Studies have used a PVR >3 WU or transpulmonary gradient >12 to 15 mm Hg to identify patients with pulmonary vascular pathology because these thresholds are associated with increased mortality.[35–38] More specific measures of CPC-PH that are less dependent on cardiac output and filling pressures include diminished pulmonary artery (PA) compliance (PAC) and elevated diastolic pressure gradient (pulmonary artery diastolic pressure–PCWP, >7 mm Hg), both of which predict mortality among patients with HFrEF and PH.[38,47] Low indexed PAC has also been shown to predict RV failure and mortality after LVAD.[48] Current consensus defines CPC-PH as group 2 PH with a diastolic pressure gradient >7 mm Hg or a PVR >3 WU.

Novel approaches are being used to better characterize the physiological and genetic basis of CPC-PH. A recent investigation found that patients with CPC-PH have an increased frequency of gene polymorphisms related to biological pathways implicated in World Health Organization Group 1 PH (pulmonary artery hypertension).[49] These findings suggest a continuum between pulmonary artery hypertension and isolated postcapillary PH with CPC-PH espousing features of both and may support a potential role of pulmonary vasodilators in these patients. Moreover, these data argue that adverse pulmonary vascular remodeling in patients with HF may be determined by the interaction between genetic factors and elevated left heart filling pressures. Importantly, CPC-PH may also represent the confluence of isolated postcapillary PH and either pulmonary artery hypertension, intrinsic lung disease/sleep apnea, or chronic thromboembolic disease. Therefore, appropriate screening for alternative causes of elevated PVR in HF patients with CPC-PH is necessary to ensure appropriate therapy.

TREATMENT OF PH IN LEFT HEART DISEASE

The principle tenet of management for patients with group 2 PH is to target the passive component of PH through maintenance of a low PCWP. Although pulmonary vasodilators may have a role in reversing adverse pulmonary vascular remodeling, there are concerns that these medications may overcome appropriate adaptive changes in the pulmonary vasculature that prevent increased left-sided venous return and pulmonary edema.

Despite these concerns, several studies in patients with HFrEF have demonstrated favorable short-term hemodynamic effects with pulmonary vasodilators. Sildenafil has been shown to acutely lower mPAP, PVR, and systemic vascular resistance while increasing cardiac output in patients with HFrEF and PH, with more robust reductions in PVR and systemic vascular resistance and enhanced cardiac output with coadministration of NO.[25] Short-term epoprostenol has also been shown to reduce PVR, systemic vascular resistance, and PCWP in HFrEF while improving cardiac output.[50] Also, selective endothelin receptor antagonists (ERAs) have been shown to acutely reduce mPAP and PVR without worsening left-sided filling pressures.[51,52]

Further, longitudinal nonrandomized studies have demonstrated beneficial effects of sildenafil on PA pressures, PVR, and cardiac output, as well as exercise capacity, peak VO_2, and patient-reported measures of breathlessness, fatigue, and emotional functioning in patients with HFrEF and PH.[27–30] Low-dose bosentan has

also been associated with improvements in PVR, transpulmonary gradient, and survival among patients with CPC-PH on the transplant waiting list, findings which may have implications in patients on LVAD support.[53]

Large randomized clinical trials have failed to replicate encouraging findings during long-term follow-up (Table).[50,54–61] Sildenafil did not improve VO_2 max or exercise capacity in HF with preserved ejection fraction, even among those with PH, and adversely affected renal function, NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide), and endothelin-1 levels.[60] Another important investigation of tadalafil among patients with HFrEF and secondary PH was terminated because of enrollment difficulties, limiting the randomized patient experience with PDE-5 inhibitors (NCT01910389). The soluble guanylate cyclase stimulator riociguat has also been studied in patients with HFrEF and PH, and although the study failed to meet its primary end point of reduction in mPAP, improvements in cardiac index and PVR were demonstrated.[61] An ongoing investigation of vericiguat in a similar patient population should shed further light on the role of these medications (NCT02861534). ERAs have had neutral-to-harmful effects on clinical outcomes in patients with PH and left heart disease.[54–57] Finally, an investigation of long-term epoprostenol use in HFrEF was abandoned because of a trend toward increased mortality (Table).[50] Lack of clinical benefit with pulmonary vasodilators in HF may be linked to study design limitations, including suboptimal target populations (no studies targeting HFrEF and CPC-PH) and inadequate volume status optimization.

A more specifically targeted study has completed enrollment and aims to assess the safety and tolerability of the ERA macitentan versus placebo in patients with CPC-PH, paving the way for further studies to assess therapeutic benefit (NCT02070991). In the meantime, the substantial cost of therapy and potential risks remain important concerns that argue against widespread use of pulmonary vasodilators in the absence of clear clinical benefit. Further, the lack of an efficacy signal in large-scale clinical investigations has implications for the application of these medications to patients on LVAD support.

REDUCTION IN PH WITH LVADS

LVADs have emerged as an effective modality to improve PH in end-stage HF. Several studies have highlighted substantial improvements in both mPAP and PVR in patients supported with LVADs, allowing for successful heart transplantation in many previously unsuitable candidates with fixed PH.[6–14] The effects of LVAD support on mPAP and PVR can be seen within days and sustained for several months.[6–10,15,16] However, the absence of core laboratory adjudication of pre- and post-LVAD hemodynamics is a major limitation of these studies. Further, use of oral pulmonary vasodilators has often been omitted from reported results, leaving the relative benefits of medications on top of LVAD support unclear.

PERSISTENT PH AFTER LVAD

Although left ventricular (LV) unloading with LVAD support leads to improvements in the passive components of PH and often decreases PVR owing to enhanced cardiac output and improved PAC, many patients on LVAD support are left with persistent PH.[18–20] Tedford et al[20] reported that >40% of patients had persistent PH with a PVR >3 WU at 1 to 2 weeks post-LVAD with several patients having a PVR in excess of 5 WU. More recently, it was shown that among stable outpatients on LVAD support, mPAP was 25.4±8.1 mm Hg (mean transpulmonary gradient, 11.6 mm Hg; mean pulmonary vascular resistance, 2.7 WU), despite reasonable LV unloading (mean pulmonary capillary wedge pressure, 13.8 mm Hg), indicating persistent PH may occur in a significant subset of patients on LVAD support.[19]

RV-PA COUPLING AFTER LVAD

RV dysfunction and RV failure are important determinants of both short- and long-term outcomes after LVAD. Using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definition, RV failure occurs in 20% to 40% of patients after LVAD.[22,24,62,63] Post-LVAD, RV failure is associated with postoperative morbidity, short- and long-term mortality, increased hospital length-of-stay, and lower rates of successful bridging to heart transplant.[21–24] Importantly, RV failure is not restricted to the perioperative period with >10% of patients developing late RV failure, which is also associated with poor prognosis.[63]

The RV and pulmonary vasculature should be considered a coupled unit upstream of the LVAD. It is now appreciated that LVAD implantation itself impacts this unit at many levels that are relevant to clinical management. Immediately after LVAD implantation, a marked increase in systemic venous return because of enhanced cardiac output elevates RV preload. RV preload stress may be further exacerbated by perioperative volume loading with intravenous fluids and blood products. As a result, RV work must dramatically increase to maintain cardiac output. LVAD insertion can also produce unfavorable geometric changes that may worsen RV performance. The RV relies heavily on the LV contribution to septal function and contractility—a reliance that is enhanced in the presence of severe RV dysfunction or PH.[64–66] During LVAD support, the combination of decreased LV contractility and increased RV free wall to septal distance because of LV unloading reduces RV contractility.[66] When RV contractility is impaired and RV preload is elevated, RV work can only be maintained through a reduction in RV after-

Table. Completed Longitudinal Randomized Controlled Trials of Pulmonary Vasodilators in Patients With Heart Failure

Study (Year)	Author	Drug	Inclusion	PH, %	Subjects, n	Study Duration	Primary Outcome	Results
FIRST (1996)	Califf et al[50]	Epoprostenol	HFrEF, NYHA IIIB/IV	NR	471	>36 wk	Survival	Early termination for decreased survival
HEAT (2002)	Lüscher et al[54]	Darusentan	HFrEF, NYHA III	NR	179	3 wk	Hemodynamics (CO, PCWP)	Increased cardiac output, no change in PAP
EARTH (2004)	Anand et al[55]	Darusentan	HFrEF, NYHA IIIB/IV	NR	642	24 wk	Change in LVESV (MRI)	No benefit
ENABLE (2002)	Kalra et al[56]	Bosentan (low dose)*	HFrEF, NYHA IIIB/IV	NR	1613	18 mo	Mortality, hospitalization	No benefit, increased early HF
REACH-1 (2005)	Packer et al[57]	Bosentan (high dose)†	HFrEF, NYHA III/IV	NR	174	26 wk	Change in clinical state	Early termination for fluid retention, elevated LFTs
Guazzi (2007)	Guazzi et al[58]	Sildenafil	HFrEF, NYHA II/III	NR	46	24 wk	Peak VO_2	Improved exercise performance, breathlessness
Guazzi (2011)	Guazzi et al[59]	Sildenafil	PH because of HFpEF	100	44	12 mo	PA pressure/RV function	Improved PAP, RV function
RELAX (2013)	Redfield et al[60]	Sildenafil	HFpEF, NYHA II-IV	53	216	24 wk	Change in peak O_2 consumption	No benefit
LEPHT (2013)	Bonderman et al[61]	Riociguat	PH because of HFrEF	100	201	16 wk	Change in mPAP	No change in PAP, decrease in PVR, increase CI

Data adapted from Fang et al.[32] Ongoing trials: Sildenafil-HF HFrEF/PH. CI indicates cardiac index; CO, cardiac output; EARTH, Endothelin A Receptor Antagonist Trial in Heart Failure; ENABLE, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure; FIRST, Flolan International Randomized Survival Trial; HEAT, Heart Failure ET(A) Receptor Blockade Trial; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LEPHT, Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial; LFT, liver function test; LVESV, left ventricular end systolic volume; MRI, magnetic resonance imaging; NR, not reported; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; REACH-1, Research on Endothelin Antagonist in Chronic Heart Failure; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; and RV, right ventricle.

*125 mg BID.

†500 mg BID.

load. In general, LVAD support will decrease RV afterload owing to a lower PCWP, improved PAC, and often, a fall in PA pressure; however, the presence of CPC-PH can cause persistent RV afterload stress, precipitating RV failure. This is particularly relevant in light of recent data indicating that the RV is more sensitive to afterload stress early after LVAD implant.[67] The unique interplay between PH and RV dysfunction in patients on LVAD support highlights the importance of RV afterload reduction as a strategy to improve clinical outcomes (Figure).

USE OF PULMONARY VASODILATORS IN THE POSTOPERATIVE SETTING AFTER LVAD

In the immediate post-LVAD setting, RV function is optimized by enhancing RV contractility and reducing RV afterload to maintain RV-PA coupling. The former is accomplished through the use of both inotropic support and if necessary, RV assist device placement. Given the poor outcomes associated with RV failure, additional pharmacological measures, such as pulmonary vasodilators, are frequently used to facilitate early weaning of both RV assist device and inotropic support.

Use of pulmonary vasodilators in the immediate postoperative setting has gained favor to reduce RV afterload. Milrinone—a phosphodiesterase type 3 inhibitor frequently used after LVAD for both its positive inotropic effects and vasodilatory properties—has been shown to reduce mPAP after LVAD.[68] Inhaled NO has also been demonstrated to reduce mPAP and improve LVAD flow in patients with persistently elevated PVR.[69] Sildenafil use in the early post-LVAD period is also associated with rapid decreases in PA pressures and may facilitate weaning from inhaled NO and inotropic support.[70,71] Based on several small studies suggesting safety and efficacy and clinical experience supporting use, pulmonary vasodilators are commonly used in the short-term management of patients post-LVAD.

USE OF PULMONARY VASODILATORS DURING LONG-TERM SUPPORT WITH LVADS

The beneficial effects seen with pulmonary vasodilators in the short-term have been extrapolated to long-term

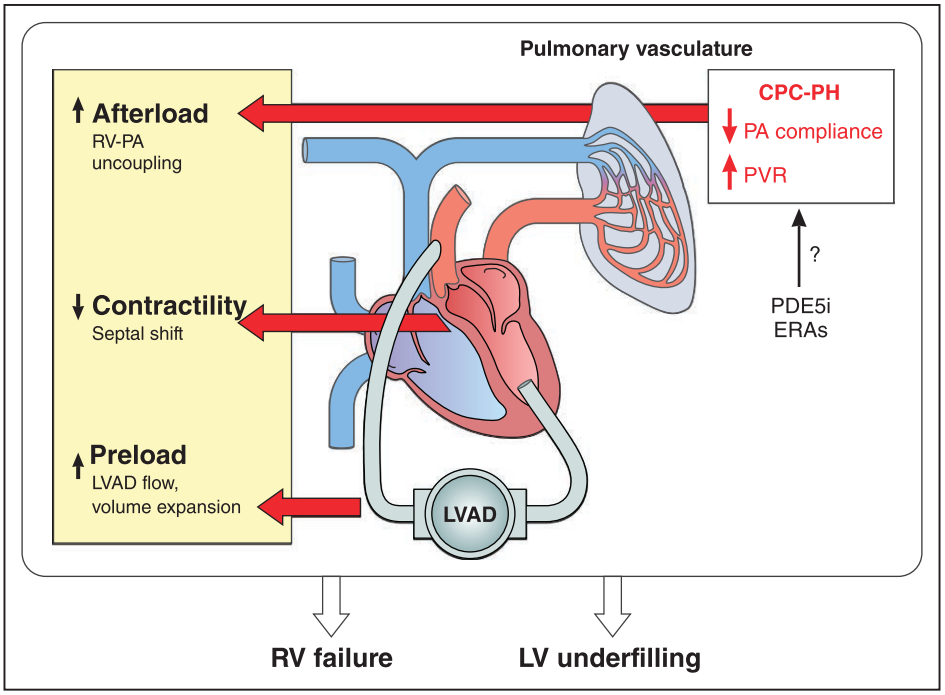

Figure. Interplay between left ventricular assist device (LVAD) support, combined post- and precapillary pulmonary hypertension (CPC-PH), and right ventricular (RV) function.
With LVAD unloading, left-sided filling pressures decrease and systemic venous return is augmented, which together with the infusion of blood products and crystalloid can increase RV preload. As the precapillary component of PH can persist after normalization of left ventricular (LV) filling pressures in those with CPC-PH, the RV also faces a pulmonary vasculature that is less compliant and has a greater resistance. These factors augment RV afterload. LV unloading will also shift septal geometry, which can impair RV contractility. The combination of preload stress, increased afterload, and decreased contractility increases the risk of clinical RV failure and the attendant consequences, including persistent heart failure, hepatic congestion, gastrointestinal bleeding, renal dysfunction, and increased mortality. At the same time, reduced RV-PA coupling leads to LV underfilling, which can result in suck-down events, ventricular arrhythmias, and presyncope/syncope. In patients with CPC-PH, pulmonary vasodilators, such as phosphodiesterase type 5 (PDE-5) inhibitors or endothelin receptor antagonists (ERAs), may reduce pulmonary vascular resistance (PVR) and increase pulmonary artery compliance leading to an improvement in RV-PA coupling. Although unproven, this approach may reduce complications association with impaired RV function in LVAD-supported patients.

management of RV dysfunction and persistent PH in clinical practice. International Society of Heart and Lung Transplant guidelines recommend treating persistent PH and RV dysfunction after LVAD with PDE-5 inhibitors with the caveat that the benefit of this strategy has not been sufficiently proven.[72] As a result, significant heterogeneity exists among LVAD centers in the use of pulmonary vasodilators. The goals of PH treatment in patients with LVAD are 3-fold: (1) reduction of PVR in patients awaiting heart transplant, (2) improvement of symptoms and morbidity associated with chronic RV dysfunction, and (3) prevention of late RV failure and its complications.

Reduction of PVR in Patients Awaiting Orthotopic Heart Transplantation

International Society of Heart and Lung Transplant listing criteria suggest PVR >5 WU or inability to reduce PVR to <2.5 WU with vasodilator challenge without significant hypotension as relative contraindications to heart transplantation because of risk of early graft dysfunction and mortality related to RV failure.[1,4] Numerous studies support the use of LVADs to unload the LV and lower PVR to allow for successful transplantation.[5–17] Unfortunately, many of these studies did not report pulmonary vasodilator use, leaving the role of these medications in improving pulmonary hemodynamics uncertain. In small studies of non-LVAD patients with elevated PVR, pulmonary vasodilators have been used to successfully bridge patients to heart transplant.[2,3] Based on these proof-of-concept, nonrandomized studies, the use of sildenafil has also increased in bridge to transplant patients supported with LVADs.

In the largest clinical study of PDE-5 inhibition in patients with LVAD, Tedford et al[20] identified 58 of 138 patients with a PVR >3 WU 1 to 2 weeks after LVAD implant and treated a subset with sildenafil. Use of sildenafil resulted in marked reductions in PVR (5.87±1.93>2.96±0.92 WU) and mPAP (36.5±8.6>24.3±3.6 mm Hg), whereas patients who did not receive sildenafil had persistently

elevated PVR (>4 WU) at 12 to 15 weeks.[20] Overall, 24 of 26 patients in the treatment group achieved a PVR <3 WU with 19 of these patients becoming eligible for transplant. Although nonrandomized, these data suggest a possible role for pulmonary vasodilators among potential heart transplant candidates with persistent elevations of PVR on LVAD support.[20]

There has also been renewed interest in the use of ERAs for patients with persistent PH after LVAD. In a study of LVAD-supported patients, low-dose bosentan was well tolerated during prolonged therapy and resulted in a reduction in echocardiographically derived PVR from 3.93±1.53 WU in the preoperative setting to 2.58±1.05 WU 3 to 6 months post-LVAD.[18] Although the relative benefits of bosentan on top of LVAD support in this study are unclear, the tolerability of this medication was encouraging.

Improvement of Symptoms and Morbidity Associated With Chronic RV Dysfunction

Many patients who survive post-LVAD RV failure are left with long-term RV dysfunction, and others may develop late RV dysfunction.[22–24,62,63,73–75] Among these patients, low cardiac output can result in fatigue and end-organ dysfunction, whereas elevated right-sided pressures can lead to increased HF hospitalizations, increased diuretic requirements, renal failure, cirrhosis, coagulopathy, malnutrition, and gastrointestinal bleeding.[22,24,60,73–76] Improving PVR and PAC with vasodilators has the potential to restore RV-PA coupling, which could reduce the effects of RV failure.[77] Sildenafil has been associated with improved hemodynamic and echocardiographic measures of RV function in patients with elevated PVR on LVAD support.[20] PDE-5 inhibitors are generally well tolerated in patients with LVAD, and no major adverse drug effects have been reported.[20,78] Bosentan has also been associated with an improvement in right atrial pressure, RV end-diastolic dimension, and RV Tei index in patients on mechanical support.[18] Whether these imaging improvements will translate into a reduction in symptoms related to right-sided congestion (lower extremity edema, ascites, and abdominal pain) or LV underfilling (suck-down events, syncope, and ventricular arrhythmias) will require additional study.

Prevention of Late RV Failure and Its Complications

The occurrence of late RV failure is one of the most challenging complications to manage in LVAD-supported patients. This is particularly problematic for patients in whom transplant is not a viable bailout option. Among this cohort, reduced RV output often results in refractory HF symptoms and recurrent hospitalizations. Additionally, as RV failure worsens, low LVAD flows, reduced pulsatility, and leftward shift of the interventricular septum can occur, resulting in impaired LV filling. This downward spiral is frequently associated with an increased frequency of LVAD alarms, suction events, and ventricular arrhythmias.[22–24,72–74,79] Use of PDE-5 inhibitors and ERAs is common to prevent late RV failure in high-risk patients; however, the safety, efficacy, and relative benefits of these 2 classes of medications are unknown in this challenging population.

OUTSTANDING QUESTIONS AND ONGOING INVESTIGATION

Who Are the Target Populations to Study?

Ongoing clinical trials of group 2 PH are currently aimed at answering the question of whether pulmonary vasodilators are safe and effective in reducing PVR and improving clinical outcomes, particularly in patients with CPC-PH. The SOPRANO (Clinical Study to Assess the Efficacy and Safety of Macitentan in Patients With Pulmonary Hypertension After Left Ventricular Assist Device Implantation) is a multicenter, randomized, placebo-controlled trial currently enrolling patients with CPC-PH on LVAD support to assess the impact of macitentan on pulmonary hemodynamics with a primary outcome of change in PVR from baseline to 3 months (NCT02554903). Patients are eligible for enrollment if they are clinically stable with a mPAP >25 mm Hg, PVR >3 WU, and PCWP <18 mm Hg after LVAD implant. The first step is to determine whether pulmonary vasodilators provide hemodynamic benefit in this population. If successful, a focus on clinical outcomes will be critical. Importantly, the placebo group in this study will provide a previously unseen window into the natural history of CPC-PH in LVAD-supported patients. In order for trials like these to succeed, collaboration and engagement are necessary across the community of LVAD centers to overcome enrollment challenges.

It is important to note that SOPRANO will not evaluate patients with RV dysfunction and milder elevations of PVR—a separate but potentially important additional subgroup for future investigation of pulmonary vasodilators. Where clinical equipoise exists, every effort should be made to enroll eligible patients in ongoing clinical trials or to store patient data in a registry format.

What Is the Most Effective Strategy to Treat PH in Left Heart Disease?

Given the limited data currently available to guide clinical practice, the relative efficacy of different classes of pulmonary vasodilators remains unclear. The car-

diovascular and systemic effects of PDE-5 inhibition include mild reductions in systemic vascular resistance and blood pressure because of systemic vasodilation in addition to pulmonary vasodilation.[80,81] The effects of ERAs are augmented by the presence of endothelin receptors in the myocardium in addition to the pulmonary and systemic vasculature, which may promote fluid retention. It remains unclear whether these differences favor one strategy in the treatment of PH in patients with HF.[82–84] Additionally, combination therapy using both PDE-5 inhibition and ERAs—a favored strategy in the initial management of pulmonary artery hypertension—does not yet have a defined role in the management of CPC-PH. Uncovering the pathways that drive endothelial dysfunction and structural arterial remodeling in patients with CPC-PH will help guide therapy in this patient population. Additionally, more sophisticated phenotyping of patients with CPC-PH may help identify specific subgroups that might benefit more strongly from specific classes of pulmonary vasodilators. The pulmonary vascular disease omics study seeks to identify both novel biomarkers and pathways relevant to pulmonary vascular disease and RV function through assessment of genetic, molecular, and cellular processes to better focus PH management strategies (NCT02980887).

How Should Candidacy and Response to Therapy Be Monitored?

The role of invasive hemodynamic assessment in patients with HF and LVAD remains unclear. Early invasive hemodynamic assessment may identify those patients most likely to benefit from pulmonary vasodilator therapy. If true, routine hemodynamic assessment at prescribed intervals may be warranted to monitor the response to therapy. Of relevance, a recent study found <50% of clinically stable LVAD recipients had optimal hemodynamics, further supporting routine hemodynamic assessment for optimization of both RV-PA coupling and LV unloading among this population.[19] In the future, ambulatory PA pressure monitoring may also have a role in the management of these patients. This strategy is supported by evidence that in HFrEF patients with PH, treatment directed by ambulatory PA pressure monitoring resulted in a reduction in the composite end point of HF hospitalization and mortality.[85] Additional study is warranted for patients on LVAD support.

CONCLUSIONS

CPC-PH is common in the advanced HF population and persists in a subset of patients on LVAD support. Despite active investigation, the role of pulmonary vasodilator therapy in advanced HF and during LVAD support remains unclear at the present time. Large clinical trials in the HF population have been limited by challenges in enrolling the appropriate patients. Moreover, the use of pulmonary vasodilators for the management of PH and RV dysfunction post-LVAD remains largely unexplored. The substantial burden of RV failure in LVAD-supported patients supports ongoing efforts to determine the effects of pulmonary vasodilators in these patients. Future investigation should begin in patients with CPC-PH and expand to target additional groups, particularly those with RV dysfunction. If successful, such approaches have the potential to reduce the burden of pulmonary vascular disease and RV failure in the advanced HF and LVAD population.

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None.

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FOOTNOTES

Circ Heart Fail is available at http://circheartfailure.ahajournals.org.

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Intersection of Pulmonary Hypertension and Right Ventricular Dysfunction in Patients on Left Ventricular Assist Device Support: Is There a Role for Pulmonary Vasodilators?

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