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Pulmonary Hypertension in Advanced Heart Failure: Assessment and Management of the Failing RV and LV

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Abstract

Purpose of Review In patients with heart failure with reduced ejection fraction, the presence of pulmonary hypertension (PH-LHD) has a significant impact on their prognosis. The purpose of this review is to explain the methods of diagnosing PH-LHD and then discuss the available therapeutic options.

Recent Findings We begin by examining the methods of assessment of PH-LHD—echocardiography, cardiopulmonary exercise testing, and right heart catheterization—with a particular focus on the importance of accurate measurement to ensure the proper determination of PH-LHD. We then focus primarily on management of PH-LHD, with an examination of trials of therapeutic options, use of mechanical circulatory support, and transplantation.

Summary This review highlights the complexities in diagnosis and management of PH-LHD. We outline a number of useful ways to maximize the yield of diagnostic testing, as well as give suggestions on the use of medical therapies, the role of both temporary mechanical support and left ventricular assist device, and finally the ways to best bridge these patients to transplantation.

Keywords Pulmonary hypertension · Heart failure · Post capillary · Ventricular dysfunction, left · Ventricular dysfunction, right

Introduction

Heart failure (HF) is a growing problem, with associated morbidity and mortality placing an enormous burden on the healthcare system. Within the overall HF population due to left heart disease, the subset of patients who develop pulmonary hypertension (PH-LHD) is increasingly recognized and at higher risk for poor outcome [1]. Unfortunately, not only are limited treatment options available for this cohort, but the presence of PH-LHD often complicates standard treatment approaches for advanced HF. HF itself is a broad diagnosis, encompassing patients with left ventricular ejection fraction (LVEF) < 40% (heart failure with reduced ejection fraction (HFrEF)), patients with LVEF > 50% (heart failure with preserved ejection fraction (HFpEF)), and patients with isolated valvular lesions. This review will specifically focus on PH in the HFrEF population, outlining the complexity in achieving a diagnosis and the evolving management options.

Definition, Prevalence, and Prognosis

The World Health Organization (WHO) previously defined PH as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, with PH-LHD, also known as WHO Group II PH, defined as a mPAP ≥ 25 mmHg in the setting of a pulmonary artery wedge pressure (PAWP) > 15 mmHg [2]. More recently, the threshold to define PH has decreased from ≥ 25 mmHg to > 20 mmHg [3]. PH-LHD is remarkably common, accounting for 65–80% of all PH

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patients [4] and with the prevalence of PH in the HFrEF population estimated at 40–75% [5–7]. PH is a poor prognostic indicator in all HF patients, with PASP > 45 mmHg on echo being associated with increased 5-year mortality, independent of the severity of HF and other comorbidities [8, 9]. Specifically, in the HFrEF population, those with evidence of PH on RHC had the worst prognosis [5].

Since the initial definition was proposed, advances in our understanding of the pathophysiology have led to a recognition that there is likely a continuum of disease comprising PH-LHD—from elevated left-sided filling pressures causing a direct elevation in pulmonary pressures to long-term elevations in pulmonary pressures leading to secondary pulmonary vascular remodeling [10].

In order to differentiate between these two sub-groups, further hemodynamic variables have been incorporated into the definition of PH-LHD, namely the diastolic pressure gradient (DPG) which is defined as the difference between the diastolic pulmonary artery pressure and the PAWP, and more recently the pulmonary vascular resistance (PVR) defined as the transpulmonary gradient (mPAP-PAWP) divided by the cardiac output.

Isolated post-capillary PH (Ipc-PH), defined as PH-LHD with PVR < 3, represents the majority of PH-LHD, with the predominant causative factor being elevation in left-sided pressures. By comparison, combined post- and pre-capillary PH (Cpc-PH), the group previously referred to as "out-of-proportion" or "reactive" PH-LHD, is defined as PH-LHD with PVR ≥ 3 and occurs in 12–38% of all HF patients [4]. This subdivision has implications across PH-LHD, as the presence of Cpc-PH is associated with increased morbidity and mortality, with potential limitations of and complications with therapeutic options [4] including heart transplantation and left ventricular assist device (LVAD) [11], as we will discuss in detail below.

Diagnosis

Noninvasive Testing

Echocardiography

Echocardiography is one of the mainstays of investigation in LHD in general and in HFrEF specifically. Furthermore, efforts have been made to identify features to diagnose and monitor PH-LHD using routinely acquired echo-Doppler images [12–14]. Direct estimation of pulmonary artery systolic pressure is able to be calculated by adding estimates of right ventricular systolic pressure (calculated by applying the Bernoulli equation to the peak tricuspid regurgitation velocity) and estimates of right atrial pressure (based on a number of factors including inferior vena cava size, tricuspid inflow filling pattern, tricuspid e/e', right atrial volume) [15–19]. Studies have shown a good correlation with invasive hemodynamic measurements [20], with the caveat of high-quality images and Doppler signals. In day-to-day practice, this becomes less accurate as estimates are effected by numerous factors—the technical ability to acquire quality images; tricuspid regurgitation velocity is low, absent, or of poor quality; and when right atrial volume is unable to be assessed or is inaccurately estimated. Furthermore, the presence of an elevated PASP does not inform as to the underlying hemodynamic state, specifically the presence of elevated RV afterload [12].

Given these inherent limitations, many have sought to identify other measures on echo that are more easily reproducible, less prone to measurement error, and more informative as to the state of RV-PA interaction. Parameters including degree of septal flattening, particularly in systole, RV dilatation, and RV to LV ratio, RV apex angle, and RV dysfunction by RV fractional area change or tricuspid annular plane systolic excursion (TAPSE) are routinely available on clinical echocardiography [12]. Furthermore, parameters assessing the pulse-wave Doppler profile in the right ventricular outflow tract (RVOT), including acceleration time, velocity time integral (VTI), and notching profile have been seen as a marker of elevated PVR across the spectrum of PH [12, 21] and correlated with worse prognosis in patients with PAH [22]. More recently, the ratio of TAPSE/PASP has been described as an index of right ventriculo-arterial coupling (independent of LV dysfunction) and shown to be associated with functional capacity and prognosis in HFrEF [23, 24]. Recently, we described the RVOT-VTI/PASP relationship as a noninvasive estimate of PA compliance which stratified patients across the PH spectrum (from Ipc-PH to Cpc-PH to PAH) and was correlated with 6-min walk distance [25].

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET), primarily with standardized exercise minute oxygen consumption (VO_2 max) protocols, is routinely used to prognosticate progression and severity of HFrEF [26, 27]. A study of 320 HFrEF patients showed that PH-LHD was associated with reduced exercise tolerance, with a direct correlation with severity of PH-LHD and degree of exercise impairment [28]. Furthermore, other parameters including ventilatory inefficiency, as expressed by increased minute ventilation to carbon dioxide production (VE/VCO_2), are associated with increased morbidity and mortality in patients with HFrEF and have been linked with severity of RV dysfunction and PH [29, 30].

Based on the above information, we recommend routine transthoracic echocardiography with serial assessment of biventricular structure and function, parameters of RV afterload, and the use of CPET to describe disease pathophysiology, severity, and prognosis in this population.

Invasive Testing

Guidelines indicate that a right heart catheterization (RHC) is needed to definitively make a diagnosis of PH, and in the case of PH-LHD, it is vital in determining not only the diagnosis, but to differentiate between Ipc-PH and Cpc-PH. Although invasive, this procedure is relatively safe and is now routine practice in most centers. The predicament is that the crucial recording—the PAWP—also happens to be the one that is most prone to error in measurement during the procedure. We recommend that extra time and care be taken while documenting the PAWP. We have identified the following three strategies for ensuring an accurate PAWP measurement:

1. Ensuring that the reference level is appropriately set at the mid thoracic position, and that it has been zeroed prior to measurement [31]
2. Confirm catheter tip position with either fluoroscopy or with aspiration and assessment of PAWP blood (ensuing appropriately high oxygenation as representative of PAWP blood)
3. Minimize the effect of respirophasic changes in intrathoracic pressure by measuring the PAWP at the end of the expiratory phase during normal respiration [32]

In addition to standard measurements, PH-LHD is a common situation where additional procedural techniques are performed. There are no standardized protocols though a growing consensus is forming that this testing will assist in both clarifying diagnosis and may aid with tailoring appropriate therapy. The commonly used additional testing maneuvers include:

- *Fluid challenge*: Patients are often on diuretic therapy, which, when combined with peri-procedural fasting, can lead to significantly lower PAWP measurements than are normal for the patient. If this occurs, a small (no more than 500 mL) intravenous fluid challenge can be performed and then hemodynamic measurements reassessed, with specific focus on increases in PAWP and TPG [33]. This can be very helpful in PH-HFpEF and may have less of a pivotal role in PH-HFrEF.
- *Exercise*: Invasive hemodynamic testing during exercise can help illicit if there is exercise-induced PH, the presence of exercise-induced diastolic dysfunction, worsening mitral regurgitation, and relative imbalances in changes in PVR and/or SVR with exercise. The definitive method is to perform an invasive cardiopulmonary exercise test (iCPET), during which the invasive measurement of cardiac output and peripheral oxygen consumption can be correlated with CPET measures to assess if there is truly exercise-induced PH in addition to the resting HFrEF [34].
- *Vasodilator testing*: As will be discussed below, the reversibility of PH-LHD has most traditionally been used in assessing patients for orthotropic heart transplantation (OHT), where a response to vasodilator challenge, defined by a reduction in PA pressures and increase in CO with resultant decrease in PVR, would suggest safety and success of OHT alone. We recommend using intravenous sodium nitroprusside (dose 0.5–1.5 μg/kg/min, titrated in 25–50 μg/min increments) [35] or inhaled nitric oxide (dose 20 to 80 ppm) [36] due to their relatively short half-life and ease of use. We would advise caution with using inhaled nitric oxide, specifically if PAWP is elevated. Alternatives described include intravenous milrinone (dose 50 μg/kg bolus) [37] and intravenous prostaglandin E1 (dose 0.02–0.4 μg/kg/min, titrated upwards in doubling doses) [38].

Management

Optimizing HFrEF Treatment

In our opinion, the main tenet of management in this population is optimization of HFrEF management, with optimization of hemodynamics including reduction in PAWP and LV unloading to allow for improved systemic output. Only in the situations where this fails, and in the context of parameters from the above-described testing, do we consider further interventions (both medical and surgical). Therefore, adequate diuretic therapy, an often under emphasized avenue of therapy, is vital to symptom control. Recently, the CHAMPION trial [39] showed that invasive monitoring of left-sided filling pressures using the pulmonary artery diastolic pressure (as a surrogate marker of PAWP) to guide diuretic therapy reduces heart failure hospitalizations in a homogenous heart failure population. This study has led to much excitement for the potential role of this form on monitor-guided diuretic therapy in PH-LHD, and upcoming studies using the CardioMEMS device may provide more evidence for its future use [40]. In addition to diuretics, the role of optimizing medical therapy, utilizing device therapy, and addressing mitral regurgitation should remain a major focus for both symptomatic and prognostic improvements. We believe that this should include the consideration of long-term inotropic support ("vasodilator conditioning"), which has been shown to significantly reduce PH [41], and may be especially useful in those for consideration of OHT.

Pulmonary Hypertension-Specific Therapy

The use of PH-specific therapy in PH-LHD has always seemed mechanistically viable, considering many similar changes in vasoactive mediators occur in patients with PAH and PH-LHD [42]. This has led to a number of trials being performed to test this treatment avenue, and we have summarized these in Table 1.

Table 1 Summary of Clinical Trials of Pulmonary Hypertension Specific Therapy in Heart Failure

Study name	Year	Drug studied	Patient population	Number of subjects	Primary outcome	Result
FIRST [41]	1996	IV epoprostenol	NYHA class IIIB/IV, no specific requirement for PH	471	Mortality	Terminated early due to mortality
HEAT [42]	2002	Darusentan	NYHA class III, no specific requirement for PH	179	Change in invasive hemodynamics	Improvement in cardiac output with no change in PA pressures
EARTH [43]	2004	Darusentan	NYHA class IIIB/IV, no specific requirement for PH	642	Change in LV size	No benefit
REACH-1 [44]	2005	Bosentan (500 mg twice a day)	NYHA class III/IV, no specific requirement for PH	174	Improvement in HF symptoms	Early termination, although trend to benefit in those that completed study
Guazzi [45]	2007	Sildenafil	NYHA class II/III, no specific requirement for PH	46	Peak VO_2	Improved exercise capacity
Guazzi [46]	2011	Sildenafil	NYHA class II/III, no specific requirement for PH	45	Diastolic function, cardiac geometry, exercise capacity	Improvement in all parameters
LEPHT [47]	2013	Riociguat	LV ejection fraction $\leq 40\%$, mPAP ≥ 25 mmHg by right heart catheterization	201	Change in mPAP	No benefit
PITCH-HF [48]	2014	Tadalafil	NYHA class II/III, documented PH within 6 months	23	Mortality and HF hospitalizations	Terminated due to poor enrolment
SIL-HF [49]	2014	Sildenafil	NYHA class II/III, SPAP > 40 mmHg on TTE	75	Patient-reported symptoms, 6 min walk test	Enrolment complete, results pending
ENABLE [50]	2017	Bosentan (125 mg twice a day)	NYHA class IIIB/IV, no specific requirement for PH	1613	Mortality	No benefit
MELODY-1 [51]	2018	Macitentan	HFrEF, NYHA class II/III, Cpc-PH by right heart catheterization	63	Safety (fluid retention or worsening NYHA class)	Increased fluid retention in study arm

Initial clinical trials using intravenous prostacyclins [43]; darusentan, a selective endothelin A antagonist [44, 50]; and bosentan, a dual endothelin A and B antagonist [52, 53], were negative, although it is important to note these studies included all HFrEF patients, failed to focus specifically on the PH-LHD population, and often studied dosing several times higher than those used in PAH.

Further studies have been performed to assess the use of sildenafil, a PDE5 inhibitor, in this population. This was based on initial data showing that sildenafil acutely reduces mPAP and PVR when co-administered with inhaled nitric oxide [45]. In a single-arm, open-label study of 13 patients with HFrEF, Lewis et al. showed a significant improvement in hemodynamics and CPET parameters including VO_2 and VE/VCO_2 after 50 mg of sildenafil [46]. Guazzi et al. prospectively studied the role of sildenafil in HFrEF in a single-center, randomized trial and showed improvements in hemodynamics, echocardiographic markers of left ventricular diastolic function, and cardiac geometry, as well as functional status (by CPET) and quality of life [48, 49]. Larger randomized, double-blind placebo-controlled trials with PDE5 inhibitors were then begun, but have been plagued by poor recruitment and funding. PITCH-HF [47], evaluating tadalafil, was terminated due to enrollment difficulties, while SIL-HF [51], a small multicenter trial of 78 patients, assessing sildenafil, has just finished recruitment.

Finally, two studies using other PH-specific therapy have recently been published. LEPHT [54], a study using riociguat, a nitric oxide pathway soluble guanylate cyclase stimulator, was performed which also failed to show any significant reduction in PAP or PVR after 16 weeks of treatment. MELODY-1 [55], which was a phase II exploratory study in the Cpc-PH population using macitentan, a dual endothelin A and B antagonist, showed increased fluid retention in the treatment arm within 4 weeks of starting therapy. Thus, at this time, large multicenter data are lacking supporting the use of PH-specific therapy in HFrEF.

Mechanical Circulatory Support

Temporary Mechanical Circulatory Support

There have been recent advances in technology in the development of devices for temporary mechanical circulatory support (MCS), but the majority are focused at LV support which is insufficient in patients with PH-LHD who will often require simultaneous support for both the LV and the RV. There are two percutaneous devices that are approved for percutaneous temporary RV support—the Impella RP (Abiomed Inc., Danvers, MA) and the Tandem Heart RVAD/Protek Duo (TandemLife, Pittsburgh, PA)—which have both being used in conjunction with percutaneous LV support. Both of these devices are configured to bypass the RV, mechanically moving blood from the RA to PA, which has the net effect of increasing the mPAP [56] and therefore may introduce difficulty in managing patients with PH-LHD.

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is configured to bypass the whole heart and mechanically moves blood from the RA to the femoral artery. This configuration has no direct effect on the mPAP, but has been well described to have an increase in LV afterload resulting in increased PAWP, which in turn can cause increased mPAP. As such, we recommend approaching the use of temporary MCS in PH-LHD with caution, and if faced with this situation, our strategy is to use VA-ECMO as our primary temporary MCS platform with careful monitoring of PA pressures and a low threshold for the addition of a second device (such as Intra-aortic Balloon Pump [57], Impella LV device [58], transeptal puncture [59], or direct LV drainage [60]) to decompress the left ventricle.

Durable Mechanical Support

Left ventricular assist device (LVAD) therapy has become a mainstay in the treatment of end-stage HFrEF, with multiple devices now FDA approved for both bridge-to-transplant (BTT) and destination therapy (DT) indications [61]. Pre-implant PH-LHD has been identified as a risk factor for both 30-day mortality [62] and risk of early right heart failure post-LVAD implant [63]. Several markers of RV-PA uncoupling pre-LVAD implantation have been described as predictive of RV failure post-LVAD including right atrial pressure (RAP), RAP/PAWP ratio, PA pulsatility index (PAPi; PA pulse pressure/RAP), and indexed PA compliance [64]. Despite much study, RV failure post-LVAD, both early and late, remain an Achilles heel of isolated LVAD technology, with poorly performing predictive models when applied to external validation cohorts [65].

Many studies over the years have shown reversal of PH-LHD with LVAD support thought to impact both acute mechanical unloading of the left ventricle and the persistent reduction in filling pressures postulated to lead to reverse remodeling of the pulmonary vasculature as seen in Cpc-PH. This has been shown in a number of single-center observational studies in the pre-transplant population [66–68] and in a more recent study which showed significant reduction in PH when compared to medical therapy in a similar population [69].

In a recent study, Tsukashita et al. [70] compared outcomes of patients who underwent BTT LVAD support and dichotomized them by pre-LVAD PVR (low and high; $<$ and ≥ 5 Wood units [WU], respectively). While LVAD placement led to a reduction of PVR in the high PVR group to a level similar to that of the low PVR group (<3 WU), there was an increase in 30-day post-OHT mortality in the pre-LVAD high PVR group, with a pre-LVAD PVR ≥ 5 WU strongly associated

with early mortality (odds ratio, 5.99; 95% confidence interval, 1.25–28.9; $P < .05$). More recently, Imamura et al. [71, 72] highlighted the prognostic importance of a sustained or de novo DPG elevation after LVAD placement and with ramp study. This underscores the notion that LVAD therapy does not uniformly address the underlying pulmonary vascular abnormalities, requiring us to better hone our understanding and abilities in the assessment and management of these patients.

In an effort to address this, both inhaled milrinone [73] and inhaled NO [74] have been used in the early post-LVAD period to successfully reduce mPAP. Despite the clear hemodynamic effects, Potapov et al. [75] showed that inhaled NO did not show any benefit in preventing right ventricular dysfunction, duration of mechanical ventilation, length of stay, or the need for mechanical right ventricular support after LVAD implantation.

In the group that are successfully supported through the early post-operative period, the majority of patients appear to reduce the degree of PH-LHD over time with LVAD support. However, there is a subgroup that do not seem to achieve this benefit, and there is still no consensus as to the ideal treatment modality for this group. There have been several small, mostly single-center trials evaluating the role of sildenafil after LVAD placement. For example, Tedford et al. [76] performed a single-center study where they identified patients who did not normalize their PVR within 1 month of implant who received sildenafil as compared to those who did not. In this small, non-randomized study, sildenafil treatment ($n = 26$) led to a significant reduction mPAP, improved CO, and reduction in PVR. This and other similar data led to the International Society for Heart and Lung Transplantation (ISHLT) recommending the use of PDE-5 inhibitors in patients with RV dysfunction and PH post-LVAD (Class IIb, Level of Evidence C) [77]. Additionally, there has been interest in the role of other agents including bosentan for the treatment of PH after LVAD implantation [78] and the ongoing SOPRANO trial (Clinical Study to Assess the Efficacy and Safety of Macitentan in Patients with Pulmonary Hypertension After Left Ventricular Assist Device Implantation) [79] which aims to assess the efficacy of the macitentan in those with persistent Cpc-PH after LVAD implantation.

Thus, while the data suggest that LVAD therapy is associated with improvements in cardiopulmonary hemodynamics both acutely and over time, there are patients who have persistent PH and/or RV failure (early or late) after LVAD implantation. While several smaller trials suggest hemodynamic benefit from the use of PH-specific therapy, and we use such therapy in isolated cases, there is currently a lack of large, randomized data to support its use more broadly across this population. Finally, in patients with severe biventricular failure precluding LVAD alone and/or RV failure post-LVAD, the use of durable mechanical RV support (i.e., Heartware HVAD (Medtronic, Minneapolis, MN) [80, 81] and Heartmate 3 (Abbott, Abbott Park, IL) [82] in the right-sided position) is becoming more widespread. As these pumps are not designed for the RV, questions remain about optimal placement (RA vs RV cannulation), impact of RV trabeculations, avoidance of pulmonary overflow, and potential for suction events in the lower pressure and more compliant right ventricle, with relatively poor outcomes in this population [56]. Prior use of the Syncardia Total Artificial Heart (SynCardia Systems, Tucson, AZ) has been limited by its large size, mechanical failure, diminished quality of life compared with continuous flow pumps, and lack of temporary use as it requires ventricular excision, among other issues.

Transplantation

Despite advances in LVAD technology and outcomes, OHT is still considered the definitive treatment for end-stage HFrEF. Unfortunately, patients with PH-LHD have significantly worse outcomes post transplantation, with RV failure accounting for nearly 20% of early deaths after OHT [83]. In the early 1990s, the Stanford program identified key hemodynamic markers associated with improved survival despite the presence of PH pre-OHT [35]. Specifically, they assessed the role of nitroprusside challenge on those with PVR > 2.5 WU and found that those with reversibility of their PVR to < 2.5 WU while maintaining a systolic blood pressure > 85 mmHg had similar survival to those without PH. Conversely, those who did not reverse their PVR < 2.5 WU or did so with a concomitant decrease in systemic blood pressure to < 85 mmHg had significantly higher risk of mortality due to RV failure at 3 months (33%; 14% related to RV failure vs 6%). As we discussed earlier, agents such as inhaled NO and prostacyclins are commonly used to assess response of PVR prior to OHT. The ISHLT guidelines also suggest the use of intra-aortic balloon pump to augment output and reduce PVR [84], although there are no studies that show a sustained reduction in PVR and many centers not prefer to progress directly to LVAD implantation.

An analysis of the United Network for Organ Sharing (UNOS) registry in 2012 [85] showed that pre-transplant PVR of > 2.5 WU was an independent predictor of mortality, although interestingly the degree of elevation of PVR above this threshold did appear not increase mortality in a linear fashion. More recently, Tedford et al. evaluated the prognostic role of the DPG to predict post-OHT survival. In this UNOS analysis, they found that an elevated DPG at various cut points, nor TPG or PVR predicted survival post-OHT. Of note, as this was a UNOS analysis, it evaluated these parameters in patients who were "cleared" for and had undergone transplant, thus a selected population that presumably had shown encouraging hemodynamic responses to reversibility testing previously. Taken together, these studies and the approach of the guidelines underscore the fact that evaluation of PH-LHD in the context of OHT must be dynamic,

provocative, and serial, such that reliance on one specific parameter to characterize the degree/type of PH prior to OHT is inadequate. The most recent ISHLT guidelines have suggested a stepwise approach to the transplant candidate with an elevated PVR, which we have summarized in Fig. 1.

Our practice is to carefully and serially assess patients with PH-LHD who are being considered for OHT. In addition to nitroprusside challenge, we will often tailor medical therapy with the help of an indwelling PA catheter. This entails the use of inodilator support (milrinone), standard vasodilators used in HFrEF along with selected use of sildenafil to ensure that the PVR remains < 3 WU, which is based on a number of single-center studies that have used this in the pre-OHT population [86, 87]. In those patients who have ongoing elevated PVR, we will then consider the appropriateness of long-term mechanical support and implant an LVAD with intent to list for transplant after normalization of the PVR. In those patients who undergo OHT despite the presence of PH-LHD (deemed reversible with PVR < 3 WU), we have a detailed perioperative management protocol that involves the use of inhaled NO or inhaled Flolan with a slow wean, while optimizing ventilator support for longer than typical post-OHT to prevent hypoxic vasoconstriction. We also carefully monitor hemodynamics while titrating vasoactive support, diuresis, and often reinitiation of sildenafil should there be signs of RAP elevation, RV dysfunction, CO reduction, and/or PVR elevation. If there is early graft dysfunction (whether LV, RV, or both), careful consideration is given to mechanical unloading with intra-aortic balloon pump or EMCO support. These measures are in place to ensure optimization of RV preload, afterload, coronary perfusion, and pulmonary mechanics [88].

Finally, in those patients whom the PVR remains elevated, and without a viable mechanical support option as may be the case in the congenital population, selected patients may be eligible for combined heart-lung transplantation. This option, however, is not without significant pitfalls, as this procedure is performed at only a select number of centers and has a high post-operative morbidity and mortality when compared to

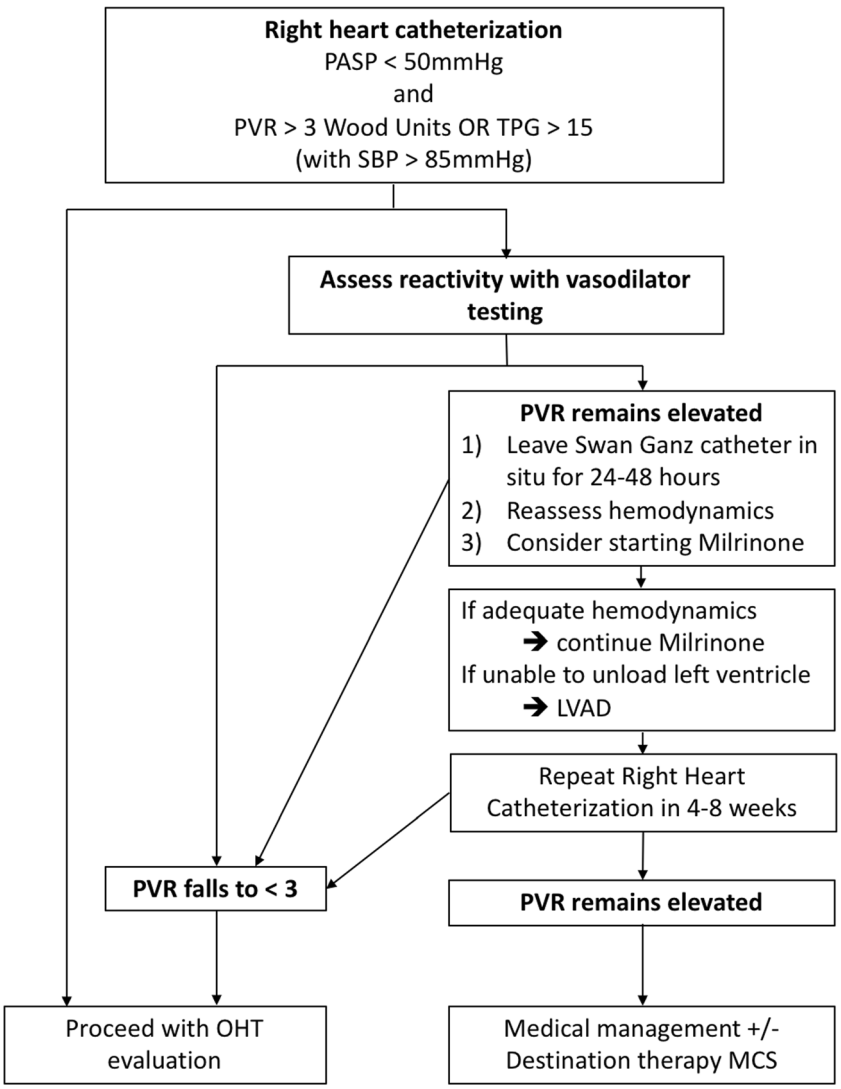

Fig. 1 Proposed investigation and management algorithm for patients with PH-LHD being assessed for advanced therapies

OHT. In fact, in a recent ISHLT report [89], only 58 procedures were reported in 2016. Interestingly, while the majority of patients undergoing this procedure are young, nearly 1/3 of recipients in North America between 2004 and 2017 were over the age of 50. The median survival for heart-lung transplant recipients has improved over the last 30 years, currently 5.8 years for those transplanted between 2004 and June 2016—a figure significantly less than that of OHT alone. Therefore, we believe it should be reserved for those in which all other options have been exhausted, and in particular those who are unable to undergo LVAD implantation due to technical/anatomical reasons.

Conclusion and Future Directions

As the above review has shown, PH-LHD remains a significant issue in the context of advanced HFrEF and one that complicates many treatment options in this population. Further studies, including the SIL-HF trial which has completed recruitment but has yet to report, along with the recently opened SILHF-US study [90] and ongoing SOPRANO trial [79], may help grow our knowledge in the field. Finally, the recent launch of the PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) [91] initiative will hopefully allow us to gain further insight into the "omics" (including genomics, transcriptomics, proteomics, metabolomics, coagulomics, and cell biomics) across the spectrum of pulmonary vascular disease to one day actualize the promise of personalized medicine for our patients with advanced cardiopulmonary disease.

Compliance with Ethical Standards

Conflict of Interest Sriram D. Rao and Jonathan N. Menachem declare no conflict of interest. Dr. Birati reports personal fees from Luitpold Pharmaceuticals, Inc. Dr. Mazurek reports personal fees from Actelion Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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