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STATE OF ART: ISHLT SUMMARY STATEMENT

World Health Organization Pulmonary Hypertension Group 2: Pulmonary hypertension due to left heart disease in the adult—a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation

James C. Fang, MD,[a] Teresa DeMarco, MD,[b] Michael M. Givertz, MD,[c] Barry A. Borlaug, MD,[d] Gregory D. Lewis, MD,[e] J. Eduardo Rame, MD, Mphil,[f] Mardi Gomberg-Maitland, MD, MSc,[g] Srinivas Murali, MD,[h] Robert P. Frantz, MD,[i] Dana McGlothlin, MD,[j] Evelyn M. Horn, MD,[k] and Raymond L. Benza, MD[l]

[a]From the Division of Cardiovascular Medicine, Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, Ohio; the [b]Division of Cardiology, University of California, San Francisco, California; the [c]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the [d]Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, Minnesota; the [e]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; the [f]Cardiovascular Research Institute, University of Pennsylvania, Philadelphia, Pennsylvania; the [g]Department of Medicine, University of Chicago Medical Center, Chicago, Illinois; the [h]Gerald McGinnis Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania; the [i]Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, Minnesota; the [j]Division of Cardiology, University of California, San Francisco, San Francisco, California; the [k]Perkin Heart Failure Center, Weill Cornell Medical College, New York, New York; and the [l]The Gerald McGinnis Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania.

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Pulmonary hypertension associated with left heart disease is the most common form of pulmonary hypertension encountered in clinical practice today. Although frequently a target of therapy, its pathophysiology remains poorly understood and its treatment remains undefined. Pulmonary hypertension in the context of left heart disease is a marker of worse prognosis and disease severity, but whether its primary treatment is beneficial or harmful is unknown. An important step to the future study of this important clinical problem will be to standardize definitions across disciplines to facilitate an evidence base that is interpretable and applicable to clinical practice. In this current statement, we provide an extensive review and interpretation of the current available literature to guide current practice and future investigation. At the request of the Pulmonary Hypertension (PH) Council of the International Society for Heart and Lung Transplantation (ISHLT), a writing group was assembled and tasked to put forth this document as described above. The review process was facilitated through the peer review process of the *Journal of Heart and Lung Transplantation* and ultimately endorsed by the leadership of the ISHLT PH Council.

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Overview

Pulmonary hypertension (PH) is a consequence of an increase in pulmonary vascular resistance (PVR), pulmonary blood flow, pulmonary venous pressure (PVP), or a combination of these elements (Table 1). Generally, a mean pul-

Reprint requests: James C. Fang, MD, Case Western Reserve University, Cardiovascular Division, 11100 Euclid Ave, Lakeside 3001, Cleveland, OH 44120. Telephone: 216-844-8242. Fax: 216-844-8318.

E-mail address: james.fang@uhhospitals.org

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Table 1 (A) World Health Organization Classification for Pulmonary Hypertension

Group	Description	Example
1	Pulmonary arterial hypertension	Idiopathic PAH
2	PH owing to left heart disease	Mitral stenosis
3	PH owing to lung diseases and/or hypoxemia	COPD
4	Chronic thromboembolic PH	Chronic pulmonary embolism
5	PH with unclear or multifactorial mechanisms	Histiocytosis X

COPD, Chronic obstructive pulmonary disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

monary arterial pressure (mPAP) > 25 mm Hg[1] in the presence of an abnormally elevated pulmonary capillary wedge pressure (PCWP > 15 mm Hg) or left ventricular (LV) end-diastolic pressure (LVEDP > 18 mm Hg)[2] is required to define PH secondary to LV dysfunction (LVD) or some other form of left heart disease (LHD). The PCWP threshold defines the 95% upper limit of normal, as reported in a thorough systematic review of normal hemodynamic values.[3]

In this situation, pulmonary venous congestion is the primary determinant of an increased PAP. Therefore, the accurate measurement of LV filling pressure becomes the most critical aspect of defining the nature of PH. If the transpulmonary pressure gradient (TPG = mPAP – PCWP) is normal (< 10 mm Hg) and the PVR is not elevated (< 1.5 Wood Units [WU]),[3] the increase in PAP is of a "passive" or "congestive" nature, also known as post-capillary PH or pulmonary venous hypertension (PVH). Commonly, the pulmonary arterial diastolic pressure will then also fall within 2 to 3 mm Hg of the LVEDP. For the purposes of this review, we will refer to this description as passive PH. This type of PH (eg, World Health Organization [WHO] Group 2) is to be distinguished from primary pulmonary arterial hypertension (PAH) where there is no concomitant increase in LV filling pressure (ie, pre-capillary PH).

The PVR or TPG may, however, be abnormally increased (eg, PVR > 1.5 WU and/or TPG > 12 mm Hg) in the setting of an increased left-sided filling pressure, producing a "mixed" picture with hemodynamic features of both PVH and PAH. In clinical practice, this scenario is often referred to as PH out of proportion to the LV filling pressure. For the purposes of this review, we will refer to this definition as mixed PH. The increase in PAP in this situation is a reflection of both pulmonary arterial vasoconstriction ("acutely reversible") and fixed or non-reactive anatomic pulmonary arteriolar and venous narrowing/remodeling ("acutely irreversible"), combined with the elevation in PVP due to elevated left heart filling pressures.

It is important to acknowledge that these definitions and thresholds are not uniform in practice or in the published literature (Table 1B and Table 2). In general, they have been extrapolated from small observational cohorts and random clinical experiences (usually obtained with patients resting supine) rather than from a large prospective evidence base. In fact, there is no clear consensus how race, sex, activity, body position, and age affect these definitions. For example, the normal resting supine mPAP is rarely > 20 mm Hg but the normal peak mPAP with exercise does increase with increasing age.[3] Moreover, many clinicians view a modest increase in PVR (eg, PVR 1.5–2.5 WU) in heart failure (HF) of minimal prognostic importance, but this has not been firmly established. These issues are important limitations to the interpretation and study of PH-LHD.

Broadly, the category of LHD and concomitant HF is the most common cause of PH.[4] In the updated classification of PH from the Fourth World Symposium at Dana Point,[5] the increased recognition of HF with preserved ejection fraction (EF), so-called diastolic HF, led to a modification of the WHO Group 2 (PH owing to LHD) sub-categories to include three distinct etiologies: left heart systolic dysfunction, left heart diastolic dysfunction, and left heart valvular disease (Figure 1). In clinical practice, more than one of these categories is often present in a particular case of PH-LHD.

PH in LHD has a highly variable prevalence and can be viewed as a "symptom" of LHD. In large part, this variability reflects (1) the severity (and duration) of the LHD, (2) the degree of hemodynamic decompensation, and (3) the pulmonary vascular response to 1 and 2.[6] Consequently, studies have varied in sample size, duration of follow-up, concomitant medical therapy, and nature of the LHD. Not surprisingly, PH-LHD is invariably accompanied with greater disability and decreased survival.[7] Furthermore, as the severity of HF increases, mixed PH (ie, an elevated PVR with an increase in PCWP) is more likely to be present.[8] Although concomitant causes of pulmonary vascular disease (eg, sleep-disordered breathing, pulmonary disorders, chronic pulmonary embolism) should be sought in such situations, most cases are ultimately due to chronic untreated passive PH.[4] Not surprisingly, exhaustion or failure of the right ventricle (RV) as a consequence of overwhelming afterload from PH is particularly ominous.[9] As will be discussed later, the cornerstone of therapy therefore becomes correction of the LHD. The efficacy and safety of selective pulmonary vasodilators combined with maximizing the treatment of LHD remains understudied and is largely unknown.

Pathophysiology

PH is common in patients with HF and reduced LVEF (HFrEF)[7] and those with HF and preserved ejection fraction (HFpEF).[10] As discussed previously, the common underlying pathophysiology is a chronic increase in left atrial pressure that causes a *passive* increase in PVP. In turn, *reactive* vasoconstriction in the pulmonary arterial bed increases PAPs beyond what is expected from the left atrial pressure alone whether at rest, with exercise, or both.[11,12] However, vasoconstriction is neither inevitable nor inexorable and is

Table 1 (B) Definitions Used in the Description of Pulmonary Hypertension

Nomenclature	Description	Physiologic definition	Hemodynamic criteria in literature
Pulmonary hypertension (PH)	Sustained elevation of PAP at rest	Pre-capillary, post-capillary, mixed, high flow state	Mean PAP $\geq$ 25 mm Hg (2 SD above normal)
Pulmonary arterial hypertension (PAH)	PH with "normal" left-sided filling pressure	Pre-capillary vasoconstriction, remodeling, thrombosis-in-situ	Mean PAP $\geq$ 25 mm Hg PCW, LAP, LVEDP $\leq$ 15 mm Hg PVR $>$ 3 WU
Pulmonary venous hypertension (PVH)	PH with elevated left-sided filling pressure	Post-capillary passive congestion	Mean PAP $\geq$ 25 mm Hg PCW, LAP, LVEDP $>$ 15 mm Hg TPG $\leq$ 12–15 mm Hg PVR $\leq$ 2.5–3.0 WU
Mixed PH or PH out-of-proportion to left-sided filling pressure	PH with elevated left-sided filling pressure and elevated pulmonary vascular resistance (PVH + PAH)	Pre- and post-capillary (passive congestion with excessive arterial vasoconstriction $\pm$ vascular remodeling)	Mean PAP $\geq$ 25 mm Hg PCW, LAP, LVEDP $>$ 15 mm Hg TPG $>$ 12–15 mm Hg PVR $>$ 2.5–3.0 WU
Reversible, reactive, or vasoreactive PH	Component of mixed PH that is acutely or chronically responsive to pharmacologic (diuretics, vasodilators, inodilators) and/or mechanical circulatory support device therapies		With vasodilators/inodilators: TPG $\leq$ 12–15 mm Hg PVR $\leq$ 2.5–3.0 WU
Irreversible, fixed, refractory, or persistent PH	Component of mixed PH that is not responsive to above strategies		Despite vasodilators/inodilators: TPG $>$ 12–15 mm Hg PVR $>$ 2.5–3.0 WU
High-flow PH	PH with high cardiac output state or high pulmonary flow	Pre-, post-, or mixed depending on etiology (eg, AV shunt, chronic anemia, thyrotoxicosis, nutritional or obesity, cardiomyopathies, congenital heart disease)	Mean PAP $\geq$ 25 mm Hg PCWP, LAP, LVEDP variable TPG variable PVR variable High cardiac output

AV, arteriovenous; LAP, left atrial pressure; LVEDP, left ventricular end diastolic pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, peripheral vascular resistance; SD, standard deviation; TPG, transpulmonary gradient (mean PAP – PAWP).

likely related to the duration and severity of the LHD. The PAP further depends on the status of the RV, such that marked elevation in PAPs can develop slowly along with RV hypertrophy as long as RV stroke volume is preserved.

Table 2 Normal Hemodynamics at Rest (Supine)

Variable	Mean $\pm$ SD
PAP, mm Hg	
Mean	14.0 $\pm$ 3.3
Systolic	20.8 $\pm$ 4.4
Diastolic	8.8 $\pm$ 3.0
PCWP, mm Hg	8.0 $\pm$ 2.9
Heart rate, beats/min	76 $\pm$ 14
Cardiac index, liters/min/m^2	4.1 $\pm$ 1.3
PVR, dynes $\cdot$ sec/cm^5	74 $\pm$ 30 ($<$1 WU)

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, peripheral vascular resistance; SD, standard deviation.
N = 882 healthy volunteers.
Adapted from Kovacs et al.[3]

Moreover, it is important to recognize the pulsatile component (relative to resistive load) of the total RV afterload may be particularly enhanced by an elevated PCWP, setting the stage for RV dysfunction.[13] In patients with end-stage biventricular HF, PAPs may actually decrease despite marked elevation in PVR, reflecting a fall in RV stroke volume.[14] As noted above, RV dilation and contractile dys-

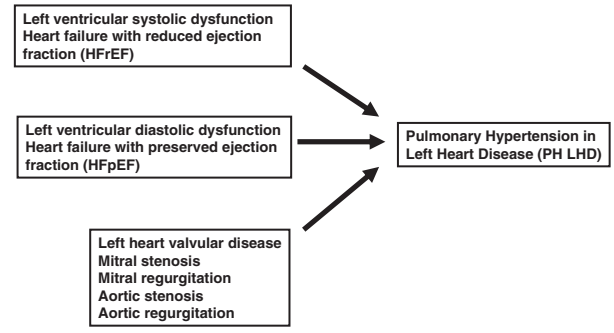

Figure 1 World Health Organization Pulmonary Hypertension Group 2.

function, along with secondary tricuspid regurgitation, are associated with poor survival (see Haddad et al[15,16] for a comprehensive review of RV failure in cardiovascular disease).

In most patients with PH-LHD, reactive pulmonary vasoconstriction may be reversed if the underlying cause of the PVH is corrected (eg, mitral valvuloplasty for mitral stenosis, diuretics for volume overload). With time, however, structural changes of the pulmonary arterial wall may occur. These changes are similar to, but often less severe, than those seen in PAH, and include abnormalities of elastic fibers, intimal fibrosis, and medial hypertrophy, although without the most advanced plexogenic lesions. Together, this pathologic "remodeling" of the arterial wall contributes to decreased vasodilator responsiveness. In addition, pulmonary occlusive venopathy with fibrous intimal thickening, lymphatic dilation, congested alveolar capillaries, and focal thickening of alveolar septa have been described and can exacerbate arterial remodeling.[17] The time course of these pathologic changes is highly variable due to genetic and biologic factors. For example, insulin resistance with decreased peroxisome proliferator-activated receptor-γ activation can accelerate this process in HF.[18] Similarly, adiponectin deficiency has been associated with PH, and type 2 diabetes mellitus and adiponectin deficiency both may be factors associated with HFpEF and PH. Hypoxemia due to pulmonary congestion, associated obstructive or central sleep apnea, or other pulmonary processes may exacerbate PH in left HF.

Several underlying mechanisms contribute to functional and structural alterations of the pulmonary vasculature and resemble changes seen in primary PAH. Studies in experimental models and in patients suggest that nitric oxide (NO)-dependent pulmonary vasodilation is impaired in HF. In vitro, pulmonary artery segments from rats with ischemic HF have impaired vasodilator response to acetylcholine.[19] In vivo, HF patients demonstrate an attenuated vasoconstrictor response to NO synthase (NOS) inhibition.[20] Decreased sensitivity of the pulmonary circulation to other cyclic guanosine monophosphate-dependent vasodilators, such as brain natriuretic peptide, also exacerbates PH in systolic HF and is reversible with phosphodiesterase (PDE) 5A inhibition.[21] Altered NO biology, including decreased NOS expression and bioavailability and increased production of endogenous NOS inhibitors (eg, asymmetric dimethylarginine), is also central to the pathophysiology of PAH. Similar to impaired NO, decreased production of prostacyclin (PGI_2) and dysregulation of PGI_2 metabolism also contribute to PH.[22] In patients with advanced HF, short-term infusion of PGI_2 reduces PVR and increases cardiac contractility.[23] This latter effect may explain the increased mortality rate observed with long-term administration of PGI_2 in HF.[24] Notably, in a dog model of acute RV failure, intravenous PGI_2 had no effect on load-independent measures of RV contractility but improved ventriculoarterial coupling through pulmonary vasodilation.[25]

Also similar to PAH, upregulation of pulmonary endothelin (ET) has also been implicated in the pathophysiology of PH due to LHD.[14] In patients with chronic HF, Cody et al[26] first described elevated ET levels that correlate with PAPs. Subsequent investigators showed a correlation between pulmonary ET-1 spillover and PVR.[27] These data suggested that ET might be a mediator of, rather than a marker for, pulmonary arterial vasoconstriction in HF. The development of ET receptor antagonists has helped to clarify underlying disease mechanisms. Acute ET_A receptor blockade in patients with moderate to severe HF caused selective pulmonary vasodilation associated with a reduction in plasma ET levels.[28] Direct intrapulmonary infusion of a selective ET_A receptor blocker caused local pulmonary vasodilation in HF patients but not in controls.[29] Upregulation of other neurohormones in HF, including catecholamines, angiotensin II, and aldosterone, may also contribute to pulmonary vascular remodeling.[30]

Importantly, biologic and neurohormonal mediators of PH exert their effects on a genetic background that may predispose a patient to abnormal pulmonary vascular remodeling.[31] Most patients with familial PAH have loss-of-function mutations in the bone morphogenetic protein type 2 receptor,[32] leading to defective Smad signaling, although thus far, a similar genetic predisposition has not been identified. In patients with PH-LHD, recapitulation of fetal gene programs in the RV, including reductions in α-myosin heavy chain and increases in fetal β-myosin heavy chain and PDE type 5 (PDE-5) may contribute to RV hypertrophy and subsequent failure.[33] Furthermore, decreased density of β-adrenergic receptors in the RV and LV has been identified in advanced HF. Basic investigations are ongoing to determine novel modifier genes and epigenetic mechanisms of enhanced susceptibility to PH at the vasculature level for a given hemodynamic insult in these patients.[31]

Specific causes of PH due to LHD

Mitral valve disease

The development of PH in the presence of mitral stenosis and mitral regurgitation has been well described for more than 40 years,[34–36] yet mechanisms mediating heterogeneity in pulmonary vascular responses to left atrial hypertension among patients with mitral valve disease remain poorly understood. In a series of 300 patients, Wood observed severe pre-capillary PH (PVR $>$ 6 WU) complicating mitral stenosis in 26% of patients.[37] In isolated mitral regurgitation with preserved LVEF, 17% of patients had PA systolic pressure (PASP) $>$ 70 mm Hg[38] and 76% had PASP $>$ 30 mm Hg. Schwammenthal et al[39] showed that elevated PAP at rest and during exercise in mitral stenosis is related to a greater extent to net atrioventricular compliance than mitral valve area. Reduced compliance (mitral valve area/mitral E wave down slope $<$ 4 ml/mm Hg) predicted the need for mitral valve replacement or commissurotomy and defined a mitral stenosis cohort in which PH was closely linked to functional capacity.[40] PH is prognostically powerful in the natural history of mitral valve disease. In a multi-center

registry of degenerative mitral regurgitation, an echocardiographically derived PASP > 50 mm Hg (present in 23%) was an independent predictor of death, cardiovascular death, and HF during a mean follow-up of 4 years.[41]

Patients with mitral valve disease and severe PH have higher rates of surgical mortality and postoperative HF than those without PH in most[42–45] but not all studies.[46] Cesnjevar et al[42] reported a large single-center experience of 2,316 patients (> 3,000 patient-years of follow-up) of mitral valve replacement surgery for mitral stenosis or regurgitation. Among the 17% of patients who had severe PH at the time of surgery (mPAP > 50 mm Hg, average PVR 690 ± 46 dyne-sec/m^2, with a 2:1 predominance of mitral stenosis vs regurgitation), the 30-day mortality was 10.6% in those with PH vs 3.6% in those with routine elective mitral valve replacement in the absence of severe PH. However, beyond the initial post-operative period, late survival curves did not differ between patients with and without severe pre-mitral valve replacement PH. PVR is reduced dramatically after mitral valve surgery, as initially reported by Reeve et al[36] and Braunwald et al[35] and subsequently corroborated in more modern series in which long-term survival has improved.[44] For this reason, the 2006 American College of Cardiology/American Heart Association guidelines recommend mitral valve surgery for PH complicating mitral valve disease.[47]

The rapid reduction in PAP and PVR after correction of valvular lesions in most patients with PH and mitral valve disease[35,36,48] indicates a predominant role of passive transmission of elevated left atrial pressures and concomitant pulmonary arteriolar vasoconstriction.[49,50] However, the continued fall in PVR in the months after mitral valve replacement[34,44,50] and persistent elevation in PVR in others[49] supports the role of more gradual pulmonary vascular remodeling in mitral valve disease–related PH. Incomplete resolution of left atrial hypertension after mitral valve replacement, resulting in persistent PH, may be related to a reduced indexed mitral valve effective orifice area attributable to patient–prosthesis mismatch.[51] Similarly, restrictive mitral annuloplasty for mitral regurgitation may also result in resting and exertional post-surgical PH from functional mitral stenosis.[52] Mitral regurgitation is also important in PH in patients with HF, as discussed below.

PH in HFrEF

PH is present in 68% to 78% of patients with HFrEF,[6,7,53] and is associated with increased morbidity and mortality.[9,54–56] PH in HFrEF can be further divided into purely passive PVH or mixed PH. Mixed PH incidence in symptomatic HFrEF ranges from 36% to 47%.[7,8] A strong inverse relationship exists between PVR and exercise capacity as measured by peak oxygen consumption.[7,57] Moreover, elevated PVR in HFrEF is closely associated with inefficient ventilation (high expired volume per unit time/volume of carbon dioxide slope),[58] contributing to hyperpnea and dyspnea on exertion while portending a poorer prognosis in HfrEF.[59] A recent study reported that among patients admitted with acutely decompensated HF, 6-month mortality increased progressively from 8.6% in no PH to 21.8% in purely passive PH to 48.3% in mixed PH.[54] PH in HFrEF appears to be intimately related to the severity of functional mitral regurgitation and diastolic dysfunction at rest and during exercise.[60,61]

PH should not be considered in isolation in HFrEF, but rather in the context of the RV-pulmonary vascular circuit. The thin-walled RV is exquisitely sensitive to changes in afterload imposed by increased PA impedance and PVR.[9] Reduced RVEF at rest and with exercise independently predicts adverse outcomes in HfrEF.[62] Indeed, Ghio et al[9] found in an observational study of 377 HFrEF patients that 1.5-year mortality in patients with an RVEF < 35% and elevated PAP was 7-fold that of patients with a preserved RVEF and normal PAP. Additional echocardiographic indices of RV systolic function include RV fractional area change, RV myocardial performance index, tricuspid annular plane systolic excursion, and RV peak systolic strain. The latter was recently shown to predict outcomes in HFrEF when serially assessed before and after treatment for decompensated HFrEF.[63]

The burden of mixed PH must be carefully assessed in individuals with advanced HF being considered for heart transplantation. Early observations that the donor RV would fail when post-reperfusion PASP exceeded 50 to 60 mm Hg led to guidelines for the assessment of PH and PVR in potential heart transplant candidates. Elevated pre-operative PVR and TPG have been associated with marked increases in death after transplant.[53,64,65] The degree of reversibility of elevated PVR in HFrEF with pulmonary vasodilators such as nitroprusside and inhaled NO predict lower post-transplant PVR and better outcomes.[53,66] Current ISHLT guidelines therefore recommend serial right heart catheterizations at 3-month intervals in patients awaiting heart transplantation, with pulmonary vasodilator testing for patients with PASP > 50 mm Hg and TPG > 15 mm Hg or PVR > 3 WU. Fixed PH, defined as PVR > 5 WU, PVR index > 6 WU/m^2, or TPG > 15 mm Hg, despite aggressive treatment with one or more inotropes or pulmonary vasodilators, represents a relative contraindication to cardiac transplantation.[67] However, this situation may be overcome with sustained LV unloading using an LV assist device (LVAD). This topic is discussed further in the section on LVADs for PH treatment.

HF with preserved EF

PH in the setting of a "normal" EF is most likely due to HFpEF.[10] HFpEF is present in approximately 50% of patients with HF, and although PH is much less studied in this population compared with HFrEF, it now well recognized that PH is extremely common in HFpEF.[10,68–70] By definition, PCWP is elevated in HFpEF, although just as in HFrEF, concomitant pulmonary vasoconstriction and pulmonary arterial remodeling may develop, leading to mixed PH.[7] A recent population-based echo-Doppler study found an 83% prevalence of PH in HFpEF, and although PAPs

correlated with estimated PCWP (Tissue Doppler E/e' ratio), PASPs were consistently elevated to a greater extent in HFpEF than in controls, regardless of estimated PCWP, suggesting a role for increased PVR as well.[10] A recent invasive study performed in patients with less advanced HFpEF, where PCWP elevation was noted only during exercise, found that PVR tends to be only minimally elevated in earlier-stage HFpEF, suggesting that preventive therapies may have a higher yield when applied at this phase.[71] Elevated PAP accurately distinguishes HFpEF from hypertensive heart disease, with more robust discrimination than traditional markers of hypertensive cardiac remodeling and diastolic dysfunction, which are commonly observed among the elderly.[10] Indeed, among older-aged patients with PH by echo, HFpEF is the most common etiology and PVH should be strongly considered as the etiology when resting or exercise elevation in PASP is noted.[11,71–75] Just as in HFrEF, the presence of PH predicts increased mortality in HFpEF.[10,68]

Exercise-induced PH

An isolated, single assessment of supine hemodynamics at rest may be insufficient to adequately assess a patient's burden of PH and the relative contributions of PAH and PVH (also see later section in Assessment). Continuous hemodynamic monitoring devices have confirmed significant intra-individual variation in PAP attributable to diurnal variation, posture, diuretic exposure, and dietary intake.[76,77] In this setting, eliciting dynamic PH with exercise or attenuating PH with vasodilator exposure can be particularly useful in characterizing PH in the setting of LHD.

In healthy individuals, passive distention of a compliant pulmonary circulation and active flow-mediated vasodilation allows the pulmonary vasculature to accommodate increased cardiac output during exercise, with only a modest increment in PAPs[3] and a fall in PVR.[78] Exercise-induced PH arises when the pulmonary vasculature is unable to accommodate increased blood flow during exercise without an abnormally high PCWP and/or PVR.[79] In addition to resting definitions, PH has traditionally also been considered to be present when exercise mPAP exceeds 30 mm Hg. However, a recent meta-analysis found the "normal" increase in PASP with exercise is exaggerated with normal aging,[3] leading a recent consensus document to recommend that exercise values be abandoned in the definition of PH.[1] In addition, very high exercise cardiac outputs in trained individuals can result in marked elevations in exercise PAP. A fall in PVR (eg, to < 1 WU) or a mean PA/cardiac output increment of < 2 mm Hg/liter during exercise [12] may better distinguish those with excessive PA responses to exercise because it accounts for heterogeneity in exercise-induced cardiac output augmentation.[79]

Ascertaining relative contributions of PCWP (ie, post-capillary component) and TPG (ie, pre-capillary component) to PH during exercise can be particularly valuable in the diagnostic evaluation of patients who experience dyspnea on exertion but have resting cardiac filling pressures within normal reference ranges.[11,79] Elevated exercise PAP, when accompanied by increased exercise PVR and a modestly increased PCWP ($<$ 15–25 mm Hg), is an intermediate PH phenotype associated with reduced exercise capacity.[79] In contrast, exercise-induced elevation in left-sided hydrostatic pressures (ie, PCWP $>$ 20–25 mm Hg), is consistent with the diagnosis of HFpEF.[11] In mixed PH, exercise permits assessment of relative augmentation in TPG and PCWP components of exercise PAP, which may have implications in selecting targeted treatment approaches to mixed PH.[12,80]

Patients with HFrEF demonstrate a steep increment in PAPs during exercise that is attributable to an exaggerated increase in TPG and PCWP compared with age-matched controls.[12] The increment in PAP relative to work during exercise predicts worse exercise capacity and outcomes independently of resting hemodynamic values.[12] In addition to invasive exercise hemodynamics, exercise echocardiography has been used in the evaluation of PH in LHD.[1] However, Doppler measures of right-sided and, particularly, left-sided pressures may be less accurate during exercise and more extensive validation is required. Intriguingly, the mechanisms of exercise-induced PH in LHD may vary according to LVEF, at least as measured by echocardiography. Exertional PH in patients with reduced EF appears to be related principally to mitral regurgitation and contractile reserve,[61] whereas in HFpEF, diastolic function and resting PAPs may be more important,[1,71] although some investigators have also observed dynamic mitral regurgitation in this population.[81]

Assessment of LHD as an etiology of PH

As previously discussed, LHD is one of the most common causes of PH and may be due to LV systolic dysfunction, diastolic dysfunction, valvular disease, or left atrial disease.[6,82] A key first step in the clinical evaluation of PH is to assess the burden of LHD and to distinguish PH due to LHD from other causes.

History, physical examination, and laboratory testing

Clues from the medical history favoring LHD as a primary etiology of PH include previously documented structural heart disease (ie, myocardial infarction, low EF, chronic hypertension), exposure to cardiotoxins, cardiac infiltrative diseases, or symptoms that are relatively specific for LHD such as orthopnea or paroxysmal nocturnal dyspnea (Table 3). Other historical findings, such as fatigue, exertional dyspnea, and peripheral edema, are non-specific and may be seen with PH due to a variety of causes.[6,82] Among patients with normal EFs, age, and comorbidities are useful to distinguish PH due to LHD from other etiologies. Older-aged patients are much more likely to have PH due to LHD, and the presence of comorbidities, such as obesity, hyperten-

Table 3 Assessment of Left Heart Disease in Pulmonary Hypertension

Initial tests	Contingent tests	Favors primary contribution of LHD to PH	Favors alternative etiology of PH
History	Targeted imaging and serologic evaluation	• Known left ventricular structural disease (eg, MI, cardiomyopathy) • Presence of comorbidities associated with LHD (eg, older age, diabetes, obesity, hypertension) • Orthopnea and paroxysmal nocturnal dyspnea	Conditions associated with WHO 1, 3–5 PAH (eg, family history of PAH, +BMPR2 mutation, HIV, collagen vascular disease, hemoglobinopathy, portal hypertension, COPD, interstitial lung disease, appetite suppressant or other toxins, previous pulmonary embolism, congenital shunts)
Physical Exam		• Left-sided S3 or S4 gallop • Left-sided murmurs (particularly mitral) • Displaced sustained apical impulse • Coarse rales	• Cyanosis, clubbing • Fine rales, protracted expiration, accessory muscle use, productive cough • Raynaud phenomenon, sclerodactyly, telangiectasia • Pulmonary vascular bruits • Splenomegaly, spider angiomata, palmar erythema
Electrocardiogram	Exercise ECG	Q waves, left ventricular hypertrophy, left atrial enlargement, left bundle branch block, atrial fibrillation, inducible myocardial ischemia during exercise	Isolated right atrial enlargement and right ventricular hypertrophy, S1Q3T3 pattern
Echocardiogram (see Table 4)	Exercise echo Transesophageal echo	• LV systolic dysfunction • LV diastolic dysfunction • LV hypertrophy • Mitral valve disease • Cor triatriatum	• Isolated right atrial or right ventricular enlargement • Intraventricular septum flattening or reverse curvature • Pericardial effusion in the absence of pericardial disease • Congenital disease with shunt
Right heart catheterization	Exercise Vasodilator test Volume loading Left heart catheterization	• PCWP or LVEDP > 15mm Hg • Abrupt increase in PCWP (to>20–25 mm Hg) with exercise or volume loading • Increase PCWP noted during pulmonary-specific vasodilator testing	• PAP > 25 mm Hg with PCWP < 15 mm Hg • Exercise PCWP and LVEDP < 20–25 mm Hg

BMPR, bone morphogenic protein receptor; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HIV, human immunodeficiency virus; LV, left ventricular; LHD, left heart disease; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; PAP, pulmonary artery pressure; PCWP pulmonary capillary wedge pressure; PH, pulmonary hypertension; S1Q3T3, S wave in lead I, Q wave and T wave inversion in lead III; WHO, World Health Organization.

sion, atrial fibrillation, diabetes, coronary disease, and metabolic syndrome, also greatly increase the likelihood of LHD.[10,72,74,75,82,83]

Physical examination findings favoring LHD include left-sided gallops, left-sided murmurs (particularly mitral), a displaced or sustained apical impulse, and rales. Electrocardiographic findings supporting LHD include Q waves, left atrial enlargement, LV hypertrophy, and atrial fibrillation.[82,83] Natriuretic peptide levels are often elevated in PH in LHD and tend to be much higher than in other forms of PH.[84] However, significant overlap exists as symptomatic class increases, regardless of etiology. Exercise intolerance is common in HF due to LHD, and the presence of PH, with or without RV dysfunction, is associated with more severely impaired exercise capacity.[7,57,58,62,85]

Imaging

Echocardiography provides valuable data in the evaluation of PH (Table 4, Figure 2A). Doppler interrogation of the tricuspid regurgitation velocity allows estimation of PAP,[86] although under-estimation and overestimation of PH severity are not uncommon.[87] When the EF is depressed, LHD is the more likely etiology of PH. When EF is normal, distinction may be more difficult, because PH due to LHD and pulmonary vascular disease may each demonstrate abnormal diastolic function by transmitral Doppler.[88] For example, grade I diastolic dysfunction (eg, E to A reversal, impaired relaxation) is common in PAH due to impaired LV filling as a consequence of a distended RV, interventricular dependence, and a normal left atrial pressure.[89,90] However, measures of LV diastolic dysfunction are more dramatically abnormal in PH due to LHD.

Table 4 Distinguishing Pulmonary Hypertension-Left Heart Disease From Pulmonary Artery Hypertension Using Echocardiography

		Likelihood of	
Echo parameter	Echo finding	PH-LHD	PAH
Ejection fraction	<50%	↑	↓
Left atrial size	LAD > 40 mm LAVI > 28 mm/m^2	↑	↓
LV wall thickness	>11 mm	↑	↓
Transmitral Doppler	Grade II/III diastolic dysfunction	↑	↓
Mitral regurgitation	Severity > 1+	↑	↓
RV size	RV-to-LV area > 1.0	↓	↑
Interventricular septum	Systolic flattening Lateral-septal TDI disparity	↓	↑
Interatrial septum	Bowing into LA	↓	↑
RV systolic function	TAPSE <1.5 cm	↓	↑
RVOT Doppler	Notching	↓	↑

LAD, left atrial dimension; LAVI, left atrial volume index; LHD, left heart disease; LV, left ventricular; PH, pulmonary hypertension; RV, right ventricular; RVOT, right ventricular outflow; TDI, tissue Doppler imaging.

Elevated tissue-Doppler E/e' ratio,[85,91] short mitral E wave deceleration time,[60] a restrictive Doppler transmitral filling pattern,[60,91] left atrial enlargement,[61,75,83] LV hypertrophy, and mitral valve disease[60,61] all favor LHD. In contrast, isolated right-sided chamber remodeling with intraventricular septum flattening or reverse curvature points to PAH and away from LHD as the primary etiology of PH.[75,92]

It is important to note that no particular echocardiographic finding is specific for LV diastolic dysfunction or PH due to LHD. For example, most patients with mild mitral Doppler inflow abnormalities (eg, E to A reversal, impaired relaxation) are not symptomatic,[93] probably because the mean left atrial pressure is typically normal at this stage. Nonetheless, echocardiography with Doppler provides invaluable data to help distinguish PH due to LHD vs other causes, assesses right heart function, and is traditionally the first diagnostic test obtained (Table 4).

Ultimately, delineating the cause of PH requires an assessment of PVR rather than just pulmonary pressures, and PVR can be estimated from echocardiography. PVR (eg, pressure/flow) can be estimated using the tricuspid regurgitation velocity and the velocity time integral of the RV outflow tract as surrogates for pressure and flow, respectively. However, this method more accurately describes total pulmonary resistance because the distal pressure is not accounted for (eg, left atrial pressure) and performs poorly when the PVR is markedly elevated.[94,95] Alternatively, notching of the RV outflow tract systolic pulse-wave Doppler envelope, created from early wave reflection (impeding RV ejection) from a stiff pulmonary arterial tree, suggests a PVR of > 3 WU.[96] Conversely, its absence is indicative of an elevated left atrial pressure and normal PVR.[96]

Exercise echocardiography is increasingly used in the evaluation of patients with exertional intolerance but requires further validation (see previous discussion). Magnetic resonance imaging (MRI) and computed tomography are little studied in the evaluation of PH in LHD but hold promise.[97–99] MRI-guided catheterization has the capacity to supplement traditional pressure hemodynamic data with dynamic volumetric assessment.[100,101] Cardiac MRI can also be used to non-invasively measure pulmonary pressures, RV size, and function, and to serially monitor PH-specific therapeutic interventions.[99] Radiographic techniques may prove useful to exclude other etiologies, such as chronic thromboembolic disease or parenchymal lung disease with hy-

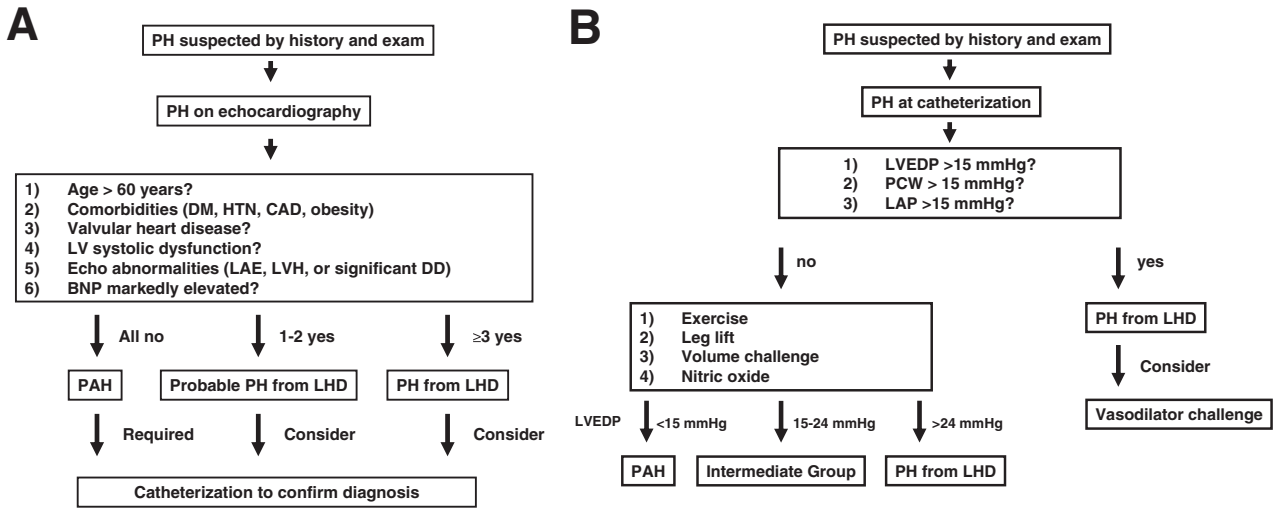

Figure 2 (A) Echocardiographic algorithm for the assessment of pulmonary hypertension (PH) and left heart disease (LHD). (B) Catheterization algorithm for the assessment of PH and LHD.

Table 5 Selective Intravenous Pulmonary Vasodilators

Agent	PVR	mPAP	PCWP	CI	SVR	Notes
Nitroprusside	↓ ↓ ↓	↓ ↓	↓ ↓	↑ ↑	↓ ↓ ↓	0.5–5.0 μg/kg/min
Milrinone	↓ ↓ ↓	↓	↓	↑ ↑ ↑	↓ ↓ ↓	50 μg/kg IV bolus
Nitric oxide	↓ ↓ ↓ ↓	↓ ↔	↑ ↑	↓	↔	80 ppm over 10 min
Prostaglandin E1	↓ ↓ ↓ ↓	↓ ↓	↓	↑ ↑	↓ ↓ ↓	0.02–0.30 μg/kg/min
Adenosine	↓ ↓ ↓ ↓	↓ ↔	↑	↑	↔	100 μg/kg/min

CI, cardiac index; IV, intravenous; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, peripheral vascular resistance; SVR, systemic vascular resistance.

Adapted from Bain DS, editor. Grossman's cardiac catheterization, angiography, and intervention. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. Used with permission.

poxic vasoconstriction.[1] Cardiac MRI is particularly valuable when restrictive or hypertrophic cardiomyopathies are potential causes of PH-LHD[102–104] and when echocardiography is limited by poor acoustic windows. Despite its ability to obtain sophisticated measures of diastolic function,[105] cardiac MRI for assessment of HFpEF is currently limited by lack of wide availability and the time-intensive nature of such data acquisition.

Invasive evaluation

Cardiac catheterization remains the gold standard for evaluating PH (Figure 2B). In general, circumstantial evidence for PH (eg, echocardiographic PH) should ideally be confirmed by invasive assessment, and invasive evaluation is mandatory before considering PH-specific therapies. As described previously, PH is considered to be due to LHD when left-heart filling pressures exceed normal references ranges (eg, PCWP $>$ 15 mm Hg), typically measured supine at rest.[1] As noted before, TPG and PVR may be concomitantly elevated in PH due to LHD (eg, mixed PH),[7] although they tend to be more abnormal in PAH.

Because symptoms of HF are often noted only during exertion, resting catheterization is often insufficient to rule in or rule out LHD as a source of PH.[11,79] Left heart filling pressures may be normal in the setting of diuresis or in early-stage HF, where pathologic neurohormonal activation and renal volume retention are not as pronounced.[11] Right-sided heart catheterization performed at rest and during exercise allows distinction of exercise-induced PAH (PH due to pulmonary vascular disease) from PH due to LHD.[79] HFpEF may be detected by an abnormal increase in PCWP during exercise, and this may be observed even when markers of volume overload from examination, echocardiography, and B-type natriuretic peptide are absent at rest.[11] PA pressures in this group track very closely with PCW, whereas in exercise-induced PAH, PCWP remains within normal reference ranges (eg, $<$ 20 mm Hg in some studies).[79,82] Although assessment of PCWP is critical to distinguish exercise-induced PAH from LHD, the partition value defining an abnormal exercise PCWP or LVEDP has no consensus, with suggested cutoff values ranging from 15 to 25 mm Hg.[11,12,79,82] These cutoffs may further vary according to whether exercise is performed with the arms or legs, upright or supine, dynamic or isometric, and whether PCWP is measured at end-expiration or the mean of the respiratory cycle (Table 5). Furthermore, cutoff values may differ by age, sex, and BMI, but their exact impact is unknown.

Because catheterization during exercise is not feasible in all laboratories, alternative maneuvers have been suggested to enhance diagnosis, such as rapid volume loading[82] or leg lifting.[11] The use of volume loading is based on prior observations of acute elevation in PCWP in patients with occult constrictive pericarditis and normal PCWP, such that "latent" diastolic dysfunction is unmasked.[106] LHD is assumed to respond in a similar manner to volume loading as to constriction, yet it remains unclear which absolute PCWP value (or change in PCWP) after saline loading establishes the diagnosis of LHD.[11,82,107] Indeed, even among patients without clinical HF symptoms, an average increase in PCWP of 7 mm Hg occurs with saline loading.[107] Moreover, the most appropriate protocol for saline loading is not established (eg, how much, how fast, central vs peripheral) and likely varies widely in catheterization laboratories. It would seem reasonable to suggest that a PCWP to $>$ 20 mm Hg is abnormal with saline loading, but prospective data are needed. Pulmonary-specific vasodilators, such as inhaled NO or prostacyclin analogs, are sometimes given during right-sided heart catheterization to assess reversibility of PAH. The development of marked increases in PCWP with such therapy should alert the physician to the possibility of LHD as a cause of PH,[108,109] although mild elevations in PCWP may also be observed in severe PAH, presumably due to interventricular dependence.[110] The use of vasodilators in the evaluation of PH-LHD is discussed in greater detail in subsequent sections.

Treatment

Treatment goals for PH secondary to LHD include (1) improvement in dyspnea and functional capacity, (2) reduction in morbidity and mortality, and (3) successfully bridging patients to advanced therapies such as heart transplantation and mechanical circulatory support.

LVAD therapy may be the best treatment of PH secondary to LHD for HFrEF in patients for whom maximal medical therapy has been achieved. The traditional primary therapeutic strategy in PH from LHD is to lower the PVP and thereby relieve the "back" hydrostatic pressure that results in PH. This approach is particularly effective when the PVR is normal or minimally increased. In such cases, vasodilators and diuretics are the mainstays of therapy.[53,111,112] Concomitant conditions that may exacerbate PH, such as sleep apnea and pulmonary embolism, should also be identified and treated aggressively. Indirect evidence suggests that effective relief of elevated LH filling pressures over time will result in favorable remodeling of the pulmonary circulation and amelioration of fixed PH when it complicates LH failure.[113,114] Intravenous agents are typically used to assess acute pulmonary vasoreactivity in bridging situations (Table 5), whereas oral agents are used for the long-term management of LVD PH to improve symptoms and exercise capacity. Ultimately, the definitive therapy for PH from LHD is correction of the LH condition, such as surgery for aortic[115] or mitral stenosis,[44] heart transplantation, or LVAD for end-stage HF.[113,116,117]

In clinical practice, the use of selective pulmonary vasodilators to relieve the concomitant reactive component (increased PVR) of mixed PH in LHD is often considered (Table 5). However, the use of agents developed for PAH should generally be avoided, outside the context of clinical trials. In fact, the few randomized clinical trials of such agents in patients with HFrEF have been largely unfavorable (Table 6 and Table 7). One potential explanation is that selective pulmonary vasodilators may increase transpulmonary flow to an extent that cannot be accommodated by a failing LV, particularly if diastolic compliance is reduced. As a consequence, LVEDP may rise rapidly and to a magnitude where pulmonary edema develops.[118–121] For these reasons, the strategy of selective pulmonary vasodilators in PH from LHD is probably best reserved when hemodynamic assessment can be provided and their routine use should be avoided. PDE-5 inhibitors and soluble guanylate cyclase activators may have characteristics that differentiate them from the other PAH therapies in their effect on LH filling pressures, and their use in PH with LHD is currently under investigation (see below).

Vasodilators (nitroglycerin, nitroprusside, nesiritide)

Traditional systemic vasodilators are commonly used to treat PH that complicates LHD (Table 5). These agents are effective in lowering PAPs by increasing venous capacitance and consequently lowering the hydrostatic component of PH-LHD. Most of the evidence for this approach comes from older studies of patients with advanced HF undergoing heart transplant evaluation.[53] In the classic report by Costard-Jackle and Fowler,[53] fixed PH or lack of pulmonary vasoreactivity without systemic hypotension was associated with early post-transplant mortality. Nitroglycerin[122] and nitroprusside[53,111,123] are commonly used in this setting and act as exogenous NO donors. In patients with acute HF, they may be used to improve hemodynamics as a bridge to a definitive procedure (eg, mitral valve replacement for acute mitral regurgitation). These intravenous agents can be transitioned to oral congeners in some patients; for example, the effects of nitroprusside can be reproduced with oral nitrates or arterial vasodilators such as angiotensin-converting enzyme inhibitors or hydralazine.[111,123] However, Murali et al[124] demonstrated the ability of such agents to lower the TPG rather than simply the PVP is modest: although nitroglycerin and nitroprusside were comparable to dobutamine and prostaglandin E1 in lowering PVR by increasing cardiac output, only prostaglandin E1 significantly lowered the TPG.

Inhaled NO is particularly attractive when the goal is to dilate the pulmonary arterial bed without lowering systemic blood pressure because it is selective for the pulmonary vascular bed when delivered as a rapidly acting gas.[125] NO is generated from L-arginine and oxygen through the activity of specific NO synthases; its effects include not only vasodilation but also bronchodilation, anti-inflammation, and anti-proliferation.[126,127] Inhaled NO will generally result in a rise in PCWP in patients with LHD, and so is of little utility in such cases aside from an acute test of the ability to lower the TPG to assess PVR before consideration of heart transplantation. Inhaled NO is generally well tolerated in PH-LHD,[66,109,128–130] although rapid elevations in PCWP have resulted in acute pulmonary edema.[118,121] Accordingly, nitroprusside is the preferred agent for assessment of PH reversibility in left HF.

NO is sometimes used to help manage residual PH after LVAD implant or for correction of other left heart filling abnormalities where right HF and PH persists post-operatively. Long-term use of inhaled NO is limited by a very short half-life, risk of methemoglobinemia, and rebound PH with planned or inadvertent discontinuation.[131] Maximal increase in cardiac output and lowering of central venous pressure, TPG, and mPAP occur at approximately 20 ppm, although up to 80 ppm are used in clinical practice. Inhaled NO is costly, and some centers require failure of other selective pulmonary vasodilators (e.g, inhaled epoprostenol) before allowing its use.

There is decreased sensitivity of the pulmonary circulation to B-type natriuretic peptides in HF,[21] and the use of nesiritide to overwhelm this decreased sensitivity may lower pulmonary pressures. However, similar to the other nonselective vasodilators, the primary hemodynamic effect is to lower PVP and increase flow rather than lower the TPG.[132,133] Like nitroprusside, nesiritide can be used as a bridge to LVAD or transplant in patients with significant PH. Systemic hypotension and renal insufficiency may complicate use of this drug at higher doses.[134] Importantly, there is no clinical benefit in the routine use of nesiritide in patients with acute decompensated HF.[135]

Table 6 Pulmonary Vasodilators Trials in Heart Failure I

Trial	Subjects	Drug	Inclusion criteria	Primary end-point	Study	Comments
FIRST	471	Epoprostenol: 4.0 ng/kg/min (median)	EF < 25%, NYHA III-IV, mPAP > 25 mm Hg	Survival	Negative	Acute—improvements in mPAP, mPCWP, and PVR Chronic—no improvement in 6MWT, QOL, or morbidity
RITZ-1	669	Tezosentan: 25 mg/h IV × 1 hr; then 50 mg 24–72 hrs	Acute hospitalization	Symptoms at 24 hrs	Negative	Time to death or worsening CHF in 24 hrs also not significantly different
RITZ-2	215	Tezosentan 50 or 100 mg/h IV	Acute hospitalization, CI < 2.5 liters/min/m2 L2 and PCWP < 15 mm Hg	CI at 6 hrs	Positive	Improvement of 0.37 to 0.38 liters/min/m2 L2 with decreased in PCWP pressure
RITZ-5	84	Tezosentan: 50–100 mg/h × 24 hrs	Acute pulmonary edema: oxygen, furosemide, morphine, isosorbide dinitrate background	Change in arterial oxygen saturation	Negative	No change in saturation, death, recurrent pulmonary edema, mechanical ventilation, and myocardial infarction
ENABLE	1613	Bosentan: 125 mg bid, 9 mos	EF < 35%, NYHA IIIB-IV	All cause mortality + CHF hospitalization	Negative	Primary end point reached: 321/808—placebo: 312/805—bosentan: worsening CHF on bosentan
REACH-1	370	Bosentan: 250 mg bid, 6 mos	LVEF < 35%, NYHA III-IV, 6MWT < 375 m	Change in clinical status	Negative	Early termination due to liver function abnormalities
HEAT-1	179	Darusentan: dose range, 3 wks: 30, 100, 300 mg	EF < 35%, NYHA III PCWP > 12 mmHg, CL < 2.6 liters/min/m2	Change in PCWP/CI	Negative	Increased CI and reduced SVR vs placebo. No significant change in PCWP, mPAP, PVR, RAP, HR, and MAP. Worsening heart failure with high dose
EARTH-2	642	Darusentan: dose range, 24 wks: 10, 25, 50, 100, 300 mg	LVEF < 35%, NYHA II-IV	Change in LV end-systolic volume measured by MRI	Negative	No significant effect on remodeling of the heart or dirical symptoms

6MWT, 6-minute walk test; bid, twice daily; CHF, congestive heart failure; CI, cardiac index; EARTH, Endothelin A Receptor Antagonist Trial in Heart Failure; EF, ejection fraction; 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; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; QOL, quality of life; RAP, right atrial pressure; REACH, Research on Endothelin Antagonism in Chronic Heart Failure; RITZ, Randomized Intravenous Tezosentan; SVR, systemic vascular resistance.

Prostaglandins

Case reports suggested that prostaglandins may be beneficial in treating PH complicating left HF and prompted a large-scale clinical trial in this setting. The Flolan International Randomized Survival Trial (FIRST) enrolled 471 patients with an EF < 25% and New York Heart Association (NYHA) class IIIB or IV HF in a trial of conventional therapy vs intravenous epoprostenol[24] (Table 6). Epoprostenol acutely improved mPAP, PCWP, and PVR. Long-term infusion, however, did not improve 6-minute walk distance, quality of life, or morbidity. The trial was stopped early by the data safety monitoring board due to a trend toward decreased survival in the patients treated with epoprostenol. However, clinicians have used prostacyclin successfully as a bridge to transplantation. Some patients do well with prostaglandin E1; that is, survived to transplant compared with those receiving dobutamine or other prostacyclin infusions.[136] Doses lower than those used in PAH, with careful inva-

Table 7 Pulmonary Vasodilators Trials in Heart Failure II

Trial	Subjects	Drug	Inclusion criteria	Primary end-point	Secondary end-points	Study	Results
PROMISE	1,088	Milrinone: 10 mg po qid	NYHA III-IV on conventional therapy; LFEF ≤ 35%	All cause mortality	CV mortality, # hospitalizations, addition of vasodilators, symptoms, adverse reactions	Negative	Increased mortality 28% (95% CI, 1%–61%; $p = 0.016$), worse in sicker pts: 53% mortality, more hospitalizations, hypotension, syncope
ESSENTIAL I + II	1,854	Enoximone: 50-150 mg tid	LVEF ≤ 30%; NYHA III-IV, 1 hospitalization or 2 clinic visits (1 yr), LVEDD > 3.2 cm/m^2	Co-primary: All-cause mortality or, cardiovascular hospitalization	6MWD, QOL	Negative	No difference in HF, 0.97 (95% CL, 0.86, 1.12); safe but ineffective
Sildenafil/placebo in Chronic Heart Failure	46	Sildenafil: 6 mos, 50 mg tid	<65 yrs, NYHA II-III; cardiomyopathy, LVEF < 45%	Change in ex capacity, ventilation efficiency, + symptoms	QOL	Positive	Improved exercise ventilation and aerobic efficiency
Sildenafil/placebo in Chronic Heart Failure	34	Sildenafil: 12 wks, 25–75 mg tid	≥ 18 yrs; NYHA II-IV on conventional therapy LFEF ≤ 40%; mPAP > 25 mm Hg	Peak Vo_2	6MWD, hemodynamics, QOL, RV/LV performance, NT-proBNP	Positive	Improved peak Vo_2, 6MWD, and QOL; decreased CHF hospitalizations
RELAX	190 (est.)	Sildenafil: 12 wks 20 mg tid, followed by 12 wks 60 mg tid	60+ yrs, NYHA II-IV, EF > 50%, NT-proBNP > 400 pg/ml	Peak Vo_2	Change in sub-max exercise capacity, change in a composite score reflective of clinical status	Ongoing	Ongoing

6MDW, 6-minute walk distance; CHF, congestive heart failure; CI, confidence interval;, CL, confidence limits; CV, cardiovascular; EF, ejection fraction; ESSENTIAL, Studies of Oral Enoximone Therapy in Advanced Heart Failure; HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; PROMISE, Prospective Randomized Milrinone Survival Evaluation; QOL, quality of life; RELAX, Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure; RV, right ventricle; tid, 3 times daily; Vo_2, volume of oxygen consumption.

sive hemodynamic monitoring, can be a viable therapeutic option in this unique situation of bridging to transplant, but is not recommended for routine management of PH from LHD on the basis of the FIRST trial.

Endothelin receptor antagonists

Endothelin, a potent endogenous vasoconstrictor and mitogen,[137] is markedly increased in HF and associated with increased symptoms, PH and increased PVR, and decreased survival.[26] There are two endothelin receptors, ET_A and ET_B. The ET_A receptors, found on vascular smooth muscle cells, mediate vasoconstriction and proliferation. The ET_B receptors, found on endothelial cells and vascular smooth muscle cells, result in NO release. ET_A receptors are upregulated in HF, whereas the ET_B receptor is downregulated.[138,139] In animal models of HF, endothelin receptor antagonists reduce hypertrophy-induced myocardial fibrosis and have been shown to improve survival.[140,141]

Early clinical studies of endothelin receptor blockade in patients with HF were encouraging (Table 5). In a study of oral darusentan (a selective ET_A receptor antagonist) in 95 patients with NYHA class II-III HF and an EF ≤ 35%,[142] hemodynamics improved in a dose-dependent fashion without altering other neurohumoral systems. Givertz et al[28] demonstrated similar findings with intravenous sitaxsentan, another selective

ET_A blocker. However, in the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH) trial, endothelin blockade with darusentan did not provide a sustainable benefit on LV remodeling (as assessed by MRI) or morbidity or mortality in 642 patients with chronic HF.[143]

Initial studies (Table 6) with non-selective endothelin antagonists focused on patients with acute HF. The Randomized Intravenous Tezosentan (RITZ) trials evaluated hemodynamics, oxygenation, and symptoms in patients with HF complicating acute myocardial infarction.[144–147] RITZ-1 did not demonstrate any difference in dyspnea, time to death, or worsening HF during the first 24 hours,[144] despite improvements in hemodynamics seen with the drug in RITZ-2.[146] RITZ-5 evaluated intravenous tezosentan therapy in addition to standard of care for acute pulmonary edema. The primary end point of improvement in arterial saturation and the secondary end points of death, recurrent pulmonary edema, mechanical ventilation, and myocardial infarction did not reach significance at 24 hours.[145] The Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study (VERITAS) trials were similarly disappointing because tezosentan failed to improve dyspnea or clinical outcomes in patients with acute HF.[148]

Non-selective endothelin receptor antagonists have also been studied in ambulatory HF patients, with similarly disappointing results. The Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) study evaluated the effects of low-dose bosentan (125 mg orally twice per day) in 1,613 patients with an EF $<$ 35% and NYHA IIIB or IV symptoms. There was no difference in the primary end point of all-cause mortality or hospitalization for HF failure.[149] More concerning was an early risk of worsening HF necessitating hospitalization, presumably due to fluid retention with bosentan. Similar concerns for harm were raised in the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) study, which evaluated bosentan in with advanced HF and impaired sub-maximal exercise.[150] The study was never completed because of a high incidence of liver function abnormalities.

There are, however, anecdotal reports of benefit in select situations. After 6 weeks of bosentan therapy, improvement in hemodynamics before and after vasodilator testing were seen in a small series of patients with severe PH awaiting heart transplant.[151] In general, the current evidence does not support the routine use of endothelin antagonists for PH-LHD. However, it should be acknowledged that the currently available clinical trial evidence has targeted patients with HFrEF rather than PH-LHD per se.

PDE inhibitors

PDE type 3 inhibitors

PDE type 3 (PDE-3) inhibitors, including milrinone and enoximone, enhance cardiac contractility by increasing intracellular cyclic adenosine monophosphate (cAMP).[152] In addition, these agents cause direct vasodilation in the pulmonary and systemic circulation. Givertz et al[153] studied the acute hemodynamic effects of milrinone in patients with severe HF and secondary PH and showed that PVR falls within 10 minutes of an intravenous bolus without systemic hypotension. The predominant effect is an increase in flow and fall in filling pressures, with little change in TPG. Although milrinone is commonly used as chronic inotropic support in patients with end-stage HF bridging to VAD or transplant, administration of intravenous milrinone may be associated with hypotension and arrhythmias.[154]

Development of oral PDE-3 inhibitors has been halted due to negative study results over 2 decades (Table 7). The Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial randomized 1,088 NYHA III or IV patients to oral milrinone (40 mg daily) or placebo.[155] Milrinone increased all-cause mortality by 28% (95% confidence interval, 1%–61%; $p = 0.016$) and was associated with more adverse events, such as rehospitalization, hypotension, and syncope. Lower dose ranges do not appear to decrease the mortality of these agents. Similarly disappointing results have been demonstrated with oral enoximone in large randomized controlled trials (The Studies of Oral Enoximone Therapy in Advanced Heart Failure [ESSENTIAL]).[156] Clearly, the long-term use of these agents in HF patients is ill advised, although bridging to advanced therapies and palliative support for organ hypoperfusion may be necessary.

PDE-5 inhibitors

Sildenafil (Table 7), through PDE-5 inhibition, prevents degradation of cyclic guanosine monophosphate (cGMP), thereby enhancing NO-dependent vasodilation without concomitant increases in cAMP in peripheral[157] and pulmonary vascular beds.[158] It also appears to potentiate the hemodynamic effects of brain natriuretic peptide in HF.[159] Inhibition of PDE-5 may potentiate the hemodynamic effects of natriuretic peptides and limit myocardial remodeling in response to stress.[160] In patients with PAH, sildenafil lowers PVR similar to inhaled NO.[158] In patients with chronic left HF, the acute hemodynamic effects of sildenafil include decreased PVR and increased cardiac index without systemic hypotension.[161–164] The effects of intravenous sildenafil appear to be comparable to milrinone and could be used to assess acute vasoreactivity before heart transplantation.[165,166] In the perioperative setting, sildenafil improves PH and right HF after heart transplantation.[167–169] In combination with mechanical circulatory support, sildenafil may decrease PVR to acceptable levels to allow for heart transplantation[170] and perhaps mitigate RV failure, but this has not been rigorously tested.

Sildenafil also safely improves symptoms in ambulatory patients with HFrEF. In a placebo-controlled randomized trial of 34 left HF patients with concomitant PH (mPA $>$ 35) who were taking maximum oral therapy for chronic HF, sildenafil (25–75 mg 3 times daily)[171] improved peak exercise oxygen consumption and 6-minute walk distance and decreased hospitalizations for HF. Ambulatory use of sildenafil in patients with chronic HF appears to produce sustained effects.[162,171] However, larger outcome studies have yet to be completed in chronic HF populations with second-

ary PH, although the National Heart, Lung and Blood Institute Heart Failure Network is currently testing the safety and efficacy of sildenafil in patients with HFpEF (clinicaltrials.gov, NCT00763867).

Soluble guanylate cyclase (sGC) is a key enzyme of the NO-signaling pathway and catalyzes the synthesis of the second messenger cGMP, which mediates a number of downstream effects, including vasodilation, platelet aggregation, and inhibition of smooth muscle cell growth.[172] Because the benefits of NO are downstream from NO binding to sGC, direct stimulation of sGC-cGMP signaling is an attractive therapeutic target. Both sGC stimulators (eg, sensitize sGC to NO) and sGC activators (eg, activate sGC in the absence of NO) have been developed for clinical use. An oral sGC stimulator, BAY 63–2521 (riociguat), has been studied in healthy human volunteers[173] and in patients with PAH[174] and chronic thromboembolic PH.[175] Riociguat and cicletanine are both currently being studied in PH and LV systolic dysfunction (clinicaltrials.gov, NCT01065454) and diastolic dysfunction (clinicaltrials.gov, NCT01172756).

Left ventricular assist devices

When pharmacologic therapies fail to lower LV filling pressures, mechanical unloading may be used to normalize cardiac filling pressures over time and thereby reverse the passive and reactive components of PH-LHD. In early reports, LVAD support was associated with a reduction in PVR over weeks to months, and this effect appears to be independent of device type.[114,176–180] In a large, retrospective, single-center experience, 63 patients who received the pulsatile HeartMate XVE (Thoratec, Pleasanton, CA) had a reduction of PVR from 5 to 3.7 WU and a mPAP from 41 to 30 mm Hg. Furthermore, of 47 patients with a mPAP $>$ 30 mm Hg and/or a PVR $>$ 4 WU, LVAD implantation was not associated with an increased need for RV support or reduced survival.[181] Other smaller series have paralleled this experience, particularly with LVAD as a bridge to successful cardiac transplantation.[114,182]

LVADs may reverse the "fixed" component of PH-LHD over relatively shorter periods of time. In a prospective 6-week study, 35 patients with severe HF and a PVR $>$ 3.5 WU, despite vasodilator therapy with nitroglycerin, PGI_2, inhaled NO, and levosimendan, underwent LVAD support (DeBakey [MicroMed Technology, Houston, TX], DuraHeart [Terumo Heart Inc, Ann Arbor, MI], Novacor [WorldHeart Inc, Oakland, CA]).[183] The average mPAP was 44.0 $\pm$ 6.2 mm Hg at baseline, with a PVR of 5.1 $\pm$ 2.6 WU. Within 3 days of LVAD implantation, the mPAP and PVR fell significantly ($p <$ 0.0001). After 6 weeks of support, the mPAP was reduced to 18.4 $\pm$ 4.3 mm Hg and the PVR to 3.0 $\pm$ 0.8 WU ($p <$ 0.001). Twenty-five patients (69%) ultimately underwent successful heart transplantation. There were no differences in transplant morbidity (including right HF) or death when compared with age-matched and sex-matched candidates at the same institution without PH who did not require LVAD therapy. Furthermore, the long-term survival of patients after heart transplantation was comparable at 1, 2, and 3 years.

The hemodynamic benefits of LVAD therapy continue to accrue over time. In a study of 34 patients who underwent LVAD implantation with the Heartmate XVE or II device, invasive hemodynamics and echocardiography were performed at baseline and 3 months after implant.[184] The mPAP fell by 47% $\pm$ 20% with the HeartMate XVE and by 41% $\pm$ 15% with the HeartMate II ($p <$ 0.05). In the face of increased cardiac index (38% $\pm$ 47% with XVE and 26% $\pm$ 50% with the HeartMate II), the PVRI fell accordingly. The TPG was also reduced, which may have been partly due to significant reductions in mitral regurgitation and left atrial area.

The type of LVAD support, pulsatile or continuous flow, may have an effect on the magnitude of PH improvement and consequent RV function.[185,186] 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 no significant changes in PVRI or mPAP in HeartMate XVE patients at follow-up. However, there were significant reductions in mPAP and PVRI as early as 1 month after HeartMate II implant. In addition, fewer HeartMate II patients required RVAD placement or inotropic support for right HF.

Concomitant vasodilator therapy may be used as an adjunct to LVAD support in patients with PH-LHD. In a retrospective study of 10 patients with post-LVAD PH, sildenafil was administered at the discretion of the medical team for failure to wean from inhaled NO or inotropic support.[187] In this cohort, systolic PAP fell significantly 90 minutes after sildenafil, without a change in systemic arterial pressure, systemic vascular resistance, or heart rate. Eight patients were weaned from inhaled NO within 12 hours, and all 10 patients were ultimately weaned from inhaled NO or inotropes within 72 hours. This observation was extended in a study of 138 consecutive patients receiving LVAD with a PVR $>$ 3 WU.[170] Of this cohort, 58 patients had persistent elevation of the PVR 1 to 2 weeks after VAD implantation.[16] Twenty-six of the patients received sildenafil (mean dose, 52 mg three times daily), and the remaining 32 patients served as nonrandomized controls. At 12 to 15 weeks after LVAD placement, the sildenafil-treated patients exhibited a reduction in PVR from 5.87 $\pm$ 1.9 to 2.96 $\pm$ 0.92 WU and a reduction in mPAP from 36.5 $\pm$ 24.3 to 24.3 $\pm$ 3.6 mm Hg ($p <$ 0.001), which were significantly lower than the control group. Sildenafil treatment also resulted in improved RV function, as determined by dp/dt and the tricuspid annular plane systolic excursion. Concomitant use of PDE-5 inhibitors to help RV function in the setting of LVAD is increasingly being used in some centers, but should be rigorously studied in randomized trials before widespread endorsement of such an approach.

Table 8 Suggested Definitions for Pulmonary Hypertension Due to Left Heart Disease

Nomenclature	Description	Physiologic definition	Hemodynamic criteria
Passive PH	PH with elevated left cardiac filling pressure	Post-capillary (passive congestion) eg, pulmonary venous hypertension	Mean PAP ≥25 mm Hg and PCW, LAP, LVEDP > 15 mm Hg and TPG ≤ 15 mm Hg or PVR ≤ 3.0 WU
Mixed PH	PH with elevated left cardiac filling pressure and increased pulmonary vascular resistance	Pre- and post-capillary (passive congestion with excessive arterial vasoconstriction ± vascular remodeling), eg, pulmonary arterial and venous hypertension	Mean PAP ≥ 25 mm Hg and PCW, LAP, LVEDP > 15 mm Hg and TPG > 15 mm Hg or PVR > 3.0 WU
Reactive PH	Component of mixed PH that is acutely or chronically responsive to pharmacologic (diuretics, vasodilators, inodilators) and/or mechanical circulatory support device therapies	With vasodilators and/or inodilators: TPG ≤ 15 mm Hg or PVR ≤ 3.0 WU	
Non-reactive PH	Component of mixed PH that is not responsive to above strategies	Despite vasodilators and/or inodilators: TPG > 15 mm Hg or PVR > 3.0 WU	

LAP, left atrial pressure; LVEDP, left ventricular end diastolic pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; TPG, transpulmonary gradient (mean PAP – PAWP).

These reports support a strategy of LVAD implantation as a viable and practical approach for managing medically refractory LVD PH to facilitate heart transplantation. Short-term percutaneous devices (eg, the TandemHeart [Cardiac Assist Inc, Pittsburgh, PA], Impella [Abiomed, Danvers, MA) may also have increasing roles in this arena, particularly because they are not associated with the obligate surgical morbidity and mortality of fully implantable devices.

Summary and future directions

PH associated with LHD is the most common form of PH encountered in clinical practice today. The primary diagnostic strategy is to determine the contribution of the LHD to the severity of PH to guide therapy. To reconcile this issue, catheterization-based evaluation is required, sometimes using targeted hemodynamic challenges such as exercise, volume loading, and vasodilators. In many patients, the degree of PH will be "out of proportion" to the distal PVP, resulting in a mixed picture of precapillary and post-capillary PH. The optimal therapeutic strategy in these patients remains unknown, but outcomes appear to be significantly worse in this group. Although the cornerstone of managing PH-LHD is primary treatment of the LHD, it remains unclear whether PH itself should be a target of therapy (eg, selective pulmonary vasodilators for some of these patients). In fact, in current clinical practice, empiric therapy is all too common without a strong evidence base and may even be harmful.

Future research will be required to provide a better understanding of this burgeoning clinical issue in HF. Recent technologic advances can now provide continuous cardiac hemodynamic assessment in ambulatory patients, which should provide new important mechanistic insights into PH-LHD. In addition, appropriately powered clinical trials based on pathophysiologic mechanisms will provide an evidence base for the efficacy and safety of PH-specific therapy, assuming PH-LHD is a risk factor rather than simply a marker of outcome. An important critical primary step to the future study of this important clinical problem will be to standardize definitions across disciplines to facilitate an evidence base that is interpretable and applicable to clinical practice. In this current statement, we provide an attempt to do so through this extensive review and interpretation of the current available literature. In Table 8, we suggest such definitions for future use and reference. We look forward to and anticipate further refinements in these standards and definitions with our colleagues and others who are interested in this difficult clinical problem.

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