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Understanding the Pathobiology of Pulmonary Hypertension Due to Left Heart Disease

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Abstract

The development of pulmonary hypertension (PH) is common and has adverse prognostic implications in patients with heart failure due to left heart disease (LHD), and thus far there are no known treatments specifically for PH-LHD, also known as Group 2 PH. Diagnostic thresholds for PH-LHD, and clinical classification of PH-LHD phenotypes, continue to evolve and therefore present a challenge for basic and translational scientists actively investigating PH-LHD in the preclinical setting. Furthermore, the pathobiology of PH-LHD is not well understood, although pulmonary vascular remodeling is thought to result from (1) increased wall stress due to increased left atrial pressures; (2) hemodynamic congestion-induced decreased shear stress in the pulmonary vascular bed; (3) comorbidity-induced endothelial dysfunction with direct injury to the pulmonary microvasculature; and (4) superimposed pulmonary arterial hypertension risk factors. To ultimately be able to modify disease, either by prevention or treatment, a better understanding of the various drivers of PH-LHD, including endothelial dysfunction, abnormalities in vascular tone, platelet aggregation, inflammation, adipocytokines, and systemic complications (including splanchnic congestion and lymphatic dysfunction) must be further investigated. Here we review the diagnostic criteria and various hemodynamic phenotypes of PH-LHD, the potential biological mechanisms underlying this disorder, and pressing questions yet to be answered about the pathobiology of PH-LHD.

Keywords

pulmonary hypertension; heart failure; pulmonary vascular disease; endothelial dysfunction; diagnosis; hemodynamics; Vascular Disease

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INTRODUCTION

Left heart disease (LHD) affects nearly 10% of the population over the age of 20 years in the United States with coronary disease as the leading cause of death.[1] Heart failure (HF), the end result of LHD, has a prevalence of 5.4% in the US with a growing burden of disease with the aging of the population.[2, 3] HF as a clinical syndrome is divided into two primary classifications, HF with preserved ejection fraction (HFpEF) in which the left ventricular ejection fraction (LVEF) >40% and HF with reduced ejection fraction (HFrEF) in which LVEF is ≤ 40%.[4] There is a growing move to subgroup patients with LVEF 41–49% as HF with mildly reduced (HFmrEF), although this population (particularly those with LVEF >45%) has been included in the epidemiologic, pathophysiologic, and clinical trial studies of HFpEF.. Of hospitalized patients with HF, HFpEF is at least 40%, and approximately half of the HF population in the community has HFpEF.[5–10] HF is a highly morbid and mortal syndrome; both HFpEF and HF with reduced ejection fraction (HFrEF) are associated with a strikingly high 35% one-year mortality and HF readmission rates range from 18–30%.[11–13] The development of concomitant pulmonary hypertension (PH) marks a significant event in the HF disease process with important survival implications.[14] LHD, and specifically HF syndromes, make up the majority of patients with PH, comprising up to 80% of cases.[15, 16] The most common etiologies of PH associated with LHD (World Health Organization Group 2 PH) in contemporary clinical practice are HFpEF and HFrEF, whereas mitral stenosis, in which Group 2 PH was initially described, is now relatively rare in developed countries. We therefore focus on Group 2 PH associated with HFpEF and HFrEF (PH-LHD). Despite the high prevalence of HF, the pathobiology of PH-LHD is not well understood, and preclinical models of PH-LHD typically do not investigate the full spectrum of hemodynamic PH-LHD phenotypes. Here we review the various hemodynamic phenotypes in patients with PH-LHD, the potential biological mechanisms underlying this disorder, and the highest priority unanswered questions.

DEFINING GROUP 2 PULMONARY HYPERTENSION

The 2018 World Symposium on PH updated the hemodynamic definitions of disease with a focus on the location of disease in the pulmonary vascular bed.[17] The recommendations incorporated hemodynamic thresholds for defining PH based on normative data rather than expert opinion by reducing the mean pulmonary arterial (PA) pressure (mPAP) indicative of PH to ≥20mmHg.[17, 18] In addition, the 2018 World Symposium highlighted the facts that pre-capillary pulmonary hypertension (defined as pulmonary vascular resistance [PVR] ≥ 3 Wood units) occurs in patients with PH-LHD and that combined pre- and post-capillary PH (Cpc-PH) represents a relatively common hemodynamic phenotype in clinical practice. Currently Group 2 PH is defined in two forms: (1) Cpc-PH (previously termed PH “out of proportion” to LHD) identified as a mPAP ≥20mmHg, PVR ≥3 Wood units, and PA wedge pressure (PAWP; a surrogate for left atrial [LA] pressure) >15 mmHg and (2) predominant pulmonary venous hypertension also known as isolated post-capillary PH (Ipc-PH), in which mPAP is ≥20mmHg, PAWP is >15 mmHg but PVR is less than 3 Wood units (Table 1).[17]

The recent evolution of the definition of Group 2 PH is an improvement; however, several gaps in our understanding of its diagnosis remain. The 2018 diagnostic criteria use PAWP

as the primary measure of left sided filling pressures and indicator of hemodynamic congestion. Clinically PAWP and LV end diastolic pressure (LVEDP) have historically been used interchangeably; however, multiple studies have shown that the two measurements frequently differ, and the 2 hemodynamic indices have different meanings.[19–22] Variable agreement between LVEDP and PAWP is demonstrated by only a moderate correlation (R^2=0.42) and impacted by the presence of atrial fibrillation, a comorbidity often seen in clinical practice.[21] The reliability of the measures of hemodynamic congestion are essential to the diagnosis of pre- versus post-capillary PH, and the ultimate implementation of therapies.[20] Rather than using these hemodynamic values interchangeably it is important to recognize that these two values measure different entities, even in the absence of mitral valvular disease or arrhythmia. Although LVEDP is often considered the gold standard for the hemodynamic diagnosis of LHD during the evaluation of patients with PH, PAWP reflects the health of the LA and is a more accurate representation of what pressures the pulmonary capillary bed sees over time. A true PAWP (as opposed to a partially damped PA pressure tracing) is easily confirmed during right heart catheterization if PAWP blood oxygen saturation is equal to systemic arterial oxygen saturation. When measured properly, PAWP is therefore a more inclusive assessment of chronic hemodynamic congestion reflecting the reaction of the LA to chronic pressure load, LA remodeling, and changes in LA compliance that develop over time.[23]

The LA response and adaptation to hemodynamic congestion is not universal between HF syndromes; HFpEF demonstrates a greater degree LA stiffness while HFrEF results in predominantly eccentric LA remodeling.[24] LA dysfunction is associated with the development of PH and right ventricular dysfunction in both HFpEF and HFrEF.[24] Impairment of LA function has prognostic value in the HFpEF population, marking an inability of the LA to buffer the pulmonary circulation against changes in LV pressure.[19, 25] LA strain is impaired in both HFpEF and HFrEF.[26] Clinically, LA strain, which is emerging as an easy-to-measure, reproducible measure of LA function that may have clinical and research utility, is divided into 3 phases: reservoir (LA filling during LV systole), conduit (LA passive emptying into the LV during early LV diastole), and booster (LA contraction at LV end-diastole).[27, 28] Clinically LA dysfunction and congestion likely determines treatment responses to pulmonary vasodilators, as increased blood flow through the pulmonary bed may result in increased pulmonary congestion in the setting of a stiff, non-compliant LA. Decongestion with diuretics and systemic afterload reduction may help offset increased blood flow into the LA but ultimately degree of LA remodeling when pulmonary vasodilator therapies are implemented may prohibit significant symptomatic benefit especially given LA dysfunction is seen early in the left heart disease process.[29] Other than treatment of atrial arrhythmias and anticoagulation, therapeutic options of LA dysfunction are non-existent at the present time.[30] Atrial arrhythmias are clearly associated with worse outcomes and RV function in HFpEF.[31, 32] Restoration of sinus rhythm by atrial fibrillation ablation has morbidity and mortality benefit in HF, but it is unclear what effect restoration of sinus rhythm has on development and severity of pulmonary hypertension, particularly when treatment of atrial arrhythmias only improves electrical function and not mechanical function of the LA.[33–35] A more complete understanding of alterations LA structure and

function in response to HFpEF and HFrEF is essential to determining risk for development of PH, differences between hemodynamic PH subtypes in HF, and potential therapeutics.

The diastolic pressure gradient (DPG), calculated as the difference between PA diastolic pressure and PAWP, and transpulmonary gradient (TPG), calculated as the difference between mPAP and PAWP, were previously key to PH diagnosis in patients with LHD and remain relevant despite their absence from the most recent diagnostic criteria in consensus guidelines. Elevated TPG and PVR in end-stage HF indicate worse prognosis and can prohibit cardiac transplantation.[36] The differentiation between Ipc-PH and Cpc-PH, or "reactive" versus "fixed" PH in end stage HFrEF is a critical part of the cardiac transplant evaluation. Often a systemic vasodilator study is recommended for those patients with PA systolic pressure ≥50 mmHg, TPG ≥15mmHg, or PVR ≥3 WU if systemic systolic blood pressure is >85 mmHg to determine severity of PH and improvement in these indices with reduction in systemic afterload.[37] Assessment of the degree of pulmonary vascular disease can be especially problematic in patients with severe, concomitant right-sided HF, where the right ventricle is unable to mount significant pulmonary pressures. Presumably the use of PVR partially overcomes this issue by incorporating the cardiac output into assessment of the pulmonary vascular disease; however, hemodynamic loading, congestion, and pulmonary vessel recruitment can all impact the TPG and DPG, although DPG less so.[38] None of the currently used variables provide a complete understanding of the degree of pulmonary vascular disease present in PH-LHD, and these nuances in the diagnostic criteria of PH-LHD are not typically considered in pre-clinical models of PH-LHD.

HEMODYNAMIC PHENOTYPES OF PH-LHD

Theoretical pathophysiologic models of PH-LHD often show the LHD process (with both HFpEF and HFrEF combined) as a continuum of advancing severity of disease that starts with Ipc-PH and evolves into a pre-capillary component due to vascular remodeling and/or vasoconstrictive response to hemodynamic loading. This load occurs when hemodynamic congestion, an increase in LVEDP and LA pressure, progresses to pulmonary congestion with an increase in extravascular fluid in the lungs, and systemic congestion in series.[39] The current progressive model of PH-LHD does not have clear longitudinal hemodynamic data to support it, and evidence has emerged that patients with Cpc-PH have overlapping features with PAH.[40, 41] This overlap may indicate that some patients have an accelerated course that leads to Cpc-PH or have a predisposition to develop pre-capillary disease simultaneously with LHD. Proposed phenotypes of PH-LHD, and their relatedness to each other, are outlined in Figure 1.

Since in the initial World Symposium on PH, much of the subgrouping, phenotyping, and implementation of therapy has been made under the assumption that patients have PH of one type or the other (pre-capillary vs. post-capillary) in isolation. In clinical practice rare is the patient who presents to the clinic or the hospital with isolated pre-capillary PH without other risk factors for LHD. The prevalence of obesity, sleep apnea, atrial fibrillation, hypertension, tobacco use, and diabetes, even in those younger than 50, means a significant proportion of the population inevitably has one or two risk factors for LHD.[42–44] The pervasiveness of these risk factors in the general population indicate that PAH and LHD cannot be

mutually exclusive, especially in patients with connective tissues diseases that are potent risk factors for both LHD and PAH. The reliance on one set of (variable and relatively poorly understood) hemodynamic data, taken almost in isolation without consideration of pre-test probability and overlapping disease processes has resulted in very strict definitions of those patients that are offered therapy for PAH. There is clear data of demographic, hemodynamic, and genetic similarities between populations of patients with PH-LHD (particularly the Cpc-PH phenotype) and PAH.[40, 41] PH-LHD patients with evidence of pulmonary vascular disease (PVR≥3 Wood Units) have worse prognosis, and as such these changes in pulmonary vascular function and structure may be markers of divergent pathophysiology and may serve as potential therapeutic targets.[16] Subgrouping PH-LHD into those with PAH risk factors may help differentiate a population of patients distinct from those with primarily congestion-driven PH. Figure 1 summarizes the 2 divergent theoretical models of PH-LHD (progressive continuum vs. risk factor overlap), which is relevant to the basic and translational scientific investigation of PH-LHD.

STRUCTURAL AND FUNCTIONAL CHANGES IN PULMONARY HYPERTENSION

Chronic hemodynamic congestion is believed to progressively drive structural and functional changes in the LA and pulmonary vasculature. In response to pressure and volume overload the LA dilates, and alterations in cardiomyocyte structure and mechanical function occur, which result in LA mechanical dysfunction. Ultimately, LA stiffness increases, and the function of the LA as a pressure and volume buffering reservoir between the LV and pulmonary circulation is impaired.[24, 45] Loss of LA function (particularly loss of LA reservoir function—the ability of the LA to fill from the pulmonary veins during ventricular systole) correlates with lower PA compliance and higher PVR in the setting of HF[46] (Figure 2), with loss of LA compliance precipitating increases in PA stiffness.[24] PA stiffness directly correlates to the severity of right ventricular dysfunction, indicative that right ventricular dysfunction in this population is impacted by both afterload (PVR) and pulsatile load (PA stiffness), of which pulsatile load appears to have a larger impact.[47, 48] These changes effectively switch the pulmonary vasculature from a low pressure, high compliance system to relatively high-pressure, low compliance system. However, some data departs from this theory as Cpc-PH had less severe cardiac structural remodeling on echocardiography compared to Ipc-PH in a large electronic health record-based cohort.[40] Patients with Cpc-PH had smaller LA and ventricular dimensions and less LV hypertrophy (smaller LV mass and lower LV thickness) on echocardiography compared to Ipc-PH.[16, 40] The lesser severity of these structural changes raise the question of a potential predisposition or increased sensitivity of the pulmonary vasculature to congestive stress, where small changes in diastolic function have a larger impact in Cpc-PH patients. Alternatively, in some Cpc-PH patients, elevated PVR may occur first, thereby resulting in reduced blood flow to the LA and LV, and PAWP increases later due to LHD risk factors. Finally, misdiagnosis is also a possibility in retrospective electronic health record-based cohorts, which may have explained the aforementioned findings.

Molecular, functional, and structural changes in the pulmonary vasculature in response to reduced LA compliance and the resultant increase in hemodynamic stress is initially adaptive, but continued pulmonary vascular wall stress appears to drive maladaptive and pathologic changes. Changes in PA compliance coincide with loss of elastin and expansion of the extracellular matrix in both animal models of PH-LHD patients.[49, 50] These structural changes are suspected to be related to “stress failure” or pressure injury of the capillary wall.[51] Edema-driven injury to this alveolar-capillary interface in animal models activates matrix metalloproteinases, reducing the strength and increasing the permeability of the vascular endothelium.[52, 53] Patients with acute cardiogenic pulmonary edema have elevated circulating levels of pulmonary surfactant proteins that leak across a stressed or disrupted alveolar-capillary interface.[54, 55] Despite treatment and resolution of acute pulmonary edema, circulating pulmonary surfactant proteins remain elevated for up to 2 weeks indicating a persistent disruption of the alveolar-capillary interface.[56] Along with pulmonary surfactant, circulating tumor necrosis factor-α (TNF-α) is elevated in acute pulmonary edema and similarly persist beyond clinical resolution. These findings suggest that injury to the capillary-alveolar interface persists past resolution of cardiogenic pulmonary edema due to LHD and may have the potential to trigger systemic inflammation.

Histologic structural modifications in the pulmonary vasculature occur frequently in PH-LHD, similar to vascular findings first described in severe mitral stenosis patients which manifested as pulmonary arteriopathy and venopathy.[57, 58] Autopsy specimens of lung parenchyma in chronic HF patients show evidence of “congestive vasculopathy” with vascular remodeling across the spectrum of the pulmonary vascular bed.[59, 60] Venous, capillary, and arterial remodeling are a result of LA hypertension and driven by adaptive and maladaptive pathways in the lung vasculature.[61, 62] Wall stress is increased in pressure-loaded vasculature and drives structural changes in the vessels to accommodate stress, resulting in vasodilation and increased vessel wall thickness. Autopsy specimens from patients with PH-LHD demonstrate increased intimal and medial thickness in pulmonary arteries and veins compared to healthy controls but less structural changes than those seen in pulmonary veno-occlusive disease (Figure 3).[60] More severe elevation of PA systolic pressure in PH-LHD correlated with greater degrees of arterial and venous remodeling with a greater percentage of arterialized veins in PH-LHD compared to pulmonary veno-occlusive disease (Figure 3). A separate examination of muscular arteries in patients with PH-LHD (defined as PA systolic pressure >30 mmHg or mPAP ≥19 mmHg) in patients with HFrEF who had undergone cardiac transplantation showed increased medial thickness in all patients without significant intimal fibrosis, although medial thickness did not correlate with post-transplant hemodynamics.[59] A study of HFrEF patients with lung biopsy at time of LV assist device (LVAD) demonstrated increased volume of vascular media, intima, and adventitia in arteries and veins compared to controls.[50] In some cases, the LVAD PH-LHD patients had media and intimal remodeling that nearly occluded the lumen indicative of the severe structural vessel changes that may occur in the setting of PH-LHD.

The differentiation between adaptive and maladaptive structural changes in PH-LHD is not well defined. The LA is sensitive to pressure and volume elevations and responds quickly to these hemodynamic derangements. A canine model of HFpEF demonstrated early adaptive response of the LA to pressure and volume stress with LA dilatation and augmented

contractile function.[63] However, with continued hemodynamic stress the pressure-volume relationship of the LA changes and LA compliance decreases, at which time these responses shift to maladaptive.[63] These LA changes result in atrioventricular uncoupling and impaired cardiac output due to reduced LV stroke volume. Reduction of LA compliance impairs its reservoir function which buffers the pulmonary vascular bed from increased LV pressures; the resultant elevation in LA pressure results in a shift of the PVR/pulmonary arterial compliance (C_{PA}) relationship to a state where compliance is lower at any given PVR. [48] Early mitigation of LA hypertension can modify these vascular changes, preventing the histologic pulmonary vascular remodeling and changes in pulmonary hemodynamics.[64] The exposure of the pulmonary vascular bed exposure to hemodynamic stress drives pulmonary venous, capillary, and arterial remodeling, with impaired endothelial function, fibrosis, and smooth muscle proliferation. [60] These changes prove to be maladaptive, as even with relief of LA hypertension the abnormalities in PVR and C_{PA} persist.[64]

There is evidence of genetic overlap between PAH and the Cpc-PH subset (but not Ipc-PH) that may contribute to the severity of pulmonary vascular disease. Single nucleotide polymorphisms (SNPs) resulting in increased lung gene expression of various proteins that have been identified in PAH have also been demonstrated in Cpc-PH.[40] These SNPs encode modifications of extracellular matrix, basement membrane structure, as well as modifications in actin binding and structural molecular activity. These genetic variants were not found in Ipc-PH, suggesting that there may be a separate genetic subgroup predisposed to the Cpc-PH pattern of PH-LHD. These findings suggest the potential for a “two-hit hypothesis” where development of pre-capillary PH in the setting of LHD requires a second insult (e.g., genetic, metabolic, or hormonal) that predisposes to pulmonary arteriopathy. Below we outline the data surrounding potential influential contributors to pulmonary vascular disease in the setting of PH-LHD disease.

ANIMAL MODELS OF PH-LHD

Few animal models of PH-LHD exist, in HFpEF specifically the variability of human disease has made it difficult to create similar animal phenotypes (Table 2).

A Zucker (ZSF1) rat model of PH-HFpEF was created by inducing metabolic syndrome via a defect in leptin receptor combined with vascular endothelial growth factor receptor-2 antagonist Sugen 5416 (SU5416) which essentially layered features of the well-known SU5416-hypoxia model of PAH over the obese metabolic syndrome found in HFpEF. [65, 67] The SU5416-exposed obese ZSF1 rats had normal LVEF but developed elevated right and left sided pressures as well as higher PVR and pulmonary vascular remodeling compared to lean rats.[65] Recently, a combined obesity and hypertensive stress (high fat diet plus L-NAME) has been utilized to produce a HFpEF phenotype in mice that mimics the human HFpEF phenotype. The *db/db* (leptin receptor-deficient) mouse is another model that mimics the HFpEF phenotype, albeit with less pulmonary congestion. SU5416 could theoretically be overlayed on top of these models to mimic the CpcPH phenotype of PH-HFpEF.

A similar mouse model was developed by observing the hemodynamics effects of a high fat diet in 36 strains of mice.[66] Of the strains investigated the AKR/J, NON/shiLtJ, and

WSB/EiJ developed hemodynamic changes consistent with PH-LHD. OF those strains the AKR/J mouse findings were the most reliably reproduced with the high fat diet inducing metabolic syndrome and the mice developing elevated right ventricular systolic pressures, LV end diastolic pressures, with biventricular hypertrophy compared to those fed a regular diet.[66] This mouse model also showed higher PVR and pulmonary vascular remodeling, and these hemodynamic abnormalities progressed with continuation of the high fat diet. These metabolic models more closely approximate clinical disease than previous models of aortic banding in which increased LV afterload induces higher LV filling pressures, elevated mPAP, and PVR.[68] While the aortic banding animal model is the most commonly used model in PH-LHD (specifically to model PH-HFpEF), this model does not mirror the metabolic syndrome component found in humans with HFpEF, and this model progresses to overt LV systolic dysfunction (HFrEF), which is not seen in the vast majority of patients with HFpEF who are followed longitudinally (i.e., in HFpEF, LVEF remains preserved over time and does not progress to HFrEF).

Similar models focusing on induction of HF without consideration of the metabolic features the co-exist in PH-LHD have been the basis of PH-LHD animal studies. Although aortic banding is the most widely used, several other models exist. Mouse models of transverse aortic constriction create phenotypes similar to aortic banding with development of HFpEF and pulmonary hypertension, although it also induced severe pulmonary fibrosis, which is not typically found in humans with HF.[69] Pulmonary venous outflow obstruction by pulmonary vein banding or creation of left atrial stenosis have also been use to pressure load the pulmonary vascular bed in animal models, and induce PH and RV failure in rats and large animal models.[70–72] The primary modality of inducing HFrEF in animal models has been coronary artery ligation to induce an ischemic cardiomyopathy, and this model can induce mild-to-moderate PH associated with low cardiac output and congestion, but infarct size is difficult to control, and the survival rates post-induced myocardial infarction can be low.[73, 84–86] The mechanical, pressure overload models of PH-HFpEF do not mirror phenotypes seen in clinical practice, rather the metabolic-driven models are closer to human phenotypes.

PROPOSED PATHOBIOLOGIC CONTRIBUTORS TO PH-LHD

The pathophysiology of Group 2 PH and contributing factors to disease severity and development of PH-LHD are not well understood, especially in HFpEF. There is emerging evidence of underlying inflammatory, hormonal, and metabolic derangements that appear to contribute to pulmonary vascular disease in LHD. Figure 4 summarizes our current understanding of the pathobiology of PH-LHD, as explained in detail below.

Endothelial Injury and Dysfunction

Both HF and PH are independently associated with systemic endothelial dysfunction in venous and arterial beds.[87, 88] Animals models of HF have demonstrated evidence of pulmonary endothelial dysfunction.[89–91] Multiple endothelial vasoactive mediators have been implicated in this dysfunction with overlap in both PH and LHD; however, the initial insult has been difficult to elucidate. Shear stress is the mechanical force on the

endothelium caused by blood flow and is instrumental in both vascular homeostasis as well as development of disease.[92] Reduced shear stress is a known driver of endothelial dysfunction in the systemic vasculature and plays a role in atherogenesis.[93] Reductions in shear stress also correlate with higher PA pressures in patients with PAH [94, 95] Changes in shear stress stimulate endothelial responses to adapt to alterations in pressure and flow; in endothelial dysfunction this response in muted or maladaptive. Here we describe a variety of mediators of endothelial function that have potential involvement in PH-LHD.

Caveolae and Caveolin-1—Changes in shear stress are sensed by endothelial cells, resulting in alterations in cellular signaling, in which caveolae and caveolin-1 expression and activity are key drivers.[96] Caveolae are plasma membrane invaginations that sense and convert hemodynamic changes in the vasculature into intracellular signals. Caveolin-1 is the main structural membrane protein within caveolae that enacts messaging across the cell membrane, with roles in intracellular calcium signaling, regulation of nitric oxide (NO) production, and activation of PA smooth muscle cell (PASMC) proliferative pathways.[97] Changes in caveolin-1 signaling are present in HF and PAH. Chronic beta-adrenergic stimulation, which occurs in HF as well as hypoxia, reduces caveolin gene expression.[98, 99] Caveolin-1 knock-out mice develop dilated cardiomyopathy with associated PH and exhibit pulmonary vascular pathologic changes similar to PH-LHD.[100, 101] In the vasculature, NO availability is partly controlled by the interaction between caveolin-1 and endothelial NO synthase (eNOS).[102] Caveolin-1 binds to eNOS rendering it inactive and unable to produce NO, a potent regulator of vascular tone.[103, 104] Caveolin-1 expression is lost in structurally normal arteries in PAH but upregulated in PASMCs surrounding remodeled arteries.[105] While caveolin-1 has been implicated in PH, the role of caveolin-3 is less clear, with inconsistent changes in HF. Murine models of HF show selective reduction in expression of caveolin-3 expression rather than caveolin-1 or 2.[106] Overexpression of caveolin-3 in rodent models reveals reduction in hemodynamically driven cardiomyocyte hypertrophy.[107] Conversely, increased expression of caveolin-3 is present in a canine pacing-induced HF model.[108]

At the present time, it is not clear how caveolin expression and function contribute to PH-LHD; decreased expression in some instances appears to modify cardiomyocyte adaptive responses, whereas caveolin gene expression is variable in pulmonary vascular disease and it is unknown whether these changes are reactive to or independent of LA hypertension. Nevertheless, caveolae and the caveolin proteins are essential to signal transduction responses to shear stress (and therefore the endothelial cellular response to hemodynamic alterations); therefore, further investigation of the role of caveolae PH-LHD is worth pursuing.

Nitric Oxide—NO is well known to be deranged in the setting of HF. Peripheral venous dysfunction is associated with imbalance in NO synthesis and degradation (resulting in reduced NO bioavailability), and increased NADPH oxidase superoxide generation, which are both also regulators of pulmonary vascular homeostasis.[109, 110] Peripheral endothelial dysfunction occurs in HFpEF, where response to flow mediated vasodilation correlates with higher PVR on invasive hemodynamics.[111] NO-mediated endothelium-dependent

vasodilation in chronic HFrEF is also impaired and has also been attributed to reduction in NO synthesis, increased degradation, and reduced vasodilatory responsiveness.[112–115] The beneficial pulmonary vascular effects of NO also include reduction in smooth muscle hypertrophy and proliferation.[116] A rodent model of HF showed impairment of alveolar-capillary endothelial function and absence of NO synthesis in response to mechanical and chemical stress driven by impairment of endothelial calcium handling.[91] Notably, the expression of eNOS was not different from controls; rather, activation of eNOS by calcium was reduced. NO production and NO-dependent pulmonary vasodilation are impaired in PH-LHD, although it is unclear to what degree the vascular response is mediated through hemodynamic-driven changes in biochemical signaling and NO synthesis or scavenging mechanisms are causal or consequential.[117] Furthermore, restoring NO-cyclic guanosine monophosphate signaling via phosphodiesterase-5 inhibition and soluble guanylate cyclase stimulation has not proven beneficial in PH-LHD (especially in PH-LHD due to HFpEF, which has been studied extensively in clinical trials).[118–124]

Endothelin-1—Endothelial cells secrete endothelin-1 (ET-1) with the primary receptors located on vascular smooth muscle cells through which ET-1 acts as a potent vasoconstrictor and pro-proliferative agent.[125, 126] The ET-1 peptide is important for maintenance of vascular tone and has mitogenic effects on endothelial and vascular smooth muscle cells.[127] Balance between vasoconstrictive and vasodilatory effects are modulated by concentrations of ET_A and ET_B receptors, respectively, on vascular smooth muscle and endothelial cells.[128, 129] Endothelin-1 levels are elevated in chronic HF and correlate with severity of PH and 1 year mortality.[130–133] The downregulation of ET_B receptors and upregulation of ET_A receptors seen in chronic HF tips the balance into predominantly vasoconstrictive and smooth muscle cell proliferative ET-1 effects [117, 130, 134] Local administration of ET_A receptor antagonist causes a dose-dependent reduction in PVR in patients with chronic HF owing to the integral role of ET-1 in pulmonary vasoconstriction.[135] Additionally, ET-1 mediates pulmonary vascular remodeling in PH-LHD by inducing smooth muscle proliferation and hypertrophy as well as collagen production.[136] The pulmonary vasculature is particularly rich in ET-1 production and sensitive to its effects.[137]

Despite the critical role of ET-1 in the pathogenesis of HF and PH-LHD, multiple clinical trials of endothelin receptor antagonists (ERAs) have failed to demonstrate benefit in the setting of PH-LHD. Vascular tone and smooth muscle tone is in part driven by the balance between ET-1 and NO activity as well as prostacyclin-, cyclooxygenase-, and thromboxane-mediated vascular effects, which may explain the lack of benefit of ERAs in PH-LHD (Figure 4).[138] ET-1 also reduces cardiomyocyte gene expression of natriuretic peptides,[139] which may counteract their beneficial vasodilatory and natriuretic effects. Indeed ERA-induced sodium and fluid retention have been the Achilles heel of ERA therapy in patients with HF. For these reasons, strategies to selectively reduce ET-1 or block endothelin receptors in the pulmonary vasculature while preventing the natriuretic peptide reduction and avoiding adverse renal effects may be a fruitful endeavor in the future.

Prostacyclin and Thromboxane A_2—In the normal pulmonary circulation, prostacyclin (also known as prostaglandin I2 [PGI_2]) is a key to contributor to vascular tone

via stimulation of cyclic adenosine monophosphate production-induced smooth muscle relaxation.[140] Thromboxane-A_2 (TXA_2), a countermeasure to the vasodilatory and anti-proliferative functions of PGI_2, drives vasoconstriction and promotes platelet aggregation.[141] Both PGI_2 and TXA_2 are products of arachidonic acid metabolism by cyclo-oxygenase (COX) activity, and the balance of PGI_2/TXA_2 activity regulates vascular tone. This PGI_2/TXA_2 ratio depends on many variables including the amount of COX isoform present with COX-1 favoring TXA_2 and COX-2 favoring PGI_2.[142] In rat models of cardiovascular disease, angiotensin-II induces production and release of PGI_2 from cardiac fibroblasts which in turn prevents TGF-β-induced upregulation of extracellular matrix genes and therefore functions as an anti-fibrotic.[143, 144] In a canine model of HF, expression of arterial eNOS and COX-1 gene expression was reduced as was resultant NO production in response to vasodilators.[145] Circulating PGI_2 is increased in chronic HF and correlates with plasma renin and angiotensin-II concentrations.[146] Conflicting data exist about the ability of TXA_2 to stimulate smooth muscle proliferation, although it appears that the presence of serotonin (5-HT) is synergistic with TXA_2 producing a mitogen effect on smooth muscle cells.[147]

Platelet Bioenergetics—Platelet aggregation occurs at the site of vascular injury and platelet-derived factors influence vascular repair and remodeling at these sites utilizing peptide growth factors, two of which are serotonin (5-HT), and TXA_2.[148] Platelet aggregation and activation at sites of “stress failure” or shear injury in the pulmonary vascular bed specifically have not been well characterized. The pulmonary vasculature exhibits metabolic abnormalities in PH that favor glycolysis and alter electron transport chain function[149, 150] Platelet metabolism and function in PH-LHD patients is similarly altered; mitochondrial maximal oxygen consumption rate and reserve respiratory capacity are both increased as is seen in Group 1 PAH patients.[151] Reserve respiratory capacity the amount of ATP that can be produced via oxidative phosphorylation in the setting of an increased demand and is a marker of mitochondrial function. The increased reserve capacity in PH-LHD platelets appears to be in part due to increased fatty acid oxidation, as has been shown in PAH.[152] Increased respiratory reserve capacity is associated with resistance to apoptosis and improved survival with oxidative stress.[153] Platelet glycolytic rate, however, is not increased in PH-LHD patients in comparison with Group 1 PAH.[151, 152] These metabolic alterations do not correlate with PVR in PH-LHD, as in Group 1 PAH, but are associated with worse right ventricular function.[151] NO-induced platelet activation did not differ from healthy age-matched controls. Platelet function is altered in PH-LHD but it is unclear to what degree these differences are reactive versus pathologic. Furthermore, while prostacyclin analogues are one of the mainstays of therapy in patients with Group 1 PAH, their use in PH-LHD has not been well studied, though in a trial of an intravenous prostacyclin (epoprostenol) with severe HFrEF was associated with worse outcomes compared to placebo.[154]

Serotonin—Serotonin hormone is released by activated platelets, can induce pulmonary vasoconstriction and smooth muscle proliferation, and is metabolized in the lung, and has been studied extensively in PAH.[155, 156] Local serotonin release is instrumental in platelet-induced vasoconstriction, as shown in acute coronary syndromes.[157] HF is associated with in enhanced platelet aggregation and activation in which the local serotonin release may drive

pulmonary vascular remodeling.[158, 159] Notably, serotonin appears to have a substantial contribution to the stimulation of platelet induced-smooth muscle cell proliferation.[160] Circulating serotonin levels are elevated in patients with HF and the degree of elevation correlates with decompensation and worse functional class.[161] Currently, it is unknown if or how much the serotonin pathway is involved in the development of PH-LHD.

Tumor Necrosis Factor-α and Interleukin-6—Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine produced by macrophages and monocytes and upregulated in HF.[162–164] Rodent models of pulmonary congestion in HF demonstrate increased circulating and pulmonary venous concentrations of Interleukin-6 (IL-6) and TNF-α which were exacerbated with increased pulmonary venous mechanical stretch used to simulate the distention that occurs in response to elevated LA pressure.[165] In other animal models, higher levels of circulating TNF-α are associated with increased circulating ET-1 levels while IL-6 induces C-reactive protein (CRP) production in the liver.[166–168] Endothelin-1 and TNF-α are ultimately stimulated by CRP-induced complement activation, thereby creating and deleterious positive feedback loop.[168, 169] Known as drivers of chronic inflammation, TNF-α and IL-6 have increased expression in patients with HF.[170, 171] Notably, IL-6 and TNF-α levels correlate with elevated PA pressures in HFrEF and HFpEF.[172] If increased levels of inflammatory cytokines are drivers of pulmonary vascular disease, targeting inflammation would be a worthwhile therapeutic target. Indeed, autoimmune disease, which is associated with increased inflammation, is known to be major risk factor for PAH and likely plays a key role in the development of pulmonary vascular disease in LHD and supports the role of a dysregulated immune system in driving PH-LHD, particularly Cpc-PH. Alternatively, increased severity of HF (which is present in patients with elevated PA pressures and pulmonary vascular disease) is known to result in increased inflammation, which would mean that therapies targeting the immune system are unlikely to be successful in PH-LHD. Both scenarios are likely true, and targeted studies of both innate and adaptive immunity aimed at deciphering the role of the immune system in the development and progression of PH in LHD remains a worthwhile pursuit, with the hope of ultimately identifying therapeutic targets in specific phenotypes of PH-LHD.

Vascular Endothelial Growth Factor—Angiogenesis is dependent on vascular endothelial growth factor (VEGF), which, in turn is often stimulated by both mechanical and metabolic stress. [173] The VEGF-D subtype appears to be most altered in HF and is instrumental in lymphangiogenesis.[174] Systemic VEGF-D levels are elevated in patients with pulmonary congestion on chest imaging, and circulating levels of VEGF-D are higher in PH-LHD.[175] In HFrEF, higher PAWP and lower cardiac output are associated with higher VEGF-D levels.[176] VEGF-D appears to be elevated in hemodynamic and pulmonary congestion, the presumptive precursors of PH-LHD, but the role of VEGF in development of PH in HF is not well characterized. Preclinical models of PAH and PH-HFpEF have used the VEGF receptor antagonist SU5416 in combination with hypoxia stimulus to recapitulate features of PH.[177] However, clinical studies of PAH and PH-LHD demonstrate significant elevation of VEGF-D, with PH-LHD demonstrating the highest concentrations. [178, 179] This presents a paradox given VEGF antagonists in combination with hypoxia induce PH in murine models, yet in clinical studies elevations in VEGF levels are associated with more

severe PH. One study hypothesized that VEGF activity through the un-blocked VEGF3 receptor (SU5416 antagonizes receptors VEGF-1 and −2) and change in expression of VEGF isoforms. In the lungs of SU5416/hypoxia rat PAH model there was increased expression of VEGF-C and VEGF-D as well as VEGF-3 receptor.[180] Interestingly the addition of a VEGF-3 antagonist prevented but did not ameliorate structural changes and development of PH in the SU5416/hypoxia model. The SU5416 model blocks VEGF-1 and VEGF-2, ultimately shifting activity to VEGF- C and VEGF-D, of which VEGF-D predominates on PH-LHD and PAH, isoforms and activation through available VEGF-3 receptor. This VEGF-3 effect produces vascular changes and lumen obliteration driving pulmonary hypertension.[180] However, VEGF-3 knockout mouse models are also associated with development of severe PH with hypoxia and VEGF-3 receptor expression is reduced in PAH and PH-LHD.[181, 182] It has been hypothesized that knock-out of VEGF-3 receptor leads to increased VEGF-C signaling through VEGF-2 receptor. [183] VEGF-2 and VEGF-3 receptors both play a role in the vascular endothelial mechanosensitive response to shear stress. [184] VEGF-C and VEGF-3 also play a primary role in lymphangiogenesis and there is increasing recognition of the importance of the lymphatic system in HF.[185] A preclinical model of HFpEF demonstrated early increase in VEGF-C and VEGF-3 protein expression which then dropped with worsening HF and decompensation.[185] VEGF antagonism results in PH and increased expression appears to have a protective effect, yet, in the presence of cardiovascular or pulmonary disease VEGF may promote cellular proliferation and vascular remodeling.[87, 186] Further preclinical studies may take advantage of combining metabolic stress (e.g., high fat diet), hypertensive stress (e.g., L-NAME), and SU5416/hypoxia to create a model of Cpc-PH in HFpEF to better elucidate the role of VEGF and VEGF receptors in the disease process. This type of strategy has been employed successfully in rat models as well, by combining the Zucker diabetic rat (ZSF1) model of HFpEF with SU5416/hypoxia, as detailed above.[187]

Estrogen—There is an association between post-menopausal reduction in estrogen production and endothelial dysfunction, partly explained by estrogen modulation of NO, endothelin, and prostacyclin pathways.[188–190] Female predominance in PAH had led to suspicion of sex hormone influence on pulmonary disease, but this association is incompletely characterized. In addition, estrogen appears to have some protective effects on RV function.[191] Visceral adipose is a primary site of estrogen production, and estrogen modulates leptin production.[192, 193] The influence of estrogen and sex hormones on development of PH-LHD requires further investigation, but seems worthwhile given the postulated role of loss of estrogen on development of HFpEF, pulmonary vascular disease, and right ventricular dysfunction.

Obesity and Metabolic Syndrome

Obesity is associated with the development of invasively diagnosed pulmonary hypertension, with risk of PH increasing in parallel with increasing BMI.[194] Hemodynamic markers of PH such as mPAP, PAWP, and TPG increase with advancing classes of obesity. There is a higher prevalence of CPC-PH and IPC-PH with more advanced obesity classes. Unsupervised machine learning (phenomapping) of HFpEF patients has shown that the pheno-group of patients who had higher prevalence of obesity, diabetes mellitus, and obstructive sleep apnea

had higher PVR.[195] Metabolic syndrome (MetS) represents a milieu of physiologic and biochemical abnormalities including central obesity, glucose intolerance, insulin resistance, and dyslipidemia; the presence of which increases risk of development of cardiovascular disease and overt diabetes mellitus. Metabolic syndrome is highly prevalent in HFpEF but also occurs in up to 39% of patients with PAH.[196]

While inflammation has been quoted as the driver of obesity related PH-LHD, the mechanisms are complex and variable, and likely go beyond inflammation alone. Adiponectin is a fat-derived hormone that in animal models reduces intimal thickening in injured arteries and suppresses proliferation of smooth muscle cells.[197, 198] Vascular effects of adiponectin are mediated by AMPK activation of eNOS which increases NO synthesis while anti-inflammatory effects stem from reduction of TNF-α (and subsequently interleukin-8) production by endothelial cells in response to injury.[199–201] COX2 expression increases with higher levels of adiponectin which favors PGI_2 vasodilatory and anti-proliferative effects and improving endothelial function in mouse models.[202] Adiponectin levels are negatively correlated with BMI, more specifically visceral adipose, as opposed to leptin which increases with increasing BMI.[203, 204] Adiponectin levels are lower in diabetic patients compared to non-diabetes, and among diabetics, those with coronary disease have less circulating adiponectin.[205] Tumor necrosis factor-α (elevated in HF) inhibits adiponectin promoter activity and may therefore modifies plasma levels of adiponectin in systemic inflammatory states. Hypoadiponectinemia appears to be integral in the development of metabolic syndrome phenotype.[206] Adiponectin and leptin have been implicated in the development of PH in MetS and obesity.

Leptin, a proinflammatory cytokine that is key in glycemic and lipid metabolism, plays a role on endothelial function and is a the product of a hypoxia-inducible factor-dependent gene.[207, 208] Leptin normally has a vasodilatory effect; however, *in vitro* pulmonary endothelial cells in PAH have been shown to overproduce leptin, and PASMCs overexpress leptin's primary receptor.[209] The subsequent activity of leptin on PASMCs augments hypoxic driven proliferation and appears to be involvement in PAH development.[209] Higher circulating leptin levels are also associated with increased risk of incident HF and disease progression.[210–213] Patients with advanced HFrEF have elevated circulating leptin levels and soluble leptin receptor even when adjusted for BMI, although there is no data in humans describing differences between those with and without PH.[214] Rodent models of PH-HFpEF have shown that elevated circulating leptin levels cause impairment of myocardial relaxation.[74, 215] Natriuretic peptides appear to decrease the secretion of leptin in adipose tissue and suppress secretion of other inflammatory cytokines, including IL-6 and TNF-α.[216]

Atrial natriuretic peptide exerts anti-inflammatory effects by suppression of circulating markers of chronic inflammation, IL-6 and TNF-α.[216] Circulating levels of these natriuretic peptides are known to be reduced in the obese HFpEF phenotype which also demonstrated more RV dysfunction and dilation, higher PAWP, and higher exercise pulmonary pressures.[217] Patients with HFpEF have lower natriuretic peptide levels compared to those with HFrEF.[218] Animal and human models of HFpEF-PH demonstrate upregulated activation of IL-6/signal transducer and activator of transcription 3 (STAT3) pathways

in MetS-LHD, which exacerbates PH, with pulmonary vascular remodeling, macrophage infiltration, and IL-6/STAT3 upregulation in human lung tissue.[74] Increased levels of IL-6 are also known to alter endothelial function and arterial stiffness.[219] Treatment with metformin and an anti-IL-6 antibody in a rodent model of MetS-LHD induced regression of pulmonary hypertension implicating a role for multimodal suppression of the leptin/IL-6/STAT3 pathway as a promising target in PH-HFpEF.[74]

Metabolic syndrome and each of its independent components are associated with increased activity of neprilysin, which degrades natriuretic peptides, which reduces normal physiologic inhibition of aldosterone secretion by circulating ANP.[220, 221] Obesity also results in increased aldosterone production and renin-angiotensin activation outside of ANP-mediated effects.[222–224] The ultimate result of these factors is hyperaldosteronism, with sodium retention, insulin resistance, increased leptin expression, and an increase in inflammatory markers. [225–227] The renin-angiotensin-aldosterone system has a role in pulmonary vascular remodeling in PAH with elevated levels of angiotensin and aldosterone correlating with hemodynamics and pulmonary vascular remodeling through similar mechanisms implicated in heart disease.[228] Pulmonary angiotensin-II levels and angiotensin-II type 1 receptor expression on myofibroblasts have been shown to be increased in post-MI rat models of PH-LHD.[229] Aldosterone antagonism may have clinical benefit in patients with PAH and prevent pulmonary vascular remodeling in pre-clinical models.[230, 231] Currently while pathologic changes in aldosterone in HF and PAH exist, the role of aldosterone in PH-LHD is less clear.

Splanchnic Circulation

Right-sided HF plays a significant role in prognosis in patients with LHD, regardless of underlying ejection fraction, and is significantly impacted by pulmonary vascular function.[232–234] The systemic venous congestion in RV failure affects multiple other organ systems, including the kidneys, gastrointestinal tract, and liver. Splanchnic venous congestion caused by RV failure has multiple potential effects on the gastrointestinal tract with increases in systemic inflammation and alteration of sodium and phosphate hemostasis.[235, 236] Venous congestion contributes to the development of cardiorenal syndrome, particularly driven by central venous pressure, and not PAWP or cardiac output.[237] Renal dysfunction results in altered calcium and phosphate metabolism which causes increased stiffness of the pulmonary artery thereby increasing RV afterload.[238] Renal dysfunction associated with splanchnic congestion causes dysregulation of mineral metabolism, specially calcium and phosphate homeostasis regulated by parathyroid hormone. A preclinical canine model of CKD showed and association between secondary hyperparathyroidism elevated pulmonary pressures and pulmonary vascular calcification.[239] Interestingly, in this model prophylactic parathyroidectomy resulted in significantly lower mPAP and RV pressure despite the same degree of renal dysfunction. Central venous congestion-induced splanchnic congestion may result in upregulation of NHE3 in the gut (by creating an acidotic environment in enterocytes due to poor blood flow and increased anerobic metabolism), thereby enhancing sodium resorption and resulting in lower pH in the gut lumen. Reduced pH in the gut lumen, in turn, can (1) reduce short-chain fatty acids (reducing integrity of gut gap junctions and increasing gastrointestinal permeability, a

risk factor for systemic infections) and (2) increase the population of bacteria that produce TMAO, which is known to increase inflammation.[235, 238] Increased sodium resorption in the gut facilitates additional fluid retention and congestion, loading the central vasculature, raising intracardial filling pressures, and driving elevation in pulmonary pressures. These abnormalities may be reasons why patients with PH-LHD, particularly those with right-sided HF, are predisposed to adverse outcomes.

Systemic inflammation is a suspected feature of splanchnic congestion that contributes to HF and development of PH-LHD. Altered gut permeability due to edema allows bacterial translocation and systemic exposure to endotoxin.[240] Decompensated HF patients have higher circulating levels of endotoxin than compensated, as well as higher concentrations of serum cytokines (CRP, TNF-α, and IL-6). Diuresis and relief of peripheral edema resulted in a significant reduction in circulating serum endotoxin levels, but cytokine levels remained elevated.[240] Gut edema contributes to the systemic inflammatory milieu in decompensated HF. Many of the circulating inflammatory markers we have described have important effects on vascular biology and endothelial function that contribute to development of PH in HF.

The splanchnic circulation holds a large proportion of the total blood volume, acting as a reservoir of volume able to be mobilized by alterations in venous tone. Venous capacitance, the ability of the vessel to accommodate changes in volume with minimal changes in pressure, is reduced in HF, obesity, diabetes, and inflammatory states, leading to increased central blood volume when stressed.[241–243] The volume loading of the central vascular compartment results in pulmonary and hemodynamic congestion, driving factors in development of PH and pulmonary vascular remodeling. Reduced PA capacitance in PH-LHD, which signals a lack of ability of the pulmonary vasculature to accommodate changes in volume loading, is associated with adverse outcomes.[244] Coupled with sodium-driven plasma volume expansion due to upregulation of gastrointestinal NHE3, the splanchnic circulation appears to play an integral role in the pathogenesis of PH-LHD. In patients with PH-LHD due to HFpEF, levosimendan (a calcium sensitizer and KATP channel opener) was associated with improved hemodynamics and exercise capacity compared with placebo.[245] Although levosimendan is known to increase contractility, it was reduction of the stressed blood volume via splanchnic vasodilation that appeared to be the underlying cause for improvement.[246] Given these encouraging results, further investigation of the effects splanchnic vasoconstriction on the development and progression of PH-LHD in animal models and humans is therefore warranted.

Lymphatic Dysfunction

The lymphatic system controls extracellular fluid volume, holding and transporting up to 8 liters per day, of which approximately 1.5L/day travels through the thoracic duct to the left subclavian vein.[247] This function is possible through both intrinsic factors, the pumping function of the lymphangion via smooth muscle, and extrinsic factors such as the respiratory cycle, skeletal muscle contraction, and surrounding blood vessel pulsations.[247] In HF, elevated central venous pressure can impede outflow from the thoracic duct, thereby increasing hydrostatic pressure and ultimately resulting in increased extracellular fluid.[248]

Recent data indicates reduced lymphatic reserve as a byproduct of microvascular disease and capillary rarefaction accompanied by dilated, dysfunctional lymphatics in HFpEF.[249]

Lymphatics may play a role in the acuity of HF and the development of pulmonary edema, as patients with longstanding HF tolerate higher filling pressures without development of pulmonary edema even as PH progresses. Hemodynamic congestion results in more equally distributed blood flow through the lung fields through capillary recruitment.[250] The thoracic lymphatics act to buffer the lungs from elevated intracardiac filling pressures by accommodating extracellular fluid influx.[251] Lymphatic vessels in the pulmonary connective tissues and pleural space can accommodate fluid removal as a high capacitance reservoir with up to ten-fold increase in volume chronically.[252] In PH-LHD, where left atrial pressure is one of the primary drivers of development of pulmonary hypertension, the capacity of the lymphatic system to act as a reservoir for excess volume serves to mitigate to some degree the hydrostatic pressure that drives PH.[253] When maximal lymphatic efflux rate is overwhelmed, both fluid and protein stalls in the interstitial compartment leading to ongoing edema development.[254, 255] Patients with HFpEF have lower numbers of lymphatic vessels with larger diameters although despite this drainage was impaired.[249] The lymphatic system contributes to pulmonary vascular hemodynamics as a reservoir for volume and pressure. In response to chronic congestion lymphatics muscularize and hypertrophy similar to the pulmonary vascular bed.[251, 252] VEGF-D, which is elevated in chronic HF, has strong lymphangiogenic and angiogenic functions. [176] The potential implications of this is important as increased circulating VEGF-D in chronic HF may, in part, be adaptive to drive the development of a larger lymphatic reservoir.[256] These changes indicate that the lymphatic system may play a critical role in the development and progression of PH-LHD given the role of lymphatic system in buffering congestion, and therefore should be studied more extensively in the pre-clinical and clinical settings.

FUTURE DIRECTIONS

Large gaps knowledge gaps exist in our understanding of PH-LHD, starting with accurate diagnostic criteria and rational pathophysiological and pathobiological disease classification. The most basic requirement for improved understanding PH-LHD is to establish a widely accepted, reproducible definition of disease, especially with provocative maneuvers. Determination of the impact of chronicity and severity of LHD as well as genetic, epigenetic, and inherited factors on risk for development of Cpc-PH versus Ipc-PH is also critical. Understanding the interplay between chronic inflammation in association with metabolic syndrome, insulin resistance, and the imbalance of vasoconstrictors and vasodilators in the pulmonary vascular bed is essential to finding intervenable pathways in these disease processes. Given the high prevalence, morbidity, and mortality of PH-LHD, it is essential that we continue to push the field forward in basic, translational, clinical, and epidemiological research so that we can identify patients at risk for PH-LHD, diagnose it early and accurately, treat it, and prevent progression of disease. Table 3 outlines important unanswered questions for improved understanding of PH-LHD and the underlying pathobiology which drives disease progression, which we hope will serve as a stimulus to the scientific community.

CONCLUSIONS

There are multiple phenotypes of Group 2 PH, which likely have significant variation in metabolic, hemodynamic, and inflammatory derangements. Hemodynamically, patients with Ipc-PH and Cpc-PH vary by severity of pulmonary vascular disease potentially driven by underlying wall stress and injury related to both the chronicity of exposure to LA hypertension over time and superimposed PAH risk factors. The current understanding of the pathobiology of PH-LHD is very limited. While endothelial dysfunction, obesity/metabolic syndrome, splanchnic vasoconstriction, and lymphatic dysfunction may all play a role, phenotypes vary, and the primary drivers of disease have not been fully identified. Furthermore, there are no direct treatments of PH-LHD, with a track record of multiple failed trials of pulmonary vasodilators. Improved understanding of the drivers of PASMC homeostasis and the biologic drivers of disease is essential to intervening in this disease process, whether via prevention or for amelioration.

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Nonstandard Abbreviations and Acronyms:

PH	pulmonary hypertension
LHD	left heart disease
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
PA	pulmonary artery
mPAP	mean pulmonary artery pressure
PVR	pulmonary vascular resistance
Cpc-PH	combined pre and post capillary pulmonary hypertension
Ipc-PH	isolated post capillary pulmonary hypertension
PAWP	pulmonary artery wedge pressure
LVEDP	left ventricular end diastolic pressure
LA	left atrium
LV	left ventricle

RV	right ventricle
DPG	diastolic pressure gradient
TPG	transpulmonary gradient
PAH	pulmonary arterial hypertension
TNF-α	tumor necrosis factor alpha
LVAD	left ventricular assist device
C_{PA}	pulmonary arterial compliance
SNP	single nucleotide polymorphisms
ZSF1	Zucker
SU5416	Sugen 5416
NO	nitric oxide
PASMC	pulmonary artery smooth muscle cells
eNOS	Endothelial nitric oxide synthase
NADPH	nicotinamide adenine dinucleotide phosphate
ET-1	endothelin-1
ET_A	endothelin receptor A
ET_B	endothelin receptor B
ERAs	endothelin receptor antagonists
PGI_2	prostaglandin I2
TXA_2	thromboxane-A_2
COX	cyclo-oxygenase
5-HT	serotonin
ATP	adenosine triphosphate
IL-6	interleukin-6
CRP	C-reactive protein
VEGF	vascular endothelial growth factor
MetS	Metabolic syndrome
AMPK	adenosine monophosphate protein kinase
BMI	body mass index

STAT-3	signal transducer and activator of transcription-3
CKD	chronic kidney disease
NHE3	sodium-hydrogen antiporter 3
TMAO	trimethylamine N-oxide
KATP	adenosine triphosphate sensitive potassium channel
RF	risk factors
PVOD	pulmonary veno-occlusive disease
PASP	pulmonary artery systolic pressure
IR	insulin receptor
TP_R	thromboxane A2 receptor
5-HTR	serotonin receptor

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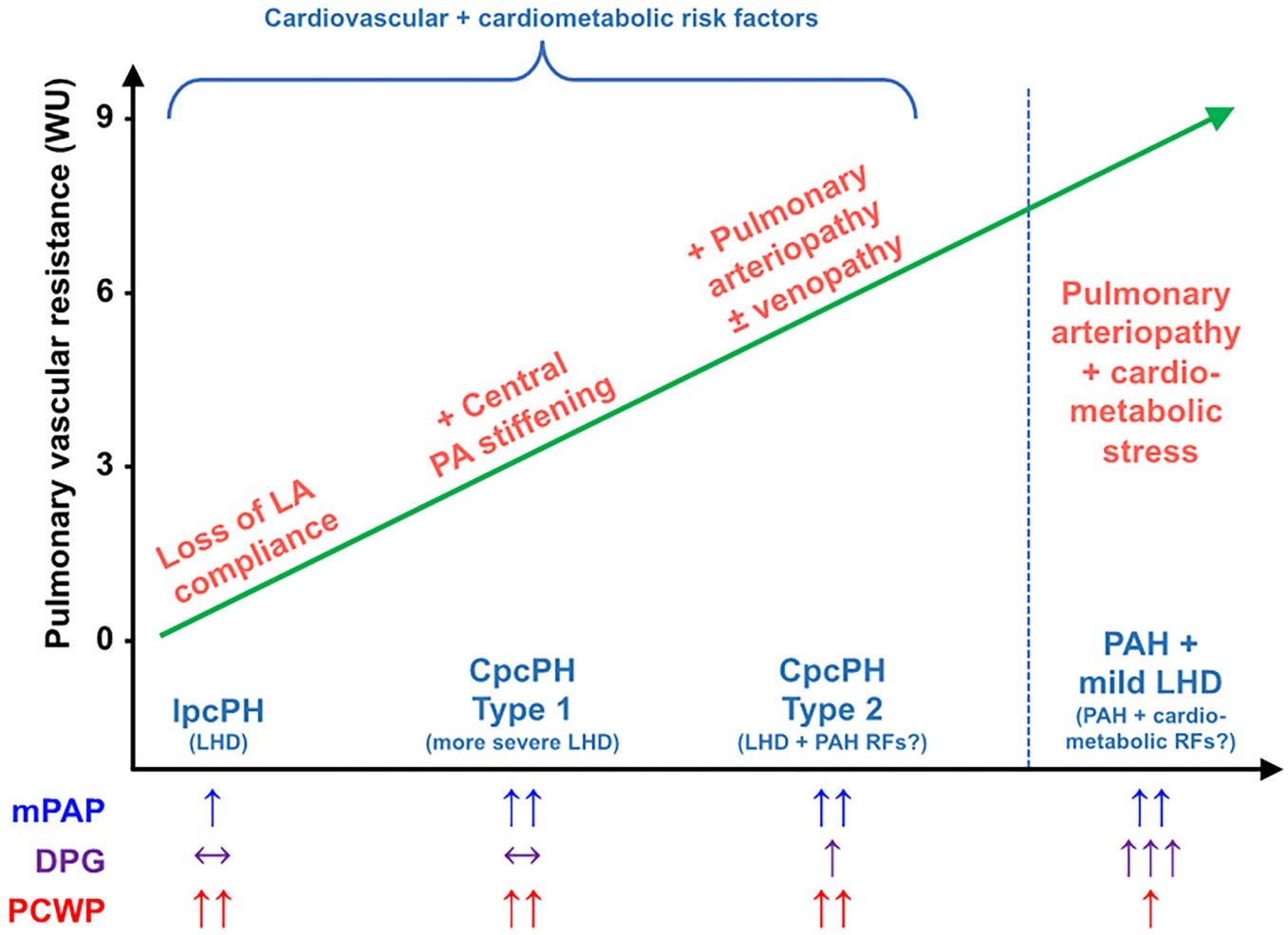

Figure 1. Hemodynamic Phenotypes of Pulmonary Hypertension in Left Heart Disease

The current understanding of PH-LHD is a progressive worsening of PH starting with Ipc-PH with the ultimate development of Cpc-PH. However, the degree of elevation in PVR in a patient with LHD likely depends on both severity of LHD and the presence of risk factors for PAH. If risk factors for PAH are present, PVR will likely be higher, and Cpc-PH will be more severe. Alternatively, there are some patients who have very high PVR and DPG with only mildly elevated PAWP. These patients likely have predominant PAH but have cardiometabolic risk factors. Technically these patients would be classified as PH-LHD due to the elevated PAWP, but from a phenotypic standpoint are much more similar to Group 1 PAH.

Ipc-PH: isolated post-capillary pulmonary hypertension; Cpc-PH: combined pre and post capillary pulmonary hypertension; LHD: left heart disease; PAH: pulmonary arterial hypertension; RF: risk factors; mPAP: mean pulmonary artery pressure; DPG: diastolic pressure gradient; PAWP: pulmonary artery wedge pressure; LA: left atrial; PA: pulmonary artery

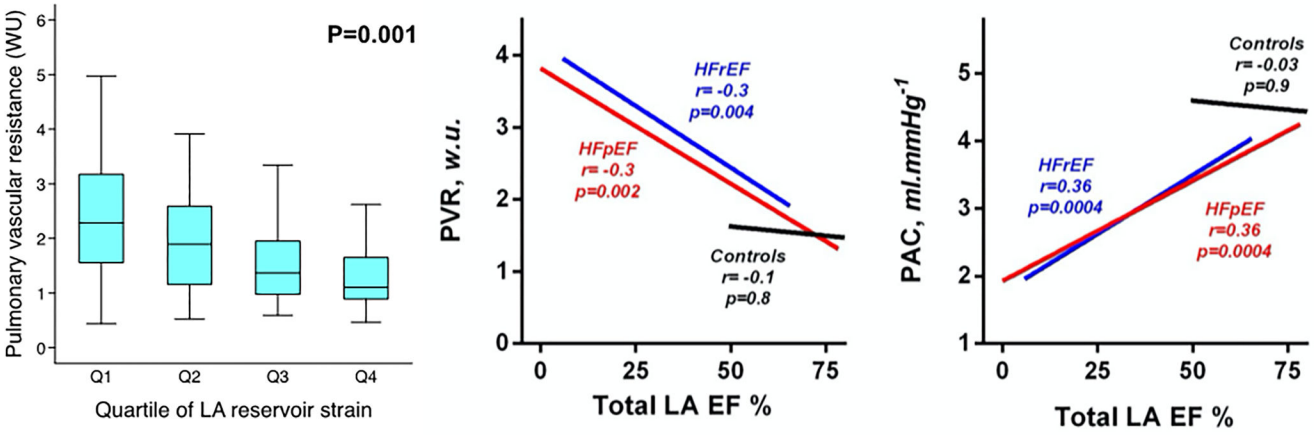

Figure 2. Left Atrial Dysfunction Correlates with Pulmonary Vascular Resistance and Compliance in Heart Failure.

Left panel: In patients with HFpEF, worse LA reservoir strain (indicative of the inability of the LA to fill from the pulmonary veins during ventricular systole) is associated with increased PVR. Middle panel: In patients with HFpEF and HFrEF, lower LA emptying fraction (indicative of worse LA function) is also associated with elevated PVR. Right panel: Lower LA emptying fraction is also associated with reduced PA compliance in both HFpEF and HFrEF. Reproduced with permission from Freed, et al. *Circulation: Cardiovascular Imaging* 2016 and Melenovsky, et al. *Circulation: Heart Failure* 2015.

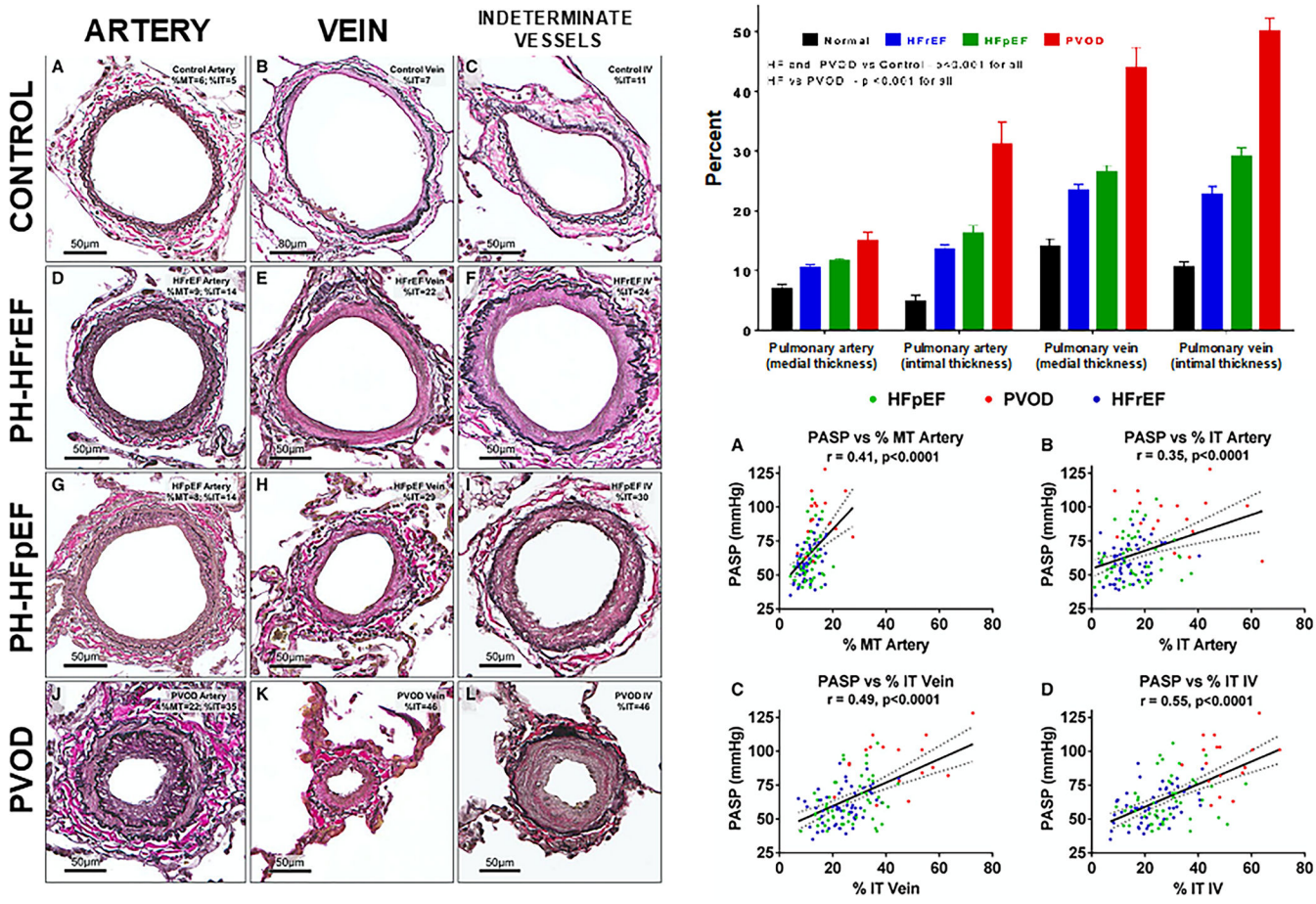

Figure 3. Histologic Pulmonary Vascular Remodeling in Pulmonary Hypertension due to Left Heart Disease.

Left panel: Comparison of pulmonary arteries, veins, and indeterminate vessels among healthy controls, PH-HFrEF, PH-HFpEF, and PVOD patients. Representative vessels with remodeling approximating the median values for medial and intimal thickening of arteries, veins, and indeterminate vessels in each group are shown. Right, top panel: There is progressive severity of medial and intimal thickening in pulmonary arteries and veins from healthy controls (normal) to PH-HFrEF to PH-HFpEF to PVOD (most severely abnormal). Right, bottom panel: increases in medial and intimal thickening in the pulmonary arteries and veins correlates with increased severity of pulmonary hypertension (increased PASP). The solid line represents the estimated PASP via linear regression based on medial/intimal thickening, and the dotted lines represent the 95% confidence interval. HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; %IT, percent intimal thickness; %MT, percent medial thickness; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; IV, indeterminate vessels; PASP, pulmonary artery systolic pressure. Reproduced with permission from Fayyaz et al., *Circulation* 2018..; and PVOD, pulmonary veno-occlusive disease. Reproduced with permission from Fayyaz et al., *Circulation* 2018.

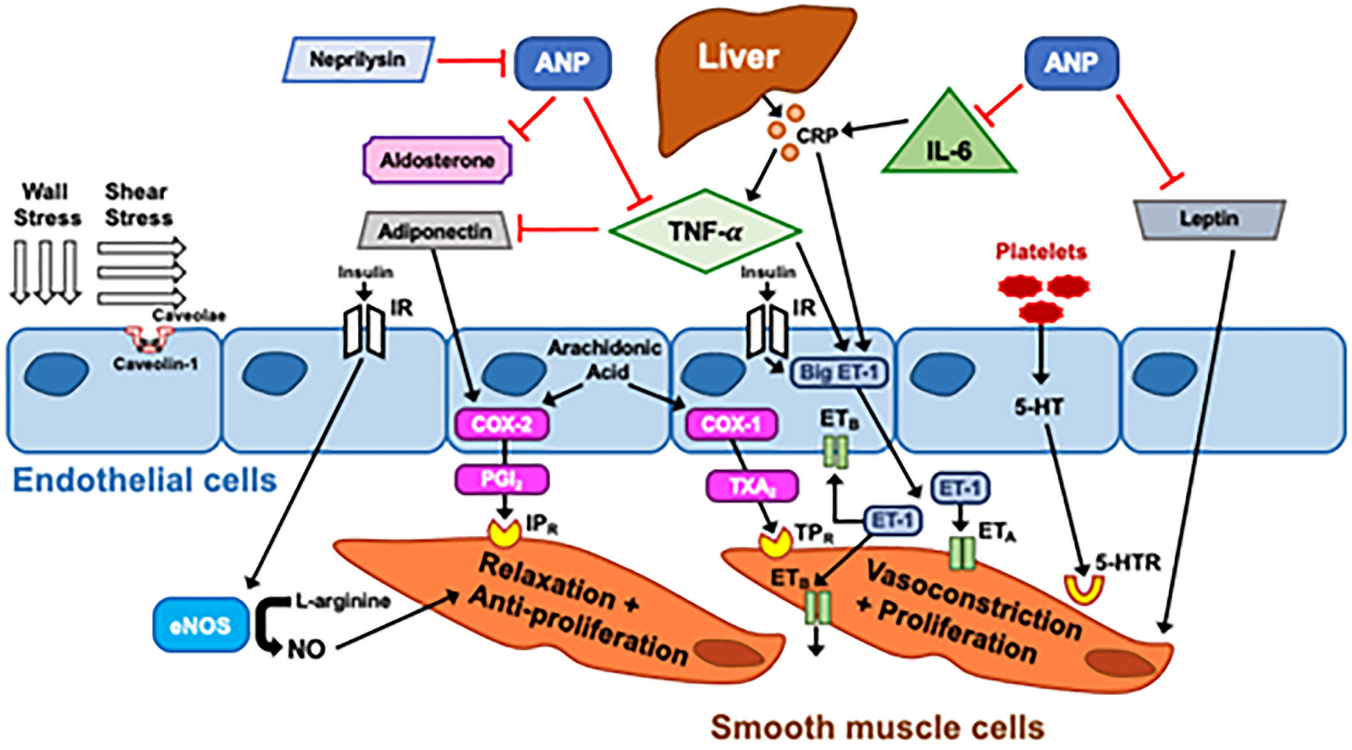

Figure 4. Pathobiologic Contributors to Pulmonary Hypertension in Left Heart Disease.

Wall stress and shear stress are drivers of adaptive and maladaptive processes resulting in endothelial dysfunction, smooth muscle hypertrophy, and inflammation. Many of these mediators of endothelial function in PH-LHD that have effects both systemically and locally. eNOS: endothelial nitric oxide synthase, IR:insulin receptor, NO: nitric oxide, ANP: atrial natriuretic peptide, TNF-α:Tumor necrosis factor alpha, COX: cyclooxygenase, PGI_2:Prostaglandin I2, IPR: Prostacyclin I2 receptor, TXA_2: thromboxane A2, $TP_{R:}$ Thromboxane A2 receptor, ET-1: endothelin-1, ET_A: Endothelin receptor A, 5-HT: serotonin, 5-HTR: serotonin receptor, IL-6: Interleukin-6, CRP: C-reactive protein

Table 1.

Hemodynamic Definitions of Pulmonary Hypertension Phenotypes in Patients with Left Heart Disease

PH-LHD Phenotype	Hemodynamic Criteria
Isolated post-capillary PH	mPAP ≥20 mmHg PAWP >15 mmHg PVR <3 WU
Combined pre- and post-capillary PH	mPAP ≥20 mmHg PAWP >15 mmHg PVR ≥3 WU

PH = pulmonary hypertension; LHD = left heart disease; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance.

Table 2.

Animal Models of PH-LHD

Model	Species	Strengths	Limitations
Metabolic Models			
Metabolic Syndrome (ZSF1 model) + SU5416/hypoxia	Rat[65]	Includes metabolic syndrome in phenotype	High Cost Limited molecular tools compared to mice Complicated phenotype
Metabolic Syndrome (ZSF1 model) + Aortic Banding	Rat[74]	Combined pressure and metabolic injury	High cost Primarily mild PH Complicated phenotype
High fat diet/Obesity	Mouse[66] Bovine[75]	Low cost Metabolic syndrome phenotype	Longer timeline needed Variation in PH-HFpEF phenotype based on mouse strain used
High fat diet + L-NAME (or *db/db* model) + SU5416/ hypoxia	Mouse	Low cost Metabolic syndrome phenotype with added pulmonary vascular disease	Needs to be further studied and validated as a PH-HFpEF phenotype
Mechanical Obstructive/Pressure Overload Models			
Aortic Banding	Mouse[68] Rat[76–78] Feline[79]	Simple Reproducible Low cost	Does not induce severe PH and RV failure Most synonymous with Aortic stenosis induced-PH, less with non-valvular HFpEF
Transverse Aortic Constriction	Mouse [69, 80]	Simple Reproducible	Associated pulmonary fibrosis Most synonymous with Aortic stenosis induced-PH, less with non-valvular HFpEF
Pulmonary vein banding	Porcine[70] Bovine[81]	Represents pulmonary venous hypertension	Higher cost Multiple operators Large animal Not representative of underlying LV disease
Left atrial stenosis	Rat[71, 72]	Simulates mitral stenosis	Not representative of underlying LV disease Difficult surgical intervention
Ischemic Models			
Left coronary artery ligation	Rat[73, 82, 84, 100] Mouse[85, 86] Porcine[83]	Primary HFrEF model	Not representative of non-ischemic cardiomyopathy Minimal control of infarct size Low survival

Table 3.

Pulmonary Hypertension due to Left Heart Disease: Unanswered Questions

1	Which provocative maneuver is most specific for the diagnosis of PH-LHD and what are the optimal diagnostic thresholds indicative of pulmonary vascular disease?
2	How does left atrial dysfunction lead to development of PH-LHD?
3	Is Cpc-PH a further progressed and more severe form of Ipc-PH or a different disease entity with specific risk factors?
4	At which point in the adaptive response to shear stress does intracellular signaling and pulmonary vascular remodeling become pathologic? What are the biologic drivers that differ between adaptive and maladaptive remodeling?
5	How does platelet aggregation and activation impact pulmonary vascular function, and which drivers of platelet activation are dominant in hemodynamic congestion?
6	In metabolic syndrome, what features are most influential in the development of PH in the setting of LHD? How does the presence of insulin resistance, chronic inflammation, and changes in natriuretic peptides influence congestion?
7	Does increased circulating adiponectin modify endothelial function in PH-LHD? How does adiponectin effect the pulmonary vasculature? Are there other adipokines that are relevant to the development and progression of PH-LHD.
8	What are the roles of venous capacitance, peripheral venous dysfunction, and stress blood volume in development and progression of PH-LHD? What are the molecular drivers of splanchnic vasoconstriction, and can those pathways be targeted with specific treatments?
9	How does lymphatic dysfunction impact different degrees of congestion and the ability of the pulmonary vasculature and RV to accommodate congestive stress?
10	What are the ideal small and large animal models for studying PH-LHD and its various phenotypes?