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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Management of Pulmonary Arterial Hypertension

Vallerie V. McLaughlin, MD,* Sanjiv J. Shah, MD,† Rogerio Souza, MD,‡ Marc Humbert, MD, PhD§

ABSTRACT

Pulmonary hypertension (PH) is common and may result from a number of disorders, including left heart disease, lung disease, and chronic thromboembolic disease. Pulmonary arterial hypertension (PAH) is an uncommon disease characterized by progressive remodeling of the distal pulmonary arteries, resulting in elevated pulmonary vascular resistance and, eventually, in right ventricular failure. Over the past decades, knowledge of the basic pathobiology of PAH and its natural history, prognostic indicators, and therapeutic options has exploded. A thorough evaluation of a patient is critical to correctly characterize the PH. Cardiac studies, including echocardiography and right heart catheterization, are key elements in the assessment. Given the multitude of treatment options currently available for PAH, assessment of risk and response to therapy is critical in long-term management. This review also underscores unique situations, including perioperative management, intensive care unit management, and pregnancy, and highlights the importance of collaborative care of the PAH patient through a multidisciplinary approach. (J Am Coll Cardiol 2015;65:1976–97) © 2015 by the American College of Cardiology Foundation.

Pulmonary hypertension (PH) defines a group of clinical conditions presenting with abnormal elevation in the pulmonary circulation pressure (1,2). The normal mean pulmonary artery pressure (mPAP) at rest is 14 ± 3.3 mm Hg, and the upper limit of normal is 20.6 mm Hg (3); nevertheless, PH is defined as an increase of mPAP ≥25 mm Hg at rest, as assessed by right heart catheterization (4). Over the past 2 decades, advances in the understanding of basic mechanisms, clinical characteristics, and treatment options have substantially changed our approach to this disease. This paper will review salient features of PH and pulmonary arterial hypertension (PAH).

CLASSIFICATION

The recognition of subgroups of patients sharing specific features has led to the most recent classification of PH (Table 1) (5). The current classification groups patients with similar pathological findings, hemodynamic profiles, and management strategies.

GROUP 1: PAH. PAH is defined by the presence of a pre-capillary pattern in the invasive hemodynamic

From the *University of Michigan Hospital and Health Systems, Ann Arbor, Michigan; †Feinberg Cardiovascular Research Institute, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ‡Pulmonary Department, Heart Institute, University of Sao Paulo Medical School, Sao Paulo, Brazil; and the §University of Paris-Sud, Le Kremlin-Bicêtre, France; AP-HP, Service de Pneumologie, DHU Thorax Innovation, Hôpital Bicêtre, Le Kremlin-Bicêtre, France; and INSERM U999, LabEx LERMIT, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France. Dr. McLaughlin has been a consultant for Actelion Bayer, Gilead, and United Therapeutics; has received research funding for clinical trials to the University of Michigan from Actelion, Bayer, Gilead, and the National Institutes of Health (R24 HL123767); and has a relationship with United Therapeutics. Dr. Shah has received research grant support from the National Institutes of Health (R01 HL107577) and Actelion Pharmaceuticals; has received generous funding from Jo Anne and Stephen A. Schiller in support of pulmonary hypertension research; has received consulting fees from the American Board of Internal Medicine, Novartis, Bayer, DC Devices, AstraZeneca, and Alnylam Pharmaceuticals; and has received speaker fees from the Pulmonary Hypertension Association and the American Society of Echocardiography. Dr. Souza has received lecture fees from Actelion, Bayer, GlaxoSmithKline, and Bristol-Myers Squibb; and has received advisory board fees from Actelion and Bayer. Dr. Humbert has served as a consultant for Actelion, Bayer, GlaxoSmithKline, and Pfizer.
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TABLE 1 Updated Classification of PH*

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent PH of the newborn
2. PH due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. PH due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic PH
5. PH with unclear multifactorial mechanisms
5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*5th World Symposium on Pulmonary Hypertension, Nice, France, February 27 to March 1, 2013. Changes since the last symposium are in **bold**.

BMPR 2 = bone morphogenetic protein receptor type 2; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

evaluation, characterized by an mPAP ≥25 mm Hg with normal pulmonary artery occlusion pressure (i.e., pulmonary capillary wedge pressure [PCWP] ≤15 mm Hg) and pulmonary vascular resistance (PVR) above 3 Wood units, in the absence of pulmonary parenchymal or thromboembolic disease. As shown in Table 1, PAH may occur in isolation or in association with several clinical conditions.

Idiopathic and heritable PAH. Although idiopathic pulmonary arterial hypertension (IPAH) might represent the most studied form of PAH, it corresponds to a rare presentation in which no family history of PAH or associated risk factor is present. Therefore, IPAH is only diagnosed after extensive investigation ruling out alternative diagnoses (4).

Heritable forms of PAH include those with identified gene mutations and familial cases with or without mutations. Up to 80% of familial cases of PAH have been linked to germline mutations in the gene coding for the bone morphogenetic protein receptor type II (*BMPR2*), a member of the transforming growth factor (TGF)-β signaling family (6). *BMPR2* mutations have also been detected in around 20% of apparently idiopathic cases without a family history of PAH (7). Other mutations in genes from the TGF-β family are also known to be associated with particular PAH presentations, such as comorbid hereditary hemorrhagic telangiectasia (*ACVRL1*, *Endoglin*) (8).

Recently, mutations in the novel PAH-associated genes *Caveolin 1* and *KCNK3* have been described. *Caveolin 1* (9) and *KCNK3* (10) are not closely related to the TGF-β family, thereby providing new and different insights in terms of potential pathophysiological mechanisms and therapeutic targets.

Drug- and toxin-induced PAH. A significant number of substances have been described as potentially associated with the development of PAH. Aminorex and fenfluramine derivatives are clear examples where a robust association between drug exposure and PAH has been demonstrated through the analysis of outbreaks of PAH in the 1960s and 1990s (11,12). More recently, benfluorex, a benzoate ester that shares structural and pharmacologic characteristics with dexfenfluramine and fenfluramine, has also been associated with the development of PAH (13). Among other classes of drugs that may be linked to the development of PAH, dasatinib, a tyrosine kinase inhibitor, gained particular attention after a case series of drug-induced PAH was reported in chronic myelogenous leukemia patients (14). Type I interferons have also been linked to an increased risk of developing PAH (15).

PAH associated with connective tissue diseases. One of the most important forms of PAH is connective tissue disease (CTD)-associated PAH. CTD-associated PAH accounts for 15% to 25% of all PAH cases in worldwide registries, with systemic sclerosis and systemic lupus erythematosus as the leading causes (16,17). These patients have a particularly poor prognosis, with an estimated 30% 1-year mortality, compared to 15% in IPAH. It was recently suggested that implementation of a systematic screening program to allow earlier diagnosis and intervention might result in better long-term outcomes for this subgroup of PAH patients (18,19). Cases of reversible PAH have been reported in PAH patients with systemic lupus erythematosus and mixed CTD.

ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

CTD = connective tissue disease

IPAH = idiopathic pulmonary hypertension

mPAP = mean pulmonary artery pressure

PAH = pulmonary arterial hypertension

PCWP = pulmonary capillary wedge pressure

PH = pulmonary hypertension

PVR = pulmonary vascular resistance

RV = right ventricle/ventricular

PAH associated with human immunodeficiency virus. Patients with human immunodeficiency virus (HIV) are at increased risk of developing PAH. The prevalence of PAH in this group is estimated to be 0.5% (20,21), with clinical and hemodynamic presentation very similar to IPAH. Prognosis of HIV-associated PAH has improved in recent years; in the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) registry, the survival of HIV-associated PAH was 93% at 1 year and 75% at 3 years (22). Cases of reversible PAH have been reported in HIV patients treated with PAH drugs and highly-active antiretroviral drugs (22).

PAH associated with portal hypertension. About 6% of patients with portal hypertension develop PAH, independent of the severity of the liver disease, although the long-term prognosis of these patients is related to the severity of both the liver and pulmonary vascular disease. Portopulmonary hypertension represents an important problem for liver transplantation programs because its presence is related to increased mortality during and after the procedure, particularly if the mPAP is >35 mm Hg. The prognosis in portopulmonary hypertension is worse than in IPAH; recently reported data suggest a 3-year survival of 40% (23).

PAH associated with congenital heart diseases. Due to the improvement in the management of congenital heart diseases (CHDs), more children with CHD survive to adulthood. Because about 10% of adults with CHD develop PAH (24), CHD-associated PAH is a significant subgroup in PH referral centers.

PAH associated with schistosomiasis. PH represents one of the most severe complications of chronic schistosomiasis (Sch), an infectious disease caused by parasitic trematode worms. A PH screening program identified a 4.6% prevalence of PAH among patients diagnosed with hepatosplenic schistosomiasis mansoni (25), highlighting the relevance of this form of PAH, considering the worldwide distribution of the infection. A recent registry demonstrated that Sch-PAH might be responsible for about 20% of all newly-diagnosed PAH cases in endemic countries. The clinical and histopathological similarities between Sch-PAH and IPAH have been recently described (26), although Sch-PAH apparently has a more benign clinical course with a 3-year mortality of about 15% (26). A recent case series also suggested that these patients might have a beneficial response to PAH targeted therapies (27).

Pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and persistent PH of the newborn. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis, rare variants within the same spectrum of disease, share some similarities with PAH, although with remarkable differences in presentation, mainly with respect to chest computed tomography findings, causal homozygous EIF2AK4 mutations in heritable cases, and clinical course (28,29). These entities remain closer to the PAH spectrum of disease than to any other PH group and, thus, are classified as 1′. Due to numerous differences with all other forms of PAH, persistent PH of the newborn has also been withdrawn from the PAH group and is classified as 1″ (5).

GROUP 2: PH DUE TO LEFT HEART DISEASE. This group encompasses the most frequent form of PH. In these patients, PH is a consequence of the elevated filling pressures of the left heart chambers transmitted backward to the pulmonary circulation. In this setting, PVR is usually normal, as is the gradient between the mPAP and the PCWP (transpulmonary gradient; <12 mm Hg) and the gradient between the diastolic pulmonary artery pressure and the PCWP (diastolic pressure gradient; <5 to 7 mm Hg). Nevertheless, in a subgroup of patients, a pre-capillary component might also be present, characterizing a mixed hemodynamic pattern (combined pre- and post-capillary PH) (30). Further studies are necessary to assess the potential benefits and risks of PAH-specific therapy in this group.

GROUP 3: PH DUE TO LUNG DISEASES AND/OR HYPOXIA. This group comprises patients with parenchymal lung diseases or other causes of hypoxia (e.g., obstructive sleep apnea) in whom the presence of PH is considered directly related to these underlying diseases. Thus, all forms of ventilatory disturbances are considered: obstructive, restrictive, and the combination of both patterns. In particular, the presence of a mixed pattern (obstructive and restrictive), as in the coexistence of pulmonary fibrosis and emphysema, results in an increased prevalence of PH. Thus far, no significant benefit from the use of targeted PAH therapies has been demonstrated in this group.

GROUP 4: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION. Up to 4% of all patients with acute pulmonary embolism may ultimately develop chronic thromboembolic pulmonary hypertension (CTEPH), which is considered a curable form of PH when performing a pulmonary endarterectomy is possible. Operability depends on several factors, including the pattern of vascular obstruction, hemodynamic severity, and experience of the referral center, among others. More recently, PAH-specific medical therapy and balloon pulmonary angioplasty have been used

for patients who were not candidates for surgery or who remained with residual PH after surgery with beneficial results.

GROUP 5: PH WITH UNCLEAR OR MULTIFACTORIAL MECHANISMS. Included in this group are numerous forms of PH in which multiple pathophysiological mechanisms might be implicated in the elevation in pulmonary vascular pressures. Given the heterogeneity of this group, further research is necessary to better establish appropriate diagnostic criteria and management strategies for each specific subform.

PATHOLOGY AND PATHOBIOLOGY OF PAH

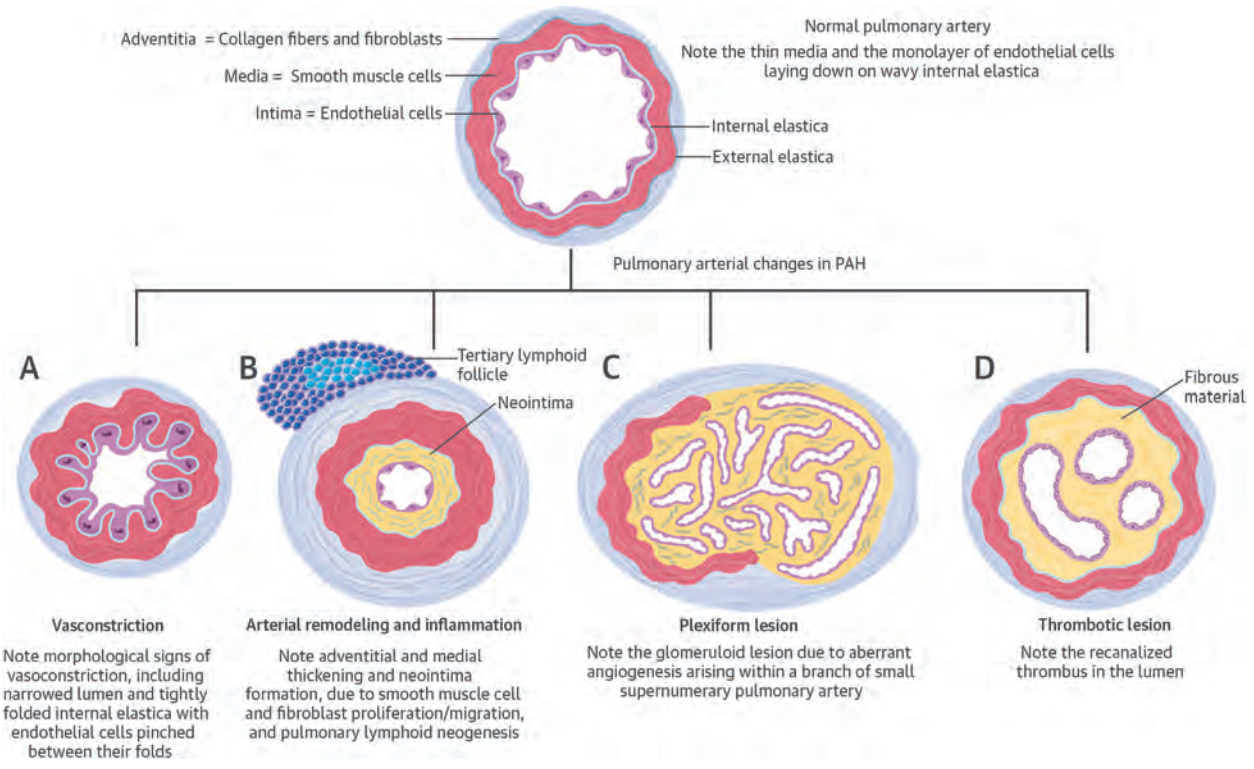
In PAH, pulmonary vascular lesions predominantly affect the small pulmonary arteries (diameter <500 μm). A wide array of changes can all occur in PAH, ranging from medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with moderate perivascular inflammatory infiltrates (which may be more pronounced and organized in tertiary lymphoid tissue), complex lesions (plexiform, dilated lesions), and thrombotic lesions (31–33). In contrast to PVOD, pulmonary veins are less affected in PAH (31). **Figure 1** highlights some key pathobiological abnormalities in PAH.

Vasoconstriction/vasodilation imbalance, thrombosis, cell proliferation, and remodeling of the pulmonary arterial walls contribute to PAH pathobiology (32,33). Several cell types play a role in the disease, including endothelial cells, smooth muscle cells, pericytes, myofibroblasts, inflammatory cells (macrophages, dendritic cells, mast cells, T and B lymphocytes), and platelets (32–35). Pulmonary vasoconstriction has long been regarded as an early event, and excessive pulmonary vasoconstriction has been related to abnormal function or expression of potassium-channels and to endothelial dysfunction characterized by reduced production of vasodilators (nitric oxide and prostacyclin) and overproduction of vasoconstrictors (endothelin-1) (32). These factors will increase pulmonary vascular tone and favor remodeling, and therefore represent logical pharmacological targets. Other mediators are also believed to play an important role in subsets of PAH patients, including proinflammatory cytokines (interleukin-1 and -6, tumor necrosis factor α), chemokines, serotonin, angiopoietins, bone morphogenetic proteins (BMPs), growth factors, and members of the TGF-β superfamily (32–36). Proteolysis of the extracellular matrix and autoimmunity are also likely to contribute to disease pathobiology. The key role of the TGF-β superfamily in pulmonary vascular remodeling has been highlighted by cases of heritable PAH due to germline mutations of *BMPR2*, *ACVRL1,* and *Endoglin* (37). The products of these genes are involved in the regulation of growth, differentiation, and apoptosis of pulmonary artery endothelial and smooth muscle cells. Idiopathic and heritable PAH affect twice as many females as males, emphasizing the likely role of additional factors in the pathobiological mechanisms leading to PAH, including sexual hormones and pregnancy (37).

NATURAL HISTORY OF PAH, LESSONS FROM REGISTRIES

Until the end of the last century, PAH was a true orphan disease, that is, a condition affecting a few individuals and overlooked by the medical and pharmaceutical world. Although rare, a number of important recent findings have significantly improved our understanding of PAH. In 1973, the World Health Organization sponsored the first international conference on a condition that was then named "primary" PH (currently idiopathic, heritable, and drug-induced PAH) in Geneva, Switzerland. The marked increase in the incidence of the disease in patients who had used an anorectic pill (aminorex fumarate) explained, at least in part, the medical world's interest in this devastating condition. The experts attending this conference recommended collection of patient information into registry databases to enable characterization of the disease in terms of demographics, clinical presentations, and outcomes. In 1981, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) launched the first national registry of patients with so-called "primary" PH. By the time the registry closed in 1987, only 187 patients (mean age 36 ± 15 years) had been recruited from 32 centers (38). These patients were described and followed for up to 5 years, leading to major advances in the understanding of the natural history of the disease, which had a poor prognosis with a median survival of 2.8 years following diagnosis. More recently, several registries have described the characteristics and survival of PAH patients in the modern management era. In the early 2000s, the French registry described consecutive adult patients from 17 expert centers. Within a year, 674 patients (age 50 ± 15 years) were entered in this registry (16). The estimates of prevalence and incidence of PAH were 15.0 cases/million and 2.4 cases/million per year, respectively. Idiopathic, familial, and anorexigen-induced PAH accounted for around one-half of the cases (39.2%, 3.9%, and 9.5%, respectively); the other one-half

FIGURE 1 Pathobiology of PAH



(A) Pulmonary vasoconstriction has long been regarded as an early event, and excessive pulmonary vasoconstriction has been related to abnormal function or expression of potassium-channels and to endothelial dysfunction characterized by reduced production of vasodilators (nitric oxide and prostacyclin), along with overproduction of vasoconstrictors (endothelin-1). Recently, a novel channelopathy due to *KCNK3* mutation has been identified in heritable cases of pulmonary arterial hypertension (PAH), which may also favor vasoconstriction. **(B)** Pulmonary vascular remodeling and inflammation: proinflammatory cytokines (interleukin-1 and -6, tumor necrosis factor α), chemokines, serotonin, angiopoietins, bone morphogenetic proteins (BMPs), growth factors, and members of the transforming growth factor (TGF)β superfamily, but also proteolysis of the extracellular matrix and autoimmunity, are key triggers in smooth muscle cells, endothelial cells, fibroblasts and pericytes proliferation and migration. Proteolysis of the extracellular matrix and autoimmunity (as evidenced here by perivascular lymphoid neogenesis) are also likely to initiate or perpetuate arterial remodeling. **(C)** Endothelial dysfunction, proliferation, and resistance to apoptosis, triggered by aberrant production of angiogenic growth factors (FGF2, PDGF, VEGF), and genetic abnormalities in TGF-β signaling (BMPR2, ACVRL1/ALK1, endoglin, SMADs), and in endothelial scaffolding protein (Caveolin-1), may favor aberrant angiogenesis (and subsequent increased vascular resistance) in PAH that is best exemplified by plexiform lesions. **(D)** Thrombotic arteriopathy, a highly prevalent pathological pattern of PAH, is an important pathophysiological feature of the disorder. Indeed, endothelial dysfunction leads to local thrombosis in PAH. Prepared from original drawings courtesy of Frédéric Perros, PhD, Inserm UMR_S 999, Université Paris-Sud, Hôpital Marie Lannelongue Le Plessis Robinson, France.

corresponded to patients with well-characterized comorbidities (diagnosis of CTD, CHD, portal hypertension, or HIV infection was made in 15.3%, 11.3%, 10.4%, and 6.2% of the population, respectively). Most patients had advanced functional impairment at the time of diagnosis, with 75% of patients in New York Heart Association (NYHA) functional class III or IV and a reduced 6-min walk distance (6MWD) of 329 ± 109 m. Severe hemodynamic impairment was present, with an mPAP of 55 ± 15 mm Hg, cardiac index of 2.5 ± 0.8 l/min/m^2, and PVR index of 20.5 ± 10.2 Wood unit index, respectively. Delay between symptom onset (mainly dyspnea on exercise) and PAH diagnosis was 27 months, similar to that observed in the NIH Registry, emphasizing the need for better PAH awareness and diagnostic strategy. Patients were then followed for 3 years and survival rates were analyzed. For incident (newly diagnosed) idiopathic, familial, and anorexigen-induced PAH, estimated survival at 1, 2, and 3 years was 85.7% (95% confidence interval [CI]: 76.5% to 94.9%), 69.6% (95% CI: 57.6% to 81.6%), and 54.9% (95% CI: 41.8% to 68.0%), respectively (39). This registry demonstrated that PAH was still detected late in the course of the

disease in the modern management era, with a majority of patients displaying severe functional and hemodynamic compromise.

An important objective of registries is to identify patient characteristics that predict outcome. The NIH Registry was the first to develop a prognostic equation. Use of this equation in the current treatment era has limitations, as it provides information only on the natural history of untreated idiopathic/heritable PAH. More recent registries have identified predictors of outcome that show similarities between studies, including disease etiology, patient sex, functional impairment, and factors reflective of right heart function. In the French registry, individual survival analysis identified the following factors as significantly and positively associated with survival: female sex; NYHA functional class I/II; greater 6MWD; lower right atrial pressure; and higher cardiac output. Multivariable analysis showed that female sex and having a greater 6MWD and higher cardiac output were jointly significantly associated with improved survival. Both the French and U.S. REVEAL equations have shown strong predictive power when cross-validated in matched patients from the U.S. REVEAL and French registries, respectively (39,40).

DIAGNOSTIC EVALUATION OF THE PATIENT WITH SUSPECTED PH

The diagnosis of PAH, especially in those without apparent risk factors, requires a high index of suspicion because typical presenting symptoms such as dyspnea, exercise intolerance, and fatigue are nonspecific (1,2,4). In contrast, signs of PH, such as elevated pulmonary artery systolic pressure (PASP) and enlarged pulmonary arteries, are often encountered on imaging tests, such as Doppler echocardiography and chest computed tomography, respectively. In these patients, PAH, which is much more rare than other causes of PH (such as left heart disease and chronic lung disease), is unlikely. Thus, clinicians must be able to both recognize clues regarding the presence of PAH (to avoid missing the diagnosis of this rare disease) and correctly determine the etiology and type of PH when found incidentally on routine testing (to avoid incorrect and potentially harmful treatment).

Although the history and physical examination are not always definitive, much information can be gathered from this initial step. Clues in the clinical history that increase the likelihood of PH include: exertional lightheadedness or syncope; symptoms of right heart failure, such as leg swelling, abdominal distension, and anorexia; and the presence of PAH risk factors, such as portal hypertension, CTD, CHD, HIV, exposure to drugs/toxins known to induce PAH (e.g., anorexigens), and a family history of PAH (4,17). Physical examination findings sometimes observed in PH and right ventricular (RV) dysfunction include: an elevated jugular venous pressure with prominent A waves (due to increased RV stiffness) and V waves (due to tricuspid regurgitation [TR]); Kussmaul's sign (increased jugular venous pressure with inspiration, due to a noncompliant RV or significant TR); an RV lift; a loud P_2; right-sided S_3 and/or S_4; murmur of TR; and signs of right heart failure (e.g., hepatomegaly, ascites, and peripheral edema) (2).

Electrocardiographic signs of PH include RV hypertrophy with strain pattern (increased R-wave amplitude with ST-segment depression and T-wave inversion in the precordial leads) and right atrial enlargement (increased P-wave amplitude in leads II and V_1). The right atrium is often quite enlarged in severe PAH and can mimic left atrial enlargement in lead V_1 (terminal negative deflection of the P-wave >1 small box), despite the presence of a small and underfilled left atrium. On chest radiography, loss of the retrosternal space on the lateral view (a sign of RV enlargement), enlarged central pulmonary arteries, and peripheral pruning can occur in PAH (1,2).

ECHOCARDIOGRAPHY. Comprehensive echocardiography, with Doppler and tissue Doppler imaging, is essential for screening and initial noninvasive assessment of PH (41). Besides evaluating for possible PH, the echocardiogram can evaluate for the cause of PH (e.g., left heart disease lesions, agitated saline bubble study to evaluate for shunt lesions). Although clinicians are often focused on the PASP when evaluating patients with PH, it is just as critical to evaluate the right heart on echocardiography because of the pitfalls of echocardiographic PASP assessment, which have been reviewed previously (41). **Table 2** displays a checklist of items to remember when evaluating the echocardiogram in a patient with known or suspected PH.

INVASIVE HEMODYNAMIC TESTING. Cardiac catheterization is an essential step in the diagnosis of PH, particularly PAH, and should be performed prior to the initiation of PAH-specific therapy (1,2,4). When performed at experienced centers, the risk of major complications from right heart catheterization is low (42). Nevertheless, invasive hemodynamic testing requires careful technique to avoid potential pitfalls. Standard good clinical practices, such as ensuring proper zeroing of pressure transducers, measuring pressures (particularly PCWP) at end-expiration, and being cognizant of artifacts in the hemodynamic

TABLE 2 Checklist for the Echocardiographic Evaluation of PH

Completed?	Action Item	Notes
☐	Record estimated PASP	• Underestimated when Doppler beam alignment is poor or when TR jet is minimal • Overestimated in patients with significant anemia or in some cases of agitated saline-enhanced TR jet on continuous wave Doppler (due to feathering) • Assumes absence of pulmonic stenosis • Echocardiographic PASP does not equal mean PA pressure (definition of PH per guidelines is on the basis of invasive hemodynamics: mean PA pressure ≥25 mm Hg)
☐	Evaluate RV size and function	• Signs of RV enlargement (apical 4-chamber view): RV shares apex with LV; RV bigger than LV; RV basal diameter >4.2 cm • RV hypertrophy (subcostal view): RV end-diastolic wall thickness >5 mm • RV systolic dysfunction: RV fractional area change <35%; TAPSE <1.6 cm; RV tissue Doppler s′ velocity <10 cm/s at base of the RV free wall (tricuspid annulus) • Septal flattening: in systole = RV pressure overload and in diastole = RV volume overload
☐	Evaluate for signs of elevated PVR	• RVOT notching on pulse-wave Doppler profile is a sign of elevated PVR • Peak TR velocity (m/s)/RVOT VTI (cm) <0.18: unlikely PVR is elevated
☐	Estimate volume status	• Use size and collapsibility of IVC (during sniff maneuver) to determine RA pressure • Hepatic vein flow: systolic flow reversal can be a sign of severe TR, RV overload, and/or increased RV stiffness • Signs of RA overload/enlargement: RA area >18 cm^2; interatrial septum bows from right to left
☐	Evaluate severity of TR	• Features suggestive of severe TR include dense TR jet on continuous-wave Doppler, V-wave cutoff sign; and systolic flow reversal on hepatic vein pulse-wave Doppler imaging
☐	Evaluate for pericardial effusion	• In patients with PAH, the presence of a pericardial effusion = poor prognostic sign
☐	Evaluate for causes of PH (left heart disease, shunt lesions)	• Left heart disease: look for overt LV systolic dysfunction, grade 2 or worse diastolic dysfunction, severe aortic or mitral valvular disease, and less common abnormalities of the left heart (e.g., hypertrophic cardiomyopathy, cor triatriatum) • Shunt lesions: perform agitated saline bubble study
☐	Differentiate PAH from PVH	• Signs favoring PVH: LA enlargement (LA size >RA size); interatrial septum bows from left to right; E/A ratio >1.2; E/e′ (lateral) > 11; lateral e′ <8 cm/s; • In patients with significantly elevated PASP at rest: grade 1 diastolic dysfunction pattern (E/A ratio <0.8) favors PAH diagnosis because of underfilled LA and decreased LV compliance due to RV/LV interaction (extrinsic compression of LV by RV). • See also **Figure 1**

IVC = inferior vena cava; LA = left atrial/atrium; LV = left ventricular/ventricle; PA = pulmonary artery; PAH = pulmonary arterial hypertension PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; PVH = pulmonary vascular hypertension; PVR = pulmonary vascular resistance; RA = right atrial/atrium; RV = right ventricular/ventricle; RVOT = right ventricular outflow tract; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; VTI = velocity-time integral.

tracings (e.g., overshoot in the pressure tracing due to an air bubble in the catheter, whip artifact due to catheter movement) are essential for making the correct diagnosis in patients with suspected or known PH. In addition, because PCWP is so important for differentiating PAH from pulmonary venous hypertension (PVH), special care should be taken to ensure that the PCWP measurement is accurate, including fluoroscopic confirmation that the pulmonary artery (PA) catheter is in the PCWP position, and that PCWP hemodynamic waveforms are appropriate. If the accuracy is in doubt, or if the PCWP value does not fit with the rest of the clinical picture, left ventricular (LV) end-diastolic pressure should be measured.

DYNAMIC TESTING DURING INVASIVE HEMODYNAMIC STUDIES. Acute pulmonary vasodilator testing is indicated in PAH patients with idiopathic, heritable, or anorexigen-induced PAH. A variety of pulmonary vasodilators can be used, with inhaled nitric oxide (iNO) used most commonly (43). Pulmonary vasodilator testing helps to determine who is most likely to respond to calcium-channel blocker therapy and also provides prognostic information. A positive response to pulmonary vasodilator testing should include all of the following: 1) decrease in mPAP to ≤40 mm Hg; 2) decrease of at least 10 mm Hg in mPAP; and 3) unchanged or increased cardiac output (43). It is important to note that a lack of acute pulmonary vasodilator response does not signify a "nonresponder" to PAH therapies. Most PAH patients will not have a positive response to a pulmonary vasodilator challenge; however, many of these patients will respond to long-term selective PAH-specific therapy (see later section "Therapy for PAH"). Pulmonary vasodilator challenge with agents such as iNO, adenosine, and prostacyclins should not be performed in patients with evidence of significant PVH (e.g., PCWP >18 to 20 mm Hg). Furthermore, although pulmonary vasodilator testing has been used commonly in patients with "associated-PAH" such as HIV, CTD, CHD, and portopulmonary hypertension, there is less rigorous data supporting its use in these patients. There is no data supporting the use of vasodilator testing or calcium-channel blockers in patients with PH other than PAH.

Exercise testing can be very helpful in the assessment of patients with suspected or known PH because

most symptoms occur with exertion. Although the diagnosis of "exercise-PH" is no longer recognized in guidelines statements, exercise can help evaluate for PVH. Given the ability to accurately document the exercise load, we prefer to use a supine or upright ergometer (instead of arm exercises) for exercise hemodynamic testing. In patients with PVH due to heart failure with preserved left ventricular ejection fraction (HFpEF), low-level exercise (25 W on a supine ergometer) typically results in significant elevations in PCWP (e.g., >20 to 25 mm Hg), and mPAP and PCWP will rise in parallel with exercise-induced increases in cardiac output (44). In patients with PAH, there will be minimal rise in the PCWP during exercise, whereas mPAP will rise, and the rise will be much steeper than the rise in PCWP.

Volume challenge during invasive hemodynamic testing can also be helpful in the diagnosis and management of PH. Typically, 10 ml/kg of warmed saline can be infused intravenously over 10 min in patients if there is still a suspicion of PAH or PVH, but the baseline hemodynamic data is insufficient for the diagnosis. Fluid challenge can be safely administered if the patient being evaluated has a resting right atrial pressure <10 mm Hg and mPAP <25 mm Hg, and may be particularly helpful if cardiac output is low-normal or decreased (e.g., cardiac index <2.5 to 3.0 l/min/m^2). In these patients, signs of PAH include a rise in mPAP ≥25 mm Hg while PCWP remains ≤15 mm Hg. Additional evidence suggestive of the diagnosis after fluid challenge are: 1) a reduction or no rise in cardiac output; and 2) rise in RA pressure greater than the rise in PCWP. Passive leg raise alone can also serve as a volume challenge. If PCWP rises significantly (to >20 mm Hg) with passive leg raise, it is likely that the patient has PVH (44). Alternatively, if PCWP changes little, but RA pressure increases to >15 mm Hg and mPAP rises to >25 mm Hg with minimal change in cardiac output, PAH may be present.

It is important to note that there is insufficient controlled data to provide firm guidelines on invasive hemodynamic pressure cutoffs for post-exercise or -volume challenge diagnosis of PAH. Thus, the aforementioned post-exercise and -fluid challenge hemodynamic criteria for the presence of possible PAH are rough estimates. Clinicians must integrate the clinical information, echocardiographic findings, and invasive hemodynamic data (pre- and post-challenge) to make an accurate diagnosis.

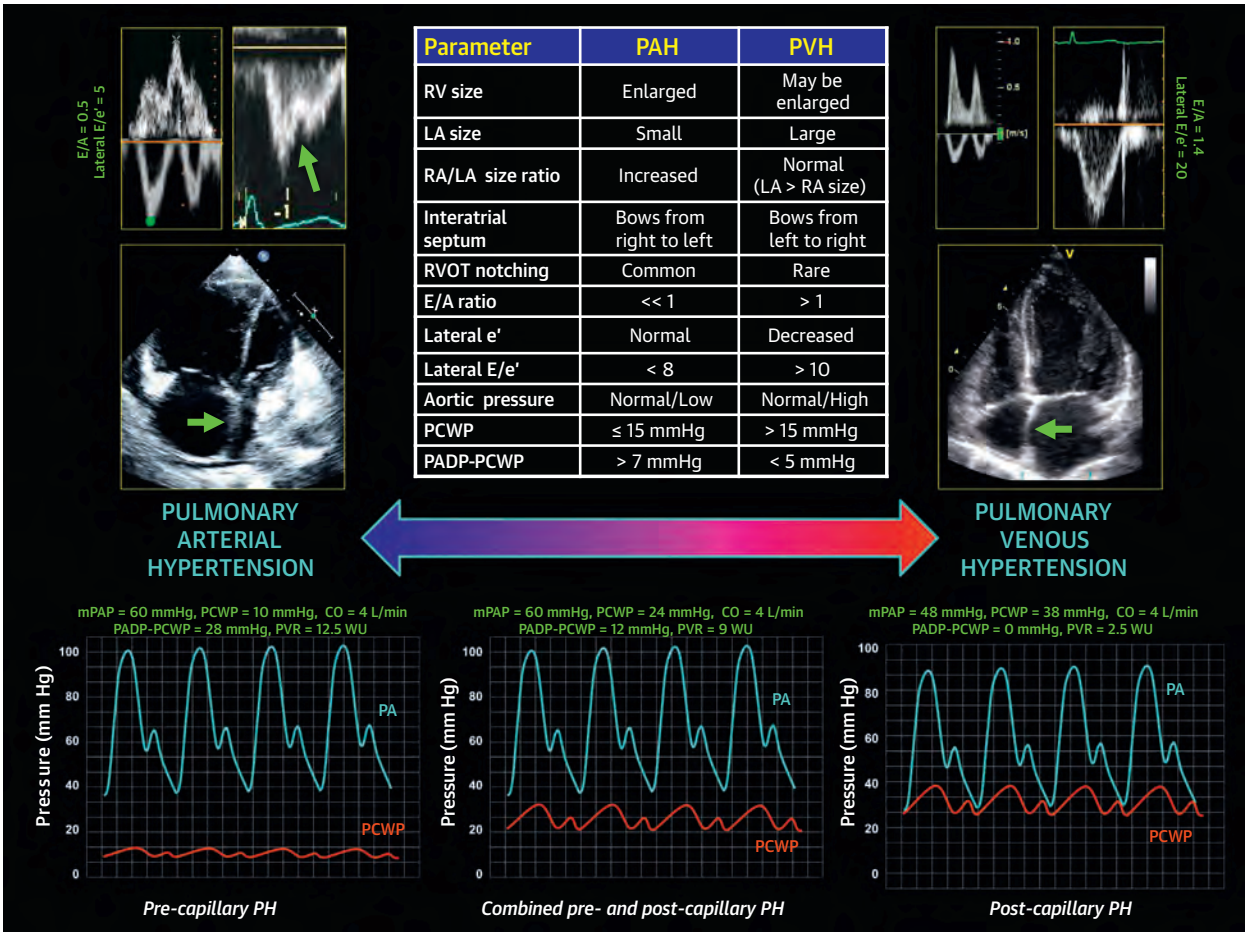
DIFFERENTIATION OF PAH FROM PVH. In clinical practice, differentiating PAH from PVH can be challenging. Given the very high prevalence of left heart disease, it is important to try to determine noninvasively the type of PH because invasive hemodynamic testing can sometimes be avoided if it is clear that the etiology of PH is left heart disease. In some patients, such as those with heart failure with reduced LV ejection fraction or severe aortic or mitral valve disease, the diagnosis of PVH (Group 2) is usually straightforward. However, many patients who are evaluated for PH have a normal LV ejection fraction and no severe valvular lesions. In these patients, differentiating PAH from PVH hypertension can be challenging. Furthermore, some patients with PVH may have superimposed PAH (the so-called combined pre- and post-capillary PH), which adds additional diagnostic complexities.

The clinical history can be helpful in differentiating PAH from PVH. Thenappan et al. (45) demonstrated that advanced age, the presence of comorbidities such as systemic hypertension and coronary artery disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output were the best variables to help differentiate PH-HFpEF (due to PVH) from PAH.

Figure 2 displays helpful criteria on echocardiography and invasive hemodynamic testing for the differentiation of PAH versus PVH and for the diagnosis of combined pre- and post-capillary PH, such as that which occurs in patients with HFpEF with superimposed precapillary PH. In a study of 44 patients with PH, Willens et al. (46) compared patients with PAH (n = 24) to those with PVH (n = 20) and found that the E/A and lateral E/e′ ratios were the 2 most helpful echocardiographic parameters in differentiating between types of PH: lateral E/e′ >9.2 had a sensitivity of 95% and specificity of 96%; E/A ratio >1.7 had a sensitivity of 75% and specificity of 91%. Crawley et al. (47) used cardiac magnetic resonance (CMR) in a similar study (n = 37 with IPAH, n = 21 with PH-HFpEF, and n = 23 without PH) and found that left atrial volume was the best parameter for differentiating PAH from PVH.

Invasive hemodynamic testing is the gold standard for differentiating PAH from PVH. In patients with invasively-documented PH (mPAP ≥25 mm Hg), PH consensus statements recommend the use of a partition value of PCWP ≤15 mm Hg (for diagnosis of PAH) versus PCWP >15 mm Hg for diagnosis of PVH (1,2,4). However, the diagnosis of PVH with superimposed precapillary PH can be challenging. Some patients with PVH, particularly those with HFpEF, will have a high PA systolic pressure that drives mPAP elevation and can result in elevated transpulmonary gradient (mPAP-PCWP) and PVR. Because these patients do not necessarily have superimposed

FIGURE 2 PAH Versus PVH: Echocardiographic and Invasive Hemodynamic Differentiation



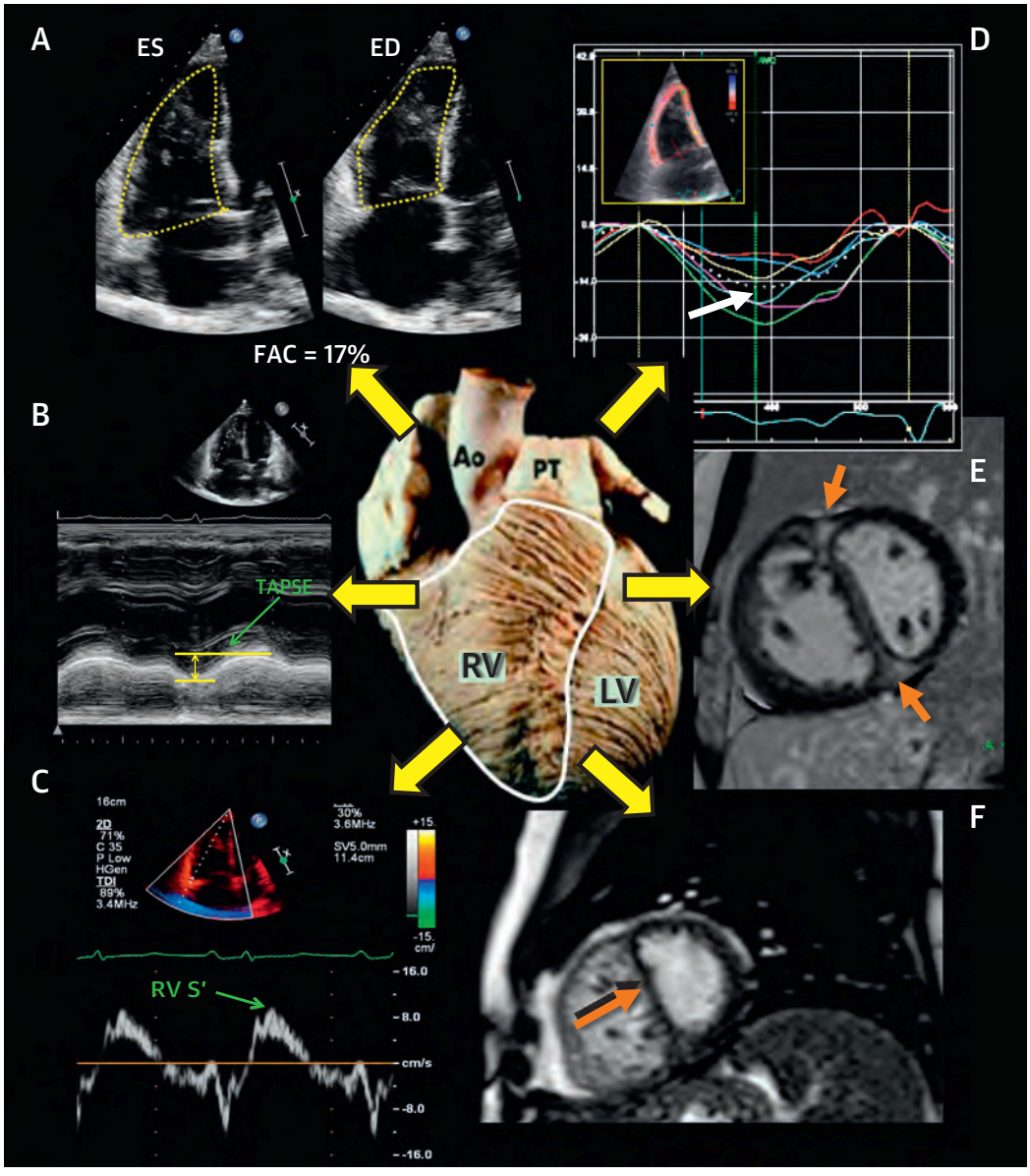
Parameter	PAH	PVH
RV size	Enlarged	May be enlarged
LA size	Small	Large
RA/LA size ratio	Increased	Normal (LA > RA size)
Interatrial septum	Bows from right to left	Bows from left to right
RVOT notching	Common	Rare
E/A ratio	<< 1	> 1
Lateral e'	Normal	Decreased
Lateral E/e'	< 8	> 10
Aortic pressure	Normal/Low	Normal/High
PCWP	≤ 15 mmHg	> 15 mmHg
PADP-PCWP	> 7 mmHg	< 5 mmHg

(Left) Prototypical echocardiographic and invasive hemodynamic findings from a patient with PAH. The RA and RV are severely enlarged, and the LV and LA are small and underfilled. The interatrial septum bows from right to left. On mitral inflow, E/A ratio <1 because of underfilling of the LA and decreased compliance of the LV due to extrinsic compression from the enlarged RV. The lateral e′ velocity and lateral E/e′ ratio are normal (<8) suggesting normal LV relaxation and filling pressures. There is notching in the RV outflow tract profile on pulse-wave Doppler imaging due to increased PA stiffness. PCWP is normal and the PADP-PCWP gradient is severely increased. **(Right)** Prototypical echocardiographic and invasive hemodynamic findings from a patient with PVH. The LA is enlarged and the interatrial septum bows from left to right. On mitral inflow, E/A ratio >1, lateral e′ velocity is reduced, and lateral E/e′ ratio is increased, suggestive of grade 2 diastolic dysfunction with impaired LV relaxation and elevated LV filling pressures. There is no notching in the RV outflow tract profile. PCWP is elevated, and there is no gradient between the PADP and PCWP. Note that although the RV in the right panel is not enlarged, RV enlargement and dysfunction can be present in patients with isolated PVH. **(Upper middle)** Parameters helpful for differentiating PAH from PVH on echocardiography and invasive hemodynamic testing. **(Lower middle)** Invasive hemodynamic findings in a patient with combined pre- and post-capillary PH (elevated PCWP and PADP-PCWP gradient). It should be noted that the most challenging patients are in this middle zone (combined pre- and post-capillary PH), with echocardiographic findings that lie in the middle of the prototypical examples of PAH and PVH shown here. In these patients, careful evaluation of the echocardiogram and invasive hemodynamics will be necessary for an accurate diagnosis. E/A = ratio of early to late (atrial) mitral inflow velocities; E/e′ = ratio of early mitral inflow velocity to early diastolic mitral annular tissue velocity; CO = cardiac output; LA = left atrial; mPAP = mean pulmonary arterial pressure; PADP = pulmonary artery diastolic pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVH = pulmonary venous hypertension; PVR = pulmonary vascular resistance; RA = right atrial; RV = right ventricular; RVOT = right ventricular outflow tract.

precapillary PH, an elevated PADP-PCWP gradient (i.e., diastolic pulmonary gradient) >5 to 7 mm Hg has been advocated as the best way to diagnose true combined pre- and post-capillary PH (i.e., PVH with superimposed precapillary PH) (30), as shown in Figure 2.

DIAGNOSTIC EVALUATION OF THE RV. The RV plays a central role in the diagnosis and management of PH.

FIGURE 3 Echocardiographic and CMR Evaluation of the RV in Pulmonary Hypertension



(A) Right ventricular (RV) fractional area change; **(B)** tricuspid annular plane systolic excursion (TAPSE); **(C)** RV tissue Doppler longitudinal (s′) velocity; **(D)** RV global longitudinal strain on speckle-tracking echocardiography; **(E)** late gadolinium enhancement of the RV insertion points on cardiac magnetic resonance (CMR); and **(F)** "D-sign" of the left ventricle (LV) due to RV overload during peak inspiration on CMR. The central image in the figure displays the superficial muscle layer of the RV (dissection by Damian Sanchez-Quintana, University of Extremadura, Spain [modified with permission from Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. Heart 2006;92 Suppl 1:i2-13]). CMR images courtesy of Benjamin Freed, MD, Northwestern University Feinberg School of Medicine. Ao = aorta; FAC = fractional area change; ED = end-diastole; ES = end-systole; PT = pulmonary trunk.

In recent years, there has been increased focus on evaluation of RV structure and function in the setting of PH, using echocardiography and CMR as the 2 primary clinical imaging modalities. Table 2 lists useful echocardiographic parameters for determining whether the RV is enlarged or dysfunctional. RV systolic function can be evaluated using 2-dimensional images (e.g., RV fractional area chance in the apical 4-chamber view) (Figure 3A); M-mode (e.g., tricuspid annular plane systolic excursion

[TAPSE]) (**Figure 3B**); and tissue Doppler imaging (e.g., RV basal free wall systolic [s′] velocity at the level of the tricuspid annulus) (**Figure 3C**) (41). These techniques are easy to apply during routine clinical echocardiography; however, RV fractional area chance can be challenging to calculate when RV images are suboptimal, and it is insensitive in cases of subtle RV dysfunction; TAPSE and RV tissue Doppler velocity are more sensitive indicators of RV dysfunction, but can be affected by M-mode or Doppler beam misalignment, respectively, or by tethering to the LV (i.e., if LV systolic function is hyperdynamic, as is often the case in PAH, TAPSE and RV velocity can be falsely elevated; alternatively, in patients with severe LV systolic dysfunction, these measures can be falsely low). Speckle-tracking echocardiography (**Figure 3D**) allows for rapid assessment of RV myocardial deformation (i.e., RV free wall strain) and is not as angle-dependent.

CMR has the advantage of being a tomographic technique that can provide 3-dimensional views of the RV without being affected by acoustic window quality. Thus, CMR provides the most accurate noninvasive measurement of RV volumes, mass, and ejection fraction. Gadolinium contrast injection during CMR can be used to evaluate for focal RV fibrosis; patients with PAH often exhibit late gadolinium enhancement at the RV insertion points (**Figure 3E**). CMR cine images during inspiration can be very helpful in understanding the ability of the RV to handle volume overload. During inspiration, as intrathoracic pressure drops, blood is drawn into the right heart from the systemic veins, filling the RA and RV. Interventricular septal flattening (“D sign”) (**Figure 3F**) at peak inspiration is indicative of a vulnerable or dysfunctional RV (in the absence of an alternate etiology of septal flattening, such as constrictive pericarditis). In the future, novel imaging techniques for the evaluation of diffuse RV fibrosis, RV metabolism, and RV perfusion will likely be possible and should further enhance our ability to understand RV pathophysiology in the setting of PH.

FURTHER TESTING FOR PATIENTS WITH PAH. In the evaluation of patients with PH, if the diagnosis of PVH has been established, the focus becomes left heart disease, with further diagnostic measures depending on the type of left heart lesion resulting in elevated left atrial pressure. Alternatively, if the initial diagnostic evaluation reveals pre-capillary PH, further testing, including laboratory testing for HIV, liver disease, and CTD; pulmonary function testing; arterial blood gas analysis; ventilation-perfusion scanning of the lung; chest computed tomography; and overnight polysomnography are helpful in classifying PH (1-3).

THERAPY FOR PAH

GENERAL MEASURES. Basic counseling and disease state education are important components in the care of PAH patients. Low-level graded aerobic exercise, such as walking, is recommended. The benefits of intensive pulmonary rehabilitation have been demonstrated (48). Patients are advised against heavy physical exertion and isometric exercise, as this may evoke exertional syncope. Oxygen supplementation to keep saturation above 90% at rest and with exertion, sleep, or altitude is advisable. A sodium-restricted diet is advised and is particularly important to manage volume status in those with RV failure. Routine immunizations, such as those against influenza and pneumococcal pneumonia, are advised.

BACKGROUND THERAPY. Despite a paucity of data, diuretic and anticoagulant agents are often appropriate therapies in PAH patients. Anticoagulant agents have been studied in 4 uncontrolled observational series: 2 prospective and 2 retrospective, primarily in IPAH patients (49-52). Improved survival was observed in all 4 studies. Most guidelines recommend warfarin anticoagulation titrated to an international normalized ratio of 1.5 to 2.5 in patients with IPAH. One prospective registry also assessed patients with associated forms of PAH and found no benefit of anticoagulation in such patients (52). Diuretic agents are indicated to manage RV volume overload. Occasionally, intravenous (IV) diuretic agents are required. Serum electrolytes and renal function should be followed closely. There are few data pertaining to digoxin, although it is sometimes used in patients with right heart failure and low cardiac output and in those with atrial arrhythmias.

CALCIUM-CHANNEL BLOCKERS. Calcium-channel blockers can be a very effective treatment for those few patients with an acute response to vasodilator testing as outlined in the previous text. Patients who meet criteria for a positive vasodilator response can be treated with a calcium-channel blocker, but should be followed closely for both safety and efficacy of therapy. If a patient meeting the definition of an acute response does not improve to functional class I or II on calcium-channel blockers, an alternative PAH-specific therapy should be prescribed. Very few patients (<7%) with IPAH do well over the long-term on calcium-channel blockers (43). Long-acting nifedipine, diltiazem, and amlodipine are the most commonly-used agents. Due to its potential for negative inotropic effects, verapamil should be avoided.

PROSTACYCLINS. Prostacyclin synthase expression is reduced in endothelial cells from PAH patients, resulting in inadequate production of prostaglandin I2 (i.e., prostacyclin), a vasodilator with antiproliferative effects (53). Administering prostanoids has been a mainstay of PAH therapy for nearly 2 decades. There are currently multiple prostanoids commercially available: epoprostenol (continuous IV), treprostinil (continuous subcutaneous, continuous IV, intermittent inhaled, and oral) and iloprost (intermittent inhaled). Prostanoids are complex therapies and are best administered by a center with expertise in the complicated delivery systems and chronic management of side effects and dosing.

Epoprostenol was the first therapy approved by the FDA for IPAH. Randomized controlled clinical trials in IPAH demonstrated improvements in exercise tolerance, as measured by the 6MWD, hemodynamics, quality of life, and survival over a 12-week period (54). Long-term observational series have also suggested improved survival on IV epoprostenol (55,56). IV epoprostenol has also been evaluated in PAH related to the scleroderma spectrum of diseases, with improvements in 6MWD and hemodynamics demonstrated by a 12-week randomized controlled clinical trial in this population (57). Observational series have also reported favorable effects of IV epoprostenol in patients with additional forms of associated PAH.

Epoprostenol must be delivered by continuous IV infusion. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. More recently, a thermostable formulation of epoprostenol, which does not require ice packs and can be mixed less frequently, has been approved. Intravenous epoprostenol is commonly started in the hospital at a dose of 2 ng/kg/min and up-titrated, depending on symptoms of PAH and side effects of the therapy. Although dosing is highly individualized, the optimal dose for most adult patients tends to be in the range of 25 to 40 ng/kg/min. Common side effects include jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening.

Treprostinil is a prostanoid currently approved as a continuous subcutaneous infusion, continuous IV infusion, or an intermittent inhaled treatment. Treprostinil was first studied as a subcutaneous infusion in a placebo-controlled, multicenter randomized trial of 470 patients over 12 weeks (58). There was a dose-related improvement in 6MWD of 16 m. Adverse effects included pain and erythema at the site of the subcutaneous infusion in 85% of patients. Other common side effects included headache, diarrhea, rash, and nausea. On the basis of bioequivalence data, treprostinil is FDA-approved for a continuous IV delivery. Treprostinil has been approved for intermittent inhaled use. In a multicenter, randomized, placebo-controlled study of 235 PAH patients who were still symptomatic despite oral bosentan or sildenafil therapy, the addition of inhaled treprostinil resulted in an improvement in the primary endpoint of 6MWD (59). Common side effects included cough, headache, nausea, dizziness, and flushing.

Treprostinil diethanolamine is a salt form of treprostinil designed to release the drug in a sustained-release osmotic tablet for twice daily dosing. Oral treprostinil has been studied as monotherapy in 349 PAH patients over 12 weeks (60). An improvement of 23 m ($p = 0.0125$) in the primary endpoint of 6MWD was observed. There were no improvements in the secondary endpoints of time to clinical worsening or functional class. The most common adverse events were headache, nausea, diarrhea, and jaw pain. Oral treprostinil has also been studied in 2 randomized controlled trials as add-on therapy to endothelin receptor antagonists and/or phosphodiesterase type 5 (PDE-5) inhibitors (61,62). The primary endpoint of 6MWD was not improved in either trial. The FDA approved oral treprostinil in December 2013 to improve exercise capacity, noting that the drug did not offer additional benefit when added to other vasodilator therapy in 2 16-week double blind, placebo-controlled trials.

A 12-week multicenter, randomized, placebo-controlled trial in 207 patients of iloprost, an inhaled prostanoid, demonstrated an improvement in a novel composite endpoint that included an improvement by at least 1 level of functional class, improvement in 6MWD by at least 10%, and the absence of clinical deterioration (63). Inhaled iloprost has also been studied in combination with bosentan in a multicenter, randomized, placebo-controlled trial. After 12 weeks, there were improvements in functional class and time to clinical worsening. The combination appeared to be safe. Common side effects of inhaled iloprost include cough, headache, flushing, and jaw pain.

ORAL PAH-SPECIFIC THERAPIES. Endothelin pathway. Increased tissue expression and increased plasma levels of endothelin-1, a potent vasoconstrictor and stimulator of cell proliferation, have been described in PAH, highlighting the potential of targeting this pathway in the treatment of PAH. Endothelin receptor antagonists act by selectively blocking endothelin-A receptors or by dual blockage of endothelin-A and -B receptors; furthermore, they constituted the first class of drugs orally administered in PAH (64–66).

Bosentan, a nonselective endothelin-A and -B receptor antagonist has been studied in multiple placebo-controlled trials in PAH. The BREATHE-1 study, a multicenter, randomized, placebo-controlled trial of 213 functional class III and IV PAH patients demonstrated an improvement in 6MWD and the composite endpoint of time to clinical worsening over 16 weeks (67). More recently, bosentan has been evaluated in functional class II patients in a 6-month multicenter, randomized, placebo-controlled trial (68). This study demonstrated an improvement in PVR and time to clinical worsening. The improvement in 6MWD was not statistically significant. Bosentan has been studied specifically in patients with congenital systemic to pulmonary shunts and Eisenmenger physiology (69). In this population, improvements in PVR, mPAP, and 6MWD were noted, and bosentan did not worsen oxygen saturation. Bosentan is currently widely used in patients with PAH. Close follow-up of both efficacy and safety is encouraged. The FDA requires liver function to be checked on a monthly basis, and an algorithm for managing elevated liver function tests is available in the package insert. Other side effects include headache, anemia, and edema.

Ambrisentan, a selective endothelin-A receptor antagonist, has been studied in 2 phase III multicenter, randomized, placebo-controlled trials in 394 PAH patients and demonstrated an improvement in 6MWD and time to clinical worsening (70). The FDA no longer requires monthly liver function test monitoring in patients on ambrisentan, although many experts continue to check liver function periodically. Other side effects of ambrisentan include fluid retention, nasal congestion, flushing, and anemia.

Macitentan, a nonselective endothelin-A and -B receptor antagonist, has increased tissue penetration and more sustained receptor blockade compared with bosentan (71). It has been studied in a phase III long-term morbidity and mortality trial (n = 742) in which the primary endpoint was the time from initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with parenteral prostanoids, or worsening PAH (72). Patients were randomized to either placebo or macitentan 3 or 10 mg daily. There were 30% and 45% risk reductions in the primary endpoint with the 3- and 10-mg doses, respectively. Both patients on PAH-specific therapy (such as PDE5 inhibitors) and treatment-naïve patients had improvements in the primary and secondary outcome measures. The most frequent adverse events were headache, nasopharyngitis, and anemia. The incidence of edema and elevation of liver function tests were similar in the placebo and macitentan groups. Macitentan was FDA-approved to delay disease progression, including death, initiation of prostanoid therapy, or clinical worsening in PAH. Unlike bosentan, monthly liver function test monitoring is not required, although physicians are encouraged to monitor as clinically indicated.

Nitric oxide pathway. Nitric oxide (NO) is a potent vasodilator of the pulmonary circulation, acting through the increase in cyclic guanosine monophosphate (cGMP), and cleared mainly as a result of degradation by PDE-5. Reduction in the expression of NO synthase has been described as a mechanism associated with the pathogenesis of PH (73). Currently, there are 2 therapeutic classes of drugs interacting in the NO pathway, aiming to increase the direct action of cGMP: PDE-5 inhibitors, which decrease cGMP degradation, and soluble guanylate cyclase stimulators, which increase cGMP production.

Phosphodiesterase type 5 inhibitors. Sildenafil has been studied in a 12-week multicenter, randomized, placebo-controlled trial and was found to improve 6MWD and hemodynamics, but not the secondary endpoint of time to clinical worsening (74). The improvement was not dose-related, and sildenafil is currently approved at a dose of 20 mg 3 times a day. More recently, tadalafil was studied in a 16-week multicenter, randomized, placebo-controlled trial and demonstrated an improvement in the primary endpoint of 6MWD (75). The highest dose studied (40 mg) also resulted in an improvement in the secondary endpoint of time to clinical worsening. Tadalafil is approved at a dose of 40 mg once daily. The most common side effects of the PDE-5 inhibitors include headache, flushing, dyspepsia, myalgias, and epistaxis.

Soluble guanylate cyclase stimulators. Riociguat is a first-in-class soluble guanylate cyclase stimulator. It directly stimulates soluble guanylate cyclase independent of nitric oxide, and increases the sensitivity of soluble guanylate cyclase to nitric oxide (76,77). A randomized controlled trial of 261 patients with either inoperable CTEPH or persistent PH after pulmonary endarterectomy demonstrated an improvement in the primary endpoint of 6MWD and the secondary endpoints of PVR, N-terminal pro-B-type natriuretic peptide (BNP), and functional class with riociguat (78). A randomized controlled trial of 443 PAH patients (44% previously treated with endothelin receptor antagonists and 6% with nonparenteral prostanoids) also demonstrated an improvement in the primary endpoint of 6MWD as well as multiple secondary endpoints including PVR, N-terminal proBNP, functional class, and time to

clinical worsening with riociguat (79). The most common adverse events included syncope, headache, dyspepsia, peripheral edema, and hypotension. Cases of hemoptysis have also been reported. Concomitant use of riociguat and PDE-5 inhibitors is contraindicated due to hypotension. The FDA approved riociguat to improve exercise capacity, functional class, and delay in clinical worsening in group 1 PAH and to improve exercise capacity and functional class in patients with persistent PH after surgical pulmonary endarterectomy, or for those with inoperable CTEPH. It must be emphasized that patients with surgically-accessible CTEPH are best treated with surgery, and should not receive riociguat instead of pulmonary endarterectomy.

LUNG TRANSPLANTATION AND BRIDGE TO TRANSPLANTATION WITH EXTRACORPOREAL LIFE SUPPORT. Despite recent advances in medical therapy, lung and heart-lung transplantation remains an essential treatment option for PAH patients in the modern management era (80–83). It is widely recognized that transplant referral should occur before the patient develops severe RV failure and that eligible patients should be counseled about lung transplant early in their diagnosis (83). Due to limited organ availability and high mortality rates while awaiting transplantation, eligible patients who are in NYHA functional class III or IV symptoms with other clinical, and/or hemodynamic predictors of poor prognosis on best standard of care including a parenteral prostacyclin have to be considered for lung transplantation. The same applies for eligible patients initially presenting with end-stage PAH in NYHA functional class IV. Bilateral sequential lung transplantation is the most common procedure. However, practice may vary from center to center, and heart-lung transplantation may be required for some patients in the context of complex Eisenmenger physiology and is also preferred by some centers in the setting of refractory RV failure. Although some patients with PVOD may respond to low-dose PAH therapy, many will have no response or will deteriorate with such therapy. Thus, PVOD patients should be managed with lung transplant teams to offer a timely listing of lung transplant candidates.

It is important to identify patients with persistent evidence of RV failure in the presence of maximal medical treatment before they develop irreversible end-organ injury. If appropriate, these patients should be considered for bridging to lung transplantation (80–83). Indeed, circulatory support may allow stabilization of patients, with improvement in organ function and increased probability of survival. Extracorporeal life support should thus be considered in PAH patients in the setting of persistent RV failure despite optimal medical management. Bridge therapy should be discussed and initiated earlier in the course of RV failure, before the occurrence of secondary organ injury. Parameters known to be associated with high mortality in PAH patients requiring inotropic support include systemic hypotension, elevated creatinine, hyponatremia, high BNP levels, and increasing inotrope requirements. Because of life-threatening RV failure, extracorporeal life support should support the heart without compromising oxygenation. Both the pulmonary artery-left atrium Novalung (Xenios AG, Heilbronn, Germany) and venoarterial extracorporeal membrane oxygenator have been used to bridge PAH patients for several weeks until transplant (80,82). One must bear in mind that extracorporeal life support complications can be serious (e.g., infection at the cannulation site, hemorrhage, renal failure, neurologic complications, vascular access site injury, thromboembolic complications), emphasizing the need for these procedures to be performed in well-selected patients treated in experienced centers (80,82). Of note, lung transplantation is a life-saving procedure in severe PAH with survival rates after 1, 5, 10, and 15 years of 70%, 50%, 39% and 26% (heart-lung transplantation) and 79%, 52%, 43%, and 30% (double-lung transplantation), respectively (81).

ATRIAL SEPTOSTOMY. Balloon atrial septostomy (artificial creation of a right-to-left shunt to decompress the right heart) can be performed percutaneously with careful graded balloon dilation. This approach has been proposed by some experienced centers to improve peripheral oxygen delivery, despite a fall in systemic arterial saturation due to a compensatory rise in cardiac output. Balloon atrial septostomy has a high periprocedural mortality in patients with markedly elevated right atrial pressure and should only be considered as a palliative therapy or bridge to transplantation in centers with experience in this procedure (84).

APPROACH TO THERAPY. The optimal therapeutic approach must be individualized for every patient, taking into account many factors including the severity of illness, route of administration of therapy, side effect profile, comorbid illnesses, treatment goals, and clinician experience and preference. Some of the factors that place patients at highest risk are listed in **Table 3**. Aggressive upfront triple combination therapy may be considered in the most seriously ill patients upon presentation (85). Emerging evidence favoring upfront dual oral combination therapy with tadalafil and ambrisentan in treatment-naïve

TABLE 3 High Risk Factors

Syncope	Yes
NYHA/WHO class	IV
6MWD	<300 m
CPET	Peak oxygen uptake <12 ml/kg/min
Echocardiographic findings	Pericardial effusion
	TAPSE <1.5 cm
Hemodynamics	RAP >15 mm Hg
	Cardiac index ≤2 l/min/m^2
CMR	RVEF <35%

CMR = cardiac magnetic resonance; CPET = cardiopulmonary exercise testing; NYHA = New York Heart Association; RAP = right atrial pressure; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; WHO = World Health Organization; 6MWD = 6-min walking distance.

patients has recently been presented. The most common treatment strategy currently employed is goal-oriented sequential combination therapy. Although the primarily observational studies described previously do not allow for definitive conclusions, reasonable goals of therapy include (86):

- Modified NYHA functional class (World Health Organization functional class): I or II
- Echocardiography/CMR: normal or near-normal RV size and function
- Hemodynamics: normal indexes of RV function (right atrial pressure <8 mm Hg and cardiac index >2.5 to 3.0 l/min/m^2)
- 6MWD >380 to 440 m
- Cardiopulmonary exercise testing: peak oxygen uptake >15 ml/min/kg and ventilatory equivalents for CO_2 <45 l/min
- BNP level: "normal" (determined by local laboratory cutoff values)

Over the years, many treatment approaches have been published, including those put forth at the 5th World Symposium on PH and by the American College of Chest Physicians (87,88). Our proposed treatment algorithm is depicted in the **Central Illustration**.

FUTURE DIRECTIONS

Oral selexipag is a pulmonary vasodilator that acts on the human prostaglandin I2 (IP) receptor. The efficacy of selexipag has been tested in multicenter, randomized controlled trials, including a recently-completed large, phase III, double-blind, placebo-controlled, event-driven, morbidity and mortality trial that enrolled 1,156 PAH patients. In that study, selexipag significantly decreased the risk of a morbidity/mortality event versus placebo by 43% ($p < 0.0001$) (89). Results of this trial were presented March 15, 2015, at the ACC.15 in San Diego, California (90).

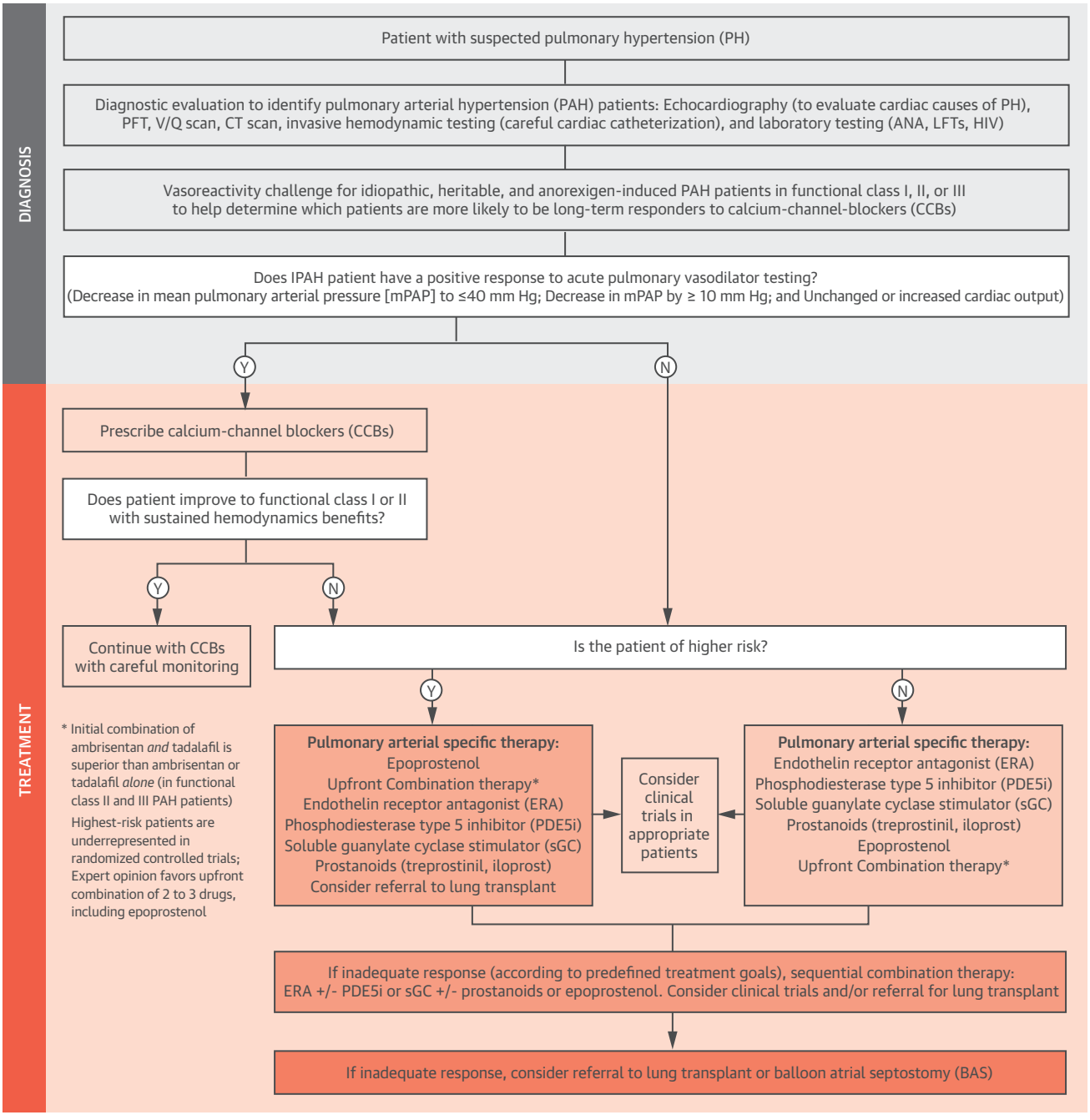
The importance of growth factors in pulmonary vascular remodeling suggests that receptor tyrosine kinase inhibition could be an interesting anti-proliferative approach in PAH. The IMPRES (Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study) study showed that imatinib therapy could improve cardiac output with a modest reduction in mPAP in a patient population with advanced disease despite therapy with at least 2 PAH drugs (91). However, the unfavorable risk-benefit profile of imatinib has resulted in cessation of its further therapeutic development in PAH, and its off-label use in PAH is not encouraged. Targeting growth factors, however, remains an attractive strategy in PAH, but a better understanding of this treatment approach will be required to facilitate the development of new drugs that could block proliferative pathways without severe side effects.

Serotonin causes pulmonary artery vasoconstriction and pulmonary artery smooth muscle cell proliferation. Terguride, a 5HT-2 receptor antagonist, was not efficacious in either hemodynamics or exercise capacity in a phase II trial. De novo synthesis of serotonin from tryptophan is catalyzed by tryptophan hydroxylase-1 (TPH-1) and overexpression of the TPH-1 gene has been found in remodeled arteries of PAH patients. Moreover, hypoxic PH is attenuated in TPH-1 knockout mice. Thus, inhibition of TPH-1 is a potential target against the serotonin system in PAH (83,92).

Rho-kinase is the downstream effector of the small GTPase, RhoA, and mediates a range of cellular functions such as cell migration and smooth muscle contraction. Fasudil is a potent Rho-kinase inhibitor, and acute IV administration has led to a 17% reduction in PVR in a small observation study of 9 PAH patients. A long-acting oral formulation of fasudil was recently tested in a pilot randomized controlled trial in Japan involving 23 PAH patients over 12 weeks. No significant differences in pulmonary hemodynamics and 6MWD were seen between the 2 groups at the end of the study. Pulmonary edema and pleural effusions occurred in 1 patient treated with fasudil, resulting in death, and a causal relationship with the drug could not be excluded (93).

A link between inflammation and PAH pathogenesis is supported by several clinical and preclinical observations. Anti-inflammatory therapies have been explored predominantly in CTD-associated PAH, and small case series have reported clinical response to immunosuppression using a combination of cyclophosphamide with glucocorticoids. However,

CENTRAL ILLUSTRATION **Treatment Algorithm for PAH**



McLaughlin, V.V. et al. J Am Coll Cardiol. 2015; 65(18):1976–97.

ANA = antinuclear antibody; BAS = balloon atrial septostomy; CCB = calcium-channel blockers; CT = computed tomography; ERA = endothelin receptor antagonist; HIV = human immunodeficiency virus; IPAH = idiopathic pulmonary hypertension; LFT = liver function test; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type 5 inhibitor; PFT = pulmonary function tests; PH = pulmonary hypertension; sGC = soluble guanylate cyclase stimulator; V/Q = ventilation perfusion scan.

beneficial effects are restricted to PAH that is associated with systemic lupus erythematosus and mixed connective tissue disorders (CTD), but not in scleroderma, the most common CTD associated with PAH (94). A phase II study investigating B-cell depletion with rituximab (monoclonal antibody against CD20) in scleroderma-associated PAH is underway (NCT01086540) (95).

Mitochondrial abnormalities with a metabolic switch favoring cytosolic glycolysis, rather than normal mitochondrial aerobic metabolism, have been demonstrated in PAH. Such metabolic abnormalities can be partially corrected by the agent dichloroacetate, which has been shown to reverse PH in animal models (96). A phase I open-label trial is currently investigating dichloroacetate in PAH (NCT01083524) (97).

The leading cause of heritable PAH is germline mutations in BMPR2. Moreover, the finding that BMPR2 function is also reduced in IPAH has led to major interest in restoring BMPR2 function in PAH patients. Interestingly, gene transfer of BMPR2 using adenovirus vector has been shown to improve PH induced by hypoxia and monocrotaline in rats. Using a transcriptional high-throughput luciferase reporter assay, the calcineurin inhibitor FK506 (tacrolimus) was recently found to be a candidate compound that can up-regulate BMPR2 signaling. Low-dose FK506 also reverses both hypoxic and monocrotaline forms of experimental PH (98).

Endothelial progenitor cells are bone marrow-derived progenitor cells involved in vascular homeostasis, which can circulate, proliferate, and differentiate into mature endothelial cells at sites of vascular injury. A study of autologous transplantation of ex vivo cultured endothelial progenitor cells has showed interesting short-term results in 31 PAH patients (99). Since this initial proof-of-concept study, no further human trials in adults have been published.

As observed in congestive heart failure, PAH is associated with neurohormonal activation, as evidenced by increased sympathetic nerve traffic and up-regulation of the renin-angiotensin-aldosterone system. Interestingly, plasma levels of renin and angiotensin I and II are increased in PAH and have been associated with worse prognosis (100). In addition, β-blockers, acetylcholinesterase (ACE) inhibitors, angiotensin-II receptor blockers, and aldosterone antagonists have produced beneficial hemodynamic effects in experimental PH (101). In clinical practice, aldosterone antagonists are already widely used in the treatment of RV failure. In contrast, there is limited data to support the use of β-blockers in PAH, and extreme caution is advocated due to reported symptom worsening with β-blocker administration.

Pulmonary artery denervation has recently been proposed for PAH in an attempt to abolish sympathetic nerve supply to the pulmonary circulation. In a first-in-human single-center proof-of-mechanism study, 13 patients underwent this procedure with a dedicated radiofrequency ablation catheter. This investigational approach resulted in significant improvement of mPAP and 6MWD, but requires further confirmation (102).

Potts shunt is a surgical method of RV decompression via the creation of an anastomosis between the descending aorta and left pulmonary artery. In case of suprasystemic PH, an advantage of Potts shunt over atrial septostomy is the sparing of the cerebral and coronary circulation from deoxygenated blood (103). Recently, an investigational small case series of adults with NYHA functional class IV PAH demonstrated the feasibility of creating a Potts shunt via an interventional percutaneous approach (104).

SPECIAL SITUATIONS INCLUDING PERIOPERATIVE CARE, PREGNANCY, AND ICU CARE

PERI-OPERATIVE CARE. Patients with significant PAH are at high risk for general anesthesia. Perioperative risk was studied in an international prospective 3-year questionnaire-based survey among 11 PH centers (105). Major complications occurred in about 6% of patients, and overall perioperative mortality was about 3.5%. The factors that increased complications and mortality were more advanced disease, manifested by a higher right atrial pressure and a lower 6MWD. The need for emergency surgery and the use of perioperative vasopressors also increased risk.

PAH can be considered a fixed obstructive cardiopulmonary lesion with intraoperative physiology similar to severe aortic or mitral stenosis. During induction of anesthesia, systemic vasodilation is common, and systemic blood pressure can decrease. Systemic hypotension can exacerbate RV ischemia by decreasing the right coronary artery perfusion pressure during systole, resulting in decreased cardiac output due to worsening RV function. The reduction in pulmonary blood flow results in more underfilling of the LA and LV, worsening the systemic hypotension. Furthermore, as the LV becomes more underfilled and the RV becomes more overloaded, increased interventricular septal flattening ensues, further decreasing the ability of the LV to fill. These abnormalities can quickly result in acute decompensation and potential death in a patient with PAH.

Given the risk of general anesthesia in a patient with PAH, the following strategies can help to ensure the best outcome perioperatively: 1) if possible, try to avoid general anesthesia (e.g., use a nerve block); 2) evaluate and treat for decompensated right heart failure; 3) in patients with severe PAH (e.g., those with functional class III or IV symptoms, or on IV or subcutaneous prostacyclins), perform pre-operative right heart catheterization and optimize hemodynamics prior to elective surgery; and 4) in the operating room, have available PA catheter monitoring, transesophageal echocardiography, and inhaled nitric oxide. All PAH patients should continue vasodilator medications perioperatively, and a PAH specialist should be involved in perioperative management, especially in high-risk PAH patients who are on advanced prostanoid therapies.

PREGNANCY. Despite the advent of multiple classes of medications for PAH patients, pregnancy is contraindicated in these patients. Although there is not much controlled data on pregnancy in PAH, a systemic review of case reports demonstrated a very high 30% to 56% mortality in PAH during pregnancy or in the early post-partum period (106). Bonnin et al. (107) found a maternal mortality rate of 36% in a series of 15 consecutive PAH patients who became pregnant in the modern era of PAH treatment. A more contemporary description is of 26 pregnancies in PAH patients at 13 PAH centers (108). There were 3 deaths (12%), and 1 patient developed refractory right heart failure and underwent heart-lung transplantation post-partum. There were 2 spontaneous and 6 induced abortions. Overall, 62% of the pregnancies resulted in a healthy baby without maternal complications. These women had well-controlled PAH (mean PVR 500 $\pm$ 352 dynes/s/cm^5). One-half were long-term calcium-channel blocker responders.

Several normal physiological changes in pregnancy can be deleterious to the patient with PAH, particularly the increase in blood volume and requirement for increased cardiac output, along with systemic vasodilation. As with other types of fixed obstructive lesions (such as aortic and mitral stenosis), pregnancy is poorly tolerated in patients with PAH. Furthermore, certain pulmonary vasodilators, such as the endothelin receptor antagonists, are contraindicated in pregnancy because of teratogenicity. Thus, all female patients with PH, particularly PAH, should avoid pregnancy, and contraception should be used in sexually-active patients (1).

Despite warnings and contraceptive measures to avoid pregnancy, some women with PAH will get pregnant. In these patients, termination of pregnancy should be discussed. If the patient desires to keep the pregnancy, the following steps should be followed to try to ensure the best possible outcome for the mother and child: 1) referral to a PAH specialist and high-risk obstetrician (with close collaboration between the PAH and obstetrics teams); 2) discontinue endothelin receptor antagonists immediately (category X) in patients who are taking them; 3) maintain patients on anticoagulation (low molecular-weight heparin), oxygen, and diuretic agents; 4) continue PDE5 inhibitors and prostacyclins (category B), and in patients with significant PAH who are not yet on prostacyclin therapy, initiation of such therapy should be considered; 5) close follow-up with monthly visits and echocardiograms to screen for and treat RV decompensation and right heart failure; and 6) perform elective, planned delivery with Caesarean section and spinal-epidural anesthesia (at 34 weeks of gestation, if possible) (1,107).

INTENSIVE CARE UNIT MANAGEMENT. With advances in pharmacological therapy for PAH, many patients can now survive with good functional status. However, the RV remains vulnerable in these patients, and they can quickly spiral downward in the setting of stressors, such as infection, medication, and/or dietary noncompliance, and become critically ill. Unfortunately, there is scant evidence for the appropriate management of PAH patients in the intensive care unit, and expert consensus is the primary basis of treatment guidelines (80).

Management of the RV is central to successfully treating PAH patients who are critically ill. Often, clinicians have a knee-jerk reaction to give fluids to patients with sepsis or hypotension, a management strategy that can have dire consequences in the setting of PAH. For example, in a patient with PAH who is septic or has a severe infection, systemic vasodilation occurs. As outlined earlier in describing the hemodynamic reaction to general anesthesia, the RV can become more ischemic due to decreased RV perfusion, resulting in further exacerbation of systemic hypotension due to decreased cardiac output. The RV enlarges and compresses the LV, further decreasing LV filling. In this setting, administration of IV fluids will only compound the problem as RV diastolic pressure rises (further impeding right coronary blood flow), and interventricular septal flattening will worsen.

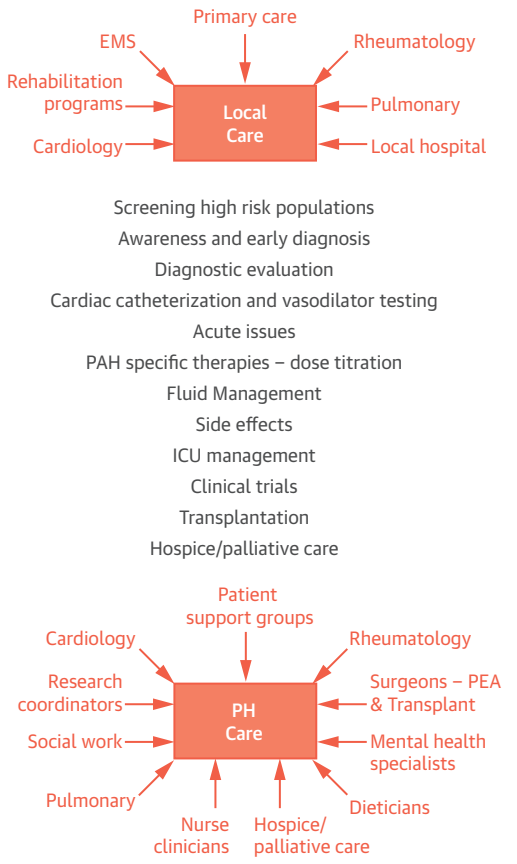
It is also important to note that acute-on-chronic RV failure in PAH is physiologically different than acute RV failure (e.g., RV myocardial infarction). Most PAH patients are not pre-load-dependent in the setting of RV failure, and even small boluses of IV

fluid can be very harmful. Finally, renal venous congestion often occurs in patients with PAH who are critically ill with RV failure. RA pressure (and therefore central venous pressure) is high in decompensated PAH, resulting in increased renal venous pressure, and systemic hypotension decreases renal perfusion. These hemodynamic changes decrease renal blood flow and result in increased fluid retention.

Given these hemodynamic abnormalities, we advocate the following steps for the management of critically ill PAH patients: 1) consider invasive hemodynamic monitoring (e.g., pulmonary artery catheter) for diagnostic purposes to determine the hemodynamic abnormality and filling pressures present; 2) increase systemic blood pressure with drugs such as dobutamine and/or phenylephrine to achieve a systolic blood pressure >90 mm Hg; 3) optimize central venous pressure to 8 to 10 mm Hg (use IV diuretic agents, ultrafiltration, or continuous venovenous hemofiltration if necessary); 4) transfuse packed red blood cells to maintain hemoglobin >10 g/dl; 5) continue pulmonary vasodilator drugs that the patient was taking previously as an outpatient; and 6) consider prescribing iNO (typical dose = 20 ppm), especially if the patient is on a ventilator, remembering to wean off slowly to avoid rebound elevations in PA pressure. If these measures fail, adding an inotropic agent to increase RV contractility can be considered. In addition, the use of short-term, percutaneous, partial ventricular support devices, such as a Tandem Heart (CardiacAssist, Inc., Pittsburgh, Pennsylvania) (inflow cannula in the RA and outflow cannula in the PA) or RV Impella catheter (Abiomed, Danvers, Massachusetts) have been described in the setting of RV failure (109,110). In severe cases, where there is a clear reversible cause of RV decompensation, extracorporeal life support (e.g., venoarterial extracorporeal membrane oxygenator) can be administered and can be life-saving; bilateral lung transplantation should also be considered in these cases (80).

COLLABORATIVE CARE OF THE PAH PATIENT. Management of the PAH patient requires a multidisciplinary approach and collaboration between local care and the PH specialty center (**Figure 4**). Given the delay from symptom onset to diagnosis, greater awareness in the community is required to achieve earlier diagnosis. Some community settings may be equipped to perform a thorough diagnostic evaluation, including a right heart catheterization with vasodilator testing, whereas others may not. An open dialogue with a PH center will help facilitate a correct and timely diagnosis in instances where local expertise is not available.

FIGURE 4 Collaborative Care



Opportunities for collaboration between local providers and pulmonary hypertension (PH) centers in the care of patients with PH. EMS = emergency medical services; PEA = pulmonary endarterectomy.

Given the complexities of the diagnosis and the cost and side effect profile of the therapies, referral to a PH center to confirm the diagnosis and comanage the patient should be considered. A recent series describing new referrals to 3 PH specialty centers demonstrated that patients are referred late, with functional class 3 and 4 symptoms, more than one-half of the time; the diagnosis is often incorrect (nearly one-half of patients receive a different diagnosis after evaluation at the referral center); and PAH-specific therapy is commonly started inappropriately (111). In fact, 30% of patients received PAH-specific therapies before referral, and 57% of the time the use of PAH-specific therapy was not in accordance with PH guidelines.

The PH center often can provide specialized care that is not available in the community. PH nurse clinicians are critical in the management of PAH patients. They provide vital education regarding the disease and its therapies, and maintain an active role in case management to titrate medications, monitor side effects, and recognize complications. Access to clinical research trials and advanced treatment options, such as parenteral prostacyclins and lung or heart-lung transplantation, are important aspects of care available at PH centers.

Collaboration is key, and it is incumbent upon the PH center to maintain an open dialogue with local health care providers. The primary care physician or local cardiologist or pulmonologist must be kept up to date on the patient's status and therapies, as they may be the first physician to encounter a complication of PAH therapy (e.g., a line infection), to recognize disease progression (e.g., fluid retention and right heart failure), or to diagnose a new problem (e.g., pneumonia). As many patients live far from the PH center, comanagement of such issues is in the patient's best interest.

CONCLUSIONS

Over recent decades, many advances have led to a better understanding of and treatment for PAH. It is critical that the appropriate diagnosis be made in a timely fashion. Differentiating PAH from PVH is important and requires a thorough evaluation. Numerous therapies are available to treat PAH, and an aggressive approach targeting multiple pathways may lead to better outcomes. The health of the RV is the key determinant of prognosis; despite advances in the treatment of PAH, management of RV failure remains suboptimal for many patients. Fortunately, this remains an area of active research with opportunities for translational discoveries that have the potential to improve patient care.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Vallerie V. McLaughlin, Pulmonary Hypertension Program, University of Michigan Hospital and Health Systems, Cardiovascular Center, 1500 East Medical Center Drive, Room 2392, Ann Arbor, Michigan 48109-5853. E-mail: vmclaugh@med.umich.edu.

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