STATE OF THE ART

Pulmonary Arterial Hypertension: Diagnosis, Treatment, and Novel Advances

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Abstract

The diagnosis and management of pulmonary arterial hypertension (PAH) includes several advances, such as a broader recognition of extrapulmonary vascular organ system involvement, validated point-of-care clinical assessment tools, and focus on the early initiation of multiple pharmacotherapeutics in appropriate patients. Indeed, a principal goal in PAH today is an early diagnosis for prompt initiation of treatment to achieve a minimal symptom burden; optimize the patient's biochemical, hemodynamic, and functional profile; and limit adverse events. To accomplish this end, clinicians must be familiar with novel risk factors and the revised hemodynamic definition for PAH. Fresh insights into the role of

developmental biology (i.e., perinatal health) may also be useful for predicting incident PAH in early adulthood. Emergent or underused approaches to PAH management include a novel TGF- β ligand trap pharmacotherapy, remote pulmonary arterial pressure monitoring, next-generation imaging using inert gas-based magnetic resonance and other technologies, right atrial pacing, and pulmonary arterial denervation. These and other PAH state of the art advances are summarized here for the wider pulmonary medicine community.

Keywords: pulmonary hypertension; treatment; risk stratification; pulmonary arterial hypertension

The Clinical Scenario

Pulmonary hypertension (PH) is a heterogeneous disease driven most often by pathogenic remodeling of distal pulmonary

arterioles or a congestive (functional) vasculopathy resulting from pulmonary venous hypertension. In practice, the clinician is faced first with clinical, imaging, and biomarker data before establishing a diagnosis

of PH by using right heart catheterization (RHC). The approach to hemodynamic classification of PH has changed recently, however, compared with the model used between 1973 and 2019. Now, patients with a

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mean pulmonary arterial pressure (mPAP) >20 mm Hg enter a diagnostic algorithm in which pulmonary vascular resistance (PVR) and pulmonary arterial wedge pressure (PAWP) are used to classify patients into one of three hemodynamic subgroups: precapillary PH, isolated postcapillary PH, and combined precapillary and postcapillary PH (Figure 1A) (1). The hemodynamic profile is then interfaced with clinical and diagnostic testing data to inform the appropriate clinical PH subgroup (Figure 1B).

There are five PH clinical subgroups, 1) pulmonary arterial hypertension (PAH); 2) PH due to left heart disease; 3) PH due to respiratory disease, hypoxia, or hypoventilatory syndromes; 4) PH due to pulmonary arterial obstructions (e.g., chronic thromboembolic PH [CTEPH]); and 5) a constellation of PH etiologies that vary widely by pathogenesis, including sickle-cell disease, sarcoidosis, and others (1, 2). In “real-world”

practice, identifying a single etiology underlying PH is challenging, particularly in patients with overlapping cardiac and parenchymal lung disease risk factors. Nonetheless, therapy diverges widely by PH clinical group, and inappropriate treatment is common and potentially harmful (3). Thus, clinicians must be familiar with the appropriate steps for distinguishing PAH from other forms of PH.

Epidemiology

The prevalence of PAH (i.e., group 1 PH) is approximately 25 cases per population of 1 million, with an incidence of approximately five cases per population of 1 million per year (reviewed in Reference 2). However, the demographic profile has changed since its original description emphasizing younger women of childbearing age as the prototypical

patients with idiopathic PAH. Today, the average age of patients with a new diagnosis in clinical trials and registries is approximately 53 years (4). This epidemiological shift reflects, in part, a wider consideration of PAH risk factors, including PAH in association with connective tissue disease, liver disease, and other age-related comorbidities. In addition, enhanced awareness among clinicians is likely to account for differences in the epidemiology of PAH today compared with the prior era.

The prevalence of PAH remains female predominant, although the sex ratio in older patients is balanced. Overall, men who present with more severe hemodynamic derangement are less responsive to contemporary medical therapy than women (5). Data from studies not hampered by selection bias reporting on PAH prevalence in self-identified Black individuals and other underrepresented minorities are sorely needed (6).

Methamphetamine use is a novel risk factor for

Figure 1. The hemodynamic and clinical classification system for pulmonary hypertension (PH). (A) Patients undergoing right heart catheterization with an mPAP >20 mm Hg are considered further for classification as having precapillary PH, isolated postcapillary PH, or combined precapillary and postcapillary PH. (B) The PH clinical subgroups. Abstracted from Reference 1. CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic PH; Developm. = developmental; HPAH = hereditary PAH; HTN = hypertension; Hypovent. = hypoventilation; iPAH = idiopathic PAH; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PAWP = pulmonary arterial wedge pressure; PVOD = pulmonary venoocclusive disease; PVR = pulmonary vascular resistance; WU = Wood units.

Figure 2. Pulmonary arterial and right ventricular (RV) remodeling in pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH). (A) A normal pulmonary artery (arrow) adjacent to a terminal Br (subpanel A); a marked medial and intimal thickening of a small pulmonary artery (arrow), partly surrounded by lymphoid cells form a cluster reminiscent of a primary follicle (arrowheads) (subpanel B); an idiopathic PH lung with a markedly muscularized, medium-sized pulmonary artery (arrow), which distally branches into a plexiform lesion (lower arrowhead) and an adjacent plexiform lesion (upper arrowhead) (subpanel C); a complex vascular lesion (circle) with a combination of telangiectasia-like dilations of the pulmonary artery (arrowheads) and a plexiform lesion (arrow) (subpanel D); a medium-sized pulmonary artery with complete lumen obliteration with loose collagen and a poorly defined cellular matrix (arrows) (subpanel E); and an intra- and/or interlobular septal, medium-sized vein (arrowhead) obliterated by loose connective tissue (arrows), likely the result of an organized thrombus, characteristic of venoocclusive disease (subpanel F). These representative images were provided courtesy of Dr. Rubin Tudor, obtained through the evaluation of the lungs collected by the PH Breakthrough Initiative, with a pulmonary vascular pathology spectrum similar to that reported in Reference 77. (B) Lipotoxicity in the RV in PAH, as indicated by ceramide deposition that corresponds to RV hypertrophy and remodeling (white arrows) on CMR. Reprinted by permission from Reference 78. (C) Compared with iPAH, RV fibrosis is observed to a greater extent in patients with SSc-PAH. Passive tension as a function of escalating sarcomere length was measured in iPAH, SScPAH, and nonfailing control myocytes. **Post hoc* $P < 0.05$ between control and IPAH; †*post hoc* $P < 0.05$ between control and SSc-PAH. Scale bar, 250 μ m. Reprinted by permission from Reference 18. (D) Uniform, random, isotopically oriented RV sections stained with fluorescein isothiocyanate-lectin show the distribution of vessels. Scale bar, 100 μ m. The relationship between RV volume and vessel length (left graph) and the diameter of RV tissue perfused by each vessel (right graph) are shown. Average radius of RV tissue served per vessel ($n = 3-4$ /group; *t* test). Reprinted by permission from Reference 19. Br = bronchiole; CMR = cardiac magnetic resonance imaging; iPAH = idiopathic PAH; Ssc = systemic sclerosis.

PAH of particular importance, owing to estimates implicating 50 million users worldwide (7).

Despite robust attention to PAH in clinical trials, isolated postcapillary PH or combined precapillary and postcapillary PH from left heart disease and precapillary PH

from obstructive lung disease are by far the most common PH subtypes in developed countries. Data on PH prevalence varies widely by study design, diagnostic modality, and patient selection, particularly with respect to the stage of underlying disease in patients with primary left heart or lung disease.

According to some estimates, the prevalence of PH is 50% and 80% in patients with heart failure with reduced left ventricular (LV) ejection fraction and in patients with heart failure with preserved LV ejection fraction (HFpEF), respectively. Approximately 90% of patients with chronic obstructive pulmonary disease

have an mPAP > 20 mm Hg, although it has not been established how many of these patients meet the contemporary definition of precapillary PH based on PVR ≥ 3.0 Wood units (WU). Similarly, an mPAP ≥ 25 mm Hg is reported in 15% of patients with mild idiopathic pulmonary fibrosis (IPF) and in two-thirds of patients with severe IPF (8). A recent meta-analysis suggested that the cumulative incidence of CTEPH ranges between 0.5 (population level) and 3% among patients seen in clinical practice after surviving acute pulmonary embolism (9). However, data on CTEPH prevalence are less clear because many at-risk patients are not assessed appropriately for CTEPH, particularly outside of referral hospital settings (10). The prevalence of PH varies widely within the group 5 subphenotypes. For example, an mPAP of ≥ 25 mm Hg is reported in cross-sectional or retrospective studies in 10% of patients with sickle-cell disease, of whom one-half receive a diagnosis of PAH (11). In patients with postsplenectomy or fibrosing mediastinitis, the prevalence of PH is 10% and 5%, respectively (12).

Pathology

Iterative arterial branching culminates in approximately 280 billion pulmonary capillaries, which underlie a high-surface-area, high-flow, and low-resistance pulmonary arterial circulation. In turn, subtle pathogenic changes to the pulmonary vascular architecture can elevate PVR, but such elevation requires extensive involvement of numerous distal vessels. The plexogenic arteriopathy is considered pathognomonic for PAH (and is observed variably in other specific subgroups with PH, such as those with sickle-cell disease) (Figure 2A); however, intimal and medial hypertrophic, fibrotic, and (micro)thrombotic remodeling is observed across the PH clinical spectrum. Sclerosis and muscularization of septal pulmonary veins are appreciated increasingly in precapillary and postcapillary hemodynamic phenotypes, including patients with PAH, patients with pulmonary venoocclusive disease, and patients with left heart disease PH (13). Active remodeling of both precapillary and postcapillary vessels over time likely contributes to disease progression in severe PAH, which occurs despite the aggressive use of current PAH therapies that primarily target vascular tone and reactivity.

Complex, overlapping, and convergent molecular pathways are a hallmark of PAH

pathobiology, although novel mechanistic insights implicate a wider range of cell types underlying PAH arteriopathy than were appreciated originally. For example, pulmonary arterial smooth muscle cells, adventitial fibroblasts, and pericytes are fundamental to the pathology of PAH by virtue of altered cellular metabolism, survival, and growth patterns (14). Oxidant stress from diverse mechanisms can induce endothelial dysfunction, phenotype switching, and paracrine signaling to other vascular cell types, which subsequently promotes vascular remodeling and fibrillar collagen deposition (15). Hemoglobinopathies, particularly sickle-cell disease, are associated with pulmonary vascular injury, in part, by nitric oxide scavenging (and subsequent changes to the redox balance of vascular cells) from erythrocyte-free Hb, reinforcing the importance of interactions between circulating intermediaries and the pulmonary blood vessel wall (16).

Right ventricular (RV) lipotoxicity and impaired oxidative glucose metabolism are observed in PAH (Figure 2B) (17), whereas a fibrosis-dominant pattern independent of hemodynamics is reported in systemic sclerosis (SSc)-PAH (Figure 2C) (18). Vascular rarefaction of the RV free wall was not observed in end-stage PAH through use of stereological analyses, although the average radius of RV tissue by each capillary increased by 15% (Figure 2D) (19). It is important to note that, unlike coronary perfusion to the LV, coronary perfusion to the RV is supplied by only a single epicardial vessel, and supply-demand mismatch causing relative ischemia may thus account for ultrastructural changes to RV cardiomyocytes. Right coronary arterial perfusion to the RV occurs in diastole and systole, but in PAH, the systolic component may be impaired because of high intracavitary pressure functioning as another potential etiology of RV ischemia (20).

Pathophysiology in PH: Key Paradigm Shifts

Refining the PH Hemodynamic Spectrum

The classical PH definition of mPAP ≥ 25 mm Hg was based largely on expert consensus opinion without normative or outcome data. In 2009, Kovacs and colleagues determined that the upper limit of normal mPAP is 20 mm

Hg (21), with little variation across age being shown. These data converge with findings from large RHC referral populations, in which all-cause mortality risk begins at 19–20 mm Hg and rises continuously through 40 mm Hg (22). In patients with well-phenotyped SSc and patients with mixed cardiopulmonary disease followed prospectively, mPAP < 25 mm Hg is also independently associated with impaired exercise capacity and adverse clinical events (23). On the basis of these collective data, a strong recommendation to change the diagnostic criteria for PH from ≥ 25 mm Hg to > 20 mm Hg was proposed (1).

Although lowering the mPAP threshold captures more at-risk patients, some physiological conditions (e.g., pregnancy) and immediately reversible high-pulmonary-flow states (e.g., anemia) can elevate mPAP without evidence of elevated PVR. This is an important point because elevated pulmonary arterial pressure (PAP) itself is not pathognomonic for pulmonary vascular disease. As described originally by Wood in 1958 ((reviewed in Reference 24), “hyperkinetic” or high-flow states may raise PAP. Under conditions of increased flow, a *decrease* in PVR is expected. Thus, to optimize the specificity of mPAP for diagnosing pulmonary vascular disease *per se*, PVR ≥ 3.0 WU was added to the criteria delineating precapillary phenotypes. This may be a conservative threshold favoring a late diagnosis of pulmonary vascular disease; however, a signal toward harm is observed in patients with portopulmonary hypertension or sickle-cell disease and PVR < 3.0 WU (25). Recent studies show that mortality is increased in patients with SSc-PAH and a PVR > 2.0 WU compared with < 2.0 WU (26), and in large referral populations with elevated mPAP, the mortality risk increases continuously beginning at about 2.2 WU (27). Furthermore, mildly elevated mPAP (20–24 mm Hg) appears to be more common in patients with preexisting left heart or lung disease, and the importance of this hemodynamic subgroup to capturing patients with PAH therefore remains uncertain (8, 28). Thus, as our understanding of long-term outcomes grows, there may be a further refinement to the hemodynamic definitions used today.

The RV and PAH

Pulmonary arterial compliance (calculated as stroke volume/pulmonary arterial pulse pressure) decreases with an increase in RV afterload before a rise in PVR is evident (29). Chronic elevation in RV afterload forces a state favoring a strong volume pulse to a state with a

Figure 3. Right ventricle (RV)–pulmonary artery (PA) coupling predicts outcomes in pulmonary hypertension (PH). (A) Compared with the LV, the RV pressure–volume relationship is triangular and defined by less discrete transition points around valvular closing and opening. This is due, in part, to the noncompacted myocardium that serves as the framework for increased cardiac chamber compliance of the RV. The ratio of end-systolic elastance to RV afterload is a measure of RV contractility. When the end-systolic elastance is expressed relatively to the RV afterload, the efficiency of RV function is quantified as RV–PA coupling. Directly measuring RV–PA coupling requires transduction catheters, which are not in use in routine clinical practice. However, determining RV volume by using cardiac magnetic resonance imaging or other methods can be combined with pressure assessment from right heart catheterization to measure RV–PA coupling indirectly. Left ventricular loop is reproduced by permission from Reference 79. The right ventricular loop is reproduced by permission from Reference 80. (B) Typical flow patterns in the RV outflow tract at different cardiac phases for a patient with manifest PH (subpanels A, D, and G), a patient with latent PH (subpanels B, E, and H), and a control subject (subpanels C, F, and I). (Subpanels A–C) At maximum outflow, flow profiles were distributed homogeneously across the cross-sections of the main PA in the group with manifest PH (subpanel A), the group with latent PH (subpanel B), and the control group (subpanel C). (Subpanels D–F) In later systole, a vortex was formed in the group with manifest PH (subpanel D). No such vortex could be found in the group with latent PH (subpanel E) or the control group (subpanel F). (Subpanels G–I) After pulmonary valve closure, the vortex in the group with PH persisted for some time. In all cases, continuous diastolic blood flows upward along the anterior wall of the main PA could be observed. Although this phenomenon disappeared quickly in control subjects (subpanel I), it was observed for a significantly longer period in those with latent PH (subpanel H) or manifest PH (subpanel G). Overall, these data show disorganized blood flow through the RV outflow tract in PH. Reprinted by permission from Reference 81. LV = left ventricle; PV = pulmonary valve.

strong pressure pulse. Functionally, this is associated with a shift in the balance of RV energy use toward maintaining pulmonary arterial pressure at the expense of energy normally committed to alveolar perfusion, which is referred to as “RV–pulmonary artery (PA) uncoupling.” Overall, RV–PA uncoupling is the sentinel pathophysiological event underlying progression to heart failure and adverse outcome in PAH. Differences in RV lusitropy, the propensity for RV cavitory dilation, and the extent of pulmonary vascular remodeling are likely to influence the RV–PA (un)coupling profile of individual patients (Figure 3A). Quantifying RV–PA coupling requires sophisticated equipment that is unavailable for routine practice; however, surrogate measures of RV–PA coupling, such as the ratio of

tricuspid annular plane systolic excursion (TAPSE) to estimated pulmonary arterial systolic pressure (PASP) measured by using echocardiography or three-dimensional magnetic resonance imaging, are emerging as informative and as establishing a framework for future studies that clarify the prognostic utility of this measurement in clinical practice (Figure 3B) (30).

Recognizing the Systemic Sequelae of PAH

Impaired LV filling, cardiac arrhythmia, renal dysfunction, neurohumoral overactivation, skeletal muscle dysfunction, and congestive hepatopathy are end-organ injury patterns that develop secondarily to PH–right heart failure (31). A notion of the right-sided cardiorenal syndrome is supported by the data

demonstrating that in PAH plasma, aldosterone is increased by 2.8-fold compared with normal levels and correlates inversely with cardiac output in the absence of left heart disease (32). Impaired renal perfusion is important prognostically in PAH; in one study of 500 patients, serum creatinine >1.4 mg/dl was associated with a mortality hazard risk that was 2.4-fold greater than that of patients with levels <1.0 mg/dl (33). In the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry, patients with PAH with a $\geq 10\%$ decline in the estimated glomerular filtration rate from the baseline that was sustained for more than 1 year had a 66% increase in their mortality hazard (34). Right atrial pressure is an independent predictor of the estimated glomerular filtration rate in PH (35),

Figure 4. Integrated pathway for diagnosing pulmonary hypertension (PH). In patients suspected of having PH on the basis of history, physical examination results, and initial diagnostic testing results (e.g., ECG, chest X-ray), a transthoracic ECHO is often used as the first quantitative test. In patients with normal diagnostic test results at rest (e.g., ECG, echocardiography) but who report exercise limitation or have a risk factor for pulmonary vascular disease (e.g., systemic sclerosis), noninvasive cardiopulmonary exercise testing (CPET) may be helpful. Abnormal results from CPET can be used to advance the diagnostic evaluation for PH. Further evaluation of those with a moderate or high probability of PH determined on the basis of echocardiographic findings and results from assessment of left heart disease and pulmonary disease is warranted through the use of various diagnostic tests, including PFT + DLCO and HRCT. Serologic assessment may include ANA testing, HIV testing, and LFT. Patients should also be assessed for CTEPH, initially by using nuclear $\dot{V}/\dot{Q}$ scanning or contrast-enhanced chest CT. The diagnosis of PH is made by using right heart catheterization and requires a mean mPAP >20 mm Hg. Patients are then classified by hemodynamic category, which, together with the clinical profile and other supporting data (e.g., serologic and genetic testing results), is used to determine the PH clinical group (as outlined in detail in Figure 1). ANA = antinuclear antibody; AT = anaerobic threshold; CT = computed tomography; CTEPH = chronic thromboembolic PH; ECHO = echocardiogram; HRCT = high-resolution CT; LFT = liver function testing; mPAP = mean pulmonary arterial pressure; PFT = pulmonary function testing; $\dot{p}\dot{V}O_2$ = peak $\dot{V}O_2$.

suggesting that increased renal interstitial edema from central pressure elevation may be involved in PH-mediated cardiorenal dysfunction. It is also proposed that disruption of normal interventricular septal dynamics driven by severely elevated RV cavity pressure and pericardial constraint disrupts left heart filling to impair cardiac output. The underlying pathophysiology that is unique to salt avidity in patients with isolated right heart failure may involve overactivation of the renin-angiotensin-aldosterone axis, but clarifying this requires further investigations.

Metabolic dysfunctions, including insulin resistance and impaired fatty acid metabolism, are common in PAH and contribute to hemodynamic derangement. Malnutrition, obesity, cachexia, and sarcopenia are also proven or likely comorbidities that are associated with PAH and are in line with the emergence of (extreme) nutritional contributions to disease pathogenesis. For example, ascorbate acid (vitamin C) is a reducing agent and cofactor for various reactions catalyzed by oxygenases, including endoglin. Endoglins hydroxylate HIF-1 α to promote its

degradation; in turn, impaired HIF-1 α degradation is associated with increased HIF-1 α -dependent pulmonary vasoconstriction and adverse vascular remodeling in PAH. This may explain converging lines of evidence linking scurvy with incident (albeit reversible) PAH (36).

Diagnosing PAH in Clinical Practice

Approach to PAH Diagnosis

The diagnosis of PAH *per se* is made in the absence of an alternative PH cause (2) (Figure

4). A thorough medical history, physical examination, and serological assessment of systemic or infectious diseases, such as SSc or HIV, is essential for evaluating comorbidities that may further or lessen the index of clinical suspicion for PAH. PAH is increasingly diagnosed in patients who are in their fifth decade of life or older. Therefore, left heart disease and parenchymal or obstructive lung disease have also become common comorbidities in individuals evaluated for PAH. As a result, supportive tests, including electrocardiography, spirometry with diffusion capacity, and chest computed tomography, are often critical in the assessment of PH. Physical examination findings exclusive to right heart dysfunction can be useful for distinguishing PAH from left heart disease PH, including the accentuated pulmonic valve component of the second heart sound and parasternal RV heave, the right-sided fourth heart sound that parallels the *a* wave of the jugular venous waveform, the loud tricuspid regurgitation murmur (suggestive of RV dilation) that accentuates on inspiration, and the loud pulmonic insufficiency murmur (37). In the absence of inspiratory crackles or other signs of left heart disease, these findings should increase suspicion for precapillary PH, particularly PAH.

Echocardiography is usually the first quantitative test that patients with PH undergo and is regarded as a useful screening tool. A TAPSE <1.8 cm, an RV fractional area change <35%, a systolic excursion velocity of the tricuspid valve (RV S') <10 cm/s, the presence of a "notch" in the RV outflow tract by pressure wave Doppler interrogation, an RV midcavitary diameter >35 mm, and a respirophasic variation in inferior vena cava size are each useful for staging end-organ injury (i.e., RV dysfunction) in PH. However, one-third of patients with PH will not have a detectable tricuspid regurgitant jet (38), which is required to estimate PASP. Moreover, population studies show a limited correlation between PASP when measured noninvasively and PASP measured directly by using RHC, and echocardiography does not provide reliable information on PVR or PAWP. LV hypertrophy, abnormal LV diastology, bowing of the interatrial septum left to right, and a long-axis left atrial dimension >4.4 cm, however, may be helpful in distinguishing postcapillary PH (e.g., HFpEF) from precapillary PH (39); mitral valvular disease and LV systolic dysfunction remain important and common causes of postcapillary PH.

Table 1. Drugs and Toxins Associated with Developing Pulmonary Arterial Hypertension

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-Tryptophan
Benfluorex	St. John's wort
Methamphetamines	Amphetamines
Dasatinib	IFN- α and - β
Toxic rapeseed oil	Alkylating agents
Mitomycin C (PVOD)	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide

Definition of abbreviation: PVOD = pulmonary venoocclusive disease.

Adapted by permission from Reference 1.

Ultimately, RHC is required for classifying patients into the appropriate hemodynamic and clinical PH subgroups and for diagnosing and staging PAH. It is important to develop a pretest hypothesis of anticipated hemodynamic results on the basis of an individual patient's medical history and the totality of their clinical data. Results from RHC that are inconsistent with the patient's clinical profile may be due to procedural/technical flaws; in some cases, a direct assessment of LV end-diastolic pressure may be useful if the PAWP seems inaccurate or the quality of the tracing appears unsound. The timing and indication of RHC in PAH continue to evolve. It has been proposed, for example, that RHC could be useful in patients with unexplained dyspnea; in patients with RV dysfunction at echocardiography, irrespective of symptoms; and before complete diuresis in patients with a first-time presentation of heart failure symptoms, as long as it can be done safely (40). The latter scenario aims to emphasize the importance of 1) diagnosing PAH early and 2) distinguishing left heart disease (HFpEF) from PAH, a task more difficult to accomplish after diuresis. The precise indications for RHC in patients with interstitial lung disease and PH are likely to evolve in light of recent data suggesting that inhaled prostacyclin (PGI₂) improves the outcome in a subgroup of these patients (41).

Focusing on Early PAH Detection

The median duration between symptom onset and diagnosis is approximately 2.5 years (4). Symptoms in PAH are often nonspecific, which is a disadvantage for prompt diagnosis of an uncommon disease and is a driver of misdiagnosis and often inappropriate use of

PAH therapy (42). The average mPAP at entry into the AMBITION (Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension) trial, which is the largest randomized clinical trial focusing on patients with incident PAH, was approximately 49 mm Hg (43). Thus, there is a major hemodynamic gap between the point at which clinical risk emerges (e.g., ~20 mm Hg) and the time of diagnosis.

Leveraging Risk to Identify PAH Early

In PAH, there are two main portals of entry into early diagnosis. First, the presence of a PAH-associated disease is useful for identifying at-risk patients. This includes patients with connective tissue disease (particularly SSc), HIV infection, portal hypertension, congenital heart disease, exposure to disease-causing drugs/toxins, or, in the developing world, *Schistosomiasis mansoni* infection. In the case of patients with SSc, the progression from "borderline" to "classic" PH has been reported in approximately 40% of patients with SSc within 4 years (44). Wider information on the temporal progression of mild PAH is needed, as longitudinal data in mixed phenotypes suggest that approximately 60% of patients with mPAP of 20–24 mm Hg will go on to develop further elevation in hemodynamics (45).

Methamphetamine exposure is recognized as a major risk factor for PAH. This addictive and potent neurostimulant has a molecular structure similar to that of aminorex fumarate and fenfluramine, and it is estimated that 50 million people use methamphetamines worldwide. Although the prevalence of PAH among users of methamphetamine is not known for certain, the 5-year event-free survival rate in one study was 47.2% for

methamphetamine PAH compared with 64.5% for idiopathic PAH (7). The tyrosine kinase inhibitor dasatinib and antineoplastic agent mitomycin C are important risk factors for PAH and pulmonary venoocclusive disease, respectively (46, 47). A list of drugs and toxins associated with PAH is provided in Table (1).

Second, asymptomatic individuals harboring rare genetic variants should be considered differently from how the general population is considered in clinical practice. In certain cases, genetic predisposition is associated with a unique clinical trajectory. Compared with patients with idiopathic PAH, patients with a *BMPR2* mutation are younger at diagnosis by an average of 10 years, are not vasoreactive, and generally have a lower cardiac index and a higher PVR (48). Furthermore, the postdiagnosis duration to death or lung transplantation is shorter. However, with a disease penetrance of 40% for women and 14% for men, *BMPR2* mutations likely require additional or “second hits” to convert a phenotypically silent mutation into a disease-causing one. For example, the female sex is a strong determinant of PAH in *BMPR2* mutation carriers (49). In addition, *BMPR2* mutant rats live full, normal lives without disease but will exhibit PH if exposed to enhanced pulmonary 5-lipoxygenase immunity (50), suggesting that perhaps pneumonia or other inflammatory insults in combination with a particular genetic context could decrease the threshold for developing PAH.

The presence of a pathogenic biallelic *EIF2AK4* mutation may be a substitute for lung biopsy in diagnosis of pulmonary capillary hemangiomatosis or pulmonary venoocclusive disease. Patients with this mutation should be considered for lung transplant earlier because of dismal clinical outcomes and a lack of response to conventional medical therapy (51). Similarly, Montani and colleagues prospectively followed a cohort of asymptomatic *BMPR2* mutation carriers ($N = 55$) for 2 years with serial clinical, hemodynamic, biological, and functional assessments. This strategy permitted diagnosis and treatment of mild PAH at an early time point in four patients, which in turn maintained a low-risk clinical profile for the affected subgroup (52). Serial surveillance of clinical symptoms and the use of noninvasive screening may be a practical approach for early detection, as it is in other systemic at-risk disorders.

Using Exercise Intolerance as an Early PAH Marker

Noninvasive cardiopulmonary exercise testing (CPET) is used to monitor the clinical trajectory of patients with established PH (see Figure E1 in the online supplement). However, CPET data may also guide early pulmonary vascular disease diagnosis, particularly in at-risk patients such as those with sickle-cell disease, connective tissue disease, HIV, lung disease, or left heart structural abnormalities despite reassuring results at initial diagnostic testing (i.e., standard ECG, echocardiography). For example, a low peak $\dot{V}O_2$, an early anaerobic threshold, abnormal ventilatory inefficiency (e.g., $\dot{V}_E/\dot{V}CO_2$) and diminished end-tidal CO_2 in patients with SSc (53) or other *bona fide* pulmonary vascular disease risk factors should prompt consideration of RHC, irrespective of results from noninvasive diagnostic data collected at rest.

Because patients with PAH often present initially with nonspecific exertional complaints, a low threshold for measuring exercise capacity with formal testing is proposed as an important strategy toward earlier diagnosis. Confirming impaired exercise tolerance by CPET or another method, in turn, obligates a further diagnostic evaluation, possibly including RHC, to clarify the etiology of symptoms. This approach is within the paradigm that exercise intolerance precedes resting symptoms in PAH, suggested initially more than 40 years ago via consideration of the subgroup of patients with “exercise-induced PH.” Achieving consensus on the parameters that distinguish normal states from pathogenic ones has been difficult, however, because of differences in the approach to testing across sites and complexities in the RV–pulmonary vasculature relationship. It is important to recognize that a slight curvilinear relationship exists between cardiac output and mPAP (54). Under pathogenic conditions that reduce pulmonary arterial compliance, this association tilts toward linearity, suggesting that a greater increase in mPAP is observed per each change in cardiac output in comparison with normal conditions. Partly for this reason (as well as because of difficulties with capturing an accurate tricuspid regurgitation jet with echocardiography to estimate PASP during exercise), focusing on PAP during exercise alone is insufficient for accurately assessing pulmonary vascular causes of dyspnea.

During invasive CPET, continuous central and peripheral hemodynamic

monitoring together with gas-exchange assessments made by using pneumotachygraphy permits an integrated assessment of heart, lung, and skeletal muscle function during exercise. Tolle and colleagues demonstrated an inverse gradient in peak $\dot{V}O_2$ across a cohort of patients with dyspnea and resting PAH, hemodynamic evidence of PAH provoked by exercise, or hemodynamic criteria for PAH that were not met at rest or during exercise (55). A similar (although inverse) gradient was observed across these groups for mPAP and PVR at peak exercise. These data helped to assemble a model by which a PAH-like hemodynamic profile observed during exercise was considered as an intermediate clinical phenotype between healthy and frank PAH. Data from perhaps the largest study thus far on exercise hemodynamics and outcomes suggest that abnormal PAP/cardiac output slope >3 mm Hg/L/min was particularly important in predicting future cardiovascular events or death in patients with preserved LV ejection fraction and unexplained dyspnea (56).

Prematurity Is an Evolving Risk Factor for Early Diagnosis of PAH

Goss and colleagues showed recently that prematurity is associated with early-onset adulthood PH. A small cohort of adults with a history of preterm birth, defined by a birth weight $\leq 1,500$ g (corresponding to a mean gestational age of 28 wk), underwent RHC at a median age of 27 years (57). Overall, 45% of preterm subjects met the criteria for unsuspected PH because of the absence of clinical symptoms. Several studies have shown strong associations of placental vascular histopathology in preterm neonates with intrauterine growth restriction and susceptibility to developing subsequent bronchopulmonary dysplasia and PH (Figure 5) (58). Epidemiologic data further demonstrate a striking incidence of preterm birth histories in adult PH populations (59). These clinical observations and extensive preclinical data suggest that perinatal or developmental events can injure and arrest growth and maturation of the lung circulation, which not only increases the risk for neonatal and childhood PH but may also be sufficient to increase the risk for PH over time, especially in response to diverse second hits, such as hypoxia (particularly important in the premature population), inflammation, hemodynamic stress, infection, drugs, toxins, and other factors.

Pulmonary Hypertension: Disease Inception

Figure 5. Pulmonary hypertension (PH): disease inception. This schematic representation reflects potential mechanisms through which adverse maternal factors and critical gene–environment interactions may impair placental structure and function, leading to intrauterine stress and altered fetal programming. As proposed, premature birth and antenatal determinants may disrupt lung vascular development and increase the subsequent risk for pulmonary vascular disease, especially with secondary postnatal “hits,” which then contribute to PH during the postnatal period. The dashed line represents the timing of term birth. Adapted by permission from References 82 and 83. PVD = peripheral vascular disease.

Assessing Risk and Prognosis

The Vasoreactive PH Subphenotype

Patients with PAH with a positive response to acute vasoreactivity testing (e.g., a decrease in mPAP ≥ 10 mm Hg to reach an mPAP ≤ 40 mm Hg with an increase [or no change] in $\dot{Q}$) may demonstrate a sustained reduction in mPAP < 30 mm Hg and New York Heart Association (NYHA) Functional Class (FC) I/II status for at least 1 year (60). This subgroup is composed primarily of patients with idiopathic PAH, hereditary PAH, or drug/toxin-associated PAH and is rarely composed of patients with hereditary PAH or PAH associated with connective tissue disease (e.g., SSc-PAH). When present, this likely represents a vasoconstriction-dominant phenotype, which may be driven by a common genetic underpinning that controls cytoskeletal function or Wnt signaling (61). In turn, intact vasoreactivity appears to be determined by signaling pathways that regulate vascular smooth muscle cell contractility. This finding may account for the observation that vasoreactive patients who are responsive to high-dose calcium channel blockade have a favorable long-term prognosis.

Point-of-Care Risk Stratification

The current goal of PAH treatment is to enable patients to achieve a low-mortality-risk status, which has been associated with improved outcomes. To enable this outcome, assessments of mortality risk should be made at diagnosis and at regular intervals during follow-up. The results of these assessments should be used to guide treatment, which should include a proactive change in therapy if a low-risk status is not achieved.

There are several valid PAH tools for point-of-care risk stratification that are used widely in clinical practice (Figure E1). An updated version of the REVEAL score (REVEAL 2.0) (62), which adds the estimated glomerular filtration rate and recent hospitalizations to many nonmodifiable variables used in earlier iterations of this scale, has emerged as a powerful predictor of mortality and clinical worsening, performs well for the incident and prevalent populations, and affords longitudinal risk-profile tracking but has not been analyzed prospectively. Recently published data demonstrated that an abridged version (REVEAL Lite 2), which includes six noninvasive variables (FC, vital signs [systolic blood pressure and heart rate], 6-minute-walk

distance [6MWD], brain natriuretic peptide/NT-proBNP [N-terminal prohormone of brain natriuretic peptide], and renal insufficiency [determined by using the estimated glomerular filtration rate]) approximates REVEAL 2.0 in discriminating among low, intermediate, and high risk for 1-year mortality in patients with the prevalent disease (63).

The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines (64) integrate (modifiable) clinical parameters across multiple dimensions to inform the risk status of individual patients (low, intermediate, or high), which corresponds to an estimated 1-year mortality of $< 5\%$, 5–10%, or $> 10\%$, respectively. The French PAH Network registry shows that patients achieving at least three low-risk 2015 ESC/ERS criteria by first follow-up had a $> 80\%$ survival rate at 5-year follow-up (65). The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERRA) registry also used 2015 ESC/ERS risk-stratification criteria to show that a modified, noninvasive, three-criteria method (using FC, 6MWD, and BNP/NT-proBNP) was more accurate than methods using invasive

Figure 6. Pulmonary arterial hypertension pharmacotherapies by molecular pathway target and delivery system. *Sotatercept is not U.S. Food and Drug Administration–approved; it is listed on the basis of data presented in Reference 70. **In addition to use in pulmonary arterial hypertension, iloprost is now supported for use in interstitial lung disease–pulmonary hypertension on the basis of clinical trial data from Reference 41.

parameters for identifying long-term survivors (66). Importantly, the extent to which achieving a low-risk clinical status (as defined by any of the validated point-of-care risk tools) modifies long-term prognosis or quality of life is not known. Thus, assembling prospective data clarifying this issue should be a priority in the field of outcomes research in PAH.

We recommend an approach that uses complementary strengths among the PAH risk-assessment tools. Specifically, the REVEAL 2.0 scale provides an instructive quantitative risk-score output, which, in our experience, has been effective when framing the prognosis in discussions with patients at the point of care. When considering the longitudinal objectives for patient care, turning to the ESC/ERS scale has been helpful for detailing common-sense clinical therapy targets across different imaging, functional, and biochemical domains. Of these, data from the COMPERA registry suggest that particular emphasis should be placed on improving FC, exercise tolerance (i.e., 6MWD), and NT-proBNP.

Combination Therapy, Staged and Goal-directed Therapy

Supportive measures with diuretics, supplemental oxygen, and, if appropriate,

aldosterone receptor antagonists are important in the management of patients with PAH to drive symptomatic relief, improve hemodynamics, and stabilize electrolytes, respectively. Routine anticoagulation therapy is not recommended in patients with connective tissue disease–PAH but may be considered in patients receiving catheter-based therapies to prevent thrombosis or may be otherwise considered on the basis of an individualized risk profile.

At present, there are 14 U.S. Food and Drug Administration (FDA)-approved medical therapies for PAH that target the endothelin receptor axis, nitric oxide–soluble guanylyl cyclase signaling, or PGI₂ signaling (Figure 6). These therapies may be available in oral, subcutaneous, inhaled, parenteral, implantable, or intravenous applications. Up-front dual-combination therapy is now the standard of care in most low- and intermediate-risk patients with PAH after diagnosis. Although ambrisentan and tadalafil have been studied in a prospective, double-blind, placebo-controlled clinical trial, other lines of evidence support the use of alternative therapy combinations in the management of treatment-naïve patients with incident PAH (64, 67).

NYHA FC IV symptoms, syncope, and chest pain remain indications for immediate parenteral PGI₂ therapy; in the absence of these features, a cardiac index <2.2 L/min/m²,

evidence of end-organ injury, the presence of severe symptoms, and high-risk-status assessment may help adjudicate initiation of parenteral PGI₂ therapy versus dual nonoral therapy in patients with a new diagnosis. Escalation of treatment should be considered in patients with established PAH if a low-risk status is not achieved and/or clinical improvement is stagnant, particularly when evidence of decline is observed (e.g., hospitalization, worsening functional status, increased dyspnea burden). In the rare subgroup of patients who are stable clinically on monotherapy or in whom the prognosis is particularly favorable, the role of sequential add-on treatment is controversial. There are fragile patients and those with comorbidities of the heart and/or lung who may not tolerate dual oral therapy and therefore should remain on oral monotherapy.

The role of up-front triple therapy in PAH is unresolved. In one small study of well-selected patients (i.e., patients with low to intermediate risk), up-front triple therapy was associated with improved long-term outcomes (68). By contrast, recent data from the TRITON (The Efficacy and Safety of Initial Triple versus Initial Dual Oral Combination Therapy in Patients with Newly Diagnosed PAH) trial did not show a significantly beneficial effect on PVR among patients with PAH randomized to receive first-line treatment either with a double combination of

Table 2. Selected Active or Completed Clinical Trials in PAH

Trial Name; Identifier (Reference)	Status	Intervention	Design and Endpoint	Phase	Outcome
PULSAR; NCT 03496207 (70)	Completed	TGF- β superfamily ligand trap	Double-blind, randomized, placebo-controlled, parallel-group study; 1° endpoint: change from baseline PVR at 168 d	2	106 patients with PAH; 0.3 mg every 3 wk: $-145 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$; 0.7 mg every 3 wk: $-239.5 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$; 2° endpoint: 0.3 mg every 3 wk: $\uparrow$ 6MWD by 29 m; 0.3 mg every 3 wk: $\uparrow$ 6MWD by 21 m
TRITON; NCT 02558231 (69)	Completed	Macitentan, tadalafil, and selexipag or placebo	Double-blind, randomized, placebo-controlled, parallel-group study; 1° endpoint: change from baseline PVR at Week 26	3b	No significant improvement in PVR vs. placebo*
TRANSFORM-UK; NCT 02676947	Completed	IL-6 inhibition with tocilizumab	6-mo open-label study; 1° endpoints: -safety: incidence and severity of AEs; change from baseline PVR	2	Results pending
Rituximab for Treatment of SSc-PAH; NCT 01086540 (84)	Completed	B-lymphocyte antigen CD20 inhibition with rituximab	Prospective, double-blind, placebo-controlled, multicenter, randomized trial will evaluate the effect of rituximab on SSc-PAH disease progression; 1° endpoint: change in 6MWD from baseline at 24 wk	2	Well tolerated; no significant difference in 6MWD at 24 wk; full results pending
ABI-009, an mTOR Inhibitor, for Patients with Severe PAH; NCT 02587325 (85)	Active	Inhibition of mTOR with ABI-099	Phase I open-label clinical trial, 16 wk; 1° endpoint: number of participants with treatment-related AEs	2	Interim analysis; $N=6$ patients with PAH; $N=3$ (of 4) patients needed dose reduction or drug discontinuation due to DLT at 10 mg/m^2 ; $N=2$ (of 2) without DLT at 1 mg/m^2
Efficacy, Safety, Tolerability, And PK of Nilotinib (AMN107) in PAH; NCT 01179737	Completed	Stabilization of the inactive confirmation of the kinase domain of the Abl protein with nilotinib	A 24-wk, randomized, double-blind, multicenter, placebo-controlled efficacy trial of safety, tolerability, and PK; 1° endpoint: change in PVR from baseline at 168 d	2	Results pending
Hormonal, Metabolic, and Signaling Interactions in PAH; NCT 01884051 (86)	Completed	Use metformin to decrease gluconeogenesis, increase fatty acid oxidation, and reduce oxidant stress	Single-center, open-label, 8-wk phase II trial; co-1° endpoints: safety inclusive of lactic acidosis and study withdrawal and change in plasma oxidant stress markers	2	$N=20$ patients with PAH; no clinically significant lactic acidosis or change in oxidant stress markers; exploratory analysis: improved right ventricle fractional area change
TransformPAH; NCT 01647945 (87)	Completed	Increase BPM signaling with FK506 (tacrolimus)	Randomized, placebo-controlled, 16-wk trial; 1° endpoint: safety	2	$N=20$ patients with PAH completed the trial; well tolerated (nausea/diarrhea were the most common AEs)
Neprilysin Inhibition for PAH (88)	Completed	Augment natriuretic peptide bioactivity and promote cGMP signaling through neprilysin inhibition	Randomized, double-blind, placebo-controlled trial, 14 d/maximum change in circulating ANP concentration	2a	$N=21$ patients with PAH; $\uparrow$ 79% in plasma ANP; $\uparrow$ 106% in plasma cGMP levels; exploratory endpoint: $\downarrow$ 14% in PVR
Hormonal, Metabolic, and Signaling Interactions in PAH; NCT 01884051 (72)	Completed	Induce Mas receptor activation by recombinant ACE2	Dose-escalation, open-label, 4 h/safety	1	$N=5$ patients with PAH; no signal toward AEs; 2° endpoint: $\uparrow$ 40% cardiac output

Definition of abbreviations: $\uparrow$ = increase of; $\downarrow$ = decrease of; 1° = primary; 2° = secondary; 6MWD = 6-minute-walk distance; AE = adverse event; ANP = atrial natriuretic peptide; BPM = beats per minute; cGMP = cyclic guanosine monophosphate; DLT = dose-limiting toxicity; mTOR = mammalian target of rapamycin; PAH = pulmonary arterial hypertension; PK = pharmacokinetics; PULSAR = A Study of Sotatercept for the Treatment of PAH; PVR = pulmonary vascular resistance; SSc = systemic sclerosis; TransformPAH = FK506 (Tacrolimus) in PAH; TRANSFORM-UK = A Therapeutic Open Label Study of Tocilizumab in the Treatment of PAH; TRITON = The Efficacy and Safety of Initial Triple versus Initial Dual Oral Combination Therapy in Patients with Newly Diagnosed PAH.

*Final results pending.

Figure 7. The CardioMEMS remote pulmonary arterial (PA) pressure (PAP)-monitoring device and the effect of right atrial pacing on hemodynamics in pulmonary arterial hypertension (PAH). (A) The CardioMEMS device was implanted in patients with PAH, and changes in PAP are shown before and after the initiation of prostacyclin therapy. (B) Tracking the effect of medication nonadherence on PAP in a patient requiring HFH. Images are courtesy of Dr. Ray Benza at Ohio State University. (C) The effect of right atrial pacing on hemodynamic parameters in a patient

macitentan (nonselective endothelin receptor antagonist) and tadalafil (phosphodiesterase type V inhibitor) followed by the placebo at 15 days ($n = 124$) or with a triple combination starting with macitentan and tadalafil and followed by selexipag (PGI₂ receptor agonist) at 15 days ($n = 123$) (69). There was a trend toward reduction in disease progression with triple therapy; full publication of these results is awaited. For most patients not requiring parenteral prostanoids, up-front double combination therapy, with careful reassessment at 3 months to ascertain the need for additional therapy, appears to be a prudent approach. Opportunity exists to consider alternative drug combinations and study designs when pursuing additional studies focusing on the potential role of triple therapy in PAH.

Evolving Areas for Optimizing Diagnosis and Treatment of PAH

Therapies Targeting Pathways Alternative to Nitric Oxide, PGI₂, and Endothelin Signaling

A summary of these therapies is shown in Table 2.

Sotatercept. This first-in-class therapy for PAH is a TGF- β superfamily therapeutic that normalizes BMPR-2 signaling. In a large phase II trial, sotatercept at 0.3 mg/kg and 0.7 mg/kg induced a significant 21% and 34% reduction, respectively, in PVR in patients on background therapy compared with placebo. Treatment also improved the change in 6MWD at 24 weeks by 50 m (70).

Seralutinib (GB002). This potent, multitargeted, platelet-derived growth factor receptor, colony-stimulating factor 1 receptor, and Kit kinase inhibitor has targeting characteristics that compare favorably with imatinib and is administered as a dry powder inhalation in an effort to more selectively target the pulmonary vasculature. It has shown promise in animal PAH models, phase 1 studies of its use in human PAH are being completed, and a phase 2 study is being planned (71).

ACE2-modulating therapies. The alternate conversion of angiotensin II to Ang-1 to Ang-7 by ACE2 stimulates Mas receptor 1, which promotes pulmonary arterial smooth muscle cell relaxation and vasodilation. In a pilot trial in patients with PAH, recombinant ACE2 administration was well tolerated and was associated with a decrease in PVR and

Figure 8. Advanced imaging in pulmonary vascular disease. (A) Ventilation, barrier uptake, and red blood cell (RBC) transfer maps show distinct patterns across a healthy control subject and patients with COPD, IPF, LHF, and pulmonary arterial hypertension (PAH). The color bins represent signal intensity (lowest, red; highest, blue; green, referent from the healthy control subject). Each map is quantified by the percentage of the D, L, and H (top). ^{129}Xe spectra are acquired every 20 ms and show cardiogenic Δ of RBC amplitude (%) and frequency shift (ppm) (bottom). Images are courtesy of Dr. Sudar Rajagopal at Duke University Medical Center. (B) Three-dimensional vascular reconstructions derived from clinically acquired computed tomographic angiography in a patient with dyspnea but no hemodynamic evidence of pulmonary vascular disease (top left) and a subject with connective tissue disease–associated PAH (top right). There is a net loss of volume in small vessels (red) as compared with a gain in volume encompassed by the larger vessels (blue and green). The bottom panels show an automated neural network–based arterial and venous labeling of each reconstruction. Images are courtesy of Dr. Farbod Rahgahi at Brigham and Women's Hospital. COPD = chronic obstructive pulmonary disease; Δ = oscillations; D = defect; H = high; IPF = idiopathic pulmonary fibrosis; L = low; LHF = left heart failure; ppm = parts per million.

improvement in cardiac output, paving the way forward for more robust clinical studies (72).

Remote monitoring devices. The CardioMEMS heart failure sensor is a device implanted in the PA that may transmit pulmonary arterial systolic, mean, and diastolic pressure and a surrogate measure of cardiac output (that latter variable is not yet part of the FDA-approved device) (Figures 7A and 7B). Implantation is a consideration for patients with NYHA FC III/IV symptoms to monitor trends in the pulmonary arterial pressure profile. Under these circumstances, use of CardioMEMS appears to be safe and may be effective for monitoring PAH therapeutic efficacy, although FDA approval for the device in PAH *per se* remains as forthcoming (73).

Imaging

Molecular and gas-based imaging. A critical frontier in PAH is the application of advanced imaging for delineating

overlapping phenotypes and quantifying the pulmonary vascular remodeling burden. Magnetic resonance imaging using hyperpolarized ^{129}Xe gas permits direct three-dimensional imaging of ventilation distribution and pulmonary gas transfer. As a result, ^{129}Xe exhibits a unique imaging profile in the signature in the alveoli, interstitial barrier, and red blood cells. Recently, imaging patterns from this method were used to distinguish among chronic obstructive pulmonary disease, IPF, left heart failure, and PAH (Figure 8A) (74). A novel methodology to create three-dimensional vascular reconstruction images generated from two-dimensional cross-sectional computed tomographic angiography studies also shows important promise for clarifying the vascular anatomy in PAH, with implications for early disease detection being shown (Figure 8B).

Interventional Therapies

Right atrial pacing. Right atrial pacing has been used to mitigate RV failure in patients

after myocardial infarction. In PAH, chronotropic incompetence is linked to impaired cardiac output. Early clinical data in a cohort of $N = 32$ patients with PAH from Khural and colleagues (75) showed that right atrial pacing decreased RV end-diastolic pressure and volume significantly and increased cardiac output to normal levels (Figure 7C). Further data on the role of various modalities of resynchronization as an effector of hemodynamics and clinical endpoints are needed.

Pulmonary arterial denervation. Fluoroscopy-guided pulmonary artery denervation (PADN) is a procedure that targets sympathetic nervous system–dependent regulation of pulmonary vascular tone in PAH. In single-center clinical studies, PADN is associated with a reduction in mPAP, an increased 6MWD, and improved RV function (76). Adaptation of PADN to routine clinical practice has been limited so far by a lack of multicenter clinical trials in PAH, a lack of unique expertise needed to ablate successfully, and uncertainty regarding its

efficacy compared with placebo or medical therapy in PAH.

Conclusions

The principal objective in the approach to PAH has evolved from delaying mortality in end-stage disease in the prior era to one defined by early diagnosis and achieving goal-directed therapeutic benchmarks.

These include having a minimal symptom burden, the restoration of normal RV morphological and functional features, improvement in cardiopulmonary hemodynamics, and wider attention to potential extrapulmonary sequelae that underlie a poor prognosis and reflect an advanced stage. Fresh data on the continuum of clinical risk related to mPAP and PVR at the lower end of the spectrum

provide an evidence-based framework by which to heighten clinician awareness, implement risk-factor modification and nonpharmacological interventions such as prescription exercise, and consider PAH therapy when the individual-patient clinical profile is within the wide range of published clinical trial data. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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