Use of pulmonary arterial hypertension–approved therapy in the treatment of non–group 1 pulmonary hypertension at US referral centers

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Abstract: Pulmonary hypertension (PH) is a frequent complication of left heart disease and parenchymal lung disease, and it portends increased mortality. A growing number of medications are approved for the treatment of World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH). However, they are not well studied in PH of other etiologies (WHO groups 2–5). We sought to assess treatment approaches used by PAH referral centers in this diverse group of patients. We developed a semiquantitative online survey designed to evaluate the use of PAH-approved therapy by pulmonary vascular disease centers in the United States for management of non–group 1 PH. Thirty of 50 centers completed the survey. Almost all centers (93%) reported using PAH therapy for patients with non–group 1 PH, including 77% with group 2 PH and 80% with group 3 PH. Elevated transpulmonary gradient or pulmonary vascular resistance and the presence of right ventricular (RV) dysfunction were commonly cited as supporting use of PAH therapy in patients with PH secondary to left heart disease. For patients with PH and concomitant parenchymal lung disease, degree of pulmonary function impairment and RV dysfunction were most important in influencing use of PAH therapy. In conclusion, pulmonary vascular disease treatment centers use PAH-approved therapy for patients with WHO group 2–5 PH, mostly relying on hemodynamics and assessment of RV function to identify candidates for therapy. Clinical trials designed to test the efficacy of PAH therapy in PH due to left heart and lung disease are needed, as clinical practice has extended beyond the evidence for these etiologies of PH.

Keywords: survey, chronic obstructive pulmonary disease, restrictive lung disease, heart failure.

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Pulmonary hypertension (PH) is defined as mean pulmonary arterial pressure (mPAP) of ≥25 mmHg and may result from several hemodynamic and pathologic mechanisms, which are grouped according to the Nice World Health Organization (WHO) classification scheme.[1] WHO group 1 pulmonary arterial hypertension (PAH) encompasses several disorders in which the precapillary pulmonary vasculature is primarily affected. PAH requires pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg and mPAP of ≥25 mmHg, and it has been extensively studied with several approved therapies available for clinical use. Guidelines have been established for the appropriate evaluation and evidence-based management of patients with PAH.[2-4]

Although much attention has been focused on PAH, it is a rare disease, and PH due to other causes (left heart disease, group 2; lung disease and/or hypoxemia, group 3; chronic thromboembolic PH, group 4; unclear or multifactorial etiologies, group 5) is far more common.[5] Thorough evaluation is imperative to accurate classification, and it is recommended that this occur in specialized PH centers. The case mix in PH centers is enriched for confirmed group 1 PAH, but patients deemed to have other causes of PH make up a large component. For instance, in three large PH centers, patients referred over 1 year were confirmed to have PAH in 41% of cases, with groups 2 and 3 combining for 33%.[6] In another center, PAH was the most common final single diagnosis, with 39 (32%) of 122 patients, but group 2 and 3 PH and mixed-etiology PH combined for 55 (45%) of 122 of the study population.[7] Frequent misclassification of patients prior to referral to a PH center highlights the complexity of appropriate diagnosis and the jeopardy of using PAH therapy prior to such a workup.[6]

Development of PH in patients with left heart disease,[8,9] chronic interstitial lung disease,[10] and chronic obstructive pulmonary disease (COPD)[11,12] is associated with worse outcome; however, the degree of PH that is observed in groups 2–5 is quite variable.[8,13,14] Some patients appear to have PH in excess of what would be expected for the degree of underlying lung disease or left atrial pressure elevation and thus may benefit from PAH-directed therapy, although this remains unproven.[15-17] Evaluation and surgical treatment of operable group 4 disease is uniformly recommended.[18,19] However, well-designed clinical studies are lacking for group 2, 3, and 5 PH; thus, there is no consensus treatment strategy other than management of the underlying disease process for these patients. Knowledge of the current treatment approach used in these patients by advanced treatment centers is limited. Use of PAH-approved ther-

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apy prior to specialty center referral is common and is often based on an incomplete workup or incorrect diagnosis.[6]

We hypothesized that the evaluation and treatment of non–group 1 PH varies by treatment center and that use of PAH-directed therapy is common. We conducted a survey of PH treatment centers in the United States to define practice patterns in the diagnosis and treatment of patients with non–group 1 PH, focusing on groups 2 and 3.

METHODS

Survey instrument and survey population

We developed an 82-question semiquantitative online survey instrument designed to collect information about practice patterns in the diagnosis and management of patients with PH. The survey was developed and survey data were collected and managed using REDCap (research electronic data capture), hosted at Vanderbilt University.[20] The survey was designed for pulmonary vascular disease specialists and asked how therapies for PAH were applied in patients with non–WHO group 1 PH. The survey contained questions not included in these results (see the supplement, available online). The survey instrument and study design were approved by Vanderbilt University's Institutional Review Board (protocol 110492) prior to survey distribution.

We identified eligible centers as those listed in a large observational US registry (the REVEAL registry)[21] and invited them to participate in the web-based survey via e-mail. Only one physician per treatment center was included.

Survey mechanics

A link to the survey was sent via e-mail to 50 participants on July 6, 2011. A reminder e-mail was sent to physicians who had not completed the survey 1 month later, and the survey was closed on October 31, 2011. Informed consent was waived, as no identifying information was collected. Physicians were required to answer a question that acknowledged their participation in this research study (see question 1 of the survey in the supplement). Respondents did not have to answer all questions to submit the survey.

Hemodynamic definitions

Transpulmonary gradient (TPG) was defined by mPAP minus PAWP or left ventricular end-diastolic pressure (LVEDP; TPG = mPAP − PAWP or LVEDP). Diastolic pulmonary gradient (DPG) was defined by pulmonary arterial diastolic pressure (dPAP) minus PAWP or LVEDP (DPG = dPAP − PAWP or LVEDP).

PAH-approved therapy

At the time of the survey, there were two phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil and tadalafil), two endothelin receptor antagonists (bosentan and ambrisentan), and three prostaglandins (epoprostenol [intravenous], treprostinil [intravenous, subcutaneous, or inhaled], and iloprost [inhaled]) approved by the Food and Drug Administration for use in PAH. These medications constitute PAH therapy for the purposes of this analysis.

Data analysis

Survey data were collected in REDCap and exported into SPSS (ver. 19; IBM, Armonk, NY). Surveys with greater than 75% of questions completed were included in the final analysis. Data are reported as the proportion of responses given and mean ± SD, unless otherwise noted. Questions with dichotomous answers (yes/no) are reported as a proportion of the number of completed responses. Comparison of proportions between groups is by Fisher's exact test. Some questions allowed multiple responses ("check all that apply"). Responses to these questions are given as the number of total responses for each question element.

RESULTS

The survey was sent to a physician at 50 centers, 30 of whom completed the survey (60% response rate) and were included in the analysis. The physicians who responded had 16.5 ± 5.8 years of experience treating PAH. Of the respondents, 23 (77%) of 30 had >50 patients receiving PAH therapy at their center, and all reported seeing >100 patients with PH in the past year.

Use of PAH therapy in non–group 1 PH was common, with 28 (93%) of 30 centers reporting use of PAH therapy for non–WHO group 1 PH patients. This practice was common in all WHO groups, with 77% reporting use in group 2, 80% in group 3, 93% in group 4, and 90% in group 5 (Fig. 1).

The decision to treat patients with WHO group 2 PH did not vary by treating physician subspecialty ($P = 0.37$; Fig. 2*A*). We examined how these experienced physicians defined the term "out of proportion" in group 2 in a question that allowed multiple responses. Most commonly an elevated TPG was used (19 of 30 respondents; Fig. 2*B*). The most frequent cutoff for TPG used to define out-of-proportion PH was >20 mmHg (range, >12 to >25 mmHg; median, >20 mmHg; Fig. 2*C*). The DPG was used less often (6 of 30 respondents), with thresholds from >5 to >20 mmHg used to define out-of-proportion PH (Fig. 2*D*). Of the 6 respondents who reported using the DPG, 5 also used the TPG. Regardless of whether

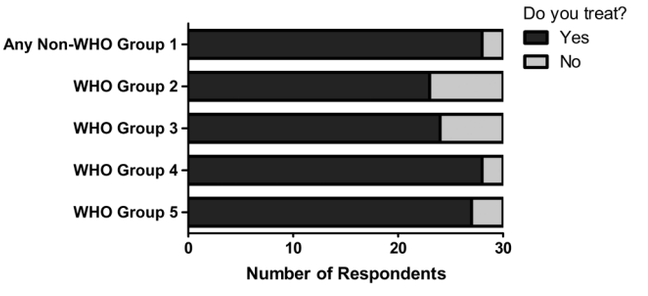

Figure 1. Use of pulmonary arterial hypertension (PAH)–directed therapy in non–World Health Organization (WHO) group 1 pulmonary hypertension by pulmonary vascular disease referral centers. Of 30 total survey respondents, the number using PAH-approved vasodilator therapy is given. Almost all centers (29 of 30) reported prescribing PAH-approved therapy outside WHO group 1.

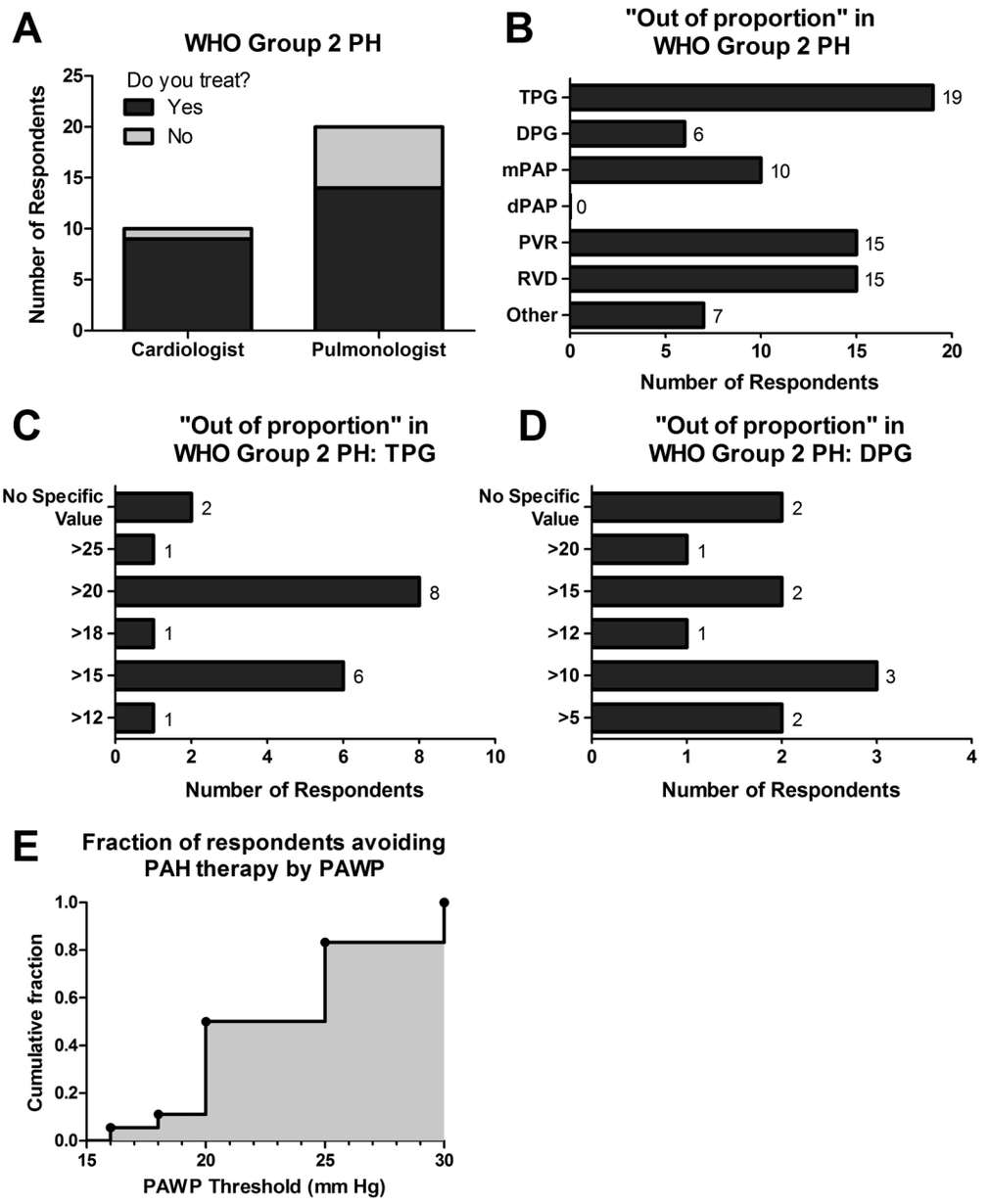

Figure 2. Use of pulmonary arterial hypertension (PAH)–directed therapy in World Health Organization (WHO) group 2 pulmonary hypertension (PH). *A*, Number of physicians who would utilize PAH-directed therapy for WHO group 2 patients by treating physician specialty. There is no difference by treating specialty in the proportion reporting that he or she would treat WHO group 2 PH (Fisher's exact test, $P = 0.37$). *B*, Criteria used to define out-of-proportion PH in WHO group 2. Respondents were allowed to report more than one criteria. *C–E*, Cutoffs for transpulmonary gradient (TPG; *C*) and diastolic pressure gradient (DPG; *D*). Eighteen respondents reported that they would not consider PAH-approved therapy above a certain pulmonary arterial wedge pressure (PAWP) threshold, the numerical value of which is shown as a cumulative fraction (*E*). mPAP: mean pulmonary arterial pressure; dPAP: pulmonary arterial diastolic pressure; PVR: pulmonary vascular resistance; RVD: right ventricle dysfunction.

centers used TPG or DPG to guide treatment of PH in group 2 patients, most respondents (18 of 30) also used an absolute PAWP above which they would not consider PAH-specific therapy (Fig. 2*E*). The majority (16 of 18) used a value of >20 mmHg (range, >16 to >30 mmHg). In addition to TPG or DPG, pulmonary vascular resistance (PVR) of >3 Wood units and right ventricular (RV) dysfunction on transthoracic echocardiogram were other commonly employed criteria used to guide use of PAH therapy (Fig. 2*B*). Almost a quarter (7 of 30 respondents) selected that they used "other hemodynamic criteria" for determining whether PH is out of proportion in patients with left

heart disease. Free responses were not collected to follow up this particular response. All respondents who reported using other hemodynamic criteria also reported using one or more hemodynamic criteria listed as alternate selections in the question stem (mPAP, $n = 5$; PVR, $n = 3$; DPG, $n = 2$; TPG, $n = 5$).

The decision to treat WHO group 3 PH was independent of treating physician subspecialty ($P = 0.37$; Fig. 3*A*), with 28 of 30 respondents reporting use of PAH therapy in group 3 PH. In this classification, most (18 of 28) used a mPAP cutoff of >35 or >40 mmHg to define out-of-proportion PH (range, >25 to >50 mmHg; Fig. 3*B*). Regarding patients with severe COPD (forced expiratory volume in 1 second [FEV_1] of <50% predicted), 5 respondents would not treat these patients, and 6 would treat regardless of FEV_1. Seven centers treated patients if FEV_1 was >1 or >1.5 L. However, the majority (17 of 28) reported that evidence of right heart failure or poor RV function on imaging studies was compelling in the decision to treat with PAH therapy. Other criteria offered by respondents included pretransplantation status ($n = 2$), relatively severe PH for degree of parenchymal lung disease as assessed by imaging or pulmonary function testing ($n = 7$), and as a last resort when other medical therapy is maximized ($n = 2$). Regarding patients with idiopathic pulmonary fibrosis (IPF) and more than mild restrictive disease, 6 respondents would not treat these patients with PAH therapy, and 5 would treat regardless of the severity of restrictive disease. Nine treated patients if they had total lung capacity of >60% or >70% predicted, and 8 treated only if high-resolution computed tomography (HRCT) showed only mild changes. Similar to patients with severe COPD, the majority (20 of 28) used evidence of right heart failure or poor RV function on imaging in their decision to treat with PAH therapy (Fig. 3*C*, 3*D*).

Almost all centers reported using PAH therapy in patients with nonoperable or residual PH due to chronic thromboembolic disease (28 of 30 respondents). Group 5 PH patients were also reported to be treated with PAH therapy (27 of 30 respondents; Fig. 1). Most centers reported encountering and treating patients with sarcoidosis and PH, with fewer reporting using PAH therapy for other forms of group 5 PH (Fig. 4).

We assessed practice pattern variation on the basis of several factors. Respondents practicing in the Northeast, Mid-Atlantic, and South ($n = 17$) were compared with those practicing in the Mid-

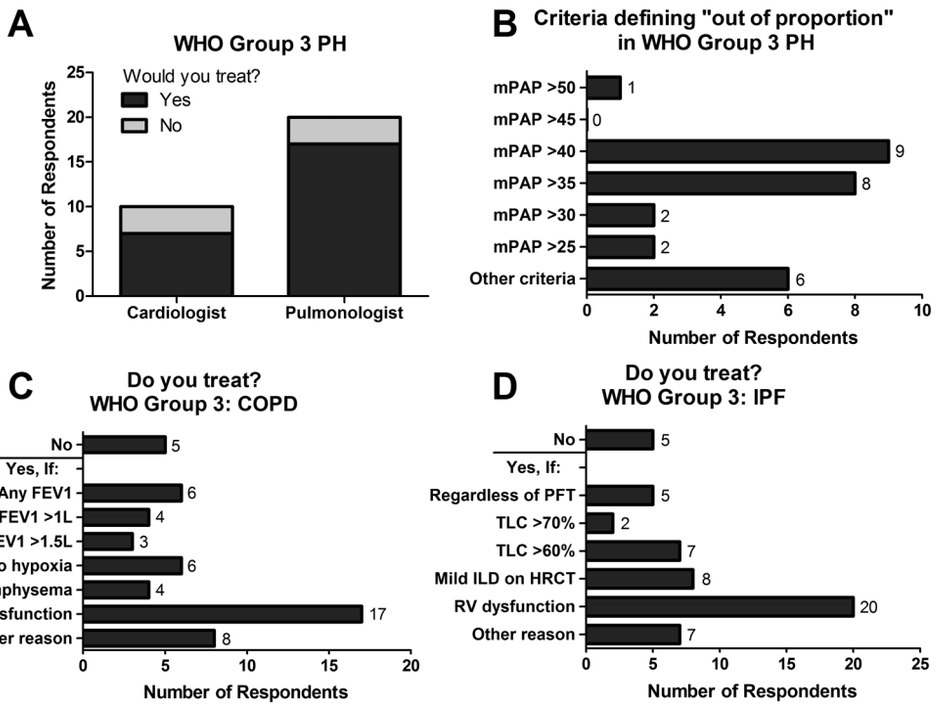

Figure 3. Use of pulmonary arterial hypertension (PAH)–directed therapy in World Health Organization (WHO) group 3 pulmonary hypertension (PH). *A*, Number of physicians who would utilize PAH-directed therapy for WHO group 3 patients by treating physician specialty. There is no difference by treating specialty in the proportion reporting that he or she would treat WHO group 3 PH (Fisher's exact test, $P = 0.37$). *B*, Criteria used to define out-of-proportion PH in WHO group 3. Mean pulmonary arterial pressure (mPAP) of >35 or >40 mmHg is reported most commonly as the hemodynamic definition of out of proportion in group 3 PH. *C*, *D*, Factors influencing the decision to treat with PAH-approved therapy in patients with chronic obstructive pulmonary disease (COPD; *C*) and idiopathic pulmonary fibrosis (IPF; *D*). Other criteria reported for COPD patients included pretransplantation status ($n = 2$), relatively severe PH for degree of parenchymal lung disease as assessed by imaging or pulmonary function testing ($n = 7$), and as a last resort when other medical therapy is maximized ($n = 2$). FEV_1: forced expiratory volume in 1 second; RV: right ventricle; PFT: pulmonary function testing; TLC: total lung capacity; ILD: interstitial lung disease; HRCT: high-resolution computed tomography imaging.

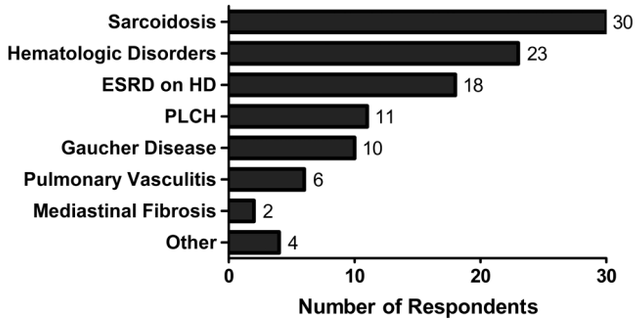

Figure 4. Subtypes of group 5 pulmonary hypertension (PH) encountered and treated at pulmonary vascular disease treatment centers. Treatment centers reported treating various causes of group 5 PH with pulmonary arterial hypertension–approved therapy. ESRD on HD: end-stage renal disease on hemodialysis; PLCH: pulmonary Langerhans cell histiocytosis.

west, Southwest, and West (n = 13). Respondents with PAH treatment experience of >15 years (n = 17) were compared with those with 15 years or less (n = 13). Cardiologist respondents (n = 10) were compared with pulmonologist respondents (n = 20). Respondents were also grouped by treatment center size as assessed by the number of patients receiving PAH therapy, using groups of 100–250 patients (n = 13) and >250 patients (n = 17). For each grouping, we assessed differences in frequency of treatment of groups 2–5 and criteria used for definition and treatment of group 2 and 3 PH. In all comparisons, no statistical differences were found. Raw P values were all >0.1 prior to correction for multiple comparisons.

DISCUSSION

Guidelines for the evaluation and treatment of PH focus on establishing the diagnosis of WHO group 1 PAH and selecting among approved therapies.[1,2] Treatment of PAH is best undertaken in PH specialty centers, but even in these centers other causes of PH predominate. PH specialty physicians rely on >2 decades of clinical trials involving patients with PAH. For patients with group 2–5 PH, there are few high-quality clinical studies of treatments. Moreover, lack of defined criteria for the expected degree of PH in left atrial hypertension or parenchymal lung disease is a major obstacle to identification of patients with PH who might benefit from treatment with PAH medications. The most recent published guidelines[15,16] acknowledge that each class of medication approved for PAH has a pharmacologic mechanism with sound theoretical benefit in patients with group 2 or 3 PH but cite a lack of quality evidence; thus, there is no evidence-based approach to pharmacologic management of PH in these patients. In the current study, we have demonstrated that most expert centers surveyed in the United States use PAH therapy in at least some patients with non–WHO group 1 PH. Practice patterns for the management of these patients did not appear to be influenced by regional location of the center, experience of the respondent, respondent subspecialty, or center size.

Outside group 1 PAH, group 2 PH has the most robust clinical evidence available for management. The prevalence of PH in patients with systolic or diastolic left ventricular dysfunction may be as high as 70%–85%.[22-24] Elevated PAWP is the key feature differentiating this group from PAH. In addition to elevated mPAP from the "passive" hydrostatic effect of increased left-sided filling pressures, patients with long-standing left-sided heart disease may develop a further "reactive" increase in mPAP manifest by TPG or DPG, PVR, and histologic evidence of vascular remodeling similar to PAH.[25-28] The term "out of proportion" as used in our survey has recently been replaced by "combined precapillary and postcapillary" PH when describing these patients.[16] There are still no generally accepted criteria for assessing the degree of precapillary PH in patients with left heart disease. Some have used TPG or PVR with cutoffs of >12–15 mmHg or 3 Wood units, respectively (Fig. 2*B*).[18,23,29-32] More recently it was reported that in group 2 patients the DPG is a more accurate indicator of pulmonary vascular disease and mortality compared with TPG, and use of DPG is now preferred.[16,33,34] Our survey identified that more than three times as many specialists surveyed use TPG rather than DPG, although our survey preceded studies demonstrating the superiority of DPG. TPG thresholds used to define out-of-proportion PH tended to be higher (>20–25 mmHg) than those reported in prior studies (>12–15 mmHg; Fig. 2*C*). Our survey also highlighted that evidence of RV dysfunction on echocardiogram is frequently used to help determine the significance of PH (Fig. 2*B*). Most of the physicians who responded to our survey noted that a PAWP of 20 mmHg or higher would prevent their use of PAH therapy (Fig. 2*E*), while some used a cutoff of 25 mmHg. Importantly, 24 of 30 centers reported using at least one hemodynamic criterion in describing PH in the presence of left heart disease, highlighting the central role that invasive hemodynamic measurements play in clinical decision making in these patients.

It is well established that treatment of underlying left ventricular dysfunction is the primary goal of therapy in patients with group 2 PH,[16,17] but PAH therapy has also been studied. Both epoprostenol[35] and endothelin receptor antagonists[36-40] have been associated with increased mortality and other adverse outcomes. Several small trials supported the use of PDE-5 inhibitors in group 2 PH.[41-44] After we obtained the results of our survey, larger subsequent studies in patients who had diastolic heart failure but were not specifically phenotyped for PH were published, and they do not show an overall benefit of PDE-5 inhibitors.[45] More targeted studies of patients with combined postcapillary and precapillary PH are warranted, as this group may have the most to gain from the use of PAH-approved medications. While almost all centers reported using PAH therapy for group 2 PH, our study did not address frequency of use or class of medications selected for subtypes of non–WHO group 1 PH. However, respondents reported that elevated PAWP was a strong deterrent to treatment with PAH therapy. In our survey, 18 of 30 respondents reported that there was an absolute PAWP above which they would not use PAH therapy, with values of 16 (n = 1), 18 (n = 1), 20 (n = 7), 25 (n = 6), and 30 (n = 3) mmHg reported. This is shown graphically

in Figure 2*E*. Therefore, for a patient with PAWP of 25 mmHg, 15 of 18 respondents would not use PAH therapy.

The presence of PH portends much higher morbidity and mortality in patients with parenchymal lung disease than in those with comparable lung disease without PH.[10,12,46] While chronic hypoxemia plays a role in pulmonary vascular disease development and should be corrected when found, other factors driving the development of PH in this group are not well understood, and there is poor correlation between the severity of PH and the degree of obstruction or restriction as measured by pulmonary function testing.[11,47-51] Data on the use of PAH-directed therapy in patients with obstructive or interstitial lung disease are limited. Endothelin receptor antagonists have no overall benefit in patients with IPF, and a recent study of bosentan in the subset of IPF patients with comorbid PH showed no benefit.[15,52] The use of sildenafil in patients with interstitial lung disease was evaluated in one randomized, double-blind, placebo-controlled study that recruited patients with IPF and enriched for PH.[53] The study did not meet its efficacy end point, but a prespecified subanalysis of patients found that those with RV systolic dysfunction on echocardiogram had a reduced decline in exercise tolerance when treated with sildenafil.[54] This was not seen in patients with RV hypertrophy on echocardiogram, and estimated RV systolic pressure was not a predictor of response to sildenafil. The number of available patients was small, limiting the conclusions that can be drawn from this study. However, there was no evidence of detriment with sildenafil use in patients with IPF with or without concomitant PH, suggesting safety if used.

Our survey demonstrates that PAH medications are used by most centers for some patients with group 3 PH. The decision to treat PH in the setting of severe obstructive lung disease (defined in our survey as FEV_1 of <50% predicted) or moderate to severe restriction in IPF was based on various factors according to respondents of our survey. For COPD, 9 of 28 respondents reported using at least one limitation to the severity of parenchymal lung disease as a criterion for treatment of PH (FEV_1 of >1 L, FEV_1 of >1.5 L, hypoxia, or minimal emphysema on imaging). Similarly, 12 of 28 respondents reported using similar features limiting severity in IPF (TLC of >70%, TLC of >60%, or only mild changes on HRCT). No single response designed to assess severity of underlying lung disease was predominantly reported for COPD or IPF. Assessment of RV performance was reported by the majority of respondents as a significant factor in PH treatment initiation.

In both group 2 and 3 PH patients, expert clinicians commonly reported that the finding of RV dysfunction was compelling in the decision to use PAH medications. About one-third of respondents (11 of 30 in COPD and 10 of 30 in IPF) selected only the response that evidence of RV dysfunction on imaging or evidence of right heart failure impacted their decision to use PAH therapy. This may reflect the opinion that RV dysfunction is more common in severe PH due to obliterative pulmonary vascular disease, as found in PAH but not in hypoxemia or left atrial hypertension. In addition, in patients with parenchymal lung disease, the presence of RV dysfunction may represent to clinicians a cardiac rather than a pulmonary limitation to exertion tolerance that warrants specific therapy.[55,56] Alternatively, it may suggest that PAH-approved medications may ameliorate RV function.[57] This study cannot reconcile these hypotheses, but future studies of pulmonary vascular therapy in group 2 and 3 PH may consider evaluation of RV metrics, such as cardiac magnetic resonance imaging–measured RV ejection fraction, to determine whether this clinical practice is founded.[58-60]

While our study asked which forms of group 5 PH had been treated, these forms of PH are rare, and the data serve only to demonstrate that centers diagnose PH on the basis of various underlying diseases and that the use of medications approved for PAH are occasionally required.

There are several important limitations to our study. We surveyed only US centers participating in the REVEAL registry. The results may not reflect practice patterns at other large centers in the United States, in other countries, or in smaller centers. In addition, due to the nature of the survey, there is potential for several types of bias. First, physicians were aware that they were part of a study, and this may have skewed their responses. Second, recall bias toward cases that may be considered outliers may make treatment of non–WHO group 1 patients appear more common than it seems. Third, some questions allowed multiple responses ("check all that apply"), a type of question that is subject to bias in that respondents may be more likely to select answers appearing earlier in the series. In addition to bias, our survey asked whether respondents treated certain subtypes of PH but did not ascertain how frequently PAH-approved medications were used for those subtypes. It cannot be implied by our data that PAH-specific therapy is used in most—or even in more than a minority—of group 2–5 PH patients, only that it is employed by most PAH specialist physicians. Although we allowed responses of "other criteria" for several survey prompts (see the supplement), we did not collect information on what other criteria were used to determine whether PH was out of proportion in the setting of IPF or left heart disease. We also did not collect data on preferred drug classes in group 2 and 3 PH. Despite these limitations, it is clear that PAH-directed medical therapy is used in the majority of these referral centers for the treatment of patients outside WHO group 1.

It should be noted that use of medications approved for use in PAH (PDE-5 inhibitors, soluble guanyl cyclase activators, endothelin receptor antagonists, and prostaglandins) for PH of other causes constitutes off-label use and is not endorsed by the authors. It is not known whether survey respondents were using these therapies off label, as part of compassionate use, or under an alternative diagnosis.

In conclusion, we found that nearly all of the pulmonary vascular disease centers responding to our survey use PAH therapy in some patients with non–group 1 PH. In group 2 PH, specialists reported relying on echocardiographic findings of RV dysfunction and invasively measured TPG and DPG to select patients for treatment; in group 3 PH, degree of mPAP elevation and RV dysfunction were reported as frequent triggers for use of PAH treatment. These data might suggest that subgroups of patients thought by experts to have a more severe pulmonary vascular disease phenotype are selected. As the availability of PAH therapy has outpaced clinical

evidence for its use in patients with PH secondary to left heart and lung disease, clinical trials with strict entry criteria for these patients are warranted to test its efficacy.

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