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Treatment Goals of Pulmonary Hypertension

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With significant therapeutic advances in the field of pulmonary arterial hypertension, the need to identify clinically relevant treatment goals that correlate with long-term outcome has emerged as 1 of the most critical tasks. Current goals include achieving modified New York Heart Association functional class I or II, 6-min walk distance >380 m, normalization of right ventricular size and function on echocardiograph, a decreasing or normalization of B-type natriuretic peptide (BNP), and hemodynamics with right atrial pressure <8 mm Hg and cardiac index >2.5 mg/kg/min^2. However, to more effectively prognosticate in the current era of complex treatments, it is becoming clear that the "bar" needs to be set higher, with more robust and clearer delineations aimed at parameters that correlate with long-term outcome; namely, exercise capacity and right heart function. Specifically, tests that accurately and noninvasively determine right ventricular function, such as cardiac magnetic resonance imaging and BNP/N-terminal pro–B-type natriuretic peptide, are emerging as promising indicators to serve as baseline predictors and treatment targets. Furthermore, studies focusing on outcomes have shown that no single test can reliably serve as a long-term prognostic marker and that composite treatment goals are more predictive of long-term outcome. It has been proposed that treatment goals be revised to include the following: modified New York Heart Association functional class I or II, 6-min walk distance ≥380 to 440 m, cardiopulmonary exercise test–measured peak oxygen consumption >15 ml/min/kg and ventilatory equivalent for carbon dioxide <45 l/min/l/min, BNP level toward "normal," echocardiograph and/or cardiac magnetic resonance imaging demonstrating normal/near-normal right ventricular size and function, and hemodynamics showing normalization of right ventricular function with right atrial pressure <8 mm Hg and cardiac index >2.5 to 3.0 l/min/m^2. (J Am Coll Cardiol 2013;62:D73–81)

As the field of pulmonary arterial hypertension (PAH) has matured, there has been a shift in our focus from short-term functional changes to improvements in long-term outcomes. Lessons from the past 2 decades provide the basis for defining important treatment goals in the hope of improving long-term survival. Indeed, the quest for clinically relevant

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide

CHD-PAH = pulmonary arterial hypertension related to congenital heart disease

CI = cardiac index

CMR = cardiac magnetic resonance

$EqCO_2$ = ventilatory equivalent for carbon dioxide

FC = functional class

HIV-PAH = pulmonary arterial hypertension related to human immunodeficiency virus infection

IPAH = idiopathic pulmonary arterial hypertension

NIH = National Institutes of Health

NT-proBNP = N-terminal pro–B-type natriuretic peptide

NYHA = New York Heart Association

PAH = pulmonary arterial hypertension

PAP = pulmonary artery pressure

PH = pulmonary hypertension

PoPH = pulmonary arterial hypertension related to portal hypertension

6MWD = 6-min walk distance

RAP = right atrial pressure

RV = right ventricular

RVEDVI = right ventricular end-diastolic volume index

SSc-PAH = pulmonary arterial hypertension related to scleroderma

SLE-PAH = pulmonary arterial hypertension related to systemic lupus erythematosus

SvO_2 = mixed venous oxygenation

prognostic predictors has been a key goal for clinicians involved in the care of patients with pulmonary hypertension (PH). The National Institutes of Health (NIH) registry was the first to show the impact of baseline hemodynamic parameters on outcome, demonstrating that factors which govern right heart function can also determine the prognosis in patients with PAH (1). Utilizing these parameters, a survival equation was derived that was the first attempt to use baseline hemodynamic factors to predict outcome. The formula included measurements of right atrial pressure (RAP), cardiac index (CI), and mean pulmonary artery pressure (PAP), each of which was shown to contribute independently toward the prediction of risk of death.

With the advent of multiple clinical trials and the success of demonstrating better outcome through improvements achieved in exercise parameters, the utility of noninvasive prognostic markers as surrogates for hemodynamic indices has been explored. In particular, the finding that the 6-min walk distance (6MWD) test correlated with hemodynamics established its role as a new baseline prognostic marker and as a treatment goal. Subsequently, a growing number of publications have identified other prognostic factors in patients with PAH, which include assessment of functional class (FC), parameters of exercise tolerance, hemodynamics, echocardiographic parameters, and biomarkers. However, investigators have recently begun to analyze the utility of these markers as prognostic indicators with the availability of long-term data, in particular the 6MWD. It is becoming clear that no single parameter can fulfill the role of a reliable prognostic indicator. Composite treatment goals have been shown to have more meaningful correlation with outcome, both as baseline predictors and as treatment targets (2).

More recently, 2 large registries have shed light on the prognosis of patients with PAH in the current therapeutic area. The French Registry characterized survival and important prognostic indicators in patients with idiopathic, familial, and anorexigen-induced PAH. The registry demonstrated that the survival of this cohort of PAH patients has improved compared with the predicted survival on the basis of the NIH registry, although it is still suboptimal, with 1-, 2-, and 3-year survival of 85.7%, 69.5%, and 54.9%, respectively, for incident cases (3). Important predictors of survival included sex, FC, exercise tolerance as measured by using the 6MWD, and hemodynamics, specifically RAP and cardiac output. Similarly, in the large, U.S.-based REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) registry, key predictors of outcome included etiology of PAH, FC, sex, exercise tolerance, and hemodynamics that reflect right ventricular (RV) function (4).

Modified New York Heart Association Functional Class

Baseline FC is an important correlate and predictor of survival. This assertion has been found in single-center cohorts from many countries, the first U.S. NIH registry of idiopathic pulmonary arterial hypertension (IPAH) patients, and, most recently, confirmed in the REVEAL registry, which enrolled 2,716 PAH patients of all subtypes (4). It should be recognized that some studies have found no association between FC and survival, and in other studies, FC was found to correlate with survival in univariate analyses, but this association was lost in multivariate analyses (1,5–8).

During the follow-up assessment of treated PAH patients, repeated assessment of FC provides important information regarding the severity of PAH and the response to therapy, as well as the prognosis for survival. After institution of effective PAH therapy, clinical improvement from initial FC III/IV to FC II is associated with improved prognosis.

There are limitations to the clinical use of modified New York Heart Association (NYHA) FC, including poor interobserver reliability and effects of demographic characteristics (e.g., age, sex, ethnicity) (9). Nevertheless, modified NYHA FC is a simple, reproducible, and clinically important assessment tool and prognostic measure in PAH patients, both at the time of diagnosis and at follow-up during PAH treatment.

6-Min Walk Distance Test

The 6MWD is a simple, noninvasive test that is inexpensive, reproducible, and well tolerated in patients with PAH. Initial studies have shown significant correlations between the baseline 6MWD and hemodynamic parameters, as well as survival (10). Furthermore, the 6MWD has been used as the primary endpoint for almost all pivotal clinical trials of PAH treatments, and it is

Table 1 Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in Patients With PAH

Functional class
I or II
Echocardiography/CMR
Normal/near-normal RV size and function
Hemodynamics
Normalization of RV function (RAP <8 mm Hg and CI >2.5 to 3.0 l/min/m^2)
6-min walk distance
>380 to 440 m; may not be aggressive enough in young individuals
Cardiopulmonary exercise testing
Peak VO_2 >15 ml/min/kg and $EqCO_2$ <45 l/min/l/min
B-type natriuretic peptide level
Normal

CI = cardiac index; CMR = cardiac magnetic resonance; $EqCO_2$ = ventilatory equivalent for carbon dioxide; PAH = pulmonary arterial hypertension; RAP = right atrial pressure; RV = right ventricular; VO_2 = peak oxygen consumption.

viewed by regulatory agencies as an acceptable surrogate endpoint because it has been shown to serve as a useful marker of treatment outcome during the pre-defined trial durations (11).

The 6MWD is widely used by clinicians as an integral component for assessing prognosis at baseline and treatment effect at follow-up. However, there are many limitations to 6MWD, including the learning effect, day-to-day variation, and impact of demographic characteristics and comorbidities. A meta-analysis recently reported on the usefulness of 6MWD in determining outcome in PAH. Savarese et al. (12) evaluated the results in 3,112 patients from 22 clinical trials, and they concluded that pharmacological treatments resulted in significant reduction of all-cause death, hospitalization for PAH, transplant, initiation of rescue therapy, and composite outcome, but the favorable effects on clinical events were not predicted by changes in 6MWD.

The other weakness of 6MWD relates to the difficulty in assessing what is a true meaningful difference in walk distance, beyond achieving statistical significance. An example of this is the "ceiling effect," which refers to the lack of sensitivity to detect changes with treatment in patients with early stage PAH and relatively high 6MWD at baseline. A similar limitation is shown by the inability to detect meaningful changes in 6MWD with the use of combination treatment as add-on therapy (13–15). Gabler et al. (16) investigated whether changes in 6MWD in the 12-week treatment period correlated with clinical events. The authors reported findings from the pooled analysis that the change in 6MWD accounted for only 22.1% of the treatment effect; the average difference in 6MWD across the trials was 22.4 m, and the significant threshold effect was calculated to be 41.8 m. Thus, the study concluded that the change in 6MWD does not explain a large proportion of the treatment effect and that, as a surrogate endpoint for clinical events, it can claim only a modest validity. Mathai et al. (17) performed a study to determine the minimal important difference from analyzing the 6MWD results of the tadalafil clinical trial. From their analysis using both distributional and anchor-based methods, the estimated minimal important difference in the 6MWD for PAH patients is approximately 33 meters. The results of the 2 studies suggest that the differences in the 6MWD seen in the recent combination trials may not indicate clinically meaningful changes.

There remain several relevant important questions in using 6MWD. These questions include which distance best correlates with exercise capacity and right heart function, and whether this should be measured as an absolute value of 6MWD that is associated with improved survival in PAH (e.g., >380 m, as suggested from Sitbon et al. [18], or >440 m, as shown by the REVEAL registry [4]). Also, should the distance be assessed based on percent predicted according to patient parameters (i.e., age, sex, height) (19)? Another question that remains to be answered is how improvement(s) in distance translate into meaningful change in quality of life or survival. There is evidence to suggest that incorporating other measurements obtained during the test, such as heart rate recovery time, may enhance the usefulness in interpreting 6MWD (20).

The current treatment goal for 6MWD is >380 m. However, we propose to increase this to 380 to 440 m; for some patients, using percent predicted may better reflect an appropriate goal of therapy.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing provides an integrative approach to assessing cardiac function, gas exchange, and muscular physiology. Peak oxygen consumption has been shown to be predictive of survival in PH, with 3 studies providing cutoff values of 10.4 ml/min/kg (21), 11.5 ml/min/kg (22), and 13.2 (23) ml/min/kg below which mortality is increased, as well as being established as a prognostic marker in other conditions, such as heart failure (24).

The development of a right-to-left shunt on exercise has been shown to be significantly and strongly associated with worse survival; in patients without a shunt, in FC III/IV, ventilatory equivalent for carbon dioxide ($EqCO_2$) at an anaerobic threshold <40 l/min/l/min was associated with excellent survival (25).

Peak oxygen consumption has been suggested as a goal of therapy, with <10 ml/min/kg indicating poor prognosis and a need to escalate treatment and with >15 ml/min/kg indicating better prognosis. In young patients, this may be a limited approach, and percent predicted peak oxygen consumption may provide a better indication in this group (26); this theory requires further evaluation. $EqCO_2$ is less age-dependent, and values <45 l/min/l/min and >55 l/min/l/min would seem appropriate goals/warning

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Table 2 Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in Patients With Pulmonary Arterial Hypertension

	Prognostic Implications at Baseline (Ref. #)	Prognostic Implications at Follow-Up (Ref. #)	Comments
Exercise tolerance			
NYHA FC	(2,4,9,10)	(2,9,10)	
6MWD	(2–4,10,61)		
Peak VO_2	(24)		
Hemodynamics			
RAP	(2,9,10,24,40,50,61,62)	(9)	In some studies, higher PAPm was associated with better survival (10,63)
PAPm	(1,4)		
PVR	(24)	(9)	
CO/CI	(2,3,9,24,40,50,61)	(2,9)	
SvO_2	(2,24,64)	(2,64)	
Echocardiographic variables			
TAPSE	(40)		
RV strain	(65)		
RA area	(40)		
Pericardial effusion	(4,40)		
Biomarkers			
BNP/NT-proBNP	(2,4,5,62)	(2,5,66)	
Troponin	(62)		
Uric acid	(24,67,68)		
CRP	(69)		
$PaCO_2$	(61)	(61)	
MRI parameters			
SV index	(8)		
RVEDVI	(8)		
LVEDV	(8)		
RVEF	(44)	(44)	
RVAC		(70)	

BNP = B-type natriuretic peptide; CI = cardiac index; CO = cardiac output; CRP = C-reactive protein; LVEDV = left ventricular end-diastolic volume; MRI = magnetic resonance imaging; NYHA FC = New York Heart Association functional class; NT-proBNP = N-terminal pro–B-type natriuretic peptide; 6MWD = 6-min walk distance; $PaCO_2$ = partial arterial pressure of carbon dioxide; PAPm = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RA = right atrial; RAP = right atrial pressure; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVFAC = right ventricular fractional area change; SV = stroke volume; SvO_2 = mixed venous oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; VO_2 = oxygen consumption.

signs for evaluation of the exercise response in relation to treatment and prognosis. The presence of a right-to-left shunt opening on exercise should be regarded as an ominous sign.

Biomarkers

Research on biomarkers has tremendously increased the understanding of different pathophysiological processes of PAH, including pulmonary vascular disease (e.g., endothelial dysfunction, in situ thrombosis, oxidative stress), RV dysfunction, and end-organ failure (e.g., renal failure). However, only a small minority of the investigated parameters have been shown to be clinically relevant. The relevance of B-type natriuretic peptide (BNP) has been demonstrated in outcome studies and as a secondary endpoint in some PAH treatment trials.

Current guidelines suggest a "normal" BNP level as a potential treatment goal. Therefore, it has to be taken into account that both BNP and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are age- and sex-dependent, leading to higher normal values (especially with age). Individual normal values are given by the manufacturer. An attempt to individualize BNP values has been suggested by dividing the measured BNP values by the age- and sex-specific normal values. This BNP ratio would be increased whenever >1 (27,28).

BNP levels have been shown to parallel hemodynamic and functional responses to PAH therapies in most clinical trials. Recent data support the hypothesis that the change in NT-proBNP levels carries prognostic information. Independently of baseline values, follow-up NT-proBNP levels <1,800 pg/ml indicated better survival in a cohort of 84 PAH patients in the current treatment era (2).

An open question remains the position of BNP in the rank order of various therapy goals. When the goal-oriented therapy approach was initially proposed for IPAH, natriuretic peptides (as many others) were not included as therapy goals (29). However, because RV failure is the main cause of death in IPAH, it seems reasonable to have an observer- and effort-independent, broadly available parameter of RV dysfunction as a main therapeutic goal. An attempt could be made when treatment of PAH is initiated to reach the "lowest possible" or "personal best" BNP and/or NT-proBNP. Comparable attempts have been made in congestive heart failure. In this context, a meta-analysis found that usage of cardiac peptides to guide pharmacological therapy significantly reduced mortality and heart failure–related hospitalization in patients with chronic heart failure (30). There is no evidence that such an approach would work in PAH, however, and it is questionable if a study size comparable to that used in congestive heart failure could be achieved in this rare condition. However, as mentioned, on the basis of the parallel development of hemodynamics and BNP/NT-proBNP levels (31) and the prognostic value of the change and follow-up values of BNP/NT-proBNP levels (2,5), as well as on the experience from other disease states, this approach has some justification.

Echocardiography

Echocardiography is widely used as an initial diagnostic test to confirm the presence of PH and/or RV abnormalities in patients suspected clinically to have PH. However, its use as a tool to provide prognostic information is based on a relatively small amount of data, specifically regarding echocardiographic assessments of RV function, which is the key determinant of outcome. The Tei index, although it has been shown to be predictive of outcome, is not as

reliable because it is affected by loading conditions and degree of tricuspid regurgitation (32). The other parameter of RV function that reportedly correlates with survival is measurement of tricuspid annular plane systolic excursion, recently shown to be predictive of survival in patients with PAH-associated scleroderma; these findings need further study for confirmation (33,34). Right atrial and ventricular enlargement and the eccentricity index have also been shown to correlate with outcome among patients with IPAH (6). The right atrial area at baseline seems to be 1 of the most robust echocardiographic determinants of outcome, but it is unclear whether this variable is also useful for guiding treatment decisions during follow-up (6,35). Furthermore, presence of a pericardial effusion to any extent has been shown to be a strong predictor of mortality (36).

The major limitations in using echocardiographic parameters for prognostic assessments, especially as a follow-up marker to guide treatment, relate to the lack of consistent method of reporting the RV size and function and the technical difficulties in obtaining reproducible right-sided chamber measurements. There is also variability stemming from differing skill levels of the technician performing the test. Furthermore, there is no consensus defining the severity of PH as assessed by echocardiographic estimates of RV systolic pressure that correlates with right heart catheterization–derived parameters.

We recommend maintaining the current recommendations regarding echocardiographic goals of treatment, specifically normal/near-normal RV size and function. The need to further define and confirm reliable quantitative measurements that can be measured, which reflect RV function (i.e., tricuspid annular plane systolic excursion, RA size) require further study.

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) is the gold standard for the investigation of right heart structure and volumes (37). Given that right heart function is accepted as the main determinant of survival in PAH, this modality would be expected to provide reliable information regarding prognosis; however, few studies are available that have assessed this variable's role in predicting survival (8,38,39). In response to chronic PH, the right ventricle hypertrophies and dilates with reducing function and stroke volume. The interventricular septum bows in to the left ventricle in diastole and systole. Commensurate with this action, right ventricular end-diastolic volume index (RVEDVI) <84 ml/m^2, left ventricular end-diastolic volume index >40 ml/m^2, and a stroke volume index >25 ml/m^2 are associated with better survival in patients with IPAH (8). RVEDVI was also shown to be an independent predictor of mortality by another group of researchers, but the number of events was too small to generate a threshold value for worse survival (39). However, according to the study by van Wolferen et al., there were no deaths in patients with RVEDVI <84 ml/m^2. Furthermore, RV mass index <59 g/m^2 showed a trend toward better survival in IPAH, and in a cohort of patients with suspected scleroderma PAH, the ratio of RV to left ventricular end-diastolic mass >0.7 predicted worse survival (40). Ejection fraction has also been assessed and a value $<35\%$ shown to be predictive of mortality (38). Importantly, even in patients with falling pulmonary vascular resistance, a decrease in ejection fraction was significantly associated with worse prognosis. Pulmonary artery stiffness increases afterload on the right ventricle and, when measured by using the relative pulmonary artery area change throughout the cardiac cycle, has also been associated with increased mortality (41,42).

Although CMR seems to hold promise for evaluation and follow-up of patients with PH, data are currently limited. It is not in widespread use for serial follow-up of patients with PH, and its main role currently resides in baseline diagnosis. It should not be assumed that myocardial indices are conserved across the different PH classifications, and further evaluation is required before it is considered part of routine clinical use.

Hemodynamic Parameters

Hemodynamic parameters are considered to be the gold standard indices of outcome in PAH. The NIH registry demonstrated that increased mean PAP, increased mean RAP, and decreased CI were associated with an increased mortality (1). Since then, hemodynamics (specifically, RA pressure, CI, and mixed-venous oxygen saturation [SvO_2] but not mean PAP) have been confirmed in numerous studies as robust independent prognostic factors (4,43,44).

However, there are several caveats and limitations in using hemodynamic parameters to assess prognosis. First, as PAH progresses and the right ventricle dilates and fails, the mean PAP declines, which is why survival estimates use mean RAP and CI in the equations. Obtaining hemodynamic measurements require an invasive procedure that is not widely available, and the associated risks, albeit small in experienced centers, limit the ability to obtain follow-up or serial hemodynamic parameters on treatment. Hemodynamic measurements also illustrate the physiological state at a single time point at rest, in a supine position, which does not account for changes associated with activity. Although exercise-related hemodynamic effects are currently undergoing active research, there is no consensus regarding the method of performing exercise right heart catheterization or interpretation of the hemodynamic effects of exercise in PAH. Furthermore, the effects of systemic processes such as anxiety, hypertension, and sedation can markedly affect the parameters.

The current recommendation advises normalization of RV function for treatment goal, which is defined as RAP <8 mm Hg and CI >2.5 l/min/m^2. There is a proposal to increase the CI to >3.0 l/min/m^2, and the

discussions include the following points. First, there is no strong evidence for the current recommendation of CI >2.5 l/min/m^2 as a hemodynamic goal; it was derived mainly from studies evaluating patients with left heart failure. The definition of normal CI for healthy subjects varies widely in the literature, from 2.4 to 4.2 l/min/m^2, depending on the sources cited (44–47). There are no direct data from PAH patients to guide this recommendation. The opinions in favor of this measure are based on the fact that we need to establish more ambitious goals in PAH, with clear mandates to "raise the bar" with the common goal of improving outcome. Clearly, there are patients who have improved symptoms and exercise capacity with treatments that result from an increase in cardiac outputs. Thus, given the lack of evidence supporting 2.5 l/min/m^2 as the best goal, the question is whether to increase the recommended CI to 3.0 l/min/m^2. The concerns raised from the panel members regarding this change include that there is no evidence that just raising the CI limit translates into better outcome, and that some physicians may feel compelled to augment treatments and/or increase doses just to reach the 3.0 l/min/m^2 target, with more risk to patients. Furthermore, from a physiological standpoint, there is a potential to increase the workload of the right ventricle in inappropriate settings and the possibility of incurring damaging effects to the RV myocardium from detrimental effects of increased catecholamine release.

Given the lack of data regarding the optimal CI in the PAH population, there seems to be support to recommend that the target CI as a hemodynamic treatment goal be adjusted for the individual patient to >2.5 to 3.0 l/min/m^2. The CI is just 1 measure in the evaluation process, however, and it must be interpreted in the context of all other hemodynamic variables as well as clinical parameters.

Current Status of Prognostic Predictors in PAH

Recently, Nickel et al. (2) reported a systemic evaluation of prognostic markers at baseline and follow-up in a series of patients with IPAH. They identified 4 variables that were independently associated with survival at baseline as well as at follow-up: NYHA FC, NT-proBNP, CI, and SvO_2. NYHA FC I and II, NT-proBNP <1,800 ng/l, CI ≥2.5l/min/m^2, and SvO_2 ≥65% during follow-up were associated with a better survival. Of note, the follow-up assessments were found to be better outcome predictors than the baseline evaluations; in fact, the outcome was almost entirely determined by the variables obtained at follow-up rather than by using the baseline measurements.

Thus, both baseline and follow-up assessments are important when assessing the risk of patients with PAH. The baseline evaluation will determine disease severity at presentation, providing important information for choosing the initial therapy. Follow-up assessments are crucial for assessing the response to treatment, and they seem to provide a more reliable prognostic estimation than the baseline evaluation. Table 1 summaries the variables used in clinical practice to determine response to therapy and progress in patients with PAH.

Notably, use of 1 parameter is not sufficient to reflect the status of RV function; multiple variables must be interpreted in the context of each individual patient. A proposal to rank the parameters has been suggested, with prioritization of markers (i.e., objective parameters such as hemodynamics ranked first/highest or categorize variables into major versus minor criteria); this proposal warrants further consideration, but current data are insufficient to validate such a ranking system. Table 2 reviews the clinical observations on specific variables.

Risk scores and prognostic equations have served as useful predictors of survival on a population basis, but currently, none has been adequately studied or validated as a goal of therapy. How an individual's change in score reflects that individual's subsequent prognosis has not yet been adequately studied. In addition, some risk scores (e.g., REVEAL) include a number of variables that cannot change, even when the response to therapy is favorable (i.e., age, sex, etiology). We advocate for a multiparameter approach to treatment goals and hope that data from large registries may aide in developing a scoring system that can be used to assess response to therapy, and to establish goals of therapy using the modifiable parameters as variables.

Are Treatment Goals Different in Different PAH Subgroups?

PAH is a heterogeneous group of diseases with numerous subgroups defined according to associated or causative conditions. Common examples include PAH related to connective tissue disease, including PAH related to scleroderma (SSc-PAH) and systemic lupus erythematosus (SLE-PAH); PAH related to congenital heart disease (CHD-PAH); PAH related to human immunodeficiency virus infection (HIV-PAH); and PAH related to portal hypertension (PoPH). It is relevant to ask whether treatment goals should differ for these various subgroups. The paucity of published data addressing this question makes it impossible to provide clear answers in most cases.

Although the prognosis for patients with SSc-PAH remains poor, it has improved, as shown in recent reports (48–50). The current treatment goals for patients with SSc-PAH are not well defined and are generally similar to those used in other types of PAH. However, functional goals (e.g., FC, 6MWD) and biomarkers (e.g., BNP) may be unreliable in SSc-PAH because of the systemic nature of scleroderma (51,52). Given the poor prognosis in SSc-PAH, it is important to explore whether more aggressive treatment goals will result in improved outcomes in the future. Outcomes for patients with SLE-PAH seem to be better than those for SSc-PAH patients (48). Intensive immunosuppression may enhance the benefit of PAH-specific

therapies in SLE-PAH and improve outcomes (53). Thus, optimal treatment of inflammation can be considered a unique treatment goal in SLE-PAH.

Patients with CHD-PAH have a better prognosis than other subgroups (54), and bosentan was shown to be safe and effective in a study performed specifically in this population (55). Patients with HIV-PAH have a worse prognosis than other subgroups, although outcomes have improved (56). There are no data currently to suggest that treatment goals in CHD-PAH or HIV-PAH should differ from those in other PAH subgroups.

Patients with PoPH have a worse prognosis than other subgroups of PAH (57), although more favorable outcomes have been reported (58), likely related to less severe liver disease in this cohort. Treatment goals in selected patients with PoPH may focus more on invasive hemodynamics because the achievement of specific PAP and pulmonary vascular resistance goals can allow for successful liver transplantation (59).

There are few data to suggest that treatment goals should differ for different PAH subgroups. Exceptions include the limited utility of functional and biomarker goals in SSc-PAH and the primacy of hemodynamic goals in patients with PoPH being considered for liver transplantation.

Conclusions

Although the primarily observational studies discussed here do not allow for definitive conclusions, reasonable goals of therapy include the following: 1) modified NYHA FC I or II; 2) echocardiography/CMR of normal/near-normal RV size and function; 3) hemodynamic parameters showing normalization of RV function (RAP <8 mm Hg and CI >2.5 to 3.0 l/min/m^2); 4) 6MWD of >380 to 440 m (which may not be aggressive enough); 5) cardiopulmonary exercise testing, including peak oxygen consumption >15 ml/min/kg and $EqCO_2$ <45 l/min/l/min; and 6) normal BNP levels.

Patients who achieve these goals, no matter which specific therapy or approach is used, seem to have a better prognosis than those who do not. A more aggressive approach to goal-oriented therapy may help us shift the survival curves farther to the right. Despite the many observations that support attainment of such goals, many patients followed up today fall far short of these targets. For example, approximately 60% of FC III patients and 50% of FC IV patients in the REVEAL registry are not being treated with a prostacyclin, despite their not being at the goal FC level of I or II (60). Both patient and physician reluctance to proceed to the most aggressive therapy are contributing factors.

Survival in PAH has improved over recent years, but outcomes are still suboptimal. Reasonable therapeutic goals that primarily reflect RV function have been established. Achieving such goals with optimal application of our current therapies and further development of novel therapies may improve long-term outcomes in patients with this previously fatal disease.

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