Recent Advances in Pulmonary Hypertension

Using Clinical Trial End Points to Risk Stratify Patients With Pulmonary Arterial Hypertension

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Regardless of the study drug being tested, as part of a clinical trial, the subject population commonly includes a range of patients with the targeted disorder. The overriding purpose of a clinical trial is to estimate the average effect of the intervention on the study population. Registration trials require the development of prospective protocols and analysis plans that describe the inclusion and exclusion criteria for patients, the treatment and its delivery, outcome assessment, and the statistical analyses. A key feature is the prospective identification of both primary and secondary outcome measures. Clinicians want to know the likely benefits and risks for an individual patient. However, applying clinical trial outcomes to study population subgroups or individual patients can be challenging.

The treatment of patients with pulmonary arterial hypertension (PAH) has changed considerably since the first PAH-specific agent, epoprostenol, was approved in 1995. Therapeutic options now target 3 pathways that include the prostacyclin pathway, the endothelin pathway, and the nitric oxide pathway, either as monotherapy or in combination.

World Health Organization Functional Class

The World Health Organization (WHO) functional classification is a measure of disease severity based on a patient’s description of their level of function and symptoms of disease in relation to their everyday activity. WHO functional class (FC) is a strong predictor of survival, both before and during treatment, but surprisingly has little correlation with degree of hemodynamic abnormality. In untreated patients with idiopathic PAH or heritable PAH, historical data showed a median survival of 6 months for WHO FC IV, 2.5 years for WHO FC III, and 6 years for WHO FC I and II. However, WHO FC is a subjective measure that is also affected by comorbidities such as connective tissue disease, obesity, and age, to name a few. Although lacking on its own, the WHO functional assessment remains an important part of ongoing assessment of patients with PAH. For example, improvement in FC during treatment is associated with an improved outcome.

Six-Minute Walk Distance

The 6-minute walk distance (6MWD) has been the mainstay of evaluation of patients with PAH. The test provides an indirect estimate of aerobic capacity and correlates with cardiac output (CO). In the original study of epoprostenol, the 6MWD had an independent correlation with survival. Since that time, treatment-associated improvements in the 6MWD in PAH patients have been used as primary end points in efficacy studies of the majority of currently Food and Drug Administration–approved therapies for PAH. The combination of the ease and consistency of testing has resulted in its widespread use in the clinical evaluation of patients. The baseline 6MWD is a good indicator of prognosis and has been shown to decrease in proportion to the severity of WHO FC, and to correlate with CO, total pulmonary resistance, and changes in pulmonary vascular resistance (PVR).

Absolute distance walked after the commencement of therapy has been shown to be predictive of outcome. Current treatment guidelines recommend that serial measurements be a part of longitudinal clinical care, and that a 6MWD >500 m be a goal of therapy. Lower-risk patients, those who walk at least 400 m, may be considered for oral monotherapy. Patients who walk <300 m fall into a higher-risk group and should be considered for more complex treatments such as prostacyclins or combination therapy. It is important to understand that these recommendations are based on primarily experiential evidence, and the 6MWD has not been studied under these conditions. In addition, the utility of the 6MWD in PAH patients who walk >450 m may be more limited.

The 6MWD as the standard in PAH clinical practice has become much more controversial. The distance walked during the baseline 6MWD correlates with the severity of WHO FC, baseline CO, total PVR, and mean right atrial pressure in patients with idiopathic PAH. Further, in those patients who walked <332 m, only 20% of patients lived 3 years, whereas, among patients who walked >332 m, survival was better than 92%. Exercise limitation, demonstrated by reduced 6MWD, has repeatedly been shown to be an excellent predictor of death in PAH (Figure 1).

However, as treatment for PAH has become more complex and the majority of patients entering clinical trials are on background vasodilator therapies, the utility of the 6MWD as a primary outcome measure has waned. Recent data demonstrate that the change in 6MWD during short-term clinical trials does not correlate with prognosis. Moreover, more recent data from

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.114.012328

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the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) demonstrated that a 15% decrease in 6MWD at any point in time significantly predicted poorer survival (no matter what the level of improvement previous to the decreased walk); in contrast, improvement in 6MWD did not have a positive effect on survival. In addition, there was no 6MWD distance threshold that provided any particular prognostic value. In sum, although improvement in 6MWD was not associated with survival, as we would expect, worsening of 6MWD (15% decrease) was strongly and significantly associated with a poorer prognosis.\textsuperscript{19} Equally important are the obvious shortcomings of the 6MWD. It is affected by mood and motivation, age, obesity, musculoskeletal limitations, and training.

An example of the divergence between 6MWD and a maximal cardiopulmonary exercise test (CPET) can be found in one of our patients, a 22-year-old man with idiopathic PAH being treated with subcutaneous treprostinil and tadalafil. He presented to clinic as a WHO FC I and walked 528 m with a Borg dyspnea index of 3. On the same day, a maximal CPET demonstrated a VO\textsubscript{2}max of 28% of predicted, and a Ve/VCO\textsubscript{2} slope of 49. Thus, assessment based on FC and 6MWD would suggest that his clinical status was good; in contrast, the CPET more clearly illustrates the status of his disease. Although the 6MWD has been the mainstay of previous clinical trials and clinical assessment, its continued utility and appropriate usage are no longer clear. It clearly cannot be used as the primary end point in clinical trials and, short of the above-mentioned highly predictive 15% decrease, should not be used as a single measure of patient status in clinical practice.

**Cardiopulmonary Exercise Testing**

Cardiopulmonary exercise testing offers a noninvasive means for assessing the cardiopulmonary limitations to exercise in patients with pulmonary hypertension. Peak VO\textsubscript{2} and peak systolic blood pressure obtained during a standardized exercise test are independent and highly accurate predictors of survival in patients with idiopathic PAH,\textsuperscript{20} which makes peak VO\textsubscript{2} an attractive end point in clinical practice and in clinical trials. CPET is safe even in established PAH,\textsuperscript{21,22} and is useful in the management and risk stratification of PAH.\textsuperscript{23} However, patients with severe PAH who present with exertional syncope, cardiac arrhythmias, or acute right ventricular failure should not undergo maximal exercise testing. Peak exercise CPET can reliably demonstrate changes in peak oxygen consumption (VO\textsubscript{2}max), rate of increase in VO\textsubscript{2}, anaerobic threshold, blood pressure, heart rate, and ventilatory efficiency (Ve/VCO\textsubscript{2} at the anaerobic threshold) in a reproducible and safe manner without complications or deaths in severely decompensated patients.\textsuperscript{22,24} In fact, CPET in PAH patients is highly reproducible, with little test-to-test variability.\textsuperscript{24} Peak exercise systolic blood pressure, and peak VO\textsubscript{2} during CPET predicts survival, which significantly improved in patients able to achieve a peak VO\textsubscript{2} >10.4 mL·kg\textsuperscript{-1}·min\textsuperscript{-1}.\textsuperscript{25} In addition to providing prognostic data, CPET could be used in goal-directed therapy.
Exercise capacity measured by CPET has been used as an end point in several clinical trials; however, in reality, its use has been problematic. In some cases, this may have been because of technical issues related to the conduct of CPET, standardization of the testing, or it may just not be appropriate for large clinical trials (we do not think so). In a study to assess the safety and efficacy of the oral prostacyclin analogue beraprost-sodium during a double-blind, placebo-controlled trial, the primary end point was disease progression based on death, transplantation, epoprostenol rescue, or >25% decrease in peak Vo2. Secondary end points included exercise capacity assessed by 6MWD and peak Vo2, Borg dyspnea score, hemodynamics, symptoms of PAH, and quality of life. Although the treatment effect did not reach statistical significance at any time point, there was no evidence of any treatment interactions when the effects of covariates were assessed in the peak Vo2 analyses.

In the Sitaxsentan To Relieve Impaired Exercise (STRIDE-1) multicenter trial, however, there was an unexpected discrepancy between the 6MWD and peak Vo2. Interestingly, during the study, there was improvement in the correlations between the 6MWD and CPET data, suggesting that this was attributable to increased experience and improved technical skills at study sites that had less experience with CPET.

In pediatrics there are additional concerns, demonstrated in the Sildenafil in Treatment-Naïve Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study. This was a 16-week, randomized, double-blind study of treatment-naïve children to evaluate the effects of oral sildenafil in pediatric PAH. The primary comparison was of treatment-naïve children to evaluate the effects of oral sildenafil on cardiac output and improved technical skills at study sites that had less experience with CPET.

The limitations of CPET in patients with PAH are several. Maximal exercise testing is needed to derive the most useful information on the physiological limitations to exercise. Although it is safe, in general, it can be difficult for some severely limited patients. CPET is more labor intensive than the 6MWD and requires specific equipment and experienced and trained personnel to operate and interpret the findings. Thus, the routine clinical use of CPET to assess exercise capacity in patients with PAH may not always be feasible, although we believe those cases are very rare.

In summary, we believe that CPET can be an integral part of future clinical trials of PAH patients, if the testing (protocol) is standardized, CPET for each participating center is validated before subject enrollment and again during the study, and CPET cores are used for uniform interpretation of data such as in the National Heart, Lung, and Blood Institute Heart Failure Network.

Assessment of Right Ventricular Structure and Function

Functional status and mortality in patients with PAH is related primarily to right ventricular (RV) structure and function. Right ventricular remodeling results from functional and structural adaptations in response to chronic pressure and volume overload. The ability of the RV to sustain stroke volume and CO in the presence of increased load determines the severity of clinical symptoms and is one of the most important determinants of clinical presentation and survival in patients with all forms of pulmonary hypertension. In fact, clinical symptoms correlate poorly with resting mean pulmonary artery pressure. It is increasingly recognized that early pulmonary vascular (PV) remodeling is met with an initial adaptive RV hypertrophy, but, with progressive PV and RV remodeling, regional myocardial ischemia develops that leads to eventual RV failure.

Chronic RV pressure overload leads to RV diastolic dysfunction in its early stages, whereas RV remodeling includes RV hypertrophy, changes in systolic function, and dilatation. Mechanisms that drive the shift from compensatory RV hypertrophy to RV failure constitute novel targets for intervention, because these changes occur when the hypertrophied RV can maintain contractile performance. RV hypertrophy is the most apparent adaptation to increased afterload, and results in increased oxygen requirement, lower oxygen extraction reserve, and higher dependence on coronary flow. Because RV perfusion during systole depends on maintenance of the normal pressure gradient between aortic pressure and RV systolic pressure, a rising RV systolic pressure attributable to an elevated PVR further compromises RV coronary perfusion pressure. In fact, patients with pulmonary hypertension and RV failure often present with evidence of myocardial ischemia including anginal chest pain. Because the state of the RV predicts mortality, there is a trend to direct therapy at RV function rather than functional status alone. Thus, direct assessment of RV function by using noninvasive techniques may provide a more informative way of determining the response to therapy and monitoring disease progression in PAH.

Echocardiography

Echocardiography provides a noninvasive assessment of right heart function that is a readily accessible, and routine method for assessment of PAH. While estimated pulmonary artery systolic pressure is neither a good surrogate of PA pressure measured by right heart catheterization (RHC) nor predictive of survival, numerous studies have demonstrated that some echocardiographic parameters can be used as surrogate markers and are predictive of survival. One of the most frequently reported prognostic factors is the presence of pericardial effusion. The tricuspid annular plane systolic excursion is a simple measure of the longitudinal movement of the lateral tricuspid annulus toward the RV apex. The tricuspid annular plane systolic excursion has been shown to correlate with RV ejection fraction, and a tricuspid annular plane systolic excursion of <1.8 cm is associated with worsening RV systolic dysfunction, and is associated with decreased survival. The Tei index, which is calculated from the sum of the isovolumic contraction and isovolumic relaxation times divided...
by ejection time, represents an estimate of global RV performance. The Tei index increases with worsening RV dysfunction, and has been shown to be a prognostic indicator in PAH. Echocardiography has other significant limitations in the assessment of PAH patients, including acoustic access being difficult in many patients because of body habitus or underlying pulmonary disease. In addition, echocardiography provides no direct measure of intracardiac pressures and is limited as far as quantitation of the structure and function of the RV.

Cardiac MRI
Increasingly, cardiac MRI (CMR) is being used as a research assessment in clinical trials. The use of CMR in clinical trials is increasingly attractive because CMR is considered the gold standard for assessment of RV volume, mass, and function. CMR is increasingly important in the diagnosis and follow-up of patients with congenital heart disease. Both 2-dimensional and 3-dimensional echocardiography have greater interobserver measurement variability over time, and require bigger sample size than with CMR. Because of the higher sensitivity of CMR and smaller sample sizes needed to detect changes in the RV, CMR is comparatively less expensive than transthoracic echocardiography in total cost. However, the number of clinical trials using CMR as an outcome measure is limited. In the Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study RV mass decreased significantly from baseline after 16 weeks of sildenafil treatment.

Noninvasive CMR provides a comprehensive picture of RV structure and function with excellent resolution. In a recent pan-European study investigating the relationship between RV structure/function and survival, a large RV end-diastolic volume, low left ventricular end-diastolic volume, and a low stroke volume at baseline were associated with a poor prognosis. Progressive dilatation of the RV, a further decrease of left ventricular diastolic volume, and a further decrease in stroke volume at follow-up predicted treatment failure and a poor long-term outcome. Assessment of mean pulmonary arterial pressure and PVR with RHC is often used in the assessment of response to therapy. In adults and children, septal curvature measured by using CMR strongly correlates with mean pulmonary arterial pressure and indexed PVR. CMR can also be used to follow reverse remodeling (Figure 2).

In patients with nonoperative chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty, there was significant improvement in RV dilatation (RV end-diastolic volume index and RV end-systolic volume index), RV systolic function (RV ejection fraction), RV hypertrophy, and interventricular septal bowing assessed by CMR. There were strong correlations between observed changes in RV remodeling, measured with CMR, and changes in invasive hemodynamic parameters. CMR has been used to demonstrate RV reverse remodeling after hemodynamically successful pulmonary thromboendarterectomy in patients who have chronic thromboembolic pulmonary hypertension in both early and later phases of recovery.

Although CMR is considered the gold standard for measurement of cardiac function, and it offers very high spatial resolution, clinicians have been slow to use CMR for a number of reasons. Some patients cannot tolerate the claustrophobia associated with the gathering of the data; some patients are too obese to access the machine; and, in addition, CMR is contraindicated in patients who have implanted defibrillators or pacemakers and is logistically difficult in patients receiving systemic prostanoids because of the effect of the magnet on the pump. In comparison with other noninvasive approaches, CMR is time consuming. CMR techniques also depend on image acquisition during repeated breath-hold maneuvers of 5 to 10 seconds. If patients are unable to perform this maneuver, an important consideration in PAH patients, image quality can be significantly degraded. Last, the quality of the images is also very dependent on the machine used, the method of collection of the images, and the expertise of the person reading the images. In sum, there is no standardization of this potentially useful imaging tool in patients with PAH.

Right Heart Catheterization
RHC remains the gold standard for the diagnosis of PAH. Specific measurements obtained during RHC are predictive of survival. In patients studied before treatment in the National Institutes of Health primary pulmonary hypertension registry, the mean pulmonary artery, mean right atrial pressures, and cardiac index were all found to be predictive of survival. The mean pulmonary artery and right atrial pressures at baseline were also found to be prognostic factors for patients treated with epoprostenol. With treatment, a reduction in total pulmonary resistance of at least 30% and improvements in cardiac index and mean pulmonary artery pressure are associated with improved survival following a period of epoprostenol treatment. Data from the French network on pulmonary hypertension, which evaluated patients who are on current therapies, showed that baseline right atrial pressure and cardiac index were significantly associated with survival in the modern treatment era. RHC has a number of obvious limitations. Although generally a low-risk procedure, especially in centers with expertise, it is invasive, can be uncomfortable, and is relatively expensive.

Biomarkers
A biomarker is a characteristic that is objectively measured and evaluated as an indicator of a biological processes, pathogenic processes, or pharmacological response to a therapeutic intervention. Changes in a biomarker as a result of therapy, to be useful, should reflect changes in clinically meaningful end points. The search for reliable biomarkers has relied on pathophysiology and has distinguished between potential biomarkers of inflammation, endothelial dysfunction, and RV pressure and volume overload. The most widely studied biomarker in PAH is brain (B-type) natriuretic peptide (BNP), which is secreted by ventricular myocytes. Pre-proBNP is secreted and cleaved into the biologically active peptide and the more stable N-terminal fragment (NT-proBNP). The production of BNP/NT-proBNP is increased with cardiac myocyte stretch. Serum levels of BNP/NT-proBNP have been correlated with worsening RV dysfunction in PAH, mean pulmonary artery pressure, right atrial pressure, total pulmonary vascular resistance, and...
RV hypertrophy. High plasma levels with additional serial increases in plasma BNP/NT-proBNP have a strong independent association with mortality. However, for BNP to be useful clinically there must be reproducible absolute levels that correlate with disease state and, more importantly, be pertinent to an individual patient, rather than to a population. Currently, none of these requirements have been fulfilled; thus, BNP/NT-proBNP cannot be used alone to accurately assess the current state of disease with or without treatment.

Composite Clinical End Points
The ability to recognize factors that affect disease progression and survival in patients with PAH is of critical interest to clinicians because it drives clinical decision making. Improving the ability to predict a patient’s disease progression or looming mortality would aid in treatment decisions, especially the necessity to escalate therapy. Based on data from both REVEAL and the French Registry, a number of prognostic variables have been identified, including the origin of PAH, age, pulmonary vascular resistance, right atrial pressure, renal insufficiency, resting systolic blood pressure and heart rate, 6MWD, BNP, presence of a pericardial effusion, and diffusing capacity of the lung for carbon monoxide.

Because, no single end point has proven ideal in measuring patient response to therapy in PAH, recent clinical trials have made use of a composite end point of clinical worsening that includes all-cause mortality, nonelective hospital stay for PAH, and indicators of disease progression. In contrast, the recent AMBrsentan and Tadalafil in patients with pulmonary arterial hypertension (AMBITION) trial used insufficient improvement as part of a composite end point (death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response). Composite end points have specific appeal in PAH because the statistical power increases with event rate, by combining a number of end points and allowing for increased detection of therapeutic benefit without the need to increase sample size. The most common approach is the time to clinical worsening (TTCW), because it is thought to be a comprehensive evaluation of disease progression. The most commonly used components of TTCW include (1) all-cause mortality, (2) need for transplant or atrial septostomy, (3) PAH-related hospitalization, and (4) additional measures of clinical worsening that usually include WHO FC progression, decline in 6MWD by at least 15%, signs of worsening right heart failure and need for additional PAH-targeted therapies. The impact of a treatment on disease progression associated with PAH can be measured by TTCW. This end point is viewed as clinically relevant by clinicians and regulatory agencies and has been used in several clinical trials as a secondary or, more recently, a primary end point. Newly completed clinical trials (Table) suggest that using a TTCW end point may be more meaningful especially when trials involve patients on background therapy. The benefit of such a TTCW composite end point is that clinicians, patients, and payers are likely to agree that the above-listed criteria better reflect real-world events that are important to prevent in their patients. The problem with using it in clinical practice is that it represents a decline in the patients’ condition, exactly what we are trying to avoid.

Figure 2. Improvement in RV structure and function documented by CMR following balloon pulmonary angioplasty (BPA). Representative cine images of CMR obtained from short-axis slices in a patient with inoperable CTEPH at end-diastole (A and D), end systole (B and E), and early diastole of the ventricle (C and F) before (A through C) and after (D through F) BPA. There is prominent RV dilatation, hypertrophy, and interventricular septal bowing (arrow) before BPA, all of which improved after BPA. CMR indicates cardiac MRI; CTEPH, chronic thromboembolic pulmonary hypertension; and RV, right ventricle. Reprinted from Fukui et al with permission of the publisher. Copyright © 2014, the European Respiratory Society. This material was not reviewed by European Respiratory Society before release; therefore, the European Respiratory Society may not be responsible for any errors, omissions or inaccuracies, or for any consequences arising therefrom, in the content.
Despite the usefulness of end points measuring disease progression and deterioration, from the standpoint of clinical practice, it may be more relevant to assess improvement in physical capacity and well-being. A composite end point was selected as the primary end point in the prostacyclin and iloprost in aerosol form in severe pulmonary hypertension (AIR) study to give a more rigorous assessment of the efficacy of iloprost. It included (1) an increase of at least 10% in the 6MWD, (2) improvement in the New York Heart Association/World Health Organization functional class (NYHA/WHO FC), and (3) absence of deterioration in the clinical condition, or (4) death. With this design, a larger proportion of subjects met the composite end point than the primary end point (increase in 6MWD and improvement in WHO FC). Use of composite improvement end points allows individual responders to be identified, lowers the placebo response, and reduces the needed number of patients and duration of the study.

It has become clear to many in the field that there is often little correlation between the patients seen in clinical practice and those patients who are enrolled in clinical trials. There are a number of reasons for this: Clinical trials only enroll a very stringent population of patients; in the real world, many, if not most, patients do not meet entry criteria for a PAH clinical trial. As such, we are looking for a reproducible objective measure of how our patients with PAH are doing. We need an approach that allows for the evaluation and quantification of symptoms, provides insight into prognosis, and can be used as a guide to therapy. This begs the question as to what makes a good outcome measure. There are a number of limitations of outcome measures that must be clarified, including the concept of what is to be measured; that is, what do we want to know about the patient population and the disease, and how it should be applied in clinical practice. For an outcome measure to be reliable it should be, as much as possible, free of random errors or chance. The measurements must be truly valid in that they measure what we want them to measure, and what we think they are measuring, and they must be able to detect change over time in a reliable and objective fashion that is understood by the providers who will use them in clinical decision making. Measurements should also be easy to obtain with respect to time, level of technology, and cost. Whatever the outcome measurements are, they should be adaptable to differences in culture and language.

Unfortunately, none of the current parameters measured as part of clinical trials or in clinical practice satisfies all these requirements. The 6MWD has some utility in clinical practice, and, as long as its limitations are recognized, it can be used as an index of the functional status (decline) of the patient. From the standpoint of prognosis, only the baseline 6MWD is helpful. There is a recognized ceiling effect in the 6MWD that may mask efficacy in some patients, and longitudinally may not fully reflect patients with extensive pathology or more severe disease, especially in younger patients. The WHO FC is very subjective and can vary from clinician to clinician. RHC is too labor intensive to be done on a regular basis. Currently, we have no validated biomarker to determine prognosis or to guide therapy reliably in these patients. The more recently adapted TTCW is really a negative parameter (maybe time to clinical betterment would be better, if we could agree on the parameters). We need a test/evaluation that can be done in every center, in exactly the same way, and that is interpreted in the same way by all practitioners. Such a test would provide information on prognosis, response to therapy, and risk stratification.

We believe that CPET might satisfy these criteria, if certain practices are followed, personnel are uniformly trained, protocols are standardized, centers are validated, and data are interpreted in a similar fashion by all centers performing CPET. Cardiopulmonary exercise testing offers a noninvasive means for assessing the cardiopulmonary limitations to exercise in patients with heart failure and PAH. CPET provides a range of physiological parameters that can detail features of pulmonary vascular and cardiopulmonary interactions beyond oxygen uptake. Patients with PAH have a similar pattern of response to exercise as patients with heart failure and pulmonary hypertension secondary to left-sided heart disease. A result of the remodeling of the pulmonary vascular bed that leads to increased PVR is heterogeneous ventilation-perfusion mismatching and increased dead-space ventilation. As the PVR increases and the disease progresses, there is a decline in CO, and impaired oxygen delivery to skeletal muscle. The decrease in oxygen delivery is the result of both diminished O2 uptake (Vo2) and compromised CO. The end result is exercise ventilation inefficiency, which can be reflected by several CPET variables.

Peak Vo2 is the standard that defines exercise limitation and is reduced in patients with PAH and, although not specific

### Table. Definition of Time to Clinical Worsening in Different Trials

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NYHA indicates New York Heart Association; PAH, pulmonary arterial hypertension; and WHO FC, World Health Organization functional class.
Adapted from Hassoun et al.58
to PAH, is a clear marker of disease severity. When the PVR is abnormally increased, or does not decrease appropriately with exercise, RV output is reduced leading to decreased left ventricular preload, decreased left ventricular stroke volume, and CO. The CO of the RV equals the CO of the left ventricle, and represents pulmonary blood flow, and thus correlates with VO₂ in the absence of an intracardiac shunt. In pulmonary hypertension, a reduced VO₂ reflects the patient’s inability to augment pulmonary blood flow during exercise.⁷¹ Peak VO₂ also provides an important prognostic marker in PAH.¹³ Improvements in VO₂ could be used to update prognosis, and provide objective confirmation of a response to therapy.

The ratio of minute ventilation (Ve) to production of carbon dioxide (VCO₂) or Ve/VCO₂ is reflective of inefficient ventilation during exercise. The Ve/VCO₂ slope, or the steepness by which the Ve increase relative to CO₂ production, is steeper in patients with pulmonary hypertension. This is reflective of worsening V/Q mismatching and increased VD/VT, and the resultant abnormalities in CO₂ tension that drive an exaggerated ventilatory response⁷² demonstrated by an abnormal reduction in end-tidal CO₂ or PETCO₂.⁷³ With impaired VO₂, there is greater dependence on inefficient anaerobic metabolism that results in an increase in CO₂ production relative to O₂ consumption. As patients approach the anaerobic threshold, there is a further increase in CO₂ production because of the dissociation of bicarbonate for lactic acid further driving ventilation.² In patients who develop hypoxemia and a right to left shunt, these variables reflect even greater gas exchange abnormalities.⁷⁴ Patients with progressive PAH often desaturate with exertion and typically have a significantly increased PVR at baseline. This would be reflected in a more severely elevated Ve/VCO₂ slope and a more significantly diminished PETCO₂.⁷³ Both PETCO₂ and Ve/VCO₂ slope provide insight into disease severity based on the degree of V/Q mismatch that is reflective of the underlying pathological remodeling of the pulmonary vasculature and the metabolic consequences of exercise. Improvements in these parameters with therapy would be reflective of reverse remodeling and improving V/Q matching and prognosis.

Submaximal exercise testing using devices that can measure breath-by-breath respiratory gas analysis can be used to predict aerobic capacity or to assess functional capacity. Their greatest utility may be in grading an individual patient’s response to therapy compared across subsequent tests over time. Measurements taken before, during, and after the test can provide valuable information regarding the person’s exercise responses. Changes in submaximal exercise responses such as heart rate, respiratory rate, blood pressure, VO₂, PETCO₂ pattern of change, O₂ uptake efficiency slope, and Ve/VCO₂ can be consistent with responses to therapy. However, there are no standard methods to assess submaximal performance, and using submaximal testing to assess prognosis has not been examined.

The primary difference between maximal and submaximal testing of the capacity of the cardiopulmonary system is that maximal testing is a measure of disease severity and has prognostic value. However, maximal testing is poorly reflective of everyday physical activity, especially when patients perform mostly submaximal effort. Whereas a change during maximal testing may imply an improvement in prognosis; in contrast, changes in submaximal indices may be more reflective of a change in symptoms.

Conclusion
For all of the reasons described above we believe that CPET could become a very useful outcome measure in clinical trials. This could include both maximal testing and sub maximal testing. If done consistently, the use of CPET would allow for a more uniform classification of patient status based on more objective measures (peak VO₂, Ve/VCO₂, and PETCO₂). This would require agreement on a specific protocol and uniform interpretation of the findings. In the clinical trial setting, that would most likely require a core laboratory with expertise in performing CPET and data analysis. In clinical practice this would require publication of clear guidelines and adherence to those guidelines.

We would also suggest that CPET be part of a composite end point that aims to assess decline or improvement in physical capacity. Overall, we suggest as a novel clinical end point the following: (1) a change of at least 10% in the peak VO₂, change in Ve/VCO₂ slope of >5% (with a goal-directed target of <34), and a 10% change in PETCO₂ (could be applied to both maximal and submaximal exercise testing), (2) improvement in the New York Heart Association/WHO FC and (3) absence of deterioration in the clinical condition, or (4) atrial septostomy, transplant, or death. These would be expected to reflect the impact of disease progression or health, lifestyle, or pharmacological changes. We believe this approach would provide the clearest indication of overall health status and prognosis in patients with pulmonary vascular disease.

Sources of Funding
Dr Waxman was supported by NHLBI 2R01HL06023412A1 and NHLBI U01 HL125215.

Disclosures
None.

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KEY WORDS: clinical trial ■ hypertension, pulmonary ■ patient outcome assessment ■ performance measure
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Circulation. 2015;132:2152-2161
doi: 10.1161/CIRCULATIONAHA.114.012328

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