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Advances in PH Journal

What Can be Learned in 6 Minutes? 6-Minute Walk Test Primer and Role in Pulmonary Arterial Hypertension

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The 6-minute walk test (6MWT) is an easy to perform and practical test that has been used in the assessment of patients with a variety of cardiopulmonary diseases including pulmonary arterial hypertension (PAH).[1,2] It simply measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Nonetheless, the result reflects the integrated exercise response of complex physiology involving the pulmonary and cardiovascular systems, systemic and pulmonary circulations, and neuromuscular function. The metabolic rate stabilizes at a level representative of maximal oxygen consumption; therefore, the test is a good measure of aerobic exercise capacity.[3] The correlation with maximal cardiac output renders the test an indirect measure of right ventricular function in patients with significant PAH.[4] An understanding of the 6MWT indications, logistics, limitations, and interpretation is important to the clinician utilizing this test to evaluate patients with PAH.

BACKGROUND

As a relatively simple measure of aerobic exercise capacity, the 6MWT has been utilized in a variety of medical conditions affecting the cardiopulmonary system. The test is “unencouraged” and therefore “self-paced” and performed at a submaximal level of exercise. The patients select their own intensity of effort, which may more accurately reflect “everyday activities” for each particular individual.[5] It should be recognized that the test is a global assessment and does not specifically identify the source of the limitation.

TECHNICAL ASPECTS

Although the instructions for both the administrator of the test and the patient are straightforward, there are several technical aspects of the 6MWT that require attention. The American Thoracic Society has published guidelines for a detailed understanding of the test logistics.[1] In addition, a document titled “Pulmonary Rehabilitation Toolkit,” is available on the following Web site: www.pulmonaryrehab.com.au/index.asp?page=19.[6] Instructions to the patient are specific. The patient should be advised to dress comfortably with appropriate footwear and use his or her usual walking aids (eg, cane, walker). A light pre-test meal is recommended. The patient should not engage in strenuous exercise for 2 hours prior to testing. In addition, the patient should rest for 10 minutes prior to the walk test, after which time baseline vital signs including oxygen saturation are assessed. As mentioned previously, the test is performed at an unencouraged intensity. In addition, the patient is allowed to stop and rest during the test. The patient should evaluate the degree of dyspnea both at baseline and at the end of the test with a validated scoring system such as the Borg dyspnea score. It is important that the patient not engage in “practice” walks. Indeed, if the walk test needs to be repeated for clinical purposes, the patient should rest for an hour and the longest distance recorded.

The equipment required includes a pulse oximeter, timer (stopwatch), and blood pressure cuff. Effort should be devoted to producing conditions that create an environment representative of the patient's normal functional status. For example, appropriate support should be available for the patient to transport their oxygen if they typically use oxygen with activity. If the patient is oxygen dependent, then an appropriate delivery device should be provided. The technician performing the test should not push or carry the oxygen delivery device for the patient. Some patients may require a mobile chair to push or pull while walking. Fortunately, advanced exercise equipment is not required. A hallway marked for distance with lap counter and/or pedometer can be used to measure distance in feet or meters. It is also reasonable to have an automatic defibrillator (AED) available in the vicinity.

CLINICAL INDICATIONS AND CONTRAINDICATIONS

There are a variety of conditions in which the 6MWT has been shown to be indicative of

disease state.[1,7] Those conditions are listed in Table 1. In addition, there are both absolute and relative contraindications to 6MWT as displayed in Table 2.[1]

Table 1:

Indications for the 6MWT

Treatment Comparison	Functional Status	Outcome Assessment
Pulmonary hypertension	Pulmonary hypertension	Pulmonary hypertension
COPD	COPD	COPD
Heart failure	Heart failure	Heart failure
Pulmonary rehabilitation	Cystic fibrosis	
Lung resection	Peripheral vascular disease	
Lung transplant	Fibromyalgia	
Lung volume reduction surgery	Older patient	

Adapted from the official statement of the American Thoracic Society: *Am J Respir Crit Care Med*. 2002;166(1):111-117. COPD = chronic obstructive pulmonary disease.

Table 2:

Contraindications to the Use of the 6-Minute Walk

Absolute	Relative
Unstable angina	Resting tachycardia (120)
Recent myocardial infarction	Poorly controlled systemic hypertension (MAP ?135)
Unable to ambulate	

Adapted from the official statement of the American Thoracic Society: *Am J Respir Crit Care Med*. 2002;166(1):111-117.

Table 3:

Patient Characteristics Or Conditions That Influence The 6-Minute Walk Distance Independent Of Cardiopulmonary Status

Shorter Distances	Longer Distances
Short stature	Tall stature
Older age	Younger age
Women	Men
Comorbidities	Prior 6MWT

VARIABILITY

Certain factors determine 6-minute walk distance variability between patients including age, sex, anthropometrics, and comorbidities (impaired cognition, cardiopulmonary disease, anemia, musculoskeletal limitations).[1,7] Variability may also be seen in an individual patient (ie, with serial tests). It should be appreciated that prior testing increases the distance walked ("learning effect").

Comparative tests ideally should be performed at similar times during the day. Reproducibility is possible for both "encouraged" and "unencouraged" walks but the process must be standardized to eliminate variability. It may be best to avoid the phrase "walk as fast as you can" to avoid premature fatigue or other limiting symptoms. Use the same oxygen flow rate if possible. If the clinical situation demands an increase in flow rate, this should be appropriately documented.

Other technical issues that may introduce variability should be noted. For example, the interaction between the patient and the person performing the test may result in the patient "tracking" the tester's pace.[8] To avoid this confounding factor, the technician should not walk with or in front of the patient. If it is necessary for the technician to accompany the patient for data monitoring or patient safety, it is recommended that the technician walk behind the patient so he or she sets the walking pace. Variations in oxygen delivery devices (portable concentrator, liquid oxygen, or gas tank), interface (nasal cannula, transtracheal oxygen, or mask), and flow delivery (continuous or pulse) must be noted. If the oxygen flow requires adjustment during the walk test, then the reason needs to be documented. Medications (type, doses, and administration times) may also potentially affect the test results and should be carefully documented.

Reference (normative) equations exist for predicting normal 6-minute walk distance based on several variables.[7] Even using such equations, 60% of the variance in 6-minute walk distance remains. In addition, although the percent predicted value may help in the interpretation of the test, its prognostic value is not superior to the absolute distance measured.[9–10] The normative equations were developed in subjects older than 40 years[7] so caution should be observed in the application to patients younger than that.

INTERPRETATION

The change in the distance walked in the 6-minute walk can be used to evaluate the efficacy of an exercise-training program or to trace the natural history of change in exercise capacity over time. The 6MWT is most commonly used as a baseline and follow-up assessment after a specific intervention or in monitoring disease progression. Unfortunately, the ideal representation of this comparison has not been determined. The available options include: absolute difference in distance walked, percentage change, or change as compared to predicted normal.

The minimally important clinical difference has not been determined for pulmonary vascular

disease. There are available criteria for both chronic obstructive and interstitial lung disease. The minimum important difference (ie, improvement) in the distance walked in the 6-minute walk has traditionally been estimated as 54 meters (with 95% confidence limits of 37 to 71 meters).[11] The value may be less for patients with chronic obstructive pulmonary or interstitial lung disease.[12–13] Percentage change in the distance walked may also be used for comparison to prior testing.

SPECIFIC ISSUES OF 6-MINUTE WALK TESTING IN PAH

The 6MWT is commonly used in the diagnosis and evaluation of patients with PAH.[14–23] The test estimates aerobic capacity and correlates with cardiac output thereby rendering the result and indirect measure of right ventricular function.[3] The 6-minute walk distance had an independent correlation with survival in the cardinal study of intravenous epoprostenol for idiopathic PAH.[14] Since that time, treatment-associated improvements in the 6-minute walk distance for PAH patients have been used as primary end points in most of the efficacy studies of currently FDA-approved pulmonary arterial vasodilator therapy.[15–16,24]

Despite the extensive deployment in the pulmonary vasodilator studies, the test has not been standardized in patients with PAH. It is our sense from conversations with staff from other pulmonary hypertension (PH) centers that 6-minute walk methodologies vary between institutions. While most centers make every effort to be in compliance with the American Thoracic Society recommendations, certain differences are dictated by the architectural design of the facilities in which the test is performed. One such example is the utilization of a single hallway vs a continuous track. Recommendations for the performance of the 6MWT have been provided in the protocol in many of the pulmonary vasodilator studies; however, the level of specificity within a trial and consistency across trials varies. In the absence of widespread standardization, there remain significant gaps in the understanding and interpretation of the 6MWT for patients with pulmonary vascular disease.

Nonetheless, the combination of the simplicity of the testing and its consistent use in efficacy studies has resulted in widespread employment in the clinical evaluation of patients. Serial measurements have been recommended by the currently available clinically based guidelines.[17–18,20,23] The 6MWT may be used to evaluate both disease progression and clinical response to therapy.[25] In addition, the distance walked has been demonstrated to correlate with WHO functional class and hemodynamic assessment of PAH.[2,24,26]

The 6-minute walk distance has also been incorporated into treatment guidelines for risk stratification. It has been suggested that lower risk patients, such as those who walk at least 400 meters, may respond to oral monotherapy.[21,23] Conversely, higher risk patients who walk less than 300 meters may require more complex prostacyclin or combination therapy. Although such stratification is based on both rational considerations and experiential evidence, it has not been rigorously studied. In addition, the utility of the 6MWT in PH patients who walk more than 450 meters may be more limited.[27]

PROGNOSIS

Early literature demonstrated a relationship to 3-year survival using a breakpoint of 332 meters.[2] Only 20% of patients lived 3 years if the distance walked was less than 332 meters compared to 92% if greater. The 6MWT was reviewed in the American College of Chest Physicians evidence-based clinical guidelines.[20] The quality of evidence for use of exercise tolerance to monitor patients was determined to be “good” with a net “substantial” benefit. Overall, the strength of recommendation for its use in PAH was an “A.”

A longer distance of 380 meters was employed in a goal-oriented approach to treatment of PAH.[19] The correlation with outcome and emphasis on objective treatment goals has resulted in risk stratification recommendations[18,21,23] involving the distance walked. Such recommendations are predicated upon the poor outcome of a low distance walked and imply that more “aggressive” therapies such as infusion prostacyclin be employed. While perhaps reasonable, such an approach to treatment selection has not been proven.

More recently, an analysis of 664 patients with idiopathic PAH from the REVEAL registry determined that the 380-meter cutoff point had a sensitivity of 79% with a specificity of 55%.[10] The use of a breakpoint distance that equated to 65% predicted was also examined. The latter had a sensitivity of 65% with a specificity of 69% indicating less sensitivity but more specificity than the absolute distance cutoff. A 70% predicted cutoff had similar sensitivity and specificity to the absolute distance of 380 meters. In addition, 1-year survival for those patients with 6-minute walk distance in excess of 380 meters was 98% compared to 89% with lower walk distances.

MISCELLANEOUS

Comorbidities

Approximately 50% of group 1 PAH patients are classified as associated PAH due to coexisting morbidities, many of which may adversely affect the 6-minute walk distance.[28] About half of the associated PAH patients have scleroderma. It should be noted that the distance walked is generally decreased in patients with scleroderma without lung disease. The distance walked is further reduced by both pulmonary vascular and parenchymal lung disease.[11–13,29–31]

It is common that non-group 1 PH patients, particularly group 3 (PH owing to lung or respiratory disease), are assessed by 6MWT for both status monitoring and prognostication. Indeed, the 6-minute walk has been incorporated into a standard tool for evaluation of chronic obstructive pulmonary disease, the BODE (the E represents exercise capacity as measured by the 6-minute walk) index.[32] The presence of PH may further decrease the distance walked.[33] Furthermore, the 6MWT has been used as the primary end point in the evaluation of treatment response in trials of bosentan in group 3 patients.[34–35]

Clinical Trials

As previously mentioned, improvement in the 6-minute walk distance was first shown to correlate with a favorable response to treatment with epoprostenol.[14] It has since been either a primary or secondary end point in most of the studies of FDA-approved vasodilator therapy. In general, the walk distance improved by approximately 40 meters (range 16 to 59) compared to placebo in short-term studies (3 to 4 months).

While the 6-minute walk distance has been used as a primary end point in most of the clinical trials in PAH, its role in this regard has come under considerable scrutiny.[25,36–37] Additional criticisms include the “ceiling effect”[38] and the insensitivity for those patients who walk more than 450 meters.[27] Unfortunately, the alternative end points also have limitations.[37] In addition, the 6-minute walk remains a FDA requirement for pharmacological studies in PAH.

Costs

The relative costs of those tests used to assess baseline function and response to treatment are an ongoing consideration, particularly in the era of declining reimbursement. Serum biomarkers may be the least expensive; eg, brain natriuretic peptide levels can be assessed for approximately $20. Echocardiography and right heart catheterization would represent the other end of the spectrum with costs that generally exceed $350 and $1000 respectively. Medicare reimbursement for a 6MWT is approximately $68. Whether the reimbursement covers the overhead has not been directly studied, but an analysis in our institution seems to indicate that this is not the case, as the cost to perform is approximately $150.

CONCLUSION

The 6MWT is an easy to perform and practical test that has been used in the assessment of patients with a variety of cardiopulmonary diseases including PAH. The correlation with maximal cardiac output renders the test an indirect measure of right ventricular function in patients with significant PAH. In addition, the test has been employed in the majority of studies evaluating the efficacy of pulmonary arterial vasodilators and has been demonstrated to correlate with prognosis. Despite the existence of testing guidelines, the test has not been standardized in patients with PAH. In order to improve our understanding and interpretation of the test results in patients with pulmonary vascular disease, this review should provide a sufficient basis for the consistent performance of the 6MWT within an institution.

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