Editorial

Six-Minute Walk Test in Scleroderma-Associated Pulmonary Arterial Hypertension: Are We Counting What Counts?

Everything that can be counted does not necessarily count; Everything that counts cannot necessarily be counted
— Albert Einstein

Scleroderma-associated Pulmonary Arterial Hypertension

Systemic scleroderma (SSc) is a multisystem disease with protean manifestations, but pulmonary involvement is the leading cause of mortality. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are 2 serious pulmonary complications of SSc that commonly cause clinical symptoms of dyspnea and exercise intolerance, can be associated with severe functional limitation, and often have a poor prognosis for longterm survival.

SSc-associated PAH (SSc-PAH) is a serious disease of progressive pulmonary vascular obliteration characterized by persistent elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Untreated SSc-PAH usually results in right-sided heart failure and high risk of death. The average survival in SSc patients diagnosed with PAH is 1–2 years[1-3]. Patients with SSc-PAH have a worse prognosis than most other PAH patients, including primary or idiopathic PAH (IPAH)[4,5].

Many new PAH-specific therapies have been studied and are available for the treatment of patients with SSc-PAH. These include prostacyclin derivatives (intravenous epoprostenol, subcutaneous or intravenous treprostinil), a novel family of oral endothelin receptor antagonists (bosentan, sitaxsentan, and ambrisentan), as well as an oral phosphodiesterase type 5 inhibitor (sildenafil)[6].

Treatment of PAH patients, including SSc-PAH, with these PAH-specific medications is associated with subjective and objective clinical benefit. Given that PAH is a disease of disturbed pulmonary hemodynamics, reductions in mean PAP and PVR, as well as improved right ventricular (RV) function, as evidenced by increased cardiac output, have been expectations of PAH therapy. However, repeated assessment of pulmonary hemodynamics by invasive right-heart catheterization is not feasible, and not necessarily indicated. Doppler echocardiographic assessment of RV systolic pressure (RVSP) is commonly used as a surrogate for systolic PAP. Moreover, other echo parameters, such as presence of pericardial effusion and degree of tricuspid annular displacement, are markers of PAH prognosis[7,8]. However, echo may not be a reliable measure of PAH severity because of lack of consensus on grading severity of these parameters, inconsistent technical rigor and expertise among echo technicians and physicians, and patient factors such as body habitus. Several studies have compared echo-estimated RVSP with systolic PAP determined by right-heart catheterization, reporting good echo specificity (85%–96%), but generally poor sensitivity (58%–80%) for the detection of elevated PAP[3,9].

Clinical parameters are commonly used in the monitoring of PAH patients over time, including symptoms and physical examination evidence of right-sided heart failure. The World Health Organization (WHO) modification of the New York Heart Association (NYHA) functional class scoring system (class I to IV) correlates with PAH survival[10], and can be used to assess stability versus decline in an individual patient. However, it remains unclear and controversial as to how to best assess the severity of PAH in an individual patient, and how to define or measure a clinical benefit of PAH treatment.

Exercise Capacity in Scleroderma-associated PAH

The most common clinical features of PAH are dyspnea and exercise intolerance. As such, the objective measurement of exercise capacity has long been considered useful and relevant in the assessment of the severity of PAH, as well as the routine monitoring of PAH patients over time. Exercise requires a global and integrated response of many systems, including cardiac (increased cardiac output), peripheral vascular (increased muscle blood flow), respiratory (increased

See Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma, *page 330*

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ventilation for O_2 uptake and CO_2 clearance), hematologic (blood carries and delivers O_2), and musculoskeletal and metabolic systems (aerobic and anaerobic generation of ATP or energy).

The gold standard for evaluation of exercise capacity is the incremental, maximal, symptom-limited, treadmill, or cycle cardiopulmonary exercise test (CPET). CPET is a robust technique for assessment of the function of several major systems involved in exercise, including cardiovascular, respiratory, and metabolic. As such, CPET quantifies overall exercise capacity, and can identify the specific physiologic limitation to exercise, including unfitness, obesity, hypoxemia, and cardiovascular or respiratory disease. However, in order to obtain the most useful diagnostic information on physiologic limitations to exercise, CPET also requires a maximal effort by the patient, and this can be difficult and risky for some severely ill patients with PAH. Moreover, CPET requires specific exercise equipment and measurement systems, staff technical expertise, and significant medical/scientific physiologic expertise and experience with exercise testing. All these aspects are essential to obtain valid, reliable CPET data and an accurate interpretation.

Because of these concerns, the routine clinical use of CPET to assess exercise capacity in PAH patients may not be feasible or appropriate. Indeed, among the randomized clinical trials (RCT) of PAH therapies, maximal exercise capacity by CPET was selected as the primary outcome measure in only a single study of the endothelin receptor antagonist sitaxsentan. The lack of experience of many centers with CPET contributed to a negative outcome, as there was no significant difference between sitaxsentan and placebo-treated subjects in CPET maximal exercise capacity, despite significant improvements in several other parameters of PAH[11].

A practical and simple alternative to CPET to determine exercise capacity is the 6-minute walk test (6MWT). The 6MWT is a simple, safe, noninvasive, reproducible test of exercise capacity[12,13]. In contrast to CPET, the 6MWT reflects a submaximal level of exertion that is more consistent with the effort required for daily physical activities. It is noteworthy that unlike CPET, the 6MWT does not provide information on the physiologic mechanism of exercise limitation[13].

The 6MWT does not require any special exercise equipment or advanced training for staff, and thus is a practical method to repeatedly assess exercise capacity over time. Parameters that should be recorded include the distance covered during the 6MWT (6MWD), the level of patient respiratory effort, as reflected by the Borg dyspnea index, and arterial oxygen saturation by pulse oximetry.

6MWD has been found to correlate with WHO/NYHA functional class in patients with IPAH[10,14] and specifically in SSc-PAH patients[10]. Moreover, 6MWD strongly and independently predicts prognosis for survival in IPAH[14,15]. For example, survival was significantly worse in WHO/NYHA class III and IV IPAH patients who walked ≤ 250 m at baseline prior to therapy, or < 380 m after 3 months of intravenous epoprostenol[15].

6MWT has also become the most popular primary endpoint in RCT of medical therapies for PAH. For example, in the first RCT of a PAH-specific therapy in patients with SSc-PAH, median 6MWD improved 108 m in 56 patients with SSc-PAH treated with intravenous epoprostenol versus placebo[16]. Placebo-controlled RCT of all other available PAH therapies have also reported significant improvements in mean 6MWD. Importantly, the benefit in exercise capacity with PAH therapy may not be similar in SSc-PAH and IPAH patients. For example, bosentan increased 6MWD in IPAH patients, but prevented 6MWD deterioration in SSc-PAH patients[17]. Finally, all recent RCT of PAH therapies have included more patients with milder disease, specifically WHO/NYHA functional class II. In such PAH patients with better baseline exercise capacity, as reflected by higher 6MWD, the 6MWT may be limited by a "ceiling effect," and may not be as robust in demonstrating an improvement in response to PAH-specific medical therapy.

In addition to the actual 6MWD, the degree of oxygen desaturation has been found to correlate with prognosis in IPAH patients[18]. Similarly, oxygen desaturation ≥ 4% during 6MWT in SSc patients correlated with echo-measured pulmonary artery systolic pressure ≥ 30 mm Hg, as well as advanced age, higher dyspnea index, and radiographic fibrosis[19].

Because of its simplicity, reproducibility, and validity in reflecting PAH severity, 6MWT has been widely accepted, and is now recommended and routinely used in the assessment of PAH patients, prognostication, and for monitoring response to therapy. However, the 6MWT has never been specifically validated as a measure of cardiopulmonary exercise capacity in patients with SSc-PAH. Although 6MWD is clearly sensitive to the presence of cardiovascular and pulmonary complications of SSc, such as PAH, SSc patients are also limited by musculoskeletal dysfunction and pain as shown by Garin and colleagues in this issue of *The Journal*[20].

Demographic and anthropometric variables such as age, height, and weight may have major effects on 6MWT. As such, the simple use of absolute 6MWD to assess an individual's exercise capacity may not be as valid as adjusting 6MWD for the above factors, or expressing 6MWD as a percentage of a predicted value[21].

The above limitations need to be resolved through further study before the routine use of 6MWT can be recommended for the management of SSc-PAH. It is also clear that new measures of PAH clinical disease severity, especially RV function, need to be developed, studied, and validated. Such outcome measures will be important in future RCT of new PAH therapies, as well as useful assessment tools for clini-

cians to better monitor individual PAH patients and assess the effectiveness of PAH therapy.

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