# Shuttling toward Improved Clinic-based Assessment of Exercise Capacity in Pulmonary Arterial Hypertension

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Reduced exercise capacity is a hallmark of pulmonary arterial hypertension (PAH). Not surprisingly, functional capacity is a strong prognostic marker in PAH (1, 2). The most commonly used method for gauging functional capacity in the clinic, and a ubiquitous endpoint in clinical trials, is the 6-minute-walk distance (6MWD) (3, 4). Despite widespread use, the 6MWD has important limitations as a clinical assessment, prognostic tool, and trial endpoint (5). First, the 6MWD measures submaximal exercise capacity at a snapshot in time in a clinical environment. As a result, it is subject to influences at the moment of testing, such as mood, motivation, and comfort, among others. Second, a ceiling effect of 6MWD has been observed in PAH trials that may mask evidence of efficacy in less symptomatic subjects who nonetheless have significant pathology (6, 7). For example, young, asymptomatic patients may be able to walk >500 m at baseline but may not substantially improve on this distance after therapy because of the submaximal nature of the test. For an average height person, distances greater than approximately 650 m would require jogging. Third, despite consistent associations with mortality and quality of life, change in 6MWD in treatment and placebo arms is not associated with clinical outcomes (8). One conclusion is that 6MWD is insensitive to the detection of early disease or disease progression or response to therapy. PAH investigators and clinicians recognize these limitations of the 6MWD test, but no practical, validated alternative has emerged.

In this issue of *AnnalsATS*, Lewis and colleagues (pp. 34–43) make noteworthy progress toward introducing a viable alternative to the 6MWD that has risk stratification value before and after treatment initiation (9). The authors assessed the ability of the intermittent shuttle walking test (ISWT) to predict clinical risk in a large cohort of patients with incident PAH enrolled in the Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre registry. The ISWT is a maximal exercise test previously shown by the same investigators to correlate with hemodynamic severity of PAH and to associate with prognosis at baseline and in response to treatment. The ISWT has important advantages over cardiopulmonary exercise testing (an alternative maximal exercise test), including short duration and no associated cost. In this test, the patient walks a 10-m track at a pace dictated by an audible signal. The initial level starts at a slow pace, and the pace progressively quickens in each subsequent level to a maximum of 12 levels, each of which lasts 1 minute. The test ends when the subject is too breathless to continue or is unable to reach the opposite end of the track before the next beep occurs.

The primary objective of this study was to determine whether the ISWT could be used to risk-stratify patients with PAH and to derive thresholds for stratification. Consistent with prior work, the investigators observed a stepwise inverse relationship between distance walked and all-cause mortality. Mortality at 1 year was 32% for patients who could not complete level 1 (≤30 m), and no mortality was observed among those reaching level 8 or higher (≥430 m). Using these 1-year mortality rates, the authors derived thresholds signifying high (>10%), intermediate (5–10%), and low (<5%) risk of 1-year mortality. At follow-up, baseline values correctly identified subjects at high, intermediate, and low risk, validating the value of the ISWT for risk stratification. A sensitivity analysis was performed for patients under 50 years of age to test whether the risk prediction categories remained accurate among patients more likely to walk longer distances. The thresholds again performed well but overestimated risk in the intermediate category, in which a mortality of 3% was observed rather than 5–10%. Another key finding was that those patients who achieved at least one higher level on repeat testing after stable therapy had better 1-year mortality (90%) compared with those who maintained the same level (84%) or declined (79%).

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Having shown the ability of the ISWT to discriminate risk categories, the authors then tested how well the measure performs when incorporated into contemporary risk stratification tools, replacing 6MWD. When added to the French Pulmonary Hypertension Registry score, Kaplan-Meier curves for the low-, intermediate-, and high-risk groups separated well though the score underestimated risk in the intermediate



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group (87% observed vs. 90–95% predicted 1-yr survival). However, the addition of ISWT added only modest discriminatory power, increasing the c-statistic from 0.59 with no walking test to 0.61 when ISWT was included. Several scoring conventions were considered when adding the ISWT to the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) 2.0 risk-assessment tool. The best performing approach (c-statistic, 0.71) involved adding an extra point for a very-high-risk ISWT and deducting an extra point for very-low-risk ISWT distances. Thus, inclusion of ISWT underperforms the original REVEAL 2.0 score (c-statistic, 0.76) (10). As the authors note, differences between cohorts (e.g., incident vs. incident and prevalent cases) may explain some of the discrepancy in predictive power. Exploring alternative thresholds may also lead to better performance and warrant future study.

Although the performance of ISWT in contemporary risk scores needs improvement, the authors' other findings argue in favor of more widespread use of the ISWT in clinical populations. The findings suggest several key advantages of the ISWT over the 6MWD. First, the test elicits maximal effort as evident in the fact that no patients reached the highest levels and only one reached level 9. Next, the absence of a ceiling effect was demonstrated by showing that even among those who had high baseline ISWT distances, the majority improved their absolute distance after therapy. Finally, changes in ISWT distance after treatment have prognostic value. For example, those reassigned to a lower risk category at follow-up had a similar prognosis as those starting in that category at baseline.

In addition to the many strengths of the study, some limitations should be noted. The lack of a contemporaneous 6MWD in this unique population is a missed opportunity for a direct comparison of the two tests in the same population. Another weakness relates to the test itself, which shares the same limitation as 6MWD of being only a snapshot of capacity at a single time point. It would be interesting to know whether daily activity (e.g., step counts), which is more of a behavioral measurement, adds prognostic value to clinical assessments of capacity. Finally, one underdiscussed aspect of the study was the strong association between higher ISWT distance and higher right-ventricular ejection fraction. An important unanswered question that follows from this observation is whether improvements in ISWT at follow-up were driven by improvement in right ventricular function in response to therapy.

The authors are commended for an important contribution and for their continued efforts to bring to the clinic a practical, low-cost, and low-burden test to assess functional capacity in PAH. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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