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Incremental Shuttle Walk Test as a Valuable Assessment of Exercise Performance in Patients With Pulmonary Arterial Hypertension

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Background: Nearly all clinical trials investigating patients with pulmonary arterial hypertension (PAH) have used the 6-min walk test (6MWT) to evaluate exercise tolerance. The incremental shuttle walk test (SWT), however, has been proposed as a more valid and reproducible alternative to the 6MWT in the evaluation of exercise tolerance in patients with chronic obstructive pulmonary disease. The efficacy of SWT in clinical practice to evaluate the exercise capacity of patients with PAH was investigated.

Methods and Results: The peak oxygen consumption ($pV\dot{O}_2$) and oxygen consumption at anaerobic threshold ($V\dot{O}_2$ at AT), the gold standard for measurement of exercise tolerance, 6MWT and SWT were measured in 19 clinically stable PAH patients (WHO functional class II–III) and the data compared. There was a higher correlation between SWT walk distance and $pV\dot{O}_2$ than between 6MWT walk distance and $pV\dot{O}_2$ (r=0.866 and 0.765, respectively; P<0.05), and a higher correlation between SWT walk distance and $V\dot{O}_2$ at AT than between 6MWT walk distance and $V\dot{O}_2$ at AT (r=0.775 and 0.587, respectively; P<0.05). No adverse events occurred during the exercise tests.

Conclusions: SWT is a better reflection than 6MWT of exercise tolerance in PAH patients, and thus is a preferable alternative for assessment of exercise tolerance in PAH patients. (*Circ J* 2014; **78:** 215–221)

Key Words: Exercise; Pulmonary hypertension; Rehabilitation

Achievement of reliable results in clinical trials requires an accurate assessment technique. Many clinical trials investigating pulmonary arterial hypertension (PAH) have used the 6-min walk test (6MWT) as a clinical endpoint. Measurement of peak oxygen consumption ($pV\dot{O}_2$) and oxygen consumption at anaerobic threshold ($V\dot{O}_2$ at AT) via indirect calorimetry provides an objective, reliable and non-invasive technique to assess exercise tolerance in patients with various cardiac diseases. Furthermore, $V\dot{O}_2$ at AT describes the highest $V\dot{O}_2$ that the patient can sustain without developing lactic acidosis, and appears to be an independent marker of PAH severity.[1] In the Sitaxsentan Therapy for Pulmonary Arterial Hypertension (STRIDE-1) study, $pV\dot{O}_2$ was adopted as the clinical endpoint.[2] Measurement of $pV\dot{O}_2$, however, requires sophisticated equipment, laboratory facilities, and highly trained personnel. As a result, this test is not widely used and is often confined to large hospitals or research centers. These tests are also expensive and time-consuming, and may not be practical for frequent assessments or large groups of patients. Because of these limitations, field exercise tests such as the submaximal 6MWT have been developed as inexpensive and simple alternative measures of exercise tolerance.[3]

The 6MWT measures the distance a patient can voluntarily traverse in a 6-min period. The test protocol, however, is self-paced, difficult to standardize, and potentially influenced by motivation and encouragement. In addition, the 6MWT has only a moderate correlation with $pV\dot{O}_2$,[4] and is not a reliable predictor of mortality in patients with congestive heart failure.[5] The development of a simple objective field test that is more highly predictive of $pV\dot{O}_2$ and easily standardized and used is therefore desirable for patients with PAH.

An incremental, externally paced 10-m shuttle walk test (SWT) has been developed for patients with chronic airway limitation. This test is highly reliable and reproducible after only 1 practice walk.[6] In contrast, the 6MWT requires at least 2 practice trials to obtain reliable results.[3] Most importantly, SWT performance relates strongly to $pV\dot{O}_2$ (r=0.88) in patients with chronic airway limitation,[7] and a strong relationship

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Table 1. Symptoms During Exercise Testing (Smith Categories)

Category	Severity			
	0	1	2	3
ST-segment changes (mm)	<1	1–3	>3	
SaO_2 (%)	>95	95–85	<85 or 10% drop	
Arrhythmia	No arrhythmia	Isolated premature ventricular contractions, ventricular couplets, or bigeminy; isolated supraventricular beat, couplets, or both; non-sustained SVT	Non-sustained VT, asymptomatic SVT	Sustained VT, cardiac arrest, symptomatic SVT
Symptoms	No symptoms	Chest pain or dizziness <4/5†	Symptoms of chest pain or dizziness 4–5/5†	Syncope

†Subjective rating by the patient, with 5/5 being the worst.
SaO_2, arterial oxygen saturation; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

between $p\dot{V}O_2$ and SWT performance in patients with chronic heart failure (CHF) has been reported.[8,9] The purpose of this study was to compare the utility and safety of the SWT, which is an objective, externally paced, and easily standardized field test, to that of the 6MWT in clinical practice to evaluate exercise capacity in patients with PAH.

Methods

Subjects

Clinically stable patients with a diagnosis of PAH were recruited from the University Hospital of Hamamatsu University School of Medicine. The diagnosis of PAH was based on clinical and laboratory data, which included right heart catheterization parameters, and satisfied the diagnostic criteria described by the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines.[10] Patients were classified as World Health Organization (WHO) functional class II or III. Those who were on long-term oxygen therapy or who had comorbidities such as musculoskeletal and neurological disorders that might influence exercise performance were excluded. Written informed consent was obtained from all patients. The study, which complied with the Declaration of Helsinki, was approved by the Ethics Committees of Hamamatsu University School of Medicine, Hamamatsu, Japan. Medication for all study subjects did not change during the study period.

Research Design

A repeated-measures design was used in which each patient underwent the 6MWT, SWT, and cardiopulmonary exercise test (CPET), with the order of the tests randomly selected using computer-generated numbers. Patients attended at the same time of day on a maximum of 3 occasions, separated by at least 1 day, over a maximum period of 10 days. The endpoints of this study were the correlation coefficients for the distance walked during each walk test and $p\dot{V}O_2$ or $\dot{V}O_2$ at AT; and safety.

Test Protocols

6MWT The 6MWT was conducted in a 30-m-long internal corridor by a single physiotherapist according to current standards.[3] Participants were instructed to "walk from end to end of the corridor at your own pace, in order to cover as much ground as possible." Each minute, the investigator encouraged the participants with standardized statements. Participants were allowed to stop and rest during the test but were instructed to resume walking as soon as they were able to do so. During the test, cardiac rhythm was continuously monitored by a wireless electrocardiogram (ECG) monitor (EC-12RS; Labtech, Debrecen, Hungary). On exercise cessation, the distance walked was determined and peak heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), and perceived exertion scores using a modified Borg scale were recorded.

SWT Patients performed the SWT as established by Singh et al.[6] The SWT was performed in an enclosed corridor on a 10-m-long course identified by 2 cones set 0.5 m from either end to avoid the need for abrupt changes in direction. The speed at which patients walked was dictated by an audio signal played on compact disc (CD) originally generated from a CD player. The start of the test was indicated by a triple beep. Thereafter, the CD emitted a single beep at regular intervals, at which point the subject's goal was to be at the opposite end of the course; that is, when the patient heard the signal he or she should have been rounding the cone to proceed back down the course to the start. The initial walking speed was set at 0.50 m/s; the speed for the next level was increased each minute by 0.17 m/s. A change in speed to the next level was indicated by a triple beep. The operator sat alongside the course and no encouragement was given; the only verbal contact was the advice given each minute to increase the walking speed slowly. The test was stopped when the patient was not able to maintain the required speed. Patients were continuously monitored by a wireless ECG monitor. After the test, the number of completed shuttles was recorded and the total distance walked was computed. Peak HR, SBP, DBP, modified Borg scale score, and reason(s) for test termination were also recorded.

CPET Assessment of $p\dot{V}O_2$ and $\dot{V}O_2$ at AT All patients were properly screened for possible safety concerns, and during all tests, a physician was readily available. Workload was increased on a bicycle ergometer (Aerobike 75XLIII; Combi Wellness, Tokyo, Japan) using a ramp protocol (10–20 W/min) that was individually selected for each patient. Protocol selection was then minimally adjusted based on health status, current level of activity, and previous exercise test performance. Patients exercised to volitional fatigue or until they demonstrated one of the safety-related termination criteria set by the exercise laboratory. A test was considered satisfactory when a patient exceeded a respiratory exchange ratio of >1.05, a rating of 9 or 10 out of 10 on the modified Borg scale, or both. Given that a mouthpiece was used during testing, patients were given instructions on how to describe symptoms through hand signals, but were encouraged to exercise until volitional fatigue or until they demonstrated one of the safety-related termination criteria set by the laboratory. BP was measured manually at 2-min intervals throughout the exercise period and recovery. Oxygen saturation (SpO_2) was measured continuously using a finger

Table 2. Clinical Characteristics

Parameter	Data
Age (years)	53.3±13.1
Sex	
Female	15
Male	4
Height (cm)	157.2±7.5
Weight (kg)	50.4±8.4
Dana Point classification	
Idiopathic	9
Associated with connective tissue diseases	10
WHO classification	
II	5
III	14

Data given as mean±SD or n.
WHO, World Health Organization

Table 3. Baseline Hemodynamics

Resting Hemodynamics	Data
Heart rate (beats/min)	
Before CPET	77.2±11.1
Before 6MWT	77.0±10.1
Before SWT	74.9±9.3
SBP (mmHg)	
Before CPET	116.9±13.5
Before 6MWT	118.6±14.7
Before SWT	118.2±14.5
DBP (mmHg)	
Before CPET	72.9±8.2
Before 6MWT	74.6±8.2
Before SWT	74.8±8.8
Oxygen saturation (%)	
Before CPET	95.8±2.9
Before 6MWT	95.9±2.9
Before SWT	95.9±3.0

Data given as mean±SD.
6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; DBP, diastolic blood pressure; SBP, systolic blood pressure; SWT, shuttle walk test.

sensor (WristOx2; Nonin Medical; Plymouth, MN, USA). Twelve-lead ECG was continuously monitored through the wireless exercise ECG system (EC-12RS) with Mason-Likar ECG electrode placement. During testing, breath-by-breath ventilation was analyzed with a metabolic cart (Aero Monitor AE-310S; Minato Medical Science, Osaka, Japan). $pV\dot{O}_2$ was measured as the highest 20-s average of $V\dot{O}_2$ at peak exercise. AT was calculated using the Veq-CO_2 method, which has been validated in patients with congenital heart disease.[11]

Categorization of Exercise Tests

A cardiologist reviewed each exercise test for any signs of arrhythmia and ischemia, and then summarized them into Smith categories: arrhythmia, ST-segment depression, oxygen desaturation, and symptoms (Table 1).[12] Within each category, the severity of the responses was graded on a scale of 0 to 3: 0, non-significant; 1, mild; 2, moderate; and 3, severe.

Statistical Analysis

Group data are presented as mean±SD. Differences among measured parameters were determined using paired t-test. Pearson's product-moment correlation coefficient (r) was used to detect correlations between criterion variables. The level of statistical significance was set at $P<0.05$. To explore the relation between $pV\dot{O}_2$ and potential predictor variables, candidate variables were assessed using univariate and multivariable regression. For the final statistical model, goodness-of-fit was assessed by calculating both the explained variance (R^2), and by plotting the residuals. The residuals followed an approximate normal distribution. A forwards stepwise model-building process was used to identify the best set of predictor variables using routinely collected data, including demographics data and distance walked. Statistical analysis were performed using IBM SPSS statistics for Windows version 20 (IBM, Armonk, NY, USA).

Results

Subjects

Nineteen patients (4 men and 15 women) were recruited and completed the study. Mean anthropometric data and clinical data are listed in Table 2. There were no significant differences between the resting physiological parameters of CPE, 6MWT, and SWT (Table 3). Almost all patients had received multiple-drug therapy (Figure 1). Peak HR and peak SBP were significantly higher during CPET and SWT than during 6MWT (Table 4). Mean 6MWT walking distance was significantly greater than SWT walking distance (539.4 m vs.432.7 m). Peak work rate of exercise during CPET was 67.5±32.6 W and maximum exercise duration was 8.4±3.4 min. Perceived dyspnea score was significantly higher at the end of CPET (6.6±2.0) than at the end of 6MWT (4.2±2.8) or SWT (4.8±2.7).

Walk Tests vs. CPET

Symptom-limited maximum exercise capacity was significantly reduced (mean $pV\dot{O}_2$ =15.4±3.2 $ml \cdot kg^{-1} \cdot min^{-1}$ or lower) in patients with PAH compared to the standard values for healthy subjects (Table 4). According to the Weber classification,[13] 7 patients were considered to be in class A or B (ie, $pV\dot{O}_2$ ≥16 $ml \cdot kg^{-1} \cdot min^{-1}$), 11 in class C ($pV\dot{O}_2$, 10–16 $ml \cdot kg^{-1} \cdot min^{-1}$), and 1 in class D ($pV\dot{O}_2$, 6–10 $ml \cdot kg^{-1} \cdot min^{-1}$). Similarly, $V\dot{O}_2$ at AT was severely reduced, with a mean of 11.0±1.7 $ml \cdot kg^{-1} \cdot min^{-1}$ (Table 4). Exercise tests were stopped for general fatigue (53%), leg fatigue (36%), or dyspnea (11%). The correlation coefficient for physiological responses in CPET and SWT was higher than that for CPET and 6MWT. The relationship between the distances walked in each walk test vs. $pV\dot{O}_2$ or $V\dot{O}_2$ at AT is shown in Figure 2. Almost all data points are contained within the 95% confidence interval. Although there was significant correlation between 6MWT walking distance and $pV\dot{O}_2$ ($r=0.765$, $P<0.05$), there was a higher correlation between SWT walking distance and $pV\dot{O}_2$ ($r=0.866$, $P<0.05$). A strong correlation was found between SWT walking distance and $V\dot{O}_2$ at AT ($r=0.775$, $P<0.05$), but the correlation between 6MWT walking distance and $V\dot{O}_2$ at AT was moderate ($r=0.587$, $P<0.05$; Table 5; Figure 2). There was a strong correlation between 6MWT walking distance and SWT walking distance ($r=0.769$; Table 5).

Safety of Exercise Tests

No serious complications were observed in any of the exercise tests performed. No moderate or serious arrhythmia (as defined in Table 1) occurred. One patient experienced mild arrhythmia. Two patients had mild ST-segment depression (as de-

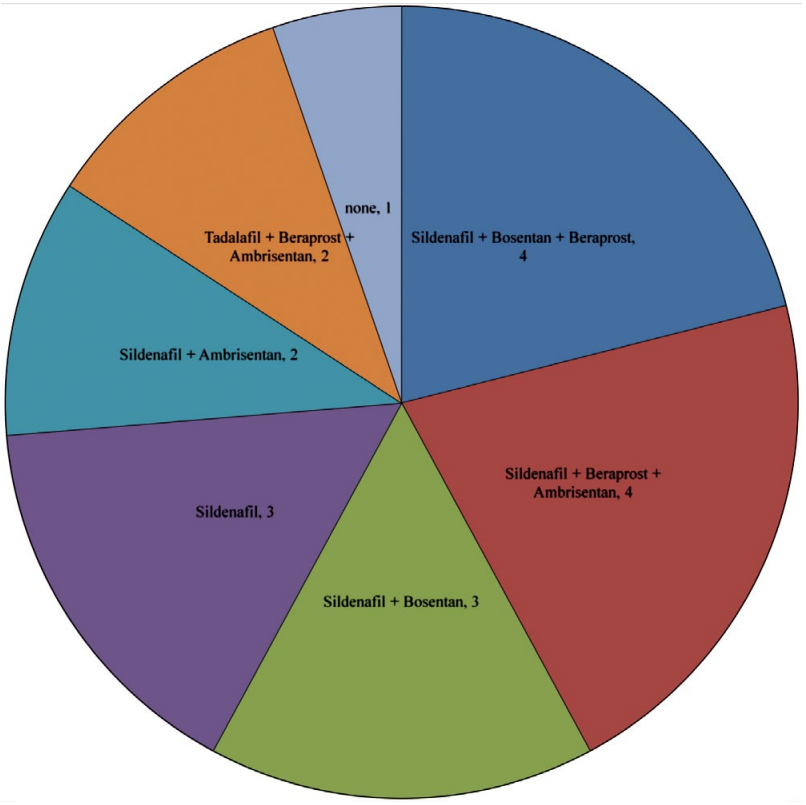

Figure 1. Subject medication. Nearly all patients were receiving multiple-drug therapy.

Table 4. Physiological and Perceptual Responses to Exercise Tests

	CPET	6MWT	SWT
Peak oxygen consumption (ml·kg^{-1}·min^{-1})	15.4±3.2	–	–
Peak oxygen consumption (% predicted)	61.5±10.8	–	–
Anaerobic threshold (ml·kg^{-1}·min^{-1})	11.0±1.7	–	–
Distance walked (m)	–	432.7±78.4§	359.4±151.6*
Peak heart rate (beats/min)	129.6±21.6*	114.7±11.7	128.7±21.3*
Peak SBP (mmHg)	140.6±17.1*	130.1±18.6	136.5±16.6*
Peak DBP (mmHg)	78.6±15.0	81.1±13.0	84.5±11.0
Oxygen saturation at peak exercise (%)	90.2±8.7	90.7±6.8	89.1±7.2
Perceived exertion (modified Borg scale)	6.6±2.0*§	4.2±2.8	4.8±2.7

Data given as mean±SD. *P<0.05 for differences between 6MWT; §P<0.05 for differences between SWT. Abbreviations as in Table 3.

fined in Table 1) during CPET. No symptoms were reported by any patients during the exercise tests. A decrease in SpO_2 to <85%, or a 10% absolute decrease from baseline, was experienced by 3 patients (16%) during CPET, 3 patients during 6MWT, and 3 patients during SWT. There were no significant adverse events such as syncope, chest pain, dizziness, or other symptoms.

Multivariate Analysis

On multivariate analysis including demographic data (WHO classification and patient age, height, and weight), hemodynamic data, and distance walked during each walk test, only walking distance was independently predictive of $p\dot{V}O_2$ and $\dot{V}O_2$ at AT. The calculated regressions are as follows: $p\dot{V}O_2$= 0.029×6MWT distance walked+2.735 (P<0.05, R^2=0.585); $p\dot{V}O_2$=0.017×SWT walking distance+9.364 (P<0.05, R^2=0.723); $\dot{V}O_2$ at AT could be estimated as: $\dot{V}O_2$ at AT=0.012×6MWT walking distance+5.960 (P<0.05, R^2=0.344); $\dot{V}O_2$ at AT=0.008× SWT walking distance+8.225 (P<0.05, R^2=0.627; Table 5). The deviation of data points for $p\dot{V}O_2$-SWT from the regression line was significantly smaller than the deviation of data points for $p\dot{V}O_2$-6MWT from the regression line (P<0.05). Similarly, the deviation of data points for $\dot{V}O_2$ at AT-SWT from the regression line was significantly smaller than the deviation of data points for $\dot{V}O_2$ at AT-6MWT from the regression line (P<0.05).

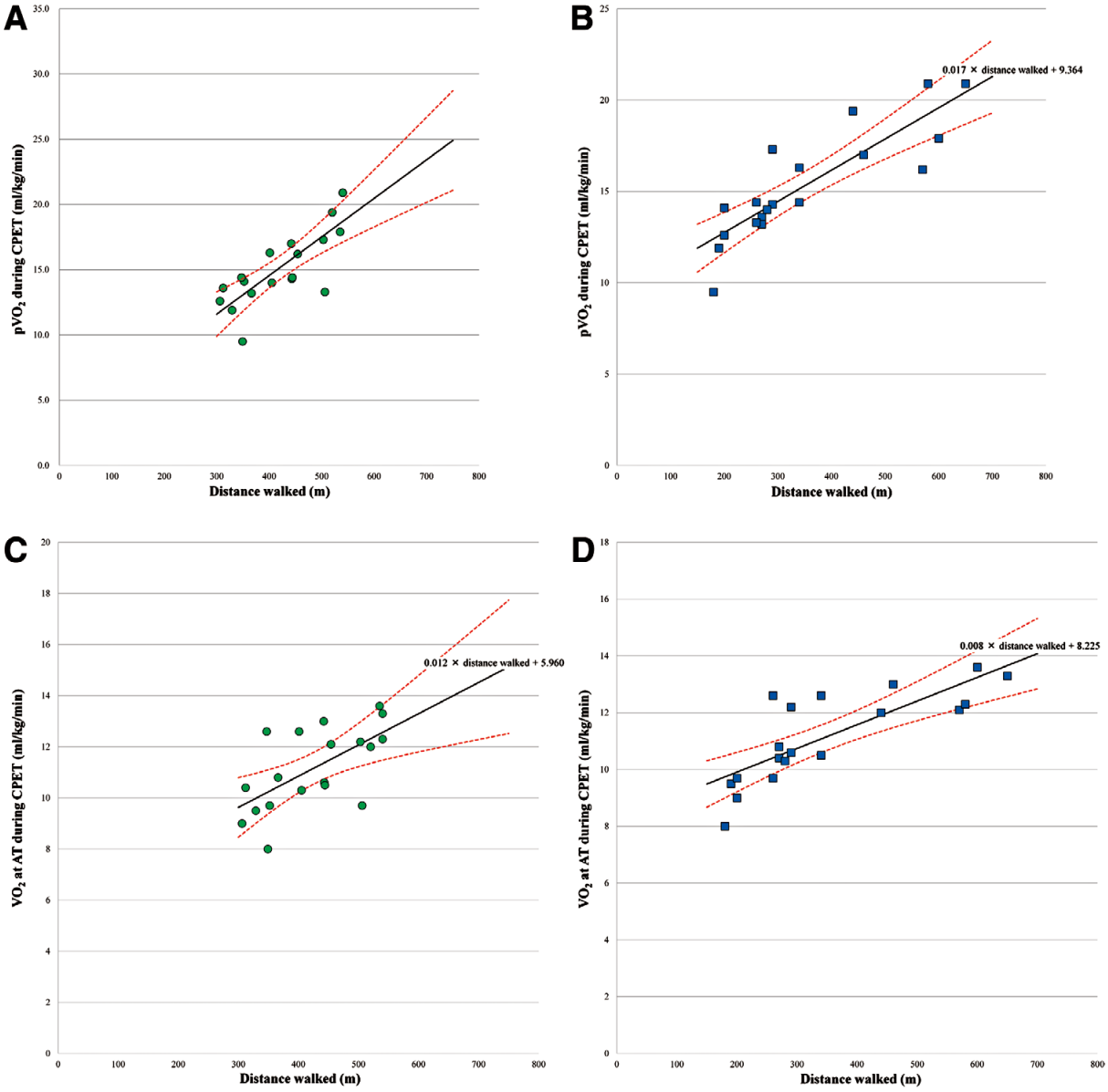

Figure 2. Relationship between (**A**) distance walked in 6-min walk test (6MWT) vs. peak oxygen consumption (pV̇O2); (**B**) distance walked in the shuttle walk test (SWT) vs. pV̇O2; (**C**) distance walked in 6MWT vs. oxygen consumption at anaerobic threshold (V̇O2 at AT); and (**D**) distance walked in SWT vs. V̇O2 at AT. There was a higher correlation between pV̇O2 and SWT walking distance than between pV̇O2 and 6MWT walking distance. There was a higher correlation between V̇O2 at AT and SWT walking distance than between V̇O2 at AT and 6MWT walking distance. Solid line, regression of pV̇O2 or of V̇O2 at AT calculated from each walk test; broken lines, 95% confidence intervals.

Table 5. Comparison Between 6MWT and SWT

	6MWT	SWT
Correlation coefficient (r)		
Between distance walked and pV̇O2	0.765	0.866
Between distance walked and V̇O2 at AT	0.587	0.775
Coefficient of determination (R^2)		
Between distance walked and pV̇O2	0.585	0.723
Between distance walked and V̇O2 at AT	0.334	0.627

Abbreviations as in Table 3.

Discussion

This study investigated whether the SWT, an objective, externally paced and easily standardized field test, is a better predictor of exercise capacity in patients with PAH. In chronic obstructive pulmonary disease or CHF patients, it has previously been reported that SWT is a better predictor of $p\dot{V}O_2$ than is 6MWT;[9,14–16] but it was not known if this would also be the case for patients with PAH. The present results show that SWT provides a valid index of functional capacity in patients with PAH that is more predictive than 6MWT of $p\dot{V}O_2$ and of $\dot{V}O_2$ at AT. Despite its incremental nature, SWT was also determined to be as safe as 6MWT.

Exercise Tolerance of PAH Patients

PAH is a progressive disease caused by small pulmonary artery obstruction from vascular proliferation and remodeling. PAH is characterized by elevated pulmonary arterial pressure and increased pulmonary vascular resistance, frequently leading to right-sided heart failure and death.[17] The increased right ventricular work eventually causes pulmonary hypertension (PH) at rest, at which time cardiac catheterization and/or echocardiography is needed to establish the diagnosis and to grade severity. CPET with gas exchange has the potential to allow non-invasive grading of the severity of exercise limitation, quantification of hypoperfusion of the lungs and systemic circulation, and assessment of responses to therapy[1,18,19] before right ventricular failure and PH are evident at rest. $p\dot{V}O_2$ assesses a subject's maximum work capacity and the maximum ability of the circulatory system to increase cardiac output. In PAH, this relates to pulmonary vasculopathy, which limits blood flow through the lungs (and thus throughout the body). $\dot{V}O_2$ at AT, which describes the highest $\dot{V}O_2$ that the patient can sustain without developing lactic acidosis, appears to be an independent marker of PAH severity.[1] In this study, $\dot{V}O_2$ at AT could be predicted from SWT more accurately, which suggests that SWT can be used to assess the severity of PAH more accurately than can 6MWT. CPET has great potential for evaluating patients with dyspnea and fatigue safely, reproducibly, and non-invasively.[20,21] It may become as useful in assessing the prognosis of PAH patients as it has been in patients with CHF,[20] or it may be used to prioritize patients for lung transplantation and to evaluate drug therapy.[18,19]

Risks of Exercise Testing in PAH Patients

Exercise testing has been widely used as a valuable means of quantifying functional capacity in a variety of patient groups. The amount of exercise data for patients with PAH, however, is limited due to the risk of developing cyanosis, syncope, and arrhythmia during exercise. Patients with PAH may also be at greater risk of complications during exercise, which may result in oxygen desaturation, syncope, or death. Therefore, data on patients with PAH undergoing exercise testing is understandably sparse because of safety concerns regarding such tests. To investigate the safety of exercise tests in these patients, we recorded the incidence of complications, including ECG changes (in particular, ST-segment changes), SpO_2, and patient-reported symptoms. Analysis of the categories related to patient safety showed that there were no severe complications related to arrhythmia or ST-segment changes during any of the tests. As expected, a moderate decrease in SpO_2 at peak exercise was found in 3 patients. Despite the frequency of desaturation with exercise, no severe complications, such as syncope, severe dizziness, or chest pain, were found.

Exercise capacity was lower for the PAH patients in the present study than what is expected from healthy, normal controls. Previous studies have outlined the specific exercise limitations of patients with PAH, including decreased pulmonary blood flow, ventilation-perfusion mismatching, and decreased adenosine triphosphate regeneration, which lead to impaired muscle contraction and dyspnea during exercise.[1] These limitations were evident from the lower $p\dot{V}O_2$ and $\dot{V}O_2$ at AT in the current study.

Advantages of SWT Over 6MWT for PAH Patients

Although the number of patients in this study was limited, the low incidence of arrhythmia and absence of significant ST-segment depression suggest that SWT and CPET are safe, functional tests for PAH patients. The main drawback of CPET is that it is difficult to perform on a daily basis without expensive equipment and highly trained testing personnel, but a simple walk test can be used routinely and safely with these patients. The current standard for assessing exercise capacity in PAH is the 6MWT; clinical trials in Japan have adopted the 6MWT as the primary endpoint.[22,23] The 6MWT, however, is time-limited, which may constrain its validity as a true measure of exercise capacity. According to the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study, when the dose of sildenafil increased, the mean pulmonary artery pressure decreased significantly.[24] There was no evidence, however, of a dose-response relationship associated with 6MWT walking distance in the SUPER study. This result has raised controversy about the reliability of the 6MWT.[24] Assessment of exercise tolerance requires both simplicity and accuracy. The present data show that peak SBP and HR were higher during SWT than during 6MWT (**Table 4**). The correlation coefficients for physiological responses ($p\dot{V}O_2$ and $\dot{V}O_2$ at AT) in CPET and SWT were higher than those for CPET and 6MWT (**Table 5**). Moreover, in multivariate analysis, the coefficient of determination for physiological responses in CPET and SWT was clearly higher than that for CPET and 6MWT (**Table 5**). This indicates that SWT can more accurately measure exercise tolerance. Based on these findings, it may be appropriate to use the SWT as an exploratory endpoint in a large-scale clinical trial on PAH to prospectively assess its diagnostic and prognostic value.

Study Limitations

The limitations of the present study include the following. First, the sample size was relatively small, but the statistical significance of the data reported here deserves consideration. Second, the results may be extrapolated only to patients who present with a well-preserved functional capacity (WHO II or III); future studies should include a broader sample base. Third, recent data from echocardiography and cardiac catheterization were not available for comparison with the present data. Future studies may also determine whether the present results are also applicable to more functionally compromised PAH patients, especially those with worsening health status as represented by those measures.

Conclusions

SWT can be performed safely in patients with PAH. SWT generates data that allow reliable prediction of $p\dot{V}O_2$ and of $\dot{V}O_2$ at AT, the gold standard for exercise tolerance assessment. In addition, SWT has the advantage of being a symptom-limited and externally paced test. It also has a progressive structure and no time limitation, similar to CPET. The present findings suggest that SWT is a better reflection of exercise

tolerance in PAH patients than is 6MWT, and is a preferable alternative assessment of exercise tolerance in PAH patients.

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Disclosures

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