Journal of
Clinical Respiratory Diseases and Care

Scharf et al., J Clin Respir Dis Care 2019, 5:1

Research Article Open Access

The Incremental Shuttle Walk Testing (ISWT) in Patients with Pulmonary Hypertension (PH): Assessment of Safety According to W.H.O. Functional Class and Etiology

Michael Leonard Scharf[1*] **and Sidharth Bagga**[2]

[1]*Department of Medicine, Pulmonary Vascular Disease Program, Division of Pulmonary, Allergy and Critical Care Medicine Jane & Leonard Korman Respiratory Institute, Thomas Jefferson University, Philadelphia, Pennsylvania, USA*

[2]*Oroville Hospital, Oroville, California, USA*

***Corresponding author:** Michael Leonard Scharf, Department of Medicine, Pulmonary Vascular Disease Program, Division of Pulmonary, Allergy and Critical Care Medicine Jane & Leonard Korman Respiratory Institute, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, Tel: 2159556591; E-mail: michael.scharf@jefferson.edu

Received date: February 07, 2019; **Accepted date**: February 25, 2019; **Published date:** March 03, 2019

Abstract

Purpose: The 6 minute walk test used to evaluate patients with PH has many limitations. The ISWT, an automated progressively incremental and more physically demanding exercise test, has been useful to assess exercise tolerance in patients with severe COPD. Its application in patients with PH and particularly, pulmonary arterial hypertension (PAH) raises the concern of eliciting cardiovascular complications during testing. We wished to evaluate the safety of ISWT in patients with PH.

Methods: A retrospective review was performed on patients with RHC-confirmed PH who had undergone outpatient ISWT, predominantly those with W.H.O. FC II and III. Eighty-four ISWTs from 46 patients were assessed according to W.H.O. functional class (FC), echocardiogram, minute distances walked, pulse oximetry, BORG dyspnea scores and fatigue, blood pressure, heart rate and adverse events.

Results: A total of 21 adverse events were reported from the 84 ISWT performed as follows: Two patients - angina, 1 - worsening dyspnea, 12 - locomotor difficulties including leg and joint pain, and 6 - lightheadedness. There were no deaths or sustained adverse events after the ISWT. There were no documented episodes of syncope or tachyarrhythmia's even in patients with right ventricular dysfunction.

Conclusions: Performance of ISWT appears to be safe in stable outpatients with PH and right-sided heart disease as an assessment of the functional capacity in the PH population and should be included in future clinical trials to assess whether it may provide a meaningful assessment of patient exercise tolerance. Its limitations are similar to those shared by the 6 minute walk and include locomotor difficulties.

Keywords: Six minute walk test; Incremental shuttle walk test; Exercise testing; Pulmonary hypertension

Introduction

The 6 minute walk test (6MWT) represents the traditional way in which most PH specialists objectively assess exercise capacity in their patients [1]. The test is inexpensive, relatively safe for the patient, requires little patient instruction and may be conducted by a non-physician [2].

Distance walked in six minutes has been correlated with prognosis in idiopathic PAH [3,4] and the FDA utilizes distance walked as a primary endpoint in determining approval for PAH-specific medications [5].

However, the 6MWT has its limitations. Several factors, including patient age, gender, height, and weight [2], make it difficult to establish a normal range of distance walked for an individual patient.

Moreover, distance walked during the 6MWT may be influenced by patient effort, particularly in patients who are only mildly impaired, i.e., W.H.O. functional class (FC) I and II [6-10] in whom, there may be a "Ceiling Effect" [11]. In fact, the most recent American Heart Association guidelines on exercise stress testing advocated against time-based walk tests to assess exercise tolerance, such as the 6MWT and instead, advocated exercise treadmill (ETT) and cardiopulmonary exercise stress testing [6].

The incremental shuttle walk test (ISWT) first described by Singh et al. [12], shown to be useful in evaluating exercise capacity in patients with chronic heart failure and COPD [12-14], may represent another clinically applicable way in which to evaluate exercise capacity in patients with pulmonary hypertension (PH).

At the time of our preliminary report, ISWT had not previously been well-studied in PH patients [15]. Subsequently, there has been interest in the ISWT in PAH [16,17].

During an ISWT, the patient shuttles back and forth between two points separated by a short distance according to timed auditory prompts set at a progressively incremental pace until the patient is too breathless to continue or cannot keep up the required pace. No verbal minute by minute communication is given to the patient and the

patient may not stop or adjust their pace to their level of comfort, features distinguishing the ISWT from the 6MWT.

Disadvantages of the ISWT include greater potential for cardiovascular problems. The exercise pace may become quite rapid and rigorous. Hodgev et al. showed in COPD patients a greater increase in heart rate and systolic blood pressure at the end of ISWT compared to 6MWT [18].

While shown to be safe and useful in COPD and chronic stable heart failure populations, we were concerned that this more demanding level of exercise may place PH patients at greater risk for sudden death, myocardial ischemia, lightheadedness and syncope [13].

We wished to determine if the ISWT might be a safe alternative to the 6MWT to evaluate exercise capacity in patients with W.H.O. Group 1, 4 and 5 PH. We present our retrospective experience using ISWT to assess exercise tolerance in this population. We believe this represents the first such assessment of the ISWT in this patient population.

Methods

We retrospectively reviewed the records of all patients with W.H.O. Groups 1, 4 and 5 PH who had undergone an ISWT between March 2009 and December 2010 as part of their routine visits in our PH outpatient practice. A total of 46 patients with right heart catheterization-confirmed W.H.O. Group 1, 4 and 5 PH were included in the study and underwent data analysis.

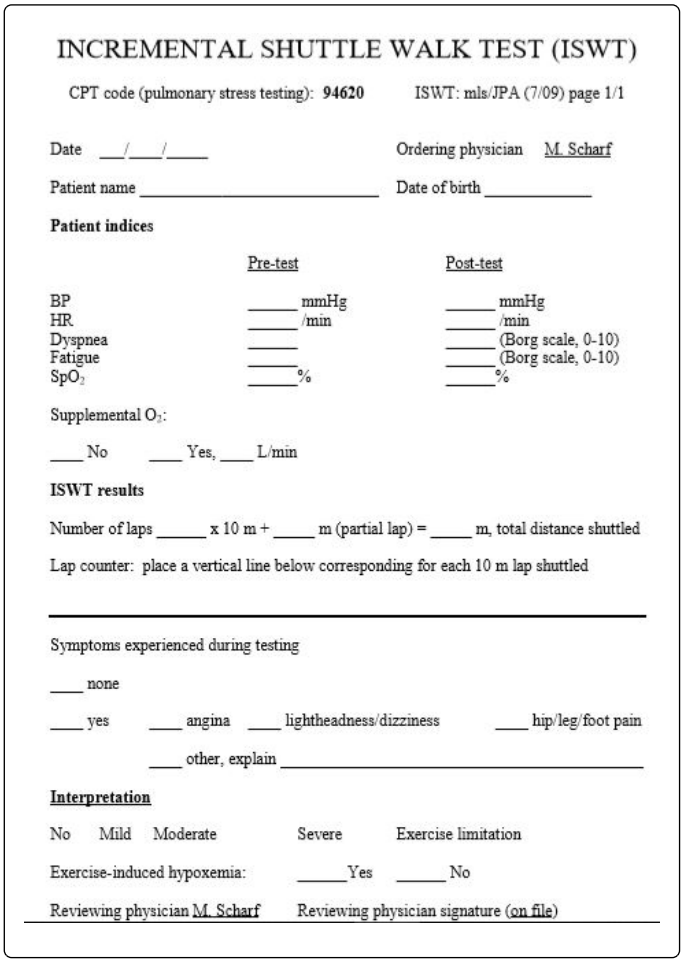
These patients underwent a total of 84 IWSTs. Patients evaluated were males and females between the ages of 25 and 84, seen at scheduled routine visits in our pulmonary vascular medicine outpatient practice. Patients unable to perform testing due to musculoskeletal pain, gait impairment, visual impairment or unwillingness did not undergo ISWT and were therefore, excluded from the data analysis. All ISWTs were performed with patients in stable condition, according to a standardized protocol described by Singh et al. [12].

Accordingly, after a brief instruction and demonstration of a single shuttle lap, the patients shuttle back and forth between 2 cones, nine meters apart in a flat hallway. The pace of the shuttles progressively increases according to shorter time intervals between pre-programmed auditory prompts, until the patient becomes either too breathless to continue or cannot reach the cone before the next prompt.

Testing was administered by a nursing assistant with a physician on site. Patients were allowed to use a cane or walker and oxygen by nasal prongs, according to their usual outpatient use.

At the time of testing, we collected data on a sheet modified after the ATS six minute walk test schedule (Figure 1), resting and post-test data including W.H.O. Functional Class (FC), pulse oximetry, Borg fatigue and dyspnea scores, blood pressure and heart rate. We recorded the interpretation of the most recently performed echocardiogram recorded. We rated RV dysfunction rated as either present or absent, based upon the description of the interpreting echo cardiographer who was un-blinded to the PH diagnosis, but unaware of the type of exercise testing conducted.

Post-procedure, we routinely asked subjects their reasons for stopping the test. These recorded responses included dyspnea, fatigue, chest pain, lightheadedness, dizziness, and musculoskeletal discomfort. We observed subjects for gait instability, routinely recorded, when present. The Thomas Jefferson University Institutional Review Board approved the study design and data collection. The study was exempted from the need for an informed consent.



INCREMENTAL SHUTTLE WALK TEST (ISWT)

CPT code (pulmonary stress testing): **94620** ISWT: mls/JPA (7/09) page 1/1

Date ___/___/_____ Ordering physician M. Scharf

Patient name _____ Date of birth _____

Patient indices

	Pre-test	Post-test
BP	_____ mmHg	_____ mmHg
HR	_____ /min	_____ /min
Dyspnea	_____	_____ (Borg scale, 0-10)
Fatigue	_____	_____ (Borg scale, 0-10)
SpO_2	_____%	_____%

Supplemental O_2:

____ No ____ Yes, ____ L/min

ISWT results

Number of laps _____ x 10 m + _____ m (partial lap) = _____ m, total distance shuttled

Lap counter: place a vertical line below corresponding for each 10 m lap shuttled

Symptoms experienced during testing

____ none

____ yes ____ angina ____ lightheadness/dizziness ____ hip/leg/foot pain

____ other, explain _____

Interpretation

No Mild Moderate Severe Exercise limitation

Exercise-induced hypoxemia: _____Yes _____ No

Reviewing physician M. Scharf Reviewing physician signature (on file)

Figure 1: Incremental Shuttle Walk Test (ISWT).

Results

As a group, patients were often late middle-aged overweight women, as commonly seen in the IPAH population, with normal vital signs and Borg scores at rest. Baseline patient characteristics (Table 1) show an average age of 61 years (range: 25-84).

Females performed 69.5% of all ISWTs. Average resting HR (77 bpm) and systolic blood pressures (129 mmHg) were within the normal range. Borg dyspnea and fatigue scores at rest were 0.87 and 1.22, respectively.

Characteristics	Number (Range)
Age (years)	60.9 (25-84)

Male (# ISWT)	25
Female (# ISWT)	59
BMI	31.9 (21-48)
Borg Dyspnea	0.87 (0-4)
Borg Fatigue	1.22 (0-3)
HR (bpm)	76.9 (45-125)
SBP (mmHg)	128.7 (86-146)

Table 1: Patient characteristics at rest.

Table 2 shows the 84 ISWTs performed, FC II and III patients are accounted for 81% of tests performed and illustrates the statistically significant differences in exercise tolerance seen between those in FC I and more advanced functional classes.

Greater impairment of exercise tolerance was reflected in the decreased distance walked associated with advancing FC.

Vital signs pre- and post-exercise reflected exercise tolerance across the FC; those of lower FC were able to augment their HR and MAP greater than those with more advanced FC.

Changes in Borg dyspnea and fatigue scores were similar across all functional classes. RV dysfunction was present commonly: - FC I-II (50%) and FC III-IV (69%) – in 60% of all ISWTs completed.

W.H.O. FC	**I**	**II**	**III**	**IV**
Total number ISWT	8	34	34	8
RV dysfunction present	4	17	23	6
Avg. distance (meters)	438.8	284.3	149.7	82.1
Avg. HR increase (bpm)	33	24.8	20.8	19.3
Avg. MAP increase (mmHg)	5.6	6.8	5.4	0.4
Avg. Borg dyspnea	2	2.9	3	2.6
Avg. Borg fatigue	0.8	2	1.9	1.4
Note: P<0.05 Unpaired t-Test: FC I-II, III-IV, Avg. distance walked, W.H.O. FC I-III, Avg. HR increase W.H.O. FC I-II, I-III, I-IV, Avg. Borg dyspnea score and W.H.O. FC I-II, Avg. Borg fatigue score.				

Table 2: Relationship between functional class, RV dysfunction and exercise outcomes.

Etiology PH	**Idiopathic**	**Limited scleroderma**	**Other CTD**	**POPH**	**Toxin**	**Others**
Total ISWTs	24	12	11	8	5	25
RV dysfunction present	20	6	4	6	4	11
Avg. dist. shuttle walked	231.46	140	225.91	291.25	208	276
Avg. HR increase	29.55	4.9	29.27	15.25	30.25	25.79
Avg. MAP increase	9.64	2.96	3.58	6.67	7.25	3.84
Avg. BORG dyspnea increase	2.95	3.94	3.45	1.63	1.25	3.25
Avg. BORG fatigue increase	1.64	2.33	2.82	0.88	1.25	1.84
Note: Others included HIV (n=2), hemolytic anemia (n=6), antiphospholipid syndrome (n=2), and splenectomy (n=2)						

Table 3: Exercise response according to etiology of PAH.

Table 3 describes the ISWTs according to etiology of PH. Idiopathic PAH, limited systemic scleroderma and other connective tissue diseases accounted for 54% of ISWTs performed.

Although findings for different etiologies of PH were not very different compared to the whole, limited scleroderma patients more commonly had RV dysfunction (50%) and averaged only 140 meters during exercise testing.

In addition to a lesser distance shuttled, as a group they had a greater post-exercise increase in Borg scores (fatigue 2.33 and dyspnea 3.94), and lesser hemodynamic response to exercise (average HR change 4.9 bpm, average MAP change 2.96 mmHg) compared to other the groups.

Table 4 shows adverse events based on FC and etiology of PH. For all etiologies, the group with CTD (limited scleroderma, other CTDs) and IPAH had the highest absolute number of adverse events, including locomotor difficulties (stumbles, near falls).

Adverse events were higher in the IPAH group of patients. Those with a more advanced FC had more adverse events, shown to be statistically significant between W.H.O. FC IV and all other functional classes. FC I-II accounted for 50% of testing and yet, in only six instances had an adverse event. FC III-IV also accounted for 50% of testing, associated with 16 adverse events.

	Adverse Events by W.H.O. FC				
Etiology of PAH	**1 (n=8)**	**2 (n=34)**	**3 (n=34)**	**4 (n=8)**	**Total (84)**
CTD (23)	-	3	2	3	8
Idiopathic (24)	-	-	5	3	8
Toxin (5)	-	-	1	1	2
CTEPH (2)	1	-	-	-	1
POPH (8)	1	1	-	-	2
Haemolytic Anaemia (6)	-	-	1	-	1
Total	2	4	9	7	22
Note: (n=number of ISWTs); (#=number ISWTs according to etiology of PH) P<0.05 Unpaired t-Test: W.H.O. FC I-IV, II-IV and III-IV.					

Table 4: Number of adverse events according to W.H.O. FC and etiology of PH.

Hypoxemia associated with performance of the ISWT, defined as greater than or equal to 4% decline in pulse oximetry, occurred commonly in 8 of the 22 ISWTs associated with an adverse event (2.57% average decline) and in 22 of the 62 ISWTs unassociated with an adverse event (4.78% average decline).

Discussion

Our findings indicate that the ISWT appears to be a safe method in which to assess exercise tolerance in patients with PH even in those with advanced W.H.O. functional class or RV dysfunction. At the time of our study, the IWST had not been utilized on a large patient PH population. Subsequently, the IWST has been employed in PH studies [16,19] findings and those of Billings, et al. and Mainguy et al. suggest that the ISWT may be worthy of consideration as an alternative to the 6MWT in this patient population.

Although the 6MWT is performed in a standardized fashion, it has several potential limitations [20]. A standard script should be utilized to prevent technician's instructions or encouragement from affecting a patient's effort. However, the Schoindre et al. observed that in some cases, those conducting the 6MWT may fail to adhere to the script resulting in aberrant distances reported often at odds with the clinical scenario. Among individual patients there may be wide swings in distance walked even on a particular day depending upon the individual's perception of the conductor's instruction. For example, an individual may walk more slowly and cautiously because he/she has been told. You will probably get out of breath or become exhausted [21].

After changing our office location, we discovered that we had no longer had a 30 meter straight hallway to conduct a 6MWT. From a practical standpoint, often physicians' offices may not have available the prescribed space available for regular use for testing. Patients often need to be directed to the hospital's pulmonary function lab for testing. For the PH population of the chronically ill and dyspneic, regular exercise testing and physician office visits at two separate sites may be cumbersome and exhausting.

Using the 6MWT in all populations is not ideal and may be particularly unreliable in the pediatric population and with various disease states [22]. In the pediatric pulmonary hypertension population, Lammers et al. found that although there existed a good correlation of 6MWT distance and VO*2* max when walk distance measured less than 300 meters, this was not the case was seen when walk distance exceeded 300 meters [23]. Takken et al. concluded that the 6MWT ought not to replace the maximal stress test in children [24]. In patients with PAH due to scleroderma, musculoskeletal limitations rather than dyspnea may significantly reduce the distance walked in the 6MWT [25].

Although the 6MWT does well in predicting disease progression and survival, it is not sensitive to interval smaller changes in functional status [26]. Redelmeier et al. has shown that changes in distance walked by persons with stable COPD are poorly associated with an individual's subjective lessening of dyspnea [27]. For patients with

minimal functional impairment, measures other than 6MWT may be more meaningful. Frost et al. demonstrated the so-called "ceiling effect" in which individuals with better FC were less able to a show a treatment effect based upon distance walked in the 6MWT [11]. A recent study of a single clinical trial suggested that a minimally important difference in 6MWT of a 33 meter improvement corresponded to a patient-reported treatment response [28]. However, a study including multiple placebo-controlled randomized clinical trials by Gabler et al. found that the 6MWT distance walked may not explain the treatment effect and concluded that the 6MWT has only "modest validity as a surrogate end point for clinical events, and may not be a sufficient surrogate end point". Previous studies of complete cardiopulmonary exercise testing with exhaled gas measurement in IPAH have shown it to be a generally safe and reproducible test [18,26,29]. Unfortunately, exercise equipment with ergometers and expired gas analyzers may not be routinely available in an office setting. When available, testing requires close supervision by an ACLS-certified physician and BLS-certified technician(s), both with special knowledge and training to direct such testing [20]. Although cardiopulmonary exercise testing has been found to be safe and reproducible in studying IPAH and to predict survival in IPAH patients, the study by Wensel et al. excluded patients deemed unfit for such testing and the study by Hansen, et al. did not describe the W.H.O. Group of PAH studied [26,29]. Limited use in an office setting with unknown response in patients with poor functional status suggests that exercise testing with exhaled gas measurement may not be the ideal way to assess PH patients for functional impairment.

Ambulatory testing has limitations regarding patient effort and external encouragement. The ATS has suggested standard specifications to help eliminate this bias [20]. Adherence to the strict scripts and guidelines presented by ATS in testing may be inconsistent amongst the various operators responsible for performing the testing. When originally developing the ISWT, Singh et al., paid particular attention to limit bias related to technician encouragement [12]. The ISWT only prompts the patient via a series of auditory prompts and after the instructions are given to the patient, requires no verbal cues from the technician.

The ISWT has been found to provide a safe and informative way in which to assess exercise tolerance in patients with COPD [12]. A study of exercise tolerance in patients with COPD by Singh et al. showed a strong correlation between VO_2 max and distance walked during an ISWT [30]. The ISWT was found to generate a similar distance walked compared to the 6MWT in patients studied while recovering from a COPD exacerbation [31]. Fowler showed that the ISWT correlates well with VO_2max during rehabilitation following CABG [32]. Jolly showed the role of the ISWT in an outpatient cardiac rehabilitation setting [33]. Pulz et al. reported strong correlation between distances walked in the 6MWT and ISWT, a greater difference between the two in more functionally impaired subjects with NYHA FC 2-4 CHF [13]. Indeed, the 2014 European Respiratory and American Thoracic Societies Guidelines on field walking tests describe a literature almost solely comprised of the study of ISWT in the COPD population [17].

ISWT also has some limitations. There is concern regarding limited validation, limited use, and increased risk of cardiovascular adverse events. The pace of ambulation during testing can become quite rapid and rigorous. While shown to be safe and useful in selected populations with COPD and heart disease, the safety of performing this more demanding level of exercise in the PAH population had not been studied prior to this report. Many of these patients have complex heart and lung interactions placing them at risk for sudden death and syncope due to acute worsening of right heart failure or arrhythmia.

The locomotor difficulties could be ascribed to pain due to musculoskeletal disease associated with their medical condition and/or leg ischemia. Our study could not make this differentiation.

Conclusion

Our findings showed that ISWT can be performed safely in an office setting with a population of W.H.O. Group 1, 4 and 5 PH patients despite RV dysfunction or advanced W.H.O. FC. Adverse events, when they occurred, were transient and not life-threatening. Although some patients experienced locomotor difficulties, including hip or knee discomfort, there were no recorded falls or injuries. Patients generally tolerated the test well and achieved dyspnea-limited exercise with a rise in HR and BP.

Our study indicates that the ISWT may be performed safely in W.H.O. FC II-IV with relatively little physical space and minimal supervision. In most cases, performance was limited by dyspnea rather than an untoward event or musculoskeletal difficulties. ISWT allowed us to uncover exercise-induced hypoxemia in many cases. This experience should be followed by a prospective investigation of the ISWT compared to the 6MWT as an appropriate assessment of exercise tolerance in patients with advanced W.H.O. FC PH.

References

1. Oudiz Ronald J (2005) The role of exercise testing in the management of pulmonary arterial hypertension. Semin Respir Crit Care Med 26: 379-384.
2. Rich S (2006) The current treatment of pulmonary arterial hypertension: Time to redefine success. Chest 130: 1198-1202.
3. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, et al. (2000) Clinical correlates and prognostic significance of six minute walk test in patients with primary pulmonary hypertension: Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 161: 487-492.
4. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, et al. (2002) Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol 40: 780-788.
5. McLaughlin V, Badesch DB, Delcroix M, Fleming TR, Gaine SP, et al. (2009) End points and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol 54: 97-107.
6. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, et al. (2007) Assessment of functional capacity in clinical and research settings: A scientific statement from the american heart association committee on exercise, rehabilitation, and prevention of the council on clinical cardiology and the council on cardiovascular nursing. Circulation 116: 329-343.
7. Hoeper MM, Oudiz RJ, Peacock A, Tapson VF, Haworth SG, et al. (2004) End points and clinical trial designs in pulmonary arterial hypertension: Clinical and regulatory perspectives. J Am Coll Cardiol 43: 48S-55S.
8. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JGF, et al. (2005) Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: A systematic review. Eur Heart J 26: 778-793.
9. Oudiz RJ, Barst RJ, Hansen JE, Sun XG, Garofano R, et al. (2006) Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. Am J Cardiol 97: 123-126.
10. Gaine S, Gomberg-Maitland M. (2009) Have we found the hidden treasure? Endpoints in PAH trials. Int J Clin Pract 63: 1-3.

11. Frost AE, Langleben D, Oudiz R, Hill N, Horn E, et al. (2005) The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: Demonstration of a ceiling effect. Vascul Pharmacol 43: 36-39.
12. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE, et al. (1992) Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 47: 1019-1024.
13. Pulz C, Diniz R, Alves A, Tebexreni A, Carvalho A, et al. (2008) Incremental shuttle and six-minute walking tests in the assessment of functional capacity in chronic heart failure. Can J Cardiol 24: 131-135.
14. Turner SE, Eastwood PR, Cecins NM, Hillman D, Jenkins S, et al. (2004) Physiologic Response to Incremental and self-paced exercise in COPD: A comparison of three tests. Chest 126: 766-773.
15. Scharf ML, Bagga S (2013) A call to apply the minimal important difference in pulmonary arterial hypertension beyond the flawed 6-minute-walk test. Am J Respir Crit Care Med 187: 659.
16. Mainguy V, Malenfant S, Neyron AS, Saey D, Maltais F, et al. (2014) Alternatives to the six-minute walk test in pulmonary arterial hypertension. PLoS One 9: e103626.
17. Singh S, Puhan MA, Andrianopoulos V, Hernandes N, Mitchell K, et al. (2014) An official systematic review of the european respiratory society/ american thoracic society: Measurement properties of field walking tests in chronic respiratory disease. Eur Respir J 44: 1447-1478.
18. Hodgev VA, Aliman OI, Marinov Bl, Kostianev SS, Mandulova PV, et al. (2003) Cardiovascular and dyspnea response to six-minute and shuttle walk tests in copd patients. Folia Med (Plovdiv) 45: 26-33.
19. CG Billings, JA Hurdman, R Condliffe, Elliot CA, Smoth IA, et al. (2017) Incremental shuttle walk test distance and autonomic dysfunction predict survival in pulmonary arterial hypertension. J Heart Lung Transplant 36: 871-879.
20. ATS/ACCP Statement: Guidelines for the Six-Minute Walk Test (2003) Am J Respir Crit Care Med 166: 111-117.
21. Schoindre Y, Meune C, Dinh-Xuan AT, Avouac J, Kahan A, et al. (2009) Lack of specificity of the 6 minute walk test as an outcome measure for patients with systemic sclerosis. J Rheumatol 36: 1481-1485.
22. Groot JF, Takken T (2011) The six-minute walk test in paediatric populations. J Physiother 57: 128.
23. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, et al. (2011) Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child 96: 141-147.
24. Takken T (2010) Six-minute walk test is a poor predictor of maximum oxygen uptake in children. Acta Paediatrica 99: 958.
25. Impens AJ, Wangkaew S, Seibold JR (2008) The 6-minute walk test in scleroderma--how measuring everything measures nothing. Rheumatology 47: 8-9.
26. Hansen JE, Xing-Guo S, Yasunobu Y, Garafano R, Gates G, et al. (2004) Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. Chest 126: 816-824.
27. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH, et al. (1997) Interpreting small differences in functional status: The six minute walk test in chronic lung disease patients. Am J Respir Crit Care Med 155:1278-1282.
28. Matthai SC, Puhan MA, Lam D, Wise R (2012) The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Cri Care Med 186: 428-433.
29. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, et al. (2002) Assessment of survival in patients with primary PAH: Importance of cardiopulmonary exercise testing. Circulation 106: 319-324.
30. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA (1994) Comparison of oxygen uptake during a conventional treadmill test and the shuttle walk test in chronic airflow limitation. Eur Respir J 7: 2016-2020.
31. Vagaggini B, Costa F, Antonelli S, Simone C, Cusatis G, et al. (2009) Clinical predictors of the efficacy of a pulmonary rehabilitation programme in patients with COPD. Respir Med 103: 1224–1230.
32. Fowler SJ, Singh SJ, Revill S (2004) Reproducibility and validity of the incremental shuttle walking test in patients following coronary artery bypass surgery. Physiotherapy 91: 22-27.
33. Jolly K, Lip GYH, Sandercock J, Greenfield S, Raftery J, et al. (2003) Home-based versus hospital-based cardiac rehabilitation after myocardial infarction or revascularization: Design and rationale of the Birmingham Rehabilitation Uptake Maximisation Study (BRUM): A randomized controlled trial. BMC Cardiovasc Disord 3: 10.