Repeatability of the 6-Minute Walk Test in Adolescents and Adults With Cystic Fibrosis

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OBJECTIVE: To determine the repeatability of the 6-minute walk test (6MWT) in adolescents and adults with cystic fibrosis (CF). METHODS: This was a prospective cross-sectional study. We included consecutive patients ages ≥ 15 years attending an adult CF program. The patients underwent the 6MWT, pulmonary function tests, and clinical evaluation. The second 6MWT was performed following a rest period of 60 min. RESULTS: Thirty-one patients were included. The mean ± SD age was 23.5 ± 6.7 y, and the mean FEV_1 was 61 ± 28% of predicted. The mean ± SD walked distance in the first 6MWT was 583.6 ± 68.6 m and in the second 6MWT was 590.0 ± 72.2 m. The mean difference between the first and second 6MWT was −6.5 m, with limits of agreement between −74.9 m and 61.9 m, and the coefficient of variation was 4.3%. The mean oxygen desaturation in the first 6MWT was 2.5 ± 4.5%, and in the second test it was 1.8 ± 4.0%. The mean difference between the first and second test was 0.6%, and the coefficient of variation was 104%. CONCLUSIONS: Although the 6MWT distance was reproducible, the wide limits of agreement exceeded the minimum important difference for this test. These findings indicate that, in the routine evaluation of CF patients, at least two 6MWTs are required on any testing occasion to obtain a reliable estimate of the 6MWT distance. *Key words: cystic fibrosis; 6-minute walk test; pulmonary function; exercise capacity; repeatability.* [Respir Care 2010;55(8):1020–1025. © 2010 Daedalus Enterprises]

Introduction

Cystic fibrosis (CF) is a genetic autosomal recessive disease, associated with decline of pulmonary function, pancreatic insufficiency, and important physical limitation.[1-3]

The 6-minute walk test (6MWT) is a submaximal exercise test that has been largely used for the periodic evaluation of exercise tolerance in patients with pulmonary and cardiac disease. The 6MWT has also been used to measure outcomes before and after therapeutic interventions. The distance covered in the 6MWT predicts morbidity and mortality from cardiopulmonary diseases.[4,5] The 6MWT is inexpensive, safe, and easily performed.[6]

The measurement of exercise capacity indexes is an integral part of the assessment and monitoring of patients with CF and may also provide prognostic information and facilitate treatment decisions, including timing for lung transplantation.[7] Thus, within-subject repeatability is of paramount importance.

Repeatability is the agreement between the results of successive measurements of the same measurand carried out under the same conditions of measurements. Reproducibility is the closeness of the agreement between the results of measurements of the same measurand carried out under changing conditions of measurements.[8]

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Few studies have evaluated the reliability and validity of 6MWT in pediatric patients with CF, and those studies involved small numbers of subjects.[9-11] Furthermore, there is a paucity of data on the repeatability of 6MWT in adolescents and adults with CF. The 6MWT has already been applied to healthy children, adolescents[12,13] and adults,[14] so our intention was to study 6MWT repeatability in an older and larger CF population than in previous reports.[9-11]

The objectives of this study were to determine the within-subject repeatability of the 6MWT in adolescents and adults with CF, and the repeatability of the 6MWT according to the disease severity.

Methods

Study Design

This was a single-center, prospective, cross-sectional study that recruited consecutive patients from the adult CF program at Hospital de Clínicas de Porto Alegre. The protocol was approved by the ethics committee of the hospital, and written informed consent was obtained from all patients or the parents if the patient was younger than 18 years.

Patient Population

Patients were recruited from the adult CF program at Hospital de Clínicas de Porto Alegre. which is a general, tertiary-care, university-affiliated hospital with 750 beds and is a reference center for CF in southern Brazil. The CF program has approximately 220 CF patients, 60 of whom are adults.

This study included CF patients aged 15 years and older, diagnosed as having CF according to the usual consensus criteria.[15] All patients were in clinically stable condition, defined as no medication change in the previous 30 days, and at least 30 days since completion of the last intravenous antimicrobial course or the use of oral antibiotics for pulmonary exacerbation, and no change $> 5\%$ in FEV_1 or forced vital capacity (FVC) in the previous 2 out-patient evaluations. One patient was receiving oral steroids during the research period. The exclusion criteria were pregnancy, cardiac or orthopedic disease, refusal to participate, and clinical conditions that would prevent performing the tests adequately.

Physical activity (running, soccer, swimming) was performed regularly by 18 patients (2 patients twice a week, and 16 patients more than twice a week). Thirteen patients did not exercise regularly.

We included 31 of the 60 CF patients in the adult CF program. To determine if the study sample represented the center's CF population we compared the FEV_1, FVC, age, sex, body mass index of participants and non-participants. There were no significant differences in age ($P = .52$), sex ($P = .10$), body mass index ($P = .84$), FVC ($P = .91$), or FEV_1 ($P > .99$).

Study Procedures

The clinical scoring was performed by the physician of the CF team at the out-patient evaluation, using the Shwachman-Kulczycki scoring system.[16]

The 6MWTs were done according to the American Thoracic Society (ATS) guidelines.[6] In a 30-meter corridor the patients were instructed to walk as far as possible for 6 min, under the supervision of a physiotherapist. The physiotherapist encouraged the subject with the standardized statements "you are doing well" and "keep up the good work," and was asked to refrain from using other sentences. The patient or the physiotherapist could interrupt the 6MWT if the following symptoms appeared: chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, or pale or ashen appearance. All the 6MWTs were administered by the same person. The measurements included: 6-min walk distance, S_{pO_2} before and immediately after 6MWT, heart rate, and Borg dyspnea score before and after the 6MWT.[17] Cutaneous oximetry (Nellcor NPB-40, Puritan Bennett, Pleasanton, California) was obtained with a finger probe. Oxygen desaturation was calculated as the difference between the at-rest and post-6MWT S_{pO_2} values.

The second 6MWT was performed in the same manner as the first, following a rest period of 60 min. All the patients had performed a 6MWT at least once before. It was recommended that patients not exercise vigorously within 2 hours of beginning the test. The 6MWT was performed with supplemental oxygen if the at-rest S_{pO_2} was $< 91\%$. A difference of > 54 m was taken as a clinically important difference between the two 6MWTs.[18] For statistical analysis the 6MWT distance was expressed in meters and in percent-of-predicted values.[19]

Pulmonary function tests were with a computerized spirometer (Lab Manager, v 4.34a, Jaeger, Würzburg, Germany). In our practice all patients undergo spirometry every 2 or 3 months. The FVC, FEV_1, and FEV_1/FVC were measured 3 times; the best trial was reported as percent-of-predicted for age, height, and sex.[20] The patients were classified as having mild, moderate, or severe lung disease.[21]

Statistical Analysis

Data are expressed as mean ± SD or median and interquartile range. The method of Bland and Altman[22] was used to evaluate the difference between the 6MWT distances in relation to the mean of those values individually. The limits of agreement were defined as the average dif-

Table 1. Characteristics of 31 Patients With Cystic Fibrosis

	Mean ± SD	Range
Age (y)	23.5 ± 6.7	15–49
Body mass index (kg/m^2)	20.8 ± 2.2	16.4–26.1
Shwachman-Kulczycki score	77.9 ± 13.6	55–100
FEV_1 (% predicted)	61 ± 28	15–119
Forced vital capacity (% predicted)	71 ± 23	30–130

ference of ± 1.96 SD. Measurement variation was quantified as the within-subject coefficient of variation, the intraclass correlation coefficient for average measures, or the weighted kappa coefficient of agreement (linear set of weight), as appropriate.[23] The root mean square method was used to calculate the coefficient of variation, as proposed by Bland.[24] We found the coefficient of variation for each subject separately, squared these, found their mean, and took the square root of that mean. Confidence intervals were calculated for coefficient of variation and intraclass correlation coefficient.

Repeatability refers to test conditions that are as constant as possible, where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator, using the same equipment within a short time interval. Repeatability can be defined as the strength of agreement between repeated measurements obtained under similar circumstances.[8]

Data analysis was carried out with statistics software (SPSS 13.0, SPSS, Chicago, Illinois, and MedCalc 9.4.2.0, MedCalc Software, Mariakerke, Belgium). The statistical significance level was set at $P < .05$. All probabilities reported are 2-tailed.

Results

Thirty-one patients (19 female, 61%, and 12 male, 39%) from our adult CF program were included in the study between March and August 2007. Four patients were excluded: two failed to repeat the second 6MWT, one was pregnant, and one did not want to be included. All patients were white. As shown in Table 1, the mean age was 23.5 ± 6.7 y (8 patients were 15–20 y, 21 patients were 20–30 y, and 2 patients were > 30 y). At-rest S_{pO_2} was ≥ 91% in all subjects, so none required supplemental oxygen during the 6MWT.

Table 2 shows the results and repeatability of the two 6MWTs. In general, the distance walked was reproducible. The within-subject coefficients of variation were 4.3% for the walk distance, 4,3% for the percent-of-predicted walk distance, 11.1% for the at-rest heart rate, 6.8% for the post-test heart rate, 0.9% for the at-rest S_{pO_2}, 1.7% for the post-test S_{pO_2}, and 104% for the oxygen desaturation. What could be considered as learning effect was observed in the second test, in which 3 patients (10%) increased their walk distance more than the clinically important threshold of 54 m, and one patient had a shorter walk distance in the second 6MWT. In contrast, the oxygen desaturation was less reproducible in these patients.

Figure 1 shows the Bland-Altman plot of the agreement between the distance walked and oxygen desaturation between the 6MWTs. The mean difference between the 2 paired 6MWTs was −6.5 m, and the limit of agreement was between −74.9 m and 61.9 m. The mean difference for the desaturation during the 6MWT was 0.6%, and the limit of agreement was between –3.9% and 5.2%.

The Borg dyspnea scores were also reproducible; the kappa coefficient of agreement was 0.79 for the at-rest score and 0.71 for the post-test score. The Borg leg-fatigue scores were less reproducible; the kappa coefficient of agreement was 0.34 for the at-rest score and 0.52 for the post-test score (Table 3).

Table 4 shows the results and repeatability of the 6MWTs according to the severity of lung disease. The 6MWT distance was reproducible independent of the baseline lung function.

Discussion

In this study we looked, in a consecutive fashion, at 31 CF patients aged 15 years and older attending an adult CF program. We found that the distance walked in the 6MWT was reproducible in a subsequent 6MWT following a rest of 60 min (limits of agreement −74.9 to 61.9 m, coefficient of variation 4.3%, and mean difference in distance walked −6.5 m), whereas the oxygen desaturation had large measurement variations (limits of agreement −3.9 to 5.2%, coefficient of variation 104%, and mean difference 0.6%). There was acceptable repeatability for both the at-rest and post-6MWT Borg dyspnea scores, but the Borg leg-fatigue scores were fairly reproducible.

Our study sample differed from patients included in the previous studies in some respects: older age (mean age 23.5 ± 6.7 y) and more severe pulmonary disease (mean FEV_1 61 ± 28% of predicted). And our study had a different corridor layout. However, the mean difference between the 6MWT distances (−6.5 m), the limits of agreement (−74.9 and 61.9 m), and the standard deviation of the difference in the mean values (5.9%) were similar to the previous studies, which included patients with fibrotic interstitial pneumonia.[25]

In our study the coefficient of variation was 4.3%. The ATS 6MWT guidelines[6] cite a coefficient of variation of 8% for 6MWT and note that the 6MWT has superior repeatability of FEV_1 in patients with COPD, providing a benchmark for what is considered a good repeatability of 6MWT in CF patients.

Table 2. 6-Minute-Walk Test Results and Reproducibility

Variable	First 6MWT (mean ± SD)	Second 6MWT (mean ± SD)	SD of Difference*	CV (%)	CV 95% CI (%)	ICC	ICC 95% CI
6MWT distance (m)	583.6 ± 68.6	590.0 ± 72.2	0.003	4.3	2.6–5.5	0.94	0.87–0.97
6MWT distance (% predicted)	77.0 ± 9.0	78.0 ± 9.0	0.003	4.3	2.6–5.5	0.93	0.86–0.97
At-rest heart rate (beats/min)	89.7 ± 11.7	89.2 ± 12.6	0.030	11.1	4.2–15.1	0.52	0.008–0.77
Post-test heart rate (beats/min)	129.8 ± 22.2	134.3 ± 22.1	0.013	6.8	1.5–9.6	0.28	–0.49 to 0.65
At-rest S_{pO_2} (%)	96.7 ± 2.5	96.3 ± 2.4	0.0001	0.9	0.6–1.1	0.94	0.87–0.97
Post-test S_{pO_2} (%)	94.2 ± 6.1	94.5 ± 5.9	0.001	1.7	0.0–2.5	0.97	0.94–0.99
Oxygen desaturation (%)†	2.5 ± 4.5	1.8 ± 4.0	3.250	104.0	ND	0.92	0.84–0.96

* Standard deviation of the difference between the two measurements.
† S_{pO_2} difference between before and after the 6-min walk test (6MWT).
CV = coefficient of variation
ICC = intraclass correlation coefficient for average measures
ND = no data available because it was not possible to generate 95% CI for the CV of oxygen desaturation.

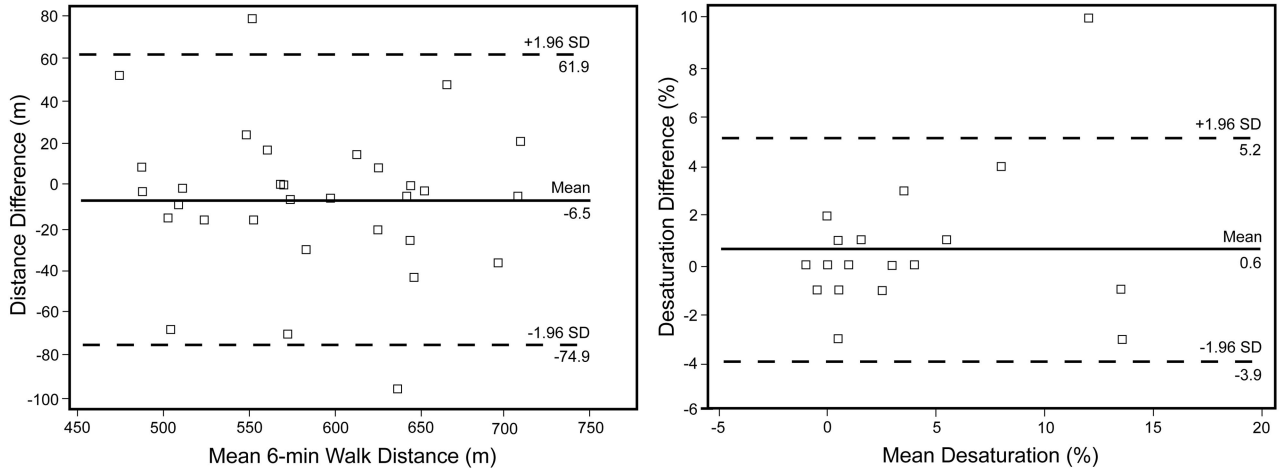

Fig. 1. Bland-Altman plot of agreement in the distance walked and oxygen desaturation between the 6-minute walk tests (6MWTs).

Table 3. Borg Scores Reproducibility

	First 6MWT Median (IQR)	Second 6MWT Median (IQR)	Kappa*
At-rest Borg dyspnea score	0 (0–1)	0 (0–0)	0.79
Post-test Borg dyspnea score	1 (0–3)	0 (0–3)	0.71
At-rest Borg leg-fatigue score	0 (0–1)	0 (0–5)	0.34
Post-test Borg leg-fatigue score	1 (0–3)	2 (0–3)	0.52

* Weighted kappa coefficient of agreement.
6MWT = 6-min walk test

The recent ATS 6MWT guidelines[6] do not require a practice walk. They do recommend, however, that if a practice walk is done, the repeat test should be done on the same day, at least one hour later, and that the higher of the 2 values should be recorded. The subjects in this study all rested for one hour between tests. Otherwise, other recommendations suggest a longer rest between 6MWTs.[10-12] The performance of 2 practice walks has been advocated by some because of the training effect related to factors such as anxiety and coordination. Conversely, we are aware that in CF patients with more severe pulmonary impairment a second 6MWT can result in excessive strain. In our study we found a small learning effect in the second 6MWT. The mean difference between the first and second 6MWTs was −6.5 m, and 10% of the patients increased their 6MWT distance more than the clinically important threshold of 54 m. Despite that fact, the at-rest and post-test Borg fatigue scores were higher in the second test. Otherwise, only one patient had a decreased 6MWT distance of 54 m, which suggests that that patient was getting tired in the second test.

We acknowledge the wide limits of agreement in the walk distance, which exceed the minimum important difference for this test. This is extremely important, particularly if the test is to be used to measure change following an intervention. If only a single test is performed at baseline, one could not be sure that an observed change at

Table 4. 6-Minute-Walk Test Results and Reproducibility Relative to Lung Disease Severity

	Severity of Lung Disease			
	Mild (FEV_1 > 65% predicted) (n = 14)	Moderate (FEV_1 40–65% predicted) (n = 7)	Severe (FEV_1 < 40% predicted) (n = 10)	P^*
Age (mean ± SD y)	20.4 ± 3.1	25.7 ± 6.1	26.2 ± 9.1	.056
Body mass index (mean ± SD kg/m^2)	21.7 ± 2.2	19.5 ± 2.2	20.4 ± 1.6	.057
FEV_1 (mean ± SD % predicted)	86 ± 17	52 ± 6	32 ± 8	< .001
Shwachman-Kulczycki score (mean ± SD)	88.2 ± 8.0	72.1 ± 11.1	67.5 ± 11.6	< .001
6MWT Distance				
First 6MWT (mean ± SD m)	593.9 ± 65.2	594.0 ± 56.3	561.7 ± 81.5	.49
Second 6MWT (mean ± SD m)	597.6 ± 65.3	603.6 ± 83.2	569.9 ± 77.0	.57
CV (%)†	7.5	5.0	4.3	ND
Post-6MWT Heart Rate				
First 6MWT (mean ± SD beats/min)	129.1 ± 24.5	123.1 ± 17.9	135.4 ± 22.3	.54
Second 6MWT (mean ± SD beats/min)	134.7 ± 25.5	127.6 ± 14.8	138.5 ± 22.1	.62
CV (%)†	9.2	8.5	4.0	
Oxygen Desaturation‡				
First 6MWT (%)	0 ± 0.88	1.3 ± 1.9	6.8 ± 5.8	< .001
Second 6MWT (%)	–0.21 ± 0.58	0.57 ± 1.27	5.6 ± 5.3	< .001
CV (%)†	77	223	58	ND

* P for the differences between the disease-severity groups.
† Coefficient of variation (CV) between the first and second 6-min walk test (6MWT).
‡ S_{pO_2} difference between before and after the 6MWT.
ND = no data available because not calculable.

follow-up was due to real clinical change, even if it exceeded the minimum important difference.

In our work, all 6MWT were administered by the same operator, which might have improved our results. Multiple operators could increase the variability of the study. According to the guidelines,[6] the walk course must be 30 m in length, but previous studies used corridors of 8 m (Gulmans et al[11]), 28 m (Cunha et al[9]), and 35 m (Guillén et al[10]).

It is not known whether it is best for clinical purposes to express change in 6MWT as an absolute value, percentage change, or percentage change of predicted value. Until further research is available, the ATS guidelines[6] recommend that change in 6MWT be expressed in absolute values. In our research we found similar 6MWT repeatability in the absolute and percent-of-predicted values (see Table 2).

In addition, there are some considerable aspects to be discussed relating to the 6MWT. In this study the heart rate after test 2 was higher than after test 1, and the Borg leg-fatigue score had a kappa coefficient of agreement of 0.34. The tests all had a one-hour rest interval between them. Probably one hour was a relatively short rest period for the patients with the worst lung function, but one hour to recover was recommended by the ATS 6MWT guidelines. Besides the large variability in FEV_1 in our sample there were no significant differences obtained in the distance walked or heart rate in the patients with the worst lung function.

The large differences in oxygen desaturation probably reflect the fact that during the exercise the patient enters the steep part of the oxygen desaturation curve. It appears that minor differences in patient tolerance and apparently trivial delays in stopping the test may have a disproportionate effect on the final saturation.[25] Measurement variation is likely to be further exacerbated by the inherent noise of cutaneous oximetry, for which the 95% confidence limits may be as wide as ± 4–5%.[26] Previous studies with CF patients and 6MWT did not mention the repeatability of the peripheral oxygen saturation.[6,9-11,27] Eaton et al[25] studied 29 patients with fibrotic interstitial pneumonia and found that the peripheral oxygen saturation at the end of the 6MWT (performed according to the ATS standards) and the maximal exercise test was not reproducible (SD/mean > 25%).

Previous studies have examined the repeatability of 6MWTs in CF patients.[9-11,28] Gulmans et al,[11] Cunha et al,[9] Balfour-Lynn et al,[28] and Guillén et al[10] studied CF patients ages 8–23 years. These studies found no significant difference between the two 6MWT tests. They also demonstrated a good correlation and a small mean difference between the distances walked in the 2 tests. They conclude that the 6MWT is a valid, repeatable, and easy-to-perform test in children and adolescents with mild to moderate symptoms of CF, to assess exercise tolerance.

Repeatability measurements could be reported by multiple statistical methods, as no single measure is appropriate in every circumstance. In this work, we presented Bland-Altman plots, coefficient of variation, and intraclass correlation coefficient. However, these methods can be misleading when the coefficient of variation mean is close to zero and the intraclass correlation coefficient is under 95%. Also, the magnitude of the intraclass correlation coefficient is dependent on the variability in the data. An intraclass correlation coefficient of 0.95 means that an estimated 95% of the observed score variance is due to true score variance and 5% is attributable to error.[29] In our work, despite a relatively" good" intraclass correlation coefficient and coefficient of variation, a single 6MWT may not be repeatable due to wide limits of agreement. The limits of agreement were greater than the clinically important threshold of 54 m for the distance walked.

Conclusions

Although the distance walked during 6MWT is reproducible in CF patients ≥ 15 years old, the wide limits of agreement in this study exceeded the minimum important difference for this test. These findings indicate that, in the routine evaluation of CF patients, at least 2 6MWTs are required on any testing occasion to obtain a reliable estimate of the distance walked in the 6MWT.

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