

Exercise tolerance in children with cystic fibrosis undergoing lung transplantation assessment

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Exercise tolerance in children with cystic fibrosis undergoing lung transplantation assessment. P. Aurora, S.A. Prasad, I.M. Balfour-Lynn, G. Slade, B. Whitehead, R. Dinwiddie. ©ERS Journals Ltd 2001.

ABSTRACT: The aim of this study was to compare the 6-min walk test against the recently developed 3-min step test, as measures of exercise tolerance in children with moderate to severe cystic fibrosis (CF) lung disease referred for lung transplantation assessment.

Twenty-eight children with CF (16 girls, 12 boys), with a mean age of 13.7 yrs (range 7.2–17.8 yrs) and mean forced expiratory volume in one second of 34% predicted (range 17%–67%) were recruited. All subjects performed both the 6-min walk and 3-min step-tests. Outcome measures were maximum rise in heart rate (HR), and maximum fall in arterial oxygen saturation (S_{a,O_2}).

There was no significant difference in resting HR or S_{a,O_2} prior to starting the two tests. Both step and walk tests produced significant rises in median HR (from 114–149 min^{-1} , $p < 0.0005$, and 119–138 min^{-1} , $p < 0.0005$, respectively) and significant falls in S_{a,O_2} (both from 94–92%, $p < 0.0005$). The step test produced a significantly greater percentage rise in HR (30% versus 18%, $p < 0.0005$) and a significantly greater percentage fall in S_{a,O_2} (4% versus 2%, $p = 0.002$). Bland-Altman analysis gave wide 95% limits of agreement (10.7–29.3% for rise in HR, -2.1–4.6% for fall in S_{a,O_2}). The step test was well tolerated.

The 3-min step test produced a greater fall in S_{a,O_2} and a greater rise in HR than the 6-min walk test in children with moderate to severe CF lung disease. It may be of value when assessing a child's suitability for lung transplantation.

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Measurement of exercise tolerance is considered an essential component of the lung transplantation assessment procedure, since it may predict life expectancy and provide valuable information regarding the patient's quality of life. A variety of tests have been considered for measurement of exercise tolerance in children, the most commonly used being the self-paced walking test. In this test, the subject is asked to walk as far as possible during a set time (2, 6 or 12 min) and the distance covered, the increase in heart rate (HR), and the change in arterial oxygen saturation (S_{a,O_2}) are recorded [1–3].

Although distance covered during a walk test has been shown to correlate with survival in adults with lung disease [4], data from children with cystic fibrosis (CF) suggest this measure may be a less useful prognostic indicator [5], possibly because results from walk tests can vary with encouragement and patient motivation. A 3-min step test has been developed, which might rely less on patient motivation than a self-paced walk test. During a walk test the subjects are asked to cover as much distance as possible in the allotted time but are allowed to choose their own pace of walking and rest during the test. Poorly-motivated subjects may walk more slowly than well-motivated subjects. During a step test the intensity of exercise is

predetermined, so a poorly motivated subject may stop the test early (though this is rare in practice), but may not slow down.

A previous study demonstrated that, in a diverse population of children with CF, the step test produces a greater increase in HR and greater increase in breathlessness (measured by a modified Borg score) than the 6-min walk. However, the two tests produced a similar fall in S_{a,O_2} [6]. In the current study the 3-min step test was compared with a 6-min walk test in a population of children with moderate to severe CF lung disease referred for lung transplantation assessment.

Materials and methods

Study subjects

All children with CF attending Great Ormond Street Hospital for Children, London, UK for lung transplantation assessment between January 1998 and November 1998 were recruited to this study. A total of 28 children with moderate-to-severe CF lung disease were enrolled. All children had been referred from CF centres in the UK or Republic of Ireland. There were

Table 1. – Change in heart rate (HR) and oxygen saturation (S_{a,O_2}) during the two tests

	Pretest HR·min ⁻¹	Maximum HR·min ⁻¹	p-value	Pretest S_{a,O_2} %	Minimum S_{a,O_2} %	p-value
6-min walk test	119 (106–128)	138 (130–150)	<0.005	94 (93–95)	92 (90–94)	<0.005
3-min step test	114 (104–125)	149 (139–156)	<0.005	94 (92–96)	92 (88–94)	<0.005
p-value	NS	NS		NS	NS	

Data are presented as medians (interquartile ranges).

16 girls and 12 boys with a mean age of 13.7 yrs (range 7.2–17.8 yrs), and a mean forced expiratory volume in one second (FEV₁) of 34% predicted for height, age and sex [7] (range 17–67%).

Study design

All subjects performed both the 6-min walk test and the 3-min step test. Order of testing was alternated. Baseline S_{a,O_2} and HR were recorded, then subjects were trained in performance of both tests, practised, and rested. The second test was performed 30 min after HR and S_{a,O_2} had returned to baseline levels. HR and S_{a,O_2} were measured continuously during exercise by pulse oximetry, and outcome measures were maximum fall in S_{a,O_2} and maximum rise in HR during exercise.

Methods

The step test required subjects to step up and down a 15 cm step at a rate of 30 steps·min⁻¹ for 3 min. The stepping rate was controlled by a metronome. S_{a,O_2} and HR were measured by pulse oximetry (Ohmeda Biox pulse oximeter, Boulder CO, USA) with a flexiprobe attached to the patients finger and its lead strapped to the patients arm. Subjects stopped if their S_{a,O_2} fell to <75% or if they felt over-tired. Patients were shown how to change the leading leg to reduce localized muscle fatigue and standardized encouragement was given. The 6-min walk test required subjects to walk up and down a 17 m corridor for 6 min accompanied by the investigator. The test was self-paced with subjects asked to cover the maximum possible distance in the allotted time. If subjects wished to rest they could do so but the clock continued to run. S_{a,O_2} and HR were measured as for the step test. The test was discontinued if the S_{a,O_2} fell to <75%. Total distance walked was also recorded.

Data analysis

Wilcoxon signed ranks tests were used to compare outcome measures before and after exercise and to compare changes in outcome measures for the two tests. Bland-Altman plots [8] were also used to compare changes in the outcome measures for the two tests. In this analysis, the difference between the percentage change in HR (or S_{a,O_2}) obtained by the two tests is plotted against their mean value. The group mean difference can also be calculated, as can

the limits of agreement (defined as 2SDs from the group mean difference).

Results

Of the 28 children tested, six had an FEV₁>40%, and 22 had an FEV₁<40%. There was no significant difference between the resting S_{a,O_2} or resting HR prior to starting the two tests. Both tests produced a significant fall in S_{a,O_2} and a significant rise in HR (table 1, fig. 1 and 2). The step test produced a significantly greater percentage rise in HR (median of 30% versus 18%), and a significantly greater percentage fall in S_{a,O_2} (median of 4% versus 2%), than the

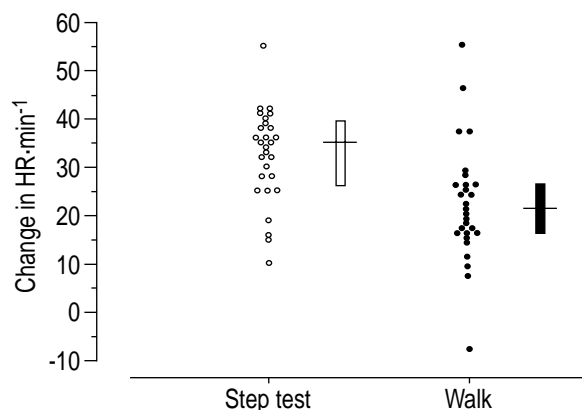


Fig. 1. – Absolute changes in heart rate (HR) during step test (○) and walk test (●). Also shown are medians (line) and interquartile ranges (bars).

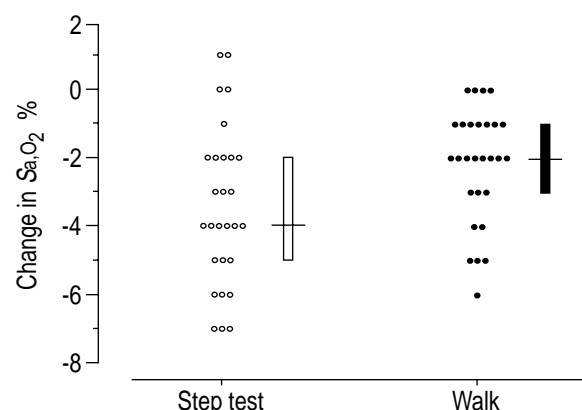


Fig. 2. – Absolute changes in arterial oxygen saturation (S_{a,O_2}) during step test (○) and walk test (●). Also shown are medians (line) and interquartile ranges (bars).

Table 2.—Percentage fall in heart rate (HR) and percentage fall in arterial oxygen saturation (S_{a,O_2}) for the two exercise tests.

	6-min walk	3-min step	p-value
Percentage rise in HR	18 (13–26)	30 (20–36)	<0.0005
Percentage fall in S_{a,O_2}	2 (1–4)	4 (2–6)	0.002

Data are presented as medians (interquartile ranges).

walk test (table 2). When the study population was divided according to order of testing, no significant difference was found between the two groups for FEV₁, median desaturation for either test, or median rise in HR for either test.

Bland-Altman analysis of the two tests gave wide 95% limits of agreement for rise in HR (-10.7–29.3%). Twenty-four of the 28 children had a greater increase in HR with the step test than with the walk test (fig. 3). Bland-Altman analysis for fall in S_{a,O_2} also showed wide 95% limits of agreement (-2.1–4.6%), though examination of the plot shows that the difference between the two tests was most marked in those patients who showed the greatest desaturation on exercise (fig. 4). Four subjects had little desaturation on exercise, whereas of the 24 subjects who showed a mean desaturation of $\geq 1\%$, the majority had greater desaturation with the step test than the walk test, and none had a greater desaturation with the walk test than with the step test.

Discussion

In the present study, the recently developed 3-min step test was compared with the well-established 6-min walk test in a population of children with moderate to severe CF lung disease. Both tests produced a significant rise in HR, and a significant fall in S_{a,O_2} . The step test produced a significantly greater rise in HR and a significantly greater fall in S_{a,O_2} than the walk test, with the greatest difference between the two tests noted in those patients with the

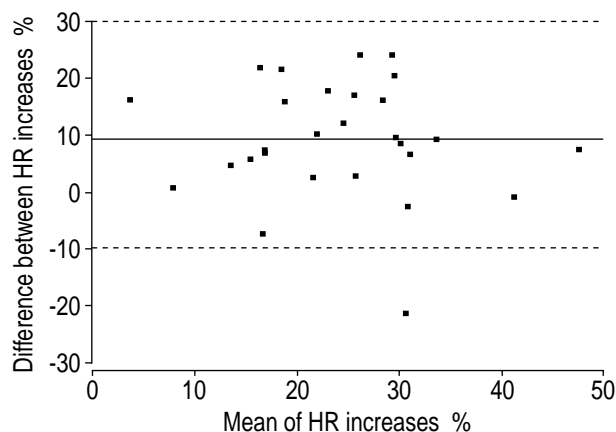


Fig. 3.—Bland-Altman plot of percentage change in heart rate (HR) between 6-min walk test and 3-min step test versus mean of the two tests. Unbroken and broken lines represent mean and mean \pm SD, respectively.

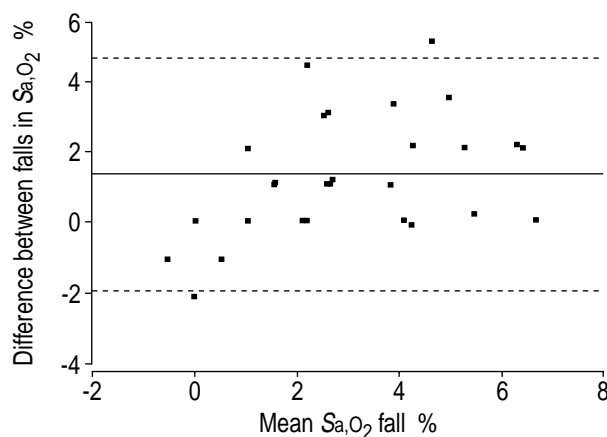


Fig. 4.—Bland-Altman plot of percentage change in arterial oxygen saturation (S_{a,O_2}) between 6-min walk test and 3-min step test versus mean of the two tests. Unbroken and broken lines represent mean and mean \pm SD, respectively.

greatest propensity to desaturate on exercise. This last finding was not observed in a previous study of CF patients with mild-to-moderate lung disease [6], and is the most important finding of this study.

On initial viewing there may appear to be a discrepancy in the data presented in tables 1 and 2. Table 1 shows no difference in median pre- and postexercise S_{a,O_2} between the two tests, but does show a lower first quartile S_{a,O_2} poststep test compared with the first quartile S_{a,O_2} obtained post-walk test. When the desaturation recorded during each test is examined, there is a clear difference between the two tests (table 2, figs. 2 and 4). This apparent discrepancy is seen because some patients had a similar degree of desaturation with both tests, whilst some had a markedly greater desaturation with the step test.

One difficulty when conducting a study that compares two exercise tests, is the effect of fatigue upon the results of the second test. The present study followed a previous protocol [6] of waiting for 30 min after S_{a,O_2} and HR had returned to baseline before commencing the second test. As these parameters may not measure fatigue or tendency to fatigue, the order of testing was alternated, and it was found that the order of testing had no effect upon results.

Measurement of exercise tolerance is considered an essential component of lung transplantation assessment, with reduced exercise tolerance considered a poor prognostic indicator. However, the interpretation of exercise test results is based upon limited data. NIXON *et al.* [9] reported an 8-yr follow-up of 107 patients with CF (mean age 17 yrs, range 7–35 yrs, mean FEV₁ 59%, range 24–95%) who had initially undergone maximal exercise testing on a cycle ergometer in the 1970s. They found that aerobic fitness (as measured by maximal oxygen uptake ($\dot{V}O_{2,max}$)) was the best predictor of survival over the study period. A similar study reported by MOORCRAFT *et al.* [10] in 1997 followed 92 adult patients over a 5-yr period and found that although $\dot{V}O_{2,max}$ was a predictor of survival, the FEV₁ was a better predictor. However,

the form of exercise testing employed in these studies is expensive, time consuming, and requires a specialized laboratory. Few transplant centres assess exercise tolerance of lung transplant candidates in this way; the majority of centres use a submaximal test, most commonly the 6-min walk test. The distance walked during self-paced walk tests has been shown to correlate with resting pulmonary function and with aerobic fitness in both adults and children [2, 11, 12]. Furthermore, the minimum S_{a,O_2} recorded during a walk test has been shown to correlate with the minimum S_{a,O_2} recorded during progressive maximal exercise testing on a cycle ergometer [3]. However, there are limited data on the value of the walk test in predicting prognosis in pulmonary disease, with just four published survival studies [4, 5, 13, 14]. Three of these studies were performed in adult subjects, one in subjects undergoing lung transplantation assessment [4], and two in subjects undergoing pulmonary rehabilitation. All three studies found timed (either 6-min or 12-min) walking distance to be a valuable predictor of survival. None of the studies evaluated minimum S_{a,O_2} as a predictor of survival. The one paediatric study analysed survival of 181 children with CF referred to Great Ormond Street Hospital for Children for lung transplantation assessment between 1989 and 1999 [5]. This study suggested that minimum S_{a,O_2} during a walk test is a better predictor of prognosis than distance covered.

Neither the step test nor the self-paced walk test is a true maximal exercise test. In the walk test, subjects are allowed to choose their own pace. In the step test the intensity and duration of the exercise is predetermined. The previous study suggested that the 3-min step test was harder exercise than the 6-min walk test, but also did not demonstrate any difference in desaturation between the two tests [6]. In the present study it has been shown that some children with more advanced CF lung disease desaturate dramatically during the 3-min step test, but not during the 6-min walk. This may be a consequence of lower resting arterial oxygen tension (P_{a,O_2}) in these children. As the relationship between P_{a,O_2} and S_{a,O_2} is not linear, a small fall in P_{a,O_2} in a child with normal resting P_{a,O_2} (e.g. a fall from 12–11 kPa) will result in little desaturation. However, a small fall in P_{a,O_2} in a child with mild hypoxia (e.g. a fall from 8–7 kPa) will produce a much greater desaturation. Thus the dramatic desaturation seen in some children undertaking the 3-min step test may represent greater oxygen consumption in a child who already has mild hypoxia.

This has implications for lung transplantation assessment. There is little doubt that resting P_{a,O_2} and resting arterial carbon dioxide tension (P_{a,CO_2}) are of value in predicting prognosis of patients with CF [15, 16]. However, arterial blood sampling can be painful and technically difficult, so many transplant centres do not include this investigation as part of their paediatric assessment protocol [17]. None of the patients included in this study underwent arterial blood gas analysis. If the 3-min step test is able to discriminate between children with normal resting P_{a,O_2} and good exercise tolerance, and children with

lower resting P_{a,O_2} and poorer exercise tolerance, it may prove to be a valuable prognostic indicator in children being considered for lung transplantation. Longitudinal studies to evaluate this are underway.

In conclusion, the 3-min step test is easy to perform and is well tolerated even in children with moderate to severe cystic fibrosis lung disease. Furthermore, it produces a greater rise in heart rate and a greater fall in arterial oxygen saturation, particularly in those patients prone to desaturate during exercise, than the 6-min walk test. The 3-min step test may be of value when assessing a child's suitability for lung transplantation.

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