

Original Article

How does heart rate recovery after sub-maximal exercise correlate with maximal exercise testing in children with CF?

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Abstract

Background: Disease progression in cystic fibrosis (CF) is marked by worsening exercise tolerance. Further, maximal exercise capacity (VO₂ peak) correlates with survival in CF, but maximal tests are uncomfortable and resource-intensive. A three-minute step test (STEP) has been validated in CF. Heart rate (HR) recovery after exercise correlates with all-cause mortality in adult non-CF populations. We compared HR recovery after the three-minute step test with VO₂ peak in children with CF.

Methods: Twenty-four children with CF performed STEP and a maximal exercise test. Correlation between the tests was assessed.

Results: Maximum HR on STEP was lower than on the maximal test (140 vs. 190, $p < 0.01$). Peak HR during STEP correlated inversely with VO₂ peak. In subjects with mild lung disease, faster HR recovery after STEP correlated with higher VO₂ peak.

Conclusions: The three-minute step test is a feasible submaximal test in this patient population. HR during and after a three-minute step test may reflect VO₂ peak in children with CF.

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Keywords: Cystic fibrosis; Exercise testing; VO₂max; heart rate recovery

1. Introduction

Exercise intolerance is a hallmark of increasing disease severity in patients with cystic fibrosis (CF) [1]. Further, exercise tolerance is a robust correlate of mortality in CF [2,3]. Exercise tests are used in a variety of cardiopulmonary diseases, including CF, to determine functional capacity and causes for exercise intolerance, and to evaluate disease progression and response to treatment [4]. The best studied measure of exercise tolerance in cystic fibrosis is peak oxygen consumption (VO₂ peak), as measured by a maximal exercise test. Current recommendations state that patients with cystic fibrosis should have a maximal exercise test annually [5]. However, a survey of German CF centers revealed that on average, patients were performing a maximal exercise test only once every

4.7 years [6]. This is due both to limitations in resource availability as well as patients' dislike of the test itself [7]. In fact, in one study, 50% of subjects said that they would not want to perform a maximal exercise test annually as recommended [8].

In light of the value of but significant problems with maximal exercise tests, various submaximal tests that can be performed outside an exercise physiology laboratory have been suggested for patients with CF [9]. These tests have the added benefit of being more reflective of usual physical activity patterns [10]. Both six-minute walk tests and modified shuttle tests have been shown to correlate with maximal exercise tests in patients with cystic fibrosis [11–13]. However, walk tests and shuttle tests both require a substantial amount of open space, and walk tests especially are highly dependent on motivation and encouragement [14].

Step tests provide a possible solution to the space requirements and motivation problems that plague walk tests and shuttle tests. Step tests are not motivation dependent, are easy to perform, and require little space [15]. When compared to the six-minute walk

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test, the three-minute step test is more physically strenuous, potentially providing for better discrimination among relatively healthy patients [16–18]. Holland et al. found that the three-minute step test was able to predict 12-month outcomes in adults with CF [19]. However, even though the three-minute step test has been shown to predict short-term outcomes in patients with CF, there are currently no data correlating variables from the three-minute step test with VO_2 peak.

The only study to compare the three-minute step test and a maximal test found that the step test was less strenuous than the maximal exercise test. That study did not find a correlation between heart rate (HR), SpO_2 , or breathlessness scores during the three-minute-step test and VO_2 peak [20].

Heart rate recovery after submaximal exercise is used in non-CF adult populations as a measure of overall fitness, and has even been shown to predict all-cause mortality in healthy adults [21]. We designed this study to assess whether, among children with cystic fibrosis, heart rate recovery after the three-minute step test correlates with peak oxygen consumption. Hypotheses were that in children 8 years and older with CF, a shorter time to return to resting HR and a greater percent change from maximum HR one minute following the three-minute step test, a submaximal exercise test, would correlate with greater percent predicted VO_2 peak as measured by a maximal exercise test.

2. Methods

Children 8 years of age and older with cystic fibrosis were recruited from the Antonio J. and Janet Palumbo Cystic Fibrosis Center at the Children's Hospital of Pittsburgh of UPMC. CF had been diagnosed by sweat test, the presence of two disease-causing mutations in the CFTR gene, or both. Exclusion criteria were limited to major comorbidities, at the discretion of the subject's CF clinician, or inability to perform reliable pulmonary function tests or exercise tests.

Subjects performed either pre- and post-bronchodilator spirometry or full pulmonary function tests, including lung volume measurements, determined by clinical need and scheduling constraints, immediately before the exercise testing. Written informed consent was obtained from each subject's parent or legal guardian or from the subjects themselves if they were over eighteen years of age. Subjects under eighteen years of age provided verbal or written assent. Subjects were shown how to perform the stepping exercise, and then allowed a practice period. The subjects then rested until a stable baseline resting heart rate was reached and recorded, then each subject performed a three-minute stepping exercise on a 15 cm step at a cadence of 30 complete steps (both feet on and off of the step) per minute. Heart rate and oxyhemoglobin saturation were measured at rest, during, and after the step test. Immediately after the exercise, subjects were instructed to rest in a seated position until their heart rate returned to within five beats per minute of their resting heart rate. Subjects then performed a maximal oxygen consumption test on a treadmill, using a modified Bruce protocol. At least ten minutes were allowed between the step test and the maximal test.

Data were analyzed as a whole as well as after stratification by FEV_1 . Desaturation was defined as a decrease in SpO_2 of

greater than 4%, and CO_2 retention during the maximal test was defined as rise in PETCO_2 greater than 5 mm Hg as compared to PETCO_2 at rest. The maximum heart rate reached during the three-minute step test was compared to the maximum heart rate reached during the maximal exercise test with a paired two-tailed student's *t*-test. Spearman's correlation coefficients were calculated to assess correlation between variables. Stepwise linear regression was performed to assess predictive value of variables from the three-minute step test for maximal oxygen consumption. A *p*-value of less than or equal to 0.05 was considered significant.

3. Results

Twenty-four children (62% male) performed the three-minute step test and a maximal exercise test. Subject characteristics may be seen in Table 1.

All subjects were able to complete the three-minute step test, with no adverse events or desaturations (fall in $\text{SpO}_2 > 4\%$). Resting HR, but not FEV_1 , correlated with the maximum heart rate reached during the step test ($\rho = 0.436$, $p < 0.05$ for resting HR). No other subject characteristics correlated with outcome measures from the step test. Fifty percent of subjects returned to their resting HR less than one minute after completing the three-minute step test.

All subjects were able to exercise maximally on the maximal exercise test, as determined by their achieving of a respiratory exchange ratio approximately equal to or greater than one. The mean HR reached on the maximal exercise test was significantly higher than the mean HR reached with the step test (190 vs 139, $p < 0.01$ — Fig. 1).

Subjects with a lower maximum heart rate on the three-minute step test tended to have a higher percent predicted VO_2 peak ($\rho = -0.40$, $p = 0.05$, Fig. 2). Overall, time to resting HR after the three-minute step test did not correlate with percent predicted VO_2 peak. However, when stratified based on percent predicted FEV_1 , interesting trends were revealed. In subjects with an FEV_1 greater than 80% predicted, a shorter time to return to resting heart rate after the step test (faster HR recovery) correlated with higher percent predicted VO_2 peak ($\rho = -.538$, $p < 0.05$). This trend was also seen in subjects who did not retain CO_2 during the maximal test ($\rho = -0.557$, $p < 0.05$), though there was no correlation between FEV_1 and change in PETCO_2 during exercise. On the other hand, in subjects with an FEV_1 of less than 80% predicted, a longer time to return to resting heart rate after the step test (slower HR recovery) actually correlated with a higher percent predicted VO_2 peak ($\rho = 0.865$, $p < 0.02$). This trend was not seen in

Table 1
Subject characteristics.

	Average	Range
Age (years)	12.8	8–19
BMI (kg/m^2)	17.7	14.9–23.3
Resting SpO_2	98.6%	96–100%
Resting HR (bpm)	88	70–110
FEV_1 (% predicted)	87%	36–111%
VO_2 peak (% predicted)	110%	83–137%

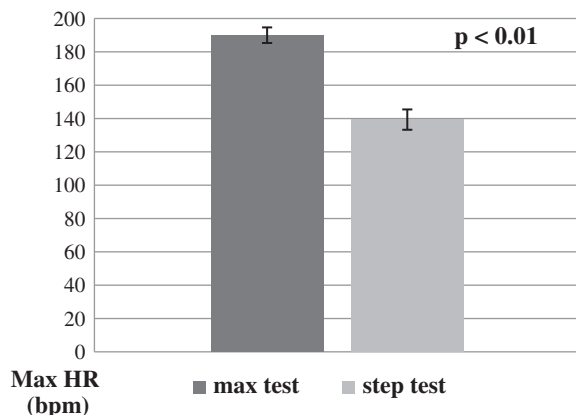


Fig. 1. Comparison of maximum HR on the three-minute step test vs. maximal test.

subjects who retained CO_2 during the maximal test. There were no significant differences between the subjects in different FEV_1 categories that could explain this phenomenon (Fig. 3).

Increased age and height both correlated with lower percent predicted VO_2 peak ($\rho = -0.46$, $p < 0.05$ for age; $\rho = -0.51$, $p < 0.02$ for height), and height and age were closely linked ($\rho = 0.873$, $p < 0.02$). However, age and height were not related to the step test max HR. The three-minute step test max HR alone was sufficient to predict percent predicted VO_2 peak ($y = -0.578x + 191$, $p < 0.02$), with no significant additional predictive value gained from including height in the model.

4. Discussion

As all subjects were able to complete the three-minute step test without any adverse events or desaturation, the three-minute step test is a feasible test in this population. The maximum heart rate reached on the three-minute step test was significantly lower than the maximum heart rate reached during the maximal exercise test, indicating that the three-minute step test truly is a submaximal test for children and adolescents with cystic fibrosis. Narang et al. had previously shown that there is not an order effect for the exercise tests in this population [18]. As fifty percent of subjects returned to

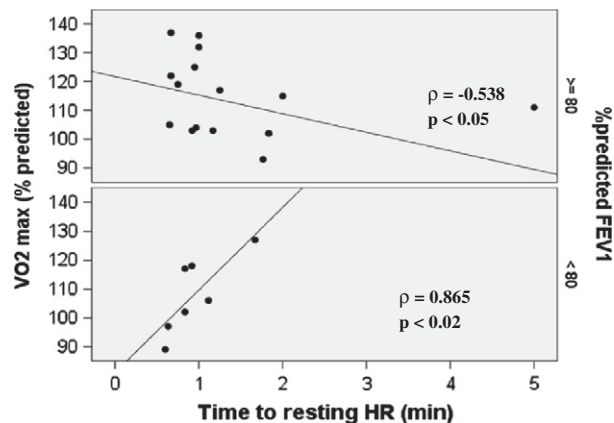


Fig. 3. VO_2 max (%predicted) vs. time to return to resting HR after the three-minute step test, stratified by FEV_1 .

resting heart rate within one minute of completing the three-minute step test, change in percent of maximal heart rate at one minute after the three-minute step test is not a useful measure of heart rate recovery in children with cystic fibrosis, at least in those with relatively mild lung disease and relatively good aerobic fitness, as represented in our sample. Further studies on the role of heart rate recovery in cystic fibrosis should include subjects with more severe pulmonary impairment than our sample.

Maximum heart rate during the three-minute step test emerged as a potentially useful measurement as regression showed it was related to percent predicted VO_2 peak. The story with time to resting heart rate after the three-minute step test, however, is not quite as simple. We predicted that the more aerobically fit patients would have a quicker return of their heart rate after exercise, and this proved to be true in the children with mild lung disease ($\text{FEV}_1 > 80\%$ predicted, and in those who did not retain carbon dioxide during the maximal exercise test). To our surprise, however, the relationship between time to resting heart rate after the three-minute step test and percent predicted VO_2 peak behaves in exactly the opposite manner in children with more severe lung disease ($\text{FEV}_1 < 80\%$ predicted). The relatively small sample size represented by the children with more severe lung disease ($n = 7$) precluded further analysis of this phenomenon. Future studies of the three-minute step test in children with more severe CF lung disease and lower aerobic fitness may help to elucidate why the children with more severe lung disease seemed to oppose the expected trend.

Increased age (and therefore height) was related to a lower maximal exercise capacity, likely reflective of the progressive nature of the lung disease in cystic fibrosis. However, these parameters were not associated with performance on the step test.

Though this study focused on evaluating the correlation between the three-minute step test and maximal exercise tests, submaximal field exercise tests like the three-minute step test are uniquely poised to evaluate functional capacity because they are more similar to typical activity patterns than are maximal tests [10]. Additionally, the simplicity and portability of the three-minute step test makes it feasible to use as an office-based evaluation of response to treatment [22]. Future studies could further investigate applications of the three-minute step test in these areas.

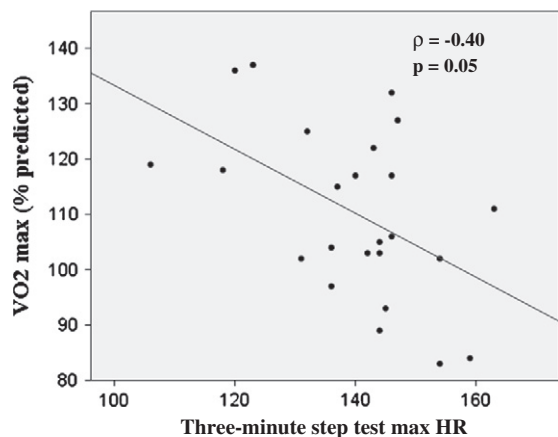


Fig. 2. VO_2 max (%predicted) vs. three-minute step test max HR.

Holland et al. found that the 3-minute step test could predict worse 12-month outcomes in adults with cystic fibrosis [19]. Since maximal exercise tolerance has been shown to be strongly linked to outcomes in cystic fibrosis, our study's finding that a 3-minute step test correlates with maximal exercise tolerance fits with previous literature and provides additional support to the further exploration of the use of the three-minute step test in clinical practice for patients with cystic fibrosis [2,3].

Conflict of interest statement

The authors have no conflicts of interest related to this work.

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References

- [1] Klijn PHC. Longitudinal determinants of peak aerobic performance in children with cystic fibrosis. *CHEST J* 2003;124(6):2215.
- [2] Nixon P, Orenstein DM, Kelsey S, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992;327:25.
- [3] Pianosi P, Leblanc J, Almudevar A. Peak oxygen uptake and mortality in children with cystic fibrosis. *Thorax* Jan 2005;60(1):50–4.
- [4] Ferrazza AM, Martolini D, Valli G, Palange P. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. *Respir Int Rev Thorac Dis* 2009;77(1):3–17.
- [5] Standards of care and good clinical practice for the physiotherapy management of cystic fibrosis. Association of Chartered Physiotherapists in Cystic Fibrosis; 2011.
- [6] Barker M, Hebestreit A, Gruber W, Hebestreit H. Exercise testing and training in German CF centers. *Pediatr Pulmonol* 2004 Apr;37(4):351–5.
- [7] Stevens D, Oades PJ, Armstrong N, Williams CA. A survey of exercise testing and training in UK cystic fibrosis clinics. *J Cyst Fibros* Sep 2010;9(5):302–6.
- [8] Kent L, O'Neill B, Davison G, Nevill A, Murray J, Reid A, et al. Cycle ergometer tests in children with cystic fibrosis: reliability and feasibility. *Pediatr Pulmonol* 2012 Dec;47(12):1226–34.
- [9] Orenstein DM. Exercise testing in cystic fibrosis. *Pediatr Pulmonol* 1998;25:223–5.
- [10] Rogers D, Prasad SA, Doull I. Exercise testing in children with cystic fibrosis. *J R Soc Med* 2003;96:23–9.
- [11] Nixon PA, Joswiak ML, Fricker F Jay. A six-minute walk test for assessing exercise tolerance in severely ill children. *J Pediatr* 1996;129(3).
- [12] Lesser DJ, Fleming MM, Maher CA, Kim SB, Woo MS, Keens TG. Does the 6-min walk test correlate with the exercise stress test in children? *Pediatr Pulmonol* 2010 Feb;45(2):135–40.
- [13] Bradley JM, Howard J, Wallace E, Elborn S. Validity of a modified shuttle test in adult cystic fibrosis. *Thorax* 1999;54:437–9.
- [14] Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman LB, Jones NL, et al. Effect of encouragement on walking test performance. *Thorax* 1984;39:818–22.
- [15] Radtke T, Stevens D, Benden C, Williams CA. Clinical exercise testing in children and adolescents with cystic fibrosis. *Pediatr Phys Ther* 2009 Fall;21(3):275–81.
- [16] Balfour-Lynn IM, Prasad SA, Lavery A, Whitehead BF, Dinwiddie R. A step in the right direction — assessing exercise tolerance in cystic fibrosis.pdf. *Pediatr Pulmonol* 1998;25:278–84.
- [17] Aurora P, Prasad SA, Balfour-Lynn IM, Slade G, Whitehead B, Dinwiddie R. Exercise tolerance in children with cystic fibrosis undergoing lung transplantation assessment. *Eur Respir J* 2001;18:293–7.
- [18] Prasad SA, Randall SD, Balfour-Lynn IM. Fifteen-count breathlessness score — an objective measure for children. *Pediatr Pulmonol* 2000;30:56–62.
- [19] Holland AE, Rasekaba TM, Wilson JW, Button BM. Desaturation during the 3-minute step test predicts impaired 12-month outcomes in adult patients with cystic fibrosis. *Respir Care* 2011;56(8).
- [20] Narang I, Pike S, Rosenthal M, Balfour-Lynn IM, Bush A. Three-minute step test to assess exercise capacity in children with cystic fibrosis with mild lung disease. *Pediatr Pulmonol* 2003 Feb;35(2):108–13.
- [21] Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000;132(7):552–5.
- [22] Kazmerski T, Orenstein DM. The ease of breathing test tracks clinical changes in cystic fibrosis. *J Cyst Fibros* 2012 Sep;11(5):383–6.