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Effect of Intravenous Antibiotics on Exercise Tolerance (3-Min Step Test) in Cystic Fibrosis

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Summary. Most children with cystic fibrosis (CF) feel better and display more energy after a course of intravenous antibiotics (IVABs), but this is not always reflected by a satisfactory improvement in lung function. We assessed the change in exercise tolerance after treatment with IVABs using the 3-min step test, and compared it with changes in spirometric lung function and arterial oxygen saturation (SaO_2). Thirty-six children (mean age, 13.8 years) were enrolled from two tertiary CF centers during an inpatient stay for IVABs.

After 10–14 days of treatment, there was a significant improvement in median FEV_1 from 43% to 57% of predicted values ($P < 0.0001$), and median FVC from 66% to 73% of predicted values ($P < 0.0001$), while median SaO_2 significantly increased from 95% to 96.5% ($P < 0.05$). This was accompanied by a reduction in resting heart rate (median 118 bpm to 109 bpm, $P < 0.005$) and subjective breathlessness at rest (median visual analogue score 2.2 to 0.8, $P < 0.005$). All outcomes of exercise tolerance were improved after IVABs. There was a reduction in maximum heart rate (median 156 bpm to 150 bpm, $P < 0.05$) and an increase in minimum SaO_2 (median 93.5% to 94.5%, $P = 0.08$) measured during the step test. There was also a reduction in subjective breathlessness (median visual analogue score of 5.5 to 4.2, $P < 0.005$) and objective breathlessness (median 15-count score of 3 to 2, $P < 0.0001$) measured immediately after the step test.

Exercise testing was a useful outcome measure for monitoring effectiveness of inpatient therapy, and complemented spirometry and SaO_2 monitoring. The simple ward-based 3-min step test was found to be a particularly suitable method for measuring changes in exercise tolerance in children with CF. **Pediatr Pulmonol. 2001; 32:38–43.** © 2001 Wiley-Liss, Inc.

Key words: cystic fibrosis; exercise testing; exercise tolerance; step test; antibiotics; children.

INTRODUCTION

After a course of intravenous antibiotics (IVABs), most children with cystic fibrosis (CF) feel noticeably better and display more energy during exercise training. However, this may not always be reflected by a satisfactory improvement in lung function as measured by spirometry. This can be disappointing for children and their parents who often scrutinize results of their lung function, which is not surprising considering that these results are often used to guide length of therapy and hospital stay. The aim of this study was to assess changes in exercise tolerance after an inpatient course of IVABs, using the 3-min step test.[1] This could then be compared to changes in lung function and arterial oxygen saturation. It might also provide additional information on the use of the step test as a method for assessing response to a therapeutic intervention in children with CF.

MATERIALS AND METHODS

The study was approved by the Hospital Research Ethics Committee; parents and/or patients gave written informed consent.

Subjects

Subjects were patients with CF admitted for IVABs to one of two tertiary pediatric CF centers in London. Exclusion criteria were age under 6 years, current oxygen therapy, or resting $SaO_2 < 90\%$. There were 36 patients

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(20 boys, 16 girls) with a mean age of 13.8 years (range, 6–18 years). On admission, their mean baseline forced expiratory volume in 1 sec (FEV_1) was 47% of predicted values adjusted for gender and height (range, 24–78%), and mean resting SaO_2 was 95% (range, 90–100%). Patients could be divided into two groups: those admitted for treatment of a symptomatic chest exacerbation that their clinician felt warranted a course of IVABs, i.e., unplanned admissions (n = 28), and those being admitted electively for routine 3-monthly IVABs (n = 8). All patients received intravenous therapy with two antibiotics based on microbiological sensitivity of sputum culture, from a combination of the following: amikacin, azlocillin, aztreonam, ceftazidime, colomycin, flucloxacillin, gentamicin, meropenem, piptazobactam, and tobramycin. Standard inpatient management was carried out, including regular physiotherapy and nutritional support. Additional therapies included inhaled bronchodilators (n = 20), long-acting β_2-agonists (n = 8), inhaled corticosteroids (n = 24), oral corticosteroids (n = 2), nebulised antibiotics (n = 22), and Dornase alfa (n = 14).

Study Design

Patients performed lung function tests and the non-incremental 3-min step test on admission (before or within 24 hr of starting IVABs), and again after 10–14 days of therapy (median, 13 days). Lung function was assessed by standard spirometry, using a compact spirometer (Vitalograph®, Buckingham, UK) which was calibrated daily to within 1%. FEV_1 and forced vital capacity (FVC) were recorded as percent predicted for gender and height. Maximal expiratory flow at 25% of remaining vital capacity ($MEF_{25\%}$) was recorded in absolute figures. A maximum of three measurements was recorded for each parameter. Resting SaO_2 and pulse rate was measured using a Biox 3700e® pulse oximeter (Ohmeda, Boulder, CO), with a flexiprobe attached to the finger and its lead strapped to the subject's arm.

The Step Test

Subjects stepped up and down a commercially available single step set at a height of 15 cm (6 inches).[1] The stepping rate of 30 per minute for 3 min was controlled by a metronome. Patients could stop if they felt tired or if the SaO_2 fell below 75%, in which case the total number of steps taken was calculated. Patients were given standardized encouragement and shown how to change the leading leg to reduce localized muscle fatigue. The step test was performed 30 min after physiotherapy, to standardize the effects of the latter on exercise testing. If the child used routine bronchodilators before physiotherapy, this was done 10 min before the start of physiotherapy, and the pretesting regimen was kept the same for the two sets of measurements.

Measurements were made of minimum SaO_2 and maximum pulse rate at rest and then during exercise. Two scores of breathlessness were assessed before and immediately after exercise. These scores were a subjective visual analogue score (VAS) and the objective 15-count breathlessness score.[2] The former consists of a 10-cm horizontal line with two anchor points, one at each extreme. On the left (zero) it is labelled, "I am not at all short of breath," while at the other end (10 cm) it is labelled, "The most short of breath I have ever been." The subject puts a mark through the line where they think their breathlessness fits on the scale, which is then measured (in centimeters) from the zero point. For the 15-count score, the subject takes a deep breath and counts out loud to 15, taking about 8 sec to do so. The number of breaths needed to complete the count, including the initial breath, is the score (thus, the minimum score is 1).

Statistical Analysis

Statistical analysis was performed using Minitab® software (Minitab, Inc., State College, PA). Nonparametric Wilcoxon tests were used to compare the outcomes before and after exercise, and Mann-Whitney tests to compare different groups. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Lung Function

Intravenous antibiotics led to a significant increase in lung function; there was also a significant increase in SaO_2, although the clinical effect was small (Table 1, Fig. 1). Differences after IVABs were less marked in the

ABBREVIATIONS

bpm	Beats per min
CF	Cystic fibrosis
FEV_1	Forced expiratory volume in 1 sec
FVC	Forced vital capacity
IVABs	Intravenous antibiotics
$MEF_{25\%}$	Maximal expiratory flow at 25% vital capacity
ns	Not significant
SaO_2	Arterial oxygen saturation
VAS	Visual analogue score

TABLE 1—Median FEV_1 and FVC (% Predicted), $MEF_{25\%}$ (L/sec), and SaO_2 (%) Before and After Intravenous Antibiotic Therapy (IVABs)[1]

	Pre-IVABs (% pred.)	Post-IVABs (% pred.)	Difference (% pred.)	*P*-value
FEV_1	43.0	57.0	+9.5	<0.0001
FVC	66.0	73.0	+9.0	<0.0001
$MEF_{25\%}$	0.23	0.33	+0.1	<0.01
SaO_2	95.0	96.5	+1.0	<0.05

[1]pred., predicted.

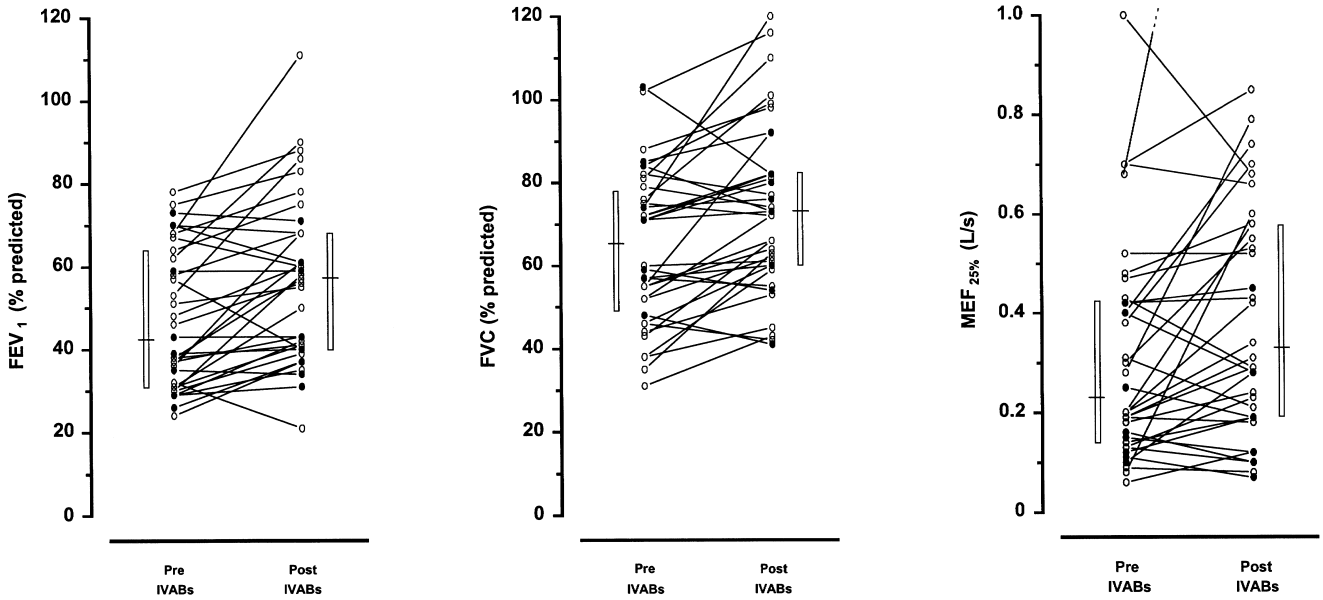

Fig. 1. FEV_1 (% predicted), FVC (% predicted), and $MEF_{25\%}$ (L/sec) before and after IVABs. Open circles are patients admitted for chest exacerbations (n = 28); solid circles are those admitted for regular IVABs (n = 8). Also shown are medians (lines) and interquartile ranges (bars).

children admitted for regular IVABs (n = 8) compared to those with exacerbations (n = 28); median differences were 0 (regular IVABs) vs. +10% (exacerbation) predicted ($P < 0.05$) for FEV_1, −1.5 vs. +10.5% predicted ($P < 0.005$) for FVC, −0.04 vs. +0.08 L/sec ($P < 0.05$) for $MEF_{25\%}$, and 0% vs. +1% (P = ns) for SaO_2 (Fig. 1).

Exercise Tolerance

Baseline

After IVABs, there was a significant decrease in resting heart rate and subjective breathlessness (VAS) at rest, but no difference in objective breathlessness score (15-count score) at rest (Table 2). However, before IVABs, 12/36 (33%) had a 15-count score >1 compared to 5/36 (14%) after IVABs (a score of 1 is the expected score at rest[2]). One child could not understand the concept of the VAS, so results for VAS relate to 35 patients only. Changes seemed less marked in those admitted for regular IVABs compared to those with exacerbations (with median differences of −3 vs. −21 bpm for heart rate, and −0.6 vs. −0.3 for VAS), but statistical significance was not reached.

TABLE 2—Median Resting Heart Rate (bpm), Visual Analogue Score (VAS), and 15-Count Score Before and After Intravenous Antibiotic Therapy (IVABs)

	Pre-IVABs	Post-IVABs	Median difference	*P*-value
Heart rate	118.0	109.0	−9.0	<0.005
VAS	2.2	0.8	−1.1	<0.005
15-count score	1.0	1.0	0.0	ns

Effects of exercise

All patients completed the 3 min of step test, apart from one child who was stopped after 2 min 20 sec due to SaO_2 falling to 75% during pretreatment testing.

Exercise led to significant changes ($P < 0.0001$) in heart rate (rise), SaO_2 (fall), and breathlessness (rise in VAS and 15-count score) (Fig. 2). After IVABs, the exercise-induced maximum heart rate was significantly less than at the start of treatment (median difference 10 bpm, $P < 0.05$). The minimum SaO_2 during exercise was higher after treatment but did not quite reach significance (median difference 1%, $P = 0.08$), although this difference was significant in those admitted for exacerbations (median difference 1%, $P < 0.05$). Exercise-induced breathlessness (both subjective and objective measures) was significantly less after IVABs (for VAS, median difference 1.0, $P < 0.005$; for the 15-count score, median difference 1.0, $P < 0.0001$). Looking at the actual exercise-induced changes, the differences in heart rate, SaO_2, and VAS were not altered by treatment, although the exercise-induced increase in 15-count breathlessness score was significantly reduced ($P = 0.001$) after IVABs (Table 3). Using a cutoff of 2 for the postexercise 15-count score (which has been shown to be useful in discriminating CF children from normal children[2]), the

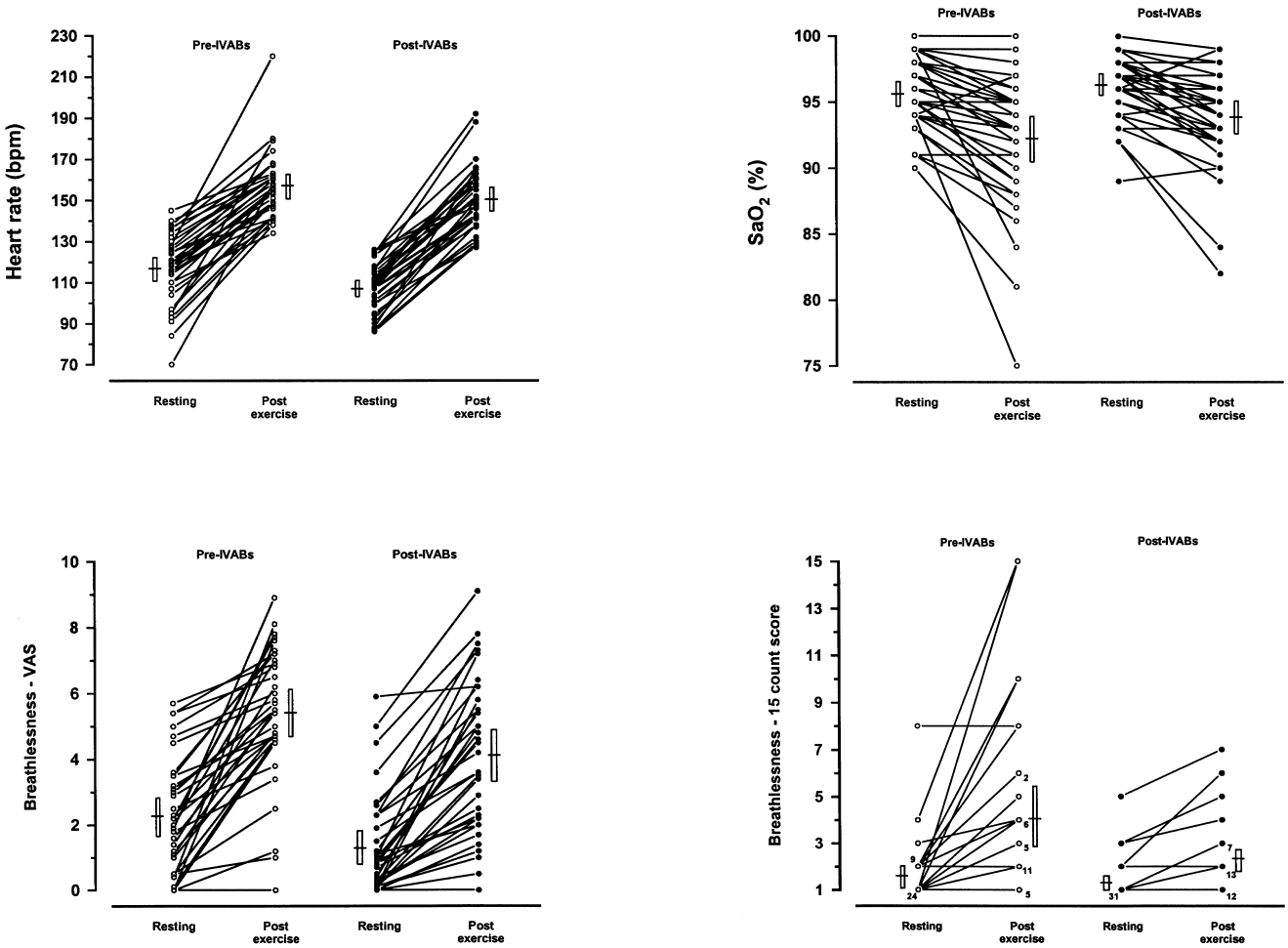

Fig. 2. Maximum heart rate (bpm) and minimum SaO_2 (%) at rest and during exercise, VAS, and 15-count breathlessness score at rest and after exercise, measured both before (open circles) and after (solid circles) a course of IVABs. Also shown are medians (lines) with interquartile ranges (bars). Overlapping data points for the 15-count breathlessness score are indicated by the adjacent numbers.

score after exercise was greater than 2 in 20/36 (56%) children before IVABs, compared to 11/36 (31%) after IVABs. These changes were all similar when dividing the subjects into the two groups of those admitted for regular IVABs vs. exacerbations, apart from the reduction in exercise-induced increase in 15-count score after IVABs, which was found significant only in the group admitted for exacerbations. Response to exercise and subsequent changes after treatment correlated poorly with baseline measures of lung function.

DISCUSSION

After a 10–14-day inpatient course of IVABs, spirometric lung function and SaO_2 were significantly increased, while resting heart rate and subjective symptoms of breathlessness were reduced. All outcomes of exercise tolerance were improved after the stay in hospital, although the reduction in the drop of SaO_2 did not quite reach statistical significance ($P = 0.08$). This is in keeping with the subjective impression that the children seemed to feel better and were more active as their hospital stay progressed. The finding that lung function was significantly increased after IVABs in the children is in keeping with previous work.[3,4] The improvement could also have been due to the inpatient physiotherapy and nutritional management as well as the "enforced adherence" to prescribed treatment regimens. However, the increase was disappointingly small in clinical terms, and indeed less than that which may be accounted for by the known variability in spirometric measurements found in children with CF.[5,6] The improvement in SaO_2 was also relatively small. However, one of the exclusion criteria for the study was "current oxygen therapy or

TABLE 3—Median Maximum Heart Rate (bpm) and Minimum SaO_2 (%) During Exercise, Visual Analogue Scores (VAS), and 15-Count Score After Exercise, Before and After Intravenous Antibiotic Therapy (IVABs)

	Pre-IVABs	Post-IVABs	Median difference	*P*-value
Heart rate	156.0	150.0	−10.0	<0.05
SaO_2	93.5	94.5	+1.0	0.08
VAS	5.5	4.2	−1.0	<0.005
15-count score	3.0	2.0	−1.0	<0.0001

resting SaO_2 <90%," and it would have been in those excluded children that the greatest improvement in SaO_2 might have been seen after IVABs.

The resting heart rate was significantly reduced after IVABs, particularly in those admitted with acute exacerbations. Presumably this is due to a reduction in the high metabolic rate and increased work of breathing associated with a chest infection. However, even after treatment, the resting heart rates remained above the expected normal range (70–110 bpm) in half the children. Heart rate is probably an underutilized measure of well-being in CF, but our study suggests that it is an important and useful variable. After the 2-week treatment period, the children also felt less breathless at rest, as measured by the subjective visual analogue score. This, together with the reduction in tachycardia, probably explains why they often feel better and display more energy by the end of a hospital admission. The objective measure of breathlessness (15-count score) at rest was unaltered by treatment, but this is not too surprising, as this score is more discriminatory at determining exercise-induced breathlessness.[2] After treatment, the children had significantly smaller postexercise increases in 15-count scores. Previous work on repeatability of the 15-count score[2] would indicate that the changes found in this study were not simply due to factors relating to repeat testing, but were a genuine finding. Breathlessness is a symptom and sign that is paid little attention to in pediatric practice and the pediatric literature, and yet it is important. The results of this study confirm the feasibility and usefulness of measuring breathlessness.

After the treatment period, the exercise-induced maximum heart rate and breathlessness scores (both subjective and objective measures) were significantly lower than at the start of treatment. The minimum SaO_2 during exercise was higher, but this difference did not quite reach significance, although it did reach significance in those admitted for exacerbations. It would seem, therefore, that exercise tolerance was improved by the hospital stay, which is in keeping with previous work in which inpatient therapy, including IVABs, led to improvement in exercise capacity in children[4] and adults[4,7] measured by cycle ergometry or a modified shuttle test.[8] This study also confirms the usefulness of exercise testing in assessing response to treatment in children with CF. Standard spirometry and resting SaO_2, which are the standard outcome measures used in clinical practice, do not give the full picture and are not usually predictive of exercise tolerance.[1,9] Exercise testing is an important outcome, and the UK CF Trust has recommended its use as part of annual assessments for all patients.[10] The 3-min step test was previously shown to be a useful, simple, and quick method for exercise testing in children over age 6 years.[1,2] It has now been shown to be sensitive to changes after a therapeutic intervention, and it is important that a method of exercise testing can do this.[11] Exercise testing is a good marker of physiological function, and the CF Foundation consensus on outcome measures for clinical trials has recommended exercise testing as a useful measure in phase I and II trials in children over age 6 years.[12] The step test is so portable and easily taught (to patients and participating centers) that it may well have a place in phase III trials, even when multicenter.

The comparison of children admitted with a chest exacerbation vs. those admitted for routine 3-monthly IVABs is interesting. The striking finding was that IVABs did not seem to improve any measures of lung function or exercise tolerance in those having a routine elective admission (Fig. 1). However, this must be put into the context of the relatively small numbers in this group; the study was not sufficiently powered to look for differences between the two groups, which means it is not possible to draw major conclusions.

In conclusion, a 2-week hospital stay for IVABs and optimization of chest physiotherapy and nutritional management led to an improvement in lung function, SaO_2, resting heart rate, and subjective breathlessness. It also led to an improvement in exercise tolerance measured with the 3-min step test. Exercise testing and breathlessness measurements are useful and important outcome measures for monitoring therapy in children with CF, and particularly so when using simple ward-based tests such as the step test and the 15-count breathlessness score.

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