Unique Pattern of Pulmonary Function After Exercise in Patients With Cystic Fibrosis

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The purpose of this study was to assess the incidence, degree, pattern, and time course of pulmonary function test (PFT) changes measured after a dynamic exercise challenge. Forced expiratory maneuvers were performed before and serially after a 7-min run-walk in 44 patients with cystic fibrosis (CF). Twenty-four patients met at least one PFT criterion for exercise-induced bronchospasm (EIB) within 21 min after exercise, and 38 patients had ≥5% increase in a PFT parameter at some point after exercise. The mean time of greatest increase in PFTs occurred sooner than the greatest decrease, which was later than for 22 patients with asthma or allergic rhinitis found to have EIB. Age was inversely related to percentage fall in forced expiratory volume in 1 s (FEV₁) after exercise. These results demonstrate a distinct pattern of PFTs measured after exercise in most patients with CF, with an early bronchodilation followed by a significant decrease in PFTs.

Many patients with cystic fibrosis (CF) complain of shortness of breath often accompanied by coughing during or after exercise. These symptoms are also typical of exercise-induced bronchospasm (EIB), an increase in bronchial obstruction to airflow that can occur after aerobic activities (2). Studies that have attempted to quantify the incidence of EIB in patients with CF have assessed changes in pulmonary function tests (PFTs) using varying techniques. These investigations have produced conflicting results, ranging from no patients having EIB to as high as 28% (3, 7, 17, 19, 21, 23). Issues surrounding the interpretation of serial PFTs in all patients (1, 18), especially those with CF (6, 8, 18), have complicated the analysis of data.

There is also evidence that bronchodilators can have a paradoxical bronchoconstricting action in some patients with CF due to aggravating the airway wall instability characteristic of chronic bronchiectatic disease (9). Therefore, routine use of bronchodilators for general therapy or for prophylaxis of EIB may not be indicated. Some studies have found that many patients with CF actually have notable degrees of increase in PFTs in the immediate post exercise period (3, 7, 19).

The purpose of this retrospective study was to assess the incidence, degree, pattern, and time course of PFT changes brought on after a heart-rate controlled...
dynamic exercise challenge. A large number of the stable members of our CF clinic population were studied, allowing statistical analysis of subgroups within the patients studied. The patients were cleared of the short-term effects of inhaled bronchodilators at the time of testing. While analysis of forced expiratory volume in 1 s (FEV₁) is emphasized, as recommended in comparing PFTs in asthmatics, more complete PFT data was collected to allow study of changes occurring in smaller airways of the patients.

Materials and Methods

Clinically stable patients with CF were referred for exercise evaluations that included a pulmonary function evaluation before and after a separate exercise challenge. Testing was not attempted on children less than 5 years old. Any prescribed short-acting bronchodilator medications, typically inhaled or oral beta-adrenergic agonists, were withheld on the day of testing (≥12 hours). One patient, who was on a long-acting oral theophylline medication, in addition to an inhaled bronchodilator, was instructed to continue taking the theophylline but to withhold the inhaled bronchodilator. Testing was supervised by a physician, who first determined that the patient was medically stable, having no signs of wheezing, acute respiratory distress, or acute illness.

Forced expiratory maneuvers were performed and analyzed on a computerized spirometer using a pneumotachograph (Multispiro LT-plus, Medical Equipment Designs, Laguna Hills, CA). Flow-volume loops were produced, and the following pulmonary function test parameters and their percentage of predicted values (16) were monitored: forced vital capacity (FVC), FEV₁, peak expiratory flow rate (PEFR), and forced expiratory flow between 25 and 75% of FVC (FEF₂₅₋₇₅).

Three to four preexercise efforts were obtained, until two consistent best performances were produced or until there was any diminution in performance. Choice of a best test was based on the test with the highest FVC and FEV₁, unless there was another test with an FVC and FEV₁ within 5% and significantly higher values in the other primary PFT variables. This was done to allow consideration of smaller airway performance, reflected in the FEF₂₅₋₇₅, in choice of best and worst tests. Testing was performed in an air-conditioned environment with temperature ranging from 22 to 25 °C and humidity from 60 to 70%.

The treadmill run-walk exercise challenge used was designed to maximize the sensitivity of provoking EIB based on studies that compared the mode, duration, and intensity of exercise (10, 12). Warm-up, which can diminish the bronchospastic response, was not allowed (2). The test duration was 7 min. The treadmill was set at a 10% grade, which was not adjusted except upwards in one tall, relatively athletic patient. Heart rate was monitored during the test with a chest strap system (CIC Heartwatch, Computer Instruments Corp., Hempstead, NY). Speed was adjusted based on the heart rate response and the patients' comfort with the treadmill.

The heart rate target was to equal or exceed 170 bpm as quickly as possible; the treadmill speed was reduced if the heart rate continued to rise after passing 170. This rate is approximately 85% of the predicted maximal heart rate for this young population. The object was to give all patients, regardless of size and
physical conditioning, a challenge of similar minimal intensity that would strongly elevate ventilation without producing exhaustion. Most patients walked most of the test, although they were encouraged to try to run at least part of the time and to not hold onto the handrails. Average exercise heart rate, reflective of exercise challenge “dose,” was 156 ± 13 bpm, which is reduced from the target by the lower heart rates occurring at the beginning of the exercise challenge, before achievement of steady state.

The chest strap heart rate sensor was removed immediately after exercise challenge. Starting at 2 min postexercise, and then every 3 min until 20–21 min, single forced expiratory maneuvers were performed as described previously. Albuterol by inhaler or nebulization was administered after the test to any patients who still had any significant decrease in pulmonary function or any symptoms after the seven postexercise spirometry efforts, or who had omitted regular bronchodilator treatment on that day.

A “worst postexercise test” was selected based on the greatest fall in FEV$_1$ and FEF$_{25-75}$ that was of a greater extent than FVC and indicative of increased obstruction. EIB was diagnosed in any patient who had a fall from baseline in FEV$_1$ or PEF of ≥15% or in FEF$_{25-75}$ of ≥25% or any of the seven efforts collected after exercise. A “best postexercise test” was also selected, again based primarily on greatest increase, or smallest fall, in FEV$_1$ and FEF$_{25-75}$. In addition, the results for the best two preexercise efforts and all seven postexercise efforts were combined and plotted versus time for analysis of the group’s time-response pattern. The patients’ clinical responses were not systematically recorded.

All exercise challenge tests performed on patients with CF were reviewed. Testing using the same procedures done by the same physician on 30 patients with asthma and/or allergic rhinitis, most of whom were part of another study (14), was reviewed for comparison with the CF group. Repeated measures ANOVA and a Dunnett’s post hoc comparison with baseline were used to compare the fall in spirometry parameters between best pretest and best and worst posttests. An independent two-tailed $t$ test was used to compare time of best and worst posttests and results of patients below and above the median age of 14.6 years. Least-squares regression analysis was used to assess the relationship between resting PFTs or age and changes in PFTs with exercise.

**Results**

Table 1 contains a profile of the study group. There were 44 patients with CF tested, 21 males and 23 females. Six patients were black, 17 white Hispanic, and 18 white non-Hispanic. Twenty-four (54.5%) met the pulmonary function criteria for EIB. The 1 patient who continued to take oral theophylline on the day of testing still had one of the largest postexercise responses (42% fall in FEV$_1$). Of the 30 tests in non-CF patients used for comparison and evaluated using the same criteria (14), 22 (73.3%) had positive results for EIB.

Table 2 displays the average timing of the best and worst tests and the degree of PFT changes found in the entire group of 44 patients after exercise. The time of the worst test (12.2 ± 6.0 min) is delayed compared to the typical EIB pattern expected in asthma. By comparison, the mean time of worst test for the 22 atopic patients with EIB was 7.7 ± 5.3 min ($p < .005$ compared with CF).
Table 1  Selected Characteristics of 44 Patients With CF

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151.0</td>
<td>19.6</td>
</tr>
<tr>
<td>% FVC</td>
<td>79.3</td>
<td>17.2</td>
</tr>
<tr>
<td>% FEV₁</td>
<td>63.2</td>
<td>20.6</td>
</tr>
<tr>
<td>% PEFR</td>
<td>72.8</td>
<td>25.9</td>
</tr>
<tr>
<td>% FEF₂₅₋₇₅</td>
<td>42.6</td>
<td>29.4</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>68.6</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Note. FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; PEFR = peak expiratory flow rate; FEF₂₅₋₇₅ = forced expiratory flow between 25 and 75% of FVC.

Table 2  Group Results for 41 Patients With CF:
Timing and Degree of Bronchial Reactivity

<table>
<thead>
<tr>
<th></th>
<th>% Rise</th>
<th>SD</th>
<th>% Fall</th>
<th>SD</th>
<th>Positives</th>
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<tr>
<td></td>
<td>M</td>
<td></td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁</td>
<td>8.4</td>
<td>8.6</td>
<td>8.7</td>
<td>11.1</td>
<td>11</td>
</tr>
<tr>
<td>PEFR</td>
<td>8.9</td>
<td>23.5</td>
<td>11.1</td>
<td>18.5</td>
<td>16</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅</td>
<td>18.3</td>
<td>21.8</td>
<td>16.3</td>
<td>16.8</td>
<td>12</td>
</tr>
<tr>
<td>At least 1 positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

Time best test (min) 8.9 6.3
Time worst test (min) 12.2 6.0

Note. FEV₁ = forced expiratory volume in 1 s; PEFR = peak expiratory flow rate; FEF₂₅₋₇₅ = forced expiratory flow between 25 and 75% of FVC. p = .037 by independent t test for time of best test vs. time of worst test.

Figure 1, demonstrating mean falls in PFTs, helps to further illustrate the degree of EIB found in the 24 patients with CF with EIB as compared to the 22 asthma/allergy patients with EIB. The falls in pulmonary function parameters were significantly different between the two groups, most strongly so for the smaller airways represented in FEF₂₅₋₇₅. It is also apparent that the non-CF group had more bronchospasm in the smaller airways (p < .05), reflected in FEF₂₅₋₇₅, while the patients with CF had a statistically uniform (p > .05) degree of PFT change for all three monitored parameters. Due to relative uniformity of response between PFT parameters in the patients studied, and since FEV₁ is recognized...
as a more reliable indicator of PFT change in patients with CF, more emphasis will be placed on changes in FEV₁ in the subsequent analysis of the patients with CF.

Figure 2 shows individual changes in FEV₁. The group mean percentage of predicted FEV₁ (%FEV₁) was significantly higher for the best test and significantly lower for the worst test than at baseline ($p < .05$). Postexercise lability (7)—defined as the difference between postexercise tests with most and least evidence of obstruction ($FEV₁ = 16.8\%, PEFR = 21.6\%, FEF_{25-75} = 33.6\%$)—was greater than pre- to postexercise reactivity, due, in part, to the increase in PFTs evident in the early postexercise period.

The best test was observed at a mean time of 3.3 min before the worst test. This early postexercise rise, seen in pulmonary function in most patients, is reflected in one of the example patterns of the graphs of pulmonary function response throughout the test (Figure 3). The overall pattern seen for the group was bronchodilation early, peaking in the first few postexercise efforts, followed by bronchospasm later on. Twelve (27.3\%) patients had a different pattern, with decreased
FEV$_1$ at 2 and 5 min postexercise (Figure 3). All but 2 of these met the PFT criteria of EIB at some point postexercise (83% positive predictive value for EIB).

Figure 4 demonstrates an opposite pattern of the comparison group of atopic patients. Their pattern of an immediate postexercise obstructive pattern followed by recovery is more classical for EIB (2).
Regression analysis of the relationship in patients with CF between age and percentage change in FEV\textsubscript{1} for the worst test after exercise showed a significant inverse relationship ($r = .40$, $p = .006$). The percentage fall in FEV\textsubscript{1} after exercise was significantly less severe ($p = .02$) for the 22 oldest patients ($>14.6$ years old) than for the 22 youngest ($4.9\%$ vs. $12.4\%$).

A significant positive correlation using percentage change was found between the preexercise value and percentage rise in PEFR (Table 3). Additional positive relationships, involving rise in FEV\textsubscript{1} and FEF\textsubscript{25-75}, and an inverse relationship (fall FEF\textsubscript{25-75}) were significant when using the absolute values of PFT changes versus baseline.

Twenty-eight patients with CF were given albuterol (by inhaler or nebulizer) after the seventh postexercise PFT measurement (20–21 min postexercise). They had their PFTs measured 5 and (for 27 of them) 10 min after this treatment. Only minimal changes in PFTs were seen ($1.8\%$, $4.1\%$, $7.6\%$ improvements in FEV\textsubscript{1}, PEFR, and FEF\textsubscript{25-75}, respectively, at 10 min).

**Discussion**

Using methodology designed to maximize sensitivity, we found evidence of PFT changes compatible with EIB in $55\%$ of 44 patients with CF. The prevalence of EIB found in the present study is higher than that reported previously. The...
Figure 4 — Changes in FEV₁ before and after an exercise challenge for patients with asthma and/or allergic rhinitis also meeting the criteria for exercise-induced bronchospasm. Ex = 7 minute walk-run exercise challenge.

Table 3  Correlations of Baseline Pulmonary Function for the Best and Worst Postexercise Tests

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Change</th>
<th></th>
<th></th>
<th>% Change</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Best</td>
<td>Worst</td>
<td>Best</td>
<td>Worst</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>.33*</td>
<td>-.16</td>
<td>% FEV₁</td>
<td>.01</td>
<td>-.06</td>
</tr>
<tr>
<td>PEFR (L/sec)</td>
<td>.11*</td>
<td>-.01</td>
<td>% PEFR</td>
<td>.40*</td>
<td>-.03</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (L/sec)</td>
<td>.26*</td>
<td>.50*</td>
<td>% FEF₂₅-₇₅</td>
<td>.09</td>
<td>-.15</td>
</tr>
</tbody>
</table>

Note. FEV₁ = forced expiratory volume in 1 s; PEFR = peak expiratory flow rate; FEF₂₅-₇₅ = forced expiratory flow between 25 and 75% of FVC. *p < .05.
protocol of Zambie et al. (23) included postexercise spirometry efforts at only three points after exercise. They found a 28% prevalence of >15% postexercise fall, using only PEFR for comparison with preexercise performance. Day and Mearns (7) also used only PEFR (measured every 2 min during and for only 15 min after exercise) and found a total frequency of abnormal (defined as >10% fall in PEFR) bronchoconstriction of 25% (13 of 52 subjects).

Van Haren et al. (21) tested their subjects 7 times after exercise, but analyzed only for fall in FEV₁ of 15%, which they did not find in any of their subjects. While the subjects of Skorecki et al. (19) performed the same number of postexercise PFTs as our subjects, they report only group averaged results and found no significant difference versus controls with no known respiratory disease. It is possible that if multiple pulmonary function parameters were examined at each point, some of their subjects may have demonstrated evidence of significant bronchospasm.

Using our techniques, we have found a significant prevalence of EIB in a nonasthmatic control group (15). The EIB in that study was in a pattern similar to the atopic comparison group presented in the current study. Conversely, if we compared only PEFR or FEV₁, as has been done previously, the prevalence of EIB would be reduced to 36% or 25%, respectively, in the patients with CF. This is still slightly higher than has been previously reported (3, 7, 17, 19, 21, 23). The inclusion of additional parameters increases the sensitivity of the analysis at the cost of increasing the chances of finding chance differences. As seen in Figure 1, there is a statistically greater fall in PFTs and stronger differentiation between the three parameters analyzed in patients with atopic conditions than is seen in patients with CF. This may indicate a greater need to explore other parameters besides FEV₁ in the non-CF population.

Notably, only 12 (27%) patients had an early postexercise fall in PFTs, similar to the response expected in patients with asthma (5). The degree of this early postexercise bronchospasm was probably blunted by a competing “CF-type” improvement of pulmonary function, possibly involving shifting of respiratory mucus. Whether the improvement in flow in the more common CF pattern occurs during or after exercise was not addressed in this study. We have not attempted to distract our subjects during the exercise challenge with maximal expiratory efforts. Therefore, we do not have data on their pulmonary function during exercise. In studies that have examined changes in PEFR or FEV₁ during exercise, bronchodilation was found to occur during exercise (11, 13, 20), especially in patients with CF (7, 19). The bronchodilation is then thought to wane after exercise, leaving milder bronchodilation in the CF response described in our study, returning close to baseline in the normal response, or crossing over to bronchospasm in patients with reactive airways.

Another difference in the study of Skorecki et al. (19), compared to ours, is that bronchodilators were withheld for as little as 6 hours before testing in their study. The possibility of a continued presence of bronchodilating medications may have further decreased the prevalence and degree of bronchospasm in their subjects.

Both the study of Skorecki et al. (19) and that of Zambie et al. (23) used a slightly different treadmill protocol, with 15% grade and 3 mph speed, not adjusted to the response of the individual patient, as was done in the present study. Most of our larger patients went at speeds faster than 3 mph, which
encouraged running. Running has been found to increase the sensitivity of the exercise challenge to produce EIB (10, 12). Heart rate was used to adjust the speed and slopes in the study of Van Haren et al. (21), but a 2-min acclimation period was allowed, which may have prophylaxed the subjects from EIB (2).

Our patients were older than those tested in the other studies, except for those studied by Van Haren et al. (21), who were all adults. Van Haren et al. found no fall in FEV₁ in their adult subjects, and we found a lesser average degree of fall in FEV₁ in our older patients. This may indicate a lessening in airway reactivity in older patients with CF.

Although complete baseline pulmonary data were not provided in other studies, from the data available, our patients seem to have had similar pulmonary function. We did not find a difference in degree of FEV₁ changes between patients with higher versus lower baseline FEV₁, nor did we find a significant correlation between baseline FEV₁ and fall in FEV₁ after exercise. This indicates that disease severity of the tested patients did not necessarily affect the changes in FEV₁ after the exercise challenge.

These data point out a need to consider EIB in the differential diagnosis of respiratory symptoms occurring with exercise in these patients. Conversely, since over 30% of patients did not have EIB, a blanket recommendation to treat all patients with a bronchodilator would not be appropriate, especially given the paradoxical response seen in some patients with CF (9). Objective evaluation is probably necessary to separate patients with or without EIB and to determine which patients would benefit from preexercise prophylaxis with a bronchodilator or other methods used in the control of EIB (2). The minimal mean bronchodilation seen in the patients given albuterol in this study provides further emphasis of this point.

Exercise has been advocated as a tool in the clearance of respiratory mucus and as a possible complement to chest physical therapy (4, 22). The early post-exercise improvement in pulmonary function demonstrated in this study may help foster mucus clearance, especially if followed by exercise-induced coughing, and may help to explain the observed benefit on pulmonary toilet. Conversely, shifts in mucus caused by exercise could be causing the changes in pulmonary function, rather than the PFT changes only being due to changes in airway smooth muscle tone.

The results of Van Haren et al. (21) shed some light on the mechanism of PFT changes in patients with CF. While they did not detect EIB in their subjects, they did find postexercise bronchodilation (13% increase in FEV₁). Despite no tests being positive for EIB, 10 of 18 subjects (56%) had positive responses to histamine challenge, equal to the frequency of EIB found in our study. All had mild to large amounts of bronchodilation on challenge with terbutaline, a bronchodilator, and with ipratropium, an inhaled anticholinergic agent and atropine derivative. Their findings confirm the role of airway smooth muscle tone and its vagal control in PFT changes seen in patients with CF.

An inverse relationship between baseline pulmonary function and degree of fall with exercise, as was previously examined by Skorecki et al. (19) and Day and Mearns (7), was found in our study only for FEF₂₅₋₇₅. Unlike the present study, their studies found that the lower the baseline PEFR expressed as a percentage of predicted value, the greater the percentage rise in PEFR with exercise. While this relationship may be viewed as a mathematical probability
(regression to the mean), this possibility should be reduced by using actual values and changes in actual values, as done here. Our results display the opposite relationship of baseline PEFR with percentage rise in PEFR and bring to light three additional direct relationships. This type of relationship was also examined in a slightly different manner by Zambie et al. (23), and a significant relationship was not found for PEFR, but was present for FEV₁ and FVC.

The distinct pattern of PFT changes after exercise found in patients with CF, unique from the pattern of other patients found to have EIB (e.g., those with asthma, allergic rhinitis, no atopic disease), was first brought to light in the study of Day and Mearns (7). Skorecki et al. (19) demonstrated the pattern by one example of a patient with CF, one patient with asthma, and one nonreactive normal control subject. Our findings confirm this pattern in the early postexercise period for most patients; however, our patients had more of a spontaneous recovery in pulmonary function by 20 min postexercise than did the example subjects provided by Skorecki et al. Based on these prior studies that measured PEFR during exercise, this dilation probably begins during exercise in most patients, continuing in the early postexercise period. Also, a minority of our patients had a predominating "atopic-type" response with an early postexercise bronchospasm (5). These included some of the few known "wheezing" patients in our clinic population.

In conclusion, we found that 55% of patients with CF in our population had evidence of EIB by using sensitive technique and analysis methodology. This pattern includes an immediate postexercise increase in PFTs compared to preexercise values, a later onset of decrease in PFTs, and a minimal bronchodilator response. The pattern of bronchial reactivity in CF is distinct from that of atopic and other patients without CF. Despite this pattern in our population of patients with CF, a high degree of individual variation requires individual assessment of each patient.

References


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