Time Point to Perform Lung Function Tests Evaluating the Effects of an Airway Clearance Therapy Session in Cystic Fibrosis

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BACKGROUND: Lung function parameters are used as end points in most clinical and therapeutic trials in cystic fibrosis (CF) and to evaluate the effects of airway clearance techniques. The aim of the study was to identify at what time point after a physiotherapy session spirometry (FEV₁ and FVC) should be performed to obtain the highest result compared to baseline and to determine whether there are inter-individual and intra-individual differences in children and adults with CF.

METHODS: This was a prospective study. Twenty-four subjects with CF and mean FVC 70 ± 30% and FEV₁ 61 ± 30% of predicted were included. Each subject performed spirometry before their airway clearance session and then immediately after, 30 min after, and 1, 2, and 3 h after their physiotherapy session for 2 consecutive days.

RESULTS: In adult subjects, mean FEV₁ improved 30 min (P < .001), 1 h (P < .002), and 2 h (P < .006) after physiotherapy compared to baseline. In pediatric subjects, it improved immediately after the session but was not statistically significant for recommendation. There were no intra-individual variations, but there were inter-individual variations (not statistically significant).

CONCLUSIONS: Performing spirometry 30 min (adults) and immediately (children) after a session might be optimal if individual peak time values cannot be used. Key words: chest physiotherapy; cystic fibrosis; spirometry; time point. [Respir Care 2014;59(10):1–•. © 2014 Daedalus Enterprises]
 ance techniques offered for CF care is thus essential. Spi-
rometry has been the accepted standard in disease moni-
toring, mostly forced expiratory maneuvers, such as FEV₁
and FVC.⁴

There are standard recommendations from the European
Respiratory Society (ERS) and the American Thoracic So-
ciety (ATS) ² about lung function tests and how spirometry
should be performed.⁵,⁶ However, the ERS and ATS give
no recommendations regarding the timing of spirometry in
relation to physiotherapy, and to our knowledge, there are
no studies investigating at what specific time point spi-
rometry should be performed after a physiotherapy ses-
tion. Thus, the time points to perform a lung function test
after respiratory physiotherapy are still unclear.

The aim of the study was to identify at what time point
after a physiotherapy session spirometry (FEV₁ and FVC)
should be performed to obtain the highest result compared
to baseline and to determine whether there are inter-indi-
vidual and intra-individual differences in children and
adults with CF.

**Methods**

**Design of the Study**

The study was a prospective design. Spirometry was
performed after a physiotherapy session for 2 consecutive
days at different time points. The time points were arbitrarily
chosen to obtain possible time-dependent results. The study
was approved by the regional ethical review board in Stock-
holm, Sweden.

**Subjects**

Inclusion criteria were confirmed diagnosis of CF based
on clinical features, ≥ 2 positive sweat tests (chloride
> 60 mmol/L),⁷ and/or the presence of a known disease-
causing mutation on each CFTR gene. Exclusion criteria
were upper airway infection, cognitive dysfunction, pres-
ence of nasal polyps, associated asthma, incapable of per-
forming a technically acceptable lung function test, and no
possibility to stay at the clinic for the required 4 h. The
subjects were included consecutively from the out-patient
clinic of the Stockholm CF Center. Of the 28 subjects
screened, 24 were enrolled in the study.

Informed consent was obtained from the adult and pe-
diatric subjects participating in the study; when the pedi-
artic subjects were < 18 y of age, informed consent was
obtained from their parents. Of the 24 subjects included,
16 were adults (mean age 32 ± 9 y) and 8 were children
(mean age 15 ± 2 y) (Table 1).

**Quick Look**

**Current knowledge**

Studies evaluating airway clearance in cystic fibrosis
commonly use changes in lung function parameters (eg,
FEV₁) as clinical end points. The optimal timing to
perform lung function studies following an intervention
has not been elucidated.

**What this paper contributes to our knowledge**

The optimal time to perform spirometry following an
airway clearance session varies between individual sub-
jects but not within individuals. Optimal timing appears
to be 30 min following airway clearance in adult sub-
jects and immediately after lung clearance maneuvers
in pediatric subjects.

**Procedures**

The daily physiotherapy performed by all subjects in the
study, which was the standard treatment indicated by the
physiotherapist and doctor according to age and lung func-
tion, consisted of inhalation twice each day with the fol-
lowing medications: β₁ agonist + hypertonic saline (12
adult subjects and one pediatric subject), β₂ agonist + ace-
tylcysteine (4 adult and 6 pediatric subjects), and β₂ ago-
nist + bromhexine (one pediatric subject). The daily res-
piratory physiotherapy (airway clearance techniques)
performed by all subjects consisted of autogenic drainage
for 10 min, positive expiratory therapy for 10 breaths, and
3 huffing maneuvers. Autogenic drainage, positive expi-
ratory therapy, and huffing were repeated 3 times accord-
ing to recommendations from the International Physiother-
apy Group for Cystic Fibrosis.⁸ No subject received recombinant human deoxyribonuclease, and all subjects
had performed inhalation and respiratory physiotherapy
since diagnosis.

The medication and respiratory treatment remained con-
sistent for an individual subject during the study. Physio-
therapy was performed in a sitting position at the same
time of day for 2 d, and the lung function test was per-
formed in a sitting position at the same time of day for the
study according to ATS/ERS recommendations (3 techni-
cally acceptable and reproducible efforts, maximum dif-
ference between the 2 best measurements of 5% or
150 mL).⁵

Subjects performed spirometry with a portable micro-
spirometer (MS01 Gold Standard MicroPlus, CareFusion,
San Diego, California) before their airway clearance ses-
sion and immediately after, 30 min after, and 1, 2, and 3 h
after their airway clearance session. Spirometry was per-
formed in a sitting position. FEV<sub>1</sub> and FVC were taken as the best value out of the 3 technically satisfactory forced expirations. Lung function as percent of predicted was calculated from the reference values presented by Hedenström et al<sup>9,10</sup> (≥ 19 y) and by Solymar et al<sup>11,12</sup> (< 19 y). All subjects performed the series of measurements on 2 consecutive d to identify intra-individual variations. No subjects withdrew from the study.

### Statistics

A sample size of 17 will have 80% power to detect a difference in means of .05 assuming that the common SD is 0.480 using a single group t test with a .05 significance level. The Student t test was used to compare the paired data. Calculations were made with statistics software (Statistica 7.0, StatSoft, Tulsa, Oklahoma). P values < .05 were considered significant.

### Results

The mean FEV<sub>1</sub> in adult subjects was increased after the physiotherapy session at each time point but was statistically significant 30 min (P < .001), 1 h (P < .002), and 2 h (P < .006) after physiotherapy in comparison to baseline. The mean FVC increase was statistically significant at 30 min (P < .02) and 2 h (P < .04) after physiotherapy. The mean FEV<sub>1</sub> increase in adult subjects was 7% compared to baseline (30 min after physiotherapy). In comparison to baseline, the highest FVC mean increase was 10% (30 min after physiotherapy) (Table 2 and Fig. 1).

The mean FEV<sub>1</sub> and FVC in pediatric subjects showed no statistically significant difference from baseline at any time point, but there was a trend to increase immediately after physiotherapy (Table 2 and Fig. 1). The mean increase in FEV<sub>1</sub> for pediatric subjects was 1% (immediately after physiotherapy) and in FVC was 2% (immediately after physiotherapy) compared to baseline. If we consider peak time in liters compared to baseline, mean FEV<sub>1</sub> in adults increased by 11%, and mean FVC in adults increased by 17%. If we consider peak time in liters compared to baseline, mean FEV<sub>1</sub> in children increased by 7%, and mean FVC in children increased by 9%. Furthermore, there were no intra-individual variations regarding peak time point.

### Discussion

This is, to our knowledge, the first study investigating at what time point after chest physiotherapy spirometry should be performed. The main result was the difference in FEV<sub>1</sub> in adult subjects, which depended on time point, from a mean of 56% (baseline) to 60% of predicted. Other main findings were that patients showed a different FEV<sub>1</sub> after their physiotherapy sessions with inter-individual variations but not intra-individual variations. Also, there was a difference between adult and pediatric subjects.

Not taking time points after physiotherapy sessions into consideration in designing clinical and therapeutic studies may lead to underestimation as well as overestimation of outcome results. In most therapeutic studies, spirometry is performed at the same time of day by the individual subjects, thereby indirectly minimizing the effect of physiotherapy sessions, and it is not considered how chest physiotherapy could affect lung function test results.<sup>13</sup> We have shown in this study that it is important to determine an individual subject’s peak time point after physiotherapy, which may be of clinical importance. In evaluating the effect of different chest physiotherapeutic sessions, choosing the right time point for lung function tests might be considered.

Adult subjects showed a statistically significant improvement in mean FEV<sub>1</sub> and FVC after 30 min and 2 h, whereas pediatric subjects showed an improvement immediately after physiotherapy (not significant). Unexpectedly, there was a deterioration trend in FEV<sub>1</sub> and FVC in pediatric subjects over time. Sixty-nine percent of adult subjects had a baseline FEV<sub>1</sub> < 70% of predicted, and 100% were sputum producers. The corresponding values for pediatric subjects were 50 and 75%, respectively. Sputum producers were those subjects who expectorated > 25 mL during airway clearance. Due to the progression of the disease, a more severe disease status in adult CF subjects is to be expected. After a physiotherapy session, adult subjects may experience an obstruction of their airways, and sputum that has not been evacuated could remain in the central airways, possibly affecting the results of the spirometry. This could be a possible reason for adult subjects performing spirometry better 30 min or later following chest physiotherapy. Pediatric subjects may have performed spirometry better immediately after chest physiotherapy due to lesser amounts of sputum and better lung function at baseline. The fact that they performed slightly worse over time

### Table 1. Subjects’ Characteristics at Inclusion

<table>
<thead>
<tr>
<th></th>
<th>Adult Subjects (n = 16)</th>
<th>Pediatric Subjects (n = 8)</th>
<th>Total (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>32 ± 9</td>
<td>15 ± 2</td>
<td>26 ± 10</td>
</tr>
<tr>
<td>Female/male, n</td>
<td>6/10</td>
<td>1/7</td>
<td>7/17</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, mean ± SD, % predicted*</td>
<td>56 ± 29</td>
<td>70 ± 32</td>
<td>61 ± 30</td>
</tr>
<tr>
<td>FVC, mean ± SD, % predicted*</td>
<td>67 ± 27</td>
<td>76 ± 37</td>
<td>70 ± 30</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 70% predicted, n</td>
<td>11</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Sputum producers, n</td>
<td>16</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Chronic pseudomonas colonization, n</td>
<td>14</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

* Values are reference values based on sex, age, and height.
might be due to having to perform 18 spirometry maneuvers during the 3-h time period prior to chest physiotherapy. It might have been difficult for the pediatric subjects to stay highly motivated and to perform their very best repeatedly. Because the study was not designed to identify which factors might affect time points for peak performance after chest physiotherapy, more studies are necessary.

While observing individual subjects, it was noted that their increases in FEV₁ after their physiotherapy sessions

Table 2. Spirometry Values Before and After Chest Physiotherapy

<table>
<thead>
<tr>
<th></th>
<th>Adult Subjects (n = 16)</th>
<th></th>
<th>Pediatric Subjects (n = 8)</th>
<th></th>
<th>Total (n = 24)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁, mean ± SD, % of predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>56 ± 29</td>
<td></td>
<td>70 ± 32</td>
<td></td>
<td>61 ± 30</td>
<td></td>
</tr>
<tr>
<td>Immediately after</td>
<td>58 ± 30</td>
<td>.20</td>
<td>71 ± 31</td>
<td>.69</td>
<td>63 ± 30</td>
<td>.22</td>
</tr>
<tr>
<td>30 min after</td>
<td>60 ± 30</td>
<td>&lt;.001</td>
<td>66 ± 32</td>
<td>.12</td>
<td>63 ± 30</td>
<td>.33</td>
</tr>
<tr>
<td>1 h after</td>
<td>59 ± 30</td>
<td>&lt;.002</td>
<td>64 ± 30</td>
<td>.11</td>
<td>61 ± 30</td>
<td>.95</td>
</tr>
<tr>
<td>2 h after</td>
<td>58 ± 30</td>
<td>&lt;.006</td>
<td>68 ± 32</td>
<td>.51</td>
<td>62 ± 30</td>
<td>.26</td>
</tr>
<tr>
<td>3 h after</td>
<td>57 ± 29</td>
<td>.39</td>
<td>67 ± 28</td>
<td>.27</td>
<td>61 ± 28</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>FVC, mean ± SD, % of predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>67 ± 27</td>
<td></td>
<td>76 ± 37</td>
<td></td>
<td>70 ± 30</td>
<td></td>
</tr>
<tr>
<td>Immediately after</td>
<td>69 ± 28</td>
<td>.53</td>
<td>78 ± 37</td>
<td>.12</td>
<td>72 ± 31</td>
<td>.24</td>
</tr>
<tr>
<td>30 min after</td>
<td>74 ± 27</td>
<td>&lt;.02</td>
<td>74 ± 32</td>
<td>.46</td>
<td>74 ± 28</td>
<td>.08</td>
</tr>
<tr>
<td>1 h after</td>
<td>72 ± 27</td>
<td>.10</td>
<td>75 ± 32</td>
<td>.66</td>
<td>73 ± 28</td>
<td>.22</td>
</tr>
<tr>
<td>2 h after</td>
<td>72 ± 27</td>
<td>&lt;.04</td>
<td>74 ± 31</td>
<td>.38</td>
<td>72 ± 28</td>
<td>.26</td>
</tr>
<tr>
<td>3 h after</td>
<td>71 ± 27</td>
<td>.15</td>
<td>70 ± 27</td>
<td>.16</td>
<td>70 ± 26</td>
<td>.79</td>
</tr>
</tbody>
</table>

Values are reference values based on sex, age, and height.

Fig. 1. Spirometry values and before and after chest physiotherapy (PT).

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were higher at different time points. The intra-individual variations showed no difference.

The main limitation of the study was its size. It was not powered for subanalyses.

FEV₁ is certainly one of the best and widely used markers of prognosis in CF. However, the measurements lack sensitivity, particularly in mild early stages of disease or when looking for small changes in response to an intervention.

Another limitation is that the subjects in the study were treated differently regarding inhaled medications, and therefore, this difference in treatment may influence the results.

In our study, we used spirometry because it is still one of the most used outcome parameters, and although highly technique-dependent and effort-dependent, it is easy to consecutively perform in an out-patient setting. Subjects in the study were used to performing spirometry every month from the age of 4–5 y.

Because of the arbitrary termination, we used spirometry (the highest value of the 3 technically satisfactory efforts). This may have underestimated the results, especially in those individuals who may have benefitted from a warm-up period.

Lung function parameters have been used as end points in most therapeutic trials in CF to date. It has been suggested that the lung clearance index could be a more sensitive early marker and a stronger indicator of disease progression than spirometry.¹⁴

FEV₁ is still an important outcome parameter in clinical trials, and we believe that our findings are important and have to be taken into account in designing studies in the future.

Conclusions

The optimal time point to perform accurate spirometry after an airway clearance session varied between individual subjects with CF but not within individuals. However, there was a trend showing that performing spirometry immediately after the session for children and 30 min after the session for adults might be optimal (statistically significant), but individual peak time should also be considered.

REFERENCES

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