Effects of Exercise on Respiratory Flow and Sputum Properties in Patients With Cystic Fibrosis

Cystic Fibrosis

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Background

The physiologic mechanisms by which exercise may clear secretions in subjects with cystic fibrosis (CF) are unknown. The purpose of this study was to compare ventilation, respiratory flow, and sputum properties following treadmill and cycle exercise with resting breathing (referred to as “control”).

Methods

In 14 adult subjects with CF, ventilation and respiratory flow were measured during 20 min of resting breathing, treadmill exercise, and cycle exercise in a 3-day crossover study. Treadmill and cycle exercise were performed at the work rate equivalent to 60% of the subject's peak oxygen uptake. Ease of expectoration and sputum properties (solids content and mechanical impedance) were measured before and immediately after the interventions and after 20-min recovery.

Results

Ease of expectoration improved following exercise. Ventilation and respiratory flow were significantly higher during treadmill and cycle exercise compared with control. Sputum solids content did not change following treadmill or cycle exercise. There was a significantly greater decrease in sputum mechanical impedance following treadmill exercise compared with control, but no significant decrease in sputum mechanical impedance following cycle exercise compared
with control.

Conclusions

The improvement in ease of expectoration following exercise may have been due to the higher ventilation and respiratory flow. The reductions in sputum mechanical impedance with treadmill exercise may have been due to the trunk oscillations associated with walking.

Trial Registry

Australian and New Zealand Clinical Trials Registry; No. 12605000422628; URL: www.anzctr.org.au

Abbreviations

CF

cystic fibrosis

PEF

peak expiratory flow

PIF

peak inspiratory flow

E

minute ventilation

Cystic fibrosis (CF) lung disease is characterized by depleted airway surface liquid volume and thickened mucus, which results in impaired mucus clearance.[1] Retained mucus is a nidus for chronic infection associated with a cascade of inflammation and progressive lung damage.[2] Airway clearance is, therefore, an integral component of the respiratory management of CF.[3]

Exercise often is promoted as an airway clearance technique in CF because of reported improvements in expectorated sputum volume. [4] , [5] As well, systematic reviews have concluded that the addition of exercise to chest physiotherapy significantly improves lung function compared with chest physiotherapy alone. [6] , [7] However, the physiologic mechanisms by which exercise alone may act as an airway clearance technique have not been evaluated and may aid treatment selection.

Exercise is proposed to improve mucus clearance by changes to airflow and mucus. Exercise increases ventilatory demand, which is met by increases in tidal volume and respiratory flow. In CF, the increase in ventilation and peak expiratory flow (PEF) with exercise [8] , [9] could increase propulsion or mechanical clearance of mucus.[10] If this increase in PEF is sufficient to create an expiratory airflow bias (ie, PEF is 10% higher than the peak inspiratory flow [PIF]), exercise also could augment the annular flow of mucus toward the oropharynx[11] through two-phase gas-liquid flow where the acceleration of one fluid transfers its momentum to another.[12] The effect of exercise on airflow bias is unknown.

Exercise has been proposed to increase the water content of CF mucus [13] , [14] on the basis of research that exercise inhibits sodium conductance channels of CF nasal respiratory epithelium. [13] , [15] As well, it is postulated that an increase in airway surface hydration occurs following exercise[14] because of the creation of an osmotic stimulus associated with high levels of ventilation.[16] Increasing airway surface hydration increases the airway surface liquid volume, which has been shown to improve mucus clearance in CF.[17] The effect of exercise on mucus water content is unknown.

There is a potential for the increase in ventilation with exercise to reduce mucus viscosity and elasticity, as increases in tidal volume and airflow impart shear forces to airway surfaces.[18] A previous study in CF showed reductions in mucus viscosity and elasticity with the application of in vivo oscillations and shear forces.[19] In addition, exercise that creates oscillations of the trunk (eg, walking or jogging) may reduce mucus viscosity and elasticity. The ground reaction forces from heel strike during walking, known as the heel-strike transient, are associated with a shock wave of oscillations attenuated through the lower limbs and trunk. [20] These trunk oscillations, between 2 Hz and 5 Hz, [21] could potentially be transferred to the lungs and reduce mucus viscosity, as in vitro oscillations as low as 3 Hz reduce mucus viscosity and in vivo chest wall vibrations as
low as 5 Hz increase mucus clearance. None of these theories, however, has been tested in relation to exercise, and the effect of exercise on mucus viscosity and elasticity is unknown.

The aim of this study was to evaluate mechanisms by which treadmill and cycle exercise may increase mucus clearance in persons with CF. We hypothesized that treadmill and cycle exercise would increase ventilation and respiratory flow and favorably alter the physical properties of sputum to aid mucus clearance. Our secondary hypothesis was that treadmill exercise would result in a greater change in sputum properties than cycle exercise because of the trunk oscillations occurring during treadmill exercise.

Materials and Methods

Subjects

Adults with CF were recruited from the CF Clinic at Royal Prince Alfred Hospital in Sydney, New South Wales, Australia. Subjects were excluded if they had received a lung transplantation, were infected with *Burkholderia cepacia* complex, or were not clinically stable. Research procedures were approved by the Sydney South West Area Health Service Ethics Committee (Protocol X-05-0020), and subjects provided written informed consent prior to participation.

Study Design

Subjects participated in a 3-day crossover study (Fig 1) registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR #12605000422628). The three visits were scheduled at the same time in the morning within a 2-week period, and medication, chest physiotherapy, and exercise regimens were unchanged throughout the study. On each visit, sputum samples were collected immediately before a 20-min intervention (referred to here as “pre”), after a 20-min intervention (referred to here as “post”), and after a further 20 min of resting breathing (referred to here as “recovery”). The three interventions were resting breathing (referred to here as “control”), constant-load treadmill exercise, and constant-load cycle exercise. The control intervention was performed on the first visit, and the constant-load treadmill and cycle interventions were randomized to the second and third visits.

![Figure 1](image.png)

On the first visit, after collection of the recovery sputum sample, spirometry and plethysmography were measured (VMax229; SensorMedics; Yorba Linda, California) according to American Thoracic Society and European Respiratory Society guidelines [23], [24] and reported as a percentage of predicted values. [25], [26] Subjects then completed an incremental treadmill test and an incremental cycle test to peak exercise capacity (with breath-by-breath measurement analyzed by the VMax229 system), in random order, and with at least 30 min of rest in between. The results of the peak exercise tests were reported as a percentage of predicted values [27], [28], [29] and used to calculate the target work rate for the constant-load treadmill and cycle interventions.

The constant-load exercise interventions on visits two and three of the study were performed at an intensity and duration similar to that which would be prescribed for exercise training. Subjects exercised for 20 min on the treadmill or cycle ergometer at the work rate equivalent to 60% of the peak oxygen uptake achieved in the incremental peak treadmill or cycle test.

Measurements

Ease of Expectoration

Subjects were asked to record the ease of expectoration on a 10-cm visual analog scale (0 = very difficult; 10 = very easy) for each sputum sample. The visual analog scales were later measured by a blinded assessor.
Ventilation and Respiratory Flow

Minute ventilation (VE) and tidal flow-volume loops were recorded during each 20-min intervention while subjects breathed through the VMax229 system. Two tidal flow-volume loops from each minute of intervention were randomly coded to ensure deidentification at later analysis when measured by a blinded assessor to determine the PEF and PIF.

Sputum Properties

Sputum samples were manually separated from saliva and stored in 1.2-mL tubes in a -80°C freezer. The storage tubes were randomly coded to ensure deidentification at later analysis when measured by a blinded assessor. Sputum analysis procedures were followed as reported previously. [30] , [31] The percentage of solids content in the sputum from which inferences of airway hydration are made was estimated by measuring the weight of a 50-µL aliquot of sputum before and after lyophilization to dryness for 24 h using a freeze dryer (FTS/Kinetics Thermal Systems; Stone Ridge, New York). Sputum elasticity (dynamic G') and viscosity (dynamic G'') were measured using a 20-µL aliquot of sputum and a controlled stress rheometer with geometry 20 mm, 0.5° aluminum cone and plate over the frequency of 1 to 100 rad/s (AR2000; TA Instruments; New Castle, Delaware). The results were reported as sputum mechanical impedance (G*), also known as rigidity factor, which is the vector sum of viscosity and elasticity. Sputum mechanical impedance values at 1 rad/s are more representative of sputum properties during resting breathing and mucociliary clearance, whereas values at 100 rad/s are more representative of sputum properties during cough and cough clearance.

Cough

Spontaneous coughs were manually counted during each 20-min intervention and recovery period.

Statistical Analysis

Repeated-measures analyses of variance were performed to compare differences between the interventions in the ease-of-expectoration and sputum properties data. Paired t tests were used to compare ventilation and respiratory flow between the interventions. Wilcoxon signed rank tests were used to determine any differences in the number of spontaneous coughs between the interventions because these data were not normally distributed. P < .05 was considered to indicate statistical significance.

No previous data have been reported on changes in the properties of spontaneously expectorated CF sputum as measured by the same instruments in this study. Thus, the sample size was based on a previous study that showed significant differences in mucus mechanical impedance between two airway clearance techniques in 14 subjects with CF. [19] We recruited 15 subjects to allow for a 5% dropout rate.

Results

Fifteen subjects with CF were recruited, and 14 completed the study. Participant baseline characteristics are presented in Table 1. One participant withdrew after the first visit because of a respiratory exacerbation. Results for this subject on the first day were similar to those of the other 14 but have not been included in the analyses because of the crossover design of the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>27 ± 7</td>
<td>18–44</td>
</tr>
<tr>
<td>Female sex</td>
<td>4</td>
<td>...</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.7 ± 2.0</td>
<td>18.7–26.3</td>
</tr>
<tr>
<td>FEV₁ [a]</td>
<td>55 ± 27</td>
<td>19–108</td>
</tr>
<tr>
<td>RV/TLC, [%]</td>
<td>49 ± 14</td>
<td>25–75</td>
</tr>
<tr>
<td>Treadmill peak O₂ [a]</td>
<td>75 ± 20</td>
<td>37–113</td>
</tr>
<tr>
<td>Cycle peak O₂ [a]</td>
<td>62 ± 19</td>
<td>23–94</td>
</tr>
</tbody>
</table>

Data are presented for 14 subjects who completed the study. RV = residual volume; TLC = total lung capacity; O₂ = oxygen uptake.
Table 2 -- Baseline Sputum Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of expectoration, cm</td>
<td>5.0 ± 2.9</td>
<td>0.7–7.7</td>
</tr>
<tr>
<td>Sputum solids content, %</td>
<td>6.1 ± 2.9</td>
<td>2.3–12.0</td>
</tr>
<tr>
<td>Sputum mechanical impedance at 1 rad/s, Pa</td>
<td>14.0 ± 6.1</td>
<td>6.5–29.4</td>
</tr>
<tr>
<td>Sputum mechanical impedance at 100 rad/s, Pa</td>
<td>139.1 ± 37.6</td>
<td>60.3–200.7</td>
</tr>
</tbody>
</table>

Data are presented for properties for the first sputum sample collected from the 14 subjects who completed the study. Ease of expectoration was scored by the subjects on a 10-cm visual analog scale (0 = very difficult; 10 = very easy). Sputum mechanical impedance is the vector sum of sputum viscosity and elasticity.

There were no significant differences in preintervention ease of expectoration or sputum properties on the three study visits (e-Tables 1-3). As well, no carryover or order effect between the interventions was detected.

Ease-of-expectoration and sputum properties results are reported as changes from pre- to postintervention and from preintervention to recovery. Sputum property data for each intervention can be seen in e-Tables-3.

**Treadmill and Cycle Exercise Intensity**

Work rate, steady-state peak oxygen uptake, and perceived intensity [32] [33] for the 20-min treadmill and cycle interventions are presented in Table 3.

Table 3 -- Treadmill and Cycle Exercise Intensity

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Work Rate</th>
<th>(\overline{VO}_2), mL/kg/min</th>
<th>Dyspnea</th>
<th>RPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadmill</td>
<td>5.7 ± 1.0 km/h (5% ± 3% incline)</td>
<td>17.8 ± 3.3</td>
<td>3.3 ± 1.9</td>
<td>3.1 ± 2.3</td>
</tr>
<tr>
<td>Cycle</td>
<td>67 ± 28 W</td>
<td>19.2 ± 5.5</td>
<td>4.1 ± 2.9</td>
<td>5.0 ± 2.7</td>
</tr>
<tr>
<td>Treadmill vs cycle</td>
<td>…</td>
<td>1.3 (-0.6–3.3)</td>
<td>0.8 (-0.3–2.0)</td>
<td>1.9[a] (0.3–3.5)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD for group values of the work rate, steady-state \(\overline{VO}_2\), modified Borg dyspnea, [33] and modified 0-to-10-point RPE [32] for the 20-min treadmill and cycle interventions. Comparisons between the treadmill and cycle interventions are shown as group mean difference (95% CI). The work rate of the 20-min treadmill and cycle interventions was set at the work level equivalent to 60% of the subject’s peak \(\overline{VO}_2\) achieved in the incremental peak treadmill or cycle tests on the first day of the study. RPE = rate of perceived exertion. See Table 1 legend for expansion of other abbreviation.

\[a] P = .023.

**Effects of Treadmill and Cycle Exercise on Ease of Expectoration**

For treadmill exercise, there was no significant difference in the change in ease of expectoration between the pre and post sputum samples (\(P > .4\)) compared with control; however, there was a trend toward a greater improvement in ease of expectoration for treadmill exercise compared with control between the pre and recovery sputum samples (mean difference, 1.8 cm; 95% CI, -0.4–3.9 cm; \(P = .096\)) (Fig 2). For cycle exercise, there was no significant difference in the change in ease of expectoration between the pre and post sputum samples (\(P > .3\)) compared with control; however, there was a significantly greater improvement in ease of expectoration for cycle exercise compared with control between the pre and recovery sputum samples (mean difference, 2.0 cm, 95% CI, 0.2–3.8 cm; \(P = .034\)) (Fig 2).
Effects of Treadmill and Cycle Exercise on Mucus Clearance Mechanisms

Ventilation and Respiratory Flow

E, PEF, and PEF:PIF were significantly higher during treadmill and cycle exercise compared with control. Results are shown in Table 4.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>E, L/min</th>
<th>PEF, L/s</th>
<th>PEF:PIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11.3 ± 2.4</td>
<td>0.63 ± 0.20</td>
<td>0.80 ± 0.10</td>
</tr>
<tr>
<td>Treadmill</td>
<td>34.1 ± 6.8</td>
<td>1.79 ± 0.52</td>
<td>0.92 ± 0.11</td>
</tr>
<tr>
<td>Cycle</td>
<td>37.9 ± 9.8</td>
<td>1.82 ± 0.47</td>
<td>0.93 ± 0.08</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD for group values of E, PEF, and PEF:PIF during the 20-min control intervention and treadmill and cycle exercise. Comparisons among the interventions are shown as group mean difference (95% CI). PEF = peak expiratory flow; PIF = peak inspiratory flow; E = minute ventilation.

a P < .001.

b P < .01.

c P = .024.

Sputum Properties

There were no significant differences in the change in percentage of sputum solids content following treadmill or cycle exercise compared with control (P > .4) (Fig 3). There were also no significant differences in the change in percentage of sputum solids content following treadmill exercise compared to cycle exercise (P > .6).
There were significantly greater reductions in sputum mechanical impedance following treadmill exercise compared with control (pre-post mean difference at 1 rad/s, 5.3 Pa; 95% CI, 0.8-9.8 Pa; \( P = .026 \); pre-post mean difference at 100 rad/s, 47.5 Pa; 95% CI, -1.4-96.4 Pa; \( P = .056 \); pre-recovery mean difference at 1 rad/s, 6.3 Pa; 95% CI, 0.9-11.7 Pa; \( P = .025 \); pre-recovery mean difference at 100 rad/s, 53.5 Pa; 95% CI, 11.5-95.4 Pa; \( P = .016 \) (Fig 4). There were no significant reductions in sputum mechanical impedance following cycle exercise compared with control (\( P > .06 \)). There were also no significant reductions in sputum mechanical impedance following treadmill exercise compared to cycle exercise (\( P > .06 \)).
Cough

There was no significant difference in the number of spontaneous coughs during or following treadmill or cycle exercise compared with control ($P > .3$). Results are shown in Table 5.

Table 5  -- Spontaneous Coughs During and Following the Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Coughs During Intervention</th>
<th>Coughs During Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5 (1–7)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Treadmill</td>
<td>3 (0–15)</td>
<td>3 (1–3)</td>
</tr>
<tr>
<td>Cycle</td>
<td>3 (0–19)</td>
<td>3 (1–7)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) for group values of the number of spontaneous coughs during the 20-min intervention and 20-min recovery period.

Discussion

The primary purpose of this study was to determine the effects of treadmill and cycle exercise on mechanisms of mucus clearance in CF. To our knowledge, this study is the first to examine the in vivo changes in sputum properties and airflow bias (PEF:PIF) with exercise in CF. The main finding was the reduction in sputum mechanical impedance with treadmill exercise compared with control.

Ventilation and respiratory flow were higher during treadmill and cycle exercise compared with control. The increase in $\dot{V}$ and PEF is likely to have aided propulsion of mucus, potentially resulting in the improvement in subjective ease of expectoration following exercise. $\dot{V}$ was higher during cycle exercise than during treadmill exercise, which also may explain the greater improvement in ease of expectoration with cycle exercise. It is important to note that the improvement in ease of expectoration with exercise was not simply due to coughing because there was no difference in the number of spontaneous coughs between the exercise interventions and the control.

The proposed mechanism of promoting annular flow of mucus toward the oropharynx by creating an expiratory bias to airflow (PEF:PIF > 1.10)\(^\text{[11]}\) during exercise did not occur in this study. Analysis of the tidal flow-volume loops during treadmill and cycle exercise demonstrated that although the increase in PEF was proportionally greater than the increase in PIF, it was insufficient to generate an expiratory bias to airflow. Airflow bias has been measured to assess the physiologic mechanisms of other airway clearance therapies in CF.\(^\text{[34]}\) Only manual vibration of the chest wall and breathing through an oscillatory positive expiratory pressure device (Flutter [sometimes referred to as the Flutter VRP1]; Axcan Scandipharm Inc; Birmingham, Alabama) created an expiratory airflow bias. Manual percussion and positive expiratory pressure therapy did not achieve an expiratory airflow bias, yet both have been shown to improve mucociliary clearance.\(^\text{[35]}\), \(^\text{[36]}\), \(^\text{[37]}\) These results would suggest that expiratory airflow bias is not an essential mechanism to improve mucus clearance in CF and that this mechanism was not involved in the improvement in ease of expectoration following exercise observed in our study.

The hypothesis that exercise would increase the mucus water content\(^\text{[13]}\), \(^\text{[14]}\) was not observed in this study because there was no reduction in the sputum solids content following treadmill or cycle exercise. Previous studies in CF have shown that a short bout of moderate-intensity exercise decreased the nasal transepithelial potential difference to a normal level because of the inhibition of sodium conductance channels,\(^\text{[13]}\), \(^\text{[15]}\) which was proposed to cause a water flux into the airway lumen. A possible explanation for not observing a reduction in sputum solids content immediately postexercise is that the water flux into the airway lumen may have been counterbalanced by evaporative water loss from the airway surface due to the high levels of ventilation during exercise.\(^\text{[38]}\) This evaporative water loss would not have been observed in the earlier studies\(^\text{[13]}\), \(^\text{[15]}\) because in these studies, it is most probable that the subjects breathed through the mouth, thus not exposing the nasal airway, where the measurements were taken, to high levels of ventilation.

A possible explanation for not observing a reduction in the sputum solids content 20 min following exercise is that the reduction in the nasal transepithelial difference with exercise in subjects with CF is transient, lasting only 4 min after stopping exercise.\(^\text{[15]}\) Thus, had there been a water flux into the airway lumen during exercise (but not detected immediately postexercise because of the evaporative water loss), it is possible that by 20 min following exercise, the water flux into the airway lumen had ceased. Perhaps the sputum samples collected 20 min after stopping exercise were obtained too late to detect the proposed water flux into the airway lumen during and following exercise. Either way, the finding that sputum solids content did not change immediately or 20 min after exercise would suggest that the proposed mechanism of increasing mucus
We did not measure airway hydration or airway surface liquid layer volume directly. However, it is possible that the increased physical forces in the airways associated with high levels of ventilation may have stimulated airway epithelial adenosine triphosphate release, which has been shown to increase airway surface liquid layer height in in vitro CF studies in response to mechanical stress. [14] These in vitro studies also demonstrated that the increase in airway surface liquid layer height was accompanied by an increase in ciliary beat frequency to augment mucus transport. These findings help to explain the observed improvement in ease of expectoration in the recovery period following exercise in our study.

There was a greater reduction in sputum mechanical impedance following treadmill exercise compared with control. Although there were small reductions in sputum mechanical impedance following cycle exercise compared with control, these changes were not significant, but this may have been due to a small sample size. No other study has examined changes in sputum properties following exercise. The only study in CF to examine the effect of in vivo airway clearance interventions on mucus properties compared treatment with the Flutter device to autogenic drainage. [19] That study showed reductions in mucus mechanical impedance following Flutter therapy but no changes following autogenic drainage. The authors postulated that the reduction in mucus mechanical impedance was due to the oscillations associated with Flutter, which can increase shear forces in the airways. In our study, the trunk oscillations associated with treadmill exercise [21] may have created oscillations in the lungs. These oscillations, combined with the shear forces in the airways due to the increased E and PEF, may have contributed to the observed reduction in sputum mechanical impedance following treadmill exercise and helped to clarify differences between treadmill and cycle exercise on mechanisms of mucus clearance.

In summary, a single bout of moderate-intensity exercise increased the ease of expectoration of sputum in adults with CF. This improvement in ease of expectoration may have been due to the higher E and PEF, which could have increased propulsion of mucus and created shear forces in the airways to augment airway surface liquid layer height and mucus transport toward the oropharynx. In addition, treadmill exercise significantly reduced sputum mechanical impedance compared with control. The clinical implications from this study are that exercise can improve ease of expectoration in CF and that treadmill exercise appears to have a greater influence on mechanisms of mucus clearance than cycle exercise. However, treadmill exercise needs to be evaluated for its ability to improve mucus clearance and compared with chest physiotherapy techniques before it can be promoted as an adequate form of airway clearance therapy.

Acknowledgments

Author contributions: Dr Dwyer: contributed to the study design, data collection, measurement and analysis of sputum properties, interpretation of the findings, and writing of the manuscript.

Dr Alison: contributed to the study design, interpretation of the findings, and writing of the manuscript.

Dr McKeough: contributed to the study design, data collection, interpretation of the findings, and writing of the manuscript.

Dr Daviskas: contributed to the study design, measurement and analysis of sputum properties, interpretation of the findings, and writing of the manuscript.

Dr Bye: contributed to the study design, interpretation of the findings, and writing of the manuscript.

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Additional information: The e-Tables can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/139/4/870/suppl/DC1.
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