Sputum rheology changes in cystic fibrosis lung disease following two different types of physiotherapy: flutter vs autogenic drainage

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Objective: The aim of the present study was to investigate the efficacy of two frequently used physiotherapies (PTs) for the removal of bronchial secretions in cystic fibrosis (CF) lung disease: autogenic drainage (AD) and the Flutter (Desitin in Germany). AD is believed to improve mucus clearance from peripheral to central airways due to airway caliber changes in combination with a special breathing technique. The Flutter is an easy-to-use physiotherapy device based on oscillations of a steel ball during expiration through a pipe-type device.

Materials and methods: To evaluate the acute and chronic physiotherapy effects of these two techniques, 14 CF patients underwent either twice daily AD or Flutter treatment for 4 consecutive weeks in a randomized crossover design. Prior to each therapy interval, for a 1-week wash-out period, no PT was administered, but patients continued regular medication. At the beginning and end of each 4-week interval, pulmonary function was measured before and after an acute 30-min therapy. At the end of the PT session, sputum was collected, weighed, and deep frozen until analyzed. The viscoelasticity of the sputum was evaluated using a magnetic microrheometer.

Results: No significant changes were noted for FVC, FEV1, or sputum volume throughout the study. Sputum viscoelasticity (rigidity index), however, was significantly lower (p < 0.01) after therapy with the Flutter in comparison with AD, predicting improvements in mucociliary and cough clearability of the secretions. In a companion in vitro experiment, oscillations generated by passing humidified air over CF sputum lining an acrylic tube connected to a Flutter device were found to decrease sputum elasticity, as measured by a filancemeter. These findings suggest that applied oscillations are capable of decreasing mucus viscoelasticity within the airways at frequencies and amplitudes achievable with the Flutter device, and provide direct evidence that PT can reduce the viscoelasticity of sputum.

Key words: autogenic drainage; cystic fibrosis; Flutter; mucus clearance; mucus viscoelasticity; physiotherapy; pulmonary function

Abbreviations: AD=autogenic drainage; CCI=cough clearance index; CF=cystic fibrosis; MCI=mucociliary clearance index; PT=physiotherapy

Mucus clearance of the airways is a crucial mechanism for patients with cystic fibrosis (CF) and should be optimized with appropriate therapeutic interventions. A number of therapeutic strategies currently in use are aimed at improving mucus clearance in CF patients. They range from antibiotic therapy and a variety of mucolytic treatments to a number of physiotherapies (PTs).

The aim of this study was to evaluate the efficacy of two frequently used PTs, autogenic drainage (AD), and Flutter therapy. Both PTs are very frequently used in Germany to augment mucus clearance from the airways of CF patients. The functional principle of the AD technique is based on airway caliber changes in conjunction with a special breath-
ing and cough procedure. The AD technique encourages mucus clearance from peripheral airways to more central airways and gentle expectoration of sputum. AD requires a period of training, but most adolescent and adult CF patients are able to learn it.

Flutter therapy using the VRP1 or Flutter device (VarioRaw SA; Aubonne, Switzerland) is a simple method that can be performed even by small children. The functional principle is based on airflow oscillations generated by a steel ball inside a pipe-like device during exhalation through the instrument. The oscillations and the resulting airflow and pressure changes are transmitted into the airways and are believed to improve the rheologic conditions of airway secretions, thereby augmenting mucus clearance. The generated oscillating frequencies of the Flutter depend not only on the airflow through the device, but also on the angle at which the instrument is used. (See Table 1.)

In contrast to Flutter therapy, bronchial secretion during AD are mobilized not by high-frequency oscillations, pressure changes, and airflow changes, but by a special calm breathing technique. We therefore hypothesized that all detectable rheologic differences in the sputum collected at the end of every AD and Flutter PT session may be caused by the high-frequency oscillations and pressure and airflow changes produced by the Flutter device.

**Materials and Methods**

**Study Design**

In order to evaluate the acute and chronic effects of these two methods, CF patients were treated in a random crossover design with twice-daily AD or Flutter therapy for 4 weeks each. One group of patients received AD therapy first and Flutter second, while the other group underwent the PTs in the opposite order. A 1-week wash-out period without any kind of PT but with otherwise unchanged medication preceded each PT interval to ascertain baseline conditions prior to each treatment arm and also to prevent a possible therapeutic overlap. At the beginning and end of each 4-week therapy cycle, pulmonary function was measured before and after an acute 30-min course of PT. The acute PT performed at this time was the same as the one used in the respective chronic treatment arm (twice daily for 4 weeks). At the end of each acute PT period, sputum was collected, weighed, and stored at −80°C in a deep freezer for subsequent rheologic analysis.

**Patients**

Seventeen patients with CF, diagnosed by clinical history and a positive sweat test, between 7 and 41 years of age were enrolled in this study. The patients were referred from CF centers in the Munich area. The patients' basic standard medical therapy remained unchanged during the course of the investigation. The only change in therapy allowed was in the two PTs being investigated. If any other change in therapy was required, the patient was withdrawn from the study.

Prior to the study, ethics committee approval was obtained from the university medical ethics committee. Each patient or his or her parent gave written consent before being randomly assigned to one of the two treatment arms.

**Physiotherapies**

Before and after each 4-week course of twice-daily PT, the effects of an acute therapy were examined. Each 30-min acute therapy session was guided by a professional physiotherapist to ensure reliable performance. The position (elevation and orientation) of the Flutter device was chosen by the patient. In general, patients used the Flutter position they were most comfortable with and that maximized their perception of an effect on airway secretions. Although patients used the device at different positions, each patient kept the position constant during the 4-week course of PT. In contrast, AD was always performed with gentle breathing.

AD is a self-care technique designed to remove mucus from the airways. The modified AD method used in this study involves inspiration through the nose, a pause, and then expiration through the nose or mouth. Expiration consists of two phases: passive—initial rapid airflow without use of the respiratory muscles, and active—slower end-expiratory airflow with careful support of the respiratory muscles. The length of expiration is determined by the amount and position of the mucus in the airways; e.g., with less mucus in the large airways, expiration is prolonged.

The breathing maneuvers are performed in either a seated or lying position, breathing with controlled chest and diaphragm movement. Hands are laid on the chest and epigastric region to monitor the breathing and the progress of the mucus, as indicated by a rattling in the larger airways and trachea. As soon as the mucus reaches the larynx, it can be readily coughed out. When indicated, the mucus is coughed out against resistance to avoid bronchial collapse or spasm.

**Pulmonary Function Testing**

Before and after each acute PT session, pulmonary function testing was performed. The best of three measurements was used for analysis. The instrument used was a constant volume body plethysmograph (Fa. Jäger; Würzburg, Germany). Only FVC and FEV1 data were utilized for analysis of the therapy effect, except for the baseline data given in Table 2.

**Blood Oxygen Saturation**

Blood oxygen saturation was determined on the finger by means of a transcutaneous pulse oximetry technique (Nellcor pulse oximeter, Model N-10; Nellcor Puritan Bennett GmbH; Frankfurt, Germany). Three measurements were taken in order to ensure accuracy.

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**Table 1—Relationship Between Flutter Mouthpiece Position and Corresponding Expiratory Pressures, Oscillation Frequencies, and Airflows**

<table>
<thead>
<tr>
<th>Angle of Instrument</th>
<th>Expiratory Pressure, cm H2O</th>
<th>Oscillation Frequency, Hz</th>
<th>Airflow, L/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>+30°</td>
<td>12-75</td>
<td>15-32</td>
<td>1.6-5.5</td>
</tr>
<tr>
<td>0°</td>
<td>10-70</td>
<td>9-22</td>
<td>1.6-5.5</td>
</tr>
<tr>
<td>−30°</td>
<td>8-60</td>
<td>2-10</td>
<td>1.6-5.5</td>
</tr>
</tbody>
</table>

*Summarized from Lindemann.*

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1. The modified AD method used in this study involves inspiration through the nose, a pause, and then expiration through the nose or mouth. Expiration consists of two phases: passive—initial rapid airflow without use of the respiratory muscles, and active—slower end-expiratory airflow with careful support of the respiratory muscles. The length of expiration is determined by the amount and position of the mucus in the airways; e.g., with less mucus in the large airways, expiration is prolonged.

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3. Blood oxygen saturation was determined on the finger by means of a transcutaneous pulse oximetry technique (Nellcor pulse oximeter, Model N-10; Nellcor Puritan Bennett GmbH; Frankfurt, Germany). Three measurements were taken in order to ensure accuracy.
Table 2—Anthropometric and Pulmonary Function Data at Baseline*

<table>
<thead>
<tr>
<th></th>
<th>Values</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Age, yr</td>
<td>19.6 ± 10.3</td>
<td>7-41</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/8</td>
<td>—</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>44.1 ± 14.6</td>
<td>20-60</td>
</tr>
<tr>
<td>Height, cm</td>
<td>156.4 ± 19.4</td>
<td>122-175</td>
</tr>
<tr>
<td>Body mass index</td>
<td>17.3 ± 2.3</td>
<td>13.2-20.1</td>
</tr>
<tr>
<td>Arterial saturation of oxygen, %</td>
<td>94.9 ± 1.6</td>
<td>91-97</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>88.4 ± 19.5</td>
<td>53.3-115.2</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>75.0 ± 26.5</td>
<td>29.2-117.3</td>
</tr>
<tr>
<td>Residual volume, % predicted</td>
<td>135.7 ± 59.6</td>
<td>35.8-274.6</td>
</tr>
<tr>
<td>Total lung capacity, % predicted</td>
<td>100.4 ± 17.2</td>
<td>75.0-126.1</td>
</tr>
</tbody>
</table>

*Data presented as mean±SD.

Sputum Collection and Weight Analysis

During each acute 30-min PT session, sputum was gently expectorated into a plastic beaker, weighed with a Sartorius analytical balance, and stored at −80°C in a deep freezer until analyzed in a complete series. This procedure has been shown in the past to allow accurate and reproducible evaluation of sputum rheology.6–5 The quantity of sputum expectorated, as measured with the analytical balance, was expressed in g.

In vitro Flutter Application

In a companion in vitro experiment, airflow oscillations were generated by passing humidified air over CF sputum lining an acrylic tube connected at its outlet to a Flutter device. Sputum elasticity was measured by a filancemeter, as described below. The CF sputum samples were taken from our sputum bank; the patients had not been on any form of mucolytic therapy.

Mucus Rheologic Analysis

The magnetic microrheometer technique6 was used to measure the viscosity and elasticity of mucus. A steel microsphere (approximately 100 μm in diameter) is carefully positioned in a 1- to 10-μL sample of mucus and oscillated under the influence of an electromagnet. The image of the steel ball is projected onto a pair of photocells that produce a signal corresponding to the oscillating magnetic field gradient displacement of the ball. The photocell signal is plotted against time, log G*, and tan δ (viscosity/elasticity), at low (1 rad/s) and high (100 rad/s) oscillation frequency.

Two derivative parameters, mucociliary clearability index (MCI) and cough clearability index (CCI), were computed from in vitro relationships derived from model studies of clearance.7,8 The MCI, indicating clearability by normalized ciliary function, was computed from log G* and tan δ at 1 rad/s, and the CCI was computed from log G* and tan δ at 100 rad/s. Both indices correlate negatively with log G*; MCI correlates negatively with tan δ, but CCI correlates positively with it. Their respective formulas are as follows9–10:

\[
\text{MCI} = 1.62 - (0.22 \times \log G^*) - (0.77 \times \tan \delta)
\]

\[
\text{CCI} = 3.44 - (1.07 \times \log G^*_{100}) + (0.89 \times \tan \delta_{100})
\]

For the in vitro application of Flutter oscillations, sputum elasticity was determined by means of a filancemeter (type 04; SEFAM; Nancy, France), which measures mucus spinnbarkeit as thread formation in mm. Spinnability, or spinnbarkeit, is the thread-forming capacity of mucus under the influence of large-amplitude elastic deformation. This measurement is performed with a 10- to 20-μL sputum sample at a distraction velocity of 10 mm/s. An electrical signal is conducted through the sputum sample; this signal is interrupted at the time where the stretched sputum thread is broken.11 Spinnability correlates negatively with cough clearability using a simulated cough machine.12

Data Analysis

Data were tested by two-way analysis of variance with the aid of a Macintosh computer and a statistical program (Statview II). Data are presented as mean±SD unless otherwise noted. Where appropriate, specific comparisons between treatments were made using paired t tests. A value of p<0.05 was considered significant.

RESULTS

A total of 17 CF patients entered into the long-term, 4-week PT study. Two of the enrolled patients had an acute bronchopulmonary exacerbation during the course of the 4-week PT interval (one in the AD and one in the Flutter treatment arm) and had to undergo IV antibiotic therapy. Both patients were therefore withdrawn from the study. One adult patient withdrew his participation because of business-related time constraints after the first examination. Thus, the data shown include only the results of the 14 patients who completed the study.

The baseline demographic, anthropometric, and pulmonary function testing data from these 14 patients are given in Table 2. These data characterize the patients of our study as having mild to moderate lung disease with sometimes severe airway obstruction, as evidenced by an FEV1 of 29.2% predicted in one case. Overall, no significant changes in FVC, FEV1, or sputum volume were noted throughout the study (Table 3). At the end of the 9-week study, both groups (group 1 starting with AD, group 2 starting with Flutter) showed a tendency toward improved FVC, up to 200 mL on average (approximately 6.5% of the baseline value). This may be attributed to a nonspecific improvement in pulmonary function or to an overall training effect.

Sputum viscoelasticity (rigidity) was significantly lower (p<0.01) after PT with the Flutter than with AD (Fig 1) at both analytical frequencies (1 rad/s and 100 rad/s), and as a consequence, the calculated MCI (p=0.01) and CCI (p=0.04) increased significantly (Fig 2). There was also a tendency for the expectorated sputum volume to be greater when the Flutter was used than when AD was, regardless of

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the therapeutic order (Table 3) when the two sputum volumes expectorated from both acute examinations were added. This was true in both group 1, who started with AD (2.7±1.3=6.3 g) and then crossed over to Flutter therapy (4.2±1.5=7.3 g), and in group 2, who started with Flutter (2.9±4.5=7.4 g) and crossed over to AD therapy (3.9±2.2=6.1 g). These differences (1.0 to 1.3 g of sputum per patient, on average) were not statistically significant, however.

In the in vitro Flutter experiment, it was found that the elastic properties of CF sputum samples, as measured by a filancemeter, were affected significantly by application of oscillations generated by the Flutter at 15 and 30 min, as shown in Figure 3. The mean airflow velocity was approximately 1.5 L/s, and the cross-sectional area of the tube was 2.2 cm². The median frequency of the Flutter-generated oscillations was 19 Hz.

**Table 3—Pulmonary Function Values and Sputum Volumes During PT Treatments**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Visit</th>
<th>FVC, L</th>
<th>FEV1, L</th>
<th>Sputum Volume, g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Group 1 (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before AD/after 1-wk wash-out</td>
<td>1</td>
<td>2.9±1.4</td>
<td>2.9±1.4</td>
<td>2.1±1.1</td>
</tr>
<tr>
<td>After 4 wks of AD</td>
<td>2</td>
<td>2.9±1.4</td>
<td>2.9±1.5</td>
<td>2.0±1.0</td>
</tr>
<tr>
<td>Before Flutter/after 1-wk wash-out</td>
<td>3</td>
<td>2.9±1.4</td>
<td>3.0±1.5</td>
<td>2.1±1.1</td>
</tr>
<tr>
<td>After 4 wks of Flutter</td>
<td>4</td>
<td>3.1±1.5</td>
<td>3.1±1.5</td>
<td>2.1±1.0</td>
</tr>
<tr>
<td>Group 2 (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Flutter/after 1-wk wash-out</td>
<td>1</td>
<td>3.2±0.6</td>
<td>3.2±0.8</td>
<td>2.1±1.0</td>
</tr>
<tr>
<td>After 4 wks of Flutter</td>
<td>2</td>
<td>3.2±0.6</td>
<td>3.2±0.6</td>
<td>2.1±1.0</td>
</tr>
<tr>
<td>Before AD/after 1-wk wash-out</td>
<td>3</td>
<td>3.2±0.7</td>
<td>3.3±0.6</td>
<td>2.1±1.0</td>
</tr>
<tr>
<td>After 4 wks of AD</td>
<td>4</td>
<td>3.4±0.7</td>
<td>3.4±0.8</td>
<td>2.2±1.0</td>
</tr>
</tbody>
</table>

*Data presented as mean±SD.

In the in vitro Flutter experiment, it was found that the elastic properties of CF sputum samples, as measured by a filancemeter, were affected significantly by application of oscillations generated by the Flutter at 15 and 30 min, as shown in Figure 3. The mean airflow velocity was approximately 1.5 L/s, and the cross-sectional area of the tube was 2.2 cm². The median frequency of the Flutter-generated oscillations was 19 Hz.

**Discussion**

Thus far, the PTs that have been used in chronic hypersecretory lung diseases such as CF are based on the assumption that these treatments are capable of enhancing mucus clearance from the airways due to improved transport mechanisms. In this respect, changing the viscoelastic properties of the bronchial secretions may be perhaps one of the most important mechanisms. However, no in vivo evidence has been shown so far to prove this theory. Dasgupta and colleagues were recently able to demonstrate in an in vitro study that when frequencies similar to those generated by the Flutter device were applied to CF sputum, viscoelasticity was significantly reduced with increasing oscillation time. This was also true for mucous gel simulants; the higher the applied frequency, the greater the reduction in viscoelasticity. In the present study, we found that oscillations generated by the Flutter device at realistic airflow velocity and frequency led to reduced sputum spinability, a rheologic measure that is closely related to cough clearance.
higher volume expectorated with Flutter than with AD. However, it was in terms of sputum viscoelasticity that the two forms of PT distinguished themselves. The evidence presented here showed that when compared with AD therapy, Flutter therapy resulted in a significant reduction in sputum viscoelasticity (log G*) at low (1 rad/s) and high (100 rad/s) analytical frequencies, producing an improved MCI and CCI. This is in line with the hypothesis that oscillations (2 to 32 Hz) and amplitudes producible with the Flutter device are capable of reducing the mucus viscoelasticity in the airways and thus improving clearance. In our study, the tendency toward a higher volume of expectoration with Flutter therapy than with AD was not significant. This is in contrast to the study by Konstan et al., who found a large increase in expectorated sputum volume with Flutter therapy compared with cough or conventional chest PT. The reasons for the difference are not certain, but could reflect at least in part the different control PT regimens with which Flutter therapy was compared.

In order to correlate rheologic data and mucus clearance, standardized and frequency-dependent rheologic measurements, such as our magnetic microrheometer technique (1 and 100 rad/s), are required. The mucus viscoelasticity analysis of such measurements have to be therefore performed under the physiologic conditions of the clearance mechanism of interest (cough clearance or ciliary clearance). The cilia beat, for example, with a frequency between 10 to 20 Hz and an amplitude of 5 μm, resulting in a mucus transport velocity, (frequency×amplitude) of 0.5 to 2.0 cm/min in the trachea. In contrast, the velocity during a cough maneuver is about 100 times greater. Furthermore, at least in intact mucociliary systems, interactions between the mucus blanket at points of attachment should be considered. Thus, low-frequency (1 rad/s) viscoelasticity measurements are appropriate for observations of mucociliary clearance, whereas high-frequency measurements (100 rad/s) should be more predictive for cough clearance. A high tan δ (ratio of viscosity to elasticity) at high frequency suggests a viscous mucus that favors cough clearance. A low tan δ at low frequency characterizes an elastic mucus that favors ciliary clearance. A high log G* (mechanical impedance or overall resistance to deformation) inhibits both forms of clearance, Flutter therapy, as we have seen, affected both low- and high-frequency rheology.

This is to our knowledge the first in vivo evidence demonstrating this mechanism. A previous in vitro study further elaborated this mechanism and showed a frequency-dependent (0, 12, and 22 Hz) decline in sputum rigidity, and further rheologic effects were seen using physiologic saline and recombinant human deoxyribonuclease. The frequencies used in this in vivo study...
are comparable to the frequencies under investigation in these previous in vitro studies, and thus oscillations are most likely responsible for the obtained results. The mechanism or mechanisms for the reduction in viscoelasticity or degree of crosslinking of the mucus gel by mechanical oscillation are not known. The most likely possibilities involve the cooperative unfolding of the physical entanglements between the primary network of mucous glycoproteins and other structural macromolecules, the rupture of crosslinking bonds such as disulfide bridges, or perhaps the fragmentation of larger molecules such as DNA or F-actin, which are present as a byproduct of infection and can increase mucus viscoelasticity due to their interactions with glycoproteins.

Mucus clearance from the airways of CF patients is of vital interest in order to prevent mucus plugging, mucus impaction, and further deterioration of lung function. This is more critical in CF than in chronic bronchitis since it has been demonstrated that CF patients do not cough as efficiently as patients with chronic bronchitis, and thus CF patients lack a sufficient secondary mucus clearance mechanism when mucociliary clearance is decreased or abolished by ongoing inflammatory processes. Airway collapse may at least in part be responsible for this insufficient cough clearance. Flutter therapy, therefore, seems an elegant way to improve cough clearance, as illustrated in Figure 2. Keeping the airways open during lightly forced expiration, through the added positive airway pressure produced by the Flutter during expiration, may be an additional factor. The shear rates during such a cough maneuver, with the consequent flow and pressure changes, have to be high enough to move bronchial secretions, but not so high that airway collapse occurs.

Because there is an optimal range for the viscoelasticity of bronchial secretions and very often a clinical need to improve mucus clearance from the airways, each therapeutic intervention that modifies the viscoelasticity of mucus should be monitored, and changes expressed as the percent change from baseline, with a standardized rheologic method.

In summary, these results are in line with recent in vitro experiments demonstrating the efficacy of externally applied frequencies to sputum aliquots in reducing the viscoelasticity of bronchial secretions. This mucotropic effect of oscillation is confirmed by the in vitro results (Fig 3); the oscillations generated by the Flutter device were of a comparable magnitude and frequency to those observed in our in vivo study. This advantageous effect on rheology and clearability was also hypothesized for the in vivo situation, but to our knowledge has not been demonstrated yet. The overall lower viscoelasticity of Flutter sputum samples suggests that the Flutter PT device is capable of reducing the viscoelasticity of mucus in vivo. This point is further reinforced by the crossover design of the study: lower viscoelasticity values returned to higher values during AD therapy and viscoelasticity values decreased during Flutter therapy.

The best benefit from the investigated PTs is illustrated in Figure 2, which shows that CCI was better with Flutter therapy than with AD. This suggests that Flutter treatment modifies the mucus, allowing it to be cleared more easily by cough and airflow mechanisms. These findings are even more important, because neither lung function nor expected sputum volume showed any significant differences between the two PTs in terms of efficacy and side effects. The improved mucus clearability (MCI and CCI) caused by the reduction in sputum viscoelasticity suggests that Flutter therapy may be most successful when used in more severe stages of illness, and also in patients with severe sputum expectoration problems.

These findings are consistent with the view that applied oscillations can decrease mucus viscoelasticity within the airways at the frequencies and amplitudes achievable with the Flutter device. This is, to our knowledge, the first in vivo evidence that PT can reduce the viscoelasticity of sputum.

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