Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: a randomised crossover trial

Philippe Reix1,2,3, Françoise Aubert1, Marie-Christine Werck-Gallois1, Agnès Toutain1, Corinne Mazzocchi1, Nathalie Moreux1, Gabriel Bellon1,3, Muriel Rabilloud2,3,4 and Behrouz Kassai1,2,3

1Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, 2Laboratoire de Biométrie et Biologie Evolutive, Equipe Bio-statistique-Santé, Villeurbanne, 3Université Claude Bernard Lyon, Villeurbanne, 4Hospices Civils de Lyon, Service de Bio-statistique, Lyon France

Question: Can a session of exercise with incorporated expiratory manoeuvres substitute for a session of breathing techniques for airway clearance in children with cystic fibrosis? Are children with cystic fibrosis as co-operative and satisfied with the exercise regimen as with the breathing techniques? Design: Randomised, cross-over trial with concealed allocation and intention-to-treat analysis. Participants: 34 children with cystic fibrosis in a stable clinical state. Interventions: Participants underwent two 20-min airway clearance interventions on two scheduled clinic days: one involving three bouts of various whole-body exercise modalities each followed by independent expiratory manoeuvres, and the other involving breathing control, thoracic expansions with manual expiratory compressions, and the forced expiratory technique. Outcome measures: Wet weight of expectorated sputum, change in lung function, co-operation with treatment, perceived treatment quality, and satisfaction with treatment were all assessed after each intervention. Results: The wet weight of sputum after exercise was 0.6 g higher after the exercise intervention, which was not statistically or clinically significant (95% CI –0.2 to 1.4). However, lung function and participant satisfaction with the treatment were both significantly better after the exercise intervention. Co-operation with treatment and perceived treatment quality were equally high for each intervention. Conclusion: A session of various whole-body exercises interspersed with independent expiratory manoeuvres could be an acceptable substitute for a session of breathing control, thoracic expansions with manual expiratory compressions, and the forced expiratory technique in children with mild cystic fibrosis lung disease. Trial Registration: NCT01509235. [Reix P, Aubert F, Werck-Gallois M-C, Toutain A, Mazzocchi C, Moreux N, Bellon G, Rabilloud M, Kassai B (2012) Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: a randomised crossover trial. Journal of Physiotherapy 58: 241–247]

Key words: Exercise, Children, Cystic fibrosis

Introduction

People with cystic fibrosis have a genetic mutation that dehydrates the airway epithelium, impairing the clearance of airway secretions by mucociliary clearance and cough (Boucher 2007). This impaired clearance leads to a cycle of mucus obstruction, infection, and inflammation. The chronic lung infection that ensues is characterised by gradual progressive decline in lung function interspersed with acute exacerbations, and eventual respiratory failure (Ratjen 2009). Although prognosis has improved markedly for people with cystic fibrosis over the past few decades, cystic fibrosis remains a life-shortening disease with respiratory failure still accounting for the majority of mortality (Viviani et al 2012). Therefore, it is important to identify and use interventions that target this pathogenic pathway.

Several categories of interventions are used to treat mucus obstruction and infection in people with cystic fibrosis. Antibiotics are used to suppress infection (Doring et al 2000), various mucoactive medications are used to improve both the patency of the airways and the physical properties of the mucus to aid its clearance (Heijerman et al 2009, Bishop et al 2011), and a range of physical techniques are used to dislodge mucus and to facilitate its expectoration. These physical techniques may include positioning, manual techniques, positive pressure devices, breathing techniques, and exercise (van der Schans et al 2000).

Although airway clearance is a widely recommended goal of treatment in the management of cystic fibrosis lung disease (Flume et al 2009), people with cystic fibrosis typically have low adherence to their airway clearance regimen despite being aware of its importance (Myers 2009). At various stages of disease progression, people with cystic fibrosis may view airway clearance as an inconvenience. When patients have mild lung disease and minimal sputum production, an airway clearance session may be perceived as time-
consum ing and ineffective, or useless. In the more severe stages of the disease, an increase in the duration of airway clearance sessions may be appropriate. However, when airway clearance is prolonged, motivation and adherence may decrease. Also, some airway clearance techniques are not well tolerated clinically. Therefore, it is important to compare the effects of the various physical interventions for airway clearance, considering their relative effects on sputum clearance, lung function, and patient satisfaction.

Exercise offers some potential advantages over other physical airway clearance interventions (van Doorn 2010). In addition to enhancing mucus clearance (Salh et al 1989, Bilton et al 1992), it improves cardiorespiratory fitness (van Doorn 2010), muscle mass, strength, and body image (Sahlberg et al 2008), as well as emotional wellbeing and perceived health (Selvadurai et al 2002, Hebestreit et al 2010). Perhaps most importantly, a recent systematic review examining trials of exercise in children with cystic fibrosis concluded that a long-term exercise program may protect against pulmonary function decline (van Doorn 2010). Furthermore, exercise is often more readily accepted by patients, especially the youngest (Moorcroft et al 1998, McIlwaine 2007), than other airway clearance methods (Bilton et al 1992). This may be because it is a more ‘normal’ activity and because it can be tailored for greater enjoyment (Kuys et al 2011).

Although substantial evidence shows that exercise is better than no exercise, fewer trials have been conducted to evaluate the usefulness of acute exercise as a substitute for or assistance in airway clearance. Most of these trials have studied adults (Bilton et al 1992, Baldwin et al 1994, Salh et al 1989, Lannefors & Wollmer 1992) with fewer studying children (Zach et al 1981, Zach et al 1982, Cerny 1989). However, the trials by Zach and colleagues were not randomised and the trial by Cerny examined the effect of substituting exercise for two of three sessions per day of manual airway clearance techniques in postural drainage positions. These features make it difficult to compare the effects of exercise to those of breathing/manual techniques for airway clearance. Therefore, we sought to compare the effect on airway clearance of exercise and chest physiotherapy in children with stable cystic fibrosis lung disease. The research questions for this study were:

1. Can a session of exercise with incorporated expiratory manoeuvres substitute for a session of breathing techniques for airway clearance in children with cystic fibrosis?
2. Are children with cystic fibrosis as co-operative and satisfied with the exercise regimen as with the breathing techniques?

Method

Design

A randomised cross-over trial with concealed allocation and intention-to-treat analysis was conducted at the Lyon Paediatric Cystic Fibrosis Centre in France to compare a regimen of exercise combined with expiratory manoeuvres against a control regimen of breathing techniques. Each intervention was tested once on non-consecutive days scheduled to coincide with quarterly clinic appointments. Each intervention lasted 20 minutes. Between the two interventions, patients continued their usual treatments and airway clearance techniques.

Participants, therapists, centres

Participants were recruited from the Paediatric Cystic Fibrosis Centre between March and December 2006. Children attending the clinic were eligible to participate if they were aged 7–18 years; had a confirmed diagnosis of CF (two positive sweat tests and/or two cystic fibrosis transmembrane conductance regulator gene mutations with compatible clinical signs), regardless of their basal pulmonary function status; were clinically stable; and able to expectorate and understand the protocol instructions. Patients were deemed stable when they had no signs of pulmonary exacerbation as defined by Rosenfeld and colleagues (2001), together with a predicted forced expiratory volume in 1 s (FEV1) that was not below 10% of the mean FEV1 calculated with the four previous values of the year. Patients with pulmonary exacerbation or deemed clinically unstable were adequately treated and invited to participate later, whenever possible. Exclusion criteria were haemoptysis greater than 50 mL in one day and permanent non-invasive ventilation.

After eligibility was confirmed, one investigator (BK) at the Clinical Investigation Centre used a computer-generated randomisation list to allocate participants to commence the study protocol beginning with either the exercise with expiratory manoeuvres (experimental) intervention or the breathing techniques (control) intervention. Participants started their first session of the study at the next scheduled quarterly clinic appointment to avoid making additional visits.

Intervention

Experimental intervention: The experimental intervention consisted of three periods of exercise each lasting 5 min, supervised by a physiotherapist (FA). The first period consisted of 2 min of indoor jogging, 1 min of stair climbing (three floors), and 2 min of cycling on an ergometer. Resistance on the ergometer was adjusted to ensure that the participant’s respiratory rate was elevated during the 2 min of cycling. At the end of the first period, the patient performed several prolonged and brief expiratory flow accelerations with open glottis, the forced expiratory technique, and finally cough and sputum expectoration. These clearance manoeuvres were performed over 1.5 min. The second period consisted of 1 min of stretching repeated five times, followed by the same expiratory manoeuvres for 1.5 min, as described above. The third period consisted of continuous jumping on a small trampoline. It included 2 min of jumping, 2 min of jumping while throwing and catching a ball, and 1 min of jumping while hitting a tossed ball. This was again followed by expiratory manoeuvres for 1.5 min. The entire regimen was followed by 40 min rest.

Control intervention: The control intervention consisted of a regimen of breathing and manual techniques usually prescribed by physiotherapists in our centre to promote airway clearance. Initially, participants instilled a small amount (~2.5 mL) of normal saline into each nostril and blew their nose, to facilitate nasal airflow during the intervention. The intervention then consisted of three steps modelled on the active cycle of breathing technique: breathing control, thoracic expansion, and forced expiration. Initially, participants were positioned in supported long sitting with the trunk inclined at 30 degrees and commenced quiet breathing around tidal volume. They were then encouraged to increase the diaphragmatic component to inspiration...
by achieving expansion of the abdomen and lower chest while relaxing the upper chest and shoulders. This was continued for 1.5 min. Participants then commenced deeper inspirations (towards total lung capacity) without inspiratory pauses. With this increasing use of the inspiratory reserve volume, participants were still encouraged to use lower chest expansion. This was also continued for 1.5 min. Next, in order to facilitate the movement of secretions to the proximal airways, prolonged forced expiratory flows were performed, accompanied by anterolateral thoracic manual compression by the physiotherapist at the end of expiration, and finally huffing (usually two) and/or coughing when secretions had reached the proximal airways. Typically, participants sat up at the end of the forced expiratory manoeuvre to cough and expectorate. This typically took 1 min. Therefore, one completion of the breathing techniques usually lasted ~5 min, and this was completed four times. The entire regimen was followed by 40 min rest.

Outcome measures

Primary outcome: The wet weight of expectorated sputum was the primary outcome measure. The sputum produced by all phases of each intervention and during the 40-min rest period that followed was collected in a sterile container and weighed. Participants were strongly encouraged not to swallow any secretions cleared from the lungs and to place all expectorated material in the container during the collection period.

Secondary outcomes: Lung function was measured using spirometry according to American Thoracic Society standards (Miller et al 2005). FEV₁ was measured using a calibrated spirometer. Pre- and post-bronchodilator spirometry was performed on each day immediately before the intervention was commenced. The bronchodilator was 200 to 400 µg of salbutamol, according to each participant’s usual dose and kept consistent between study days, via a spacer device. The best FEV₁ value obtained (either before or after bronchodilators) was kept for analysis. Spirometry was repeated 10–30 min after the 40-minute rest period. FEV₁ was expressed as a percentage of the predicted values for the participant’s height and gender (Bellon et al 1982). In addition to the analysis of the data when expressed as a percentage of predicted values, change in FEV₁ was also analysed in relative percent, ie,

\[(\text{FEV}_1 \text{ end} - \text{FEV}_1 \text{ start}) * 100 / \text{FEV}_1 \text{ start}\]

Participant co-operation with each intervention was rated by the treating physiotherapist. Ratings were recorded on a Likert-type scale from 1 (participant refused to co-operate with the intervention) to 5 (excellent co-operation).

The quality of each intervention was rated by the participant. Ratings were recorded on a Likert-type scale from 1 (poor) to 5 (excellent). The ratings of treatment quality were made at the end of the 40-min rest period for each intervention.

Participant satisfaction with each intervention was rated by participants on a visual analogue scale from 0 (not satisfied at all) to 100 (fully satisfied). The ratings of satisfaction were made at the end of the 40-min rest period for each intervention.

Any adverse changes in a participant’s clinical status were noted as an adverse event. Non-invasive pulse oximetry was used throughout each intervention to monitor for oxyhaemoglobin desaturation.

Data analysis

We calculated the sample size based on the primary outcome. For the smallest worthwhile effect of one intervention versus another, we nominated a 1.5 g difference in the wet weight of expectorated sputum produced. We anticipated a standard deviation of the difference between the two values for the same patient at 2.8 g, based on data reported by Bilton et al (1992). With an alpha risk of 5% and a study power of 80%, a total of 30 patients were required. To allow for 10% loss to follow-up, this sample was increased to 34 participants.

The characteristics of the participants were described using means and standard deviations for continuous variables and using numbers and percentages for categorical variables. An analysis of variance, which took period and sequence effects into account, was used to estimate the effect of the intervention on sputum weight and FEV₁. In the absence of period and sequence effects, a paired t-test was calculated. Co-operation and perceived treatment quality were analysed as the relative risk of a rating of good to excellent. Adverse events were also analysed using relative risk. A mixed-effect Tobit model was used to analyse the effect of the intervention on satisfaction while taking a ceiling effect into account.

Results

Flow of participants through the study

Fifty-five patients were assessed for eligibility, of whom 34 underwent randomisation (Figure 1). Among the 10 patients who refused to participate, 4 stated that they did not enjoy sport and 6 stated that they did not like spirometry. The baseline characteristics of the participants who completed the study are presented in Table 1. The two groups of participants were comparable at the start of the intervention arms in terms of pulmonary function, nutritional status and therapeutic requirements (Table 2 and the first two columns of data in Table 3). There was also no statistically significant difference in FEV₁ values between the start of the first and second intervention arms (p = 0.6).

Compliance with the trial method

All randomised participants completed their first allocated intervention. One participant was withdrawn before undertaking the control intervention due to unstable lung disease and one participant was withdrawn before undertaking the experimental intervention for psychological reasons. The second intervention arm occurred at the next scheduled quarterly visit for 18 participants. For the remaining participants, because of unavailability or clinical instability, the second session was done at 5 months for one patient, 6 months for ten patients, and at 9, 10 and 14 months for one participant each.

Effect of intervention

Primary outcome: The wet weight of expectorated sputum was slightly higher after the experimental intervention than after the control intervention, but the mean difference of 0.6 g (95% CI –0.2 to 1.4) was not statistically significant in the analysis, which took into account sequence and period effects (Table 4). Individual data are presented in Table 5 (see eAddenda for Table 5).

Secondary outcomes: On average, FEV₁ as a percentage of the predicted value improved by 2% after the experimental
Figure 1. Design and flow of participants through the trial.

Table 1. Baseline characteristics of study completers.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean (SD)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Gender, n male (%)</td>
<td>18 (56)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>F508del homozygote</td>
<td>13 (41)</td>
</tr>
<tr>
<td>F508del heterozygote</td>
<td>17 (53)</td>
</tr>
<tr>
<td>other</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>146 (14)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>36 (11)</td>
</tr>
<tr>
<td>Long-term medication use, n (%)</td>
<td></td>
</tr>
<tr>
<td>rhDNase</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Colimycin</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Chronic Pseudomonas aeruginosa</td>
<td>15 (47)</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of study completers at entry to the first intervention arm by randomly allocated group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exp first (n = 17)</th>
<th>Con first (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>16.5 (2.0)</td>
<td>16.5 (1.7)</td>
</tr>
<tr>
<td>Therapy use, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rhDNase use</td>
<td>11 (65)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>antibiotic use</td>
<td>8 (47)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Airway clearance sessions/wk, mean (SD)</td>
<td>4.7 (1.7)</td>
<td>4.2 (1.4)</td>
</tr>
</tbody>
</table>

Exp = experimental intervention, Con = control intervention, BMI = body mass index.
Forced expiratory volume in one second (FEV₁) improved with the experimental intervention by 2.7% (SD 6.8%) and deteriorated with the control intervention by 0.5 (SD 6.0%), which equated to a statistically significant mean difference of 3.2% (95% CI 0.5 to 6.0).

After the experimental intervention, cooperation was rated as excellent or good for 30 (94%) of the 32 completing participants and poor for two (6%) participants. The results were similar after the control intervention with cooperation rated as excellent or good for 31 (97%) of participants and poor for one (3%). This difference was not statistically significant (RR = 1.03, 95% CI 0.93 to 1.15).

The quality of the experimental intervention was rated as excellent or good by 27 (84%) of the 32 completing participants. The quality of the control intervention was rated as excellent or good by 30 (94%) participants. No participants rated either intervention as poor. This difference was again not statistically significant (RR = 1.11, 95% CI 0.93 to 1.32).

The mean satisfaction score was 89 (SD 16) after the experimental intervention and at 72 (SD 27) after chest physiotherapy (Table 4). The result of the Tobit model, taking into account period and sequence effects, estimated a mean between-group difference of 24, which was statistically significant (95% CI 10 to 38). A period effect was also identified with a greater satisfaction score after the first period than after the second period. The difference in mean score between the two periods was estimated at 19 (95% CI 5 to 32). In a post hoc subgroup analysis, the difference in the mean satisfaction score between the two interventions was greater in children aged 12 years or less than in children over 12 years old. The difference was 35 (95% CI 15 to 55) in favour of the experimental intervention among the younger children and 9 (95% CI –6 to 24) in favour of the experimental intervention among the older children.

Four participants experienced adverse events during the experimental intervention and one participant experienced adverse events during the control intervention, which was not statistically significant (RR = 4.00, 95% CI 0.47 to 33.86). The adverse events were fatigue, breathlessness, and oxygen desaturation below 92%, all of which required interruption of the intervention but resolved swiftly.

**Discussion**

This randomised trial conducted in children with cystic fibrosis compared an exercise regimen with expiratory manoeuvres against a regimen of breathing and manual techniques for airway clearance. The primary outcome did not show significantly greater wet weight of sputum expectorated with one intervention or the other. However, the estimate of the mean difference had a confidence interval of –0.2 g to 1.4 g, which is sufficiently precise to exclude the nominated smallest worthwhile effect of 1.5 g. Therefore we can conclude that the effects of the two interventions on
sputum expectoration do not differ to a clinically important extent. This is an important finding because it indicates that one intervention or the other may be chosen based on, eg, its effects on other outcomes or acceptability to the child with cystic fibrosis.

In the analyses of lung function in this study, exercise tended to have the better effect of the two interventions. Although no smallest worthwhile effect was nominated for FEV$_1$, the lower limit of the confidence interval was clearly clinically trivial, while the upper limit is arguably a clinically worthwhile difference to achieve with a single application of the intervention. This suggests that children who prefer to achieve airway clearance through exercise would not do so at the expense of their lung function. This result is consistent with the study by Bilton et al (1992), in which FEV$_1$ improved within 20 min of exercise. However, an important caveat here is that the long-term effects of these interventions may not be a simple extrapolation of their effects after a single treatment. Nevertheless, if the effect does persist, this may explain how short-term training programs increase pulmonary function (Selvadurai et al 2002) and long-term programs protect against lung function decline (Schneiderman-Walker et al 2000).

The acceptability of an airway clearance intervention to children with cystic fibrosis is an important consideration because they are recommended to perform airway clearance regularly on an ongoing basis (Lester et al 2009, Schechter 2007). If adherence is to be maintained with this indefinite prescription to perform airway clearance, the acceptability of the clearance regimen is crucial. Therefore, another important finding of the study was that the secondary outcomes that reflect acceptability were also similar between the interventions as well. The perceived quality of both interventions and the child's co-operation with them was good or excellent for almost all participants, with no important differences between the interventions. Satisfaction scores were also high for both interventions, although notably satisfaction with the exercise intervention was significantly higher, especially among the children younger than 12 years. The higher satisfaction scores corroborate our and others' experience that people with cystic fibrosis get frustrated with conventional airway clearance techniques and prefer exercise or a combination of both interventions (Moorcroft et al 1998, Bilton et al 1992, Baldwin et al 1994). The fact that satisfaction is greater after one treatment is promising for exercise, given that there are many ways it can be modified to keep it novel, enjoyable, and challenging while maintaining a suitable exercise load (Kuys et al 2011).

Two more caveats are worth noting here. Some other exercise modalities may not have the same airway clearance effects and any exercise modality may not be effective without the incorporation of the short bouts of expiratory manoeuvres. Therefore extrapolation of these results should be done with caution until further assessment of the airway clearance effects of other exercise regimens is available.

As well as being a satisfying alternative to traditional airway clearance techniques, the exercise regimen we examined appears to be a safe alternative. Adverse events were few, mild and transient.

Our results indicate that the participants had relatively low quantities of sputum to expectorate compared to adult studies, which report higher sputum production, eg, 10 to 20 g over periods of 50 to 150 min (Bilton et al 1992, Baldwin et al 1994, Salh et al 1989). The smaller amount of sputum in our participants is likely to be due to their mild lung disease. Given our efforts to ensure expectoration, we do not think that the small amount of sputum indicates that sputum was swallowed. However, this is a theoretical source of bias that must be considered. The vigour of the exercise intervention may have entailed a higher risk of accidental or unnoticed swallowing of secretions than the control intervention. However, if such bias did occur, this would only further support our conclusion that the exercise intervention was a suitable substitute for the control intervention in this study.

The conclusions of our study are limited because each intervention was only applied once for 20 min, and in a hospital environment, where treatment co-operation and quality may surpass that achieved at home. Also, although eligibility was not restricted to a specific FEV$_1$ range, most of the children had excellent lung function so the results may not apply to more severely affected children. Another limitation of the study was the long period between the two interventions, although the patients' clinical status appeared to remain comparable at the start of the two study arms.

This study showed that several bouts of different exercises interspersed with expiratory manoeuvres could be an acceptable substitute for a regimen of breathing and manual techniques for airway clearance in children with mild cystic fibrosis lung disease. In the setting of a chronic paediatric lung disease with a high burden of care and poor adherence to therapy, especially for airway clearance and aerosol therapy, this subset of patients could sometimes perform these exercises as their airway clearance regimen without detriment to their lung function.

**Footnotes:** *Masterscreen PFT, Jaeger, Hoechberg, Germany. Aerochamber, Boehringer Ingelheim Ltd, Bracknell, UK*

**eAddenda:** Table 5 available at jop.physiotherapy.asn.au.

**Ethics:** This study was approved by the local institutional review board: the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (CCPRPB) LYON A (number 2005/100A). Informed consent was obtained from parents and children before enrolment.

**Competing interests:** None.

**Support:** Financial support for this study was provided by a grant from the Hospices Civils de Lyon 'Projet Hospitalier Paramédical’ in 2004, contract number 27313, and ALLP, contract number D20381.

**Acknowledgements:** Investigators are grateful to the children and parents for their active participation in this study. The authors would like to thank Kent Neal (supported by the French Cochrane Center) for proofreading the manuscript.

**Correspondence:** Dr Philippe Reix, Centre de Référence de la Mucoviscidose, Hôpital Femme Mère Enfant, 59, Boulevard Pinel, 69677 Bron Cedex, France. Email: philippe.reix@chu-lyon.fr
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