Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial

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Introduction

Airway clearance is an integral component of the respiratory management of cystic fibrosis (CF). During acute exacerbations of their lung disease, people with CF often find it difficult to maintain effective airway clearance due to increased breathlessness, lethargy and respiratory muscle fatigue. Studies have shown that the addition of non-invasive ventilation (NIV) to a single treatment of physiotherapy techniques for airway clearance assists in overcoming these issues. However, it is not known whether NIV is a beneficial adjunct to physiotherapy treatments for airway clearance if used throughout a hospital admission for an acute exacerbation of CF.

The efficacy of NIV as an airway clearance technique in CF has been examined in several single-session crossover trials. Mucus clearance, as measured by inhaled radioaerosol (a crossover trial).

KEY WORDS
Cystic fibrosis
Non-invasive ventilation
Respiratory therapy
Physical Therapy

ABSTRACT

Question: During an acute exacerbation of cystic fibrosis, is non-invasive ventilation beneficial as an adjunct to the airway clearance regimen? Design: Randomised controlled trial with concealed allocation and intention-to-treat analysis. Participants: Forty adults with moderate to severe cystic fibrosis lung disease and who were admitted to hospital for an acute exacerbation. Intervention: Comprehensive inpatient care (control group) compared to the same care with the addition of non-invasive ventilation during airway clearance treatments from Day 2 of admission until discharge (experimental group). Outcome measures: Lung function and subjective symptom severity were measured daily. Fatigue was measured at admission and discharge on the Schwartz Fatigue Scale from 7 (no fatigue) to 63 (worst fatigue) points. Quality of life and exercise capacity were also measured at admission and discharge. Length of admission and time to next hospital admission were recorded. Results: Analysed as the primary outcome, the experimental group had a greater rate of improvement in forced expiratory volume in 1 second (FEV1) than the control group, but this was not statistically significant (MD 0.13% predicted per day, 95% CI –0.03 to 0.28). However, the experimental group had a significantly higher FEV1 at discharge than the control group (MD 4.2% predicted, 95% CI 0.1 to 8.3). The experimental group reported significantly lower levels of fatigue on the Schwartz fatigue scale at discharge than the control group (MD 6 points, 95% CI 1 to 11). There was no significant difference between the experimental and control groups in subjective symptom severity, quality of life, exercise capacity, length of hospital admission or time to next hospital admission. Conclusion: Among people hospitalised for an acute exacerbation of cystic fibrosis, the use of non-invasive ventilation as an adjunct to the airway clearance regimen significantly improves FEV1 and fatigue. Trial registration: ANZCTR 12605000437662.

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people with CF may be able to perform airway clearance manoeuvres with less effort or tolerate more effective airway clearance techniques with the support of NIV, especially when most required – during an acute exacerbation.

Despite the promising results of single-session applications of NIV during airway clearance treatment in people with CF, to date, no study has examined the efficacy of NIV over a longer period of time. Therefore, the research questions for this study were:

1. In adults with moderate to severe CF lung disease and who are admitted to hospital with an acute exacerbation, does the addition of NIV to chest physiotherapy improve the rate of change and discharge values of lung function and subjective symptom severity?
2. Does it improve the change in respiratory muscle strength following chest physiotherapy?
3. Does it improve quality of life, fatigue score, exercise capacity and quantitative sputum microbiology at discharge?
4. Does it reduce the length of hospital admission and lengthen the time to next hospital admission for an acute exacerbation of CF?

Methods

Design

A parallel-group, randomised controlled trial was conducted in two tertiary Australian hospitals with specialist CF units. After signing consent to participate, patients were assigned to the control group (standard comprehensive inpatient care from the CF team) or the experimental group (standard care plus NIV during chest physiotherapy). Group allocation was determined by computer-generated block randomisation, which was stratified for hospital and gender. Randomisation was performed by a person not involved in the study and stored in sealed, sequentially numbered, opaque envelopes, which were opened after the participant had signed consent. The participants, treating therapists and independent assessors were not blinded to treatment group allocation. Participants in the experimental group used NIV during chest physiotherapy from Day 2 of admission until discharge from hospital. Spirometry and subjective symptom severity were recorded daily throughout the admission. All other outcome measures were collected on admission to and discharge from hospital.

Participants, therapists and centres

All patients who were aged over 17 years and admitted with an acute exacerbation of CF to the Royal Prince Alfred Hospital, Sydney, and Prince Charles Hospital, Brisbane, were assessed for inclusion in the study. An acute exacerbation of CF was defined as the need for intravenous antibiotics with the presence of four or more signs or symptoms, according to the criteria used by Fuchs et al. Patients with moderate to severe CF lung disease were included in the study if their forced expiratory volume in 1 second (FEV1) on admission < 60% of the predicted value. Patients were excluded from the study if they were using domiciliary NIV for the treatment of respiratory failure, had precautions to the use of NIV (eg, pneumothorax, recent severe haemoptysis), were colonised with *Burkholderia cepacia* complex, were pregnant or had already participated in the study. The physiotherapy staff rostered to the respiratory inpatient wards applied the interventions after discussion with a senior physiotherapist not otherwise involved in the study.

Interventions

A senior respiratory physiotherapist, who was not otherwise involved in the study, individually assessed all participants and determined the type, frequency and duration of chest physiotherapy treatment with the participant. During chest physiotherapy, all participants performed the active cycle of breathing technique, which consists of cycles of deep breathing, relaxed breathing, huffing and coughing in order to aid mucus clearance. In addition, the physiotherapist determined whether to incorporate any additional techniques, including manual percussion, vibration, postural drainage positioning, autogenic drainage, positive expiratory pressure (PEP) and oscillating PEP.

Non-invasive ventilation treatment

Participants assigned to the experimental group underwent an acclimatisation session on the day of admission. During this time, the appropriate inspiratory and expiratory pressures were determined, and an interface (nasal mask or mouthpiece) was chosen that maximised participant comfort and efficacy (pressure support), whilst minimising leak. On Day 2 of admission, participants assigned to the experimental group were provided with a NIV machine with inbuilt humidifier and were instructed to use NIV during all chest physiotherapy sessions for the rest of their hospital admission. NIV use was recorded with the inbuilt storage card and downloaded at discharge from hospital.

Outcome measures

Spirometry, which was the primary outcome measure, was performed daily to determine the rate of change in FEV1. Subjective symptom severity was also recorded daily for breathlessness, expectorated sputum volume and energy levels on 10-cm visual analogue scales (breathlessness: 0 = nothing at all, 10 = the maximal I have ever experienced; expectorated sputum volume: 0 = none at all, 10 = as much as I have ever had; energy: 0 = full of beans, 10 = no energy at all). Maximal inspiratory (PImax) and expiratory (PEmax) pressure were measured immediately before and after chest physiotherapy on Day 2 of admission, 1 week after admission and at discharge from hospital. At admission and discharge from hospital, participants also completed the CFQ (a CF-specific quality of life questionnaire), the Schwartz fatigue scale, and the 25-level modified shuttle test to assess exercise capacity. Sputum samples were collected at admission (prior to commencement of intravenous antibiotics), 1 week after admission and at discharge from hospital. Samples were couriered on ice to a central laboratory for quantitative microbiological analysis, which was performed by a blinded assessor. Organisms were identified with the use of standard microbiological techniques, including the API 20 NE system and quantification of organisms was performed with the use of the modifications of Wong and colleagues. The length of admission and time to next hospital admission for an acute exacerbation of CF were recorded.

Data analysis

The primary outcome measure was rate of change in FEV1 (% of predicted per day) from admission to discharge from hospital. Data from 10 patients of similar lung function severity (five from each of the hospitals in this study) showed a standard deviation of 0.49% of predicted per day. With an anticipated effect size of 0.5, 17 participants in each group would give 80% power to detect a significant difference (α < 0.05) between the two groups. To allow for a 15% dropout rate, we sought to recruit 40 people to the study. Repeated-measures analyses were performed using linear mixed models to determine if the rates of improvement in FEV1 and symptom severity were different between the experimental and control groups. The models included fixed effects for group (experimental or control), time (day of admission), and the group by time interaction. A random effect for the intercept (ie, the participant) was included. Independent-samples t-tests, adjusting for the participants’ admission values, were performed to compare the discharge values between the experimental and control groups for FEV1, symptom severity, quality of life, exercise capacity and quantitative sputum microbiology. Independent-samples t-tests were calculated to determine whether there were differences
between the experimental and control groups in the change in respiratory muscle strength following chest physiotherapy and the length of admission. Cox proportional-hazards regression was calculated to compare the time to next hospital admission in the experimental and control groups. Data were analysed on an intention-to-treat basis and statistical significance was set at $p = 0.05$ for all calculations.

**Results**

**Flow of participants, therapists and centres through the trial**

Over a 26-month period, 40 participants consented to the study protocol and underwent randomisation (Figure 1). Three participants withdrew from the study and the data from these participants were used, as available and appropriate, in the analyses of daily rate of improvement, length of stay and time to next hospital admission. The experimental and control groups were similar at baseline (Table 1 and first two columns of Table 2).

![Diagram of flow of participants, therapists and centres through the trial](attachment:image.png)

**Figure 1.** Design and flow of participants through the trial.

* B. cepacia = *Burkholderia cepacia*, CF = cystic fibrosis, FEV$_1$ = forced expiratory volume in 1 second, NIV = non-invasive ventilation.

* One participant in the experimental group did not tolerate NIV and withdrew from further intervention and data collection from Day 2, so was not able to be included in the analyses of rate of improvement or discharge, but was included in the calculation of length of stay and time to readmission.

* On Day 1, one participant in the control group withdrew without providing a reason, so was not able to be included in the analyses of rate of improvement or discharge, but was able to be included in the calculation of length of stay and time to readmission.

* One participant in the experimental group received a lung transplant at Day 19 of the admission, so was able to be included in the rate of improvement analysis but was not able to be included in the discharge analysis or the calculation of length of stay and time to readmission.

All participants performed the active cycle of breathing technique. In addition, physiotherapists applied techniques of manual percussion, vibration and postural drainage positioning, autogenic drainage, PEP and oscillating PEP (Table 3). One of the 19 participants in the experimental group did not tolerate NIV and withdrew from the study. The average inspiratory pressure was 13 cmH$_2$O (SD 2, range 10 to 19), average expiratory pressure was 5 cmH$_2$O (SD 1, range 4 to 7) and average pressure support (difference between inspiratory and expiratory pressure) was 8 cmH$_2$O (SD 3, range 6 to 15). The average daily NIV use was 65 minutes (SD 31, range 26 to 135).
Some sputum samples were unable to be collected before intravenous antibiotics commenced or no courier was available to transport samples to the centralised laboratory. Therefore, sputum samples were analysed for only 14/19 participants in the experimental group and 18/21 participants in the control group at admission and discharge.

Effect of the intervention

Most of the study outcomes are presented in Table 2, with individual participant data presented in Table 4 (see eAddenda for Table 4).

Lung function

There was a non-significant trend for the experimental group to have a greater daily rate of improvement in FEV1 (% predicted) than the control group, with a mean difference of 0.13% per day (95% CI –0.03 to 0.28), as shown in Figure 2. At discharge, the experimental group had a significantly higher FEV1 (% predicted) than the control group (Table 2).

Subjective symptom severity and quality of life

There was no significant difference in the daily rate of improvement between the experimental and control groups for any domain (breathlessness MD 0.05 cm/day, 95% CI –0.07 to 0.18; expectorated sputum volume MD 0.00 cm/day, 95% CI –0.06 to 0.06; energy MD –0.07 cm/day, 95% CI –0.20 to 0.06). At discharge, there was also no difference between the experimental and control groups in the physical, health and respiratory domains of the CFQ (Table 2).

At discharge, there was no significant difference between the experimental and control groups in the physical, health and respiratory domains of the CFQ (Table 2). The experimental group reported significantly less fatigue at discharge than the control group using the Schwartz fatigue scale (Table 2).

Respiratory muscle strength following chest physiotherapy

On Day 2 of the admission, the PImax and PEmax worsened following standard chest physiotherapy (control group) and improved in the experimental group compared to the control group (Figure 2).

Table 1
Characteristics of participants at admission to hospital.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exp (n = 19)</th>
<th>Con (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean (SD)</td>
<td>28 (7)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Gender, n female (%)</td>
<td>6 (32)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>21.4 (1.1)</td>
<td>20.4 (3.0)</td>
</tr>
<tr>
<td>FVC (% predicted), mean (SD)</td>
<td>61 (15)</td>
<td>63 (15)</td>
</tr>
<tr>
<td>Max (% predicted), mean (SD)</td>
<td>87 (32)</td>
<td>93 (30)</td>
</tr>
<tr>
<td>Max (% predicted), mean (SD)</td>
<td>70 (22)</td>
<td>92 (41)</td>
</tr>
</tbody>
</table>

BMI = body mass index, Con = control group, Exp = experimental group, FVC = forced vital capacity, PEmax = maximal expiratory pressure, PImax = maximal inspiratory capacity.

Comparisons between the experimental and control groups are shown as estimated group mean differences, adjusted for admission values, with 95% CI. Fatigue measured on the Schwartz fatigue scale (minimum score = 7, maximum score = 63, lower values represent less fatigue).

Table 2
Mean (SD) of each group at admission and at discharge from hospital, and mean (95% CI) difference between groups at discharge.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Admission</th>
<th>Discharge</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp (n = 19)</td>
<td>Con (n = 21)</td>
<td>Exp (n = 17)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>36.1 (10.4)</td>
<td>39.1 (10.2)</td>
<td>49.5 (14.3)</td>
</tr>
<tr>
<td>MST-25 distance (m)</td>
<td>737 (340)</td>
<td>776 (413)</td>
<td>914 (343)</td>
</tr>
<tr>
<td>P. aeruginosa density (log CFU/g)</td>
<td>7.44 (2.23)</td>
<td>7.57 (0.78)</td>
<td>6.77 (1.68)</td>
</tr>
<tr>
<td>CFQ – physical</td>
<td>36 (19)</td>
<td>37 (24)</td>
<td>54 (27)</td>
</tr>
<tr>
<td>CFQ – health</td>
<td>43 (23)</td>
<td>32 (19)</td>
<td>59 (24)</td>
</tr>
<tr>
<td>CFQ – respiratory</td>
<td>42 (16)</td>
<td>37 (15)</td>
<td>62 (17)</td>
</tr>
<tr>
<td>Fatigue score</td>
<td>44 (12)</td>
<td>44 (12)</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Breathlessness – VAS (cm)</td>
<td>5.6 (2.2)</td>
<td>6.0 (2.4)</td>
<td>1.9 (1.3)</td>
</tr>
<tr>
<td>Sputum volume – VAS (cm)</td>
<td>5.1 (2.1)</td>
<td>6.4 (1.8)</td>
<td>2.0 (1.4)</td>
</tr>
<tr>
<td>Energy – VAS (cm)</td>
<td>6.4 (2.0)</td>
<td>5.7 (1.9)</td>
<td>3.2 (1.7)</td>
</tr>
</tbody>
</table>

Comparisons between the experimental and control groups are shown as estimated group mean differences, adjusted for admission values, with 95% CI. FEV1 = forced expiratory volume in 1 second as percent of predicted normal lung volume, MST-25 = 25-level modified shuttle test, P. aeruginosa = Pseudomonas aeruginosa, calculated as the percentage of participants in each group colonised in sputum and density of P. aeruginosa colony forming units per gram of sputum, expressed as log values on a base 10 scale (log CFU/g), VAS = 10-cm visual analogue scale (higher values represent feeling more symptomatic).

Table 3
Physiotherapy techniques applied during the admission.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Exp (n = 18)</th>
<th>Con (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual techniques</td>
<td>18 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>PEP</td>
<td>6 (33)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Oscillating PEP</td>
<td>1 (6)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Autogenic Drainage</td>
<td>0 (0)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

All participants performed the active cycle of breathing technique. In addition, physiotherapists applied manual techniques of percussion, vibration and postural drainage positioning to all participants. Two participants in the control group performed PEP and autogenic drainage. One participant in the experimental group performed independent oscillating PEP without NIV for some physiotherapy treatments. One participant in the experimental group performed independent PEP without NIV for some physiotherapy treatments. Five participants in the experimental group performed PEP with NIV.

PEP = positive expiratory pressure.
improved following NIV-assisted chest physiotherapy (experimental group). The mean difference in PImax was 8 cmH2O (95% CI 2 to 14) and the mean difference in PEmax was 6 cmH2O (95% CI –3 to 15), as shown in Figure 3. When PImax and PEmax were re-measured before and after chest physiotherapy 1 week into the admission and on discharge from hospital, there was no difference in the change in respiratory muscle strength between the experimental and control groups.

Exercise capacity

At discharge, there was no significant difference in distance covered in the 25-level modified shuttle test between the two groups (Table 2).

Quantitative sputum microbiology

Pseudomonas aeruginosa was identified in all sputum samples, except in one sample from a participant in the experimental group at admission. On quantitative microbiology, the experimental group had a significantly lower Pseudomonas aeruginosa colony count than the control group at 1 week after admission (mean difference –1.12 log CFU/g, 95% CI –0.04 to –2.20). At discharge, there was also a non-significant trend for the experimental group to have a lower Pseudomonas aeruginosa colony count than the control group (Table 2).

Length of hospital admission and time to next hospital admission

There was no significant difference between the experimental and control groups in the length of hospital admission. The mean length of stay was 14.7 days (SD 3.9) in the control group and 14.2 days (SD 4.0) in the experimental group (MD –0.4 days, 95% CI –3.0 to 2.1). There was no significant difference between the experimental and control groups for the time to next hospital admission for an acute exacerbation of CF, as defined by the criteria of Fuchs et al., with a hazard ratio for re-admission in the experimental group of 0.78, p = 0.44 (Figure 4).

Adverse events

There were no adverse events in either group.

Discussion

Non-invasive ventilation-assisted chest physiotherapy applied during a hospital admission for an acute exacerbation of CF resulted in significantly higher FEV1 (% predicted) at discharge than standard chest physiotherapy alone. However, the group who received NIV-assistance to the chest physiotherapy only showed a non-significant trend towards a greater daily rate of improvement in FEV1 (% predicted), which was the primary outcome of the study.

At discharge, the improvement in lung function may have been related to the reduced sputum bacterial load and the preservation of respiratory muscle strength with chest physiotherapy for those using NIV during the early stages of the hospital admission. Participants in the experimental group reported significantly lower levels of fatigue on discharge from hospital compared to the control group. This reduction in fatigue was also reported in other trials of people with CF when NIV-assistance was added to a single session of chest physiotherapy. Potentially, the lower levels of fatigue are related to the preservation of respiratory muscle strength following NIV-assisted chest physiotherapy, which has been demonstrated in previous studies as well as this study. Interestingly, the improvement in respiratory muscle strength following NIV-assisted chest physiotherapy in this study was only evident when measured on Day 2 of admission. When respiratory muscle strength was measured before and after chest physiotherapy 1 week into the admission and at discharge from hospital, there was no difference between the experimental and control groups. Perhaps the unloading of the respiratory muscles with NIV during the early stages of the hospital admission.

Despite having greater improvements in lung function and fatigue, the experimental group reported similar improvements in symptom severity to the control group, both in the rate of improvement and discharge values. Perhaps the improvements in symptoms and quality of life from admission to discharge from hospital are so great that subjective scoring is unable to detect the differences between types of chest physiotherapy.

Surprisingly, considering the improvements in lung function and fatigue, the participants in the experimental group had no greater improvement in exercise capacity at discharge than those in the control group. Both groups had marked improvements in exercise capacity, from admission to discharge, with average improvements of 150 m on the 25-level modified shuttle test, where an improvement of 40 m is considered to be clinically significant.

High sputum bacterial load is a major cause of morbidity in CF. In this study, the experimental group had greater reductions in the sputum Pseudomonas aeruginosa density than the control group, both at 1 week into the admission and at discharge from hospital. It is possible that NIV-assistance augmented the mucus clearance with chest physiotherapy, to help lower the sputum bacterial load, which in turn may have contributed to the greater improvements in lung function for the experimental group.

Lung function is often the major determinant for a physician to decide when a patient should be admitted to hospital and when...
they are well enough to go home. In this study, although participants in the experimental group had slightly faster rates of improvement in lung function, there was no difference in length of hospital stay between the two groups. In addition, despite leaving hospital with significantly higher FEV₁, there was no difference in the time to next hospital re-admission for an acute exacerbation between the two groups.

Although not formally measured in this study, the addition of NIV to chest physiotherapy was well tolerated, which was similar to previous single-session trials of NIV.4–8 The average daily NIV use was 65 minutes. Only one of 19 participants in the experimental group refused NIV treatment due to poor tolerance, and there were no adverse events associated with NIV. The range in pressure support applied with NIV in this study (6 to 15 cmH₂O) was similar to that of previous trials;4–7 however, the average pressure support was only 8 cmH₂O, which may have been insufficient to adequately support inspiratory effort and unload the respiratory muscles for those receiving lower inspiratory pressure. Perhaps higher levels of inspiratory pressure could have been tolerated as participants became more accustomed to the treatment later in the admission, possibly allowing NIV treatment to have been more effective, rather than maintaining the same NIV settings as determined in the acclimatisation session on the day of admission.

This investigation into the efficacy of NIV as an adjunct to chest physiotherapy during an exacerbation of CF lung disease is a difficult setting in which to identify between-group differences. This is because the standard care received by both groups (intravenous antibiotics and comprehensive input from the CF team) is so effective, as reflected in the marked improvements in exercise tolerance and lung function for both groups in this study. Perhaps if the study had targeted more severe CF patients or those with significantly increased work of breathing and intolerance to standard chest physiotherapy, more differences would have been found between the treatment groups. Another limitation of this study was that participants, clinicians and independent assessors were not blinded to treatment allocation. Complete blinding of treatment allocation would have been impossible; however, introducing a third group with sham NIV or continuous positive airway pressure (CPAP) may have provided some blinding to participants and independent assessors.

In summary, the use of NIV as an adjunct to chest physiotherapy during a hospital admission for an acute exacerbation of CF significantly improved lung function and fatigue on discharge from hospital. This improvement in lung function, however, was not matched by improvements in symptom severity, exercise capacity, length of hospital stay, or the exacerbation-free period after discharge from hospital. It is very difficult to show improvements over comprehensive inpatient care; however, the results of this study suggest that the addition of NIV to standard chest physiotherapy is a useful tool to aid airway clearance, especially when people with moderate to severe CF lung disease are most at risk of respiratory muscle fatigue. Future trials targeting people with more-severely affected lungs or continuing the addition of NIV to chest physiotherapy after discharge from hospital would further evaluate the role of NIV in CF care.

What is already known on this topic: People with cystic fibrosis often find it hard to maintain effective airway clearance during acute exacerbations of CF lung disease due to increased breathlessness and respiratory muscle fatigue. When used as an adjunct to a single session of airway clearance techniques, non-invasive ventilation reduces these symptoms and improves ease of expectoration.

What this study adds: When non-invasive ventilation was used as an adjunct to chest physiotherapy throughout a hospital admission by adults with an acute exacerbation of cystic fibrosis lung disease, they left hospital with better lung function and less fatigability.