

CYSTIC FIBROSIS

Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis

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Background: Chest physiotherapy is essential to the management of cystic fibrosis (CF). However, respiratory muscle fatigue and oxygen desaturation during treatment have been reported. The aim of this study was to determine whether non-invasive ventilation (NIV) during chest physiotherapy could prevent these adverse effects in adults with exacerbations of CF.

Methods: Twenty six patients of mean (SD) age 27 (6) years and forced expiratory volume in 1 second (FEV₁) 34 (12)% predicted completed a randomised crossover trial comparing standard treatment (active cycle of breathing technique, ACBT) with ACBT + NIV. Respiratory muscle strength (P_{lmax}, P_Emax), spirometric parameters, and dyspnoea were measured before and after treatment. Pulse oximetry (SpO₂) was recorded during treatment. Sputum production during treatment and 4 and 24 hours after treatment was evaluated.

Results: There was a significant reduction in P_{lmax} following standard treatment that was correlated with baseline P_{lmax} ($r=0.73$, $p<0.001$). P_{lmax} was maintained following NIV (mean difference from standard treatment 9.04 cm H₂O, 95% confidence interval (CI) 4.25 to 13.83 cm H₂O, $p=0.006$). A significant increase in P_Emax was observed following the NIV session (8.04 cm H₂O, 95% CI 0.61 to 15.46 cm H₂O, $p=0.02$). The proportion of treatment time with SpO₂ ≤ 90% was correlated with FEV₁ ($r=-0.65$, $p<0.001$). NIV improved mean SpO₂ ($p<0.001$) and reduced dyspnoea ($p=0.02$). There were no differences in FEV₁, forced vital capacity (FVC) or sputum weight, but FEF₂₅₋₇₅ increased following NIV ($p=0.006$).

Conclusion: Reduced inspiratory muscle strength and oxygen desaturation during chest physiotherapy are associated with inspiratory muscle weakness and severity of lung disease in adults with exacerbations of CF. Addition of NIV improves inspiratory muscle function, oxygen saturation and small airway function and reduces dyspnoea.

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Chest physiotherapy is integral to the management of cystic fibrosis (CF) lung disease. Techniques to aid the removal of secretions from the airway have been shown to slow the rate of deterioration in pulmonary function.¹ Patients with CF are required to perform these airway clearance techniques both during acute respiratory exacerbations and periods of clinical stability.² Despite the essential nature of airway clearance techniques, they are often an onerous task for patients with CF and have been associated with increased energy expenditure, oxygen desaturation, respiratory muscle fatigue, and dyspnoea.³⁻⁶ These effects are likely to be greatest during an acute exacerbation when energy expenditure is increased due to infection and inflammation, and bronchial obstruction and respiratory muscle performance are at their worst.⁷ These factors may compromise the patient's ability to perform airway clearance techniques at a time when it is most crucial.

Non-invasive ventilation (NIV) with bilevel positive airway pressure has been shown to reduce respiratory muscle work at rest in adults with stable CF and respiratory failure.⁸ The effect of this form of NIV on airway clearance has not been examined and there is some controversy regarding its role in patients who produce copious respiratory secretions.⁹ A different mode of NIV, inspiratory pressure support ventilation, has been used to prevent respiratory muscle fatigue during airway clearance in children with stable CF.⁵ However, the results of this study may not be applicable to adults with CF because of differences in respiratory muscle performance.¹⁰ To date, no studies have evaluated the effects of NIV on airway clearance during acute exacerbations, a time when it may be most useful. The aim of this study was to

evaluate the effects of bilevel positive airway pressure during airway clearance on respiratory muscle performance, pulmonary function, oxygen saturation, and sputum clearance in adults with acute exacerbations of CF.

METHODS

Study subjects

All patients aged 18 years or over admitted to a university teaching hospital with an acute exacerbation of CF were assessed for inclusion in the study. An acute exacerbation of CF was defined as the presence of four or more of the following symptoms: change in sputum production; new or increased haemoptysis; increased cough; increased dyspnoea; malaise; fatigue or lethargy; fever; anorexia or weight loss; sinus pain or tenderness; changes in sinus discharge; loss of appetite; more than 10% (of best over last 6 months) deterioration in lung function.¹¹ Patients who produced more than 20 g sputum in 24 hours were eligible for inclusion. This was confirmed by a sputum collection conducted on admission. Subjects were excluded if they required continuous (24 hour) NIV; had decreased level of consciousness, pneumothorax, symptomatic gastro-oesophageal reflux requiring modification of treatment, major haemoptysis (200 ml or more over 24 hours), or oxygen saturation (SpO₂) <90% on room air at study entry. Subjects were also excluded if they had started home antibiotic treatment before day 5 of admission.

The study was approved by the hospital ethics committee and written informed consent was obtained from each subject before testing.

Study design

Subjects participated in two treatment sessions—standard treatment and NIV assisted treatment—on days 3 and 4 of hospital admission. A within subject crossover design was used with subjects randomly allocated to treatment order. Treatments were conducted at the same time each morning and by the same physiotherapist. All measurements were obtained by an independent data collector who was blinded to treatment order.

Treatment methods

Active Cycle of Breathing Technique (ACBT)

The Active Cycle of Breathing Technique (ACBT)¹² was used in both the standard and NIV assisted treatments. The ACBT cycle consisted of a sequence of six thoracic expansion exercises, breathing control (quiet breathing), six thoracic expansion exercises, breathing control, the forced expiration technique (one or two huffs from mid to low lung volume combined with breathing control), and cough as required. The number of cycles performed and number of coughs were recorded. The treatment was performed in body positions determined by the patient's usual treatment regimen or the presence of focal chest signs on assessment, with a minimum of 10 minutes in each position. Treatment duration was 30 minutes.

NIV assisted treatment

During NIV assisted treatment NIV was administered with a bilevel device (BIPAP Duet LX Bi-Level System; Respironics, Pittsburg, USA) for the entire duration of the treatment. Inspiratory and expiratory pressure settings were determined at an acclimatisation session conducted on the day before the start of the study and were chosen to maximise both patient comfort and the level of pressure support delivered. A minimum expiratory pressure of 4 cm H₂O was given. The patient interface consisted of a nasal mask (Mirage Mask System; ResMed, Sydney, Australia) and expectoration occurred without removal of the mask. A warm water humidifier (HC100, Fisher and Paykel Healthcare Pty Ltd, Breakfast Creek, Australia) was connected in series between the bilevel device and the nasal mask. A disposable bacterial filter (Suregard; RJ and VK Bird, Melbourne, Australia) was used to prevent cross infection.

Both sessions were performed without supplemental oxygen. Use of bronchodilators and dornase alfa on study days was standardised with respect to timing and dosage for each subject. Subjects continued with their usual predetermined physiotherapy regimens of airway clearance and exercise for the remainder of the day. These regimens were held constant until the end of the data collection period.

Measurements

Inspiratory and expiratory muscle strength were measured before and immediately after each treatment using maximal static respiratory pressures produced at the mouth (Pmax Monitor; PK Morgan Ltd, Kent, UK). P_{imax} was measured at residual volume (RV) and P_Emax was measured at total lung capacity (TLC) with the subject seated in a hard backed chair. Each pressure was measured at 1 minute intervals, a minimum of three times until there was less than 5% difference between the two highest values. The highest value obtained for P_{imax} and P_Emax was recorded and compared with predicted values.¹³ P_{imax} was reported as a positive value for simplicity of recording. Subjects had been trained to carry out these manoeuvres on the day before the study to ensure that reproducible values were obtained. Standard pulmonary function testing was performed using a Vitalograph spirometer (Vitalograph Ltd, Buckingham UK)

before and immediately after each treatment according to American Thoracic Society guidelines¹⁴ with the subject seated in a hard backed chair. Oxygen saturation (Sp_{o2}) was measured continuously throughout treatment using a pulse oximeter and finger probe (Oxypleth; Novametrics, Wallingford, CT, USA). Mean Sp_{o2}, minimum Sp_{o2}, and proportion of treatment time with Sp_{o2} ≤ 90% were obtained. Sputum expectorated during treatment, 4 hours after treatment, and for the remainder of the 24 hour period was collected and weighed (FX320 electronic balance; A&D Ltd, Tokyo, Japan). Breathlessness was measured at the beginning and end of each treatment using the Borg scale¹⁵ and preference for treatment type was recorded following the final treatment session.

A baseline measurement of static lung volumes was obtained during the 48 hour period before the treatment sessions in a constant volume body plethysmograph (Medgraphics 1085D Series with BREEZPF software; Medical Graphics Corporation, St Paul, Minnesota, USA). Body mass index (BMI), sputum pathogens, and current medications were recorded for all subjects.

Analysis of data

Crossover two sample *t* tests were used to analyse for effects attributable to treatment (standard *v* NIV assisted), period (day 3 *v* day 4), and carryover (the contribution of treatment on day 3 to response on day 4).¹⁶ The relationship between variables was assessed with correlations. Alpha was set at 0.05.

RESULTS

Twenty seven subjects fulfilled the selection criteria and were randomised to treatment order. One subject withdrew at the start of testing because of pain on respiratory muscle testing. The demographic data for the remaining 26 subjects are shown in table 1. Inhaled bronchodilators were used by all subjects and 15 subjects also used dornase alfa. All subjects were colonised with *Pseudomonas aeruginosa* and none were colonised with *Burkholderia cepacia*. One subject used nocturnal NIV for hypercapnic respiratory failure and another had previously used NIV for respiratory support during a severe acute exacerbation. All other subjects were naive to NIV. Inspiratory pressures delivered during the NIV assisted session ranged from 10 to 20 cm H₂O and expiratory pressures from 4 to 5 cm H₂O. There was no correlation between level of pressure support and FEV₁; however, there was a weak correlation between level of pressure support and RV/TLC (*r* = 0.42, *p* = 0.04).

Baseline P_{imax} varied between subjects, ranging from 56 to 171 cm H₂O (47–173% predicted normal). There was a moderate association between baseline P_{imax} and BMI (*r* = 0.43, *p* = 0.03). There was a significant reduction in P_{imax} following standard treatment (*p* = 0.04, fig 1). The

Table 1 Mean (SD) demographic data of study subjects

Male/female	21/5
Age (years)	27.04 (6.42)
BMI (kg/m ²)	20.63 (2.36)
FEV ₁ (litres)	1.32 (0.43)
FEV ₁ (% predicted)	33.85 (11.85)
FVC (litres)	2.50 (0.75)
FVC (% predicted)	54.15 (15.17)
RV/TLC (%)	52.92 (11.08)
RV/TLC (% predicted)	205.53 (46.74)
24 hour sputum weight (g)	77.96 (42.76)

BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity.

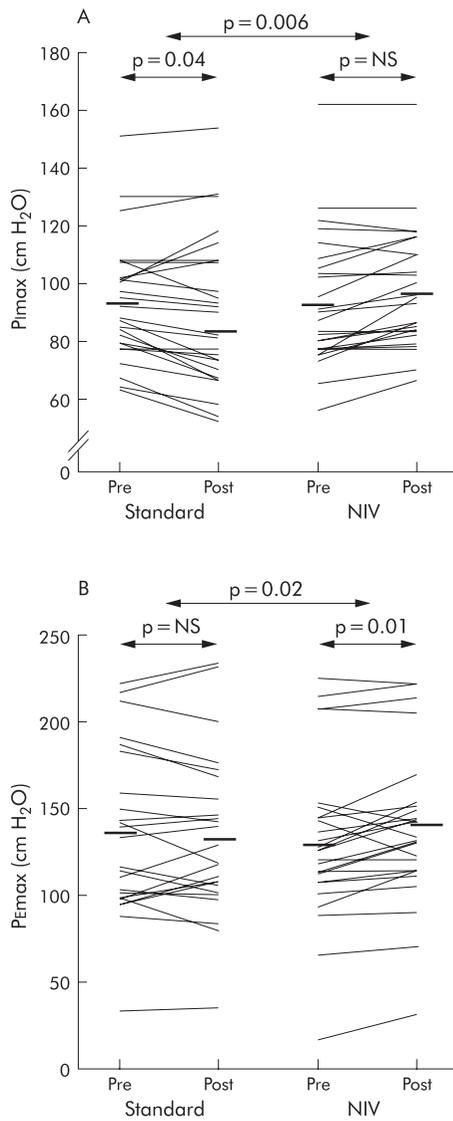


Figure 1 Effect of standard and NIV assisted treatments on maximal inspiratory (A) and expiratory (B) pressures. Individual data. Group means are represented by bold horizontal lines.

largest reductions were observed in those with lowest baseline inspiratory muscle strength ($r = 0.73$, $p < 0.001$) and lowest BMI ($r = 0.61$, $p < 0.001$). In contrast, PImax was maintained following NIV assisted treatment, resulting in a significant difference compared with the standard treatment (mean difference 9.04 cm H₂O, 95% CI 4.25 to 13.83 cm H₂O, $p = 0.006$). Baseline PEmax also varied widely (40–148% predicted normal) and had a moderate association with BMI ($r = 0.45$, $p = 0.02$). However, PEmax did not change significantly following standard treatment but increased following NIV assisted treatment (mean difference 8.04 cm H₂O, 95% CI 0.61 to 15.46 cm H₂O, $p = 0.02$; fig 1).

Mean and minimum SpO₂ were significantly lower during standard treatment than during the NIV assisted session (fig 2). The proportion of standard treatment time spent with SpO₂ ≤ 90% was correlated with FEV₁ ($r = -0.65$, $p < 0.001$). Addition of NIV resulted in a significant reduction in the proportion of treatment time with SpO₂ ≤ 90% ($p < 0.001$).

FEV₁, FVC, and forced expiratory ratio (FEV₁/FVC) did not change significantly following either treatment, but there was a significant increase in FEF_{25–75} following NIV assisted

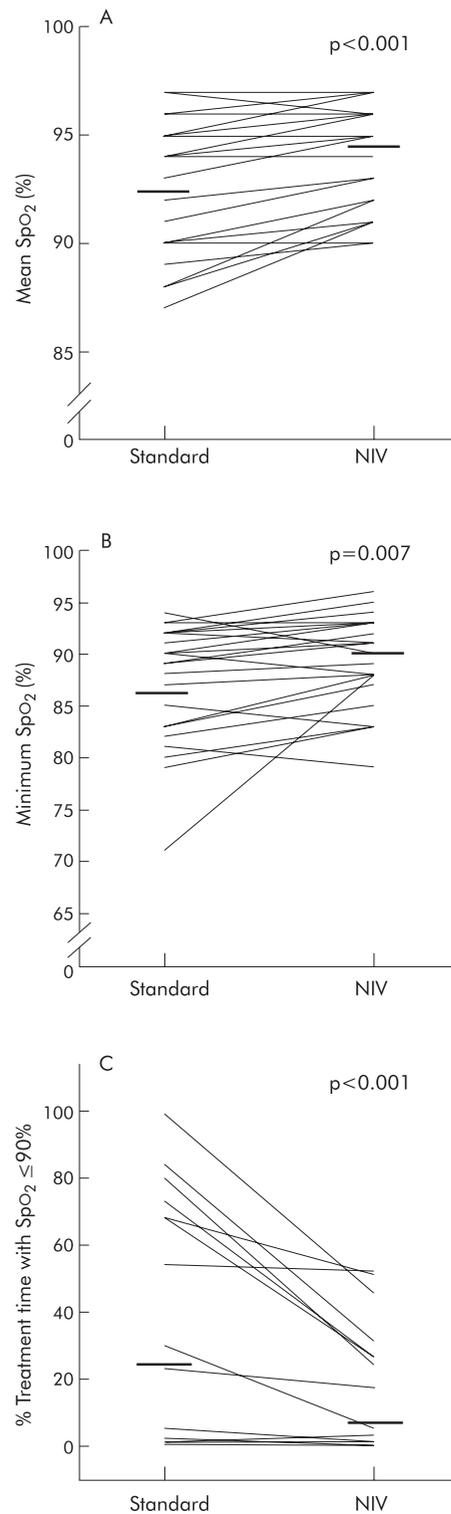


Figure 2 Effect of standard and NIV assisted treatments on oxygen saturation: (A) mean SpO₂, (B) minimum SpO₂ and (C) % of treatment time with SpO₂ ≤ 90%. Individual data. Group means are represented by bold horizontal lines.

treatment (table 2). There were no differences between standard and NIV assisted treatment in mean (SD) weight of sputum expectorated during treatment (15.92 (6.44) v 15.32 (6.20) g, $p = NS$), 4 hours after treatment (11.57 (9.65) v 13.97 (9.86), $p = NS$) or for the remainder of the 24 hour period (44.14 (23.26) v 41.35 (25.59), $p = NS$). Breathlessness

scores increased following both treatments but to a slightly lesser extent following NIV assisted treatment (Borg score after treatment 2.69 (1.82) v 2.26 (1.96), $p = 0.02$). Fifteen subjects preferred treatment with NIV, eight subjects preferred standard treatment, and three subjects did not have a preference.

No carryover or period effects were identified for any of the outcome variables. There was no significant difference in the number of ACBT cycles or coughs between the treatment sessions.

DISCUSSION

In this study of adults with acute exacerbations of CF and moderate to severe lung disease, standard chest physiotherapy with ACBT resulted in reduced inspiratory muscle strength and oxygen desaturation. These findings were associated with impaired baseline inspiratory muscle strength, reduced BMI, and more severe bronchial obstruction. The addition of NIV during treatment resulted in preserved inspiratory muscle strength and improved expiratory muscle strength. Improvements in oxygen saturation and small airway function were observed without change in the wet weight of sputum expectorated. No adverse effects were observed and NIV was well tolerated, with 58% of patients preferring it to the standard treatment.

The improvements in respiratory muscle strength during NIV assisted airway clearance are consistent with observations in children. Fauroux and colleagues⁵ evaluated the effects of the forced expiratory technique (FET) on respiratory muscle strength in 16 children with CF, all of whom had reduced respiratory muscle strength at baseline. A significant reduction in P_{Imax} was evident after 20 minutes of FET in all subjects. There was a significant increase in P_{Imax} following an identical treatment with the addition of inspiratory pressure support ventilation (PSV). The reduction in P_{Imax} was less consistent across subjects in our study. Our results suggest that, in adults, decreased inspiratory muscle strength following airway clearance is most likely when baseline inspiratory muscle strength and BMI are low. P_{Imax} was maintained in our subjects following NIV assisted treatment, but an increase was not observed.

We did not observe a reduction in P_{Emax} following standard treatment. This difference in response of inspiratory and expiratory muscles may be related to differences in the force-volume relationship. As P_{Emax} is not related to hyperinflation,¹⁷ the load imposed by the repeated inspiratory and expiratory manoeuvres associated with airway clearance may not be as great for the expiratory muscles in these severely hyperinflated patients. There may also be differences in response due to the nature of the airway clearance technique employed. The FET used by Fauroux *et al* consisted of slow active expirations from TLC to RV. The ACBT routine used in our study incorporated a more conventional form of FET consisting of forced expirations from mid to low lung

volumes, hence the expiratory muscles were not required to generate force over such a wide range of lung volumes. An increase in P_{Emax} was observed following NIV assisted treatment, the significance of which is unclear.

Significant falls in Sp_{o2} occurred during standard treatment with ACBT. The effect of airway clearance on oxygen saturation has been inconsistently reported, with some studies indicating significant desaturation^{4,5} and others suggesting that this can be avoided by incorporating periods of breathing control.¹⁸ In our study the falls in Sp_{o2} were observed mainly during the FET and this was not prevented by periods of breathing control. We also observed a relationship between the proportion of treatment time with Sp_{o2} ≤ 90% and FEV₁, with the most desaturation evident in subjects with the greatest degree of airflow obstruction. The largest increases in Sp_{o2} with NIV were seen in these same subjects. Improvement in oxygen saturation is likely to be associated with increased effective alveolar ventilation during NIV, which has previously been observed in adults with advanced CF.⁸ NIV may also have a role in the prevention of airway closure during the prolonged expirations required for airway clearance, similar to that postulated for positive expiratory pressure breathing.¹⁹

In concordance with previous short term studies of airway clearance techniques, standard treatment with ACBT had no effect on lung function parameters.²⁰ Spirometric testing was performed to evaluate the safety of NIV as an adjunct to treatment, especially in light of concerns regarding impaction of secretions in the small airways as a result of positive pressure. No deleterious effects on small airway function were observed in this short term study and a small increase in FEF₂₅₋₇₅ was observed. A weak but significant relationship between small airway function and mucociliary clearance has previously been reported.²¹

Wet weight of sputum is a simple, clinically available measurement that has been shown to impact on quality of life in CF.¹¹ However, it may not accurately reflect the degree of mucus clearance as it does not account for concomitant mucus production, swallowing of secretions, or contamination with saliva. The crossover design used in this study attempted to control for some of these factors. In addition, we recruited only subjects who expectorated more than 20 g of sputum per day, as the relationship between mucus transport measured with radioactive aerosol tracer and expectorated mucus is thought to be stronger in patients who produce a large volume of secretions.²² Future investigations into the direct effect of NIV on bronchial mucus transport are required.

NIV delivers a high flow of gas at low relative humidity. This has been associated with impaired mucociliary clearance and drying of airway secretions within 30 minutes of exposure.²³ To avoid these potentially confounding effects on airway clearance, we chose to incorporate a heated humidifier into the NIV circuit. It has previously been shown

Table 2 Mean (SD) lung function parameters before and after treatment

	Standard		NIV assisted		p value
	Pre	Post	Pre	Post	
FEV ₁ (l)	1.35 (0.47)	1.35 (0.48)	1.33 (0.42)	1.35 (0.44)	0.31
FVC (l)	2.50 (0.74)	2.51 (0.98)	2.53 (0.74)	2.55 (0.75)	0.77
FER	0.54 (0.09)	0.54 (0.10)	0.53 (0.10)	0.54 (0.10)	0.22
FEF ₂₅₋₇₅ (l/s)	0.53 (0.40)	0.53 (0.42)	0.52 (0.33)	0.57 (0.33)	0.006

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; FER = forced expiratory ratio (FEV₁/FVC); FEF₂₅₋₇₅ = forced expiratory flow rate between 25% and 75% of FVC.
p values represent delta standard v delta NIV assisted treatment.

that exposure of sputum to 100% relative humidity does not increase wet weight at 1 hour.²⁴ It is unlikely that deposition of water in the airway occurred at the temperature and relative humidity delivered during treatment, as there would have been no exchange of heat and moisture with the mucosa and the inspired gas did not contain aerosolised water.

A ventilatory mode that combined inspiratory and expiratory pressure was chosen for this study as it has been shown to provide better unloading of the diaphragm than inspiratory support alone in patients with COPD.²⁵ Expiratory pressure settings in our study were kept at 4–5 cm H₂O as other authors have reported interference with coughing at higher pressure settings.²⁶ Inspiratory pressures were set to achieve the maximal level of pressure support associated with patient comfort. The level of pressure support delivered thus ranged from 6 to 15 cm H₂O. This method of determining ventilatory settings reflects clinical practice but does not provide information on the degree of respiratory muscle unloading that was achieved. Vitacca and colleagues²⁷ compared the effects of pressures set according to patient comfort with those set according to invasive measurement of respiratory mechanics. They found that both methods were effective in achieving respiratory muscle unloading. The weak correlation found in our study between the level of pressure support and degree of hyperinflation suggests that we did provide increased support to those with the greatest mechanical load during breathing.

Patients with CF now frequently survive to adulthood. The course of the disease is nonetheless characterised by progressive airflow obstruction and respiratory failure. Physiotherapists are frequently required to provide treatment to these severely unwell patients, including those requiring NIV for prolonged periods before transplantation.²⁸ We have shown that NIV can safely be used to assist airway clearance during acute exacerbations in adults with CF, and that beneficial effects may be seen in those with severe bronchial obstruction and reduced inspiratory muscle strength. Further study is required to evaluate longer term effects and direct effects on secretion clearance.

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