The Acute Effects of Nasal Positive Pressure Ventilation in Patients With Advanced Cystic Fibrosis*

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Objective: To evaluate the acute effects of noninvasive positive pressure ventilation (NPPV) in patients with stable chronic respiratory failure secondary to cystic fibrosis.

Patients: Eight patients (29±5 years of age) with severe airflow limitation (mean FEV₁, 24±3% predicted) and chronic respiratory failure (PaO₂=67±15 mm Hg and PaCO₂=50±4 mm Hg) were evaluated.

Methods: Tidal volume, respiratory rate, minute ventilation, oxygen saturation, and transcutaneous CO₂ (TcCO₂) measurements were made over a 20-min period before and after the application of NPPV (inspiratory pressure of 10 to 12 cm H₂O and expiratory pressure of 4 to 6 cm H₂O).

Results: NPPV increased saturation from 88±2% to 90±1% (p<0.05) and decreased TcCO₂ from 51±3 mm Hg to 50±2 mm Hg (p<0.05). Tidal volume increased from 219±20 mL to 256±37 mL (p=not significant [NS]) and respiratory rate decreased from 24±2 to 18±1 (p<0.01). Minute ventilation decreased from 5.3±0.8 L/min to 4.6±0.6 L/min (p=0.08). There was no change in duty cycle (32±5% to 34±5%, p=NS). In two patients, esophageal pressure measurements were also recorded. There was a decrease in pressure from −21±1 cm H₂O to −11±2 cm H₂O and −14±1 cm H₂O to −7±1 cm H₂O.

Conclusions: In patients with stable, severe cystic fibrosis, NPPV (1) acutely improves gas exchange, (2) decreases minute ventilation, suggesting either a reduction in CO₂ production or an increase in alveolar ventilation, and (3) reduces work of breathing.

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Key words: cystic fibrosis; noninvasive ventilation; oxygenation; work of breathing

Abbreviations: CF=cystic fibrosis; CPAP=continuous positive airway pressure; EMG=electromyograph; EPAP=expiratory positive airway pressure; IPAP=inspiratory positive airway pressure; NPPV=noninvasive positive pressure ventilation; PEEP=positive end-expiratory pressure; Pes=esophageal pressure; TcCO₂=transcutaneous CO₂; Ti=inspiratory time; T/TOT=duty cycle; VT=tidal volume

Noninvasive positive pressure ventilation (NPPV) has been successfully used to treat patients with chronic respiratory failure secondary to neuromuscular and skeletal disorders. In patients with COPD, enthusiasm for noninvasive ventilation was initially tempered by the failure of a prospective study of negative pressure ventilation to demonstrate an improvement in quality of life, gas exchange, or pulmonary function. Lack of compliance and the development of upper airway obstruction during negative pressure ventilation were cited as reasons for failure.

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The problems with negative pressure ventilation prompted the evaluation of NPPV in patients with COPD. Ambrosino et al demonstrated that pressure support ventilation via nasal mask improved PaO₂ and decreased PaCO₂ and led to a reduction in surface diaphragmatic electromyograph (EMG) in eight patients with chronic hypercapneic respiratory failure. NPPV, which has been shown to be useful in managing COPD patients with acute respiratory failure, reduces the requirement for intubation and mechanical ventilation. Experience with NPPV in COPD patients with stable hypercapneic respiratory failure is evolving. Nasal continuous positive airway pressure (CPAP) may reduce respiratory effort during sleep. NPPV when combined with domiciliary oxygen has been shown to improve daytime blood gas values and estimates of quality of life beyond that obtained using oxygen alone.

Respiratory failure is responsible for most morbid-
ity and mortality in adult patients with cystic fibrosis (CF). Of those CF patients who require intubation and ventilation for acute respiratory failure, most (70%) will die while receiving ventilatory support and only 6% will survive 1 year. However, with the advent of lung transplantation, it may be desirable to offer these patients NPPV as a bridge to transplantation. Experience with NPPV in patients with CF in the literature is limited. Piper et al demonstrated that NPPV improved oxygenation and reduced PaCO₂ in four CF patients with acute deterioration in respiratory function. These patients continued to receive NPPV following discharge from hospital for up to 18 months. In CF patients with stable respiratory function, nasal CPAP has been shown to improve exercise tolerance and reduce sleep disturbances when administered through the night. Thus, NPPV represents a potentially useful modality to treat CF patients with chronic respiratory failure.

To evaluate the potential benefits of NPPV therapy in CF, we sought to examine its immediate effects on gas exchange and breathing pattern in patients with chronic respiratory failure and stable lung function. We hypothesized that NPPV would acutely improve gas exchange and reduce respiratory effort.

**Materials and Methods**

**Patients**

Patients with CF >18 years of age were eligible for study if their PaO₂ was <50 mm Hg on room air or had a PaCO₂ >40 mm Hg. In addition, patients were required to be in clinically stable condition and free from an exacerbation of respiratory failure requiring hospitalization in the preceding month. Patients with an active infection, history of recent hemoptysis, or recent pneumothorax were excluded.

**Measurements**

All studies were performed in the pulmonary research laboratory of the Toronto Hospital. Patients were seated in a semirecumbent position and breathed room air. Heart rate, pulse oximetry (Biox 3700; Ohmeda, Louisville, Colo), and transcutaneous CO₂ (TeCO₂ ) (model 634; Kontron Medical; Zurich, Switzerland) were measured continuously. Rib cage and abdominal movements were measured during quiet breathing by respiratory inductance plethysmography (Respirac; Ambulatory Monitoring Inc; White Plains, NY). The system was calibrated prior to each patient’s study using the volume of isoflow method. Surface EMG (P15 A.C. Preampifier; Grass Instruments; Quincy, Mass) of the medial scapular muscle was measured continuously.

Two patients consented to a measurement of esophageal pressure (Pes). Pes was measured by a latex balloon inflated with 0.5 mL of air and positioned 10 cm above the gastroesophageal junction and its position was confirmed by an occlusion test. Pressures were measured by connecting the balloon to a differential pressure transducer (Validyne Corp; Northridge, Calif).

This system is linear from 50 to −60 cm H₂O. All data were recorded continuously on an eight-channel recorder (ES 1000; Gould Instruments; Cleveland). Data were analyzed at 1-min intervals by planimetry using the average of three consecutive breaths. Tidal volume (VT) was calculated as the sum of chest wall and abdominal excursions. Respiratory rate, inspiratory time (TI), and duty cycle (TI/Ttot) were obtained from the volume signal. To provide an estimate of patient effort, we calculated the Pes-time index (Pes · Ti) as the product of Pes and Ti.

**Noninvasive Positive Pressure Ventilation**

NPPV was provided using a ventilatory support system (BiPAP; Respironics Inc; Monroeville, Pa) applied through a nasal mask. This device consists of a nasal CPAP delivery system modified to provide delivery of positive airway pressure at two different levels. In addition, the system allows for either spontaneous breathing and/or cycled machine-generated breaths. For purposes of this study, all breaths were patient initiated. The level of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) used was determined 1 to 2 days prior to the study by titrating levels to patient comfort.

**Protocol**

The protocol was approved by the Toronto Hospital Committee for Research on Human Subjects. All participants provided informed consent prior to enrollment into the study. Patients were first allowed to acclimate to the measuring equipment for 15 min. Next, continuous recordings were made for 20 min. Subsequently, patients were started on a regimen of NPPV (IPAP, 10 to 12 cm H₂O; EPAP, 4 to 6 cm H₂O). After 15 min of acclimatization, recordings were repeated for another 20 mins.

**Data Analysis**

All data are presented as mean±SD. Values before and after NPPV use were compared using the paired t test. A level of significance of p<0.05 was considered significant.

**Results**

**Demographics**

Eight patients (six male, two female) with CF (mean age, 29±5 years) were evaluated. All patients had severe airflow limitation (mean FEV₁=24±3% predicted). The mean PaO₂ was 67±15 mm Hg and mean PaCO₂ was 50±4 mm Hg. Only one patient met the hypoxemia inclusion criteria. All patients were awaiting lung transplantation.

**Effects on Gas Exchange and Pattern of Respiration**

NPPV increased saturation from 88±2% to 90±1% (Fig 1, top; p<0.05) and decreased TeCO₂ from 51±3 mm Hg to 50±2 mm Hg (Fig 1, bottom; p<0.05). During NPPV, VT increased slightly (219±20 mL to 256±37 mL; p>0.05; Fig 2, top left) and respiratory rate decreased from 24±2 to 18±1 (Fig 2, bottom left; p<0.01). The net effect was a
nonsignificant decrease in minute ventilation from 5.3±0.8 L/min to 4.6±0.6 L/min (Fig 2, top right; p=0.08). There was no change in duty cycle following NPPV (32±5% to 34±5%; p=not significant). There was no relationship between the magnitude of the ventilatory response to NPPV, baseline spirometry, arterial blood gas values, or the change in saturation or TeCO₂ during NPPV. One patient had a dramatic response to NPPV administration. VT increased from 253 to 481 mL, and respiratory rate decreased from 34 to 15, resulting in a decrease in minute ventilation. In this patient, saturation increased from 82 to 90% and TeCO₂ decreased from 45 to 43 mm Hg. Exclusion of this patient from the analysis did not alter the results of the study.

All subjects tolerated the NPPV trial. We did not measure patients’ sensation of breathlessness during the trial.

**Esophageal Balloon Studies**

In the two patients who consented to measurement of Pes, there was a decrease in Pes from -21±1 to -11±2 cm H₂O and -14±1 to -7±1 cm H₂O. A recording of the first patient before and after NPPV is shown in Figure 3. There was a decrease in Pes · Ti from 18 to 15 cm H₂O in the first patient and no change (10.1 to 10.4 cm H₂O · s) in the second patient. A representative tracing from one patient is shown in Figure 3.

Technical difficulties precluded interpretable EMG recordings in patients due to difficulty in reducing baseline interference.

**DISCUSSION**

CF is characterized by progressive destruction of lung parenchyma, airflow limitation, and progressive respiratory failure. In patients with advanced airflow limitation, the respiratory muscles and diaphragm are placed at a mechanical disadvantage. This pump inefficiency in addition to a breathing strategy aimed at reducing mechanical work is thought to lead to hypercapnia and to increased stress on respiratory muscles. We therefore attempted to assess the effects of a strategy aimed at alleviating the increased work of breathing that would occur in chronic respiratory failure secondary to CF. We demonstrated that in patients with CF and stable respiratory failure, NPPV acutely improved oxygenation and decreased minute ventilation. As TeCO₂ did not rise, there was either a reduction in CO₂ production or an improvement in alveolar ventilation. In the two patients in whom Pes values were recorded, there was a significant reduction in pressure swings, suggesting a reduction in work of breathing.

In patients with advanced CF, respiratory failure is the most common cause of death. Physiotherapy, exercise, attention to nutrition, inhaled medication, and therapy directed at treatment of acute infectious exacerbations represent the mainstay of treatment. Lung transplantation represents one potential option for these patients. Unfortunately many patients will die before a suitable organ becomes available. Therefore, NPPV represents an option that may potentially prolong life while awaiting suitable lung allografts.

While NPPV improved arterial oxygen saturation, we were disappointed by the very modest reduction in TeCO₂ in our study. Two possibilities for this finding exist. First, Ferguson and Gilmartin observed that CO₂ rebreathing occurs using the ventilatory support (BiPAP) system when CO₂ is not completely removed through the exhalation port (Whisper swivel), enters the tubing, and is inhaled during the subsequent breath. They demonstrated that the application of at least 6 cm H₂O of EPAP was required to eliminate rebreathing of CO₂ from
The tubing. Our patients used 4 to 6 cm H₂O EPAP. Thus, there may have been a small contribution of rebreathing to the observed changes in TcCO₂. Second, relatively low inspiratory support pressures were used in this study. IPAP ranged from 10 to 12 cm H₂O and EPAP from 4 to 6 cm H₂O. This resulted in a driving pressure on average of only 6 cm H₂O. Ambrosino et al.⁵ evaluated the physiologic effects of 2 h of NPPV without EPAP (using either a ventilatory support system [BiPAP] or pressure support by a standard ventilator) in seven patients with stable COPD. IPAP was titrated to achieve V̇e of 10 to 15 mL/kg and consequently, greater levels of IPAP were used (17 to 20 cm H₂O). In contrast to our study, minute ventilation increased from 8.2 to 11.1 L/min owing to significant increases in V̇e. There was a significant decrease in PaCO₂ from 60 to 49 mm Hg over a 12-h period. Similar results were obtained by Brochard et al.¹² in their study of acute respiratory failure in patients with COPD where 15 to 20 cm H₂O was applied by face mask using a modified pressure support system. Our patients had significant airflow limitation and potentially may have benefited from higher IPAP levels. In addition, the longer observation period used by Ambrosino's group may have contributed to the dissimilarities between the two studies.

The observation of a decrease in minute ventilation during NPPV without a concomitant increase in TcCO₂ suggests that there was either an increase in effective alveolar ventilation (reduction in dead space) or a reduction in CO₂ production. The latter effect may be the result of a decrease in inspiratory work and oxygen consumption by the respiratory muscles. Alternatively the decrease in respiratory rate and minute ventilation along with the increase in V̇e may simply represent the normal response to a resistive load, as previously noted in healthy normal subjects given CPAP.¹³ We were concerned that during NPPV and with the generation of higher lung volumes that dynamic hyperinflation would develop if insufficient time was available for expiration. This in turn would have resulted in a decrease in effective alveolar ventilation. With the application of NPPV we observed a decrease in respiratory rate, while there was no change in Ti/Ttot. In addition, there was no change in the baseline of the plethysmographic tracing, suggesting that end-expiratory lung volume did not increase. Consequently the time spent in exhalation increased (data not shown) and provided sufficient time for the exhalation of the larger V̇e.

In both patients in whom Pes values were measured, there was a dramatic reduction in Pes swings.
during the application of NPPV. This reduction was roughly equivalent to the amount of inspiratory pressure applied. However, only one of the patients had a reduction in the Pes-Ti product suggesting a reduction in work of breathing. A reduction in work of breathing is supported by earlier studies of NPPV. In COPD patients, Ambrosino et al\(^8\) noted a decrease in surface diaphragm EMG signal decreased during NPPV. In a related study, Nava et al\(^14\) recorded transdiaphragmatic pressures before and after the application of pressure support and positive end-expiratory pressure (PEEP) in patients with hypercapnic, stable COPD. Both transdiaphragmatic pressure and the tension time index significantly decreased, which suggested that diaphragm activity was reduced.\(^{14}\) In a recent study of CPAP during exercise in CF patients, oxygen consumption at equivalent work loads was decreased and Pes was reduced compared with breathing at ambient pressure.\(^8\) This suggested that CPAP reduced work of breathing. We did not measure dead space or oxygen consumption during this study and therefore cannot comment on the relative contributions of these factors. Another possibility for a reduction in Pes swings is that intrinsic PEEP was reduced.

In a study in patients with acute exacerbations of COPD, Appendini and coworkers\(^15\) demonstrated that CPAP, when titrated to the level of intrinsic PEEP, reduced diaphragmatic effort. In addition, intrinsic PEEP was reduced from 5.4 to 3.1 cm H\(_2\)O. We did not specifically measure airflow during this study and therefore cannot precisely comment on pleural pressure changes that occurred before the onset of flow (intrinsic PEEP). However, when the two available Pes tracings were examined, there appeared to be a 4 to 5 cm H\(_2\)O pressure generation before any deflection in VT trace. This was not seen during NPPV and suggests that these two patients did have intrinsic PEEP that was reduced with EPAP. This decrease in intrinsic PEEP may have also improved effective alveolar ventilation leading to the observed reduction in TeCO\(_2\).

Theoretically, therapy aimed at reducing the work of breathing or placing the diaphragm in a more optimum position in its length-tension curve should improve gas exchange. In patients with acute exacerbations of COPD, NPPV improves gas exchange, reduces the requirement for intubation and mechanical ventilation, and reduces mortality as compared with conventional medical management.\(^3,12,16,17\) In

**Figure 3.** Scalene EMG signal and Pes variation in one patient before and after the application of a ventilatory support system (BiPAP) (IPAP=12 cm H\(_2\)O/EPAP=4 cm H\(_2\)O).
contrast to patients with acute respiratory failure, the efficacy of NPPV in patients with stable COPD has not been evaluated rigorously. Recent studies suggest that intermittent use of NPPV in patients with stable COPD facilitates respiratory muscle function during sleep and improves daytime gas exchange, quality of life, sleep time, and sleep efficiency as compared with oxygen alone.\(^6,\(^7\) In contrast, in a recent small prospective study, NPPV failed to improve any physiologic parameter despite an improvement in neuropsychological function.\(^8\) Early studies in patients with acute respiratory failure from a variety of causes suggest that NPPV may not be tolerated by patients with bronchiectasis.\(^9\) However, all our patients tolerated the NPPV well and rapidly adapted to the ventilatory support. Similarly, in an earlier study in four CF patients with acute respiratory failure, NPPV was able to improve gas exchange and was well tolerated for periods up to 18 months.\(^7\)

In summary, the short-term application of NPPV in patients with end-stage lung disease secondary to fibrosis modestly improves gas exchange and reduces work of breathing. Given the encouraging acute effects of NPPV, further studies examining the long-term benefits of NPPV in patients with CF awaiting lung transplantation need to be explored.

References

6. Davis PB, di Sant'Agnese PA. Assisted ventilation for patients with cystic fibrosis. JAMA 1978; 239:1851-54