Effects of Noninvasive Positive Pressure Ventilation on Gas Exchange and Sleep in COPD Patients*

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**Study objective:** The role of nocturnal noninvasive positive pressure ventilation (NPPV) in the treatment of patients with hypercapnic COPD remains controversial. Beneficial effects reported after prolonged use have included an improvement in gas exchange. The purpose of this study was to examine the short-term effects of NPPV on gas exchange and sleep characteristics in patients with hypercapnic COPD and to determine if similar acute changes in gas exchange are associated with improved sleep quality.

**Design:** Prospective, randomized, controlled trial.

**Setting:** Sleep laboratory of a university hospital.

**Patients:** Six patients with severe but stable hypercapnic COPD (PaCO₂ = 58±4 [SE] mm Hg). Mean age was 63±6 (SD) with an FEV₁ = 0.58±0.09 L.

**Interventions and measurements:** Patients were studied in the sleep laboratory for a total of three nights. On nights 2 and 3, arterial catheters were placed prior to the study. Following an acquaintance night, patients were randomized to either a control-sham night on 5 cm H₂O nasal continuous positive airway pressure (CPAP) or an NPPV night using a ventilatory support system (BiPAP; Respirronics Inc; Murrysville, Pa) at previously determined optimal settings. The third night consisted of the opposite for each patient, either a control-sham or an NPPV night. On the second and third nights, three arterial blood gas readings were obtained: (1) baseline wakefulness; (2) non-rapid eye movement (NREM) sleep; and (3) rapid eye movement (REM) sleep.

**Results:** During NREM sleep, NPPV in comparison to the control-sham night on low level CPAP caused no significant change in PaCO₂ (60±4 to 59±3 mm Hg [p=0.6]) and a decrease in PaO₂ (96±9 to 72±5 mm Hg [p=0.04]). During REM sleep, NPPV in comparison to the control-sham night on low level CPAP caused no significant change in either PaCO₂ (63±7 to 57±2 mm Hg [p=0.46]) or PaO₂ (67±7 to 75±8 mm Hg [p=0.51]). Sleep efficiency and total sleep time (TST) increased significantly with NPPV in comparison to the control-sham night on low level CPAP: from 63±7% to 81±4% (p<0.05) and from 203±32 to 262±28 min (p<0.05), respectively. Sleep architecture, expressed as a percentage of TST, was unchanged on the NPPV night compared to the control-sham night on low level CPAP. The number of arousals during the night was also unchanged with NPPV in comparison to the control-sham night on low level CPAP (45±11 to 42±9 [p=not significant]).

**Conclusions:** NPPV acutely improved sleep efficiency and TST in patients with hypercapnic COPD without significantly improving gas exchange. Other sleep parameters, including sleep architecture and the number of arousals during the night, remained unchanged during NPPV. These data suggest that the beneficial effects of NPPV in patients with hypercapnic respiratory failure are not solely due to an improvement in gas exchange but may be more complex with other factors potentially having contributing roles.

**Key words:** chronic obstructive pulmonary disease; gas exchange; noninvasive positive pressure ventilation; sleep quality

**Abbreviations:** ABG=arterial blood gas; CPAP=continuous positive airway pressure; EELV=end-expiratory lung volume; EMG=electromyogram; FIO₂=fraction of inspired oxygen; IPAP=inspiratory positive airway pressure; NPPV=noninvasive positive pressure ventilation; NREM=non-rapid eye movement sleep; PEEP=intrinsinc positive end-expiratory pressure; PtCO₂=transcutaneous CO₂; REM=rapid eye movement sleep; TST=total sleep time; VRU=ventilator rehabilitation unit; VT=tidal volume

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Noninvasive positive pressure ventilation (NPPV) is effective in the treatment of chronic respiratory failure in patients with restrictive ventilatory disorders, particularly those with neuromuscular disease and kyphoscoliosis. However, the use of NPPV in patients with severe hypercapnic respiratory failure due to COPD is controversial, with...
conflicting results reported on its efficacy in improving gas exchange, respiratory mechanics, and functional capabilities. In most patients, long-term intermittent NPPV is implemented during sleep to avoid interrupting daytime activities, as well as to attenuate sleep-related breathing disturbances in patients with significant underlying respiratory disorders. However, to our knowledge, no study has examined the short-term effects of nocturnal NPPV on gas exchange and/or the pattern of sleep in COPD in a prospective, controlled manner. Herein, we examine the effects of NPPV on gas exchange and sleep characteristics in a prospective, randomized controlled trial in patients with severe COPD and chronic respiratory failure.

Materials and Methods

Patient Selection and Treatment

Six patients with severe, stable hypercapnic COPD were studied. Patients were in clinically stable condition for at least 1 month prior to the study. The protocol was approved by our institutional review board and informed consent was obtained from all patients prior to study enrollment. Patients were excluded from the study if (1) they had a COPD exacerbation within 1 month of the study period, (2) their PaCO2 was <45 mm Hg, or (3) they were unable to give informed consent.

All patients were admitted to a special noninvasive ventilatory rehabilitation unit (VRU). This unit is designed to evaluate and treat, in a multidisciplinary fashion, patients difficult to wean from mechanical ventilation or to institute noninvasive mechanical ventilation in patients suffering from chronic respiratory failure. Unit admission criteria and a description of its treatment plans have been described previously.17

Pulmonary Function Testing

All patients had baseline complete pulmonary function tests obtained prior to the study, including routine spirometry (SensorMedics Inc, model 2200, Yorba Linda, Calif) and measurement of lung volumes by body plethysmography (SensorMedics Inc, model 6200). In addition, baseline daytime awake arterial blood gas (ABG) values (IL BG3 blood gas analyzer and IL 482 co-oximeter; Instrumentation Laboratory Company, Lexington, Mass) were obtained while receiving supplemental oxygen.

NPPV Technique

NPPV was initiated in the VRU using a standard nasal continuous positive airway pressure (CPAP) mask (Respironics Inc; Murrysville, Pa) connected to a ventilatory support system (BiPAP, Respironics Inc). Nasal-oral or full face masks were used as needed to minimize mouth or mask leaks, optimize patient comfort, or to attain the ventilatory goal targets. An in-line pressure transducer and pneumotachograph were used to monitor inspiratory and expiratory airway pressures, flows, and volumes. After baseline measurements were obtained, the inspiratory pressure was increased to a level of 10 cm H2O. Further increases in the inspiratory pressure were done in 2 cm H2O increments until the minute ventilation was increased 20%. Increases in the expiratory pressure were performed to match any "intrinsic positive end-expiratory pressure" (PEEP) noted to be present at end expiration. In addition, supplemental oxygen was bled into the system to maintain the PaO2 above 60 mm Hg and the arterial oxygen saturation above 92%. Thus, optimum settings for NPPV were determined by increasing minute ventilation 20% above baseline, alleviating dyspnea, and improving gas exchange (eg, increased oxygenation and reduced hypercapnia).

To ensure that the patients received their set pressure boost with NPPV during the study nights (see below), estimated exhaled tidal volume and mask leak (L/min) were initially measured while the patient was awake after the mask was fitted with no observable leak. Measurements were obtained with the use of the detachable control panel of the ventilatory support system (BiPAP S/T-D) unit. This device also allowed for continuous measurements to be obtained throughout the night to ensure that no significant leaks developed (as compared to their initial values) that might have limited their set pressure boost with NPPV.

Sleep Studies

Prior to the study, a radial arterial line was placed with extension tubing to allow ABGs to be drawn during the night without waking the patients. The polysomnogram recording consisted of breathing pattern (abdominal and rib cage motion), pulse oximetry (Criticare 504-US; Waukeesa, Wis), and nasal thermistors, ECG, electrooculograms, digastic electromyogram (EMG), bilateral anterior tibials EMG, and EEG. All variables were recorded continuously on a 16-channel EEG polygraph (Grass model 9-21B; Quincy, Mass). Sleep stage was classified by the standard criteria of Rechtschaefen and Kales.18 Other sleep parameters that were determined included the following: (1) total sleep time (TST); (2) sleep efficiency, defined as the TST divided by the time in bed; and (3) arousals, defined as the appearance of alpha waves on EEG that were 3 to 15 s in duration.19

Protocol

All patients were studied for a total of three nights. The first night consisted of an "acquaintance night" to allow the patients to become familiar with the sleep environment. No arterial catheters were placed during this initial study.

During the second night, patients were randomized to either a control-sham night, with a continuous mask pressure of 5 cm H2O or an NPPV night on their previously determined optimal ventilatory support system (BiPAP) settings. The third night consisted of the opposite; an NPPV night on a ventilatory support system (BiPAP) or a control-sham night on low level CPAP. During both nights, supplemental oxygen was bled into the system at a level previously determined during NPPV optimization.

During nights 2 and 3, ABGs were drawn for analysis during three different phases of the study: (1) baseline wakefulness; (2) non-rapid eye movement (NREM) sleep; and (3) rapid eye movement (REM) sleep.

Statistics

Data are represented as the mean±SE, except where noted. Comparisons between groups were made using paired Student t tests. One patient did not have a long enough REM period during the control-sham night to allow an ABG to be drawn; therefore, comparisons during REM sleep were made using unpaired Student t tests. A p<0.05 was considered significant.
RESULTS

Patient Characteristics

Six patients (five male and one female) with a mean age of 63±6 (SD) years were studied (Table 1). All patients had severe, but stable COPD (FEV1, 0.58±0.09 L) and moderate to severe hyperinflation (total lung capacity, 127±15.1% predicted). Baseline daytime awake gas exchange demonstrated resting hypercapnia (PaCO2, 58±4 mm Hg) and a PaO2 of 92±9 mm Hg while receiving supplemental oxygen (fraction of inspired oxygen [FIo2]=0.27±0.01 by nasal cannula). During the NPPV night, mean inspiratory pressure was 22±0.3 cm H2O, and mean expiratory pressure was 3±1 cm H2O. During both the control-sham night on low level CPAP and the NPPV night, a similar amount of supplemental oxygen (FIo2=0.27±0.01) was bled into the system.

Gas Exchange During Sleep

During NREM sleep (Fig 1), NPPV in comparison to the control-sham night on low level CPAP caused no significant change in PaCO2 (60±4 to 59±3 mm Hg [p=0.6]) and a decrease in PaO2 (96±9 to 72±5 mm Hg [p=0.04]). During REM sleep (Fig 1), NPPV in comparison to the control-sham night on low level CPAP caused no significant change in either PaCO2 (63±7 to 57±2 mm Hg [p=0.46]) or PaO2 (67±7 to 75±8 mm Hg [p=0.51]).

Sleep Characteristics

Sleep efficiency significantly increased by 14% with NPPV in comparison to the control-sham night on low level CPAP, from 63±7% to 81±4% (p<0.05) (Fig 2). TST also significantly increased with the use of NPPV in comparison to the control-sham night on low level CPAP, from 205±32 to 262±28 min (p<0.05) (Fig 2). Sleep architecture, expressed as a percentage of TST, was unchanged on the NPPV night compared to the control-sham night on low level CPAP, including the percentage of sleep stages 3 and 4 and REM sleep. The number of arousals did not change significantly with NPPV in comparison to the control-sham night on low level CPAP, from 45±11 to 42±9 (p=0.46).

![Figure 1. Effects of NPPV on gas exchange during sleep. Compared to the control-sham night on low level CPAP (left, A), NPPV during NREM sleep did not cause a significant change in PaCO2, while PaO2 was noted to decrease (p=0.04). Right, B: NPPV during REM sleep did not cause a significant change in either PaCO2 or PaO2. Patients were studied on the same level of supplemental oxygen (FIo2=0.27±0.01) during both nights.](image-url)

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*TLC=total lung capacity; % pred=percent predicted; DCO=diffusion capacity of carbon monoxide; O2 Sat=oxygen saturation; VA=alveolar volume; N/A=not available.
1Measured by helium-dilution technique.
in COPD patients with nasal CPAP, as measured by esophageal and gastric pressure tracings and diaphragm EMG. Belman et al. were also able to demonstrate an acute reduction in transdiaphragmatic pressure generation and diaphragm EMG activity with NPPV via a volume-cycled ventilator in severe, hypercapnic COPD patients. Other investigators have found similar reductions in transdiaphragmatic pressure in patients with hypercapnic COPD using NPPV.3,14,15 We did not measure the effects of NPPV on respiratory muscle function in our patients, but it is conceivable that a reduction in the work of breathing and an associated decrease in central respiratory drive during NPPV could account for the improvement in sleep efficiency and TST that we observed.

Patients with severe COPD often have PEEP that requires the inspiratory muscles to overcome an opposing positive recoil pressure before inspiratory airflow begins.11 Dynamic hyperinflation seems to persist during NREM sleep.23,24 Petrof et al.21 have demonstrated that the administration of CPAP to both awake intubated23 and sleeping nonintubated patients11 with severe COPD decreases inspiratory muscle effort. The expiratory positive airway pressure used on our patients could have partially compensated for their PEEP, thus reducing the inspiratory threshold load needed to trigger the inspiratory positive airway pressure (IPAP) boost. This could have decreased inspiratory muscle work and central drive. Yet, it should be noted that during the control-sham night, patients received 5 cm H2O of CPAP, which could have had a similar effect of reducing inspiratory threshold load. Thus, this does not completely explain the observed improvements in sleep efficiency and TST. A decrease in inspiratory threshold load, allowing a triggered IPAP-related increase in tidal volume (Vt), may be more important in decreasing inspiratory work and central drive.

NPPV-induced increases in both inspiratory and end-expiratory lung volume (EELV) could potentially stimulate slowly adapting stretch receptors in the pulmonary parenchyma, decreasing central drive to inspiratory muscles, thereby inhibiting inspiration and allowing more time for exhalation. This possibility, however, appears unlikely. Petrof et al.11 demonstrated only a minimal increase in EELV in a group of COPD patients when given 5 cm H2O nasal CPAP. Additionally, no changes in inspiratory time, expiratory time, Vt, or respiratory rate were noted. A similar finding has been reported in intubated patients despite using higher levels of CPAP with associated further increases in EELV.23 In both studies, inspiratory flow, a measure of central respiratory drive, remained unchanged. Thus, decreased central drive secondary to changes in lung volume

**DISCUSSION**

Using a randomized, sham-controlled design, we were able to demonstrate that NPPV improved sleep efficiency and TST in patients with hypercapnic COPD without significantly improving gas exchange. Other sleep parameters, including sleep architecture and the number of arousals during the night, remained unchanged with the use of NPPV. Patients with COPD are known to have disturbed sleep, with an increased sleep latency, decreased TST, and increased number of arousals during the night.20,21 This does not necessarily improve with the supplemental oxygen.20 The beneficial effect of NPPV on sleep efficiency and TST noted in our patients is not solely due to improvement in gas exchange, but may be more complex and involve other mechanisms, including effects on central respiratory drive, which is known to be elevated in patients with COPD.22

Several investigators have demonstrated that NPPV can result in a reduction in the work of breathing9,11,13-15 Petrof et al.11 were able to significantly reduce inspiratory muscle effort during NREM sleep

![Figure 2. Effects of NPPV on TST and sleep efficiency. Compared to the control-sham night on low level oxygen, NPPV caused a significant increase in both (A) TST and (B) sleep efficiency during the night.](image-url)
seems an unlikely mechanism to account for the changes in sleep seen in our study.

Other studies have reported similar improvements in sleep efficiency and TST using NPPV, but this was evaluated only after more prolonged use. Elliott et al noted a significant increase in sleep efficiency after patients had been using NPPV for a total of 6 months. This could have been secondary to becoming more comfortable with the equipment over this period. More recently, Meecham Jones et al noted a significant increase in both sleep efficiency and TST after 3 months of NPPV with oxygen compared to oxygen alone. These patients showed a significant increase in PaO₂ and decrease in PaCO₂ that may have contributed. Strumpf et al actually noted a decrease in sleep efficiency in their seven patients after 3 months of NPPV. Mezzanotte et al examined the effects of nocturnal nasal CPAP on physiologic parameters and sleep in eight patients with COPD. They showed no significant change in sleep efficiency; yet it should be noted that their patients were not hypercapnic with a mean PaCO₂ of 36.5±1.8 mm Hg. In addition, the amount of time that their patients were receiving nasal CPAP was variable, anywhere from 7 to 20 days.

In our study, the significant improvement in sleep efficiency and TST while receiving NPPV occurred regardless of the order in which they had their control-sham and NPPV nights. Thus, this improvement does not appear to be due to the patients becoming familiar with wearing the equipment or with the sleeping environment. In addition, all patients had an acquaintance night study before they were randomized to allow them to adapt to sleeping in the laboratory.

Studies showing beneficial changes in nocturnal gas exchange (ie, decrease in PaCO₂, increase in PaO₂) after prolonged use of NPPV have included patients with severe daytime and nocturnal gas exchange abnormalities. Our patients had a mean awake PaCO₂ of 58±4 mm Hg and we were able to acutely decrease their awake PaCO₂ to a mean of 46±1 mm Hg when NPPV was initiated (Table 2). However, during the NPPV study night, only a minimal decrease in PaCO₂ was noted during both NREM and REM sleep compared to the control-sham night. These differences, with decreased ventilation during nocturnal NPPV, could be secondary to mask or mouth leaks resulting in a reduction in the level of assisted ventilation. More importantly, however, all of our patients were ventilated in the spontaneous mode of ventilation, and higher nocturnal PaCO₂ levels may reflect decreased patient-initiated triggering compared to their awake values.

Other investigators have noted similar small decreases in transcutaneous CO₂ (Ptco₂) or end-tidal Pco₂ while receiving NPPV during sleep. Strumpf et al studied seven patients with COPD with a baseline PaCO₂ of 46±2 mm Hg. Mean ventilatory support system (BiPAP) settings of inspiratory pressures of 15 cm H₂O and expiratory pressures of 2 cm H₂O resulted in only a 5 mm Hg decrease in end-tidal Pco₂ during the night. Petrof et al noted no change in Ptco₂ during NREM sleep in eight patients with COPD when studied on nasal CPAP at 5 cm H₂O. More recently, Meecham Jones et al noted a small increase in Ptco₂ during the night compared to wakefulness (2.6±1.8 mm Hg) when patients were studied with NPPV and supplemental oxygen. They noted, though, that this increase in Ptco₂ during the night was less than that seen with oxygen therapy alone (8.2±4.5 mm Hg).

Similar mechanisms explaining the observed changes in PaCO₂ during the night with NPPV, such as mask and mouth leaks or a reduction in spontaneous ventilation during sleep, might also explain why the PaO₂ was noted to decrease with NPPV during NREM sleep. Other mechanisms include the possible effects of increasing EELV on worsening ventilation/perfusion inequality, as well as the effects of NPPV on venous return and cardiac output. Yet, a similar decrease in PaO₂

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*Sat=saturation; EPAP=expiratory positive airway pressure.

Table 2—Daytime Awake Gas Exchange on Optimal NPPV Settings*
during NPPV was not noted during REM sleep. Meecham Jones et al. noted no significant difference in mean overnight oxygen saturation in those patients treated with NPPV plus oxygen compared to oxygen therapy alone. To our knowledge, our study is the first to analyze gas exchange during the night in COPD patients using NPPV by serially obtaining arterial blood samples. The findings seem to indicate that reduction in PaCO₂ and elevation in PaO₂ are not always demonstrated during NPPV, nor are they essential for improvements in sleep efficiency and TST.

Limitations in our methodology need to be discussed. First, we did not use an endoesophageal balloon to measure the short-term effects of NPPV on inspiratory muscle effort. This would have also enabled us to measure PEEPi and the effects of NPPV on EELV. Second, our sham-control night consisted of a setting of 5 cm H₂O nasal CPAP. Although some improvement can be seen at this level of CPAP, we believe it is much less than that associated with the pressure boost, and associated increase in VT, during the NPPV night.

In conclusion, NPPV can be used in hypercapnic COPD patients to acutely improve overall sleep efficiency and TST. Mechanisms other than improved nocturnal gas exchange, including those effecting central respiratory drive, may be responsible. To better utilize nocturnal NPPV in hypercapnic COPD patients, future investigations should focus on the contribution that these proposed mechanisms might have on sleep.

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