Effects of Short-term NIPPV in the Treatment of Patients With Severe Obstructive Sleep Apnea and Hypercapnia*


Although nasal continuous positive airway pressure (CPAP) is effective in the treatment of most patients with obstructive sleep apnea (OSA), there is a small group of such patients in whom rapid eye movement (REM) hypoventilation and CO\textsubscript{2} retention persist despite the use of CPAP and supplemental oxygen. In this report we describe our experience with nocturnal nasal ventilation (nasal NIPPV) in such patients and its effectiveness in reversing daytime hypercapnia. Thirteen patients, aged 28 to 69 years, with severe OSA confirmed on polysomnography, failed to respond to initial CPAP therapy. All were grossly obese (body mass index [BMI] > 35 kg.m\textsuperscript{-2}) and hypercapnic (mean PaCO\textsubscript{2} > 62 mm Hg). Nocturnal nasal ventilation was commenced using a volume-cycled ventilator, which was well tolerated in all patients. After 7 to 18 days of NIPPV, significant improvements in daytime arterial blood gas values were achieved, with a rise in arterial oxygen tension from 50 ± 2.6 (SEM) to 66 ± 3 mm Hg (p < 0.001) and a fall in CO\textsubscript{2} from 62 ± 2.5 to 46 ± 1 mm Hg (p < 0.0001). Nine of the 13 patients were able to be established on a regimen of nasal CPAP after this period, while 3 patients required a longer period (up to 3 months) before adequate nocturnal ventilation could be maintained. In one patient, the improvements in ventilatory drive achieved with NIPPV could not be maintained on CPAP, and she was transferred on to NIPPV long term. These results indicate that effective nasal ventilation leads to an overall improvement in spontaneous ventilation and blood gas values both awake and asleep. We believe this improvement is the result of improved central ventilatory drive. Short-term NIPPV provides lasting benefits allowing the majority of such patients to resume CPAP therapy. Short-term intervention with this therapy should be considered as an interim measure in patients with severe hypercapnic OSA who fail to respond to initial CPAP therapy.

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The widespread use of nasal continuous positive airway pressure (CPAP) had been a major advance in the treatment of patients with obstructive sleep apnea (OSA) and is now generally accepted as the treatment of choice for this condition. Despite severe oxyhemoglobin desaturation at night, many patients remain eucapnic, with only a small number exhibiting daytime CO\textsubscript{2} retention. Even in those patients who do develop CO\textsubscript{2} retention, nasal CPAP has been shown to be an effective treatment modality in the majority of cases.\textsuperscript{1} However, in a subgroup of patients with severe OSA and hypercapnia, nasal CPAP may prove to be only partially effective despite the reversal of upper airway obstruction. In such patients, significant desaturation and CO\textsubscript{2} retention persist, particularly during rapid eye movement (REM) sleep, despite high levels of CPAP pressure and the use of supplemental oxygen.\textsuperscript{2} With careful management and the addition of supplemental oxygen, such patients can show slow but progressive improvement in nocturnal breathing, but this may take weeks or months.\textsuperscript{3}

Therapeutic options for such patients, in controlling nocturnal respiratory failure and reducing daytime hypercapnia, have in the past been somewhat limited, but they included such invasive measures as intubation and tracheostomy. However, such approaches in this population pose particular problems and limitations.\textsuperscript{3,5}

In this study, we considered the possibility that a more rapid control of the sleep-linked respiratory failure could be achieved with nocturnal nasal positive pressure ventilation (NIPPV), leading to an improved overall level of ventilatory drive\textsuperscript{1,3} and clinical well being so that nasal CPAP alone would become a more effective long-term therapy. We report herein our experience with NIPPV as a short-term intervention in the treatment of 13 patients with severe OSA and hypercapnia who were refractory to initial CPAP therapy.
METHODS

Thirteen patients with a clinical history indicative of severe OSA and daytime hypercapnia presented to our unit for management. Eleven patients were newly referred for assessment and treatment. The remaining two patients had been using CPAP for some time (6 and 18 months) and were reassessed because of recurrence of symptoms, including sleepiness, frequent nocturnal awakenings, morning headaches, or inability to tolerate their current CPAP pressure.

All-night sleep studies using continuous monitoring of EEG, EOC, EMG, ECG, and ear oximetry (Biox 3700e; Boulder, Colo) were performed to establish the diagnosis of sleep apnea. Airflow was monitored via nasal cannula attached to a pressure transducer. Detection of chest wall and abdominal movement was made using inductance plethysmography (Respirtrace, Ambulatory Monitoring Inc, Ardsley, NY). Data were recorded on a polygraph (Grass model 8-24E, Grass Instruments; Quincy, Mass). In eight patients, continuous transcutaneous CO₂ measurements were performed. Sleep stage was classified by the standard criteria of Rechtschaffen and Kales.⁶

During the second sleep study night, nasal CPAP pressure was determined. Nasal CPAP was adjusted with the aim of preventing apneas and hypopneas in all sleep states, including REM, with oxygen being added if required.

Arterial blood gas tensions and standard respiratory function tests were measured in the sitting position. Respiratory muscle strength was assessed by multiple measurements of the maximal inspiratory mouth pressure generated against an occluded airway at residual volume. Values are given as percent predicted according to Wilson et al.⁷

Nasal CPAP was considered to have failed if apneas and hypopneas with significant oxygen desaturation persisted despite the use of high pressures, or if significant hypventilation with oxygen desaturation occurred in REM sleep while receiving CPAP.

Nocturnal nasal ventilation therapy was then commenced and continued for 7 to 18 days before a repeated sleep study was performed to determine the patient’s current response to CPAP therapy. A volume-cycled, portable ventilator (such as the PLV-100, LifeCare, Lafayette, Colo) was used in the assist/control mode. Rate, volume, and inspiratory flow were set initially according to patient comfort and tolerance while awake. Adjustments were then made during sleep periods to maximize ventilation. This was achieved by close monitoring of transcutaneous CO₂ tensions and arterial oxygen saturation, with CO₂ levels being maintained at or below spontaneous daytime values, and saturation kept above 90 percent. In general, respiratory rates of

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*Pimax = maximal inspiratory mouth pressure.

FIGURE 1. Top panel shows the slow recording of oxygen saturation, demonstrating a low baseline, and drops in SaO₂ during NREM sleep. In REM sleep, more prolonged periods of hypoxemia became apparent, without recovery of SaO₂ to baseline values. The lower panel illustrates the response to initial CPAP therapy. There was some improvement in breathing and saturation during NREM periods, but during REM sleep, prolonged periods of desaturation persisted, not associated with frank apnea. Bars indicate REM periods.
between 18 and 24 breaths/min with tidal volumes of 700 to 1,200 ml were required to achieve effective ventilation. If necessary, supplemental oxygen, usually at 0.5 L/min, was added. Eleven patients required the addition of a positive end-expiratory pressure (PEEP) valve (5 to 10 cm H2O) on the expiratory port of the patient circuit to prevent residual upper airway obstruction. Chin straps were necessary in all patients to minimize mouth leaks and ensure effective PEEP was not lost.

**Results**

Of the 13 patients studied, 9 were men. Mean age (± SE) was 54 ± 3.6 years, with a range of 28 to 69 years. All patients were grossly obese with a body mass index (BMI) > 35 kg·m² (normal, 20 to 25 kg·m²). At presentation, all were hypercapnic (mean PaCO₂, 62 ± 2.5; range, 49 to 78 mm Hg), and 10 of the 13 patients had a PaO₂ of less than 60 mm Hg (Table 1). Overnight sleep studies confirmed severe OSA in all patients, with hypoventilation and CO₂ retention especially during REM sleep.

There were two patterns of response to initial CPAP therapy in these patients. In some patients, CPAP therapy effectively controlled obstructive apnea and hypopnea and prevented desaturation in non-REM (NREM) sleep. However, during REM sleep, substantial desaturation and CO₂ retention continued, although notably the level of desaturation was usually less severe than without CPAP (Fig 1).

In the second type of response, obstructive apneas continued to occur in all sleep states despite high mean CPAP pressures (up to 18 to 20 cm H₂O depending on patient tolerance) (Fig 2).

Nasal ventilation readily prevented apnea and hypoventilation throughout all sleep states and was well tolerated by all patients, resulting in improved sleep quality and marked improvement in daytime function. Skilled staff and monitoring are necessary on the first few nights of therapy to ensure ventilation is optimized and the patient comfort is maximized. When ventilation parameters were set correctly, patients readily relaxed, and we found 9 of the 13 patients fell asleep during the initial practice sessions, possibly as a consequence of severe hypoxemia being relieved. In those patients in whom full polysomnography was performed during the initial NIPPV trials, large epochs of uninterrupted slow-wave and REM sleep were observed, attesting to the acceptability of the technique, despite mouth leaks and the compensatory high tidal volumes. After the first few days of ventilation, peak inspiratory pressures during ventilation decreased, and with reduction in mouth leaks, tidal volume could be reduced. Nocturnal ventilation resulted in the normalizing of daytime blood gas values with mean arterial oxygen tension increasing from 50 (± 2.6) to 66 (± 3) mm Hg (p <0.001), and a corresponding fall in arterial CO₂ from 62 (± 2.5) to 46 (± 1) mm Hg.

**Figure 2.** Slow recording of oxygen saturation. The first section of the recording represents the typical SaO₂ of the patient during the initial diagnostic study. At A, CPAP therapy was commenced, which increased baseline SaO₂ but failed to prevent continued apneas and hypopneas at 14 cm H₂O. Use of higher pressures resulted in awakening the patient.

**Figure 3.** Bar graphs demonstrate the normalization of daytime arterial blood gas values after short-term intervention with nocturnal nasal intermittent positive pressure ventilation. The open bars represent awake blood gas measurements prior to ventilation while the shaded bars represent the awake values after ventilation.
(p <0.0001) (Fig 3). Thus, effective control of the sleep-induced respiratory failure led to improved overall ventilation and arterial blood gas values in these patients even when awake and without assisted ventilation.

During the initial CPAP trials, the mean rise in transcutaneous CO₂ was 15 (± 0.9) mm Hg, most commonly seen during REM periods. Although transcutaneous CO₂ was not measured in all patients during their diagnostic night, in those cases where it was, the rise was similar to that seen during the subsequent CPAP trial. When the patients were retested on a regimen of nasal CPAP after 7 to 18 days of NIPPV, the mean rise was markedly reduced to 6 (± 1.7) mm Hg (p <0.001).

After short-term intervention with NIPPV, ten of the patients were able to be established or recomenced on a regimen of nasal CPAP. In these patients, repeated polysomnography demonstrated that CPAP was now effective in preventing clinically significant desaturation in all sleep states, including REM sleep (Fig 4). In one patient, daytime hypercapnia and sleepiness returned within 2 months of discontinuing ventilation, even though she remained on a regimen of CPAP and oxygen. On two further occasions, short-term NIPPV was again initiated, but the improvements could not be sustained and the patient has since been transferred onto NIPPV on a long-term basis. Her condition has now remained stable with no recurrence of awake decompensation over a period of 12 months.

In three patients, extended use of nasal ventilation was required, as major REM hypventilation on a regimen of CPAP persisted despite improvements in daytime arterial blood gas values. These patients continued to desaturate significantly (to a minimum of 60, 47, and 60 percent) during REM sleep on a regimen of CPAP. Although this was better than on control studies (where minimum oxygen desaturation was to 25 percent, 43 percent, and 13 percent), we considered that they were likely to decompensate without continued nasal ventilation. After 3 months of ventilation therapy, they were again retested on a regimen of CPAP (with oxygen in two patients or alone in one) which was then found to be sufficient to maintain adequate nocturnal ventilation in all sleep states.

**DISCUSSION**

Although nasal CPAP therapy is effective for a majority of patients with severe OSA, its use may be limited in some patients because of a number of factors. These include extreme upper airway narrowing that exceeds the ability of the CPAP to maintain airway patency, unacceptably high levels of CO₂ retention during CPAP therapy, or the continuation of significant arterial desaturation especially during REM sleep despite the abolition of apneas and hypopneas (the emergence of hypoventilation). The latter appears to be particularly likely in the presence of gross obesity where upper airway loading with complete or partial obstruction is not the dominant mechanism of hypoventilation.

In this clinical report, we have demonstrated that NIPPV during sleep is an effective method of treatment for patients with severe OSA and hypercapnia, so that continuing use of nasal CPAP now may be possible. Importantly, once established, effective nasal ventilation leads to an overall improvement in spontaneous ventilation and blood gas values both asleep and awake. The improved ventilation after short-term NIPPV is similar to that reported by Sullivan et al and Berthon-Jones and Sullivan using nasal CPAP. However, our results indicate that an initial period of nasal intermittent positive pressure ventilation in sleep is a more efficient and rapid method of reversing respiratory failure in this subgroup of patients. It has also proved to be an effective alternative to intubation or tracheostomy and intensive care unit admission in patients with severe cardiopulmonary failure, in whom CPAP therapy is ineffective or intolerable. There have been a number of articles outlining the use of...
NIPPV in nocturnal hypoventilation. Becker et al. reported the effectiveness of NIPPV in seven patients with central and two with mixed apnea and chronic lung disease unresponsive to CPAP therapy. However, these authors used nasal ventilation for their patients on a long-term basis. Sanders and Kern have reported the use of a BiPAP device in the management of hypoventilation of patients with OSA. However, the patients in their study were normocapnic, and during CPAP trials they demonstrated a relatively good response to therapy with an apnea/hypopnea index of 2.3/h and a mean minimum oxygen saturation of 86 \pm 5 percent in NREM and 86 \pm 7 percent REM. In contrast, the patients in our study were all hypercapnic, and initial use of nasal CPAP failed to prevent significant oxygen desaturation (30 to 65 percent in REM sleep).

Waldhorn used bilevel pressure ventilation in eight patients, three of whom had obesity-hypoventilation. He reported that in two of his patients, nasal CPAP eliminated apnea but not REM-related “non-apneic” desaturation. In his patients, relatively low inspiratory pressures (16 to 22 cm H\textsubscript{2}O) were sufficient to improve ventilation and reduce CO\textsubscript{2} retention. Initial peak inspiratory pressures needed to effectively ventilate our patients were significantly higher than those of Waldhorn. Volume-cycled ventilation has the distinct advantage of being able to generate higher peak inspiratory pressures, which may be advantageous when chest wall impedance is particularly high. Certainly, volume-cycled ventilation should be considered in those patients in whom bilevel airway pressure fails to give satisfactory results.

Our results indicate that short-term intervention with NIPPV in hypercapnic OSA can improve the clinical status of such patients, permitting the eventual transfer of the patient back to CPAP therapy, which can maintain the patient indefinitely. Certainly, ventilators are considerably more expensive than standard CPAP machines. However, our findings strongly suggest that short-term NIPPV, in many cases, will allow the patient to be reestablished on the much cheaper form of long-term treatment. Clearly, some patients will require long-term ventilation, similar to patients with neuromuscular disease and kyphoscoliosis. However, the fact that short-term intervention can lead to long-term stability has important implications for the treatment of these patients with the so-called obesity-hypoventilation syndrome.

We believe the improvement in ventilation both during the day and at night, as demonstrated by a progressive return toward normal of the arterial blood gas tensions, is the result of improved central respiratory drive. The mechanism of this improved drive is unclear, but it may include improved chemoreceptor function or the removal of asphyxial induced changes in central respiratory control mechanisms. The improved daytime and nighttime ventilation in these patients on regimens of NIPPV has similarities to patients with hypercapnic OSA or chronic respiratory failure from chest wall dysfunction, where either CPAP alone or NIPPV led to a sustained increase in both daytime and sleep ventilation. Thus, severe sleep-linked respiratory disturbance can induce a secondary cycle of depressed respiratory drive. While factors such as respiratory muscle rest and improved lung function can contribute, there is also considerable evidence that overall central drive is improved.

By definition, all of the patients in this report had classic obesity hypoventilation syndrome, as evidenced by daytime hypercapnia and a BMI greater than 35 kg/m\textsuperscript{2}. However, in all but one patient, daytime control of breathing, as seen in the normalization of daytime CO\textsubscript{2} tensions, improved with intervention by short-term NIPPV. Thus, despite the fact that these patients did not lose substantial amounts of body weight, their awake hypoventilation was reversed with effective control of sleep-induced respiratory failure.

It is not clear why hypercapnia develops in some patients with OSA and not in others. Reduced or defective ventilatory responses to both hypercapnia and hypoxia were identified many years ago in the obesity-hypoventilation syndrome. Abnormalities in the mechanical properties of the chest wall associated with obesity are also considered to be a significant factor.

A common feature of those patients with daytime hypercapnia and OSA is the greater degree of oxyhemoglobin desaturation that occurs during sleep compared with eucapnic OSA patients. During periods of apnea and hypopnea, CO\textsubscript{2} tensions will rise and remain elevated during the period of the obstruction. In patients with normally functioning carotid bodies, such changes in blood gas values would stimulate ventilation and return CO\textsubscript{2} to normal between apneic periods. However, in those patients with depressed ventilatory responses to chemical stimuli, extended apneic periods will occur, and there will be less respiratory effort between obstructive events. Sullivan and colleagues have suggested that the depressed chemosensitivity has a “protective” effect on the upper airway. With less effort during inspiration, there will be partial upper airway obstruction rather than complete apnea, permitting some, though reduced, ventilation to occur. An overall hypoventilation will ensue, resulting in sustained blood gas abnormalities. Chronic hypoxemia and sleep
fragmentation may further depress the arousal response to the apneic periods contributing to the continuing cycle of worsening hypoxemia and further depression. Under such circumstances, and in the presence of low chest wall compliance associated with obesity, the patient will be unable to recover between apneic periods with the normal compensatory hyperventilation response. Hence, the pattern of ventilation between apneic periods is probably crucial in the development of hypercapnia in these patients.

With long-term adaptation to these acute episodes of asphyxia and hypercapnia during sleep, depression of ventilatory drive occurs even when awake. This was demonstrated in our patients by the daytime CO₂ retention and its reversal after effective treatment. Although not specifically studied in this series, all the patients reported long histories consistent with OSA. Several other studies suggest that hypercapnic obese patients with OSA tend to be older than their eucapnic counterparts, adding support to the concept that both the degree of severity of nocturnal breathing abnormality and the period of time over which it occurs are important in the adaptation process and the evolution of daytime hypercapnia.

Although part of the improved ventilation may have resulted from improved lung function and weight loss, the time course of improvement in daytime clinical state occurred prior to the changes in these two variables. Indeed, in one patient in whom ventilation was continued over 3 months, improved daytime and nocturnal respiratory drive were maintained despite the addition of 4 kg of weight.

An additional mechanism of improved overall ventilation in some subjects may have been improved upper airway function. There was generally a reduction in peak airway pressure during the course of nocturnal ventilation, indicating reduced impedance of the respiratory system. We believe the greater part of this is the result of better upper airway function rather than any significant change in lung mechanics or weight loss.

Whatever the mechanisms of improvement involved, we have demonstrated that sleep-disordered breathing in these patients can induce a secondary reversible depression of respiratory drive both awake and asleep. Some period of time on a regimen of nasal ventilation is necessary to reverse the deceleration brought about by this prolonged and severe upper airway dysfunction. Typically we have found a week to 18 days is a sufficient period to see improvement, although as long as 3 months of NIPPV therapy may be necessary. If no improvement has occurred by this time, then it is likely that CPAP will not be a viable option for the patient, and decisions regarding long-term therapy and management need to be made.

In conclusion, in patients with hypercapnia and severe OSA who appear to be unresponsive to conventional CPAP therapy or who are slow to respond, short-term intervention with nasal ventilation should be considered as an interim measure until ventilatory decompensation is reversed. After this time, CPAP can be recommended and, in most cases, will prove to be effective long term.

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REFERENCES
1 Berthon-Jones M, Sullivan CE. Time course of change in ventilatory response to CO₂ with long-term CPAP therapy for obstructive sleep apnea. Am Rev Respir Dis 1987; 135:144-47
10 Waldhorn RE. Nocturnal nasal intermittent positive pressure ventilation with bi-level positive airway pressure (BiPAP) in respiratory failure. Chest 1992; 101:516-21

CHEST / 105 / 2 / FEBRUARY, 1994 439
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