REVIEW ARTICLE

Noninvasive ventilation and sleep

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Introduction

Sleep has several physiological effects on respiration that assume significance in the presence of respiratory insufficiency (1). These relate to the decrease in respiratory drive and respiratory muscle activity during sleep. This may result partly from lung mechanics in the supine position, pathological breathing pattern, and reduced chemosensitivity during REM sleep (2).Also, the diaphragm is essential for ventilation in REM sleep (3) since in REM sleep a marked reduction in intercostal muscle activity is found (4). During NREM sleep there is an increased contribution of the rib cage to breathing (5)

Conditions that may be associated with sleep-related respiratory insufficiency range from pulmonary disorders (such as chronic obstructive pulmonary disease (COPD)), to central respiratory insufficiency (such as central alveolar hypoventilation), neurological and neuromuscular disorders (such as polio and muscular dystrophy), and thoracic cage disorders such as kyphoscoliosis. In all these conditions a relative alveolar hypoventilation occurs during sleep with resulting hypoxemia and hypercarbia that may persist into the daytime. These abnormalities have also been shown to be associated with poor sleep quality and health-related quality of life (6). Assisted ventilation using NIV during sleep has a rational basis in the presence of blood gas abnormalities in these conditions. Use of NIV during the night is associated with beneficial effects during the day, particularly improved awake gas exchange and respiratory muscle strength, in addition to less dyspnoea and improved quality of life. This review aims to evaluate the evidence for its use in the above-mentioned conditions.

Mechanism of improvement

There may be 3 principal mechanisms by which nocturnal NIV may produce improvement: a) increased ventilatory sensitivity to CO_2, (b) respiratory muscle rest/increased respiratory muscle strength, and (c) enhanced pulmonary mechanics.The exact mechanism remains unknown.

In a recent study (7), 20 patients with restrictive disease on nocturnal NIV were studied at baseline,1 week and 3months.It was found that daytime PCO2 progressively decreased along with improved ventilatory response to hypercapnia. No improvement was found in inspiratory muscle strength , lung function tests or diaphragm function.

These findings suggest that increased ventilatory response to carbon dioxide is the principal mechanism underlying the long term improvement in gas exchange following NIV in patients with restrictive thoracic disease.

The mechanisms for progressive improvement over time with NIV use remains speculative. There may be

several other explanations for these findings for example, increased adaptation to the NIV and interface or slowly improving neurophysiological phenomena (8).

Other studies of patients with neuromuscular diseases or chest wall disorders have concluded that the correction of sleep disordered breathing and the associated arousal responses are the main mechanisms for the beneficial effects of NIV (9,10).However, in another study it was found that daytime NIV in awake patients with chronic respiratory failure (CRF) also leads to an improvement in both spontaneous daytime and nocturnal ventilation without direct treatment of the associated sleep disordered breathing itself (11). These findings imply that improvement obtained with daytime NIV is not directly mediated by an effect on sleep quality, and suggest that NIV does not exclusively need to be directed at what is functionally the worst period of hypoventilation. CRF may therefore be at least partially reversed without primarily preventing sleep disordered breathing. However, the greatest improvements in quality of nocturnal ventilation and sleep appear to be still achieved during nocturnal NIV (8).

Neuromuscular disease

In one of the earliest studies on the subject, Piper and Sullivan reported findings on 14 patients with documented nocturnal respiratory failure, who had been treated with nocturnal NIV for at least 6 months (9). All were reviewed with an all night polysomnograph on a night without ventilatory support. The severity of nocturnal desaturation both in NREM and REM sleep without nocturnal ventilation was compared to desaturation measured during the initial diagnostic study. Spontaneous daytime blood gas values and inspiratory muscle strength and spontaneous breathing during sleep were significantly improved at follow-up compared to values obtained prior to nasal ventilation. During NREM sleep and REM sleep without ventilatory support, minimum oxygen saturation was significantly higher compared to the initial study and where transcutaneous carbon dioxide was measured continuously during sleep on both occasions less CO2 retention was observed during follow-up compared to control studies both in NREM and REM sleep states.Thus, long-term nocturnal ventilation produces improved respiratory drive both while asleep and awake and improved arousal responses to abnormal blood gases.

Simonds and Elliot studied the outcome of long term domiciliary NIV in 180 patients with hypercapnic respiratory failure predominantly due to chest wall restriction, neuromuscular disorders, or chronic obstructive lung disease (12). 138 patients were started on NIV electively, and 42 following an acute hypercapnic exacerbation. Outcome measures were survival , pulmonary function, and health status. Five year acturial probability of continuing NIV for individuals with early onset scoliosis (n = 47), previous poliomyelitis (n = 30), following tuberculous lung disease (n = 20), general neuromuscular disorders (n = 29), and chronic obstructive pulmonary disease (n = 33) was 79% (95% CI 66 to 92), 100%, 94% (95% CI 83 to 100), 81% (95% CI 61 to 100), 43% (95% CI 6 to 80), respectively. Most of the patients with bronchiectasis died within two years. One year after starting NIV electively the mean PaO2 ,mean PaCO2 values in patients with extrapulmonary restrictive disorders and in patients with obstructive lung disease improved significantly.Further,health status measures improved most in patients with early onset scoliosis, previous poliomyelitis, and following tuberculous lung disease.

Overall the long term outcome of domiciliary NIV in patients with chronic respiratory failure due to scoliosis, previous poliomyelitis, and chest wall and pulmonary disease secondary to tuberculosis was encouraging, while the outcome in end stage bronchiectasis was poor (12).

Chronic obstructive pulmonary disease (COPD)

Domiciliary long-term oxygen therapy (LTOT) is one of the few interventions in patients with chronic obstructive pulmonary disease (COPD) that improves survival when used for ≥ 15 h/day (13,14). LTOT, however has less clear beneficial effect on other factors including health-related quality of life or reduction in frequency of exacerbations. Many of these COPD patients manifest as derangement of blood gases and ventilatory muscle dysfunction during sleep, which may contribute to the progressive deterioration seen in this group (15). It has therefore been suggested that ventilatory support may confer further advantages when used in addition to LTOT.

COPD may often be associated with chronic respiratory muscle fatigue, and improvements in lung

mechanics and reduction in the work of breathing may facilitate muscle rest and relief of fatigue. The application of noninvasive ventilation, using both positive- and negative-pressure techniques, have been shown to produce significant reductions in diaphragmatic electromyogram (EMG) activity and work of breathing (16,17) However, no long-term controlled study has yet shown an improvement in measures of ventilatory muscle strength with the addition of assisted ventilation.

Patients with hypoxic COPD also have sleep disruption, although the effects of supplemental oxygen therapy on sleep quality have been variable (18). Coincident sleep apnoea may exist, but sleep disruption in COPD is not usually caused by the effects of upper airway obstruction.Arousals with oxygen desaturation may occur in paatients with COPD, although sleep disruption is also present in patients with COPD who do not desaturate at night (19). Hypercapnia may be worsened overnight with the addition of supplemental oxygen therapy. An acute elevation of $PaCO_2$ during the night may contribute to arousals and thus impaired sleep quality (19). Control of nocturnal hypercapnia through nasal ventilation may improve sleep quality and thus result in increased neuropsychological performance and quality of life.

There is now robust evidence for the use of NIV for acute exacerbations of COPD , but its effect when added to LTOT has not been determined.

Early uncontrolled studies showed that arterial blood gases improved in patients treated with NIV, with improvement in sleep quality (20,21), with more favourable results compared to those achieved previously with negative-pressure ventilation. However, in these studies compliance with ventilation was not as good as in patients with restrictive chest disease. Patients who showed benefit were the patients who also had significant daytime hypercapnia and whose nocturnal hypercapnia could be successfully reduced by overnight ventilation (21). Supplemental oxygen was not used routinely with the NIV in some early studies. This may have reduced benefit because overnight oxygen saturation levels were not adequately corrected with NIV alone (22).

Strumpf *et al.* (23) performed a randomised crossover study of nasal ventilation using a bilevel ventilator in 19 patients with COPD. Compliance proved to be a major problem in the study and only seven patients completed both arms of the protocol; the poor compliance mainly resulting from problems with the nasal/mask interface. This study showed no changes in pulmonary function, respiratory muscle strength, gas exchange, exercise endurance, sleep efficiency, sleep quality, oxygenation or dyspnoea ratings between the two arms of the trial. The only improvements observed were in neuropsychological function. Although these patients had severe airflow obstruction, they showed less severe derangement of blood gases and in particular lesser degrees of hypercapnia, with some patients in the normocapnic range.

Meecham –Jones et al (24) reported a randomized crossover study of the effect of the combination of NIV and domiciliary LTOT as compared with LTOT alone in stable hypercapnic COPD. Fourteen patients were studied . A 4 wk run-in period (on usual therapy) was followed by consecutive 3-mo periods of: (1) oxygen therapy alone, and (2) oxygen plus NIV in randomized order. Assessments were made during run-in and at the end of each study period. There were significant improvements in daytime arterial PaO2 and PaCO2, total sleep time, sleep efficiency, and overnight PaCO2 following 3 months of oxygen plus NIV as compared with run-in and oxygen alone. Quality of life with oxygen plus NIV was significantly better than with oxygen alone. The degree of improvement in daytime PaCO2 was correlated with the improvement in mean overnight PaCO2. They concluded that NIV may be a useful addition to LTOT in stable hypercapnic COPD.

As progressive COPD is associated with significant disturbances in activities of daily living, measures of quality of life are essential for assessing the effectiveness of therapies. Meecham Jones *et al.* (24) measured quality of life in their study using the St George's Respiratory Questionnaire (SGRQ), which provides a disease-specific measure of quality of life, with three component scores (symptoms, activities and impacts) and a total score. The combination of NIV with oxygen therapy produced significant improvements in symptom, impact and total quality of life scores as compared to oxygen alone. There was no change in the activity component in the two study groups and no change in 6-min walking distance after ventilation. A study involving patients with restrictive ventilatory disorders showed that quality of life was related to sleep quality (25). Although these findings were not confirmed in the study by Meecham Jones *et al.*, it is possible that improvements in sleep time and efficiency contribute to parallel improvements in health-related quality of life. Seemungal *et al.* (26) have recently shown

that quality of life, as assessed using the SGRQ, is strongly related to exacerbation frequency. It is possible that the improvement in health status observed reflects reduction in exacerbation frequency, although this was not addressed in this particular study. NIV may also protect the patient against deterioration in blood gases during an exacerbation, and this may be the mechanism of any observed survival benefit.

Perrin *et al*. (27) followed 14 patients with hypercapnic COPD over a 6-month period and found similar improvements in daytime arterial blood gases. This study is also of interest in that improvements were also found in the total SGRQ score and in the impacts component of the SGRQ score. Another small study investigated the effects of the addition of NPPV to oxygen therapy in severe COPD, but found no significant benefit of NIV after only 2 weeks of therapy (28), which could be too short a time for assessment.

A study of NIV in COPD patients who were unable to tolerate LTOT showed that survival was similar to those able to take oxygen therapy and better than historical controls (29). A high overnight transcutaneous CO_2 tension, correlated with poor survival again showing that control of nocturnal hypoventilation is an important factor in the use of NIV in hypercapnic COPD. Another recent small uncontrolled study of NIV in COPD found that hospital admissions and primary care consultations were halved with NIV, although this type of analysis is subject to bias as the use of NIV involves more supervision and hospital visits (30). A recent study assigned patients with hypercapnic COPD to two groups depending on whether or not they were able to tolerate NIV. Although there was no difference in mortality between the two groups, patients taking NIV had a reduction in intensive care admissions compared to those on LTOT alone (31). The results of randomised controlled trials, comparing long term outcome of NIV to oxygen therapy, are awaited.

In a recent review, Elliot (32) concludes that a trial of noninvasive positive pressure ventilation can only be justified in patients with chronic obstructive pulmonary disease who either have significant symptoms of nocturnal hypoventilation (morning headaches, daytime sleepiness, *etc*.) despite maximal bronchodilator therapy or cannot tolerate long-term oxygen therapy because of symptomatic hypercapnia. It should also be considered in patients with repeated episodes of hospitalisation as well as those with hypercapnic ventilatory failure requiring acute noninvasive positive pressure ventilation.

Conclusions

There is clearly a pathopyhysiological rationale for considering nocturnal domiciliary support with NIV for chronic respiratory failure, in view of ventilatory decompensation during sleep in these patients and its impact not only on survival, but also on sleep quality and quality of life indices. While it is widely accepted therapy for neuromuscular and restrictive chest wall disorders, domiciliary NIV is indicated in only selected cases of COPD

Table 1: Noninvasive positive-pressure ventilation (NIV) in chronic obstructive pulmonary disease: selection criteria of patients for long-term therapy (19)

Established on long-term oxygen therapy
Daytime hypercapniaEnd stage disease excluded
Blood gas tensions stable
Evidence of nocturnal hypoventilation
Poor sleep quality with frequent arousals
Nocturnal hypoventilation confirmed to be controlled by NPPV
Appropriate support and education for patient
Adequate patient motivation

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