Current status of noninvasive ventilation in stable COPD patients

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Abstract: Noninvasive ventilation (NIV) has been one of the major advances in respiratory medicine in the last decade. NIV improves quality of life, prolongs survival, and improves gas exchange and sleep quality in restrictive patients, but evidence available now does not allow us to establish clear criteria for prescribing NIV in patients with chronic respiratory failure due to COPD. On the basis of the available studies, NIV should not be used as a treatment of choice for all patients with COPD, even when disease is severe. However, there is more evidence that NIV has an important effect in these patients. In fact, a selected group of patients may well benefit from domiciliary mechanical ventilation, and we need to be able to identify who they are. Moreover, NIV can be a new strategy to improve exercise tolerance in COPD patients.

Keywords: noninvasive ventilation, COPD

Introduction

Noninvasive ventilation (NIV) has been one of the major advances in respiratory medicine in the last decade. The 1990s can be considered the decade of NIV and home ventilation thanks to the important invention of the nasal mask (Díaz-Lobato and Mayoralas 2003). No doubt remains about the efficacy of NIV in patients with chronic respiratory failure arising from thoracic restriction. Research has shown that NIV improves quality of life, prolongs survival, and improves gas exchange and sleep quality in restrictive patients (Lèger et al 1994; Mehta and Hill 2001; Nauffal et al 2002) (see also Tables 1 and 2). Debate continues, however, on the usefulness of long-term ventilation of COPD patients. Evidence available now does not allow us to establish clear criteria for prescribing NIV in patients with chronic respiratory failure due to COPD (Wedzicha and Muir 2002; Wijkistra et al 2002; Plant and Elliot 2003). Despite of lack of evidence for the effectiviness of NIV in COPD patients, this is one of the most common reasons for long-term home mechanical ventilation worldwide (Lloyd-Owen et al 2005).

Early uncontrolled studies on NIV in COPD patients, mainly using nasal masks, have shown that NIV is feasible at home in these patients, as had been previously found in chest wall and neuromuscular disease. During NIV, overnight abnormal physiology can be corrected, with improvements in gas exchange during sleep and sleep quality, exercise capacity, and diurnal arterial blood gas tensions (Elliot et al 1992; Krachman et al 1997; Sivasothy et al 1998; Costes et al 2003; Ambrosino and Strambi 2004). Use of health care resources may also be reduced and quality of life and functional score improved (Perrin et al 1997; Criner et al 1999; Hill 2004). Survival appears to be prolonged when the NIV outcomes are compared with those of the NOTT and MRC trials (Jones et al 1999).

However, there have been few controlled trials and these have had small numbers of patients followed over a short period of time (Strumpf et al 1991; Meecham-Jones

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Table 1 Guidelines for use of noninvasive ventilation in severe stable COPD

Symptomatic patient after optimal therapy
Sleep apnea excluded
$PaCO_2$ >55 mmHg *or*
$PaCO_2$ 50–54 mmHg and evidence of nocturnal hypoventilation based on nocturnal oximetry showing sustained desaturation to < 89% for > 5 min while patient is on his or her usual FIO_2
Repeated hospitalizations

Adapted from Consensus Conference (1999).

Table 2 Potential benefits of noninvasive ventilation in severe stable COPD

Can improve respiratory muscle strength in these patients
Increases in maximum inspiratory pressure
Improvement (or at least prevention of deterioration) in nocturnal and daytime gas exchange, and better quality-of-life scores
May increase walking distance, particularly if combined with rehabilitation
Prolongation of total sleep time in severely hypercapnic patients with some sleep-disordered breathing
Reduces the need for hospitalization

et al 1995; Lin 1996). Only one study has shown any benefit from the combination of NIV and long-term oxygen therapy (LTOT) in stable COPD patients (Meecham-Jones et al 1995). These authors reported a randomized crossover study of nasal pressure support ventilation plus oxygen therapy, compared with domiciliary oxygen therapy alone in 18 hypercapnic COPD patients. The aim of this study was to investigate the effect of the addition of NIV for patients already established on LTOT. Following a run-in period, each patient received NIV plus oxygen and oxygen alone in random order for 3-month periods. There was significant improvement in daytime arterial blood gases, with the mean oxygen tension in arterial blood (PaO_2) rising from 44.3 mmHg after the oxygen period to 50.2 mmHg after the addition of NIV and arterial carbon dioxide tension ($PaCO_2$) falling from 57.0 mmHg to 52.5 mmHg. There were also improvements in overnight $PaCO_2$, total sleep time, and sleep efficiency, suggesting that control of hypoventilation in these patients was effective and leads to improved sleep quality. The improvement in daytime blood gas values was correlated with the change in overnight $PaCO_2$, suggesting that the patients who showed the greatest improvement in $PaCO_2$ with NIV were likely to gain the greatest benefit from the treatment.

As noted above, this is the only study showing any benefit from the combination of NIV and LTOT. There are a number of possible explanations for this, related to the way in which patients were acclimatized to NIV, the different hypercapnia levels between studies, and the differences in the type and settings of the ventilators.

Acclimatization to NIV

Patients were acclimatized to NIV in different ways. Strumpf et al (1991) performed a randomized crossover study of nasal ventilation using a bilevel device in 19 patients with COPD. Compliance proved to be a major problem in the study and only 7 patients completed both arms of the protocol; the poor compliance resulted mainly from problems with the nasal mask interface. In this study acclimatization was performed as an out patient, but with regular visits from a respiratory therapist. It is important to know that many patients do not find NIV easy initially and in uncontrolled studies a higher success rate was achieved when patients started NIV in hospital under close supervision.

Another small study investigated the effects of the addition of NIV to oxygen therapy in severe COPD, but found no significant benefit of NIV after only 2 weeks of therapy (Lin 1996). Practical experience with both NIV and continuous positive airway pressure (CPAP) has suggested that most patients require several weeks of acclimatization before they are comfortable and confident with the delivery of ventilatory support during sleep. Therefore, a study time of 2 weeks was considered too short. In this study, patients had problems with higher levels of inspiratory positive airway pressure (IPAP $\geq$ 15 cm H_2O) and this also suggests that they probably required a longer period of acclimatization to the ventilator.

When we are trying to facilitate a stable patient's adaptation to NIV, his or her comfort and tolerance of the technique is what should concern us in the initial stages. Once the patient has been adapted to the ventilator, the time comes to optimize ventilation. The long-term objectives of NIV are mainly to prolong survival, and improve quality of life and the functional status of the patient. Such achievements will not be feasible unless adaptation to the respirator and good tolerance have already been established, and that is why it becomes our principal aim. Only in few medical disciplines can we see such a direct relationship between adherence to treatment and success as we see in patients undergoing NIV (Mehta and Hill 2001; Díaz-Lobato

and Mayoralas 2003). Criner et al (1999) have clearly established how a comprehensive follow up and support is necessary for all patients on home ventilation programs.

Hypercapnia levels

In the studies of Strumpf et al (1991) and Lin (1996), patients were not particularly hypercapnic (mean $PaCO_2$ 46 mmHg and 50.5 mmHg respectively), whereas those in the study of Meecham-Jones et al (1995) had a mean $PaCO_2$ of 55.8 mmHg. In studies using negative pressure devices, any benefits observed have usually been in those with daytime hypercapnia (Braun 1984; Zibrak et al 1988; Celli et al 1989; Dubois 1990; Shapiro et al 1992).

Ventilator type and setting

The type and settings of the ventilators differed in reported studies. Meecham-Jones et al (1995) used pressure support ventilation with a mean IPAP of 18 cm H_2O (Meechan-Jones et al 1995). Strumpf et al (1991) used a timed mode because it is more likely to reduce inspiratory muscle effort than patient-initiated ventilation, but noted that approximately 25% of the night was spent with the patient breathing out of synchrony with the ventilator. Asynchrony between the patient and ventilator may cause worsening of gas exchange with both negative and positive pressure devices (Calderini et al 1999; Rabec et al 2004). The best synchrony between the patient and the respirator facilitates the reduction of work load for the diaphragm and increases the patient's sense of well-being (see also Table 3).

Effective ventilation

It is important to confirm that effective ventilation has been delivered before it can be concluded that NIV has no effect. The absence of these data does not allow us to know if failure in effectiveness is related to NIV itself or to optimal parameters not being chosen for performing NIV (Díaz-Lobato et al 2004). In the study of Strumpf et al (1991) carbon dioxide control during sleep was assessed on the basis of spot measurements of end-tidal CO_2 monitoring ($EtCO_2$) (Strumpf et al 1991). $EtCO_2$ is an unreliable measure of $PaCO_2$ in patients with severe airways obstruction (Levine 2000). In the study of Lin (1996) no data were given about the effect of NIV on blood gas tensions during ventilation and there was no statistically significant improvement in sleep hypoventilation with NIV. In the study of Gay et al (1996) CO_2 tensions were not measured and there was no change in mean or nadir PaO_2, during overnight polysomnography, which suggests that nocturnal hypoventilation was not controlled. By contrast Meecham-Jones et al (1995) showed a reduction in transcutaneous CO_2 tension during sleep and this correlated with the improvement in daytime $PaCO_2$ that was seen. Since a primary aim of NIV delivered during sleep is to control nocturnal hypoventilation, it can be argued that this was not achieved in the other studies and therefore a therapeutic effect with NIV cannot be affirmed. It may also be significant that Meecham-Jones et al (1995) used higher inflation pressures (mean IPAP 18 cm H_2O) than the other studies. Gay et al (1996) were the only group to compare active NIV with sham, and importantly two patients in the sham group reported that their breathing improved, despite unchanged results of the objective measures, suggesting a significant placebo effect.

Two prospective, randomized, controlled trials including reasonable numbers of patients have been recently published (Casanova et al 2000; Clini et al 2002). In a 1-year controlled trial Casanova et al randomized 52 patients with severe stable COPD to either NIV plus "standard care" (96% patients with LTOT) or to standard care alone (93% patients with LTOT). The adequacy of ventilation was determined by close observation of the patient, during the day and night, but was not confirmed objectively. One-year survival was similar in both groups (78%) as was the number of acute exacerbations. The number of hospital admissions was less at 3 months in the NIV group (5% vs 15%, $p < 0.05$), but this difference was not seen at 6 months (18% vs 19%, respectively). No statistically significant differences in respiratory lung function or survival were found, although the authors did not analyze important variables such as quality of life or sleep. In this study the level of support was modest, mean

Table 3 Monitoring noninvasive ventilation in COPD: basic aspects in a chronic setting

Patient comfort
Mask fit and leak
Hours of use
Problems with adaptation (eg, nasal congestion, dryness, gastric insufflation, conjunctival irritation, inability to sleep)
Symptoms (eg, dyspnea, fatigue, morning headache, hypersomnolence)
Gas exchange: daytime, nocturnal oximetry, blood gases measured periodically to assess $PaCO_2$
Polysomnography if symptoms of sleep disturbance persist or nocturnal desaturation persists without clear explanation

IPAP 12±2 cm H_2O. Ventilatory parameters should be selected considering changes of gas exchange parameters in response to night-time NIV together with effects seen during the day. Thus, the poor results of the trial carried out by Casanova et al (2000) could simply be attributable to failure to achieve effective ventilation.

In the second study Clini et al (2002) undertook a 2-year, multicenter, prospective, randomized, controlled trial to assess the effect of NIV + LTOT on severity of hypercapnia, use of healthcare resources, and health-related quality of life (HRQL), in comparison with LTOT alone. One hundred and twenty-two stable hypercapnic COPD patients on LTOT for more than 6 months were consecutively enrolled. After inclusion and 1-month run-in, 90 patients were randomly assigned to NIV + LTOT (n = 43) or to LTOT alone (n = 47). Arterial blood gases, hospital and intensive care unit (ICU) admissions, total hospital and ICU length of stay, and HRQL were primary outcome measures; survival and drop-out rates, symptoms (dyspnea and sleep quality), and exercise tolerance were secondary outcome measures. Follow-up was performed at 3-month intervals up to 2 years. In this study, compliance with LTOT was excellent and among NIV patients the mean night-time use of 9 hours compares very favorably with reported use in other studies. Lung function, inspiratory muscle function, exercise tolerance, and sleep quality score did not change over time in either group. By contrast the CO_2 tension in arterial blood on usual oxygen, resting dyspnea and HRQL, changed differently over time in the two groups in favor of NIV + LTOT. Hospital admissions were not different between groups during the follow-up. Nevertheless, overall hospital admissions showed a different trend to change in the NIV + LTOT (decreasing by 45%) as compared with the LTOT group (increasing by 27%) when comparing the follow-up with the follow-back periods. ICU stay decreased over time by 75% and 20% in the NIV + LTOT and LTOT groups, respectively. Survival was similar. Compared with long-term oxygen therapy alone, the addition of noninvasive positive-pressure ventilation (NPPV) to long-term oxygen therapy in stable COPD patients with chronic ventilatory failure slightly decreased the trend to CO_2 retention in patients receiving oxygen at home and improved dyspnea and HRQL (Clini et al 2002).

NIV was deemed to be adequate when the $PaCO_2$ was reduced by 5% during wakefulness. We think this reduction in CO_2 during NIV when awake is very modest. The changes in diurnal $PaCO_2$ were small and it remains to be seen whether more aggressive ventilation would have resulted in a bigger change in this and other end points. The average IPAP was 14 ± 3 cm and EPAP 2 ± 1 cm H_2O, suggesting that there was room to increase the pressures, at least to levels closer to those seen in the study of Meecham-Jones et al (1995). End-expiratory pressure must be set to prevent rebreathing, to maintain alveoli open in patients with very low residual functional capacity and, particularly, in patients with COPD, to counterbalance intrinsic positive end-expiratory pressure. A low expiratory positive airway pressure (EPAP) could be responsible of certain degree of rebreathing and higher $PaCO_2$ levels.

The fact that the effectiveness of ventilation during sleep was not confirmed is an important limitation of the study and it is possible that there was in fact no change in $PaCO_2$ overnight, given that the pressures used were comparable with those used in the study of Lin (1996), in which no effect of NIV was seen upon sleep hypoventilation. If this is correct the question arises as to why patients reported less dyspnea and an improved quality of life.

Firstly, this could have been a placebo effect, as was seen in the study of Gay et al (1996). A significant placebo effect has been seen with sham CPAP and the placebo effect of a "breathing machine" should not be underestimated (Jenkinson et al 1999).

Secondly, exacerbations have been shown to have a detrimental effect upon quality of life in patients with COPD (Seemungal et al 1998). NIV offloads the respiratory muscles and reduces the sensation of dyspnea associated with an acute exacerbation at ventilator settings similar to those used in this study (Bott et al 1993; Appendini et al 1994; Plant et al 2000). It is possible that NIV therefore reduced the impact of exacerbations upon the patient; this may also have contributed to the trend towards reduced hospitalization. Compliance was considered to be acceptable if NIV use was greater than 5 hours per day on average; in fact the mean daily use in those who achieved this minimum was much higher at 9 ± 2 hours per day. This suggests that at least some patients were using the ventilator during wakefulness, which lends some support to this hypothesis. Further data suggesting that NIV may be important in reducing the impact of exacerbations come from a small case series (Tuggey et al 2003), in which domiciliary NIV both reduced the frequency of hospitalization and was also economically advantageous. Patients who have received NIV in hospital for an acute exacerbation of COPD are at high risk for re-admission and death in the following year (Conti et al 2002;

Chu et al 2004) and may be a particularly important group to target for chronic domiciliary NIV, though this needs to be evaluated in a prospective controlled trial (Elliot 2004).

Thirdly, no data are given about input from health care givers; this may affect quality of life and dyspnea (Cockcroft et al 1987). It is possible that patients receiving NIV, which requires considerable staff input at least initially, had greater contact with medical and paramedical staff than those on LTOT alone.

Two final studies opening new research areas merit discussion (Schonhofer et al 1997; Díaz et al 2002). Schonhofer et al (1997) have shown that NIV can be equally effective when administered during the day or overnight during sleep. In this sense, Díaz et al (2002) have also shown that NIV administered during the day for 3 hours per day for 5 days in the week during wakefulness can improve arterial blood gases. This suggests that even relatively short periods of NIV can produce useful benefit and for some patients, particularly those who cannot sleep with NIV this may be an attractive option. The "dose" of effective NIV may be relatively small. The primary aim of both of these studies was to investigate the mechanism by which NIV brings about improvement. There is no clear answer to this question but it is likely to be multifactorial, with different factors being more important in some patients than others. In this sense, respiratory muscle rest, restoration of chemosensitivity, improved compliance of the chest wall and lungs, improved sleep quality, and reduced respiratory system load would be factors to take into account.

Identifying COPD patients to NIV

So where do things now stand with regard to NIV in stable COPD? On the basis of the available studies, NIV should not be used as a treatment of choice for all patients with COPD, even when disease is severe (see Table 4). However, there is more evidence that NIV has an important effect in these patients. In fact, a selected group of patients may well benefit from domiciliary mechanical ventilation, and we need to be able to identify who they are. Patients must have sustained hypercapnia, and control of nocturnal hypoventilation with NIV must be confirmed. A NIV trial should be initiated as an inpatient and patients should be motivated to comply with therapy and willing to be trained. The effect of NIV upon exacerbations and the amount of input from medical and paramedical staff should be quantified. Survival must be included as an end-point, but quality, rather than prolongation, of life at any cost is more important to most patients with severe disability due to chronic disease. Finally, a detailed economic evaluation should be included. Such patients should be enrolled by researchers carrying out the next wave of randomized, controlled trials if we are to answer the question of whether to administer ventilation to patients with COPD.

Until such a study is completed a trial of NPPV is recommended by the British Thoracic Society (BTS 2002) for COPD patients needing more than 7 days of NIV in the acute setting, for patients with severe hypercapnia even after adequate oxygenation, or for those who have been hospitalized 3 or more times in 1 year with hypercapnic respiratory failure. The 1999 Consensus Conference (Consensus Conference 1999), on the other hand, suggested that nocturnal ventilation be prescribed when $PaCO_2$ is greater than 55 mmHg in the presence of hypoventilation symptoms. If $PaCO_2$ falls to between 50 and 55 mmHg, the consensus was to recommend starting NIV if the patient had nocturnal desaturation defined as a pulse oximeter reading of less than 88% for longer than 5 consecutive minutes in spite of receiving oxygen at 2 L/min. Finally, along the lines of the BTS recommendations, night-time ventilatory support was considered appropriate for COPD patients with $PaCO_2$ between 50 and 55 mmHg who had been hospitalized with hypercapnic respiratory insufficiency at least twice in 1 year. Moreover, the Consensus Conference suggested also overlap syndrome as an indication of NIV in COPD patients. From a clinical perspective, the absence of clearly defined indications means that the use of NIV in stable COPD patients with hypercapnia tends to differ considerably from one group prescribing these techniques to another.

Finally, we would like to consider two new aspects of great interest concerning NIV in COPD patients. As we have seen before, perhaps the technique of NIV application might

Table 4 Relative contraindications to long-term noninvasive ventilation for COPD patients

Severe comorbidity that is likely to shorten survival more than lung disease (end-stage malignancy, liver disease). Congestive heart failure may respond favorably
Unmotivated patient
Nonadherence to oxygen or medical therapy
Cognitive impairment that interferes with patient's ability to understand therapy
Insufficient financial resources
Insufficient caregiver resources
Unable to tolerate or fit mask, claustrophobic patient

be a major factor determining success of NIV treatment in patients with stable COPD. All published, randomized, controlled trials used either inspiratory pressures from 10 to 18 cm H_2O or/and a spontaneous mode of ventilatory support for NIV that achieved only modest reductions in $PaCO_2$ (Meecham-Jones et al 1995). There is increasing concern that inspiratory pressures of < 18 cm H_2O might have been insufficient to reduce the $PaCO_2$ sufficiently during spontaneous breathing in order to provide a clinical benefit for the patient (Elliot 2002; Windisch et al 2002). However, there is increasing evidence that chronic hypercapnia is a poor prognostic sign in patients with COPD. In addition, long-term survivors of patients with chronic respiratory failure due to COPD have been shown to have higher reductions in mean $PaCO_2$ during the first 2 years following initiation of NIV (Leger et al 1994). Accordingly, indirect evidence supporting the hypothesis that more aggressive ventilation aimed at maximally decreasing $PaCO_2$ could provide beneficial effects for patients with stable hypercapnic COPD has been published (Leger et al 1994). Nevertheless, studies have not been undertaken to investigate this. Recently, controlled NIV using relatively high inspiratory pressures with a mean of 28 cm H_2O has been shown to significantly improve lung function and blood gas levels during spontaneous breathing in patients with stable hypercapnic COPD (Wendisch et al 2005). The high mean inspiratory pressure was well tolerated over a prolonged period by patients after careful adaptation to NIV in the hospital. These results suggests that further randomized controlled trials using NIV with higher inspiratory pressures are needed to verify the benefits of NPPV on outcome in these patients.

On the other hand, NIV has also been considered as a new strategy to improve exercise tolerance in COPD patients. It is known that NIV during exercise reduces dyspnea and work of breathing and enhances exercise tolerance in COPD patients. A systematic review identified 15 physiological studies dealing with use of NIV during exercise (van't Hul et al 2002). Seven of these studies met the inclusion criteria, including a total of 65 patients with COPD. The methodological quality of the included studies varied from 31%–54% of the maximum score of 13 points. Statistically significant summary effect sizes were found in the analysis of exertional dyspnea as well as in the analysis of exercise endurance, indicating improvements in these outcomes in favor of NIV. Nevertheless, the role of NIV in pulmonary rehabilitation is still to be defined.

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