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EDITORIAL

Noninvasive ventilation in chronic ventilatory failure due to chronic obstructive pulmonary disease

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Noninvasive ventilation (NIV) has been one of the major advances in respiratory medicine in the last decade. In particular, it has found widespread application in the management of patients with chronic obstructive pulmonary disease (COPD). There is a robust evidence base for its use in acute exacerbations of COPD, but the evidence that it is effective in chronic COPD is much less strong. Despite this, COPD is one of the most common reasons for long-term home mechanical ventilation.

Early experience was with negative pressure devices, usually used for short periods in hospital [1–4]. Studies were uncontrolled and with small numbers of patients, but did suggest possible benefits. The use of negative pressure devices at home and during sleep in patients with COPD has been largely unsuccessful [3, 5]. In two controlled trials, patients were generally unable to sleep during negative pressure ventilation, and most either failed to complete the protocol because of lack of improvement or discomfort associated with the use of the equipment [5], or did not wish to continue treatment after the study was completed [3]. Negative pressure devices are cumbersome and relatively inefficient, particularly when the impedance to inflation is high, and may not be able to provide adequate ventilation during sleep. They predispose to the development or accentuation of upper airway collapse [6], and this may be a particular problem during sleep in the obese patient with COPD.

In most studies of negative pressure ventilation in COPD, the primary focus of therapy was to rest respiratory muscles, which were thought to be in a state of chronic fatigue. Unfortunately, in the absence of any reliable test of respiratory muscle fatigue this approach remains speculative. In an attempt to definitively answer whether respiratory muscle fatigue exists in stable chronic COPD and whether respiratory muscle rest leads to any benefits, SHAPIRO *et al.* [7] randomised 184 patients (mean carbon dioxide (CO_2) tension in arterial blood (P_{a,CO_2}) of 5.8 kPa (44 mmHg)) to active or sham-negative pressure ventilation at home using a poncho wrap ventilator. Compliance with treatment was much less than anticipated and no significant difference was shown between the two groups. There was no relationship between the primary end-point, a 6-min walking test with the total duration of ventilation serving as an index of the "dose" of respiratory muscle rest actually delivered. SHAPIRO *et al.* [7] concluded that respiratory muscle fatigue did not exist and that little was to be gained by resting the respiratory muscles. However, the 6-min walking distance test is an unconventional measure of respiratory muscle fatigue and is affected by other factors. This study does not preclude the possibility of an important effect upon respiratory muscle function, but the main conclusion is that negative pressure ventilation at home is not feasible in most patients with COPD.

Noninvasive positive pressure ventilation (NPPV) is effective in patients with extra pulmonary restrictive disorders [8, 9], and a number of studies have shown that NPPV is feasible at home in patients with COPD [8–14]. During NPPV overnight abnormal physiology can be corrected, with improvements in gas exchange and sleep quality [11], as well as improved exercise capacity and diurnal arterial blood gas tensions [11, 13]. Use of healthcare resources may also be reduced [14], and quality of life [15] and functional score [16] improved.

In contrast to negative pressure ventilation, NPPV is usually delivered during sleep. There have been few controlled trials, those of which used small numbers of patients followed over a short period of time [17–20]. Only one study showed any benefit from the combination of NPPV and long-term oxygen therapy (LTOT) [19], with the others failing to show any advantage to using NPPV. There are a number of possible explanations for this. Firstly, there were differences in the way in which patients were acclimatised to NPPV. In the study of STRUMPF *et al.* [17], acclimatisation was performed as an outpatient, but with regular visits from a respiratory therapist. Many patients do not find NPPV easy initially, and in uncontrolled studies, a higher success rate was achieved when patients started NPPV in hospital under close supervision [10, 12, 21, 22]. In the study of LIN [18], patients only received NPPV for 2 weeks. Practical experience with both NPPV and continuous positive airway pressure (CPAP) suggests that some patients require several weeks of acclimatisation before they are comfortable, and confident, with the delivery of ventilatory support during sleep. CRINER *et al.* [16] observed that comprehensive follow-up and support was necessary for all patients on home ventilation programmes. Secondly, the patients in the studies of

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STRUMPF *et al.* [17] and LIN [18] were not particularly hypercapnic (mean P_{a,CO_2} of 6.1 kPa (46 mmHg) and 6.7 kPa (50.5 mmHg), respectively), whereas those in the study of MEECHAM JONES *et al.* [19] had a mean P_{a,CO_2} of 7.4 kPa (55.8 mmHg). In studies using negative pressure devices, where benefit has been seen, it has usually been in those with daytime hypercapnia [2–4, 23, 24]. Thirdly, there were differences in the type and settings of the ventilators. MEECHAM JONES *et al.* [19] used pressure support ventilation with a mean inspiratory positive airway pressure (IPAP) of 18 cmH_2O. STRUMPF *et al.* [17] used a timed mode because it is more likely to reduce inspiratory muscle effort than patient-initiated ventilation, but noted that ~25% of the night was spent with the patient breathing out of synchrony with the ventilator. With both positive and negative pressure devices, asynchrony between the patient and ventilator may cause worsening of gas exchange.

It is important to confirm that effective ventilation has been delivered before it can be concluded that NPPV has no effect. In the study of STRUMPF *et al.* [17], CO_2 control during sleep was assessed on the basis of spot measurements of end-tidal carbon dioxide ($ETCO_2$). This may have missed periods of hypoventilation, for instance those associated with asynchrony; in addition, $ETCO_2$ is an unreliable measure of P_{a,CO_2} in patients with severe airways obstruction. In the study of LIN [18], no data were given about the effect of NPPV on blood gas tensions during ventilation, and there was no statistically significant improvement in sleep hypoventilation with NPPV. In the study of GAY *et al.* [20], CO_2 tensions were not measured and there was no change in mean or nadir arterial oxygen saturation during overnight polysomnography, which suggests that nocturnal hypoventilation was not controlled. By contrast, MEECHAM JONES *et al.* [19] showed a reduction in transcutaneous CO_2 tension during sleep, and this correlated with the improvement in daytime P_{a,CO_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. Therefore, a therapeutic effect with NPPV cannot be excluded. It may also be significant that MEECHAM JONES *et al.* [19] used higher inflation pressures (mean IPAP of 18 cmH_2O) than the other studies. GAY *et al.* [20] were the only group to compare active NPPV with sham, and importantly, two patients in the sham group reported that their breathing improved despite unchanged results of the objective measures, thus suggesting a significant placebo effect.

In a 1-yr controlled trial, CASANOVA *et al.* [25] randomised 52 patients with severe stable COPD to either NPPV 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. The level of support was modest (mean IPAP of 12 ± 2 cmH_2O). 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 NPPV group (5% *versus* 15%, $p<0.05$), but this difference was not seen at 6 months (18% *versus* 19%, respectively). There was either little or no difference between the groups in dyspnoea scales, gas exchange, haematocrit, pulmonary function, cardiac function and neuropsychological performance. However, the number of patients was too small to avoid a type II error and the period of follow-up was too short to fully evaluate the effect upon outcome.

In summary, the negative pressure studies, largely targeted at reducing respiratory muscle effort and relieving hypothetical muscle fatigue, showed that negative pressure ventilation during sleep was poorly tolerated. When it could be instituted, it did not result in any benefit, except in a small number of hypercapnic patients. The question about the importance of respiratory muscle fatigue remains unanswered because it is likely that offloading of the respiratory muscles was less than ideal [4, 7]. Positive pressure ventilation is better tolerated, but a significant proportion of patients still struggle with the technique, although it should be appreciated that there have been significant improvements in the technology, particularly interfaces, since these early studies. In the only positive study [19], patients who were significantly hypercapnic (mean P_{a,CO_2} of 7.4 kPa (55.8 mmHg)), were acclimatised to NPPV as inpatients, and had a documented improvement in nocturnal hypoventilation; this was achieved with higher levels of inspiratory pressure support (mean IPAP of 18 cmH_2O).

Case series of patients with COPD [8, 9] suggest survival comparable to that seen in the oxygen-treated patients in the Medical Research Council and Nocturnal Oxygen Therapy Trial group studies [26, 27]. Although direct comparison cannot be made with historical controls from 20 yrs ago, it is important to note that the patients with COPD selected for home ventilation were often those who had "failed" (not rigorously defined) on oxygen therapy and were usually hypercapnic. Hypercapnia is a poor prognostic sign in COPD [28, 29] and is a marker for a lack of benefit from oxygen therapy [26]. However, a study from Japan of 4,552 patients with obstructive lung disease did not show any difference in outcome between patients with hypercapnia and those who were normocapnic [30]. Indeed, hypercapnic patients who had had a thoracoplasty had a better prognosis than those who were normocapnic. It is therefore possible that the patients with a better prognosis are being selected for home NPPV.

In this issue of the *European Respiratory Journal*, CLINI *et al.* [31] report the first prospective, randomised controlled trial of NPPV in chronic stable COPD patients, with a significant number of patients followed for a reasonable period of time. One hundred and twenty-two patients with stable chronic hypercapnia who had been on LTOT for $\geqslant 6$ months were considered and 90 were randomised to continuing LTOT or LTOT and NPPV. Compliance with LTOT was excellent, and amongst NPPV patients, the mean night-time use of 9 h compares favourably with reported use in other studies. There were small improvements in the NPPV group (in resting P_{a,CO_2},

dyspnoea and health-related quality of life), but no improvement in survival or hospital stay. There was, however, a trend towards less time in hospital in the NPPV group compared to an increase in the LTOT group, when compared with the period before the study. Intensive care unit stay was reduced in both groups, but more so in the NPPV than in the LTOT group.

NPPV was deemed to be adequate when the P_{a,CO_2} was reduced by 5% during wakefulness; this reduction in CO_2 during NPPV when awake is very modest. The changes in diurnal P_{a,CO_2}, which was the primary end-point that informed the power calculation, 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 cmH_2O and expiratory positive airway pressure 2 ± 1 cmH_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.* [19]. 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 P_{a,CO_2} overnight, given that the pressures used were comparable to those used in the study of LIN [18], in which no effect of NPPV was seen upon sleep hypoventilation. If this is correct, the question arises as to why patients reported less dyspnoea and an improved quality of life. First, this could have been a placebo effect, as was seen in the study of GAY *et al.* [20]. A significant placebo effect has been seen with sham CPAP [32] and therefore the placebo effect of a "breathing machine" should not be underestimated. Secondly, exacerbations have been shown to have a detrimental effect upon quality of life [33] in patients with COPD. NPPV offloads the respiratory muscles [34] and reduces the sensation of dyspnoea [35, 36] associated with an acute exacerbation at ventilator settings similar to those used in the study of CLINI *et al.* [31]. Therefore, it is possible that NPPV reduced the impact of exacerbations upon the patient; this may also have contributed to the trend towards reduced hospitalisation. Compliance was considered to be acceptable if NPPV use was >5 h·day^{-1} on average; in fact, the mean daily use in those who achieved this minimum was much higher at 9 ± 2 h·day^{-1}. This suggests that at least some patients were using the ventilator during wakefulness, which lends some support to this hypothesis. Thirdly, no data are given about input from healthcare givers; this may impact upon quality of life and dyspnoea [37]. It is possible that patients receiving NPPV, which requires considerable staff input at least initially, had greater contact with medical and paramedical staff than those on LTOT alone.

So, where do things now stand with regard to NPPV in stable COPD? On the basis of the CLINI *et al.* [31] study, the widespread use of NPPV for this patient group cannot be advocated. It does, however, strongly suggest (more than previous studies) that NPPV has an important effect in these patients. In addition, it paves the way for, and helps to inform the design of a definitive study of NPPV in patients with chronic ventilatory failure due to COPD. Patients must have sustained hypercapnia, and control of nocturnal hypoventilation with NPPV must be confirmed. NPPV is probably best initiated as an inpatient. The effect of NPPV upon exacerbations and the amount of input from medical and paramedical staff should be quantified. Ideally, there should be a sham limb, but this would greatly escalate the cost of the study and there are important concerns about the safety of providing inadequate ventilation. The use of a placebo is probably not practical. 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, as this will be of major interest to those who pay for healthcare; severe chronic obstructive pulmonary disease is a major financial burden [29, 38]. Until such a study is completed, 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, even with careful administration using Venturi masks or a low-flow meter. 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 [39].

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