

## **EDITORIAL**

# **The changing role of mechanical ventilation in COPD**

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For many years, mechanical ventilation has been employed in patients with chronic obstructive pulmonary disease (COPD) but the recent development of noninvasive techniques, particularly nasal and face mask ventilation, have considerably increased its use. The enthusiasm for these methods, however, has not been matched by the results from well-constructed studies, and the role of ventilatory support both in acute and chronic respiratory failure is still not settled.

### **Acute respiratory failure**

The steadily increasing number of publications on the use of noninvasive ventilation in acute infective exacerbations of COPD are hard to evaluate for several reasons. Firstly, most of the studies are uncontrolled or use historical or other unsatisfactory control groups. The definition of an infective exacerbation and its severity also varies considerably between the studies. Some studies compare the results of ventilation against "standard" medical treatment but this is frequently unspecified and, where details are given, oxygen appears to have been provided in flow rates sufficiently high to risk precipitating hypercapnia. Lastly, the criteria for the success or failure of noninvasive ventilation, such as the need for intubation, differ between studies.

Series published before the use of noninvasive ventilation indicated that the intubation rate was around 25% for hospitalized COPD patients with an acute infective exacerbation [1, 2]. Their survival to discharge from hospital was around 60–75%, and at 1 year was around 50% and 2 years around 35% [3–6]. The major areas of interest with noninvasive techniques have been to show whether they can adequately ventilate these patients, reduce the intubation rate and improve survival. Approximately 60–80% of patients tolerate both positive pressure ventilation by face or nasal mask [7, 8] and negative pressure ventilation [9]. With mask ventilation, the arterial blood gases can usually be improved within 1–2 h, especially if the initial arterial carbon dioxide tension ( $P_{a,CO_2}$ ) is raised [10–16], although in a controlled study there was no difference in the blood gases between the ventilated and nonventilated patients [17]. Early studies with negative pressure ventilation also showed that ventilation could be adequately supported [18–22], and these findings have been confirmed in subsequent uncontrolled studies [9, 23–25]. The mechanisms by which noninvasive ventilation achieves these effects have not been established.

It can reduce respiratory muscle activity [26] and increase maximum inspiratory pressures [9, 24], but whether these or any changes in respiratory drive or mechanics are clinically significant is still uncertain.

There are few data regarding the ability of negative pressure systems to avoid or delay intubation, but this question has been addressed in several reports of mask ventilation. Three series using historical controls suggested that the intubation rate could be reduced [27–29]. The results of a fourth are published in this edition of the Journal [30]. Patients were matched with a control group of 24 subjects selected from 72 who had been admitted during the previous 2 yrs. The matching criteria were age and  $P_{a,CO_2}$ , pH and Acute Physiology and Chronic Health Evaluation (APACHE) score on admission. The intubation rate was significantly less in the nasal ventilation group than in the historical controls (8 *versus* 38%), although the arterial oxygen tension ( $P_{a,O_2}$ ) and  $P_{a,CO_2}$  at discharge were similar in the two groups.

Two randomized, controlled studies have also investigated this problem. In one [31], only 9% of the patients treated by nasal ventilation required intubation, compared with 67% in the control group. The patients in this series were, however, highly selected from those that were eligible for the study and the high intubation rate in the control group also suggests that there may have been a bias in the patient's studied. No details about the inspired oxygen concentration or flow rate in the control group were given and it is possible that this precipitated the need for intubation in some of the patients. In the second study [32], 85 patients were randomized either to face mask ventilation or standard treatment, but the subjects were a selected group from the 275 who were eligible for the study. The most severely ill patients, for instance, were intubated initially and excluded from the study. This was also marred by the provision of up to 5 L·min<sup>-1</sup> of oxygen in the standard treatment group in order to maintain the oxygen saturation above 90%. This almost certainly precipitated hypercapnia in some patients and, thereby, increased the intubation rate, which was as high as 74%. Intubation was required in only 26% of the group with face mask ventilation, which presumably protected many of these patients from oxygen-induced hypercapnia.

The results of all the controlled and uncontrolled studies suggest that face and nasal mask ventilation is associated with an intubation rate of 10–30%, which is similar to the 25% recorded in the pre-mask ventilation era. This overall lack of detectable effect could be the result of mixing patients of different severities of respiratory failure

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in the series. Those with a severe acute illness, particularly if they are unconscious or have profuse secretions and a poor cough, would usually require intubation whether or not they are treated noninvasively initially, and those with a mild acute illness, whilst often tolerating mask ventilation [33], would avoid intubation whether or not they are ventilated noninvasively. The potential benefit of the new techniques is probably in the group of intermediate severity, where a mask or negative pressure system may adequately support ventilation until either the patient has improved clinically or clinical data, necessary to assist the decision whether or not to intubate, has been collected from sources such as relatives.

The survival rates using nasal ventilation have been the subject of three controlled studies. In two there was no difference between the mortality of the control and treated group [31, 32]. The other [34] was carried out in three centres, but patients with only mild respiratory failure ( $P_{a,CO_2}$  greater than 6 kPa and with only a mild acidosis) were entered. There was no difference in blood gases at 1 h after treatment or in the survival at 30 days between the ventilation and control groups on an "intention to treat" basis. The high (30%) mortality in the conventionally treated group was ascribed to differences between the individual centres but may also have been related to the low intubation rate. There are no controlled series using negative pressure ventilation but in two reports of a large series of patients with severe acute respiratory failure [25, 35] the survival rate using tank ventilation ("iron lung") was as high as 90%.

The provision of adequate ventilatory support whether noninvasively or with intubation should prevent death due to hypoxia, hypercapnia or acute respiratory acidosis but these are not the only causes of mortality in this group of patients. This also depends on the age, the overall performance status before the acute illness, the severity and duration of the infection, its response to treatment and any complications from the treatment. Noninvasive ventilation would only be expected to show a survival advantage over intubation if it either provides better respiratory support or is associated with fewer potentially fatal complications. Intubation usually requires sedation and immobilization, which increase the risk, for instance, of pneumonias and pulmonary emboli, but the chance of these complications may not nowadays be sufficiently large for any difference in survival rates to be apparent in studies of the size that have been carried out. Larger studies or those focusing on high risk patients, such as those who require prolonged ventilatory support because of difficulties in weaning, might show a survival difference.

The report in this edition of the Journal [30] found a higher survival rate at 6 and 12 months in patients who had received nasal ventilation during an episode of acute respiratory failure, even though the treatment after discharge from hospital was similar in the two groups. Whilst this could have been due to some, as yet unidentified, long-term benefit from short-term ventilatory support, it is more likely to reflect imperfect matching of the control and patient groups. Only the patient's age and

markers of the severity of the acute illness were taken into account, whilst other determinants of long-term survival, such as the severity and progression of their air-flow obstruction, were not allowed for.

Even if there is no survival advantage to using noninvasive ventilation, there could be a financial advantage in avoiding the need for transfer to an Intensive Care Unit if intubation is not required. However, in the one report which has studied this [31], no difference in hospital charges was found and the use of face and nasal masks did not appear to reduce the length of hospital stay [31, 34], although this was documented in the study reported in this edition of the Journal [30]. The length of stay is determined mainly by the speed of resolution of the acute illness, this being independent of whether noninvasive or invasive ventilation is provided. Nasal ventilation has also been tried as an assistance in the weaning process of patients who require prolonged tracheostomy ventilation, but the results are inconclusive [36, 37]. This is hardly surprising, since the ability to provide partial and intermittent ventilatory support, whilst important, is only one element in the overall programme of care that is required to overcome weaning difficulties [38].

The data that are available do not allow firm recommendations to be made about the best techniques for ventilating these patients. Many subjects develop substantial leaks through the mouth when a nasal mask is used and require a face mask which encloses the mouth as well as the nose, despite its greater dead space. Of the negative pressure methods, tank ventilation appears to be more effective than the cuirass or jacket [39]. There are no adequate studies comparing positive and negative pressure systems and any differences between them may relate more to the sophistication of the ventilators than to whether positive or negative pressure is applied. All the negative pressure ventilators work in the controlled mode as pressure preset ventilators, whereas the positive pressure systems have a wider range of modes. No clear difference in the effectiveness of volume and pressure preset ventilation is apparent from the large number of uncontrolled studies or from two reports looking specifically at this question [28, 40]. Use of positive expiratory pressure might be expected to reduce the work of triggering by overcoming intrinsic positive end-expiratory pressure (PEEP) and to be of benefit in those patients with obstructive sleep apnoeas. However, there is no evidence to support its routine use, especially since it may lead to hyperinflation and a fall in cardiac output. The expiratory flow limitation and instability of the respiratory pattern in COPD both during wakefulness and sleep, and particularly during acute infective exacerbations, require close attention to the details of the ventilator settings.

Regarding the duration of noninvasive ventilation, most studies have employed it for around 6 h-day<sup>-1</sup> for 1–7 days, but it is not known whether this is optimal or what should determine the length of treatment. It would seem reasonable to continue until the  $P_{a,CO_2}$  has been normalized for about 24 h and until conventional medical treatment has begun to improve the underlying infection, but further studies are required.

### Chronic respiratory failure

The physiological changes during noninvasive ventilation in chronic stable COPD have been well-demonstrated but their clinical significance is uncertain. Nasal ventilation can improve the blood gases whilst patients are awake [41–43] and asleep [41, 44, 45], although two controlled studies have not shown any change [46, 47]. Controlled [48] and uncontrolled [49–52] studies with negative pressure ventilation have also demonstrated an improvement in blood gases during wakefulness.

The mechanisms by which the blood gases alter have not been established but are probably multifactorial. No increase in respiratory drive has been found [44] but this might improve either by relief of sleep deprivation or through a reduction in the cerebrospinal fluid bicarbonate concentration, which would increase the carbon dioxide sensitivity. Ventilatory support might also improve respiratory mechanics. It could alter the chest wall mobility and, thereby, increase its compliance. It could also increase lung compliance either by recruiting previously collapsed alveoli or by reducing lung water. There is no evidence for either of these, however, and the lack of improvement in spirometry [41] argues against these mechanisms being clinically significant.

The role of ventilation in improving respiratory muscle strength has been extensively investigated. Although no effect on maximal inspiratory and expiratory mouth pressures has been seen in prolonged studies [46, 47, 53, 54], an improvement in these pressures or a reduction of diaphragmatic electromyographic (EMG) activity has, with one exception [55], been documented in short-term studies with negative pressure systems [48, 49, 56–61], as well as a reduction in diaphragmatic activity with nasal ventilation [62]. The small changes in maximal mouth pressures may, however, have been due to alteration in the configuration of the chest wall or the length of the muscles rather than any change in the contractile properties of the muscles themselves.

The significance of any changes in respiratory muscle function is uncertain, particularly since respiratory muscle endurance appears to be only slightly increased if at all [47, 63]. The question of whether chronic respiratory muscle fatigue was present and might be relieved by negative pressure ventilation was examined in the large Montreal study but this did not prove decisive because of problems with its design [64]. Firstly, the criterion for assessing the adequacy of ventilation was taken as a reduction of peak diaphragmatic EMG of more than 50% but this was not validated in any way. The main outcome criterion was a change in the 6 min walking distance, which is, at best, only indirectly related to any change in respiratory muscle fatigue. Lastly, the patients only used the treatment for a mean of 2.5 h·day<sup>-1</sup> and this was mainly while they were awake rather than asleep. The negative finding of this study does not, therefore, provide evidence either way concerning the role or relief of respiratory muscle fatigue.

It is hard to predict on theoretical grounds what effect these physiological changes might have on the survival of patients with chronic stable COPD, since the causes

of death other than during an acute infective exacerbation have not been well identified. A poor prognosis is associated with severe and rapidly progressing airflow obstruction [65, 66] but this is probably unaffected by ventilatory support. It is the patients whose  $P_{a,CO_2}$  is persistently elevated without any acute exacerbation, and those in whom it remains elevated after an acute exacerbation (60%) [67], who are least likely to tolerate long-term oxygen treatment without worsening of hypercapnia. In these subjects, domiciliary ventilatory support needs to be considered in order to relieve symptoms and complications, and to improve the prognosis.

Two large series have examined long-term survival in COPD using tracheostomy ventilation. The first [68] reviewed 50 subjects treated with 11–17 h ventilation per day, but little blood gas and no sleep study data are available to evaluate its efficacy. The survival rates were 88, 72, 54, 34 and 18% at 1–5 yrs, respectively. Slightly better results have been reported recently [69] in an Association Nationale pour le Traitement a Domicile de l'Insuffisance Respiratoire (ANTADIR) multicentre French trial, which included 259 patients, although 24% of these did not require any ventilation through their tracheostomy. The majority of these were also receiving long-term oxygen therapy (LTOT). The 2, 3, 5 and 10 year survival rates were 70, 60, 44 and 20%, respectively, for the whole series but only 56, 41 and 22% at 3, 5 and 10 yrs, respectively, for the ventilated patients. A better prognosis was associated with an age of less than 65 yrs, use of an uncuffed tracheostomy tube and  $P_{a,O_2}$  greater than 7.3 kPa (55 mmHg) 3 months after the tracheostomy was performed.

A recent study of 33 COPD patients using nasal ventilation, some of whom also received oxygen treatment, showed the 1, 3 and 5 year probabilities of still using nasal intermittent positive pressure ventilation (NIPPV) to be approximately 85, 75 and 43, respectively [70]. At 1 year, the  $P_{a,O_2}$  had risen by 0.8 kPa and the  $P_{a,CO_2}$  had fallen by 1.9 kPa. The results of this study and the two tracheostomy studies do not show any significant differences from those of the Nocturnal Oxygen Therapy Trial (NOTT) and Medical Research Council (MRC) trial of long-term oxygen therapy using 12–24 h of oxygen per day [71, 72]. Accurate comparisons between the studies are impossible, however, since it is not known whether the patients were started on oxygen and mechanical ventilation at a similar stage in their natural history and none of the studies controlled for smoking, which may be a more important factor affecting survival than either of the treatments.

The lack of difference between the survival rates has led to the use of the combination of nasal ventilation and oxygen. A randomized controlled study [73] showed that the daytime  $P_{a,O_2}$  and  $P_{a,CO_2}$  and night-time  $P_{a,CO_2}$  were improved with bi-level pressure support plus oxygen, compared with oxygen alone but, unfortunately, the oxygen was given at a standard rate of 2 L·min<sup>-1</sup> and not individually optimized. The  $P_{a,CO_2}$  in the oxygen only group may, therefore, have been iatrogenically raised, so that this study does not show whether ventilation with oxygen is any better than no treatment alone. In

addition, patients with more than five apnoeas-h<sup>-1</sup> were excluded from the study because of lack of a back-up rate on the ventilator. In a separate study of 50 COPD patients [74], who all received long-term oxygen as well as nasal ventilation, approximately 70% were still using the ventilator at 1 yr and 56% at 2 yrs. The only physiological change was a reduction in the  $P_{a,CO_2}$  at 1 and 2 yrs. These figures, which approximate to the survival rate, are not significantly different from the large studies of ventilation without oxygen or the NOTT and MRC LTOT series.

There results suggest that either mechanical ventilation provides very little, if any, survival advantage or that it only improves the prognosis in a subgroup of COPD patients and that death in the other is related to changes, such as progression of airflow obstruction or cardiac dysfunction, which are not improved by mechanical ventilation. More selective use of ventilation in patients with hypoxia- or hypercapnia-related complications, or in those who are at risk of developing these, might prove more effective. It would also seem prudent to give supplemental oxygen to those in whom hypoxia persists despite normalization of the  $P_{a,CO_2}$  with ventilation. It is not known whether pressure preset ventilation might be more effective than volume preset ventilation used in the assist-control mode as in most of the large studies [70, 74]. A single short-term study during wakefulness did not show any significant differences between the two techniques [43].

A separate indication for long-term ventilation is to try to improve the quality of life, or reduce the symptoms in patients with COPD. No improvement in exercise ability was found in the only controlled study to examine this [46], although these patients did show an improvement in neuropsychiatric function. There are few other quality of life data available. In one study, patients with nasal ventilation had a reasonable quality of life but no measurements were made before treatment to examine its effect [70]. In another report, there was no overall change in quality of life when nasal ventilation was compared with LTOT, but symptom relief was improved [73]. Ventilation might not be expected to significantly alter, for instance, exertional breathlessness, which is more closely related to the severity of airflow obstruction, but it could improve symptoms that result primarily from sleep disruption due to respiratory problems. The total sleep time and the sleep efficiency are improved with nasal ventilation, although sleep architecture and the number of arousals are unchanged, both without [44] and with [73] added oxygen. Further studies of quality of life looking both at the benefits and the intrusiveness of the ventilator are required. Compliance with long-term ventilation is likely to be poor even if it improves ventilation, unless it results in symptomatic benefit or an overall improvement in the quality of life [53].

### The future

The evidence regarding the use of ventilatory support that is available suggests that it should be used selectively both during acute infective exacerbations and in

the chronic stable phase of chronic obstructive pulmonary disease. Its indications should be guided by an understanding of the possible mechanisms by which it might work. In the acute situation, for instance, it is likely to provide most benefit in patients of intermediate severity and those who are able to tolerate either a mask or tank ventilator, whereas in the stable patient it should be targeted at those whose symptoms, quality of life, complications or prognosis are related to hypoxia, hypercapnia or to sleep disruption, and in whom maximum medical treatment has already been instituted. If hypoxia cannot be corrected by ventilation alone, despite the arterial carbon dioxide tension being normal, supplemental oxygen should be considered.

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