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SERIES "NONINVASIVE VENTILATION IN ACUTE AND CHRONIC RESPIRATORY FAILURE"
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Noninvasive ventilation for acute respiratory failure

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ABSTRACT: Noninvasive ventilation (NIV) has emerged as a significant advance in the management of respiratory failure. There is now a wide body of prospective randomized-controlled trial data to support its use, particularly in the management of patients with acute or respiratory failure due to exacerbations of chronic obstructive pulmonary disease (COPD). Its successful application results in a more rapid resolution of the physiological derangements, reduces the need for intubation and, in larger studies, improves survival. A reduction in the number of infectious complications is a particular advantage.

In patients with acute exacerbations of COPD there is evidence of benefit when NIV is introduced earlier in the course of the illness than would be the case for invasive ventilation and it should now be considered even with mild acidosis (pH<7.35) and tachypnoea (respiratory rate >23 breaths·min^{-1}) after initial medical therapy.

There is less clinical-trial data in patients with hypoxaemic respiratory failure, but again as with COPD those with less severe physiological disturbance are more likely to benefit. By contrast noninvasive continuous positive airways pressure, while being widely used has not been shown to reduce the need for intubation or to improve survival in patients with hypoxaemic respiratory failure, with the exception of acute cardiogenic pulmonary oedema.

Noninvasive ventilation has been a real advance in the treatment of the critically ill. Most of the studies published to date, have excluded patients needing immediate intubation and it should be viewed as a complimentary technique rather than an alternative to invasive ventilation. It is best viewed as a means of preventing the need for endotracheal intubation and as a result should be introduced earlier than would be the case for invasive ventilation.

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Noninvasive ventilation (NIV) has emerged as a new and important tool in the treatment of acute respiratory failure (ARF). It can reduce substantially the need for endotracheal intubation and mechanical ventilation (MV) in a number of conditions. It can reduce the incidence of complications associated with MV and stay in the intensive care unit (ICU), the hospital length of stay and mortality in selected patients. Patients with hypercapnic forms of ARF are more likely to benefit from NIV, but it may also benefit selected patients with hypoxic respiratory failure. This article reviews the evidence for the use of NIV in acute and chronic respiratory failure.

Patients with acute exacerbations of chronic obstructive pulmonary disease

NIV in the hospital setting was first used in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and it is in this group of patients that there is the most prospective randomized-controlled trial data (table 1). Acute exacerbation of COPD is a frequent cause of hospital and ICU admission. During these episodes, major deterioration in gas exchange accompany a clinical worsening, characterized by a rapid and shallow breathing pattern, dyspnoea, right ventricular failure and encephalopathy. The pathophysiological pathway involves the inability of the respiratory system to maintain adequate alveolar ventilation in the presence of major abnormalities in respiratory mechanics. This can be modified by the use of NIV, which allows the patient to take deeper breaths with less effort. A pressure-targeted mode of ventilation is frequently used, delivering a constant positive pressure in synchrony with the patient's inspiratory effort, and maintaining atmospheric pressure during expiration or a low positive end-expiratory pressure. The ability of these modes to improve the volume of gas delivered to the lung explains how NIV may improve gas exchange and decrease the effort needed to

Table 1. – Prospective randomized controlled trials of noninvasive ventilation (NIV) in patients with chronic obstructive pulmonary disease (COPD)

[Ref. no.]	Disease n	Setting	Baseline data pH or $P_{a,O_2}/F_{i,O_2}$	ETI or "surrogate"	Mortality	Mode plus settings cmH_2O Use on day 1
[1]	COPD 60	Ward	7.35	0/30 *vs* 5/30	3/30 *vs* 9/30	VCV Use 7.63 h on day 1
[2]	COPD 85	ICU	7.28 *vs* 7.27	11/43 *vs* 31/42*	4/43 *vs* 12/42*	PSV 20 Use $\geqslant$6 h·day^{-1}
[3]	Subgroup COPD 23	ICU	7.29 *vs* 7.27	9% *vs* 67%*		IPAP 11.3 EPAP 2.6 Use 20.1 h on day 1
[4]	COPD 24	Casualty Ward	7.33	0/12 *vs* 0/12	0/12 *vs* 0/12	IPAP 14.8 EPAP 5 Use 2×3 h·day^{-1}
[5]	COPD 17	Ward	7.31 *vs* 7.30	0/9 *vs* 5/8	0/9 *vs* 3/8	IPAP 14–18 cmH_2O
[6]	Subgroup COPD 6[#]	Casualty	7.35 *vs* 7.34			
[7]	COPD 30	ICU	7.27 *vs* 7.28	1/16 *vs* 6/15*	0/15 *vs* 1/15	PSV 15.4 Use mean of 26.7 h
[8]	COPD 30	Ward	7.36 *vs* 7.39	1/15 *vs* 2/15	0/15 *vs* 1/15	IPAP 13 EPAP 3
[9]	Subgroup COPD 23	ICU	7.27 *vs* 7.28 103 *vs* 110	25% *vs* 45% 5.26 *vs* 100 ICU days	8% *vs* 9%	IPAP 11 EPAP 5.7
[10]	COPD 236	Ward	7.32 *vs* 7.31	15% *vs* 27%*	10% *vs* 20%*	IPAP 10–20 EPAP 5 h Use median 8 h on day 1

P_{a,O_2}: oxygen tension in arterial blood; F_{i,O_2}: inspiratory oxygen fraction; ETI: endotracheal intubation; ICU: intensive care unit; VCV: volume cycled ventilators; PSV: pressure support ventilation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure. [#]: two NIV and four controls. *: $p<0.05$.

breathe, thus reversing the clinical abnormalities resulting from hypoxemia, hypercapnia and acidosis [11–13]. At baseline, the transdiaphragmatic pressure generated by these patients can be considerably higher than normal and represents a high percentage of their maximal diaphragmatic force, a situation posing high risk for respiratory muscle fatigue [11]. Negative pressure ventilation has also been used in a few centres where it may have a comparable efficacy to invasive ventilation in COPD patients [14, 15]. The cumbersome nature of the devices used, the fact that they are not widely available and the success of positive pressure ventilation mean that it is unlikely that the technique will become widely available.

There have been a number of studies that exclusively recruited patients with hypercapnic acute exacerbations of COPD and others with a more mixed population, which included patients with COPD [3, 6, 9], though not always hypercapnia [9]. The studies with a more heterogeneous study population were more difficult to interpret because of the differences in prognosis from ARF of different aetiologies. These studies are discussed in this section on COPD.

BROCHARD *et al.* [2] showed that NIV in patients with exacerbations of COPD in the ICU, reduced intubation and mortality rates compared to conventional medical therapy. NIV also improved pH, oxygen tension in arterial blood (P_{a,O_2}), respiratory rate and encephalopathy score at 1 h and was associated with a shorter hospital stay (23 days *versus* 35 days, p=0.005) and a lower complication rate (16% *versus* 48%, p=0.001). Most of the excess mortality and complications, particularly pneumonia, were attributed to endotracheal intubation (ETI). This data suggests that NIV may be superior to invasive mechanical ventilation (InMV), although this was a highly selected group of patients with the majority (70%) of potentially eligible patients excluded from the study for various reasons. In a smaller study (n=31) in two North American ICUs, KRAMER *et al.* [3] showed a marked reduction in intubation rate, particularly in the subgroup with COPD. However mortality, hospital stay and charges were unaffected. Those enrolled had a severe exacerbation, as evidenced by a mean pH of 7.28. In a further ICU study, CELIKEL *et al.* [7] showed a more rapid improvement in various physiological parameters, but there was no difference in intubation rate or survival. However, some patients randomized to standard therapy subsequently received NIV and there was a significant reduction in treatment failure rate, defined as the need for ventilatory support. At the time of failure all patients had a decrement in pH. MARTIN *et al.* [9], in a prospective randomized controlled trial comparing NIV with usual medical care in 61 patients, including 23 with COPD, showed, in common with other studies, that there was a significant reduction in intubation rate (6.4 *versus* 21.3 intubations·100 ICU days^{-1}, p=0.002). However there was no difference in mortality (2.4 *versus* 4.3 deaths·100 ICU days^{-1}, p=0.21). Although the intubation rate was lower in the COPD subgroup (5.3 *versus* 15.6 intubations·100 ICU days^{-1}, p=0.12) this did not reach statistical significance, possibly reflecting the small sample size. Three patients in the NIV group and one in the control group required ETI to maximize the safety of other procedures (*e.g.* bronchoscopy) and two patients in the NIV group required ETI because of haemodynamic compromise related to massive gastrointestinal bleeding. All other patients required ETI because of progressive ventilatory failure. In summary, only

four of the intubations in the NIV group were because of an inability to control respiratory failure compared with 16 in the control group.

The use of NIV opens up new opportunities in the management of patients with ventilatory failure, particularly with regard to location and the timing of intervention. The issue of location for NIV will be addressed in the next article in this series but the six prospective randomized-controlled studies of NIV outside the ICU also have implications for the timing of the initiation of NIV [1, 4–6, 8, 10]. The mean pH is higher than that seen in the ICU studies reflecting a milder physiological disturbance and NIV was therefore introduced at an earlier point in the natural history of the exacerbation before assisted ventilation would usually be considered necessary.

BOTT *et al.* [1] randomized 60 patients with COPD to either conventional treatment or NIV. NIV initiation, by research staff, took on average 90 min (range 15 min–4 h) and it led to a more rapid correction of pH and carbon dioxide tension in arterial blood (P_{a,CO_2}). In an "intention to treat" analysis there was no significant benefit from NIV, but when those unable to tolerate NIV were excluded a significant survival benefit was seen (nine of 30 *versus* one of 26, p=0.014). The high mortality rate (30%) in the control group was surprising considering that the mean pH was only 7.34. In addition the low intubation rate, while probably reflecting UK practice, has been criticized.

ANGUS *et al.* [5] compared NIV and Doxapram in patients with COPD and type-II respiratory failure in a small randomized trial that primarily addressed the effect of both interventions on arterial blood gas tensions. NIV resulted in a significant improvement in both P_{a,O_2} and P_{a,CO_2} at 4 h. In contrast, no fall in P_{a,CO_2} occurred in patients treated with Doxapram and an initial improvement in P_{a,O_2} was not sustained at 4 h. At both 1 and 4 h pH was significantly better in the NIV group as compared to the Doxapram group. All the patients in the NIV group were discharged home, although one required Doxapram in addition to NIV during their acute illness. Three out of eight patients in the Doxapram group died and a further two received NIV. This small study suggests that NIV is more effective than Doxapram in the treatment of respiratory failure associated with COPD. However no comparisons were made of nursing work load, patient tolerance or complication rates between the two groups.

BARDI *et al.* [8] found no significant differences in hospital outcome between NIV and conventional therapy in a study of 30 patients with COPD, with the majority of patients in both groups recovering without the need for invasive ventilation. Because there was no ICU on site NIV was started early, and as the mean pH in the two groups were 7.36 and 7.39 and no patient in either group had a pH <7.30 these results are not surprising. However, a surprising finding was that the outcome in the patients who had received NIV was better than in those who had not at 3, 6 and 12 months. On admission there was no difference between the forced expiratory volume in one second (FEV_1) in the two groups. However, at discharge FEV_1 in the NIV-treated group was 49.4% of predicted and in the standard therapy group 40.5%. It seems unlikely that this increase in FEV_1 was an effect of NIV and suggests that these patients had less severe chronic disease. Furthermore a number of the patients who died had significant coexistent disease.

A multicentre randomized controlled trial of NIV in acute exacerbations of COPD (n=236), on general respiratory wards, in 13 centres, has recently been reported [10]. NIV was applied, by the usual ward staff, using a bilevel device in spontaneous mode according to a simple protocol. Treatment failure, a surrogate for the need for intubation, defined by *a priori* criteria, was reduced from 27% to 15% by NIV ($p<0.05$). In-hospital mortality was also reduced from 20% to 10% ($p<0.05$). Subgroup analysis suggested that the outcome in patients with pH<7.30 after initial treatment was inferior to the outcome reported in the studies performed in the ICU. This study suggests that, with adequate staff training, NIV can be applied with benefit outside the ICU by the usual ward staff, and that the early introduction of NIV on a general ward results in a better outcome than providing no ventilatory support for acidotic patients outside the ICU. Furthermore, it suggests that earlier intervention (pH<7.35) than would normally be considered when only invasive ventilation is available, is advantageous.

BARBE *et al.* [4] initiated NIV in casualty in patients presenting with acute exacerbation of COPD and continued it on a general ward. To ease some of the problems of workload and compliance NIV was administered for 3 h, twice a day. In this small study (n=24) there were no intubations nor deaths in either group and arterial blood gas tensions improved equally in both the NIV group and in controls. However, the mean pH at entry in each group was 7.33 and at this level of acidosis significant mortality is not expected, in other words it was unlikely that such a small study would show an improved outcome when recovery would be expected anyway [16].

WOOD *et al.* [6] randomized 27 patients with acute respiratory distress, due to a variety of different conditions, to conventional treatment or NIV in casualty. Intubation rates were similar (seven of 16 *versus* five of 11) but there was a nonsignificant trend towards increased mortality in those given NIV (4/16 *vesus* 0/11, p=0.123). The authors attributed the excess mortality to delay in intubation as conventional patients requiring invasive ventilation were intubated after a mean of 4.8 h compared to 26 h in those on NIV (p=0.055). It is difficult to draw many conclusions from this study given its small size, the fact that the numbers of patients in each group was different and that the patients were not matched for aetiology of respiratory failure.

Another possible reason why these studies in which NIV was initiated in casualty [4, 6] both failed to show any advantage to NIV over conventional therapy includes the fact that most patients presenting in casualty have not received any treatment. A proportion will improve after initiation of standard medical therapy, including controlled oxygen therapy. In a

Table 2. – Prospective randomized controlled trials of noninvasive ventilation (NIV) in patients with nonchronic obstructive pulmonary disease

[Ref. no.]	Disease n	Setting	Baseline data pH or $P_{a,O_2}/F_{i,O_2}$	ETI or "surrogate"	Mortality	Mode plus settings cmH_2O Use on day 1
[3]	Mixed 31	ICU	7.28 *vs* 7.27	31% *vs* 73%*	1/16 *vs* 2/15	IPAP 11.3 EPAP 2.6 Use 20.1 h
[6]	Mixed 27	Casualty	7.35 *vs* 7.34	7/16 *vs* 5/11	4/16 *vs* 0/11	
[22]	Hypoxic ARF 64	ICU	116 *vs* 124	10 *vs* 32	28% *vs* 47%	PSV Use continuous for first 24 h
[23]	Post transplant ARF 40	ICU	129 *vs* 129	20% *vs* 70%	35% *vs* 55%	PSV 14–20 PEEP $\leqslant$10
[24]	Pneumonia 56	ICU	183 *vs* 167	21% *vs* 61%	7/28 *vs* 6/28	PSV 14.8 PEEP 4.9
[9]	Mixed 38	ICU	7.27 *vs* 7.28 103 *vs* 110	6.4 *vs* 21.3·100 ICU $days^{-1}$*	2.4 *vs* 4.27·100 ICU $days^{-1}$*	IPAP 11 EPAP 5.7
[25]	Hypoxic ARF	ICU	140 *vs* 148	21% *vs* 24%	19% *vs* 18%	CPAP
[26]	Immune compromized 52	ICU	141 *vs* 136	46% *vs* 77%*	38% *vs* 69%*	PSV Use $\geqslant$45 min every 3 h

P_{a,O_2}: oxygen tension in arterial blood; F_{i,O_2}: inspiratory oxygen fraction; ETI: endotracheal intubation; ARF: acute respiratory failure; ICU: intensive care unit; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; PSV: pressure support ventilation; PEEP: positive end-expiratory pressure; CPAP: continuous positive airway pressure. *: $p<0.05$.

1-yr period prevalence study [17] of 983 patients admitted through casualty in Leeds (UK) with acute exacerbations of COPD, 20% were acidotic on arrival in the department and of these 20% had completely corrected their pH by the time of arrival on the ward. There was a weak relationship between the P_{a,O_2} on arrival at hospital and the presence of acidosis, suggesting that in at least some patients, respiratory acidosis had been precipitated by high-flow oxygen therapy administered in the ambulance on the way to hospital. These casualty studies therefore lack the statistical power to pick up any advantage from very early NIV.

Long-term effects of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease

The avoidance of intubation may have beneficial effects in the long term. CONFALONIERI *et al.* [18] looked at the outcome at up to 1 yr in 24 patients who received NIV during their acute exacerbation of COPD and compared this with 24 well-matched historical controls. Mean admission pH was 7.29 and all were hypoxic and hypercapnic. The survival at 1 yr was 71% in the NIV group compared with 50% in the controls. Further days in hospital during that year with exacerbations were also significantly lower in the NIV group (7±10 *versus* 25±22 days, p=0.003). These findings were confirmed in another retrospective study [19] comparing face mask ventilation with ETI and MV. Although no differences were seen in in-hospital survival there was a marked difference at 3 (23% *versus* 48% mortality) and 12 (30% *versus* 63% mortality) months favouring the noninvasive approach. In addition the number of new ICU admissions during the follow-up at 1 yr was reduced in those ventilated noninvasively (0.12 *versus* 0.30, $p<0.05$). Within each group 1-yr mortality was greater ($p<0.01$) in patients with pneumonia. Imperfect matching is one possible explanation but patients who are intubated and mechanically ventilated may lose a considerable amount of muscle bulk [20] rendering them susceptible to further episodes of ventilatory failure. The observation of a better long-term outcome with NIV needs to be confirmed in further prospective trials. Longer-term follow-up from the study of PLANT *et al.* [21] failed to show any statistically significant benefit from NIV compared with conventional therapy, though importantly the study showed a median survival in both groups of >1 yr indicating that the patients salvaged by NIV were not just those who had a very poor prognosis. It may be significant that few patients in either group were intubated and ventilated and this is an important difference when compared with the studies mentioned earlier.

Nonhypercapnic respiratory failure

There is convincing evidence for the use of NIV in patients with acute or chronic respiratory failure secondary to COPD (table 2). The situation in patients with ARF is less clear. Early studies in predominantly hypoxaemic patients failed to show an advantage to NIV [6, 27]. One small, randomized study in patients with no previous history of chronic lung disease did not show clear benefits of NIV, except in a subgroup of patients with acute hypercapnia [27]. However more recent studies have suggested a role for NIV in selected patients.

ANTONELLI *et al.* [22] compared intubation and conventional MV with NIV in patients with acute hypoxic respiratory failure. Patients were randomized at the time they reached predefined criteria for intubation, between endotracheal intubation or NIV.

Improvement in oxygenation was similar with the two modes of support but 10 out of 32 patients in the NIV group eventually required intubation. Delays in intubation may explain the worse outcome in the intubated patients. Although all the patients who required ETI after NIV died, 15 patients who were intubated from the outset also died, making this unlikely. Patients receiving NIV had significantly lower rates of serious complications and those successfully treated with NIV had shorter ICU stays. One concern in this study, is the high mortality rate observed in the NIV patients eventually requiring endotracheal intubation. *Post hoc* subgroup analysis of patients with simplified acute physiological scores (SAPS) of <16 and those ⩾16 showed that patients in the latter group had similar outcomes irrespective of the type of ventilation. However NIV was superior to conventional MV in patients with SAPS <16.

CONFALONIERI *et al.* [24] evaluated the early application of NIV in patients with ARF due to severe community acquired pneumonia, on three intermediate respiratory ICUs. Twenty-eight patients were randomly assigned to standard treatment and 28 to NIV. The study included both COPD patients with hypercapnic ARF (23 subjects) and non-COPD patients with pure hypoxaemic ARF (33 subjects). NIV resulted in a significant reduction in intubation. Six patients (21%) in the NIV group and 17 (61%) in the standard treatment group met the preselected criteria for intubation (p=0.007). In total, twenty patients were intubated, six in the NIV group and 14 in the standard treatment group (p=0.03). The three remaining patients in the standard treatment group, who met the preselected criteria for intubation but were not intubated, were all successfully treated with NIV. Patients randomized to NIV had significantly shorter ICU stays (1.8±0.7 days *versus* 6±2 days p=0.04) and required a similar nursing care intensity to those in the standard treatment group. The two groups did not differ significantly in terms of duration of hospital stay, complications, hospital and 2-month mortality. However, there was a beneficial effect of NIV upon the 2-month outcome in the subgroup with COPD (89% *versus* 37.5% survival, p<0.05).

ANTONELLI *et al.* [23] evaluated the use of NIV in patients undergoing solid organ transplantation. They found a sustained improvement in the P_{a,O_2}/inspiratory oxygen fraction (F_{i,O_2}) ratio in more patients (60% *versus* 25%, p=0.03) and a reduction in the intubation rate (20% *versus* 70%, p=0.002), rate of fatal complications (20% *versus* 50%, p=0.05), length of stay in the ICU by survivors (5.5 *versus* 9 days, p=0.03) and ICU mortality (20% *versus* 50%, p=0.05). However there was no difference in hospital mortality.

HILBERT *et al.* [26] conducted a prospective, randomized-controlled trial of NIV compared with standard treatment with supplemental oxygen and no ventilatory support, in 52 immunosuppressed patients with pulmonary infiltrates and fever. Patients were recruited at an early stage of hypoxaemic respiratory failure. NIV (for at least 45 min) was alternated every 3 h with periods of spontaneous breathing with supplemental oxygen. Each group of 26 patients included 15 patients with haematological malignancy and neutropenia. Fewer patients in the NIV group required endotracheal intubation (12 *versus* 20, p=0.03), had serious complications (13 *versus* 21, p=0.02), died in the ICU (10 *versus* 18, p=0.03) or died in hospital (13 *versus* 21, p=0.02).

These studies all suggest that there is an emerging role for NIV in nonhypercapnic patients. There is no data to suggest that it is worse than intubation and MV and certainly in the less severely affected patients the early introduction of NIV reduces the need for subsequent intubation and infectious complications, which have a high morbidity and mortality.

Noninvasive continuous positive airway pressure

Respiratory failure due to lung disease

The issue of whether mask continuous positive airway pressure (CPAP) should be considered as NIV is debatable but it has been used in ARF [28–32], during weaning [33] and for postextubation respiratory failure [34–36]. In patients with restrictive lung disease it improves oxygenation and reduces the work of breathing by recruiting atelectatic lung, improving ventilation/perfusion relationships and increasing functional residual capacity. In patients with COPD it counterbalances intrinsic positive end-expiratory pressure (PEEP) thereby reducing the work of breathing [37] but the benefit seen is not as great as when PEEP is added to pressure support ventilation [38]. CPAP may also be useful in splinting the upper airway during sleep when there is upper airway obstruction, which in the acute setting may further compromise effective ventilation. It has been shown to reduce inspiratory muscle effort during sleep in chronic stable patients with COPD, but without any beneficial effects upon gas exchange or daytime symptoms [39]. Most of the studies reported earlier confirm short-term physiological benefits, but there is little controlled trial data to support the use of noninvasive CPAP in ARF. DELCLAUX *et al.* [25] compared noninvasive CPAP plus oxygen with oxygen alone in 123 patients of whom 102 had acute lung injury. After 1 h of treatment, subjective responses to treatment (p<0.001) and median (5th–95th percentile) $P_{a,O_2}/F_{i,O_2}$ ratios were greater with CPAP (203 (45–431) mmHg *versus* 151 (73–482) mmHg, p=0.02). No further difference in respiratory indices was observed between the groups. There was no difference in endotracheal intubation rate (21 (34%) *versus* 24 (39%), p=0.53), hospital mortality (19 (31%) *versus* 18 (30%), p=0.89), or median (5th–95th percentile) ICU length of stay (6.5 (1–57) days *versus* 6.0 (1–36) days, p=0.43). A higher number of adverse events occurred with CPAP treatment (18 *versus* 6, p=0.01). A number of patients in the CPAP group had respiratory arrests, suggesting that noninvasive CPAP delayed intubation. Despite early physiological improvement, CPAP neither reduced the need for intubation nor improved outcomes in patients with acute hypoxaemic,

nonhypercapnic respiratory insufficiency, primarily due to acute lung injury.

Acute cardiogenic pulmonary oedema

Three randomized-controlled trials have been performed comparing standard medical treatment plus CPAP and standard medical treatment alone in patients with cardiogenic pulmonary oedema (CPO) [40–42] . The earliest of these studies [40] showed significant improvement in oxygenation within the first 10 min of treatment, in the patients randomized to 10 cmH_2O of CPAP as compared with control. Seven of 20 patients in the CPAP group and 13 of 20 in the standard treatment group failed (p=0.068). There was also no difference in mortality rates between the two groups. The largest study [42] involved 100 patients (50 in each group) admitted to a Coronary Care Unit with acute pulmonary oedema. Haemodynamic and pulmonary function parameters were recorded over the first 6 h following admission. Using predetermined criteria, CPAP resulted in a reduced intubation and therapeutic failure rates at 6 h (eight of 50 *versus* 18 of 50, p<0.01 and 12 of 50 *versus* 25 of 50, p<0.01, respectively). During the first 3-h the CPAP group also showed significant improvements in oxygenation, alveolar arterial oxygen gradient and intrapulmonary shunt, a lower rate-pressure product and a higher stroke/volume index as compared with the control group. There was, however, no difference in hospital or 1-yr mortality or hospital length of stay between the groups. BERSTEN *et al.* [41] randomized 39 patients admitted to ICU with acute CPO to receive standard medical care (n=20) or CPAP (n=19). At enrolment the patients were more acidotic than those in the other two randomized-controlled trials (pH 7.18± 0.08 CPAP, 7.15±0.11 control). Receiving a total of 9.3±4.9 $h \cdot day^{-1}$ of CPAP led to a reduction in intubation rate (seven of 20 *versus* zero of 19, p=0.005), a shorter ICU stay (1.2±0.4 days *versus* 2.7±2.0 days, p=0.006) and more rapid improvement in respiratory rate, respiratory acidaemia and oxygenation. Again there was no difference in mortality rate between the two groups.

Pooled results of these three randomized-controlled trials [43] showed a risk reduction for intubation of 26% (95% confidence interval (CI): 14–38%) with CPAP indicating that four patients with pulmonary oedema need to be treated with CPAP to prevent one intubation. The pooled results also suggest a trend towards a reduction in hospital mortality, with a risk difference of 6.6% between the two treatment groups, however the CI were wide (95% CI: -16–3%) and thus do not allow the exclusion of harm with CPAP.

Only one study has compared bilevel positive airway pressure (BiPAP) and CPAP in the treatment of acute pulmonary oedema [44]. Performed in casualty, this study of 27 patients showed that BiPAP improved ventilation and vital signs more rapidly than CPAP. At 30 min the BiPAP group had significant improvements in pH, P_{a,CO_2}, respiratory rate, cardiac frequency and dyspnoea scores. In contrast only respiratory rate improved, from baseline values, in the patients treated with CPAP. When the two therapeutic groups were compared a greater reduction in P_{a,CO_2} was seen in the BiPAP group although this failed to reach a significant level (p=0.057). The BiPAP group did however have a significantly greater reduction in systolic (p=0.005) and mean blood pressure (p=0.03). The outcome variables were similar in both groups, with no difference or trends towards difference in intubation rates (7% *versus* 8%, p=NS), mortality rates (7% *versus* 15%, p=NS) and ICU or hospital length of stay. The study was terminated early, following interim analysis, because of an increased rate of myocardial infarctions in the BiPAP group (10 of 14 *versus* four of 13, p=0.06). Baseline characteristics of the two groups of patients were well matched except for a higher, although nonstatistically significant, incidence of chest pain (10 of 14 *versus* four of 13, p=0.06) and left bundle branch block on the electrocardiogram in the BiPAP group. It is therefore unclear as to whether the increased infarction rate is due to BiPAP ventilation *per se*, the specific settings used or due to the higher incidence of chest pain at the outset.

Another prospective randomized-controlled trial [45] compared NIV with oxygen therapy in addition to standard medical therapy in 40 patients and showed a reduction in the intubation rate and more rapid resolution of abnormal physiology. Endotracheal intubation was required in 5% of patients assigned to NIV and in 33% of those treated conventionally (p=0.037). The time to reach an oxygen saturation of $\geqslant$96% and respiratory rate <30 $breaths \cdot min^{-1}$ was significantly shorter in the NIV group (median 30 (interquatile range (IQR) 15–53) *versus* 105 (50–230) min, p=0.002). However there was no difference in survival or hospital length of stay. Further larger studies comparing CPAP and NIV are needed.

When noninvasive ventilation fails

Some patients require ETI and MV from the outset or after a failed trial of NIV and in this situation NIV may have a role in facilitating weaning from MV. NAVA *et al.* [46] performed a prospective multicentre randomized-controlled trial of the use of NIV as a means of weaning patients with COPD, who had failed a T-piece weaning trial after 48 h of ETI, controlled MV and aggressive suctioning to clear secretions. A total 56% of the patients had required immediate ETI on presentation and 44% after a failed trial of NIV (mean pH at presentation 7.18). If patients failed the weaning trial they were randomized to further intubation and MV or NIV. NIV was associated with a shorter duration of ventilatory support (10.2 days *versus* 16.6 days), a shorter ICU stay (15.1 days *versus* 24 days), less nosocomial pneumonia (zero of 25 *versus* seven of 25) and an improved 60-day survival (92% *versus* 72%). GIRAULT *et al.* [47] in a further randomized-controlled trial involving 33 patients showed a reduction in the

duration of InMV (4.6±1.9 *versus* 7.7±3.8 days) and a reduced mean daily ventilatory support, but an increased total duration (11.5±5.2 *versus* 3.5±1.4 days) of ventilatory support when the noninvasive approach was used. There was no difference in percentage of patients successfully weaned or in complication rates. In patients not suitable for NIV from the outset or those who fail, ETI for 24–48 h to gain control, and then early extubation onto NIV may have advantages over prolonged endotracheal intubation.

A proportion of patients weaned from invasive ventilation subsequently deteriorate and require further ventilatory support. HILBERT *et al.* [48] reported 30 patients with COPD who developed hypercapnic respiratory distress within 72 h of extubation. They were treated with mask bilevel pressure support ventilation. Only six of these 30 patients as compared to 20 of 30 historical controls required reintubation. Although in-hospital mortality was not significantly different, the mean duration of ventilatory assistance and length of ICU stay related to the event were significantly shortened by NIV. Further studies are needed before NIV becomes a routine method of weaning from MV. The role of NIV in weaning is described in more detail in another article in this series.

Patients may fail NIV "late", after a period of successful NIV, with rates reported at 0–20% and this has been associated with poor outcomes. MORETTI *et al*. [49] studied 137 patients admitted with COPD and acute hypercapnic respiratory failure, initially treated successfully with NIV. Of these, 106 continued to improve and were discharged home. The remaining 23% deteriorated after 48 h of NIV. These so called "late failures" were then assigned to either an increased number of hours of NIV (the mean number of hours per day of NIV at the time of late failure was 9.2) or intubation and MV, depending on the patients/relatives wishes. Patients assigned to increased NIV did significantly worse, with a mortality of 92% compared with 53% in those invasively ventilated. At the time of relapse those patients treated with increased NIV were more acidotic than those who were intubated (pH 7.1 *versus* pH 7.29) and though this difference was not statistically significant it is clinically significant. The lack of statistical significance probably reflects the small number of patients. The difference in pH suggests that the patients who were treated with continuing NIV were sicker than those who were intubated. There is also the possibility that patients who were not intubated were self-selected as a group with more advanced disease, since they were not offered or declined ETI. At the time of admission "late failures" had significantly lower activities of daily living (ADL) scores and blood pressure, were more tachycardic and more likely to have associated complications, in particular hyperglycaemia. pH was not different between the groups at admission, at 1 h or 24 h. Using logistic regression analysis a low pH, a low ADL score and the presence of associated complications at admission were more likely in patients who failed after $\geqslant$48 h of NIV. Interestingly neither the Acute Physiology and Chronic Health Evaluation (APACHE) II score nor age were predictive of failure.

In summary, patients who fail NIV "early" have a reasonable prognosis with subsequent InMV. However, decisions about subsequent management must be based upon individual circumstances. The published data do not distinguish between failure of NIV due to intolerance of the technique and when NIV could be applied appropriately, but despite this the patient still deteriorated. It is possible that the outcome in these two situations with subsequent InMV might be different. In one case the failure is of the application of assisted ventilation, whereas in the second it is a failure of assisted ventilation to improve gas exchange *etc.* The prognosis in patients who fail "late" after initial successful NIV is poor and further data, particularly on the quality of life in those who do survive, are needed before informed decisions can be made about the appropriate action in this situation.

Patients with contraindications to endotracheal intubation

Several reports have described the application of NIV to patients with ARF who are poor candidates for endotracheal intubation for a variety of reasons: advanced age or poor physiological condition, advanced disease and "do not resuscitate" directives [50, 51]. The overall success rate in these reports is ~60–70%. Successfully treated patients rapidly improved gas exchange. Even when respiratory failure did not resolve, NIV can be effective in providing symptomatic relief of dyspnoea.

Noninvasive ventilation in the "real" world

NIV is very dependent upon the skill, expertize and enthusiasm of the attending medical, therapist and nursing staff. Inevitably, clinical trials are performed in units with a particular interest in the subject under investigation and it is possible that the results seen in the clinical trials are not generalizable to everyday clinical practice. The study of PLANT *et al.* [10] attempted to address this, in that the majority of centres involved had no particular expertize in NIV, but inevitably participation in a trial with access to a full-time research doctor and nurse may have improved the application of NIV. A recent survey was undertaken among 42 ICUs in France over a 3-week period [52] including all the 689 patients who needed ventilatory support. Patients treated with NIV represented 16% of all patients and 35% of the patients admitted without previous endotracheal intubation and needing ventilatory support. NIV was employed in <20% of all hypoxic ARF, in one-half of patients with hypercapnic respiratory distress and was never used in patients with coma. It was followed by ETI in 40% of cases. The incidence of both nosocomial pneumonia (10% *versus* 19%, p=0.03) and mortality (22% *versus* 41%, p<0.001) was lower in NIV patients than in those with ETI. After adjusting for differences at baseline, Simplified Acute

Physiology Score (SAPS) II (odds ratio (OR)=1.05 per point; CI: 1.04–1.06), McCabe/Jackson score (OR=2.18; CI: 1.57–3.03), and hypoxaemic ARF (OR=2.30; CI: 1.33–4.01) were identified as risk factors explaining mortality. Success of NIV was associated with a lower risk of pneumonia (OR=0.06; CI: 0.01–0.45) and of death (OR=0.16; CI: 0.05–0.54). In NIV patients, SAPS II and a poor clinical tolerance predicted secondary ETI. Failure of NIV was associated with a longer length of stay.

A reduction in the incidence of nosocomial infection is a consistent and important advantage of NIV compared with InMV [53, 54]. In intubated patients there is a 1% risk per day of developing nosocomial pneumonia [55]. This complication of invasive ventilation is associated with a longer ICU stay, increased costs and a worse outcome [56]. The reduction in nosocomial infections is probably the most important advantage of avoiding ETI and using NIV.

Contraindications to noninvasive ventilation

The boundaries for the use of NIV continue to expand. However intubation and conventional ventilation remain the "gold standard" in the management of many patients with ARF. Local protocols need to be developed in order to avoid inappropriate trials of NIV in patients who require urgent intubation. NIV is not appropriate in well-documented end-stage disease or when several comorbidities are present. There are no absolute contraindications although a number have been suggested [57, 58]. These include coma or confusion, inability to protect the airway, severe acidosis at presentation, significant comorbidity, vomiting, obstructed bowel, haemodynamic instability (two studies have shown only small changes in cardiac output when NIV is initiated [59, 60] but haemodynamic collapse comparable to that often seen when patients are intubated is seldom seen), radiological evidence of consolidation, and orofacial abnormalities which interfere with the mask/face interface. In part, these "contraindications" have been determined by the fact that they were exclusion criteria for the controlled trials. It is therefore more correct to state that NIV is not proven in these circumstances. In addition other factors, such as failure of pH to improve within 1 h [57] are a self-fulfilling prophecy if they have been determined from the outset as indicating a failure of treatment. Whether NIV is contraindicated or not must depend on individual circumstances. For instance if invasive ventilation is not considered appropriate, but NIV would be acceptable, there is nothing to be lost by a trial of NIV and there are no contraindications. By contrast in an individual moribund with life threatening asthma, who may be very difficult to ventilate noninvasively, but in whom no problems with weaning *etc.* would be anticipated, there is little to be gained and much to be lost by attempting NIV.

NIV has been used in patients with an undrained pneumothorax, without apparently causing the pneumothorax to increase in size [61]. However, in most patients with a pneumothorax it will be appropriate to insert an intercostal drain before commencing NIV.

Conclusion

Noninvasive ventilation can be very effective for reversing the severe physiological abnormalities in acute or chronic respiratory failure. Indeed it should now be regarded as a new standard of care in the management of acute exacerbations of chronic obstructive pulmonary disease [62]. It may also be useful in selected patients with hypoxic respiratory failure, although patient selection and administration of the ventilatory support may prove more difficult in this group. Noninvasive ventilation can reduce the need for endotracheal intubation and its associated complications, improving the outcome of patients. When successful it can be associated with a reduction in the duration of intensive care unit and hospital stay, which may have important economic implications. It is important to note that, to date, no direct comparison between InMV and noninvasive ventilation has been published and the two techniques should be viewed as complementary, with noninvasive ventilation considered a means of obviating the need for endotracheal intubation rather than as a direct alternative. Noninvasive ventilation should be available in all hospitals admitting patients with acute respiratory illness. Motivation of the staff and education of personnel are essential for the success of the technique.

References

1. Bott J, Carroll MP, Conway JH, *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; 341: 1555–1557.
2. Brochard L, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817–822.
3. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 151: 1799–1806.
4. Barbe F, Togores B, Rubi M, Pons S, Maimo A, Agusti AGN. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. *Eur Respir J* 1996; 9: 1240–1245.
5. Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax* 1996; 51: 1048–1050.
6. Wood KA, Lewis L, Von Harz B, Kollef MH. The use of noninvasive positive pressure ventilation in the Emergency Department. *Chest* 1998; 113: 1339–1346.
7. Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. *Chest* 1998; 114: 1636–1642.

8. Bardi G, Pierotello R, Desideri M, Valdisseri L, Bottai M, Palla A. Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. *Eur Respir J* 2000; 15: 98–104.
9. Martin TJ, Hovis JD, Costantino JP, *et al.* A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. *Am J Respir Crit Care Med* 2000; 161: 807–813.
10. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; 355: 1931–1935.
11. Brochard L, Isabey D, Piquet J, *et al.* Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med* 1990; 323: 1523–1530.
12. Thorens JB, Ritz M, Reynard C, *et al.* Haemodynamic and endocrinological effects of noninvasive mechanical ventilation in respiratory failure. *Eur Respir J* 1997; 10: 2553–2559.
13. Diaz O, Iglesia R, Ferrer M, *et al.* Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156: 1840–1845.
14. Corrado A, Bruscoli G, Messori A, *et al.* Iron lung treatment of subjects with COPD in acute respiratory failure. Evaluation of short- and long-term prognosis. *Chest* 1992; 101: 692–696.
15. Corrado A, De Paola E, Gorini M, *et al.* Intermittent negative pressure ventilation in the treatment of hypoxic hypercapnic coma in chronic respiratory insufficiency. *Thorax* 1996; 51: 1077–1082.
16. Jeffrey AA, Warren PM, Flenley DC. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease: risk factors and use of guidelines for management. *Thorax* 1992; 47: 34–40.
17. Plant PK, Owen J, Elliott MW. One year period prevalance study of respiratory acidosis in acute exacerbation of COPD; implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000; 55: 550–554.
18. Confalonieri M, Parigi P, Scartabellati A, *et al.* Noninvasive mechanical ventilation improves the immediate and long-term outcome of COPD patients with acute respiratory failure. *Eur Respir J* 1996; 9: 422–430.
19. Vitacca M, Clini E, Rubini F, Nava S, Foglio K, Ambrosino N. Non-invasive mechanical ventilation in severe chronic obstructive lung disease and acute respiratory failure: short- and long-term prognosis. *Intensive Care Med* 1996; 22: 94–100.
20. Coakley JH, Nagendran K, Ormerod IE, Ferguson CN, Hinds CJ. Prolonged neurogenic weakness in patients requiring mechanical ventilation for acute airflow limitation. *Chest* 1992; 101: 1413–1416.
21. Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. *Thorax* 2001; 56: 708–712.
22. Antonelli M, Conti G, Rocco M, *et al.* A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; 339: 429–435.
23. Antonelli M, Conti G, Bufi M, *et al.* Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA* 2000; 283: 235–241.
24. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Meduri UG. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999; 160: 1585–1591.
25. Delclaux C, L′Her E, Alberti C, *et al.* Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. *JAMA* 2000; 284: 2352–2360.
26. Hilbert G, Gruson D, Vargas F, *et al.* Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001; 344: 481–487.
27. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. A randomized comparison with conventional therapy. *Chest* 1995; 107: 761–768.
28. de Lucas P, Tarancon C, Puente L, Rodriguez C, Tatay E, Monturiol JM. Nasal continuous positive airway pressure in patients with COPD in acute respiratory failure: a study of the immediate effects. *Chest* 1993; 104: 1694–1697.
29. Brett A, Sinclair DG. Use of continuous positive airway pressure in the management of community acquired pneumonia. *Thorax* 1993; 48: 1280–1281.
30. Covelli HD, Weled BJ, Beekman JF. Efficacy of continuous positive airway pressure administered by face mask. *Chest* 1982; 81: 147–150.
31. Gachot B, Clair B, Wolff M, Regnier B, Vachon F. Continuous positive airway pressure by face mask or mechanical ventilation in patients with human immunodeficiency virus infection and severe *Pneumocystis carinii* pneumonia. *Intensive Care Med* 1992; 18: 155–159.
32. Suter PM, Kobel N. Treatment of acute pulmonary failure by CPAP *via* face mask: when can intubation be avoided? *Klin Wochenschr* 1981; 59: 613–616.
33. Petrof BJ, Legare M, Goldberg P, Milic-Emili J, Gottfried SB. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990; 141: 281–289.
34. DeHaven CB, Hurst JM, Branson RD. Post extubation hypoxaemia treated with continuous positive airways pressure mask. *Crit Care Med* 1985; 13: 46–48.
35. Putensen C, Hormann C, Baum M, Lingnau W. Comparison of mask and nasal continuous positive airway pressure after extubation and mechanical ventilation. *Crit Care Med* 1993; 21: 357–362.
36. Kilger E, Briegel J, Haller M, *et al.* Effects of noninvasive positive pressure ventilatory support in non-COPD patients with acute respiratory insufficiency after early extubation. *Intensive Care Med* 1999; 25: 1374–1380.
37. Goldberg P, Reissmann H, Maltais F, Ranieri M, Gottfried SB. Efficacy of noninvasive CPAP in COPD with acute respiratory failure. *Eur Respir J* 1995; 8: 1894–1900.
38. Appendini L, Purro A, Patessio A, *et al.* Partitioning of inspiratory muscle workload and pressure

assistance in ventilator-dependent COPD patients. *Am J Respir Crit Care Med* 1996; 154: 1301–1309.
39. Petrof BJ, Kimoff RJ, Levy RD, Cosio MG, Gottfried SB. Nasal continuous positive airway pressure facilitates respiratory muscle function during sleep in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 143: 928–935.
40. Rasanen J, Heikkila J, Downs J, Nikki P, Vaisanen I, Viitanen A. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Am J Cardiol* 1985; 55: 296–300.
41. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *N Engl J Med* 1991; 325: 1825–1830.
42. Lin M, Yang YF, Chiang HT, Chiang BN, Cheitlin MD. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema. Short-term results and long-term follow-up. *Chest* 1995; 107: 1379–1386.
43. Pang D, Keenan SP, Cook DJ, Sibbald WJ. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: a systematic review. *Chest* 1998; 114: 1185–1192.
44. Mehta S, Jay GD, Woolard RH, *et al.* Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary oedema. *Crit Care Med* 1997; 25: 620–628.
45. Masip J, Betbese AJ, Paez J, *et al.* Non-invasive pressure support ventilation *versus* conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. *Lancet* 2000; 356: 2126–2132.
46. Nava S, Ambrosino N, Clini E, *et al.* Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998; 128: 721–728.
47. Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure. A prospective, randomized controlled study. *Am J Respir Crit Care Med* 1999; 160: 86–92.
48. Hilbert G, Gruson D, Porel L, Gbikpi-Benissan G, Cardinaud JP. Noninvasive pressure support ventilation in COPD patients with post extubation hypercapnic respiratory insufficiency. *Eur Respir J* 1998; 11: 1349–1353.
49. Moretti M, Cilione C, Tampieri A, Fracchia C, Marchioni A, Nava S. Incidence and causes of noninvasive mechanical ventilation failure after initial success. *Thorax* 2000; 55: 819–825.
50. Benhamou D, Girault C, Faure C, Portier F, Muir JF. Nasal mask ventilation in acute respiratory failure. *Chest* 1992; 102: 912–917.
51. Meduri GU, Fox RC, Abou-Shala N, Leeper KV, Wunderink R. Noninvasive mechanical ventilation *via* face mask in patients with acute respiratory failure who refused endotracheal intubation. *Crit Care Med* 1994; 22: 1584–1590.
52. Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L. Noninvasive *versus* conventional mechanical ventilation. An epidemiologic survey. *Am J Respir Crit Care Med* 2001; 163: 874–880.
53. Nourdine K, Combes P, Carton M-J, Beuret P, Cannamela A, Ducreux J-C. Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. *Intensive Care Med* 1999; 25: 567–573.
54. Girou E, Schortgen F, Delclaux C, *et al.* Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; 284: 2361–2367.
55. Fagon JY, Chastre J, Hance A, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; 94: 281–287.
56. Torres A, Aznar R, Gatell JM. Incidence, risk and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990; 142: 523–528.
57. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M. Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive airways disease: correlates for success. *Thorax* 1995; 50: 755–757.
58. Soo Hoo GW, Santiago S, Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. *Crit Care Med* 1994; 22: 1253–1261.
59. Ambrosino N, Nava S, Torbicki A, *et al.* Haemodynamic effects of pressure support and PEEP ventilation by nasal route in patients with stable chronic obstructive pulmonary disease. *Thorax* 1993; 48: 523–528.
60. Confalonieri M, Gazzaniga P, Gandola L, *et al.* Haemodynamic response during initiation of noninvasive positive pressure ventilation in COPD patients with acute ventilatory failure. *Respir Med* 1998; 92: 331–337.
61. Haworth CS, Dodd ME, Atkins M, Woodcock AA, Webb AK. Pneumothorax in adults with cystic fibrosis dependent on nasal intermittent positive pressure ventilation (NIPPV): a management dilemma. *Thorax* 2000; 55: 620–622.
62. Brochard L. Non-invasive ventilation for acute exacerbations of COPD: a new standard of care. *Thorax* 2000; 55: 817–818.