The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis

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Summary Study Objectives: To compare the effect of noninvasive mechanical ventilation (NIV) in severely acidotic with mildly acidotic patients with acute hypercapnic chronic obstructive lung disease (COPD).

Design: Comparison of NIV in consecutively enrolled patients with acute hypercapnic COPD with mild (pH 7.25–7.35) or severe (pH ≤ 7.25) acidosis on time to normalise pH and improve $\text{PaCO}_2$, duration of NIV treatment, length of stay in hospital and survival.

Results (median (IQR)): Twenty-nine patients had 36 episodes of acute hypercapnic respiratory failure: Seventeen with pH ≤ 7.25 and 19 with pH 7.25–7.34. Compared with the mildly acidotic group, the severely acidotic group took a similar length of time for pH to normalise and $\text{PaCO}_2$ improve (12 (6–34) vs 12 (4–28) h, respectively, $P = 0.42$), with similar duration of NIV treatment (60 (35–96) vs 68 (36–48) h, respectively, $P = 0.25$) and hospital length of stay (8 (7–18) vs 9 (5–17) days, respectively, $P = 0.61$). Overall survival was 89%, with 95% in the mild and 82% in the severely acidotic groups.

Conclusions: Noninvasive ventilation is effective in the treatment of patients with severe acidosis due to acute hypercapnic COPD.

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Introduction

Noninvasive mechanical ventilation (NIV) has been shown to be an effective adjunct to standard medical treatment (controlled oxygen, bronchodilators, corticosteroids and antibiotics) in the treatment of acute hypercapnic respiratory failure.
(ARF) caused by exacerbations of chronic obstructive pulmonary disease (COPD).

Previous studies have shown NIV treatment to reduce length of hospital stay and the need for mechanical ventilation via endotracheal intubation (MV-ETI) plus improve arterial blood gases at 1 h faster than with standard medical treatment alone. In reducing the need for MV-ETI, the risks associated with this intervention (e.g. barotrauma or ventilator-associated pneumonia) are also significantly reduced.

Previous studies have suggested that the initial pH upon presentation is important in determining outcome from NIV. A large multicentre European analysis of 1033 patients with acute hypercapnic COPD requiring NIV suggested that if the initial pH was <7.25, there was a significantly higher odds ratio (OR 1.97, 95% CI 1.23–3.15) of failure with NIV, with pH being the most important biochemical variable. Moreover, if the pH measured 2 h later was <7.25, the odds ratio of NIV failure was 21.02 (95% CI 10.07–43.87). Similarly, Moretti and colleagues found that following the pre-admission activity level, the initial pH was the strongest physiological predictor of NIV success in a group of 137 patients with acute hypercapnic COPD. Squadrone et al. reported a high failure rate (~63%) with the use of NIV in a severely acidic (pH <7.25) group of 64 COPD patients managed in their intensive care unit (ICU). In many studies a pH <7.20 is regarded as an indication for ETI.

The largest randomised controlled study examining the effects of NIV delivered in UK general district hospital medical wards on ARF in COPD exacerbations found that the subgroup of patients with a pH <7.30 tended to have a worse outcome when treated with NIV than less acidic patients. However, this study was not specifically powered for this subgroup analysis. As a result of such data recently published guidelines for the use of NIV usually include pH thresholds of 7.25, below which NIV may not be as effective and safe.

The location of NIV delivery within a hospital varies between countries and is influenced by local factors including nurse (or respiratory therapist) to patient ratio, monitoring facilities and adequacy of staff training. There are variations in the guidelines published by learned bodies including the degree of respiratory acidosis at which NIV can be instituted on the ward and the severity of acidosis at which ETI should be considered.

Thus, patients with severe ARF are common and frequently present physicians with dilemmas as to how best to manage them both in terms of the type of respiratory support offered and the best location for this support. Given that NIV use has become more widespread with increasing clinician experience over the past decade and that guidelines are based upon data usually collected 5–10 years earlier, we therefore sought to examine our recent experience of the use of NIV in a dedicated nonICU respiratory ward for patients with acute hypercapnic exacerbations of COPD and varying degrees of respiratory acidosis.

Methods

Consecutive patients with COPD admitted during the 12 months of 2004 to the Alfred Hospital Emergency Department who were treated with standard medical treatment and had required NIV were studied. The Alfred Hospital is a 300 bed university-based teaching hospital and tertiary referral centre. The study was approved by the Alfred Hospital Ethics Committee (number 175/05) and all patients provided informed consent.

The NIV service has been active for over 10 years and is run by two specialist physicians with support from one respiratory nurse specialist and one pulmonary fellow and liaison with emergency and intensive care wards. All patients receive NIV on the respiratory ward staffed by nurses who receive six monthly NIV updates and provide a nurse: patient ratio of 1:4. Portable monitoring is available in the respiratory ward with continuous oximetry with heart rate and regular arterial blood gas sampling but no invasive monitoring. Close links are maintained with a geographically separate ICU (1:1 nurse:patient ratio) by means of an ICU liaison team who are readily accessible. All hypercapnic COPD patients admitted to our hospital are referred to our service.

Patients were regarded as having COPD based upon clinical history, radiological and lung function and were included if they were dyspneic, hypercapnic (PaCO₂ >45 mmHg), acidotic (pH <7.35) and breathing spontaneously on presentation in the emergency department. Patients were excluded if they had cardiac instability or pulmonary oedema, pneumothorax, impaired conscious state (Glasgow Coma Scale <8), inability to protect their airway or a history of asthma as indicated by significant reversibility to β₂ agonists (improvement in FEV₁ by >15% and 200 ml from baseline) on prior testing. Anthropometric data on height, weight and derived body mass index (BMI) and long-term oxygen therapy (LTOT) prior to admission were recorded.

The duration of admission and need for ETI were recorded. The initial blood gases on referral to our
NIV service, supplementary FiO\textsubscript{2}, ventilator settings, time (in hours) to pH > 7.35 and duration of NIV use were noted. Severity of illness was assessed using the Simplified Acute Physiology Score II (SAPS II),\textsuperscript{17} a severity score mainly based on physiological parameters. Higher scores are associated with higher probability of ICU mortality. Arterial blood gases and respiratory rates were recorded at initiation and after 1 h of NIV with repeat blood gases performed 1–4 hourly until clinical stability and improved blood gases (pH > 7.35 and PaCO\textsubscript{2} reduced) were achieved. Failure of NIV was defined as a worsening of pH or increased PaCO\textsubscript{2} despite correct NIV administration, the need to protect the airway, hemodynamic instability or agitation, inability to tolerate the mask, unexpected death or if MV-ETI was considered appropriate by the treating team.

NIV was delivered via Vision, Synchrony or BiPAP-ST (Respironics, Murrysville, USA) device. The Vision was commenced in ED and then patients were transferred to the Synchrony or BiPAP-ST for ward use. A back-up rate of 12 breath per minute was routinely set on the latter machines. Inspiratory pressure (IPAP) of 10 cmH\textsubscript{2}O and expiratory positive airway pressure (EPAP) of 5 cm H\textsubscript{2}O were initially set and pressures adjusted depending on comfort, arterial blood gases and clinical response with oxygen added to maintain SpO\textsubscript{2} 88–92\%, as per our institution’s guidelines which are based upon published recommendations.\textsuperscript{12–15} The mask used was usually a full face mask (Resmed, New South Wales, Australia) initially and later changed to nasal mask (Resmed Ultra Mirage Nasal, New South Wales, Australia) once clinical stability and/or improvement was achieved. Special care was taken to ensure comfortable mask fit and adequate seal. Standard clinical observations (respiratory and heart rate, SpO\textsubscript{2}, blood pressure) were recorded.

Patients were initially managed in emergency department (ED) for ~4 h and later in the respiratory ward. Usual treatment with antibiotics (if clinically appropriate), steroids, bronchodilators and oxygen plus nursing and allied healthcare (e.g. physiotherapy) and was provided equally to both groups.

**Statistical analysis**

All statistical analysis was performed using SPSS version 11.0 (Statistical Package for Social Sciences, Chicago, USA). All data were tested for normality of distribution using Shapiro–Wilk W-tests. Parametric data is expressed as mean ± SD and nonparametric data as median (IQR) unless otherwise stated. Parametric data measured on one occasion was compared using the unpaired Student’s t-test and for nonparametric data comparisons were made for unpaired samples using the Mann–Whitney U-test. Correlations were performed using Spearman’s rank correlation test. Chi squared was used to compare nominal data. P values < 0.05 were accepted as statistically significant.

**Results**

Within the 12 month data collection period, there were 153 patient admissions to the NIV service. Thirty six admissions fulfilled the entry criteria of the current study (Fig. 1). The 36 patient admissions involved 29 patients, 5 patients having two separate admissions and 1 patient having three admissions. There were no admissions to ICU with acute hypercapnic COPD requiring NIV during this period.

![Figure 1 Flow diagram of patient inclusion in study.](image-url)
Of the 36 patient admissions with acute hypercapnic COPD, there were 17 episodes with severe acidosis and 19 episodes of mild acidosis and their demographic data and SAPS II scores are shown in Table 1. The two groups were similar in terms of age, sex, BMI, spirometric values (FEV1 and FVC) and the number in each group who had been prescribed LTOT. There was a tendency for patients with a severe acidosis to have higher SAPS II score although this did not reach statistical significance \( P = 0.08 \).

Initial blood gas values on admission, initial FiO2 and during NIV are shown in Table 2, and as expected the pH was significantly lower and PaCO2 was significantly higher in the severe group \((P<0.01, P<0.01, \text{respectively})\). While there was no statistical difference in PaO2 between the groups, it did tend to be higher in the more severe group \((P = 0.15)\) and a negative correlation between the pH and initial FiO2 was noted \((r = -0.66, P<0.01)\). There was no difference between the initial mean (so) HCO3 values between the severe acidotic and mild acidotic groups \((38.0 (8.4) \text{ vs } 33.5 (7.1) \text{ mmol/l}, P = 0.08)\).

The changes at 1 h in respiratory rate and pH after initiation of NIV are shown in Figs. 2 and 3, respectively. There was a significant improvement in respiratory rate after 1 h of NIV in both the severe acidotic \((28.6 \pm 4.9 \text{ breaths/min, } P<0.01)\) and mild acidotic groups \((28.5 \pm 7.9 \text{ to } 22.5 \pm 6.9 \text{ breaths/min, } P<0.01)\). There were similarly significant improvements in pH \((7.15 \pm 0.03 \text{ to } 7.27 \pm 0.04, P = 0.01 \text{ and } 70.7 \pm 15.3 \text{ to } 63.8 \pm 12.1 \text{ mmHg, } P = 0.01)\). There were no significant differences between the two groups in change in respiratory rate, pH or PaCO2 over 1 h. No serious side-effects attributable to the use of NIV were noted.

The median (IQR) NIV settings used were similar in both severe and mild acidotic groups (IPAP 12 (11–13) and EPAP 6 (5–6) cmH2O). The time to normalise pH, duration of NIV use and hospital stay for the two groups are shown in Table 3. There were no significant differences between the groups in any of these indices. To investigate the possible impact of hyperoxia on the results, admissions were analysed in terms of patients who were relatively hyperoxic on admission (defined arbitrarily as PaO2 > 70 mmHg) and those who were relatively hypoxic (PaO2 < 70 mmHg). There were no differences between the normoxic and hyperoxic groups in respiratory rate after 1 h of NIV in both the severe acidotic \((28.6 \pm 4.9 \text{ breaths/min, } P<0.01)\) and mild acidotic groups \((28.5 \pm 7.9 \text{ to } 22.5 \pm 6.9 \text{ breaths/min, } P<0.01)\). There were similarly significant improvements in pH \((7.15 \pm 0.03 \text{ to } 7.27 \pm 0.04, P = 0.01 \text{ and } 70.7 \pm 15.3 \text{ to } 63.8 \pm 12.1 \text{ mmHg, } P = 0.01)\). There were no significant differences between the two groups in change in respiratory rate, pH or PaCO2 over 1 h. No serious side-effects attributable to the use of NIV were noted.

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in terms of the pH on admission or initial \( \text{PaCO}_2 \) values, the time to normalise pH, duration of NIV use and hospital stay (Table 4).

Four patients died during the admission, three in the severe acidotic group (initial pH values of 7.00, 7.15 and 7.19) and one in mild acidotic (initial pH value of 7.30) group. Each of these patients had severe end-stage COPD. Each had improved with NIV without the need for MV-ETI (i.e. each had normalised their pH and \( \text{PaCO}_2 \) fallen), however they were difficult to wean from NIV, volunteered their desire for palliation and expressed a wish not to undergo intubation. They were palliated and subsequently died. Although the death rates were 18 and 5% in the severe and mild acidotic groups, respectively (11% overall), all were “expected” and accordingly the NIV failure rate was zero. All patients who survived the exacerbation were still alive at 28 days.

### Discussion

To the best of our knowledge, this is the first study to compare the effectiveness of NIV in patients with severe and mild acidosis secondary to acute hypercapnic COPD. The major finding was that the time to normalise pH and improve \( \text{PaCO}_2 \), the duration of NIV use, length of stay in hospital and failure rates with NIV were similar in hypercapnic COPD groups with severe (pH \( < 7.25 \)) and mild (pH 7.25–7.35) acidosis. The mortality rate was 11% overall with 5% in the mild and 18% in the severe acidotic groups which compares favourably with published figures of 7–62%.4,10 All such deaths were not unexpected and included palliative care management. Importantly, this study was conducted in a nonICU dedicated respiratory ward.

The two groups of acute hypercapnic COPD patients were divided upon an arbitrary pH value.
of 7.25. This value was derived from both published guidelines and from a previous study suggesting that patients with acute COPD and a pH < 7.25 have a significantly greater mortality compared with patients with pH > 7.25. However, in the latter study the more acidotic patients were also noted to be more hypotensive and uraemic suggesting that they may have been more systemically unwell. None of the patients included in our study were hypotensive or had significant renal impairment. We observed no difference between the two groups in terms of lung function, BMI, age and frequency of prior use of LTOT. However, the severe acidotic group had a tendency to have a higher SAPS II score than the mild acidotic group indicating a more severe acute presentation.

It is known that initial low pH is an indicator of NIV failure and that in many studies a low pH (< 7.25) would signal the need for MV-ETI. Other studies suggest that the change in pH is predictive of success. All patients with severe acidosis in our
The study had a good initial response to NIV as shown by the improvements in pH after 1 h of NIV and therefore were more likely to succeed with this modality. It must also be acknowledged that some patients had multiple admissions and thus there may have been a learning effect in that these patients were perhaps more likely to succeed with NIV.

Although the two groups had similar initial PaO₂ values, we noted a significant negative correlation between pH and FiO₂ suggesting the possibility that the degree of acidosis may be related to the initial FiO₂. This finding has been reported by other investigators. Whether the hyperoxic group in our study would have normalised their pH and PaCO₂ values with back titration of oxygen without the need for NIV was not tested. Indeed we are not aware of any study which has specifically addressed the issue as to whether back-titration of oxygen alone would satisfactorily treat acute respiratory failure in this group of patients. In addition, the fact that there was no difference in time to normalise pH, duration of NIV use or length of hospital stay between patients who were hyperoxic, and those who were not, would suggest that hyperoxic patients are not different from other patients in terms of their likelihood of NIV success. Plant et al. noted that only 20% of their mildly acidotic patients (pH 7.25–7.35) normalised their pH without the need for NIV. Moreover, Moloney et al. have reported only ~13% COPD patients with an acute hypercapnic exacerbation developed worsening of hypercapnia with controlled oxygen therapy. Thus, the likelihood of hyperoxia as being the main or only contributor to NIV success in our study is unlikely.

The long-term morbidity and mortality of those who suffer acute respiratory failure is known to be very high. Of those who survive an episode of ARF requiring NIV, 80% will be admitted in the subsequent year and 50% will have died in the same period.22 Within hospital mortality for patients with severe COPD is estimated to be ~12%,20 which is not dissimilar to the overall 11% mortality we observed. Of note, the mortality rate was higher in the severe acidotic group compared with the mild acidotic group (18 vs 5%) but as stated above, all patients who died, did so with palliative intent due to extremely severe and disabling end-stage COPD.

In a study specifically examining the outcome of severely acidic patients in an ICU setting Squadrone et al. compared 64 patients with hypercapnic respiratory failure due to an exacerbation of COPD (mean age ~70 years, pH ~7.18 and FEV₁ ~35% predicted normal) who received NIV to a historical matched group who had been treated with MV-ETI. NIV failed in 40 (62.5%) patients who went on to be intubated. Conti et al. undertook a prospective randomised trial of NIV vs MV-ETI in an ICU setting in acidemic hypercapnic COPD patients with similar age (~72 years), FEV₁ (~30%), PaCO₂ (~86 mmHg) and pH (~7.20) to those in our study group. Their overall mortality was 22%, NIV failure (requiring MV-ETI) was 52%, average length of NIV treatment was 28 h and average ICU length of stay 7 days. In comparison, although our severe acideamic group had similar mortality (18%), important differences were the absence of NIV failure and longer mean NIV use (48 h) yet similar hospital length of stay (9 days) without the need for ICU. Thus, important differences exist in the NIV failure rates of Conti and in our series. The reasons for this are not entirely clear to us. It is known that studies performed in an ICU setting tend to have higher rates of MV-ETI despite similar blood gas data. Patients who are treated promptly and efficiently in ED and on the nonICU wards may well respond quickly to standard medical and NIV therapy and thus may have better outcomes than those who remain acidic despite multiple interventions and are subsequently managed in the ICU. Avoiding the noisy sleep disturbing environment of ICU may also be advantageous and a formal study to compare NIV delivery in ICU vs a respiratory ward would be of great interest.

| Table 4 The effects of initial oxygenation on time to normalise pH, duration of NIV use and length of hospital stay (results shown as median (IQR)). |
|-----------------|-----------------|-----------------|
|                  | PaO₂ < 70 mmHg  | PaO₂ > 70 mmHg  |
|                  | (n = 14)        | (n = 22)        |
| PH               | 7.26 (7.19–7.32)| 7.25 (7.18–7.28)|
| PO₂ (mmHg)      | 50 (46–60)*     | 96 (82–134)*    |
| PCO₂ (mmHg)     | 88 (64–112)     | 80 (61–109)     |
| Time to normalise pH (h) | 12 (5–34)  | 13.5 (6–33)   |
| NIV duration (h) | 55 (45–110)   | 47 (32–73)    |
| Length of stay (days) | 10 (7–17)   | 9 (6–18)     |

*P < 0.01.
Experience with NIV within an institution also allows greater use of NIV outside of an ICU setting. Carlucci et al.\textsuperscript{25} reported the in-hospital NIV failure to be 17\% and overall mortality 8\% in 248 patients with acute hypercapnic COPD (mean pH $\sim$7.23, PaCO\textsubscript{2} $\sim$86 mmHg) over a 7 year period. Importantly, they noted that the use of NIV outside the ICU ward was increasing in patients with a greater severity of respiratory disease without alterations to survival rates. The shift from ICU dominated to a combined ICU and medical ward use of NIV was rewarded by 16\% reduction in daily healthcare costs. The authors comment that while initial pH may be a predictive factor in the treatment of ARF, factors such as staff familiarity with the use of NIV and refinements of its use over a period of time may be more important and influence greatly the chance of success of NIV in a particular unit. Thus, it is possible that the results we achieved may not be found in an institution with less experience, regardless of the actual location of delivery.

It is important that institution of a trial of NIV does not delay other therapies including MV-ETI if necessary. Squadrone et al.\textsuperscript{10} showed that in severely acidic patients in whom NIV succeeded there was a significant reduction in ICU mortality, ICU stay and serious complications as compared to those who required MV-ETI. When comparison was made between those who failed NIV and went on to be intubated and those who were initially intubated there were no significant differences in ICU or hospital mortality or in the numbers who developed serious complications. This would suggest that in this group of patients a trial of NIV is worthwhile in view of the reduction in serious complications in the patients who succeed. It also demonstrates that a trial of NIV is not detrimental to the outcome as compared to patients who are intubated immediately.

In summary, this study provides strong data that the provision of NIV is similarly effective in severe and mild acidic hypercapnic COPD patients. Second, this can be achieved in a nonICU respiratory ward with educated staff. Whether this is related to the experience of the unit providing care is as yet unknown. However, given the prevalence of patients presenting with severe respiratory acidosis and the current controversies regarding this group, this is an area which deserves further study.

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References


