Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome

P K Plant, J L Owen, M W Elliott

Abstract

Background—Non-invasive ventilation (NIV) reduces the need for intubation and the mortality associated with an exacerbation of chronic obstructive pulmonary disease (COPD). This study aimed to identify factors that could be used to stratify patients according to their risk of requiring invasive mechanical ventilation. The second aim was to determine the long term survival of patients treated with and without NIV.

Methods—In this prospective multicentre randomised controlled trial 118 patients were allocated to standard treatment and 118 to NIV between November 1996 and September 1998. Arterial blood gas tensions and respiratory rate were recorded at enrolment and after 1 and 4 hours. Prognostic factors were identified using logistic regression analysis. All patients were followed until death or 1 January 1999.

Results—At enrolment the H^+ concentration (OR 1.22 per nmol/l, 95% CI 1.09 to 1.37, p<0.01) and Pa_{CO_2} (OR 1.14 per kPa, 95% CI 1.14 to 1.81, p<0.01) were associated with treatment failure. Allocation to NIV was protective (OR 0.39, 95% CI 0.19 to 0.80). After 4 hours of treatment improvement in acidosis (OR 0.89 per nmol/l, 95% CI 0.82 to 0.97, p<0.01) and fall in respiratory rate (OR 0.92 per breaths/min, 95% CI 0.84 to 0.99, p=0.04) were associated with success. Median length of survival was 16.8 months in those treated with NIV and 13.4 months in those receiving standard treatment (p=0.12). The trend in improved survival was attributable to prevention of death during the index admission.

Conclusion—Initial pH and hypercapnia can be used to stratify groups of patients according to their risk of needing intubation. NIV reduces this risk and progress should be monitored using change in respiratory rate and pH. The long term survival after NIV is sufficiently good to render treatment appropriate.

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Keywords: non-invasive ventilation; chronic obstructive pulmonary disease; long term survival

Department of Respiratory Medicine, St James's University Hospital, Leeds LS9 7TF, UK
P K Plant
J L Owen
M W Elliott

Correspondence to:
Dr P K Plant
Paul.Plant@
gw.sjsuh.northy.nhs.uk

Non-invasive ventilation (NIV) has been shown in randomised controlled trials to improve arterial blood gas tensions and dyspnoea and to prevent the need for intubation in patients admitted to hospital with an exacerbation of chronic obstructive pulmonary disease (COPD) associated with decompensated respiratory acidosis.[1–7] In the two largest trials in-hospital mortality was also reduced. Brochard *et al*, in the ICU environment, reduced the need for intubation from 74% to 25% and mortality from 29% to 9%.[1] In a 14 centre randomised controlled trial we have shown that NIV used early in the admission in the ward environment was, firstly, feasible but also reduced the need for intubation using a priori criteria from 27% to 15%, real intubation rates from 10% to 6%, and in-hospital mortality from 20% to 10%.[7]

If ward based NIV is to be widely adopted into clinical practice, it would be useful to identify individuals who are likely to fail to respond to NIV either before or shortly after a trial of therapy. This will allow such patients to be managed in a higher dependency area or an ICU with ready access to invasive mechanical ventilation. The failure to do this may lead to a delay in intubation and an increase in mortality.[8]

It is also possible that the subgroup in which death is avoided is a high risk group who will die shortly after discharge in association with another exacerbation. If this occurs, the appropriateness of offering NIV in the first place may need to be questioned. This paper reports the long term survival of patients recruited into the randomised controlled trial and explores the data set for factors associated with treatment failure during the hospital admission.

Methods

CLINICAL TRIAL

The methods for this 14 centre randomised controlled trial have been described previously.[7] Between November 1996 and September 1998, 236 patients admitted to hospital with an acute exacerbation of COPD with a respiratory rate >23/min and a mild to moderate respiratory acidosis (pH 7.25–7.35, Pa_{CO_2} >6 kPa) were randomised to receive standard treatment with (n=118) or without (n=118) the addition of bi-level NIV. Arterial blood gas tensions and respiratory rate were measured at enrolment and 1 and 4 hours after randomisation. The primary end point was "need for intubation". This was defined using a set of objective criteria, avoiding the inconsistencies associated with intubation on clinical grounds. Patient were considered to have "needed intubation" if they met any of the following criteria within 14 days of admission: (a) pH <7.20, (b) pH 7.20–7.25 on two occasions 1 hour apart,

Table 1 Characteristics of patients with acute exacerbations of chronic obstructive pulmonary disease assigned to standard treatment or non-invasive ventilation

Characteristic	Standard treatment (n=118)	NIV (n=118)
Mean (SD) age (years)	69 (8)	69 (7)
M:F	63:55	54:64
Respiratory rate (breaths/min)★	28 (24–40)	28 (24–36)
pH★	7.31 (7.26–7.35)	7.32 (7.25–7.35)
Mean (SD) $Paco_2$ (kPa)	8.65 (1.70)	8.82 (1.51)
Pao_2 (kPa)★	7.00 (4.71–12.31)	6.88 (4.50–13.8)
FEV_1 at discharge (l)★	0.68 (0.37–2.00)	0.71 (0.28–1.47)

$Paco_2$, Pao_2 = arterial carbon dioxide and oxygen tensions; FEV_1 = forced expiratory volume in one second.
★Median data with 5th and 95th centiles.

Table 2 Variables at enrolment associated with failure of treatment

Variable	Univariate analysis p value	Multivariate analysis	
		Odds ratio	p value
Age	0.569		
Sex	0.526		
H^+	<0.001	1.22 (1.09 to 1.37) per nmol/l	<0.01
Pao_2	0.035		
$Paco_2$	<0.001	1.14 (1.14 to 1.81) per kPa	<0.01
Respiratory rate	0.330		
Radiographic consolidation	0.136		
Allocation to NIV	0.038	0.39 (0.19 to 0.80)	<0.01

$Paco_2$, Pao_2 = arterial carbon dioxide and oxygen tensions; NIV = non-invasive ventilation.

Table 3 Relative risk of failure judged at enrolment compared with a patient with a pH of 7.35 and $Paco_2$ 6 kPa treated without NIV

pH	Treatment	$Paco_2$			
		6 kPa	8 kPa	10 kPa	12 kPa
7.35	Standard	1.00	1.30	1.69	2.19
	+ NIV	0.39	0.51	0.66	0.86
7.30	Standard	2.96	3.84	5.00	6.49
	+ NIV	1.15	1.50	1.95	2.53
7.25	Standard	9.98	12.97	16.85	21.90
	+ NIV	3.89	5.06	6.57	8.54

(c) hypercapnic coma (Glasgow coma scale <8 and $Paco_2$ >8 kPa), (d) Pao_2 <6 kPa despite maximum tolerated Fio_2, and (e) cardiorespiratory arrest. Secondary end points included in-hospital mortality.

ANALYSIS OF FACTORS ASSOCIATED WITH FAILURE
The identification of factors associated with failure was carried out using three analytical steps. Univariate analysis was performed between subjects who were managed successfully and those who met the a priori failure criteria. Continuous variables were compared with unpaired *t* tests for parametric data and the Mann-Whitney U test for non-parametric data. Categorical data were compared using Fisher's exact test. All tests and p values were two tailed and analysed on an intention to treat basis. Variables with p values <0.10 were then entered into a forward stepwise logistic regression analysis. Variables with a p value <0.05 were considered statistically significant and are reported as odds ratios (OR) with 95% confidence intervals (CI). Finally, the ability of the derived regression equation to identify those who failed in the trial was considered. Sensitivity, specificity, positive and negative predictive values are reported.

The analysis was firstly performed for variables available at enrolment to try to identify those who will fail before NIV is commenced; these variables were age, sex, pH, $Paco_2$, Pao_2, respiratory rate, consolidation on

chest radiograph, and the decision to offer NIV. pH was converted to H^+ concentration in all analyses. A second analysis was made using variables available 4 hours after randomisation. These included the variables above plus absolute values of H^+ concentration, $Paco_2$, Pao_2, and respiratory rate at 1 and 4 hours as well as change in H^+ concentration, $Paco_2$, Pao_2, and respiratory rate between randomisation and 1 and 4 hours. Analyses were performed using version 7 of the SPSS statistical software package.

LONG TERM SURVIVAL
The survival of the two cohorts of patients was assessed to 1 January 1999 (minimum follow up 3 months, maximum 26 months) by writing and telephoning the patients' general practitioners (GPs). Where GPs were unknown or the patient had subsequently changed their GP, the hospital computerised patient administration systems (PAS) were searched. To allow for data entry onto the hospital PAS, the systems were searched 6 months after the census date. Survival was taken from enrolment in the study and not from the point of discharge. Kaplan-Meier curves were generated for survival data and compared using the log rank test.

Results
CLINICAL TRIAL
One hundred and eighteen patients were allocated to standard treatment and 118 to NIV. The characteristics of both groups were similar (table 1). Thirty two of the 118 patients (27.1%) in the standard treatment group met the primary end point "need for intubation" compared with 18 of the 118 (15.3%) in the NIV group (p<0.02). In-hospital mortality was also reduced: 24/118 (20.3%) of the standard group died compared with 12/118 in the NIV group (10.2%) (p=0.046).[7]

FACTORS ASSOCIATED WITH THE FAILURE OF TREATMENT
At enrolment only three variables were associated with subsequent failure of treatment on univariate analysis (table 2): severity of acidosis (p<0.001), degree of hypercapnia (p<0.001), and severity of hypoxia (p=0.035). Allocation to NIV was protective (p=0.038). On multivariate analysis only three variables remained: H^+ concentration (OR 1.22 per nmol/l, 95% CI 1.09 to 1.37, p<0.01), $Paco_2$ (OR 1.14 per kPa, 95% CI 1.14 to 1.81, p<0.01), and allocation to NIV (OR 0.39, 95% CI 0.19 to 0.80, p<0.01). However, this model had poor discriminant value, only predicting 82% of the outcomes correctly with a sensitivity of 22% and a specificity of 97%. The predictive value of failure was 67% and of success was 83%. Despite this, these three variables are useful for stratifying patients according to risk (table 3). Compared with a patient with a pH of 7.35 and a $Paco_2$ of 6 kPa, a patient with a pH of 7.25 and a $Paco_2$ of 12 kPa has a 22-fold higher risk of meeting criteria for intubation. It can also be seen that the degree of acidosis is a greater risk factor clinically than the extent of hypercapnia.

Table 4   Variables at 4 hours associated with failure of treatment

Variable	Univariate analysis p value	Multivariate analysis	
		Odds ratio	p value
At enrolment			
H^+	<0.001	1.23 (1.05 to 1.43) per nmol/l	<0.01
PaO_2	0.035		
$PaCO_2$	<0.001	1.77 (1.28 to 2.45) per kPa	<0.01
Allocation to NIV	0.038		
At 1 hour			
Fall in H^+	0.119		
Change in PaO_2	0.193		
Change in $PaCO_2$	0.276		
Change in respiratory rate	0.209		
At 4 hours			
Fall in H^+	0.035	0.89 (0.82 to 0.97) per nmol/l	<0.01
Change in PaO_2	0.896		
Change in $PaCO_2$	0.104		
Change in respiratory rate	0.009	0.92 (0.84 to 0.99) per breath/min	0.04

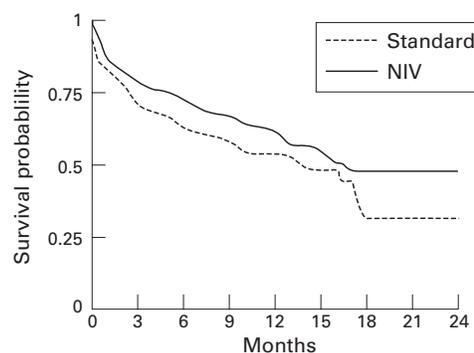$PaCO_2$, PaO_2 = arterial carbon dioxide and oxygen tensions; NIV = non-invasive ventilation.

Figure 1   Kaplan-Meier plot of survival from enrolment. Median survival 13.4 months in standard treatment group v 16.8 months in NIV group (p=0.12).

After 4 hours of treatment two additional variables were associated with treatment success on univariate analysis (table 4): fall in respiratory rate (p=0.009) and an improvement in H^+ concentration (p=0.035). All six univariate variables were entered into the multivariate analysis of which four remained. At 4 hours the factors associated with a worse outcome were severity of acidosis (OR 1.23 per nmol/l, 95% CI 1.05 to 1.43, p<0.01) and hypercapnia (OR 1.77 per kPa, 95% CI 1.28 to 2.45, p<0.01) at enrolment. Fall in respiratory rate between admission and 4 hours was associated with success (OR 0.92 per breaths/min, 95% CI 0.84 to 0.99, p=0.04) as was fall in H^+ ion concentration over the same time period (OR 0.89 per nmol/l, 95% CI 0.82 to 0.97, p<0.01). Allocation to NIV was no longer a statistically significant variable. However, this model also lacked discriminant ability, only predicting 85% of the outcomes correctly with a sensitivity of 30% and a specificity of 97%. The predictive value of failure was 69% and of success was 87%.

Despite this, the changes in H^+ concentration and respiratory rate can be used to assess risk in a clinically meaningful fashion (table 5). An improvement in pH over the first 4 hours from 7.30 to 7.35 is associated with a 47% reduction in the risk of failure. Similarly, a fall in respiratory rate of 8 breaths/min is associated with a 49% reduction in risk.

LONG TERM SURVIVAL
Follow up was achieved for all 236 patients to either death or 1 January 1999. The median survival for all patients enrolled into the study was 15.9 months (95% CI 12.6 to 19.2) with 58.4% surviving at 1 year. There was a trend to improved survival in the group receiving NIV

(fig 1). The 1 year survival in the NIV group was 61.6% compared with 53.9% in the standard treatment group. The median survival rates were 16.8 and 13.4 months, respectively. However, these differences were not statistically significant (p=0.12). The curves suggest that the decline in survival was parallel after the first 3 months. Indeed, at 1 year 78.2% of the NIV patients who were alive at 3 months remained alive, which is very similar to the 75.7% of the standard treatment group.

Discussion
This study shows that the long term survival after NIV for acute exacerbations of COPD is worthwhile and identifies factors which can be used to monitor patients during the in-hospital period. Factors associated with long term survival were not analysed because of the lack of control during the follow up period and the paucity of data on co-morbidity.

LONG TERM SURVIVAL
The patients enrolled in the randomised controlled trial had a 1 year survival of 58%. This is comparable to other long term studies of patients with COPD admitted with respiratory failure where 1 year survival has ranged from 57% to 88% in series where only a proportion of patients required ventilatory support,[9–11] and from 34% to 56% in series where all patients receive ventilatory support.[12–16] This suggests that our survival rates are typical. However, it is difficult to make accurate comparisons between these studies because of variations in study population (especially co-morbidity), the interventions received during the exacerbation (for example, invasive mechanical ventilation), and subsequent outpatient care.

There was a non-significant trend to improved survival in the NIV group compared with the standard treatment group with 1 year

Table 5   Relative risk of failure at 4 hours compared with admission

Initial pH	pH at 4 h	RR −8/min	RR −4/min	RR no change	RR +4/min	RR +8/min
7.30	7.35	0.27	0.38	0.53	0.74	1.03
	7.30	0.51	0.72	1.00	1.40	1.95
	7.25	1.05	1.46	2.04	2.85	3.97
7.25	7.35	0.13	0.19	0.26	0.36	0.51
	7.30	0.25	0.35	0.49	0.68	0.96
	7.25	0.51	0.72	1.00	1.40	1.95

RR = respiratory rate.

survival rates of 62% and 58%, respectively, despite the fact that the study design was biased against such a finding. The control element of the study was lost at the point of discharge. No control was maintained over outpatient care or the management of future exacerbations. The latter is important as some patients would have received NIV in subsequent exacerbations and others—for example, in centres where NIV was only available in trial—would not have received NIV due to prior enrolment. Hence, the comparison of long term survival was biased against showing a survival advantage.

Three other controlled but not randomised trials[17–19] assessing the long term survival of patients with COPD treated with NIV have reported similar findings with 1 year survival rates of 64% (95% CI 49 to 79, n=39),[18] 71% (95% CI 53 to 89, n=24),[17] and 87% (95% CI 69 to 100, n=15).[19] The equivalent survival rates in the standard treatment groups were less at 30% (95% CI 12 to 47, n=27),[18] 50% (95% CI 30 to 70, n=24),[17] and 53% (95% CI 28 to 79, n=15).[19] However, the survival advantage in our study and that of Confalonieri *et al*[17] appeared to be related to the reduction in in-hospital mortality during the index admission rather than a long term protective effect as the decline in survival after 3 months was identical in the two groups.

The data therefore suggest that the benefit of NIV is in improving survival during the exacerbation itself, and that those in whom in-hospital death was avoided do not represent a high risk group. If they had a very poor prognosis, the survival curves would have converged as these patients died early in the follow up period. Moreover, the median survival of 15.9 months is not sufficiently poor to render NIV inappropriate, at least in terms of survival.

FACTORS ASSOCIATED WITH THE FAILURE OF TREATMENT

On admission patients with the worst degree of acidosis and the highest level of $PaCO_2$ were the most likely to meet criteria for intubation (table 3). Of these two variables, acidosis was the most important clinically. The risk of needing intubation was reduced by NIV. After 4 hours improvements in respiratory rate and in acidosis were associated with success (table 5), but had to be interpreted in the light of the initial pH and $PaCO_2$. However, at neither enrolment nor in the first 4 hours was it possible accurately to predict on an individual basis who will or will not meet the criteria for intubation. However, these variables can be used as a clinical guide.

The findings of this study are consistent with previously published studies. A low pH has been shown to be associated with increased mortality[20 21] and the need for intubation[22] in cohorts of patients admitted to hospital with COPD. Moreover, in controlled and uncontrolled trials of NIV a low initial pH[3 23] and a high $PaCO_2$[3 23 24] have been associated with a poor outcome. A fall in $PaCO_2$[23 24] and improvement in pH[4 23–25] have also been shown to be protective.

A change in respiratory rate has not previously been reported as a prognostic factor. The fall in respiratory rate is probably explained by an increase in tidal volume which allows the respiratory rate to fall, thus protecting against fatigue but allowing minute ventilation to be maintained. The improvement in tidal volume may occur due to medical treatment and/or NIV. The absence of "allocation to NIV" as a prognostic variable at 4 hours is initially a little surprising. However, NIV has been shown in randomised controlled trials to improve acidosis and reduce respiratory rate.[1 4 7] These variables therefore reflect not only allocation to NIV, but also response to NIV and, as such, the NIV variable is lost from the logistic regression analysis.

It is also valuable to consider variables that were not significant in the analysis, notably hypoxia and radiographic consolidation. Hypoxia on admission in acute exacerbations has not been shown to be associated with mortality or the need for intubation and, as such, the findings in this study are not surprising.[3 4 20–25] Radiographic consolidation has been shown to be a poor prognostic factor.[18 23 26] However, Rieves *et al*[26] also studied 19 patients with less severe disease and could not find an association with consolidation. They suggested an interplay between disease severity and consolidation. All three studies included patients who were more seriously ill than those in our study. The explanation suggested by Rieves *et al*[26] may explain the lack of association in our study finding. Alternatively, these studies were small (n=59, 33, and 57, respectively) and the finding may be a statistical anomaly which does not appear in our larger study (n=236).

The lack of discrimination in the prognostic models reflects the methodology used. This was a post hoc analysis and potentially important variables were therefore not considered. For example, Ambrosino *et al*[23] found that a low body mass index, a high Apache II score, tachycardia, decreased consciousness, and poor compliance with NIV were associated with failure. These factors were not included in the above analyses because they were not available or, in the case of consciousness, those with a low consciousness were excluded from the trial. The lack of these factors may explain the failure of the models to discriminate in a clinically useful fashion. Notably, health status and lung function before admission were not included. However, in the clinical situation this information is often unavailable within the first 4 hours of an admission.

In conclusion, the initial pH and $PaCO_2$ can be used clinically to stratify patients according to their risk of meeting criteria for intubation. NIV reduces this risk and, once started, the effectiveness of NIV should be monitored using respiratory rate and improvement in acidosis. Changes in $PaCO_2$ and PaO_2 are not associated with either a positive or an adverse outcome and should not be the focus of monitoring. Unfortunately, these variables are not sufficiently predictive to be able accurately to discriminate individuals who will fail and require invasive mechanical ventilation despite

NIV. Further research is required to develop a predictive model as well as to clarify the importance of radiographic consolidation and of a fall in respiratory rate. With regard to long term survival, NIV appears to be associated with a long term survival advantage but this is achieved by avoiding death during the index admission. Those in whom death is avoided seem to have a similar long term prognosis to the whole group, and the median survival is sufficiently good to support the use of NIV in acute exacerbations of COPD.

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