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Is it possible to predict the success of non-invasive positive pressure ventilation in acute respiratory failure due to COPD?

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There is now sufficient evidence that non-invasive positive pressure ventilation (NIPPV) in selected patients with severe hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease (COPD) is more effective than pharmacological therapy alone. The aim of this study was to identify prognostic factors to predict the success of this technique. Fifty-nine consecutive patients with COPD admitted to a respiratory ward for 75 episodes of acute respiratory failure treated with NIPPV were analysed: success (77%) or failure (23%) were evaluated by survival and the need for endotracheal intubation. There were no significant differences in age, sex, cause of relapse and lung function tests between the two groups. Patients in whom NIPPV was unsuccessful were significantly underweight, had an higher Acute Physiology and Chronic Health Evaluation (APACHE) II score, and a lower serum level of albumin in comparison with those in whom NIPPV was successful. They demonstrated significantly greater abnormalities in pH and $PaCO_2$ at baseline and after 2 h of NIPPV. The logistic regression analysis demonstrated that, when all the variables were tested together, a high APACHE II score and a low albumin level continued to have a significant predictive effect. This analysis could predict the outcome in 82% of patients. In conclusion, our study suggests that low albumin serum levels and a high APACHE II score may be important indices in predicting the success of NIPPV.

Key words: non-invasive mechanical ventilation; acute respiratory failure; chronic obstructive pulmonary disease.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) are prone to exacerbations, especially with progression of their disease, which can lead to hypercapnic acute respiratory failure (1). The majority of cases of acute respiratory failure can be treated in a conservative way, the frequency of use of assisted ventilation varies from 16% to 35% in reported studies (2). Endotracheal intubation and mechanical ventilation have been standard therapy when conservative treatment fails. However, this technique exposes the patient to several complications including local airway injury and an increased risk of ventilator associated pneumonia. Patients with COPD may be difficult to wean from ventilation, often require tracheostomies due to the length of intubation, and thus have prolonged stays in intensive care units. Moreover, these patients cannot be refused treatment because of the severity and chronic nature of their disease. It is important to accurately evaluate the recent and past history and to bear in mind that severe COPD patients can live many years beyond the

survival threshold indicated by forced expiratory volume in 1 sec FEV_1 (3). The introduction of non-invasive ventilatory techniques have thus been particularly useful for management of these patients.

Now there is evidence that the use of NIPPV in selected patients with severe hypercapnic acute respiratory failure due to COPD is more effective than pharmacological therapy alone (4–7). The effectiveness of NIPPV results in a significant reduction in rates of intubation and mortality (8). There is concern, however, that when this approach is unsuccessful, the delay in endotracheal intubation and mechanical ventilation may adversely affect the outcome (4, 9–11). The aim of this study was to identify prognostic factors in order to predict whether patients with COPD could be successfully treated with NIPPV and also to avoid unnecessary delay in intubation of those who deteriorate on NIPPV.

Materials and methods

PATIENTS

Between October 1996 and October 1998, 137 COPD patients with acute respiratory failure were treated with bilevel pressure support ventilation via a nasal or a facial

mask. Among this group, 59 patients (39 males and 20 females) admitted to a respiratory ward for 75 episodes of acute respiratory failure were eligible for the study. All patients, usually followed in our institution, were chronically hypoxaemic ($PaO_2 < 8 \cdot 0$ kPa breathing room air) and, moderately hypercapnic ($PaCO_2 < 7 \cdot 3$ kPa) on long-term oxygen therapy. All patients were judged to be in acute respiratory failure and at risk of requiring endotracheal intubation, based on the presence of respiratory distress (severe difficulty in breathing, increased respiratory rate, intercostal or suprasternal retraction, increasing contribution of respiratory accessoty muscles, paradoxical respiratory movements), acute onset of severe hypercapnia ($PaCO_2 > 8 \cdot 7$ kPa) and acute decrease in arterial blood pH ($< 7 \cdot 35$). Exclusion criteria were haemodynamic instability, multiple organ system failure, respiratory arrest or need for immediate intubation, inability to clear secretions and to co-operate, and inability to tolerate the mask because of discomfort. The patients were first treated in an emergency room with conventional medical therapy (bronchodilators, steroids, diuretics, controlled oxygen therapy delivered either via 24–31% venturi mask or nasal prongs at $0 \cdot 5$–$2 \, 1 \, \text{min}^{-1}$). Afterwards, patients were transferred to a respiratory ward where, if they met the criteria of the protocol they were submitted to a short (2 h) trial of NIPPV. Ventilation was delivered to the patient using a BiPAP ST-D ventilator (Respironics; Murrysville, U.S.A.) in spontaneous/timed (ST) mode, through a nasal or facial mask. Masks were connected to the ventilator by a single tube equipped with the Sanders NRV-2 valve (Respironics) (BiPAP + SV) to prevent rebreathing of CO_2. Bilevel positive pressure ventilation was performed with a median inspiratory positive airway pressure of 15 cm H_2O (minimum 10 cm H_2O, maximum 20 cm H_2O) and a median expiratory positive airway pressure of 5 cm H_2O (3–6 cm H_2O). Supplementary oxygen was added to the ventilator circuit in order to achieve an arterial oxygen saturation > 90%. If, after 2 h of BiPAP treatment, arterial gas value improved, NIPPV was continued as long as tolerated, even nocturnally, for a period ranging 6–24 h day^{-1} according to the patient's clinical status and gas exchange data.

Patients in whom severe acute respiratory failure persisted or worsened despite NIPPV were admitted to the intensive care unit for intubation and conventional mechanical ventilation. Criteria for endotracheal intubation and mechanical ventilation were at least one of the following: (i) inability for the patient to clear tracheal secretions; (ii) severe encephalopathy; (iii) increase in respiratory rate up to 20% by comparison with baseline; (iv) deterioration in gas exchange defined by greater than 20% fall in PaO_2 or greater than 20% rise in cm $PaCO_2$ compared with baseline; (iv) circulatory shock defined by a sustained systolic blood pressure less than 80 mm Hg.

DATA COLLECTION

The following data were collected from the clinical report: age, sex, weight (kg), height (cm), body mass index (kg m^{-2}) serum albumin levels (g l^{-1}), last spirometric parameters recorded during a period of clinical stability within 1 year prior to admission. Causes of relapse including the following definitions: (a) pneumonia—presence of lung infiltrates on the chest radiograph combined with any three of the following: fever, positive blood cultures, leucocytosis, or potential pathogenic bacterial cultures from sputum; (b) exacerbation of COPD—increased dyspnoea associated with no obvious cause for respiratory compromise. APACHE II score (12) was recorded at the moment of starting NIPPV. Arterial blood gases were measured by arterial radial puncture immediately before (baseline) and 2 h after onset of NIPPV, with all patients breathing oxygen. The arterial oxygen tension (PaO_2) was normalized by the fractional concentration of inspired oxygen (PaO_2/FiO_2 ratio). Failure of NIPPV was defined by the need for endotracheal intubation or death during NIPPV.

STATISTICAL ANALYSIS

Comparison of differences of successful versus unsuccessful treatment was performed using Student's unpaired *t*-test for continuous variables. Dichotomous variables were compared with χ^2-test with Yate's correction. Comparison of baseline data with those recorded during NIPPV was performed using a paired *t*-test. A *P*-value of less than $0 \cdot 05$ was considered significant. The predictive models were developed using discriminant logistic analysis. All the variables shown on Table 1 were tested to reveal differences in variables behaviour between the successful and failure group, after they have been tested by univariate procedure. A software package (SYSTAT, Inc. Evanston, IL, U.S.A.) was used for statistical analysis.

Results

NIPPV was successful in 58 episodes of acute respiratory failure (77%) and unsuccessful in 17 patients (23%) according to survival and to need for endotracheal intubation. The overall mortality was $11 \cdot 8$% (seven of 59 patients). One patient died in our respiratory ward during NIPPV, six patients in group 2 died despite endotracheal intubation and invasive mechanical ventilation performed in the intensive care unit. The most frequent cause of acute respiratory failure in all patients was an exacerbation of COPD (84%), pneumonia was found in 16%. Table 1 compares causes of acute respiratory failure, demographic, anthropometric and clinical status in the group of patients successfully treated with NIPPV and in the group in who this failed. There were no significant differences in age, sex, causes of relapse and lung function tests between the two groups. Patients in whom NIPPV was unsuccessful were significantly underweight, had a higher APACHE II score, and a lower level of serum albumin in comparison with those in whom NIPPV was successful. Arterial blood gas tension before and during the initial trial of NIPPV are shown in Table 2. Patients in group 2 had significantly lower baseline pH and higher $PaCO_2$ than those in group 1. The level of oxygenation as assessed by $PaCO_2/FiO_2$ was

TABLE 1. Demographic characteristics and physiological measurement of patients according to outcome of non-invasive mechanical ventilation*

	Group 1 (n = 47)	Group 2 (n = 12)	P-value
Number of episodes of ARF	58 (77%)	17 (23%)	
Age (years)	70 ± 10	70 ± 7	NS
Weight (kg)	75 ± 22	63 ± 17	< 0·05
Body mass index ($kg\,m^{-2}$)	28 ± 7	24 ± 5	< 0·05
Albumin ($g\,L^{-1}$)	37 ± 4	33 ± 5	< 0·01
FEV_1 % pred	38 ± 12	37 ± 14	NS
VC % pred	62 ± 11	61 ± 15	NS
FEV_1 VC %	63 ± 10	62 ± 11	NS
Pneumonia n (%)	9 (15·5%)	3 (17·6%)	
Exacerbation n (%)	49 (84·4%)	14 (82·3%)	
APACHE II	17 ± 3	21 ± 4	< 0·001
Death n	1	6	

*Data expressed as mean ± SD or absolute number and percentage.

TABLE 2. Blood gas levels (means ± SD) at baseline and during non-invasive mechanical ventilation (NIPPV)

	Group 1 successful		Group 1 unsuccessful	
	Baseline	NIPPV	Baseline	NIPPV
pH	7·29 ± 0·05*	7·33 ± 0·05°	7·24 ± 0·06*	7·26 ± 0·06
Pa_{CO_2} mmHg°	9·79 ± 1·54**	8·99 ± 1·49§	11·61 ± 1·77**	10·86 ± 1·82
Pa_{O_2}/FiO_2	27·62 ± 8·15	29·99 ± 8·15	25·65 ± 9·53	27·43 ± 8·11

*$P < 0·005$ for difference between baseline in groups 1 and 2.
**$P < 0·0001$ for difference between baseline in groups 1 and 2.
°$P < 0·001$ for difference between baseline and NIPPV in groups 1.
§$P < 0·01$ for difference between baseline and NIPPV in group 1.

similar in the two groups. NIPPV improved pH and Pa_{CO_2} in both groups (mean reduction in Pa_{CO_2} of 8·1% and 6·5% in group 1 and 2, respectively), but only significantly so in group 1. In group 2 pH and Pa_{CO_2} remained severely compromised. The logistic regression analysis demonstrated that, when these variables were tested together, a high APACHE II score (odds ratio: 1·33; 95% confidence interval: 1·74–1·02) and a low serum albumin level (odds ratio: 0·14; 95% confidence interval: 0·88–0·02) maintained a significant predictive effect. The pH values after 2 h of NIPPV were close to statistical significance. A predictive modelling formula was constructed using these covariates. The sensitivity of this model was 60·4% and the specificity was 88·4%.

Discussion

In this retrospective study the success rate of 77% and mortality rate of 11·8% are in agreement with previous studies (9–11,13,14). The most common conditions leading to acute respiratory failure in COPD are generally associated with bronchial, and sometimes parenchymal, infection (15). Pneumonia as a cause of acute respiratory failure was found in a total of 19 patients out of 75 (16%) with no significant differences between the two groups. A high failure rate among patients presenting underlying pneumonia as the cause of respiratory failure has been reported (13,16). In contrast, our study has reported much lower failure rates for patients with pneumonia, which is in accordance with previous findings (17,18). The differing results of these studies may be attributed to the diversity of patients treated: for example the patients in the Wysocki study (16) were not affected by COPD. In another study by Vitacca et al. (14) no significant difference was found in either admissions or in the 3-month mortality of all patients with or without pneumonia, but the overall 1-year mortality was greater in patients showing lung infiltrates. In our study, the patients were also comparable in the severity of their underlying respiratory disease, as assessed

by similar values of FEV_1 measured in a stable state before acute respiratory failure. Brochard et al. (5) reported spirometric tests performed in survivors at 3 months with no difference between the two study groups. Most of the literature has shown that the degree of airflow limitation is a very reliable index of the severity and the outcome of pulmonary disease (19–22). There is less evidence regarding the clinical course of the subset of patients with severe COPD. Long-term survival for these patients, variously defined as those with an FEV_1 less than 11 or 35% predicted, has been positively correlated to the presence of a bronchodilator response and smoking cessation (23). Rieves et al. (24) analysed COPD patients with acute respiratory failure and reported that the severity of the baseline obstruction alone was not predictive of short-term survival while the mortality risk associated with the presence of pulmonary infiltrates on chest X-ray increased dramatically with declining baseline lung function. These conclusions reflect the inclusion of patients with a broad range of pulmonary functional impairment. Unsuccessful NIPPV was associated with reduced body weight, expressed as absolute and as body mass index, and a lower level of serum albumin. Our data confirm that malnutrition appears to be a risk factor for prognosis confirming the findings of previous reports (13,24–26). Poor nutritional status can adversely affect pulmonary function, not only by impairment of respiratory muscle strength and excercise tolerance (27,28), but also by decreased ventilatory drive and altered lung defence mechanism (29). Some authors (30,31,32) reported worse outcomes in COPD patients with low serum albumin levels. It is possible that visceral proteins reflect the severity of disease and prognosis in critically ill hospitalized patients, more than nutritional status or adequacy of nutritional support (33,34). In our study, the most important independent predictor of outcome was the overall severity of illness on admission as measured by the APACHE II score. The APACHE II scoring system has been shown to have a significant correlation with outcome and mortality in patients with acute respiratory failure due to a variety of pathologies (12), including severe COPD (32). In a study by Vitacca et al. (21), the APACHE II score is seen to be able to prognostically stratify patients and is correlated with a nutritional profile. In a study by Confalonieri et al. (35) a high APACHE II score seems to be correlated with a failure to ventilate with NIPPV. Particularly, an APACHE II score of more than 29 seems to be predictive of failure. In our study we find a significant difference in admission level of acidosis and hypercapnia between patients successfully ventilated with NIPPV and those who failed with NIPPV. NIPPV was effective in reducing $PaCO_2$ levels and pH in both groups of patients. Nevertheless, the absolute level of $PaCO_2$ and pH after the initial trial of NIPPV are significantly lowered only in the patients which are successfully ventilated, while in group 2 patients the values remained severely compromised. Acidosis is an important prognostic factor for acute respiratory failure. A number of studies has confirmed that rapid improvement in the blood pH is crucial for successful ventilation (4,5,10,13,36). Ambrosino et al. (13) found that in a multivariate context only baseline pH had a

significant independent predictive effect of success with ventilation, which was greater when acidosis was less severe. Baseline pH showed a sensitivity of 97% and a specificity of 71%, but this analysis was related only to 41 patients. The use of arterial blood gas tension measured at different levels of FiO_2 has been questioned. However, seeing that our patients were both hypoxaemic and hypercapnic and on long-term oxygen therapy, we were obliged to administer O_2 at the lowest levels of FiO_2 maintain SaO_2 over 90%. The level of PaO_2/FiO_2 did not differ between successful and unsuccessful cases, so we are confident, in accordance with Ambrosino et al. (13), that the level of oxygenation did not influence the values in $PaCO_2$ of the two groups. The logistic regression analysis demonstrated that, when all the variables present in Table 1 were tested together, only a high APACHE II score and a low albumin level maintained a significant predictive effect. This analysis could correctly predict the outcome of NIPPV in 82% of the patients. In particular, the logistic regression analysis showed a sensitivity of 60% and a specificity of 88%. In conclusion, unsuccessful employment of NIPPV may depend not only on the severity of the underlying lung disease (FEV_1) or on the arterial blood gas values ($PaCO_2$, pH) obtained before initiating ventilation, but also on systemic factors such poor nutrition (body mass index, albumin) or on comorbidity and severity of the acute exacerbation (APACHE II score). Further research will be required to identify factors that predict success of NIPPV more accurately, and it is essential that conventional mechanical ventilation by endotracheal intubation be available promptly.

References

1. Wedzicha JA. Non-invasive ventilation for exacerbations of respiratory failure in chronic obstructive pulmonary disease. *Thorax* 1996; **51** (Suppl. 2): 535–539.
2. 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.
3. Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Clin Chest Med* 1990; **11:** 555–569.
4. 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.
5. 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.
6. Ahmed A, Fenwick L, Angus RM, et al. Nasal ventilation vs doxapram in the treatment of type II respiratory failure complicating chronic airflow obstruction. *Thorax* 1992; **47:** 858.
7. Daskalopoulou E, Teara V, Fekete K, et al. Treatment of acute respiratory failure in COPD patients with

positive airway pressure via nasal mask (NPPV). *Chest* 1993; **103:** 271S.

8. Keenan SP, Kernerman PD, Cock DJ, Martin CM, McCormack D, Sibbald WJ. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: A meta-analysis. *Crit Care Med* 1997; **25:** 1685–1692.

9. 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.

10. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. *Chest* 1991; **100:** 445–454.

11. Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. *Intensive Care Med* 1993; **19:** 450–455.

12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13:** 818–829.

13. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M. Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. *Thorax* 1995; **50:** 755–757.

14. 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.

15. Derenne JP, Fleury B, Pariente R. Acute respiratory failure of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; **138:** 1006–1033.

16. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. *Chest* 1995; **107:** 761–768.

17. Meduri GU, Turner RE, Abou-hala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask: First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest* 1996; **109:** 179–183.

18. Chevrolet JC, Jolliet P, Abajo B, Toussi A, Louis M. Nasal positive pressure ventilation in patients with acute respiratory failure: Difficult and time-consuming procedure for nurses. *Chest* 1991; **100:** 775–782.

19. Postma D, Sluiter HJ. Prognosis of chronic obstructive pulmonary disease: the Dutch experience. *Am Rev Respir Dis* 1989; **140:** 100–105.

20. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease: a 15-year follow-up study. *Am Rev Respir Dis* 1979; **119:** 895–902.

21. Vitacca M, Clini E, Porta R, Foglio K, Ambrosino N. Acute exacerbations in patients with COPD: predictors of need for mechanical ventilation. *Eur Respir J* 1996; **9:** 1487–1493.

22. Vitacca M, Foglio K, Scalvini S, Marangoni S, Quadri A, Ambrosino N. Time course of pulmonary function before admission into ICU: a two year restrospective study of COLD patients with hypercapnia. *Chest* 1992; **102:** 1737–1741.

23. Postma DS, Burema J, Gimeno F, *et al.* Prognosis in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1979; **119:** 357–367.

24. Rieves RD, Bass MS, Carter RR, Griffith JE, Norman JR. Severe COPD and acute respiratory failure: correlates for survival at the time of tracheal intubation. *Chest* 1993; **104:** 854–860.

25. Laaban JP, Kouchakji B, Dore MF, Orvoen-Frija E, David P, Rochemaure J. Nutritional status of patients with COPD and acute respiratory failure. *Chest* 1993; **103:** 1362–1368.

26. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary diseases. The National Institute of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989; **139:** 1435–1438.

27. Nishimura Y, Tsutsumi M, Nakata H, Tsunenari T, Maeda H, Yokoyama M. Relationship between respiratory muscle strength and lean body mass in men with COPD. *Chest* 1995; **107:** 1232–1236.

28. Palange P, Forte S, Felli A, Galassetti P, Serra P, Carlone S. Nutritional state and exercise tolerance in patients with COPD. *Chest* 1995; **107:** 1206–1212.

29. Rochester DF, Esau SA. Malnutrition and respiratory system. *Chest* 1984; **85:** 411–415.

30. Burrows B, Earle RH. Prediction of survival in patients with chronic airway obstruction. *Am Rev Respir Dis* 1969; **99:** 865–871.

31. Menzies R, Gibbons W, Goldberg P. Determinants of weaning and survival among patients with COPD who require mechanical ventilation for acute respiratory failure. *Chest* 1989; **95:** 398–405.

32. Connors AF Jr, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am Respir Crit Care Med* 1996; **154:** 959–967.

33. Murray MJ, Marsh HM, Wochos D, Moxness KE, Offord KP, Callaway CW. Nutritional assesment of intensive care unit patients. *Mayo Clin Proc* 1988; **63:** 1106–1115.

34. Boosalis MG, Ott L, Levine AS, *et al.* Relationship of visceral proteins to nutritional status in chronic and acute stress. *Crit Care Med* 1989; **17:** 741–747.

35. Confalonieri M, Aiolfi S, Gandola L, Scartabellati A, Della Porta R, Parigi P. Severe exacerbations of chronic obstructive pulmonary disease treated with BiPAP by nasal mask. *Respiration* 1994; **61:** 310–316.

36. Wysocki M, Tric L, Wolff MA, Gertner J, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. *Chest* 1993; **103:** 907–913.