Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial

Josep Masip, Antoni J Betbesé, Joaquim Páez, Francisco Vecilla, Rosario Cañizares, Jaume Padró, Marco A Paz, Jordi de Otero, Josep Ballús

Summary

Background Non-invasive pressure support ventilation (NIPSV) is an effective treatment for acute respiratory failure in patients with chronic obstructive pulmonary disease. We assessed the efficacy of this therapy in acute cardiogenic pulmonary oedema in a randomised comparison with conventional oxygen therapy.

Methods 40 patients were randomly assigned conventional oxygen therapy or NIPSV supplied by a standard ventilator through a face mask, with adjustment of tidal volume and pressure support in addition to a positive end-expiratory pressure of 5 cm water. Physiological measurements were obtained in the first 2 h and at 3 h, 4 h, and 10 h. The main endpoints were intubation rate and resolution time. Analyses were by intention to treat.

Findings Three patients were withdrawn on the basis of clinical and chest radiography results. Endotracheal intubation was required in one (5%) of 19 patients assigned NIPSV and in six (33%) of 18 assigned conventional oxygen therapy (p=0·037). Resolution time (defined as a clinical improvement with oxygen saturation of 96% or more and respiratory rate less than 30 breaths/min) was significantly shorter in the NIPSV group (median 30 [IQR 15–53] *vs* 105 [50–230] min, p=0·002). NIPSV led to a rapid improvement in oxygenation in the first 2 h. There were no differences in hospital length of stay or mortality.

Interpretation In this study of acute cardiogenic pulmonary oedema, NIPSV was superior to conventional oxygen therapy. Further studies should compare NIPSV with continuous positive airway pressure.

Lancet 2000; **356:** 2126–32

Intensive Care Unit and Cardiology Department, Consorci Sanitari Creu Roja de Catalunya, Hospital Creu Roja de Barcelona, University of Barcelona, Barcelona, Spain (J Masip MD, A J Betbesé MD, J Páez MD, F Vecilla MD, R Cañizares MD, J Padró MD, M A Paz MD, J de Otero MD, J Ballús MD)

Correspondence to: Dr Josep Masip, Intensive Care Department, Consorci Sanitari Creu Roja de Catalunya, Hospital Creu Roja de Barcelona, University of Barcelona, Dos de Maig 301, 08025 Barcelona, Spain
(e-mail: jmasip@medicina.ub.es)

Introduction

Acute cardiogenic pulmonary oedema is a common cause of acute respiratory failure. During the past decade, several studies have shown that continuous positive airway pressure (CPAP) is effective in this setting, through improvement in gas exchange and decrease in the need for intubation.[1–3] CPAP is usually obtained with a hermetic nasal or face mask that has an expiratory valve to maintain a positive pressure at the end of expiration. With this modality, patients do not receive any assistance with respiration. Non-invasive pressure support ventilation (NIPSV) is a new mode of mechanical ventilation without intubation, in which a certain volume of air is delivered by a ventilator during the inspiratory cycle, by means of a preset pressure and through a nasal or face mask. Addition of positive end-expiratory pressure to NIPSV results in a CPAP mode with an assisted inspiration (also called bilevel positive airway pressure). This assistance can improve ventilation indices and vital signs[4,5] more rapidly than CPAP alone and also seems to reduce the work of breathing more effectively in intubated[6] and non-intubated patients.[7] In chronic obstructive pulmonary disease, NIPSV reduces the need for endotracheal intubation, the length of stay in the intensive-care unit, and mortality compared with conventional oxygen therapy.[8–10] In patients with acute respiratory failure from other causes, the effect of NIPSV is less conclusive.[11–13] However, good results have been reported,[14] especially in hypercapnic patients.[15] No study has tested the efficacy of NIPSV over conventional oxygen therapy in acute cardiogenic pulmonary oedema,[16] and the available data come from one prematurely stopped trial of bilevel positive airway pressure versus CPAP[4] and from uncontrolled studies.[17,18] Therefore, we undertook a controlled prospective randomised study to investigate whether the use of NIPSV would decrease the need for intubation and shorten time to recovery as compared with conventional oxygen therapy in patients with acute cardiogenic pulmonary oedema.

Methods

Patients

Our institutional ethics committee approved the study design, and all patients or their next of kin gave written informed consent. We enrolled patients with acute respiratory failure. Inclusion criteria were: dyspnoea of sudden onset with physical findings consistent with pulmonary oedema (widespread rales with or without third heart sound) and typical findings of congestion on a chest radiograph (to initiate treatment as soon as possible, patients could be assigned randomised treatment on admission to the intensive-care unit, before chest radiography). Patients with mild acute cardiogenic

pulmonary oedema (acute heart failure not presenting evident shortness of breath) were not eligible. Exclusion criteria were: cardiogenic shock (systolic blood pressure <90 mm Hg); severe acute or chronic airflow obstruction without evidence of cardiogenic pulmonary oedema; severe chronic renal failure (serum creatinine concentration >265 μmol/L); any neurological impairment that would prevent adherence to the protocol; acute myocardial infarction necessitating thrombolysis; evidence of pneumonia; immediate need for intubation; and absence of pulmonary oedema on a first chest radiograph. Criteria for treatment failure were: cardiac or respiratory arrest necessitating resuscitation or refractory and progressive hypoxaemia (oxygen saturation <80%) with clinical signs of muscle fatigue.

Candidates for the study were recruited in the emergency room or in the ward and were subsequently transferred to the intensive-care unit. Oxygen administration and medical therapy were started before the transfer.

Design

Patients were randomly assigned NIPSV or conventional oxygen therapy administered with a Venturi mask (control group). The randomisation sequence was generated by a table of random numbers. The assignments were placed in closed envelopes with identification numbers that were stored in the intensive-care unit. Each patient's assignment was made on admission to the intensive-care unit by the attending physician, from the next record sheet and the attached envelope. Masking of treatment allocation was not possible.

Patients were placed in a semirecumbent position and were managed by an experienced medical and nursing team, who gave clear instructions and tried to relax the patients. Monitoring by pulse-oximetry and electrocardiography was started, and oxygen therapy was administered with an initial fraction of inspired oxygen up to 0·50, which could be increased if the oxygen saturation remained below 95% after several minutes (with a reservoir mask) in the continuous oxygen group and switching fraction of inspired oxygen on the ventilator up to 1·00 in the NIPSV group). When intravenous access had been obtained, 40 mg furosemide and 4 mg morphine were given. Continuous perfusion of glyceryl trinitrate was started at an initial rate of 1·5 mg/h. If systolic blood pressure was above 180 mm Hg, 1 mg intravenous glyceryl trinitrate was administered. Further doses of morphine (2 mg), furosemide (20 mg), and glyceryl trinitrate were unrestricted according to clinical response. Patients with fast atrial fibrillation received digoxin. An arterial catheter was inserted for blood-pressure control and to obtain blood samples in all the patients. Urinary output was monitored through a Foley catheter. Patients were intubated when the criteria for treatment failure were met. Recording of physiological measurements finished after intubation or 10 h after study inclusion. Patients who survived the acute phase were transferred to the general ward, where an echocardiogram was done.

For patients assigned NIPSV, a ventilator (Puritan Bennett 7200, CA, USA) was connected to a hermetic face mask (Respironics, Murrysville, USA). The degree of pressure support was adjusted to obtain maximum tidal volume of more than 400 mL, without leakage, and was frequently changed to achieve the best response. A positive end-expiratory pressure of 5 cm water was administered to all patients. The sensitivity of the ventilator was decreased to a minimum (0·5 cm water) to allow easier triggering of the machine. Much effort was put into adapting face masks, adjusting them to the face with head straps, sometimes with active nursing help at the beginning. Under the protocol, the duration of NIPSV was 4 h, but if a patient responded very rapidly, the treatment could be stopped earlier. Conversely, in patients with a poor clinical response, with persistent hypoxaemia (ratio of arterial pressure of oxygen to fraction of inspired oxygen <150 mm Hg), the duration of NIPSV could be extended.

Oxygen saturation (by pulse-oximetry), heart rate, respiratory rate, and blood pressure (plus pressure support and tidal volume in NIPSV), were measured every 5 min (for analysis, data every 15 min were used) during the first 2 h, then at 3 h, 4 h, and 10 h. Arterial blood samples were also taken, as soon as possible at entry, every hour for 4 h, then at 10 h, for analysis of blood gases and lactate concentrations. Cardiac enzymes (creatine phosphokinase and its MB isoenzyme) were analysed at study entry, 4 h, and 10 h. Further measurements were made in patients with acute myocardial infarction. An estimation of the illness severity and predicted probability of death was made for each patient by the APACHE II system.[19] First radiographs were assessed by the Battler classification,[20] with scoring of pulmonary oedema in four categories. Resolution of the acute pulmonary oedema was defined as evident clinical improvement with a respiratory rate of less than 30 breaths/min and oxygen saturation of 96% or more. The time for these criteria to be met was called the resolution time.

Statistical analysis

The primary endpoint was the intubation rate. We calculated that a sample size of 40 patients would allow us to detect, at p=0·05, a difference between a postulated 50% rate of intubation and mechanical ventilation in the conventional oxygen group and a 10% rate in the NIPSV group with a power of 80%.

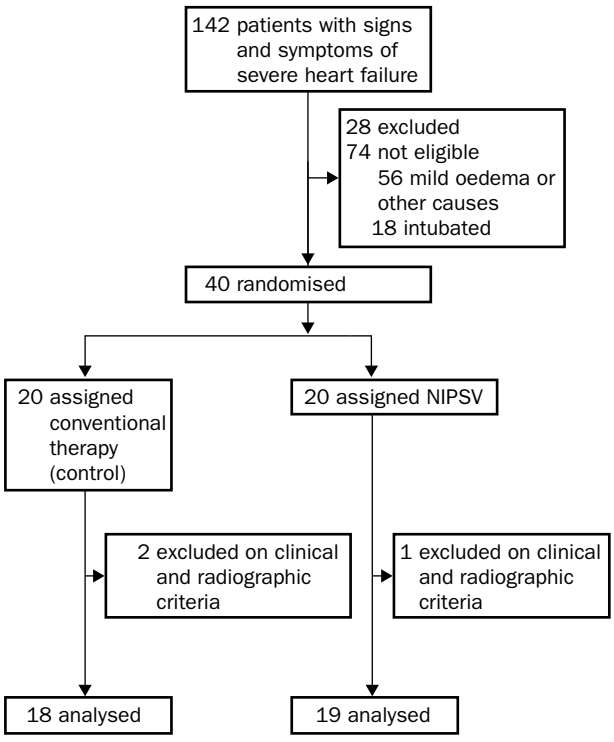

Figure 1: **Trial profile**

	Control group (n=18)	NIPSV group (n=19)
Demography		
Age (years)*	78·5 (5·0)	75·3 (11·0)
Male/female†	11/7	8/11
Condition*		
APACHE II	15·9 (6·0)	16·1 (6·0)
Battler score	3·0 (0·7)	2·8 (0·6)
New York Heart Association class	2·1 (0·7)	1·8 (1·0)
History†		
Heart failure	12 (67%)	10 (53%)
Acute myocardial infarction	12 (67%)	5 (26%)
Hypertension	14 (78%)	15 (79%)
Diabetes mellitus	10 (56%)	6 (32%)
Chronic obstructive pulmonary disease	7 (39%)	3 (16%)

*Mean (SD). †Number of patients.

Table 1: **Baseline characteristics of the patients**

Physiological measurements obtained after intubation were excluded from the analysis, because intubation would produce bias. ANOVA was used to compare the two groups at study entry and at each time. Multiple comparisons were made with ANOVA for repeated measures, with the Bonferroni test for post-hoc analysis. The Kolmogorov-Smirnov test was used to identify variables with normal distribution. Variables without homogeneous variance and normal distribution were compared by non-parametric testing (Mann-Whitney). Fisher's exact test was used for pairwise comparisons. Logistic regression analysis was done to analyse whether baseline characteristics had a significant influence on the intubation rate. All p values are for two-tailed comparisons.

Results

Between April, 1996, and December, 1998, 40 patients were enrolled in the study (figure 1). 102 other patients seen during this period were not included because they did not meet entry criteria. Three patients enrolled were later excluded because they were judged not to have had cardiogenic pulmonary oedema; two were thought to have had pneumonia/bronchopneumonia and one chronic obstuctive pulmonary disease with pulmonary fibrosis. Thus, 19 patients in the NIPSV group and 18 in the control group were included in the analyses.

NIPSV was applied for a mean of 254 min (SD 90). 14 of the 19 patients completed the first 4 h of the protocol (in three, the treatment was extended to 10 h). In the other five, the treatment was stopped early because of vomiting (one case), haematemesis (one), and discomfort from the hermetic face mask after resolution was achieved (three). Mean setting pressure support was 15·2 cm water (SD 2·4; range 10–20). Tidal volumes obtained with NIPSV ranged from a mean of 531 mL (143) at study entry to 627 mL (137) at 4 h.

Baseline characteristics of the patients are shown in table 1 and causes of cardiac decompensation in table 2.

	Number of patients	
	Control (n=18)	NIPSV (n=19)
Hypertension or progressive*	3 (17%)	6 (32%)
Respiratory-tract infection	2 (11%)	4 (21%)
Treatment non-compliance	5 (28%)	2 (11%)
Tachyarrythmia	1 (6%)	1 (5%)
Acute myocardial infarction	6 (33%)	5 (26%)
Unstable angina	1 (6%)	0
Volume overload	0	1 (5%)

*No clear cause of decompensation; the most significant finding was high blood pressure at study entry.

Table 2: **Causes of acute pulmonary oedema**

The proportions of patients with previous myocardial infarction, chronic obstructive pulmonary disease, and diabetes were higher in the control group than in the NIPSV group. The proportions of patients in the two groups with myocardial infarction as a cause of acute cardiogenic pulmonary oedema were similar.

Six (33%) patients in the control group and one (5%) in the NIPSV group needed endotracheal intubation because they met the criteria for therapeutic failure (p=0·037). Thus, the effect size of the intervention was 28% (95% CI 4·5–52·1). Intubation was necessary during the first hour in three patients, owing to cardiac or respiratory arrest, and during the third hour in the other two patients for refractory hypoxaemia (all these patients were in the control group). The remaining two patients needed late intubation (after the first 10 h of the protocol): one (control group) had a poor response to treatment with progressive respiratory failure, and the other (NIPSV group) had an initial good response to therapy but later developed atrial fibrillation and worsening cardiac failure.

Four of the seven intubated patients and seven of the 31 non-intubated patients had acute myocardial infarctions (p=0·09). Intubated patients had worse radiological scores (mean 3·4 [SD 0·5] *vs* 2·8 [0·7], p=0·02) and APACHE II scores (20 [7] *vs* 15 [5], p=0·032) than non-intubated patients. By logistic regression analysis, baseline characteristics had no significant influence on intubation rate.

Two patients assigned conventional oxygen therapy died: one of cardiogenic shock secondary to acute myocardial infarction and one of ventilator-associated pneumonia with septic shock. There were no differences between the control and NIPSV groups in total hospital stay (14·3 [4·0] *vs* 14·2 [5·0] days, p=0·93).

Resolution time was significantly shorter in the NIPSV group than in the control group (median 30 [IQR 15–53] *vs* 105 [50–230] min, p=0·002).

At 15 min, the patients assigned NIPSV showed significantly higher oxygen saturation than those assigned conventional oxygen therapy, and the difference persisted during the first 3 h of the study (figure 2). Similarly, patients assigned NIPSV showed a greater decrease in respiratory rate than those assigned to the control group at 15 min (p=0·009) and 30 min from baseline (p=0·042, table 3). Moreover, the ratio of arterial oxygen pressure to fraction of inspired oxygen was higher in the NIPSV group than in the control group during the first 2 h (figure 2), and the differences from the baseline values were also significantly greater in the NIPSV group than in the control group during the first 4 h. The fraction of inspired oxygen was slightly higher in the NIPSV than the control group during the first 30 min but subsequently it was lower in that group (table 3); the difference between the groups did not reach significance at any time. Although baseline arterial pressure of carbon dioxide was slightly higher in the control group than in the NIPSV group, there were no differences between the groups at any time (figure 2).

In the whole group, six patients (16%) had hypocapnia on admission (arterial partial pressure of carbon dioxide ⩽36 mm Hg), and 16 (43%) had hypercapnia on admission(⩾46 mm Hg), nine in the control group and seven in the NIPSV group. Throughout treatment, only the hypercapnic patients assigned to the NIPSV group showed significant decreases from baseline in arterial pressure of carbon dioxide (p=0·002, figure 3). Furthermore, four of the nine hypercapnic patients assigned to the control group needed endotracheal

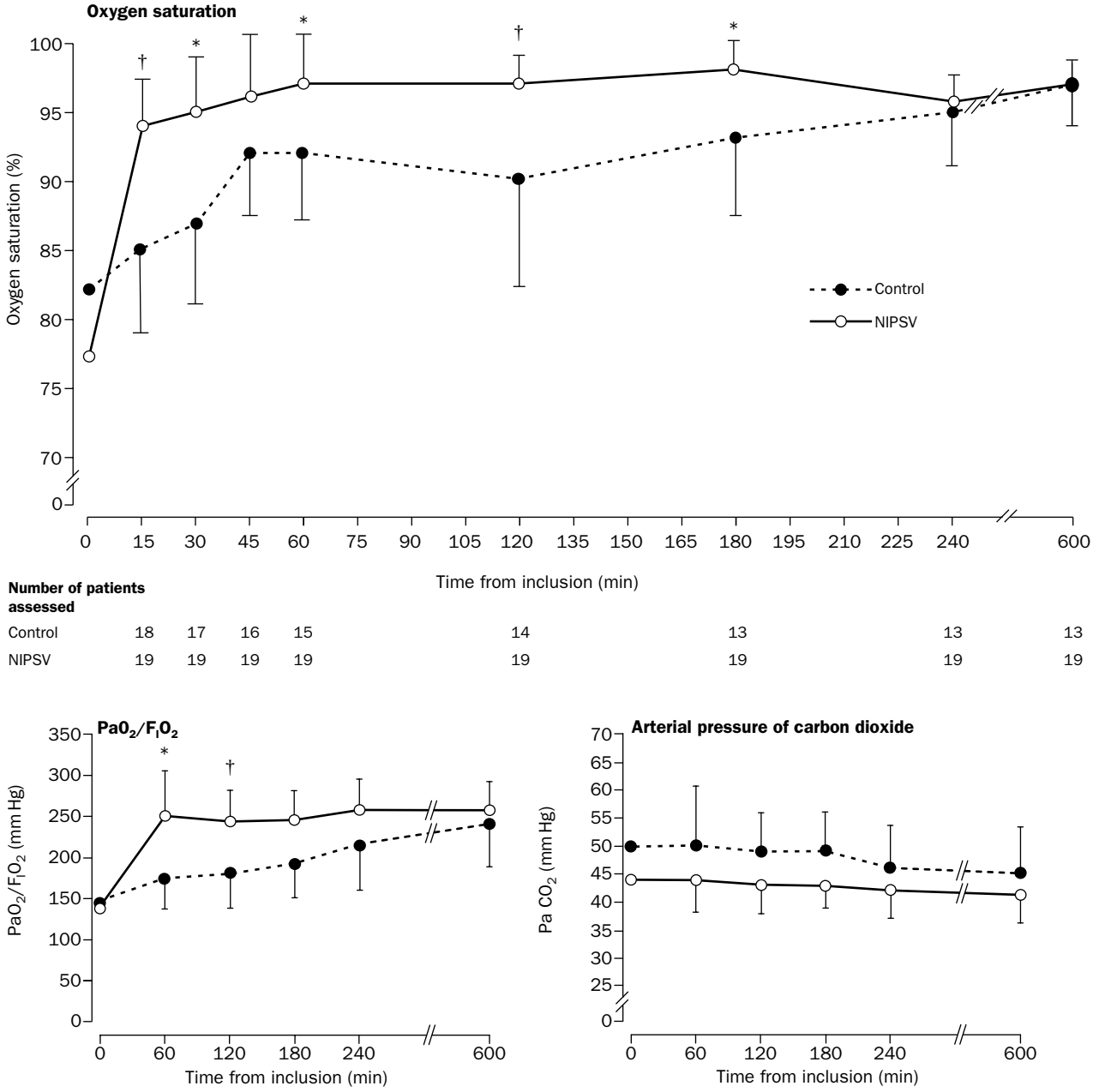

Figure 2: **Measurements of oxygen saturation, ratio of arterial oxygen pressure to fraction of inspired oxygen (PaO_2/FiO_2), and arterial pressure of carbon dioxide in NIPSV and control groups**

Note that time scales differ between sections. Error bars represent upper or lower limits of 95% CI. For difference between groups *p<0·05; †p<0·01.

intubation, compared with none of the seven patients assigned to the NIPSV group (p=0·08). In this study, patients with chronic obstructive pulmonary disease and those without a history of this disorder had similar arterial pressures of carbon dioxide (mean 48 [SD 17] *vs* 47 [13] mm Hg).

There were no differences between the groups in absolute values or proportional changes from baseline in heart rate or systolic, diastolic, or mean blood pressure (table 3). However, in relation to baseline values, arterial pH, lactate concentration, blood pressure, heart rate, and respiratory rate showed significant improvement earlier in the NIPSV group than in the control group. Furthermore, patients in the NIPSV group showed larger increases in arterial pH after 60 min and after 120 min.

We did separate analyses for patients with poor outcome (n=13), defined by resolution time longer than 120 min or need for intubation, to establish indicators of severity. Compared with the patients defined as having a good outcome, these patients had a higher Battler radiological score (3·3 [0·5 *vs* 2·7 [0·7], p=0·009), higher previous New York Heart Association functional class (2·4 [0·8] *vs* 1·8 [0·9], p=0·03), and slightly higher arterial pressure of carbon dioxide (53 [17] *vs* 44 [11] mm Hg, p=0·053) at study entry. At 30 min from baseline, oxygen saturation was lower (84 [9] *vs* 95 [6] %, p=0·003) and respiratory rate higher (34 [5] *vs* 27 [8] per min, p=0·01) in the high-risk group than in the remaining patients. At 60 min, there were also significant differences in pH, ratio of arterial oxygen pressure to fraction of inspired oxygen, arterial oxygen pressure, arterial carbon dioxide pressure, oxygen saturation, and respiratory rate.

	Baseline	15 min	30 min	45 min	60 min	120 min	180 min	240 min	600 min
Pressure support (cm water)									
NIPSV	15·3 (2·5)	15·5 (2·4)	15·5 (2·6)	15·6 (2·5)	15·4 (2·6)	15·2 (2·5)	14·3 (1·9)	14·1 (2·0)	14·7 (4·1)
Tidal volume (mL)									
NIPSV	531 (143)	533 (132)	588 (143)	596 (117)	562 (129)	577 (136)	561 (118)	627 (137)	555 (67)
Fraction of inspired oxygen									
Control	0·45 (0·18)	0·53 (0·12)	0·53 (0·13)	0·67 (0·24)	0·64 (0·24)	0·65 (0·26)	0·66 (0·28)	0·63 (0·28)	0·55 (0·30)
NIPSV	0·47 (0·17)	0·63 (0·23)	0·66 (0·23)	0·66 (0·24)	0·63 (0·23)	0·59 (0·23)	0·56 (0·19)	0·50 (0·14)	0·46 (0·16)
Arterial pH									
Control	7·31 (0·12)	. .	. .	. .	7·29 (0·10)	7·33 (0·10)	7·35 (0·09)	7·35 (0·08)	7·41 (0·06)*
NIPSV	7·29 (0·09)	. .	. .	. .	7·33 (0·07)	7·36 (0·07)	7·36 (0·07)	7·38 (0·07)†	7·41 (0·06)‡
Lactate concentration (mmol/L)									
Control	2·76 (1·76)	. .	. .	. .	2·24 (1·44)	2·22 (1·44)	2·40 (1·89)	2·16 (1·22)	2·23 (1·55)
NIPSV	3·28 (2·44)	. .	. .	. .	2·51 (1·33)	2·26 (1·22)	2·45 (1·22)	2·32 (1·22)	1·88 (0·89)
Mean blood pressure (mm Hg)									
Control	119 (30)	108 (25)	107 (23)	104 (26)	98 (24)	89 (17)*	90 (19)*	88 (15)*	85 (11)†
NIPSV	121 (32)	109 (22)	103 (18)	99 (17)	91 (17)*	92 (13)*	92 (16)†	93 (15)†	89 (10)*
Respiratory rate (breaths/min)									
Control	35·3 (8)	34·2 (9)	30·7 (8)	27·4 (8)	26·3 (8)*	23·8 (7)†	21·6 (9)‡	21·8 (8)‡	20·5 (5)‡
NIPSV	39·2 (8)	32·3 (7)*	28·0 (7)‡	25·8 (7)‡	24·8 (4)‡	19·9 (5)‡	18·8 (5)‡	18·5 (4)‡	20·7 (3)‡
Heart rate (beats/min)									
Control	107 (23)	105 (25)	104 (24)	99 (26)	96 (23)	89 (21)	88 (23)	81 (17)	79 (16)
NIPSV	113 (21)	112 (21)	103 (26)	103 (27)	99 (24)	90 (22)	88 (19)*	85 (16)†	82 (17)‡

Comparison with baseline value: *p<0·05; †p<0·01; ‡p<0·001.

Table 3: **Mean (SD) physiological measurements during the first 10 h of the study (all patients included)**

Discussion

In this study, NIPSV shortened the resolution time of acute cardiogenic pulmonary oedema in comparison with conventional oxygen therapy. This effect could be achieved by several mechanisms: more rapid improvement in oxygenation; more rapid lowering of the respiratory rate, probably as a result of a decrease in the work of breathing; and faster reversal of acidosis (essentially by decreasing hypercapnia). These results are consistent with previous uncontrolled studies of NIPSV in acute cardiogenic pulmonary oedema. The main finding of this study was the decrease in the intubation rate. We also expected to find an effect on the length of stay and mortality, but the study was probably too small to detect differences in these variables.

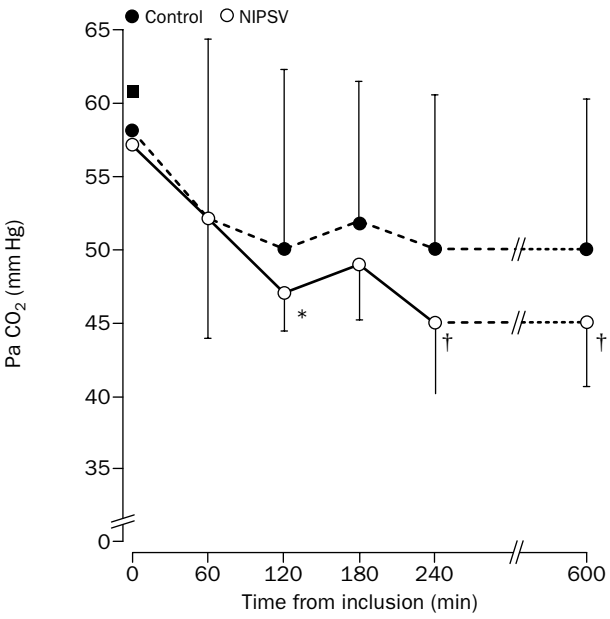

Figure 3: **Measurements of arterial pressure of carbon dioxide in patients with hypercapnia at baseline who completed the 10h of the study (control n=6, NIPSV n=7**

Error bars=upper or lower limits of 95% CI. Square on y axis is mean value for all hypercapnic patients assigned conventional oxygen therapy (n=9). For comparison with baseline *p<0·05; †p<0·01.

The study did not compare NIPSV with CPAP. Although some randomised trials have shown beneficial effects of CPAP in acute cardiogenic pulmonary oedema, the use of this technique is not yet judged standard in the guidelines of the American Heart Association[21] or the European Society of Cardiology.[22] Furthermore, a systematic review[16] highlighted the lack of studies on the usefulness of NIPSV compared with conventional therapy or CPAP. Therefore, we designed a study to compare NIPSV with conventional oxygen therapy. Moreover, assessment of NIPSV versus CPAP in terms of intubation rate would have needed a much larger sample.

Patients with acute cardiogenic pulmonary oedema are generally managed in emergency departments. Therefore, this therapy should be used in that setting. NIPSV was administered in the intensive-care unit in our trial. NIPSV is not complicated, and it has been succesfully used in general wards.[10] Furthermore, the use of a standard ventilator (as in this study) offers advantages, and the same ventilator can be used if the patient has to be intubated.

Some baseline characteristics (table 1) indicated more severe disease in the control group, but the differences did not influence intubation rate and could be counterbalanced because on admission, the NIPSV group had a slightly higher respiratory rate, lower oxygen saturation, and higher lactate concentrations. Patients in NIPSV group received a slightly higher fraction of inspired oxygen during the first 30 min, but subsequently the control group received somewhat higher fraction of inspired oxygen; despite this difference, the ratio of arterial oxygen pressure to fraction of inspired oxygen remained lower than in the NIPSV group during most of the study. We observed that several patients who were almost candidates for intubation in both groups successfully recovered after the fraction of inspired oxygen was increased to 1·00. Previous studies have used a wide range of fraction of inspired oxygen from 0·30–0·60[1,2] to 0·93–1·00.[3,18,23] We believe that high oxygen concentrations (1·00) should be recommended early in the treatment of acute cardiogenic pulmonary oedema, especially if NIPSV is used.

NIPSV was quite well tolerated, and previously decribed side-effects,[24] such as eye irritation and facial-skin necrosis, were not found in this study, probably because the

duration of therapy was short (250 min on average). In previous studies of acute cardiogenic pulmonary oedema, face masks or nasal masks were used with CPAP or NIPSV. However, face masks seem to be more appropriate in this setting because most patients are tachypnoeic, breathing through the mouth, and because nasal respiration may increase airflow resistance.

No significant haemodynamic complications were seen. At study entry, most of the patients had blood pressure high enough (mean systolic pressure 172 mm Hg) to confer protection against the hypotension associated with mechanical ventilation and positive end-expiratory pressure. There were no differences between the study groups in treatment for blood pressure or heart rate in any study interval; thus, the raised intrathoracic pressure caused by NIPSV did not impair the function of a failing heart and even could assist it, as in previous studies with CPAP.[3] Although in patients with cardiac failure and low pulmonary wedge pressure, CPAP and bilevel positive airway pressure may decrease cardiac output,[5] this is not the case for the acute cardiogenic pulmonary oedema, in which patients have high pulmonary wedge pressure. Furthermore, the positive intrathoracic pressure has been reported to increase stroke volume index and to decrease intrapulmonary shunt and left-ventricular afterload without compromising cardiac index.[3,25,26]

An interesting finding of this study was the evolution of arterial carbon dioxide pressure. There were no differences in this variable between the study groups or within a group at different times. High pressures (>45 mm Hg) were detected in fewer than half of the patients, and the values were not higher in patients with a history of chronic obstructive pulmonary disease. Hypercapnia is not a constant finding in acute cardiogenic pulmonary oedema. In our series, 16% of patients even had hypocapnia at study entry. Some investigators[1,3] have reported normal mean arterial carbon dioxide concentrations in their patients with acute cardiogenic pulmonary oedema. Conversely, others[2,4,17] have reported higher than normal carbon dioxide concentrations. Mehta and colleagues[4] found that bilevel positive airway pressure decreased arterial carbon dioxide pressure more quickly than CPAP.[5] In an uncontrolled study, Rustherholtz and colleagues[18] found higher arterial carbon dioxide pressures in patients who responded successfully to NIPSV than in those who did not respond, but these patients had a higher proportion of acute myocardial infarction, which may have biased the results. As others have reported,[4,17] we found that NIPSV lowered carbon dioxide concentrations in hypercapnic patients and tended to reduce intubation in these patients.[20]

Unlike other studies, we found no association between myocardial infarction and NIPSV. Mehta and colleagues[4] interrupted their trial of CPAP versus bilevel NIPSV when a high proportion of patients with myocardial infarction were detected in the NIPSV group, but whether the infarcts preceded or were a consequence of therapy was not clear. Rusterholtz and colleagues[18] found a higher proportion of myocardial infarction in patients who did not respond to treatment and therefore did not recommend NIPSV in patients with myocardial infarction. Nevertheless, Takeda and colleagues[27] described a good response to nasal CPAP in patients with acute cardiogenic pulmonary oedema secondary to myocardial infarction. In our study, the proportion of patients with myocardial infarction was similar in the two study groups. Post-hoc analysis suggested a poorer outlook for patients with myocardial infarction, independently of the therapy used. Myocardial infarction may well have a worse prognosis than other causes of acute cardiogenic pulmonary oedema, because it usually implies impairment of cardiac function. We believe that NIPSV can be used in patients with myocardial infarction.

Not all patients are good candidates for this therapy, because the hermetic face mask causes discomfort in anxious patients (usually needing higher doses of opioids) and the technique requires intensive attention until patients are adapted to face masks and ventilators. Furthermore, about a third of our patients had a rapid response to treatment, and many of these patients probably did not need any additional intervention. NIPSV may produce greater benefit in patients with more severe acute cardiogenic pulmonary oedema, especially in those with severe signs of alveolar oedema on chest radiograph and those with impaired functional class or high arterial pressure of carbon dioxide on admission. In patients initially managed with conventional treatment, if a new assessment is made after 30 min, as Poponick and colleagues suggested,[28] NIPSV should be considered in those who had poor response, with high respiratory rate and low oxygen saturation.

Contributors

J Masip had the original idea and designed the main features of the study and wrote the paper. J Masip, A Betbesé, J Páez, F Vecilla, R Cañizares, J Padró, and J Ballús enrolled patients in the study and they took charge of collecting data during the first 2 h of the protocol. J Betbesé was responsible for obtaining informed consent, the accomplishment of all data in the case report form, and the introduction of data in the computer program. F Vecilla prepared record sheets, randomisation envelopes, and laboratory forms, and tested several face masks and their adaptation to the ventilators. J Páez designed the record sheet, which had a digital clock. R Cañizares, J Padró, and J Ballús helped in collection of data and in the review of previous studies. M Paz took care of the patients in the cardiology ward and carried out the echocardiograms. J Masip, A Betbesé, and J de Otero did the statistical analysis and the main interpretation of the data. All the investigators discussed the results, revised the report critically, and approved the final version.

Acknowledgments

We thank Sergio Zapateria, Natalia Llorens, Cristina González, and Luisa Corral (intensive-care unit physicians), the entire intensive-care unit nursing team (especially Isaura Rodríguez), the whole Emergency Department team (especially physicians Teresa Catà and Josep A Ferreres), students Laura Gonzalez and Judith Sánchez for revision of data, Antonio Torres (UVIR Hospital Clinic, University of Barcelona) for advice, Jordi Mancebo (Hospital Sant Pau of Barcelona) for critical review of the paper, Kathleen Domingo and Joshua Morris for help with language in writing the paper, and Marta Espinalt and Ignasi Gich for statistical support.

This study was financed by the Fondo de Investigación Sanitaria (FIS Grant 1996), Ministerio de Sanidad y Consumo.

References

1 Räsänen J, Heikkilä J, Downs J, Nikki P, Väisänen I, Viitanen A. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Am J Cardiol* 1985; **55:** 296–300.

2 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:** 1825–30.

3 Lin M, Yang YF, Chiang HT, Chang MS, 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:** 1379–86.

4 Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit Care Med* 1997; **25:** 620–28.

5 Philip-Joet FF, Paganelli FF, Dutau HL, Saadjian AY. Hemodynamic effects of bilevel nasal positive airway pressure ventilation in patients with heart failure. *Respiration* 1999; **66:** 136–43.

6 Viale JP, Annat GJ, Bouffard YM, Delafosse BX, Bertrand OM, Motin JP. Oxygen cost of breathing in postoperative patients: pressure support ventilation vs continuous positive airway pressure. *Chest* 1988; **93:** 506–09.

7 Nava S, Ambrosino N, Rubini F, et al. Effect of nasal pressure support ventilation and external PEEP on diaphragmatic activity in patients with severe stable COPD. *Chest* 1993; **103:** 143–50.

8 Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; **333:** 817–22.

9 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:** 1799–806.

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 trial. *Lancet* 2000; **355:** 1931–35.

11 Wood KA, Lewis L, Von Harz B, Kollef MH. The use of noninvasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. *Chest* 1998; **113:** 1339–46.

12 Keenan SP, Kernerman PD, Cook 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:** 1685–92.

13 Wysocki M, Tric L, Wolf MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure: a randomized comparison with conventional therapy. *Chest* 1995; **107:** 761–68.

14 Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-presure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; **339:** 429–35.

15 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:** 1636–42.

16 Pang D, Keenan SP, Cook DJ, Sibbald WJ. The effect of positive pressure airway support on mortality and need for intubation in cardiogenic pulmonary edema: a systematic review. *Chest* 1998; **114:** 1185–92.

17 Hoffmann B, Welte T. The use of noninvasive pressure support ventilation for severe respiratory insufficiency due to pulmonary oedema. *Intensive Care Med* 1999; **25:** 15–20.

18 Rusterholtz T, Kempf J, Berton C, et al. Noninvasive pressure support ventilation (NIPSV) with face mask in patients with acute pulmonary edema (ACPE). *Intensive Care Med* 1999; **25:** 21–28.

19 Knaus WA, Draper EA, Wagner DP, Zimmerman JA. APACHE II: a severity of disease classification system. *Crit Care Med* 1985: **13:** 818–29.

20 Battler A, Karliner JS, Higgins CB, et al. The initial chest x-ray in acute myocardial infarction: prediction of early and late mortality and survival. *Circulation* 1980; **61:** 1004–09.

21 American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on evaluation and management of heart falilure). Guidelines for the evaluation and management of heart failure. *J Am Coll Cardiol* 1995: **26:** 1376–98.

22 Task Force of the Working group on heart failure of the European Society of Cardiology. Guidelines on the treatment of heart failure. *Eur Heart J* 1997; **18:** 736–53.

23 BouquinV, L'Her E, Moriconi M, et al. Spontaneous ventilation in positive expiratory pressure in cardiogenic pulmonary edema. *Arch Mal Coeur Vaiss* 1998; **91:** 1243–48.

24 Hillberg RE, Johnson DC. Noninvasive ventilation. *N Engl J Med* 1997; **337:** 1746–52.

25 Naughton MT, Rahman MA, Hara K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation* 1995; **91:** 1725–31.

26 Lenique F, Habis M, Lofaso F, Dubois-Rande JL, Harf A, Brochard L. Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am J Respir Crit Care Med* 1997; **155:** 500–05.

27 Takeda S, Nejima J, Takano T, et al. Effect of nasal continuous positive airway pressure on pulmonary edema complicating acute myocardial infarction. *Japan Circ J* 1998; **62:** 553–58.

28 Poponick JM, Renston JP, Bennett RP, Emerman CL. Use of a ventilatory support system (BiPAP) for acute respiratory failure in the emergency department. *Chest* 1999;**116:** 166–67.