

NON-INVASIVE VENTILATION IN CARDIOGENIC PULMONARY EDEMA : A MULTICENTER, RANDOMIZED TRIAL

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ABSTRACT (words count=199)

Studies employing Non-invasive Pressure Support Ventilation in cardiogenic pulmonary edema have been performed in the ICU when overt respiratory failure is already present and in small groups of patients. In this multicenter study, carried out in Emergency Departments, 130 patients with acute respiratory failure were randomized to receive medical therapy+O₂ (65 pts) or non-invasive pressure support ventilation (65 pts). The primary end-point was the need for intubation, while secondary end-points were in-hospital mortality and changes in some physiological variables. Non-invasive pressure support ventilation improved PaO₂/FiO₂, respiratory rate and dyspnea significantly faster. Intubation rate, hospital mortality and duration of hospital stay were similar in the two groups. In the subgroup of hypercapnic patients non-invasive pressure support ventilation improved PaCO₂ significantly faster and reduced the intubation rate compared to medical therapy (2/33 vs 9/31 p=0.015). Adverse events, including myocardial infarction were evenly distributed in the two groups. We conclude that during acute respiratory failure due to cardiogenic pulmonary edema the early use of non-invasive pressure support ventilation accelerates the improvement in PaO₂/FiO₂, PaCO₂, dyspnea and respiratory rate, but does not affect the overall clinical outcome. Non-invasive pressure support ventilation does, however, reduce the intubation rate in the subgroup of hypercapnic patients.

KEY WORDS: Cardiogenic Pulmonary Edema - Non-invasive Pressure Support Ventilation – Acute Respiratory Failure – Chronic Obstructive Pulmonary Disease

INTRODUCTION

The rationale of using continuous positive airway pressure (CPAP) in acute pulmonary edema is based on the fact that it may limit the decrease in functional residual capacity, improve respiratory mechanics and oxygenation and decrease left ventricular afterload (1,2). The best therapy for treating an episode of acute respiratory failure due to cardiogenic pulmonary edema is, however, controversial. A systematic review on the effect of CPAP on mortality and need for intubation in patients with cardiogenic pulmonary edema (3) concluded that experimental evidence exists to support its use in these patients, although the potential for harm has not been excluded; the widespread use of this ventilatory technique is still not recommended by the major clinical guidelines (4,5,6). Indeed all the randomized controlled trials using CPAP (3) excluded *a priori* the patients with pre-existing hypercapnic chronic pulmonary disease (COPD), while one study included patients with a $\text{PaCO}_2 > 45$ mmHg, but without chronic airflow obstruction (7). A recent physiological study demonstrated that NPSV was more effective at unloading the respiratory muscles than CPAP alone in patients with acute cardiogenic pulmonary edema (8).

In patients affected by COPD and hypercapnia and recovering from an acute exacerbation of their disease, the addition of an inspiratory aid (NPSV) to CPAP has been shown to further reduce inspiratory muscle effort (9), so that the application of NPSV may be particularly useful in patients with cardiogenic pulmonary edema and signs of pump failure (i.e. hypercapnia).

In one uncontrolled study using NPSV it was noted that patients who responded to NPSV had a higher baseline carbon dioxide pressure than those who did not respond, suggesting that this strategy is of potential benefit only in patients affected by chronic pulmonary diseases or by disorders in which respiratory muscle are likely to be fatigued (10). In a similar population not balanced for subgroups according to the value of PaCO_2 Masip et

al.(11) reported that NPSV, was superior to conventional oxygen therapy in reducing the intubation rate and more rapidly improving oxygenation. As a matter of fact 4/6 (66%) patients requiring intubation in the conventional therapy group were hypercapnic, whereas no hypercapnic patients in the NPSV-treated group required intubation. Unfortunately the small sample size did not allow a subgroup analysis of the impact of the different degree of hypercapnia ($\text{PaCO}_2 > \text{ or } < 45 \text{ mmHg}$) on the main outcomes. Indeed most of the previous investigations, employing either CPAP or NPSV (7,12,13,14) were performed in single, specialized Centers [usually in an Intensive Care Unit (ICU)], while often the first line intervention in “real life” is often carried-out in the Emergency Department (15). The use of non-invasive ventilation directly in this environment could theoretically allow earlier use of this ventilatory technique and at the same time widen its use, since a consistent portion of patients are admitted to the ICU already intubated. We designed a large, multicenter, randomized, prospective study in the setting of Emergency Rooms, comparing NPSV with conventional oxygen therapy in the treatment of acute cardiogenic pulmonary edema. The aim was to assess the feasibility of NPSV outside the ICU and to detect any differences in mortality, intubation rate and some physiological variables like dyspnea and respiratory rate. We also analysed separately the subgroups of patients with and without hypercapnia, since this latter group is more likely to receive a greater benefit from the application of NPSV (11).

Some of the results of these studies have been previously reported in the form of an abstract (16).

METHODS (words count: 542)

Patients

130 consecutive patients with acute cardiogenic pulmonary edema were prospectively recruited in 5 Emergency Departments. The study protocol was approved by the local research ethics committees, and oral consent was obtained from the patient or next-of-kin. Inclusion criteria were the following: severe acute respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 250$) breathing oxygen at $> 10\text{L/m}$ for at least 15 min (time needed to stabilize the patients and to make a diagnosis), dyspnea of sudden onset with respiratory rate > 30 breaths/min, and typical physical signs of pulmonary edema. Exclusion criteria were (see repository for details): immediate need for endotracheal intubation, severe sensorial impairment (Kelly score > 3) (17), shock, ventricular arrhythmias, life-threatening hypoxia ($\text{SpO}_2 < 80\%$ with oxygen), acute myocardial infarction necessitating thrombolysis, severe chronic renal failure, and pneumothorax. Echocardiography was performed in 86 patients once the clinical condition allowed. Patients were randomly assigned to receive standard medical treatment+ O_2 or standard treatment plus NPSV through a full face mask.

Standard treatment.

The patients had continuous SpO_2 and electrocardiographic monitoring. Oxygen therapy was delivered through a face mask with an inspired oxygen fraction aimed to maintain an $\text{SpO}_2 > 90\%$. Medical treatment besides O_2 therapy was also standardized.

NPSV.

A portable ventilator, furnished with an oxygen analyzer and specifically designed for non-invasive ventilation (Breas 102, Uppsala, Sweden) was connected to a full face mask (see repository for details). A common standardized protocol was used. The positive end-expiratory pressure was initially set at $5\text{ cmH}_2\text{O}$ and could be increased by $1\text{ cmH}_2\text{O}$ until a brisk increase of SpO_2 was observed, while the inspiratory pressure support was initially set at $10\text{ cmH}_2\text{O}$ and then increased in increments of $2\text{ cmH}_2\text{O}$ to the maximum tolerated.

Primary outcomes.

The primary endpoints was the need for endotracheal intubation according to standardized criteria defined in the repository.

Secondary outcomes.

Arterial blood gases, respiratory rate, systolic and diastolic blood pressure, heart rate, and dyspnea were recorded at fixed intervals. The duration of hospital stay was also recorded. Cardiac enzymes (creatine phosphokinase and its MB isoenzyme and troponins) were analyzed in all patients at study entry, and 4 hr and 10 hrs after; additional analyses were performed in patients with myocardial infarction (18).

Statistical analysis.

The scheduled sample size of 130 patients would allow us to detect, at $p=0.05$, a difference between a postulated 35% rate of intubation in the conventionally treated group (2), and 10% in the NPSV group (5,6,7) with a power of 90%. The randomization was also balanced to distribute hypercapnic ($\text{PaCO}_2 \geq 45$ mmHg) patients and non-hypercapnic ($\text{PaCO}_2 \leq 45$ mmHg) patients evenly within each treatment group.

Difference in baseline characteristics between standard treatment and NPSV groups (whole groups and subgroups according to a PaCO_2 threshold of 45 mmHg) were tested by means of unpaired t test and chi-square test for continuous and categorical variables respectively. 2x2 tables with expected counts less than five were analysed by Fisher's exact test.

Repeated measures two-ways analysis of variance was used to evaluate trends over time. Kaplan-Meier curves were generated for time data and compared by log-rank and Wilcoxon tests.

A logistic regression analysis was performed using intubation (yes/no) with input being the PaCO_2 threshold $>$ or $<$ 45 mmHg, to verify the hypothesis that hypercapnia was a determinant of intubation .

All tests and p values are two tailed and analyses were performed on an intention-to-treat basis using the SAS package (19). Results are given as means (+SD or SE when specified in the legends to the figures).

RESULTS (E tables on the repository)

Patients' characteristics.

Sixty-five patients were randomly assigned to standard treatment and 65 to NPSV (fig.1); (See table E1 for the distribution by center). The two groups had similar characteristics on admission (table E2). Patients with a PaCO₂ > or < 45 mmHg were equally distributed between the two treatment groups (table 1). Pre-existing cardiac or other disease, NYHA class, possible precipitating causes of cardiogenic pulmonary edema and echocardiographic findings were also similar in the two subgroups (table E3). Hyperthermia (i.e body temperature > 37.0 C°) was present in a consistent subgroup of patients despite them not showing any signs of pulmonary infection. Ten patients had a urinary tract infection, 12 had a suspected viral infection not related to the respiratory system (i.e. enteritis, sinusitis), 4 had a positive sputum culture (without signs of exacerbation), 2 had purulent skin infections, 1 had a dental abscess, while in the remaining patients no focus of infection was found. After the initial adjustments, the ventilator settings were set at 14.5±21.1 cmH₂O for the inspiratory support and 6.1±3.2 for PEEP. These settings were kept constant throughout the study, except in 5 patients who needed a small reduction of 2 cmH₂O in both inspiratory and expiratory levels.

Doses and frequencies of medical therapy are shown in table E4. No statistical differences in medical therapy were observed in the two groups of patients.

Primary outcome and hospital mortality.

Table 2 shows that overall there were no significant differences between the two treatment groups in the need for endotracheal intubation or hospital mortality, but when the statistical analysis was performed dividing each treatment group into subsets of hypercapnic and

non-hypercapnic patients, the percentage of patients needing intubation was significantly lower in those with a $\text{PaCO}_2 > 45$ mmHg.

The logistic regression analysis using the need or not for intubation and the level of $\text{PaCO}_2 < \text{ or } > 45$ mmHg did not however show any statistically significant correlation.

The mean duration of NPSV was 11.4 ± 3.6 hrs. The reasons for and timing of intubation are shown in table 3.

Secondary outcomes.

After 30 min. of treatment patients receiving NPSV had a significantly higher $\text{PaO}_2/\text{FiO}_2$ ratio and this was still the case after 3 hrs (fig.2). Fig.3 illustrates the changes in PaCO_2 recorded in the subset of hypercapnic patients in the two treatment groups; a significant decrease from baseline was observed in the NPSV group in the first hour of treatment. Most of the intubations in the subset of patients treated with medical therapy occurred in the first 3 hours (7/9).

In comparison with baseline values, respiratory rate, dyspnea score, blood pressure and heart rate showed significant improvement earlier in the NPSV group than in the control group (table 4).

Other clinical outcomes.

As illustrated in table E5 there were no differences between the two groups in total hospital stay, occurrence of a "new" acute myocardial infarction, infectious and non-infectious complications. Skin lesions due to the presence of the mask were assessed according to Gregoretti et al (20): area of redness were recorded in fourteen patients, initial ulcer without involvement of the muscle and/or bone in nine and area of necrosis in four. One patient complained of claustrophobia and 3 tolerated ventilation poorly during the night hours.

DISCUSSION

The present multicenter, randomized study shows that early use of NPSV in the Emergency Department to treat severe cardiogenic pulmonary edema is feasible and effective in providing a more rapid improvement in oxygenation and dyspnea compared to standard medical therapy alone. NPSV in this context did not decrease the overall endotracheal intubation except in the subgroup of patients with baseline hypercapnia. Mortality and adverse events were equally distributed in the two treatment groups.

Our study of NPSV vs standard medical therapy in patients with acute pulmonary edema is the first to balance the enrollment of hypercapnic and normocapnic patients, in each treatment group, so that a subgroup statistical analysis was feasible. The study was also designed to avoid the occurrence of some confounding variables. For example, echocardiography was performed in our study in more than half of the patients and the two groups were extremely well balanced with respect to cardiac dysfunction, so that we are confident that this potential bias in the recruitment of patients was avoided. The same can be stated for the causes of the acute pulmonary edema and baseline characteristics. Some of the previous studies (10,12) did not record the $\text{PaO}_2/\text{FiO}_2$ ratio, but only the SpO_2 , which clearly depends on the fraction of oxygen delivered. For this reason enrollment criteria were not based on the ratio, which remains the major score of severity in these patients.

The overall intubation rate in our NPSV group was relatively higher than that in Masip's study (11), and this was particularly true for the non-hypercapnic patients in whom the intubation rate was even higher than in the medically treated group. However, as illustrated in table 3, only a small number of non-hypercapnic patients needed intubation for respiratory reasons (i.e. refractory hypoxia), since most of them were promptly intubated for cardiovascular problems. It is possible that another potential reason for the lack of greater benefit from NPSV may be also related to the limited experience that most

of the Centers participating in the study had in the administration of the technique, but this should also be true for the hypercapnic subgroup in which, the intubation rate, in contrast, was fairly low.

The best therapy for treating an episode of acute respiratory failure due to cardiogenic pulmonary edema is still a controversial matter. For example the use of CPAP is not yet judged standard in the Guidelines of the American Heart Association (4), the European Society of Cardiology (5), the International Liaison Committee on Resuscitation (6), and in most textbooks of medicine. Furthermore, definitive data are not available concerning either the use of NPSV vs medical therapy (2 small studies) (11,21) and NPSV vs CPAP (1 small study) (22), so that larger randomized and controlled studies are needed.

NPSV has been the subject of some criticism, and its widespread use has not been recommended, so that the present study was designed to assess this controversial issue. We found that NPSV in hypoxemic patients is not superior to medical treatment in avoiding intubation, although it may produce faster improvement of some physiological variables. A rapid improvement in $\text{PaO}_2/\text{FiO}_2$ ratio was demonstrated in several other studies, using CPAP and NPSV, and indeed a decreased need for intubation was observed in these latter investigations (7,11,13,14). Unfortunately the design of the studies, did not allow the Authors to discriminate whether a specific subset of patients was responsible for the overall outcome.

In fact, different effects of NPSV in hypoxemic and hypercapnic acute respiratory failure have already been shown in a randomized, controlled study enrolling patients affected by pathologies other than cardiogenic pulmonary edema (23), while a trial in patients with cardiogenic pulmonary edema was underpowered to detect any possible difference (11).

Our study design allowed us to perform a sub-group analysis to eventually detect a possible difference between the outcomes of the patients with $\text{PaCO}_2 > 45$ mmHg and those with $\text{PaCO}_2 < 45$ mmHg, since a power analysis of the sample size could not be

determined a priori, simply because no data in the literature allowed us to build it. Our randomization was however balanced in order to obtain similar numbers of patients with and without hypercapnia in the two treatment groups, so that a subgroup analysis was performed. Unfortunately, despite a statistically different pattern of intubation was found between the two subgroups of patients, the logistic regression analysis did not confirm that the level of PaCO₂ > 45 mmHg was per se a determinant of intubation. This is likely to be due to the relatively small sample size of the two subgroups of patients, so that further larger, stratified, randomised controlled trials are needed to eventually confirm the hypothesis that the hypercapnic patients are more likely to benefit from the application of NPSV

Some studies have reported a high incidence of myocardial infarction when using NPSV. Mehta *et al.* (22) had to stop their trial since a high proportion of patients with myocardial infarction was detected in the patients randomized to NPSV. The Authors suggested that the prolonged increase in intrathoracic pressure during inspiration may explain their results. It is of interest to note that they delivered NPSV using a spontaneous timed mode with a ventilator that at the time of the study was not equipped with the now available sophisticated expiratory triggering system, so that airleaks, when present, may have unduly prolonged the inspiratory time (failure to cycle-off phenomenon). This problem has now been solved by the new generation ventilators. Furthermore most of the patients reported chest pain (10/14) at admission so that it is likely that acute ischemia preceded and not followed the application of non-invasive ventilation. A more recent study by Sharon *et al.* (21) also described a higher rate of myocardial infarction using NPSV, but the low inspiratory and expiratory pressures used suggest that in this group of patients the ventilatory assistance may have been inadequate. In the present study we found the same incidence of myocardial infarction as that reported by Masip and coworkers (11) and by

Takeda *et al.* (24) who described a satisfactory outcome in a group of patients with acute pulmonary edema secondary to myocardial infarction.

Overall the number of adverse events occurring in our patients during their hospital stay was similar in the two groups. The most common adverse events during NPSV were skin lesions; the rate of these was comparable to that in some other published reports, but higher than in some others. This may be a reflection of the relative inexperience of the staff and could have contributed to the lack of tolerance in a small subset of patients.

In conclusion we have shown that, compared to standard medical therapy, early use of NPSV in the Emergency Department for treatment of acute respiratory failure due to cardiogenic pulmonary edema produces faster gas exchange, dyspnea score and respiratory rate improvements, but does not affect the overall clinical outcome. The subgroup analysis showed however that the need of intubation in the hypercapnic patients may be reduced with the use of NPSV. Considering that CPAP has been shown to reduce the intubation rate, but not mortality, and to improve more rapidly the physiological variables compared to standard medical therapy (3), we can reasonably say that both NPSV and CPAP may be used in the treatment of cardiogenic pulmonary edema. Larger multicenter randomised studies are needed to compare the efficacy of CPAP vs NPSV especially regarding the rate of intubation, so that we may determine which modality should then be tested vs the medical therapy (i.e. actually the golden standard for the major clinical guidelines) to assess whether mortality may be improved.

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LEGENDS:

Table 1: Baseline characteristics of the patients.

Patients were divided in those presenting at enrolment a PaCO₂ < or > than 45 mmHg.

NPSV= non-invasive pressure support ventilation

NYHA class = New York Heart Association class

SAPS II= simplified acute physiologic score II

RR= respiratory rate

HR= heart rate

BP= blood pressure

Table 2: Intubation rate and in-hospital mortality

NPSV= non-invasive pressure support ventilation

Table 3: Reasons (n.of patient) of intubation. The time of intubation for individual patients is reported under.

MI= myocardial infarction

NPSV= non-invasive pressure support ventilation

Table 4: Physiological measurement during the first 24 hrs of the study.

+ = p < 0.01 non-invasive pressure support ventilation (NPSV) vs Standard Therapy (ST)

* = p < 0.05 non-invasive pressure support ventilation (NPSV) vs Standard Therapy (ST)

Figure 1: Trial profile

Figure 2: Oxygenation ($\text{PaO}_2/\text{FiO}_2$ ratio) over time in the two randomized groups.

n= numbers of patients not needing intubation or dead.

Closed circles= non-invasive pressure support ventilation (NPSV)

Open circles= Standard Treatment

Data are mean \pm Standard Error

+ = $p < 0.01$ NPSV vs Standard treatment

* = $p < 0.05$ NPSV vs Standard treatment

Repeated measures two-ways analysis of variance

Figure 3: Measurements of arterial pressure of carbon dioxide (PaCO_2) over time in the two randomized groups of patients presenting at enrolment a $\text{PaCO}_2 \geq 45$ mmHg

n= numbers of patients not needing intubation or dead.

Closed circles= NPSV

Open circles= Standard Treatment

Data are mean \pm Standard Error

+ = $p < 0.01$ NPSV vs Standard treatment

Repeated measures two-ways analysis of variance

Variables	Standard Treatment PaCO₂>45mmHg	NPSV PaCO₂>45mmHg	P value	Standard Treatment PaCO₂<45mmHg	NPSV PaCO₂<45mmHg	P value
n.	33	31		32	34	
pH	7.19+0.09	7.20+0.11	0.71	7.33+0.061	7.30+0.076	0.19
PaCO₂ (mmHg)	62.1+14.0	65.2+11.3	0.32	38.0+5.3	39.2+4.8	0.31
PaO₂/FiO₂	168.7+34.9	152.8+34.6	0.07	153.8+35.3	152.9+32.1	0.91
NYHA class	2.3+0.8	2.4+0.7	0.60	2.2+0.9	2.2+0.7	0.96
SAPS II	20.3+3.7	21.6+3.3	0.48	22.1+4.8	20.0+3.7	0.32
RR (breath/m)	38.9+8.8	39.1+6.9	0.26	41.5+6.9	37.5+7.2	0.19
HR (b/m)	121.7+17.7	120.1+18.4	0.56	125.3+15.8	118.5+17.2	0.19
Mean BP (mmHg)	118.3+27.2	120.6+21.3	0.47	120.5+25.0	119.1+16.8	0.65
Lactate* (mmol/L)	3.10+1.78	3.75+1.81	0.19	3.58+1.47	3.66+1.66	0.38
Serum Bicarbonate (mmol/L)	25.7+8.3	23.6+9.3	0.16	19.9+7.4	18.6+7.6	0.35

TABLE 1

	Standard Treatment	NPSV	<i>P value</i>	<i>OR</i>
<i>Intention-to-treat</i>				
Intubated	16/65 (25%)	13/65 (20%)	0.53	1.3
Died	9/65 (14%)	6/65 (8%)	0.41	1.58
<i>Subgroup analysis</i>				
PaCO₂> 45 mmHg				
Intubated	9/31 (29%)	2/33 (6%)	0.015	6.34
Died	5/31 (16%)	1/33 (3%)	0.10	6.15
PaCO₂<45 mmHg				
Intubated	7/34 (21%)	11/32 (34%)	0.21	0.40
Died	4/34 (12%)	5/32 (15%)	0.65	0.72

TABLE 2

Reasons for Intubation	Standard Treatment PaCO ₂ <45mmH		Standard Treatment PaCO ₂ >45mmHg		NPSV PaCO ₂ <45mmHg		NPSV PaCO ₂ >45mmHg	
	n. of pts	Time from admission	n. of pts	Time from admission	n. of pts	Time from admission	n. of pts	Time from admission
MI necessitating thrombolysis	1 1	2 h 22 h	1	8 h	1 1 1	2 h 3 h 10 h		
Hemodynamic Instability					1	1 h		
Stroke			1 1	1 h 10 h				
Cardiac Arrest	1	1 h			1 1 1	1 h 6 h 22 h		
Refractory Seizure			1	5 h				
GI bleeding			1	1 h				
Refractory Hypoxia	3 1	30 min 1 h	1 1	30 min 2 h				
PaCO ₂ >5mmHg from baseline after 1 hour			2	1 h	1	1 h		
Intolerance to NPSV					2	30 min	1	30 min

TABLE 3

	Baseline	30 min	1 hr	3 hr	6 hr	12 hr	24 hr
pH							
ST	7.26+0.09	7.28+0.10	7.31+0.09	7.36+0.07	7.39+0.06	7.41+0.04	7.42+0.03
NPSV	7.25+0.11	7.28+0.10	7.32+0.07	7.36+0.07	7.40+0.05	7.42+0.04	7.42+0.03
Resp Rate							
ST	38.1+6.9	36.4+9.6	32.3+7.1	29.8+8.2	26.1+8.6	24.0+11.1	18.9+4.2
NPSV	40.1+7.7	33.8+7.3*	29.3+7.1 ⁺	24.9+6.5 ⁺	20.6+5.4*	18.2+3.9*	16.1+2.9
Borg scale							
ST	7.5+1.2	7.3+1.5	7.1+1.3	4.3+1.4	2.8+1.5	1.5+1.3	0.7+1.1
NPSV	7.9+1.2	5.7+1.7 ⁺	3.8+1.6 ⁺	2.0+1.5 ⁺	1.2+1.3*	0.8+1.4	0.7+0.8
Heart rate							
ST	118+17	114+16	109+18	102+19	98+20	90+17	86+11
NPSV	123+17	111+18	104+18*	98+14	89+14	83+15	82+12
Mean BP							
ST	117+22	116+24	111+23	101+12	92+27	88+11	85+8
NPSV	119+18	111+25	106+17*	89+20*	86+14	83+11	82+9

TABLE 4

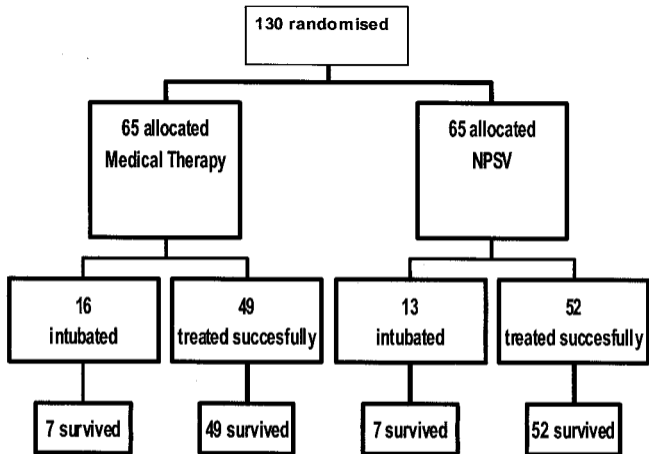


FIGURE 1

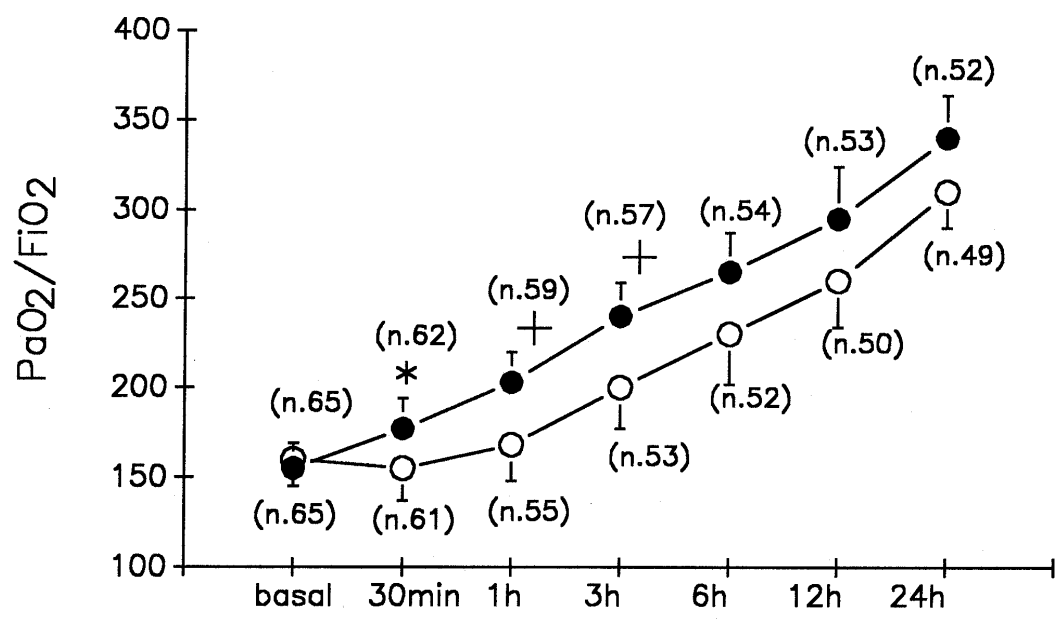


FIGURE 2

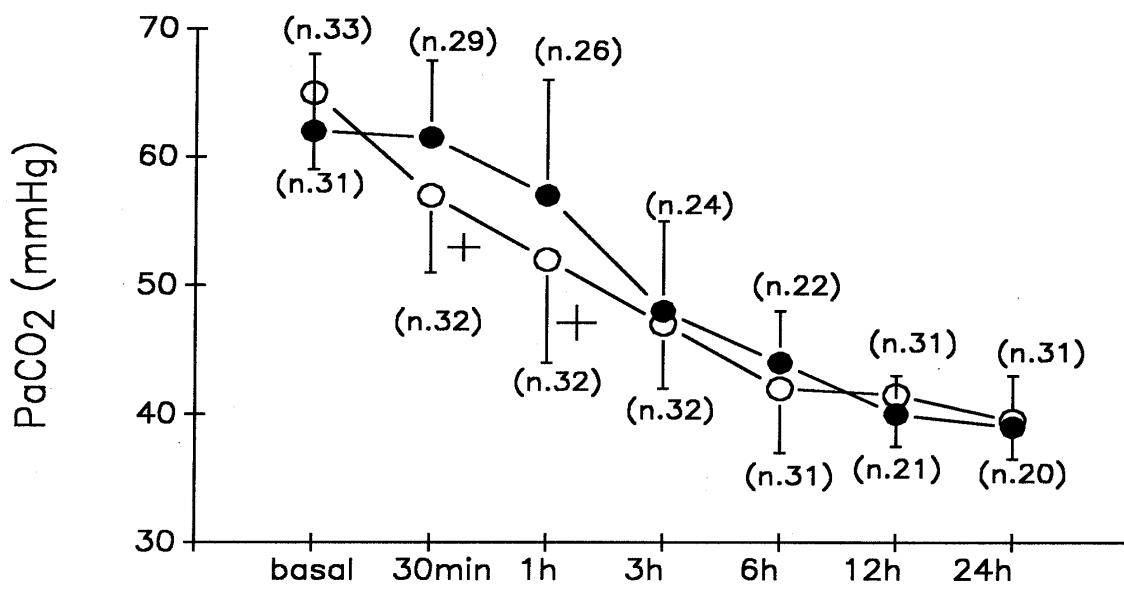


FIGURE 3

REPOSITORY DATA

NON-INVASIVE VENTILATION IN CARDIOGENIC PULMONARY EDEMA : A MULTICENTER, RANDOMIZED TRIAL

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METHODS (words count=1507)

Patients

The study was performed over a 21-month period on 130 consecutive patients with acute cardiogenic pulmonary edema prospectively recruited in the Emergency Departments of 5 Italian hospitals (Gradenigo, Torino; S.Orsola, Bologna; San Biagio, Alessandria; Policlinico, Milano; Correggio, Reggio Emilia). Gradenigo Hospital had previously participated in NPSV studies.

A formal 2 days training (mean 10 ± 3 hours total) was given by an experienced physician to the medical and paramedical staff of the other 4 Hospitals in the two months preceding the study. The training consisted of the following steps: 1) explanation of the methodology (noninvasive ventilation) 2) overview of the ventilator's functions 3) practical training on a normal subject, including the setting of the ventilator and the mask positioning 4) explanation of the protocol with particular emphasis on the monitoring procedures (i.e. use of the oximeter). The study protocol was approved by the local research ethics committees. The consent to participate in the study was asked by the attending physician to the patient or next-of-kin in the presence of a witness. The agreement to participate in the study was recorded on the data collection sheet that was signed by the attending physician. Inclusion criteria were the following: severe acute respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 250$) breathing oxygen at $> 10\text{L/m}$ for at least 15 min (FiO_2 determined by a portable oxygen analyzer, dyspnea of sudden onset with respiratory rate > 30 breaths/min, typical physical signs of pulmonary edema (widespread rales), congestion on chest X-ray, without a history of pulmonary aspiration or infection. The patients were enrolled in the protocol fifteen minutes after the arrival in the Hospital, this waiting period included the time necessary to stabilise the patients (the large majority coming directly from home) and

especially to make a diagnosis (clinical examination, and anamnesis). During this period 1 patient developed sudden respiratory arrest needing prompt intubation

Exclusion criteria were: immediate need for endotracheal intubation, severe sensorial impairment (Kelly score > 3) (E1), shock, ventricular arrhythmia, life-threatening hypoxia ($SpO_2 < 80\%$ with oxygen), acute myocardial infarction necessitating thrombolysis, severe chronic renal failure, and pneumothorax. The Kelly score (E1) was specifically designed for mechanically ventilated patients so that it could be rapidly and easily administered by nurses and physicians and it is sensitive to minor changes in mental status. It consists of 5 grades ranging from 1= alert, "*follows complex 3 step command*" to 6 "*comatose with brain stem dysfunction*".

Shock was defined as: systolic arterial pressure < 90 mmHg or a decrease in pre-morbid systolic blood pressure of 40 mmHg with or without oliguria.

Severe chronic renal failure was defined as: Estimated glomerular filtration rate <10 mL/min/1.73m² (Kt/V urea <2.0) - Normalized protein nitrogen appearance rate (nPNA) > 0.8 g/kg/day - estimated glomerular filtration rate of 10-20 mL/min/1.73m² with signs of malnutrition (normalized protein nitrogen appearance rate < 0.8g/kg/day) or patients already on dialysis (E2).

To avoid potential confounders, we decided to exclude a priori patients necessitating thrombolysis, since this procedure may per se significantly increase the risk of stroke (E3).

Echocardiography was performed in 86 patients once the clinical condition allowed. Patients were randomly assigned to receive standard medical treatment+O₂ or standard treatment plus NPSV through a full face mask (see below).

The randomization schedule had a block design for each center and was generated by an independent statistician who used random numbers. Because the level of PaCO₂ might have a substantial influence on the study results (E4,E5), the randomization was balanced

according to whether the patients had an admission PaCO₂ < or > 45 mmHg, to ensure that these two groups were equally distributed between the 2 study groups. To do that each centre received 20 different envelopes, 10 for the hypercapnic patients (PaCO₂> mmHg) and 10 for non-hypercapnic patients (PaCO₂<45 mmHg), containing the random of the treatment, equally distributed within the specific group. To ensure that the two groups were numerically balanced, once the centre had finished the envelopes for a group, no further enrolment was made in that particular group, until the enrolment in the other group of patients was finished. The individual assignment were made using opaque sealed envelopes. Patients were treated in the Emergency Department of the hospital, which was usually in close proximity to the medical ICU, so that the possibility of prompt intubation and, therefore, mechanical ventilation was present. Usually one physician and one or more specialized nurses were in charge of the patient. After the first few hours the patients who did not require intubation were admitted to the 'step-down' unit that is part of the Emergency Department and then discharged to their home or transferred to another Department after 24-48 hrs.

Standard treatment.

The patients had continuous SpO₂ and electrocardiographic monitoring. Oxygen therapy was delivered through a face mask with an inspired oxygen fraction to maintain an SpO₂> 90%. Patients received oxygen using high concentration sources through a tight fitting reservoir non-rebreathing mask (Oxinova Carburos Metalicos, Barcelona, Spain) that provides air-oxygen mixture at a flow up to 50-60 L/min. Therefore the peak inspiratory flow rate of our acute patients should not greatly exceed the flow rate delivered by the oxygen source. Oxygen therapy was continued until intubation, death or fulfilment of oxygen delivery cessation criteria (SpO₂>92% without oxygen and a respiratory rate < 30/min.)

The tip of the oxygen analyzer was introduced via a small hole in the mask.

Medical treatment besides O₂ therapy was standardized as follow: furosemide 40 mg iv or twice the patient's usual dose, repeated, if necessary, every 20 min., up to 320 mg, until a brisk urine output was evident; morphine sulfate up to 4 mg; continuous glyceryl trinitrate at an initial rate of 1.5 mg/h. A bolus dose of 1 mg iv was to be added if systolic blood pressure was above 180 mmHg. Doses and frequency of medical therapy are illustrated on table 4 repository.

NPSV.

All the centers used the same ventilator and set of masks. A portable ventilator, furnished with an oxygen analyzer and specifically designed for non-invasive ventilation (Breas PV102, Uppsala, Sweden) was connected to a full face mask (Mirage, ResMed, Waterloo, Australia).

The Breas PV102 is a 3.2 Kg weight, flow-triggered ventilator with a range of inspiratory and expiratory pressures between 4 and 30 cmH₂O. The back-up respiratory rate may be set between 6 and 40 breaths/min, and it also offers the option of modulating the initial flow rate according to the gradient chosen and the patient's inspiratory activity, so that a pressure plateau is reached after a variable time between 0.3 and 1.0 sec. The inspiratory pressure ceases when the flow reaches a predetermined value.

A common standardized protocol was used. The positive end-expiratory pressure was initially set at 5 cmH₂O and could be increased by 1 cmH₂O, until a brisk increase of SaO₂ was observed, while the inspiratory pressure support was initially set at 10 cmH₂O and then increased in increments of 2 cmH₂O to the maximum tolerated. Trigger sensitivity was set to avoid auto-triggering. The ventilator was set in spontaneous mode with a fixed back-up rate of 8 b/m. At least 4 hours of NPSV were given continuously and then discontinuously as appropriate based on the patient's tolerance and the achievement of a SpO₂ > 92% without oxygen with a respiratory rate < 30 b/m.

Primary outcomes.

The primary endpoints was the need for endotracheal intubation, defined as:

- progressive or refractory hypoxemia ($\text{SaO}_2 < 85\%$ with a FiO_2 of 100%)
- Cardiac or respiratory arrest
- inability to tolerate the mask accompanied by a worsening of the clinical status
- increase in $\text{PaCO}_2 > 5$ mmHg if baseline PaCO_2 was > 45 mmHg . In the case of baseline PaCO_2 value < 45 mmHg, intubation was eventually performed at 50 mmHg.
- clinical signs of pump exhaustion, such as active contraction of the accessory muscles with thoracic-abdominal paradoxical movement
- inability to adequately clear respiratory secretions
- hemodynamic instability without response to fluids (i.e. systolic blood pressure < 90 mmHg)
- Myocardial Infarction necessitating thrombolysis in the patients with one of the following risk factors: age > 75 yrs, transient ischaemic attack in the preceeding 6 months, Coumadin therapy, refractory hypertension (systolic blood pressure > 180 mmHg) (E3).
- Massive GI bleeding

Secondary outcomes.

Arterial blood gases, respiratory rate, systolic and diastolic blood pressure, heart rate, and dyspnea score according to Borg's scale were recorded at 30 min, at 1, 3, 6, 12, and 24 hours and thereafter twice a day. The duration of hospital stay was also recorded. Cardiac enzymes (creatine phosphokinase and its MB isoenzyme and troponins) were analyzed in all patients at study entry, and 4 hr and 10 hrs after; additional analyses were performed in patients with myocardial infarction (E6). All the adverse events and complication, including side effects due to NPSV, were recorded.

The classification of the skin lesions due to NPSV was done according to a modified published score (E7) as follows: 0= nil 1= area of redness 2= initial ulcer without involvement of the muscle and/or bone 3= skin ulcer with involvement of the muscle and/or bone 4= area of necrosis.

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Legend

Table E1: The number of patients treated in each centre and their intubation rate

NPSV= non-invasive pressure support ventilation

Table E2: Baseline characteristics of the patients

* recorded in 102 patients

BMI= body mass index

SAPSII= simplified acute physiologic score

RR= respiratory rate

Mean BP= mean blood pressure

Table E3: medical, history echocardiographic findings and precipitating causes of acute pulmonary edema. Patients were divided in those presenting at enrolment a PaCO₂ < or > than 45 mmHg.

CHF= congestive heart failure

Echocar.findings= echocardiography findings

EF%= ejection fraction %

Table E4 : Doses and frequency of distribution of the drugs

Table E5: Adverse events occurring in patients during their Hospital stay

H. length of stay= hospital length of stay

Centre	Standard Treatment (n.)	Intubated pts (n.)	NPSV (n.)	Intubated pts
# 1	16	4 (25%)	16	3 (18%)
# 2	14	4 (28%)	16	4 (25%)
# 3	9	3 (33%)	10	2 (20%)
# 4	17	3 (18%)	14	2 (14%)
# 5	9	2 (22%)	9	2 (22%)

TABLE E1

Variables	Standard Treatment (n.65)	NPSV (n.65)	P value
Sex (F/M)	13/52	16/49	0.53
Age	73.1+8.3	72.1+9.1	0.67
BMI	22.54+4.8	21.78+5.02	0.59
SAPS II	21.5+2.5	20.7+3.1	0.44
pH	7.26+0.107	7.27+0.098	0.54
PaCO₂ (mmHg)	52.4+15.7	49.5+15.9	0.29
PaO₂/FiO₂	152.9+33.2	157.9+35.6	0.39
RR (a/m)	40.1+7.7	38.1+6.9	0.20
HR (b/m)	123.1+17.5	119.6+17.0	0.38
Mean BP (mmHg)	117.2+22.2	119.5+18.5	0.51
Borg scale	7.90+1.24	7.48+1.24	0.12
Lactate (mmol/L) *	3.43+1.56	3.71+1.71	0.34
Serum Bicarbonate (mmol/L)	23.3+5.6	21.0+6.8	0.22

TABLE E2

<i>Variables</i>	Standard Treatment PaCO₂>45mmHg	NPSV PaCO₂>45mmHg	P value	Standard Treatment PaCO₂<45mmHg	NPSV PaCO₂<45mmHg	P value
<i>n.</i>	33	31		32	34	
<i>History</i>						
CHF	24 (72%)	22 (71%)	0.88	24 (75%)	26 (76%)	0.89
Hypertension	27 (82%)	23 (74%)	0.46	28 (87%)	30 (88%)	0.93
“Old” A.M.I	13 (40%)	16 (52%)	0.33	11 (34%)	12 (35%)	0.94
Chronic Bronchitis	22 (67%)	24 (77%)	0.34	4 (12%)	3 (9%)	0.63
Diabetes	18 (54%)	12 (39%)	0.21	19 (59%)	16 (47%)	0.32
<i>Precipitating causes</i>						
Acute A.M.I.	7 (21%)	5 (16%)	0.60	4 (12%)	6 (18%)	0.73
Hypertension	12 (36%)	13 (42%)		15 (47%)	12 (35%)	
Hyperthermia	11 (31%)	10 (32%)		9 (28%)	11 (32%)	
Arrhythmia	1 (3%)	0		1 (3%)	2 (6%)	
<i>Echocar. Findings</i>	n.19	n.21		n.18	n.28	
Aortic stenosis	3 (15%)	2 (9%)	0.65	3 (9%)	4 (14%)	>0.99
Mitral regurgitation	5 (26%)	4 (19%)	0.71	6 (33%)	10 (35%)	>0.99
EF %	36.6+4.9	38.1+5.0	0.34	37.4+6.2	35.1+4.8	0.16

TABLE E3

	Standard Treatment (n.65)	NPSV (n.65)
Morphine (mg)	2.2+0.9 (n.48)	2.4+1.1 (n.39)
Furosemide (mg)	77+27 (n.65)	86+21 (n.64)
Glyceryl Trinitrate (mg)	4.5+3.1 (n.60)	3.9+2.6 (n.59)

TABLE E4

ADVERSE EVENT	Standard Treatment (n.65)	NPSV (n.65)	<i>P value</i>
New Miocardial Infarction	5	7	0.76
Nosocomial Pneumonia	2	1	>0.99
Sinusitis	0	1	>0.99
Pneumothorax	1	0	>0.99
G.I. bleeding	1	2	>0.99
Cardiac arrest	1	3	0.62
Stroke	2	0	0.50
Seizures	1	0	>0.99
TOTAL	13 (20%)	14 (22%)	0.83
H length of stay	5.1+2.3	5.4+3	>0.99

TABLE E5