

Noninvasive Ventilation in Severe Hypoxemic Respiratory Failure

A Randomized Clinical Trial

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The efficacy of noninvasive ventilation (NIV) to avoid intubation and improve survival was assessed in 105 patients with severe acute hypoxemic respiratory failure (arterial O₂ tension or saturation persistently 60 mm Hg or less or 90% or less, respectively; breathing conventional Venturi oxygen at a maximal concentration [50%]), excluding hypercapnia, admitted into intensive care units of three hospitals. Patients were randomly allocated within 24 hours of fulfilling inclusion criteria to receive NIV (n = 51) or high-concentration oxygen therapy (n = 54). The primary end-point variable was the decrease in the intubation rate. Both groups had similar characteristics. Compared with oxygen therapy, NIV decreased the need for intubation (13, 25% vs. 28, 52%, p = 0.010), the incidence of septic shock (6, 12% vs. 17, 31%, p = 0.028), and the intensive care unit mortality (9, 18% vs. 21, 39%, p = 0.028) and increased the cumulative 90-day survival (p = 0.025). The improvement of arterial hypoxemia and tachypnea was higher in the noninvasive ventilation group with time (p = 0.029 each). Multivariate analyses showed NIV to be independently associated with decreased risks of intubation (odds ratio, 0.20; p = 0.003) and 90-day mortality (odds ratio, 0.39; p = 0.017). The use of noninvasive ventilation prevented intubation, reduced the incidence of septic shock, and improved survival in these patients compared with high-concentration oxygen therapy.

Keywords: acute respiratory failure; intensive care unit; noninvasive ventilation; controlled clinical trial

During the evolution of severe acute hypoxemic respiratory failure (AHRF), patients may require intubation and mechanical ventilation as a life-support measure while concomitant treatments for the underlying disease are instituted. In these patients, however, invasive mechanical ventilation is associated with an important incidence of complications and mortality (1–4).

The use of noninvasive ventilation (NIV) as an alternative to immediate intubation in these patients reduced the incidence of serious complications and length of stay in one study (5). More recently, NIV has shown to reduce the need for intubation in selected groups of patients with severe cardiogenic pulmonary edema (6), immunosuppression (7, 8), and respiratory failure after lung resection (9). A randomized clinical trial in nonchronic

obstructive pulmonary disease (COPD) patients receiving NIV failed to find significant benefits in the subset of patients without hypercapnia after a post hoc analysis (10). However, this study was not specifically powered to assess the efficacy of NIV in patients with AHRF. Therefore, whether the systematic use of NIV in these patients is effective enough to prevent intubation as compared with oxygen therapy remains to be assessed.

We hypothesized that in patients with severe AHRF unable to achieve acceptable levels of arterial oxygenation using conventional oxygen therapy, the use of NIV, providing appropriate inspired oxygen concentrations, would prevent intubation as the primary end-point variable, hence averting the poor outcome associated with the need of invasive ventilation. Accordingly, we conducted a prospective, randomized controlled trial to assess the efficacy of NIV compared with a standard regime consisting of high-concentration oxygen therapy. Some of the results of this study have been previously reported in abstract form (11).

METHODS

Patients

A prospective, randomized controlled study was conducted in three intensive care units (ICUs). Patients with severe AHRF, defined as Pa_{O₂} persistently (more than 6 to 8 hours) less than 60 mm Hg or arterial oxygen saturation by pulse oximetry (Sp_{O₂}) persistently less than 90% while breathing conventional Venturi oxygen at a maximal concentration (50%), were considered eligible for the study.

Exclusion criteria were (1) hypercapnia (Pa_{CO₂} of more than 45 mm Hg) on admission; (2) need for emergency intubation; (3) recent esophageal, facial, or cranial trauma or surgery; (4) severely decreased consciousness (a Glasgow coma score of 11 or less); (5) severe hemodynamic instability despite fluid repletion and use of vasoactive agents; (6) a lack of cooperation; (7) tracheotomy or other upper airway disorders; (8) severe ventricular arrhythmia or myocardial ischemia; (9) active upper gastrointestinal bleeding; (10) an inability to clear respiratory secretions; and (11) more than one severe organ dysfunction in addition to respiratory failure. The study was approved by the ethics committee of the three institutions, and informed consent was obtained in all cases.

Study Design

Patients were randomly allocated within 24 hours of fulfilling inclusion criteria either to the noninvasive ventilation group or the control group.

In the noninvasive ventilation group, patients were ventilated using the bilevel positive airway pressure mode (BiPAP Vision; Respicronics Inc., Murrysville, PA). A face mask was used as the first choice, but the nasal mask was optionally used if patients did not tolerate face mask. FI_{O₂} was set to achieve an Sp_{O₂} of more than 92% or a Pa_{O₂} of more than 65 mm Hg. NIV was continuously delivered after entry into the study as much time as possible. When patients received FI_{O₂} of 0.50 or less, attempts to withdraw NIV were made if they achieved Sp_{O₂} of more than 92% or Pa_{O₂} of more than 65 mm Hg while spontaneously breathing Venturi oxygen at FI_{O₂} of 0.50 or less.

In the control group, patients received oxygen using high concentration sources. The FI_{O₂} was set to achieve Sp_{O₂} of more than 92% or Pa_{O₂} of more than 65 mm Hg. NIV to avoid intubation was allowed in

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the control group if predefined criteria for spontaneous breathing failure occurred (*see* criteria in the online supplement) (12).

Definitions

Criteria for intubation were predefined (*see* criteria in the online supplement). The end of the protocol was defined as: (1) clinical improvement, when patients could persistently achieve PaO₂ of more than 65 mm Hg or SpO₂ of more than 92% while breathing Venturi oxygen at FiO₂ of 0.50 or less; (2) intubation; (3) death; (4) in the NIV group, withdrawal of NIV without intubation because of intolerance; and (5) in the control group, the use of NIV in the control group because of spontaneous breathing failure without intubation.

Data from patients were recorded, and follow-up was extended until 90 days after randomization. Respiratory frequency, heart rate, blood pressure, and arterial blood gases were recorded at baseline (before randomization) and after 1–2, 3–4, 6–8, 12, 24, 48, and 72 hours. At entry into the study, diagnosis of pneumonia (13), cardiogenic pulmonary edema (14, 15), and acute respiratory distress syndrome (ARDS) (16) were based on published criteria.

Clinical (13) and microbiologic (17) diagnoses of hospital-acquired pneumonia and septic shock and multiple organ failure (18, 19) were defined by published criteria (*see* criteria in the online supplement). Other relevant complications were recorded.

Statistical Analysis

Sample size estimation. We estimated at least 51 subjects in each group with an expected intubation rate of 58% in the control group and a 50% reduction in the NIV group (confidence level [1 – α] 95%, power level [1 – β] 80%).

Comparisons between the two groups. Qualitative or categorical variables were compared with the chi-square test or the Fisher's exact test. Quantitative continuous variables were compared using the unpaired Student's *t* test or the Mann-Whitney test. The overall time course of respiratory frequency, heart rate, blood pressure, and arterial blood gas variables was compared using a two-way analysis of variance for repeated measures. Differences between the two groups at each time point were compared with Student's *t* test and Bonferroni correction. The cumulative probability of remaining on spontaneous breathing and the 90-day survival were compared with the Kaplan-Meier estimate of survival and the log-rank test to compare the two groups. All analyses were in intention to treat, and the level of significance was set at 0.05.

Risk factors for intubation. Univariate and multivariate analyses of risk factors for intubation were performed with logistic regression.

Predictors of 90-day survival. Univariate and multivariate analyses of 90-day survival were performed with the Kaplan-Meier estimate of survival and Cox proportional hazard regression, respectively. To correct for collinearity in all multivariate analyses, a conditional stepwise forward model was chosen (p_{in} [maximal *p* value in the univariate analyses to entry in the multivariate analyses] of less than 0.05). Adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with intubation or survival.

RESULTS

Patients

One hundred five consecutive patients were studied (Figure 1): 51 were allocated to the NIV group and 54 to the control group.

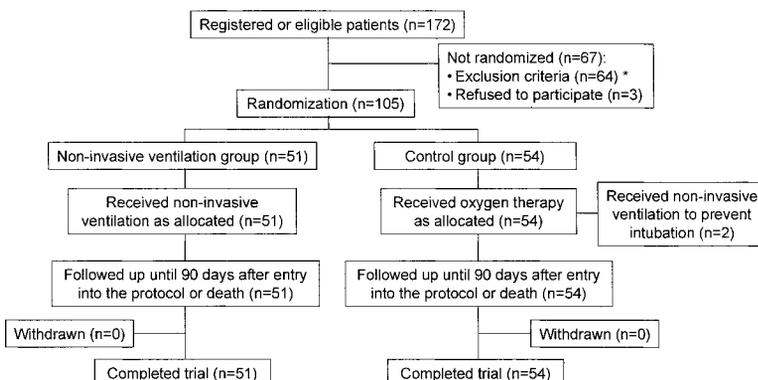


Figure 1. Trial profile. *The main exclusion criteria, as defined, were a lack of cooperation, including agitation and mild to moderate altered mental status ($n = 45$), the need for immediate intubation ($n = 10$), severely decreased consciousness ($n = 5$), and severe hemodynamic instability ($n = 4$).

General clinical characteristics and physiologic parameters of patients at entry into the study are summarized in Table 1. Additional information of patients is shown in Table E1 of the online supplement. No significant differences between the two groups were shown in age, sex, severity of illness, presence of pulmonary infiltrates, underlying diseases, respiratory frequency, heart rate, blood pressure, arterial blood gases, and causes of AHRF.

NIV was delivered for a period of 3.5 ± 2.6 days (mean \pm SD) (range, 1–13) in this group. The levels of inspiratory and expiratory positive airway pressure were 16 ± 3 cm H₂O (range, 10–24) and 7 ± 2 cm H₂O (range, 4–12), respectively, during the first day. Fourteen patients were ventilated with nasal mask because of better tolerance than face mask. Patients from the control group needed high-concentration oxygen therapy for a period of 3.2 ± 2.0 days (range, 1–10).

Intubation, Length of Stay, and Complications

The intubation rate and causes of intubation are summarized in Table 2. Compared with the control group, the intubation rate was lower in the NIV group ($p = 0.010$). Moreover, the probability of remaining without intubation with time was higher in the NIV group ($p = 0.006$; Figure 2). In two patients from the control group, the use of NIV because of spontaneous breathing failure spared intubation. NIV intolerance without intubation before achieving criteria for clinical improvement occurred in one patient from the NIV group. Separate analyses of patients by groups showed that the significant reduction in the intubation rate persisted in the subset of patients with pneumonia as the cause of respiratory failure ($p = 0.017$; Table 2). Multivariate analyses showed that NIV was independently associated with a decreased risk of intubation (Table 3). In addition, cardiogenic pulmonary edema and ARDS as the cause of respiratory failure were independently associated with a decreased risk and an increased risk of intubation, respectively.

ICU and in-hospital stays in the overall population did not change between the two groups (Table 2), but in-hospital stay among ICU survivors decreased in the NIV group ($p = 0.043$).

Complications diagnosed after entry into the study are summarized in Table 4. There was a nonsignificant trend to decrease the incidence of hospital-acquired pneumonia in the NIV group ($p = 0.093$). The incidence of other severe infections and barotrauma was not different between the two groups. In contrast, septic shock was more frequent in the control group ($p = 0.028$). The specific complications associated with NIV are shown in Table 4.

Time Course of Respiratory Frequency, Heart Rate, Blood Pressure, and Arterial Blood Gases

Arterial hypoxemia, as assessed by the PaO₂/FiO₂ ratio, and respiratory frequency improved with time in the two groups (Figure

TABLE 1. GENERAL CLINICAL CHARACTERISTICS OF PATIENTS AT ENTRY INTO THE STUDY*

	Noninvasive Ventilation Group (n = 51)	Control Group (n = 54)	p Value
Age, yr	61 ± 17	62 ± 18	0.774
Sex, male/female	30/21	28/26	0.602
SAPS-II on admission	34 ± 10	33 ± 8	0.691
Prior intensive care unit stay, days	0.6 ± 2.6	0.6 ± 1.4	0.892
Number of underlying chronic comorbidities	1.4 ± 0.9	1.1 ± 0.9	0.208
Chronic heart disorders, n (%) [†]	20 (39)	19 (35)	0.822
Chronic airflow limitation, n (%)	3 (6)	3 (6)	> 0.999
Diabetes mellitus, n (%)	17 (33)	15 (28)	0.685
Liver cirrhosis, n (%)	0 (0)	4 (7)	0.118
Immunosuppression, n (%) [‡]	9 (18)	10 (19)	> 0.999
Pulmonary infiltrates on admission, n, %	46 (91)	44 (81)	0.319
Shock on admission, n (%) [§]	6 (12)	4 (7)	0.519
Respiratory frequency, min ⁻¹	37 ± 6	37 ± 6	0.764
Heart rate, min ⁻¹	116 ± 17	115 ± 16	0.892
FiO ₂	0.58 ± 0.15	0.54 ± 0.10	0.132
PaO ₂ , mm Hg	58 ± 14	56 ± 20	0.682
PaO ₂ /FiO ₂ , mm Hg	102 ± 21	103 ± 23	0.735
PaCO ₂ , mm Hg	37 ± 7	36 ± 6	0.392
Arterial pH	7.42 ± 0.06	7.41 ± 0.07	0.178
Causes of acute respiratory failure, n (%)			0.818
Pneumonia	19 (37)	15 (28)	
Cardiogenic pulmonary edema	15 (29)	15 (28)	
Thoracic trauma	6 (12)	11 (20)	
Acute respiratory distress syndrome	7 (14)	8 (15)	
Acute severe asthma	2 (4)	2 (4)	
Postoperative respiratory failure	2 (4)	2 (4)	
Usual interstitial pneumonitis	—	1 (2)	

Definition of abbreviation: SAPS-II = simplified acute physiology score-II.

* Plus-minus values are mean ± SD.

[†] Chronic heart disorders include coronary artery disease, hypertensive and valvular heart diseases, and dilated myocardial disease of any cause.

[‡] Immunosuppression included neutropenia after chemotherapy or bone marrow transplant, drug-induced immunosuppression in solid-organ transplant or as a result of corticosteroids or cytotoxic therapy, and human immunodeficiency virus-related disorders (8)

[§] Shock was defined by published criteria (18).

3). The overall improvement of PaO₂/FiO₂ with time (from baseline to 72 hours after randomization, p = 0.029) and respiratory frequency (from baseline to 6–8 hours after randomization, p = 0.029) were higher in the NIV group. In the NIV group, PaO₂/FiO₂ and respiratory frequency became significantly higher and lower, respectively, 3–4 hours after randomization, and differences remained significant until 24 hours for PaO₂/FiO₂ and 6–8 hours for respiratory frequency. There were no differences between the two groups in the time course of heart rate, blood pressure, arterial pH, and PaCO₂.

Analyses of Mortality and Survival

The ICU mortality was lower in the NIV group (p = 0.028; Table 2), and differences between the two groups persisted in the subset of patients with pneumonia (p = 0.030). Likewise, the cumulative survival probability after 90 days of randomization, as shown in Figure 4, was higher in the NIV group (p = 0.025). The causes of death within 90 days of randomization are summarized in Table 4.

The multivariate analyses of 90-day survival are summarized in Table 5. Two different analyses were done. When entering the same variables tested to predict the risk factors for intubation, allocation in the control group, ARDS as the cause of respiratory failure, and severity of illness (Simplified Acute Physiology Score-II of more than 37 on admission) were independent predictors of decreased 90-day survival. However, when also including the follow-up variables in the analyses, the need for intubation was the only independent predictor of decreased 90-day survival (p < 0.001).

DISCUSSION

The results of this study show that the use of NIV to avoid intubation in patients with severe AHRF decreased the need for intubation, the incidence of septic shock, and the levels of tachypnea and arterial hypoxemia, and improved ICU and 90-day survival compared with patients receiving high-concentration oxygen therapy.

Significant debate exists concerning the precise indications for NIV in patients with AHRF (20, 21), as NIV was initially shown to be of limited benefit to these patients (10, 22, 23). Initial evidence for the lack of efficacy of NIV in patients with AHRF was not supported by randomized clinical trials powered to address this question (10, 22). Subsequently, however, NIV has shown to be effective in preventing intubation in selected groups of patients with cardiogenic pulmonary edema (6), immunosuppression (7, 8), and acute respiratory failure after lung resection (9).

Despite the latter studies, the efficacy of the systematic use of NIV to avoid intubation in a general population of patients with severe AHRF, defined as the inability to achieve acceptable levels of arterial oxygenation using conventional oxygen therapy at maximal concentration and flow, had not been assessed yet in a randomized fashion. We used this inclusion criteria instead of PaO₂/FiO₂ ratios below predefined thresholds because PaO₂/FiO₂ is dependent on the levels of FiO₂ delivered. In addition, using predefined thresholds for PaO₂/FiO₂ may not always reflect life-threatening consequences of the deterioration of oxygenation. These criteria selected patients with very severe hypoxemia, as

TABLE 2. INTUBATION, LENGTH OF STAY, AND OUTCOME VARIABLES*

	Noninvasive Ventilation Group (n = 51)	Control Group (n = 54)	p Value
Intubation rate, n, % [†]	13 (25)	28 (52)	0.010
Pneumonia, n/tot	5/19	11/15	0.017
Cardiogenic pulmonary edema, n/tot	1/15	2/15	> 0.999
Thoracic trauma, n/tot	1/6	5/11	0.333
ARDS, n/tot	6/7	8/8	0.467
Other, n/tot	0/4	2/5	—
Indications for intubation and other relevant features at the time of intubation [‡]			
Signs of exhaustion	11	22	
Neurologic impairment	2	5	
Respiratory pauses and gasping	1	2	
Severe hemodynamic instability	2	5	
Respiratory or cardiac arrest	2	0	
Aspiration	1	1	
Inability to clear secretions	1	2	
Major agitation	2	3	
Refractory hypoxemia [§]	2	10	
Respiratory acidosis	1	3	
Metabolic acidosis	1	11	
Respiratory rate of more than 35 min ⁻¹	5	13	
ICU stay, d	9.6 ± 12.6	11.3 ± 12.6	0.510
Among ICU survivors	8.0 ± 7.6	10.1 ± 10.7	0.339
Hospital stay, d	20.7 ± 16.6	26.8 ± 19.8	0.090
Among ICU survivors	21.1 ± 14.8	30.2 ± 21.3	0.043
Intensive care unit mortality, n (%)	9 (18)	21 (39)	0.028
Pneumonia, n/tot	3/19	8/15	0.030
Cardiogenic pulmonary edema, n/tot	1/15	2/15	> 0.999
Thoracic trauma, n/tot	0/6	3/11	0.515
ARDS, n/tot	5/7	7/8	0.569
Other, n/tot	0/4	1/5	—

Definition of abbreviations: ARDS = acute respiratory distress syndrome, ICU = intensive care unit; n/tot = number of events/total number of patients.

* Plus-minus values are mean ± SD.

[†] Results are given for the overall population and the four main subgroups of patients only.

[‡] Some patients had more than one indication or relevant feature.

[§] Refractory hypoxemia was defined as arterial oxygen saturation of less than 90% at maximal inspired oxygen fraction.

assessed by the baseline mean P_{aO_2}/F_{iO_2} ratios. In similar patients, NIV decreased the incidence of serious complications and length of stay when compared with immediate intubation and invasive ventilation (5). However, the efficacy of NIV in preventing intubation as compared with a conventional therapeutic approach was not assessed in the study mentioned (5).

NIV reduced the need for intubation in this study, and the beneficial effects were independent of other factors, as shown in the multivariate analyses. Interestingly, NIV was especially

effective in the subset of patients in whom pneumonia was the cause of respiratory failure. Pneumonia is considered a predictor both of poor response to NIV when it causes an exacerbation of COPD as compared with other causes (24) and in patients with AHRF (25). However, a randomized controlled study in patients with pneumonia showed that NIV prevented intubation in those with underlying COPD and hypercapnic respiratory failure only (26). Therefore, this is the first study showing that NIV can reduce the rate of intubation in patients with pneumonia mainly without chronic respiratory disorders. Two reasons may explain the greater efficacy of NIV in this study in patients with

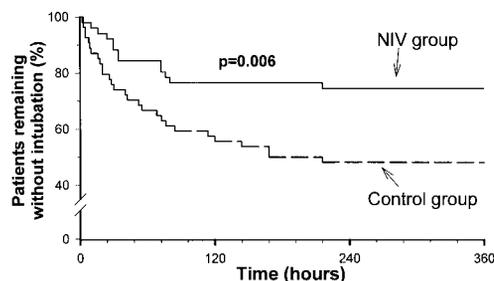


Figure 2. Kaplan-Meier curves for patients remaining without intubation after entry into the protocol. In the overall population, the cumulative probability of remaining without intubation was higher in the noninvasive ventilation (NIV) group (log-rank test). Time denotes the hours after patients were entered into the study.

TABLE 3. MULTIVARIATE ANALYSES OF RISK FACTORS FOR INTUBATION*

	Adjusted Odds Ratio	95% CI	p Value
Noninvasive ventilation [†]	0.20	0.07–0.58	0.003
Cardiogenic pulmonary edema [†]	0.14	0.04–0.56	0.005
ARDS	28.5	3.2–249.8	0.003

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval.

* Together with the randomized groups (noninvasive ventilation or control), the variables tested for association to intubation are shown in the online supplement.

[†] Adjusted odds ratio and 95% confidence intervals below one mean a beneficial effect on intubation.

TABLE 4. SERIOUS COMPLICATIONS DIAGNOSED AFTER PATIENTS WERE ENTERED INTO THE STUDY AND CAUSES OF DEATH WITHIN 90 DAYS AFTER ENTRY INTO THE STUDY

	Noninvasive Ventilation Group (n = 51)	Control Group (n = 54)	p Value
Complications after patients were entered into the study			
Hospital-acquired pneumonia, n (%)	5 (10)	13 (24)	0.093
Catheter-related sepsis, n (%)	1 (2)	2 (4)	—
Urinary tract-related sepsis, n (%)	—	1 (2)	—
Abdominal-related sepsis, n (%)	1 (2)	2 (4)	—
Bacteremia of unknown origin	—	1 (2)	—
Barotrauma, n (%)	—	2 (4)	—
Septic shock, *n (%), causes:	6 (12)	17 (31)	0.028
Hospital-acquired pneumonia [†]	3	11	
Pneumonia causing AHRF [‡]	1	2	
Abdominal-related sepsis [§]	1	2	
Catheter-related sepsis	1	1	
Bacteremia of unknown origin	—	1	
Specific complications associated to noninvasive ventilation			
Mild to moderate nasal bridge injury	13 (25)	—	
Conjunctivitis	3 (6)	—	
Gastric distension	1 (2)	—	
Causes of death within 90 days of randomization			
Shock /multiple organ failure	6	15	
Refractory hypoxemia	1	5	
Cardiac arrest	2	—	
Do not resuscitate order	1	1	

Definition of abbreviation: AHRF = acute hypoxemic respiratory failure.

* Cases of septic shock (18) developed after patients were entered into the study; cases of shock on admission are not included in this table.

[†] Cases of pneumonia diagnosed after patients were entered into the study.

[‡] Cases of pneumonia causing the episode of acute hypoxemic respiratory failure.

[§] In one case from the control group, acute respiratory distress syndrome secondary to abdominal sepsis was the cause of acute hypoxemic respiratory failure; in the remaining cases, abdominal sepsis was diagnosed after entry into the study.

In patients with thoracic trauma, pneumothorax, pneumomediastinum, or subcutaneous emphysema were not considered as barotrauma if present at entry into the study.

pneumonia. First, patients from this study with pneumonia were more severely hypoxemic than those from the previous study (26) without either COPD or hypercapnia (mean Pa_O₂/F_IO₂ ratios were 100 and 165, respectively). Therefore, NIV may be a significantly better support than oxygen therapy alone because of the higher risk of intubation using oxygen alone in those more severely hypoxemic patients. Second, this subset of patients receiving NIV in a previous study (26) were more seriously ill than those from the control group, as assessed by their higher acute physiology a chronic health evaluation-II score.

In contrast, the use of NIV had marginal effects on the needs for intubation in patients with cardiogenic pulmonary edema, unlike a recent publication from Masip and coworkers (6), showing decreased intubation rate in such patients. Several reasons may explain the differences between the two studies: (1) Because of the low intubation rate of patients with cardiogenic pulmonary edema in this study, we cannot expect benefits of using NIV in this subset of patients. (2) Those authors (6) initiated the protocol in the emergency room before admission to ICU. (3) A significant number of patients with hypercapnia on admission, recently identified as better responders to NIV than nonhypercapnic patients (27), received NIV in the previously mentioned study (6). The efficacy of NIV in patients with ARDS was also limited. The severe average levels of arterial hypoxemia and the likely impairment of pulmonary mechanics in these patients may explain the high intubation rate, regardless of NIV use. The advisability of future studies is questionable given the poor outcome of ARDS patients managed with NIV. If done, they should be performed cautiously. Finally, a nonsignificant trend to reduce the intubation rate was shown in patients with thoracic trauma.

Because all of these patients had rib fractures, and in some cases flail chest, the use of positive-pressure ventilation could facilitate chest wall stabilization and consequently prevent spontaneous breathing failure during the initial days of hospital admission. However, conclusions about the latter subset of patients are limited by the small sample size.

The efficacy of continuous positive airway pressure has been compared with oxygen therapy in a population of patients with AHRF secondary to acute lung injury with or without preexisting cardiac disease, but with less severe levels of arterial hypoxemia (28). Despite an initial improvement of arterial hypoxemia, the use of continuous positive airway pressure did not result in changes of the intubation rate nor outcome variables in this study. In our study, the use of NIV was also associated with a higher improvement of arterial hypoxemia. A possible limitation of these differences could be an overestimation of the actual F_IO₂ and therefore underestimation of the Pa_O₂/F_IO₂ ratio in the control group because the peak inspiratory flow rate of patients with AHRF may exceed in some cases the flow rate delivered by the high-concentration oxygen sources, as shown in other populations (29), hence potentially magnifying the differences between the two groups. We think that in addition to applying positive pressure to the airways to improve the physiologic determinants of abnormal pulmonary gas exchange, as well as lung mechanics and heart function, providing inspiratory support is very relevant to support the high ventilatory demands and decrease the work of breathing. This is supported by the improvement of respiratory frequency in the NIV group (Figure 3), suggesting beneficial physiologic effects of this technique compared with a standard regime. However, although the effects of NIV in decreas-

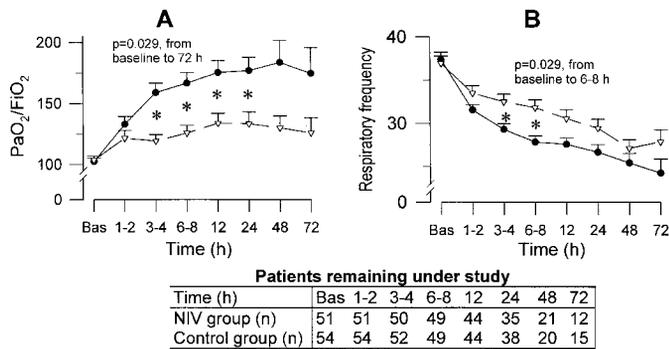


Figure 3. Time-course evolution (mean ± SEM) of arterial hypoxemia, as assessed by the Pa_o₂/F_iO₂ ratio (A), and respiratory frequency (B), in the two groups (filled circles, NIV group; open inverted triangles, control group). Both variables improved with time in the two groups. Asterisks denote significant differences between the two groups at individual time points (p < 0.05). After Bonferroni correction, the improvement of the two variables was significantly greater in the NIV group after 3–4 hours of randomization and remained significantly greater 24 and 6–8 hours after randomization for Pa_o₂/F_iO₂ ratio and respiratory frequency, respectively. The table below the graph denotes the number of patients remaining under study at each time point in the two groups. The time-course decrease of patients corresponds to those meeting criteria to terminate the protocol.

ing the work of breathing and improving the ventilatory pattern are well studied in patients with exacerbation of COPD and hypercapnic respiratory failure (30, 31), no similar information in patients with severe AHRF has been reported yet.

Survival increased in patients receiving NIV, especially in the subset of patients with pneumonia. The multivariate analyses of survival showed the need for intubation (of which NIV was an independent protective factor) as the most relevant factor related to poor outcome. Patients failing spontaneous breathing and needing intubation despite such aggressive support for respiratory failure may be a selected subset of very severely ill patients, as assessed by their high mortality rate. Perhaps because the delay in intubation permitted time for the treatment of the underlying disease so as to improve the patients' clinical condition and respiratory failure, the use of NIV prevented spontaneous breathing failure and decreased the need for invasive mechanical ventilation and improved survival. This may be especially valid

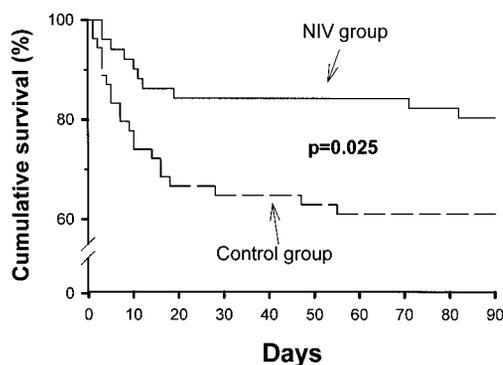


Figure 4. Kaplan-Meier curves for survivor patients within 90 days after entry into the protocol. In the overall population, the cumulative survival probability was significantly higher in the NIV group (log-rank test). Time denotes the days after patients were entered into the study.

TABLE 5. MULTIVARIATE ANALYSES OF DECREASED 90-DAY SURVIVAL*

	Adjusted Odds Ratio	95% CI	p Value
All variables			
Intubation	38.3	9.1–161.4	< 0.001
Variables present at entry into the study only			
Noninvasive ventilation†	0.39	0.18–0.84	0.017
ARDS	5.1	2.4–11.0	< 0.001
SAPS-II of more than 37 on admission	2.4	1.1–5.0	0.021

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval; SAPS-II = simplified acute physiology score-II.

* Together with the randomized groups, the variables tested for association to 90-day survival are shown in the online data supplement.

† Adjusted odds ratio and 95% confidence intervals below one mean a beneficial effect on 90-day survival.

in clinical conditions with potentially effective treatments, such as antibiotics in pneumonia. Consequently, avoiding intubation should be one of the goals in the management of patients with severe AHRF. In addition, the most frequent cause of death, namely shock/multiple organ failure, was mainly a consequence of complications associated with invasive mechanical ventilation.

In addition to an appropriate selection of patients and the experience of the attending clinicians and nurses in the use of NIV, the type of ventilator used may be one of the possible reasons to explain the efficacy of NIV. In this study, we used a ventilator specifically designed for NIV, able to provide high levels of oxygen, a proper maintenance of the positive pressure levels by leak control facilitated by a real-time assessment of mask pressure, as well as a sensitive and rapid response flow-by trigger (32, 33).

In patients with cardiogenic pulmonary edema or COPD exacerbations, the highest number of intubations and therefore the greatest efficacy of NIV for intubation avoidance are shown within hours or the first day (6, 12). In contrast, intubations in this study occurred after a longer period of time, as shown in Figure 2. This suggests that some patients with AHRF may benefit from using NIV for longer periods of time, up to 13 days as shown in this study.

Several limitations of this study have to be taken into account. The first is the difficulty for a correct blinding of the investigators, attending physicians, and patients in this type of open clinical trials, which might lead to possible bias. Despite the fact that we predefined the criteria for all relevant interventions, clinical decisions, and outcome variables, this bias could not be entirely controlled. Second, a significant number of patients were not included because of a lack of cooperation; this is inherent of this controlled clinical trials in severely ill awake patients where several features need to be under control. It does not exclude that these patients can benefit from receiving NIV in the clinical practice when such amount of cooperation is not needed. The third is the relative heterogeneity of patients with AHRF. We performed a subgroup analysis in the four main subsets of patients, but the study was powered to analyze the overall population. We recognize that this type of analysis in small sample sizes may seem inconclusive, especially when no differences among groups are shown.

In conclusion, except in patients with ARDS, the use of NIV is effective to reduce intubation in patients with severe AHRF. Avoidance of intubation and complications associated with invasive mechanical ventilation appear to be the main reasons of

improved survival. Our data provide strong evidence for the use of NIV as a first-line intervention in patients with severe AHRF in the absence of contraindications for using this technique.

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