A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome*

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Objective: **In randomized studies of heterogeneous patients with hypoxemic acute respiratory failure, noninvasive positive pressure ventilation (NPPV) was associated with a significant reduction in endotracheal intubation. The role of NPPV in patients with acute respiratory distress syndrome (ARDS) is still unclear. The objective was to investigate the application of NPPV as a first-line intervention in patients with early ARDS, describing what happens in everyday clinical practice in centers having expertise with NPPV.**

Design: **Prospective, multiple-center cohort study.**

Setting: **Three European intensive care units having expertise with NPPV.**

Patients: **Between March 2002 and April 2004, 479 patients with ARDS were admitted to the intensive care units. Three hundred and thirty-two ARDS patients were already intubated, so 147 were eligible for the study.**

Interventions: **Application of NPPV.**

Measurements and Main Results: **NPPV improved gas exchange and avoided intubation in 79 patients (54%). Avoidance of intubation was associated with less ventilator-associated pneumonia (2% vs. 20%; $p < .001$) and a lower intensive care unit mortality rate (6% vs. 53%; $p < .001$). Intubation was more likely in patients who were older ($p = .02$), had a higher Simplified Acute Physiology Score (SAPS) II ($p < .001$), or needed a higher level of positive end-expiratory pressure ($p = .03$) and pressure support ventilation ($p = .02$). Only SAPS II >34 and a Pao_2/Fio_2 ≤175 after 1 hr of NPPV were independently associated with NPPV failure and need for endotracheal intubation.**

Conclusions: **In expert centers, NPPV applied as first-line intervention in ARDS avoided intubation in 54% of treated patients. A SAPS II >34 and the inability to improve Pao_2/Fio_2 after 1 hr of NPPV were predictors of failure. (Crit Care Med 2007; 35:18–25)**

Key Words: intensive care; respiratory insufficiency; mechanical ventilators; endotracheal intubation

Noninvasive positive pressure ventilation (NPPV) is an effective technique for improving gas exchange and avoiding endotracheal intubation in selected patients with acute respiratory failure (ARF) (1). In a recent study performed in patients with acute lung injury, NPPV combined with positive end-expiratory pressure reduced inspiratory muscle effort and work of breathing (2). Considerable evidence supports the use of NPPV in hypercapnic ARF due to acute exacerbation of chronic obstructive pulmonary disease (3), and recent randomized studies have indicated a benefit to patients with hypoxemic ARF caused by severe community-acquired pneumonia (especially with chronic obstructive pulmonary disease) (4, 5), complications from solid organ transplantation (6), and following lung resection (7). A multivariate analysis of five randomized studies of patients with hypoxemic ARF of varied etiologies showed NPPV to be independently associated with a lower risk of intubation and a lower 90-day mortality rate (3). Reduction in mortality with NPPV is related to avoidance of complications associated with endotracheal intubation and a shorter duration of mechanical ventilation and intensive care unit (ICU) stay (1). Acute respiratory distress syndrome (ARDS) represents the most severe form of hypoxemic ARF and is caused by diffuse inflammation of the pulmonary lobules with breakdown in the barrier and gas exchange function of the lung (8). In ARDS, transient loss of positive pressure during mechanical ventilation may seriously compromise lung recruitment and gas exchange. For this reason, most NPPV studies have excluded patients with ARDS, and limited data are currently available in the literature. In two randomized studies, we reported that among patients with ARDS (n = 31), NPPV avoided intubation in 60% (6, 9), whereas a recent trial that included a small number of ARDS patients (n = 7) reported an

*See also p. 288.

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86% intubation rate (5). Two NPPV observational studies involving 98 ARDS patients reported an intubation rate of 50% (10, 11), which was similar in patients with ARDS of pulmonary or extrapulmonary origin (10). Overall, the findings of these studies invite a prudent approach, limiting the application of NPPV to hemodynamically stable patients who can be closely monitored in the ICU where endotracheal intubation is promptly available (9). ARDS represents one of the last frontiers in exploring the application of NPPV in patients with ARF. Achieving a 50% reduction in intubation rate would positively affect ARDS outcome if the potential complications of a delayed intubation could be avoided. In this regard, it is unclear how often and with which results expert centers apply NPPV in ARDS patients. In addition, an accurate predictor of response would be clinically useful to avoid unnecessary continuation of NPPV in those less likely to achieve a sustained improvement in gas exchange. For this reason, we prospectively investigated, under close ICU observation, the application of NPPV as first-line intervention in patients with early ARDS to describe the behavior of expert centers in everyday clinical practice and to identify factors predicting response.

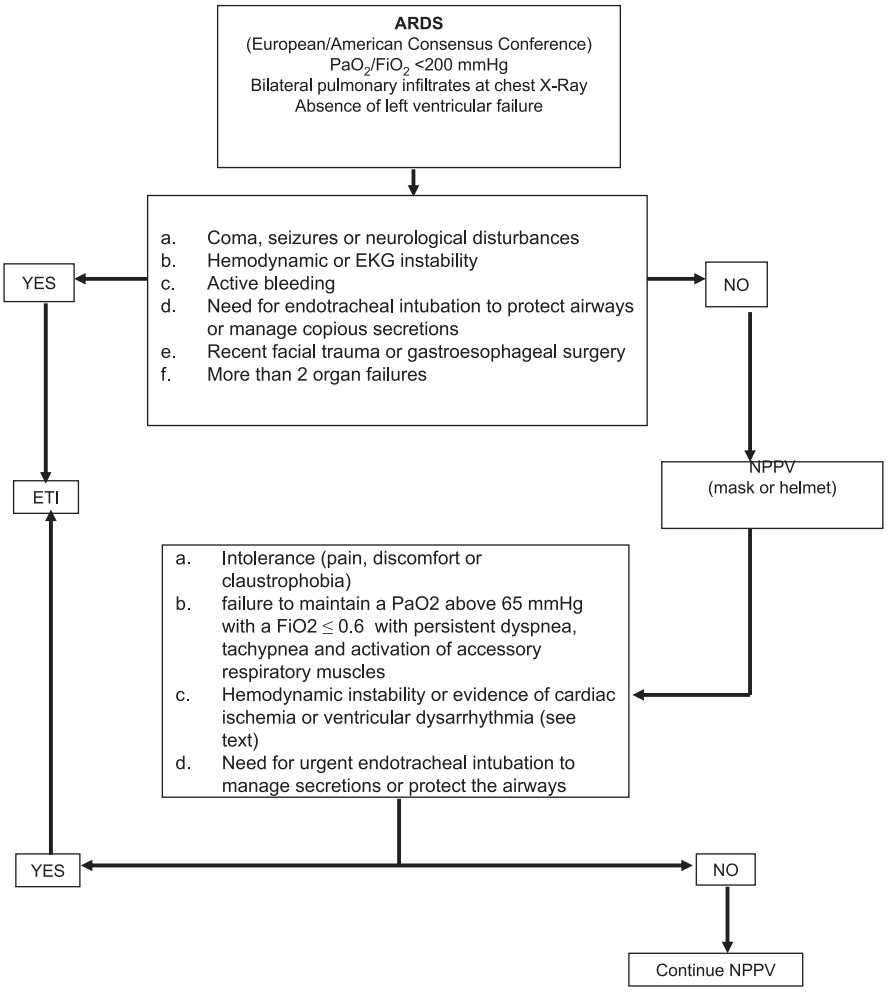

Figure 1. Study design. *ARDS*, acute respiratory distress syndrome; *EKG*, electrocardiograph; *NPPV*, noninvasive positive pressure ventilation.

METHODS

Study Design and Patient Selection

Between March 2002 and April 2004, all consecutive adult patients with early ARDS (occurring within the first 24 hrs before ICU admission) admitted to three ICUs in Italy (Università Cattolica del Sacro Cuore and Università La Sapienza, Rome) and Spain (M. Meseguer Hospital, Murcia) were considered eligible for the study. All the participating teams had accumulated a great deal of experience with NPPV in patients with hypoxemic ARF (6, 9, 10, 12, 13).

The ethics committee and the institutional review board approved the protocol, and all patients gave written informed consent. All the centers apply the same criteria to select patients candidate for NPPV treatment: a) spontaneous breathing with severe dyspnea at rest; b) respiratory rate >30 breaths/min; and c) diagnostic criteria for ARDS by the American-European Consensus Conference definition (14).

In all eligible patients, a trial of NPPV was attempted as a first-line intervention with the aim of avoiding endotracheal intubation. All centers followed a clinical flow chart reported in Figure 1. In all centers, the decision to treat patients noninvasively or not was left to the doctors in charge.

Exclusion criteria included requirement for emergent intubation for cardiopulmonary resuscitation, respiratory arrest, severe hemodynamic instability (systolic arterial pressure <90 mm Hg, despite adequate fluid replacement, presence of ventricular arrhythmias, or signs of cardiac ischemia), or encephalopathy; more than two new extrapulmonary organ failures (e.g., the simultaneous presence of renal and cardiovascular failures) (15); tracheostomy, facial deformities, or recent oral, esophageal, or gastric surgery; and inclusion in other prospective randomized studies on noninvasive ventilation. Patients had continuous electrocardiographic and arterial oxygen saturation monitoring (Biox 3700, OHmeda, Boulder, CO). Four types of mechanical ventilators were used, without preference, in all centers: Puritan Bennett 7200 (Puritan Bennett, Overland Park, KS), Servo 900C, Servo 300 (Maquette, Solna, Sweden), and Vision Respironics (Respironics, Pittsburgh, PA). The Simplified Acute Physiology Score (SAPS) II was calculated 24 hrs after admission to the ICU (16).

Noninvasive Ventilation

The head of the bed was kept elevated at a 45° angle, and patients were not sedated. The ventilator was connected with conventional tubing to a clear, full-face mask with an inflatable soft cushion seal (Gibeck, Upplands, Sweden, or Vitalsigns, Towota, NJ) or double spring soft cushion (Benefit, Puritan Bennett, Overland Park, KS) or to a clear, latex-free helmet (CaStar, Starmed, Mirandola, Italy) (12, 13). With all interfaces, pressure support ventilation (17) with positive end-expiratory pressure (PEEP) was used. Pressure support ventilation was increased in increments of 2–3 cm H_2O to obtain an exhaled tidal volume of 6 mL/kg and a respiratory rate of <25 breaths/min. When the helmet was used, part of the volume delivered to the system was spent to distend the helmet and did not reach the patient (12, 13). PEEP was increased in incre-

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ments of 2–3 cm H_2O up to 12 cm H_2O to ensure a peripheral oxygen saturation of ≥92% with the lowest F_{IO_2} possible. Ventilator settings were then adjusted on the basis of pulse-oximetry and measurements of arterial blood gases. Both flow and pressure triggers were used. Pressure trigger was set at −2 cm H_2O and flow trigger at 5 L/sec.

Duration of ventilation was standardized according to the protocol of Wysocki et al. (18). During the first 24 hrs, ventilation was continuously maintained until oxygenation and clinical status improved. Once PEEP requirements decreased to 5 cm H_2O, each patient was evaluated daily while breathing supplemental oxygen without ventilatory support for 15 mins. NPPV was reduced progressively in accordance with the degree of clinical improvement and was discontinued if the patient maintained a respiratory rate <30 breaths/min and a Pa_{O_2} >75 mm Hg, with an F_{IO_2} of 0.5 without ventilatory support and activation of the accessory muscles of respiration.

Mask Ventilation. The mask was secured with head straps to avoid a tight fit, and when necessary a hydrocolloid sheet was applied over the nasal bridge. A seal connector on the dome of the mask was used for passage of the nasogastric tube. Special care was taken to avoid air leakage by monitoring the difference between inspired and expired tidal volume.

Helmet Ventilation. The helmet (Castar, Starmed, Mirandola, Italy) is a transparent, latex-free, PVC hood, with a seal connection soft collar adherent to the neck (12, 13) joined by a plastic ring. Two arm-pit braces hooked to the ring secure the helmet to the patient during pressurization. The pressure increase during ventilation makes the soft collar seal comfortably to the neck and the shoulders, avoiding air leakage. A specific seal connector on the plastic ring was used for passage of the nasogastric tube or a straw (used for drinking). The helmet could be removed easily if endotracheal intubation was necessary.

Criteria for Endotracheal Intubation. Patients who failed NPPV underwent endotracheal intubation with cuffed endotracheal tubes (internal diameter 7.5–8.5 mm) and were mechanically ventilated. Predetermined criteria for endotracheal intubation (18) included failure to maintain a Pa_{O_2} >65 mm Hg with an F_{IO_2} ≥0.6 with persistent dyspnea, tachypnea, and activation of accessory respiratory muscles; development of conditions necessitating endotracheal intubation to protect the airways (coma or seizure disorders) or to manage copious tracheal secretions; any hemodynamic or electrocardiographic instability (i.e., systemic hypotension lasting >1 hr despite fluid resuscitation); inability to correct dyspnea; or inability to tolerate the mask or helmet. After intubation, all patients were ventilated with a lung-protective strategy, with tidal volume of 6 mL/kg and plateau pressures <30 cm H_2O (19). For all the intubated patients, the head of the bed was kept elevated at a 45°angle, but none was pronated. All intubated patients were weaned after T-piece trials (20).

End Points and Definitions

The primary outcome variables were the number of patients eligible for NPPV, requirement for endotracheal intubation and mechanical ventilation at any time during the study, and risk factors associated with failure of NPPV. Secondary end points included development of nosocomial infections after study entry (such as ventilator-associated pneumonia or extrapulmonary sepsis), duration of ventilatory assistance, length of ICU stay, and survival of ICU and hospital admission.

Arterial blood gas levels were determined at baseline, at 1 hr during NPPV, when clinically needed, and at discontinuation of support or at the moment of endotracheal intubation for those who failed NPPV. Improvement in gas exchange was defined as an increase in Pa_{O_2}/F_{IO_2} ratio above 200 or >100 from baseline (21). Improvement in gas exchange was evaluated 1 hr after study entry (initial improvement) and over time (sustained improvement). Sustained improvement in gas exchange was defined as the ability to maintain the defined improvement in Pa_{O_2}/F_{IO_2} until mechanical ventilation was discontinued.

Sepsis was defined as the systemic inflammatory response to an infectious process, with manifestations including tachycardia, tachypnea, hyperthermia or hypothermia (>38°C or <36°C), and altered white cell count (>10,000 or <4000 cells/mm^3) (22). Patients with clinical manifestation of pneumonia (23) underwent bronchoscopy with bronchoalveolar lavage. The methods and laboratory procedures followed consensus guidelines and common protocols (24, 25). The diagnosis of pneumonia was established by recovering microorganisms in quantitative bacterial cultures at a growth ≥10,000 colony-forming units of bacteria/mL (24). Multiple organ failure was defined following previously described criteria (15).

Data Analysis

Data were analyzed using the SAS system for Windows version 8 (SAS Institute, Cary, NC). Results in the failed and successful groups were evaluated with two-tailed chi-square test, unpaired Student's *t*-test, or Fisher's exact tests, when appropriate. Comparisons of median values were made using the Mann-Whitney test. Factors independently associated with endotracheal intubation were identified using a logistic regression model. A univariate analysis was initially performed, obtaining for each variable the crude odds ratio (OR). Age and SAPS II were dichotomized based on the median values of the distribution, whereas the cutoff values of the basal and post-1-hr variables of noninvasive ventilation (Pa_{O_2}/F_{IO_2}, pH, respiratory rate, and Pa_{CO_2}) were assessed with the receiver operating characteristic curve. All variables showing $p < .2$ in the univariate analysis were entered into the model. A significant improvement in the log likelihood function was the main criterion for entering variables in the model. The effect of possible confounding factors was determined by introducing these variables in the final model and calculating the change in the risk factor coefficients (26).

Receiver operating characteristic curve analysis provides a powerful means of assessing the ability of each index to discriminate between the two groups of patients (successful and failure), with the advantage that the analysis does not depend on the cutoff value selected. The cutoff values selected were those resulting in the fewest false classifications. This decision was based on the assumption that the disadvantages associated with either a false-positive or false-negative result were equal, since delayed or unnecessary intubations were considered equally deleterious. The appropriateness of the cutoff value was evaluated using a logistic regression model.

The receiver operating characteristic curve analysis was performed using a nonparametric method. With this approach, the 95% confidence interval (CI) of the area can be used to test the hypothesis that the theoretical area is 0.5: If the CI does not include this value, then there is evidence that the test has the ability to distinguish between the two groups.

RESULTS

During the 25 months of the study, 5,888 patients were admitted to the ICUs of the three participating centers. The mean (±SD) SAPS II and age were 35 ± 9 and 53 ± 17 yrs, respectively. Of the 479(8%) patients who met ARDS criteria, 332 (69%) were admitted already intubated or required immediate intubation for altered mental status, inability to manage secretions, hemodynamic or electrocardiographic instability, severe trauma, and/or more than two organ failures. One hundred forty-seven (31%) patients were eligible for study participation and received NPPV as first-line intervention. Sepsis was the leading cause of ARDS. ARDS was caused by a primary pulmonary process in 69 patients (51 nosocomial pneumonia, 13 community-acquired pneumonia, and five pulmonary contusion) and an extrapulmonary process in 78 patients (23 extrapulmonary sepsis, 33 postsurgical sepsis, 11 multiple

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blood transfusions, nine pancreatitis, two fat embolism).

Predefined criteria for improvement in Pa_{O_2}/F_{IO_2} were achieved within 1 hr in 52 (35%) patients and sustained improvement in 71 (48%). Improvement in Pa_{O_2}/F_{IO_2} within 1 hr of NPPV institution was not associated with improved mortality. NPPV was successful in avoiding intubation in 79 patients (54%), and the success rate was similar among centers. The baseline characteristics of patients who avoided or required endotracheal intubation are shown in Table 1; arterial blood gas findings, comorbid conditions, and etiology of ARDS were similar. All centers had similar outcome, and no difference was noted by using different types of ventilator or interfaces or by using a flow or pressure trigger. Patients requiring endotracheal intubation were older, had higher SAPS II, and initially received a higher level of PEEP and pressure support ventilation. Patients with pulmonary or extrapulmonary ARDS were equally distributed among those receiving ventilation via mask or helmet and had a similar rate (48% vs. 51%) of intubation (OR, 0.87; 95% CI, 0.49–2.05; $p = .84$) that was not affected by the Pa_{CO_2} value at study entry. Figure 2 shows changes in Pa_{O_2}/F_{IO_2} over time in patients who avoided or required intubation. Those who avoided intubation had a significantly higher Pa_{O_2}/F_{IO_2} 1 hr after initiation of NPPV (195 ± 66 vs. 168 ± 48; $p = .009$) and before discontinuation of ventilation (253 ± 86 vs. 146 ± 65; $p < .001$) (Fig. 2) and were more likely to have a sustained improvement in Pa_{O_2}/F_{IO_2} (Table 2). The median duration of NPPV without interruptions (Table 2) in patients who avoided intubation was 42 hrs (25th–75th, 24–51). NPPV exceeded 72 hrs in 28 patients and 100 hrs in ten patients (eight with helmet). Figure 3 shows timing to endotracheal intubation. Seventy percent of NPPV failures were intubated within 48 hrs of initiating NPPV.

Table 2 shows outcome variables and complications after study entry. Patients who required intubation had a higher rate of severe sepsis or septic shock (OR, 5.81; 95% CI, 2–17.4; $p = .01$) Ventilator-associated pneumonia was the leading infection and developed almost exclusively in patients who required intubation (Table 2). A microbiological etiology of pneumonia was established in 13 (93%) cases: five methicillin-resistant *Staphylococcus aureus*, four *Pseudomonas aeruginosa*, two *Acinetobacter* species, one *Klebsiella*, and one *Aspergillus fumigatus* (an immunosuppressed patient). Complications related to NPPV included nasal or facial skin necrosis (healed spontaneously within 10 days) in 17 (11%) patients, conjunctivitis in 2 (1%) patients, and gastric distension in 13 (9%) patients.

Overall ICU mortality rate was 28%. ICU mortality ate was significantly higher in those who required intubation (OR, 21; 95% CI, 6.4–76.5; $p < .001$) (Table 2). Causes of death for those who required and avoided intubation included ventricular fibrillation or sudden cardiac arrest (one and one), cardiogenic shock or acute myocardial infarction (four and one), and severe sepsis or septic shock with multiple organ dysfunction (31 [22 occurring after study entry] and three). Twelve pa-

Table 1. Baseline characteristics in patients who avoided and required intubation

Variable	Avoided Intubation (n = 79)	Required Intubation (n = 68)	*p* Value
Age, yrs, median (25th–75th)	53 (35–64)	60 (51–68)	.02
Male gender, n (%)	43 (54)	50 (73)	.02
SAPS II on admission, median (25th–75th)	32 (28–36)	38 (34–41)	<.001
GCS, mean (SD)	14 (1)	14 (1)	.9
PEEP[a] basal, mean (SD)	7 (2)	8 (2)	.03
PSV, cm H_2O, mean (SD)	14 (3)	16 (4)	.02
NPPV started in the ER, n (%)	17 (21)	13 (19)	.43
Patients treated with the helmet, n (%)	25 (32)	19 (28)	.37
Pa_{O_2}/F_{IO_2} at baseline, mean (SD)	116 (38)	105 (33)	.06
pH at baseline, mean (SD)	7.41 (0.08)	7.39 (0.07)	.12
Pa_{CO_2} at baseline, mm Hg, mean (SD)	40 (13)	40 (13)	.94
RR at baseline, mean (SD)	35 (5)	36 (5)	.27
HR at baseline, mean (SD)	105 (21)	106 (24)	.9
Comorbid conditions, n (%)			
None	45 (57)	37 (54)	.8
Systemic hypertension	9 (11)	9 (13)	.9
Diabetes	3 (4)	9 (13)	.09
Immunosuppression[b]	16 (20)	6 (9)	.1
Cardiac ischemia	6 (8)	7 (10)	.72
Etiology of ARDS, n (%)			
Pulmonary	36 (45)	33 (48)	.84
Extrapulmonary	43 (54)	35 (51)	.84

SAPS, Simplified Acute Physiology Score; GCS, Glasgow Coma Scale; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; NPPV, noninvasive positive pressure ventilation; ER, emergency room; RR, respiratory rate; HR, heart rate.

[a]PEEP basal refers to the value taken immediately after the institution of NPPV. pH, Pa_{CO_2}, Pa_{O_2}/F_{IO_2}, RR, and HR were all recorded at baseline, before starting NPPV; [b]Immunosuppression included hematologic malignancies (n = 5), solid tumor (n = 8), and immunosuppression for solid organ transplantation (n = 9).

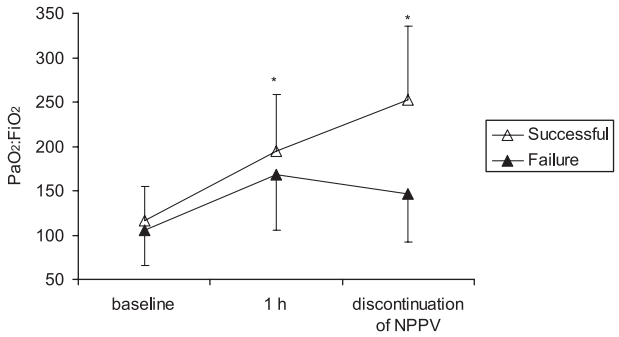

Figure 2. Pa_{O_2}:F_{IO_2} ratio over time in patients who avoided (successful) and required (failure) intubation. Discontinuation of noninvasive positive pressure ventilation (*NPPV*) corresponds to the discontinuation of ventilation for patients who avoided intubation and timing of endotracheal intubation for those who required intubation. *$p < .01$ between the two groups.

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Table 2. Outcome variables and complications after study entry

	Avoided Intubation (n = 79)	Required Intubation (n = 68)	*p* Value
Outcome variables			
Improvement of gas exchange after 1 hr, n (%)	32 (41)	20 (29)	.21
Sustained improvement of gas exchange, n (%)	59 (75)	12 (18)	<.001
Duration of NPPV (hrs) without discontinuation, median (25th–75th)	42 (24–51)	24 (21–47)	.002
ICU length of stay (days), median (25th–75th)	6 (3–11)	7 (3–18)	.24
Skin breakdown, n (%)	8 (10)	9 (13)	.32
ICU mortality, n (%)	5 (6)	36 (53)	<.001
Hospital mortality, n (%)	15 (19)	38 (54)	<.01
Complications after study entry, n (%)			
None	58 (73)	19 (28)	<.001
Sepsis	13 (16)	19 (28)	.11
Severe sepsis or septic shock	6 (7)	16 (23)	.01
Ventilator-associated pneumonia	2 (2)	14 (20)	.001

NPPV, noninvasive positive pressure ventilation; ICU, intensive care unit.

In most cases, the longer duration of NPPV was related to the use of a helmet (see text). The etiology of hospital-acquired pneumonia is reported in the text. For the definition of initial and sustained improvement, see text. For all the five patients who died in the successful group, death occurred some days after weaning from NPPV.

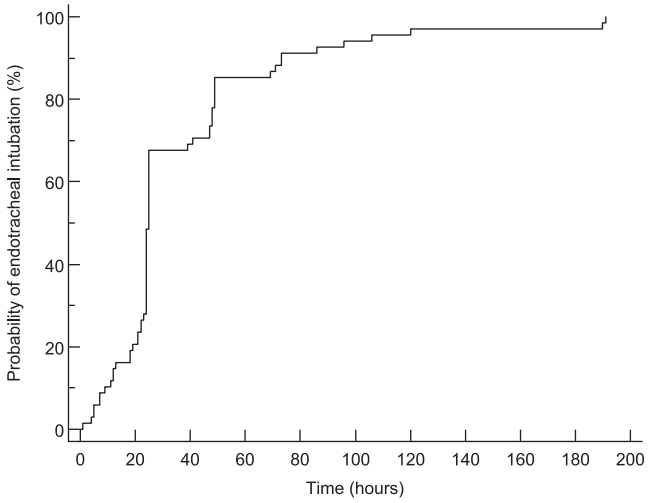

Figure 3. Kaplan-Meier curve of the probability of endotracheal intubation over time in the 68 failing patients. Most intubations occurred within the first 24–48 hrs. Reasons for intubation included inability to correct hypoxia or dyspnea (46, 67%), intolerance (17, 25%), inability to clear secretions (three, 4%), and hemodynamic instability or severe ventricular arrhythmia (two, 3%). After 48 hrs, 70% of the patients who failed NPPV were already intubated.

tients (11 who avoided intubation) died in the hospital after ICU discharge.

As shown in Figure 4 and Table 3, among the 42 patients with SAPS II ≤34 who achieved a Pao_2/Fio_2 >175 after 1 hr of NPPV, ten patients failed NPPV and were intubated and five died (50%), and 32 avoided endotracheal intubation and three (9%) died. Thirty-seven patients with a SAPS II >34 achieved a Pao_2/Fio_2 >175; 18 of them were intubated and 12 (66%) died, and 19 avoided intubation and 1 (5%) died. Of the 36 patients with a SAPS II ≤34 and a Pao_2/Fio_2 ≤175, 15 patients were intubated and eight (53%) died, and 21 avoided intubation and only one (5%) died. Of the 32 patients whose SAPS II was >34 and Pao_2/Fio_2 ≤175, 25 patients failed NPPV and were intubated and 11 (44%) died, and seven patients were successfully treated and none died. Irrespective of SAPS II value or Pao_2/Fio_2 after 1 hr of NPPV, avoidance of intubation was associated with a significantly lower mortality rate (Fig. 4).

The baseline variables and those recorded after 1 hr of noninvasive ventilation are compared in Table 4. After 1 hr of noninvasive ventilation, those who avoided intubation, in comparison to those who required intubation, had a higher Pao_2/Fio_2 (p = .009) and a lower respiratory rate (p = .0006). According to the receiver operating characteristic curve analysis, Pao_2/Fio_2 >175, pH >7.37, and respiratory rate >29 after 1 hr of noninvasive ventilation were the cutoff values that best discriminated those who avoided intubation (Table 4).

According to logistic regression model, only SAPS II >34 and a Pao_2/Fio_2 ≤175 after 1 hr of noninvasive ventilation were independently associated with the need for endotracheal intubation (Table 5).

DISCUSSION

The present study is the largest prospective investigation of noninvasive ventilation focused on patients with ARDS. In everyday clinical practice of centers expert on NPPV, no more than 31% of patients with ARDS are treated with NPPV. This clearly shows that only a small number of ARDS patients can receive NPPV in expert centers, always needing a close monitoring in the ICU setting.

We found that NPPV applied by experienced clinicians as first-line intervention to treat early ARDS avoided intubation in no more than 50% of the eligible patients. Avoidance of intubation was associated with a lower incidence of septic complications and increased ICU survival. Multivariate analysis showed that a SAPS II >34 and a Pao_2/Fio_2 ≤175 after 1 hr of NPPV were independently associated with the need for endotracheal intubation.

Thirty percent of patients admitted to the ICU with ARDS received NPPV, a fraction similar to the one in a prior study investigating NPPV as a first-line intervention in patients with ARF of varied etiology (21) but higher than in two recent studies (9, 27). This limited percent of patients underlines the need for a thorough selection and a careful respect of the exclusion criteria. Similar to the prior report (21), intubation before ICU admission was the major factor that lim-

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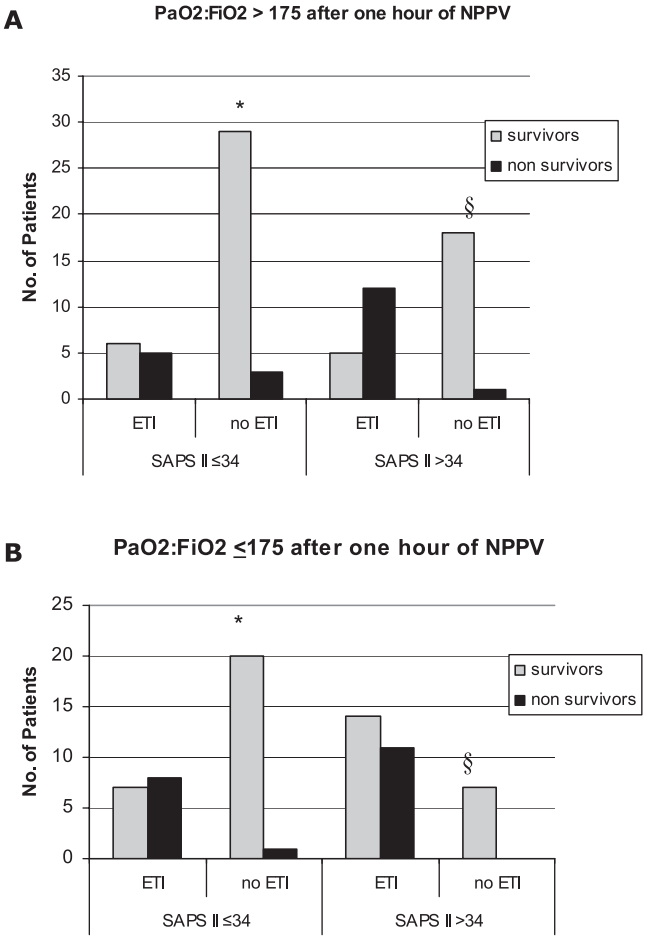

Figure 4. Survival and intubation in relation to SAPS II and Pao_2:Fio_2 findings after 1 hr of noninvasive positive ventilation (NPPV). *A*, Pao_2/Fio_2 >175 after 1 hr of noninvasive positive pressure ventilation (*NPPV*). *B*, Pao_2/Fio_2 ≤175 after 1 hr of NPPV. *ETI*, endotracheal intubation; *SAPS*, Simplified Acute Physiology Score. Irrespective of SAPS II or Pao_2/Fio_2 after 1 hr of NPPV, avoidance of intubation was associated with significant reduction in mortality: *$p < .05$; §$p < .01$.

Table 3. Noninvasive positive pressure ventilation (NPPV) failure and mortality rates stratified by Simplified Acute Physiology Score (SAPS) II and Pao_2/Fio_2 findings after 1 hr of NPPV

	SAPS II ≤34 n = 78	SAPS II >34 n = 69	Total	p^a
NPPV failure, no. of failures/no. of patients per subgroup (% of subgroup)				
Pao_2/Fio_2 >175 (n = 79)	10/42 (24)	18/37 (49)	28/79 (35)	.02
Pao_2/Fio_2 ≤175 (n = 68)	15/36 (41)	25/32 (78)	40/68 (59)	.003
Total	25/78 (32)	43/69 (62)	68/147 (46)	
Mortality, no. of death/no. of patients per subgroup (% of subgroup)				
Pao_2/Fio_2 >175 (n = 79)	8/42 (19)	13/37 (35)	21/79 (26)	.09
Pao_2/Fio_2 ≤175 (n = 68)	9/36 (25)	11/32 (34)	20/68 (29)	.28
Total	17/78 (22)	24/69 (35)	41/147 (28)	

[a]Chi-square test. Data show that the highest failure rate and subsequent endotracheal intubation occurred in the subgroup of patients with the combination of a SAPS II score >34 and a Pao_2/Fio_2 ratio ≤175.

ited implementation of NPPV. Although this factor may have biased recruitment toward patients with less severe ARDS, the baseline Pao_2/Fio_2 in our patients was similar to that in a recent study (28). Moreover, sepsis was the leading cause of ARDS in this study and is recognized as the condition precipitating ARDS associated with highest mortality rate (29). NPPV, via facial mask or helmet, was well accepted overall with a rate of intolerance (12%) similar to that in our prior study of 354 patients with hypoxemic ARF (9). In comparison to studies evaluating hypoxemic ARF of varied etiologies (9, 10), our findings show that ARDS patients have a lower rate of initial improvement in gas exchange. We previously reported that in patients with hypoxemic ARF, NPPV was equally as effective as conventional ventilation in correcting gas exchange and that improvement in Pao_2/Fio_2, with criteria similar to the present study, was observed in 62% after 1 hr of NPPV and was sustained in 69% (10). In the present study, 35% of patients achieved a Pao_2/Fio_2 200 or increased Pao_2/Fio_2 by ≥100 after 1 hr of NPPV, and sustained improvement was observed in 48%. We do not believe that this finding reflects a technical limitation of NPPV in ARDS, since the rate of improvement in Pao_2/Fio_2 was similar to the one reported with conventional ventilation (28) and the delta increment in Pao_2/Fio_2 was higher than the one reported with either low or high tidal volume conventional ventilation in the National Institutes of Health-sponsored ARDS network trial (19). In the former trial (28) of ARDS patients on conventional ventilation for <48 hrs, those who achieved a Pao_2/Fio_2 >200 after 30 mins of ventilation with standardized ventilatory settings (PEEP 10 cm H_2O and 1.0 Fio_2) had a lower mortality rate (12.5% vs.52.9%; $p = .01$) (28).

NPPV successfully avoided intubation in 54% of patients, a rate similar to our prior experience in patients with ARDS (6, 9, 10). In agreement with our prior report (9), the response to NPPV was similar in patients with ARDS caused by pulmonary or extrapulmonary condition, and arterial blood gas findings at study entry had no predictive value. Although a Pao_2/Fio_2 >175 after 1 hr of NPPV predicted avoidance of intubation (59% vs. 35%; $p < .01$), we had only three patients who met predefined criteria for intubation in the first 6 hrs of the study. In agreement with previous reports (6, 9, 10, 12, 30), most intubated patients (70%) met intubation criteria 12–48 hrs after initiating NPPV, and the main indication for intubation was an inability to improve gas exchange. In the present study, 30% of patients received NPPV through a helmet. Similar to our prior reports (12, 13), the helmet was well tolerated, allowing for prolonged and con-

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Table 4. Variables at baseline and after 1 hr of noninvasive positive pressure ventilation (NPPV) and values discriminating between patients who avoided or required intubation

Variable	Avoided Intubation, Mean (SD) (n = 79)	Required Intubation, Mean (SD) (n = 68)	*p* Value	Threshold Value[a]	AUC ± SE	95% CI	Sensitivity (95% CI)	Specificity (95% CI)
Pa_{O_2}/F_{IO_2} basal	116 (38)	105 (33)	.06	≤102	0.61 ± 0.04	0.52–0.69	0.6 (0.48–0.72)	0.66 (0.54–0.76)
Pa_{O_2}/F_{IO_2} after 1 hr	195 (66)	168 (48)	.009	≤175	0.61 ± 0.04	0.53–0.69	0.59 (0.46–0.71)	0.65 (0.53–0.75)
pH basal	7.41 (0.08)	7.39 (0.08)	.21	≤7.45	0.59 ± 0.04	0.51–0.67	0.87 (0.76–0.94)	0.37 (0.26–0.48)
pH after 1 hr	7.42 (0.06)	7.39 (0.06)	.02	≤7.37	0.61 ± 0.04	0.53–0.69	0.63 (0.51–0.75)	0.63 (0.52–0.74)
RR, basal breaths/min	35 (5)	36 (5)	.27	>31	0.54 ± 0.04	0.46–0.62	0.9 (0.8–0.96)	0.25 (0.16–0.36)
RR after 1 hr, breaths/min	27 (5)	30 (7)	.0006	>29	0.67 ± 0.04	0.59–0.75	0.63 (0.51–0.75)	0.67 (0.56–0.77)
Pa_{CO_2} basal, mm Hg	40 (13)	40 (13)	.91	>34	0.51 ± 0.04	0.43–0.59	80.6 (69–89)	27.8 (18.3–39)
Pa_{CO_2} after 1 hr, mm Hg	39 (8)	41 (13)	.46	>36	0.53 ± 0.04	0.44–0.61	0.48 (0.36–0.61)	0.71 (0.6–0.81)
Δ Pa_{O_2}/F_{IO_2}	85 (63)	65 (56)	.05	≤98	0.56 ± 0.04	0.48–0.64	0.84 (0.73–0.92)	0.3 (0.2–0.42)
Δ pH	0.0013 (0.0634)	−0.0051 (0.059)	.52	≤0.08	0.53 ± 0.04	0.44–0.61	0.22 (0.13–0.34)	0.89 (0.79–0.95)
Δ RR, breaths/min	8 (6)	6 (7)	.02	≤4	0.64 ± 0.04	0.55–0.71	0.53 (0.4–0.65)	0.72 (0.61–0.82)
Δ Pa_{CO_2}, mm Hg	0.71 (8)	−1.35 (14)	.26	>3	0.54 ± 0.04	0.46–0.66	0.69 (0.57–0.8)	0.43 (0.32–0.55)

AUC, area under receiver operating characteristic curve; CI, confidence interval; RR, respiratory rate; Δ Pa_{O_2}/F_{IO_2}, Pa_{O_2}/F_{IO_2} after 1 hr − Pa_{O_2}/F_{IO_2} basal; Δ pH, pH after 1 hr − pH basal; Δ RR, RR basal − RR after 1 hr; Δ Pa_{CO_2}, Pa_{CO_2} basal − Pa_{CO_2} after 1 hr.

[a]> and ≤ indicate whether the value above or below the threshold was predictive for endotracheal intubation. The statistical difference of pH at 1 hr was not clinically relevant.

Table 5. Univariate and multivariate analysis of risk factors for endotracheal intubation

Variable	No. of Endotracheal Intubations/Total (%)	Univariate Analysis			Multivariate Analysis		
		OR	95% CI	*p* Value[a]	OR	95% CI	*p* Value[a]
Age, yrs							
≤58	28/77 (36)	1			1		
>58	40/70 (57)	2.33	1.2–4.52	.01	1.4	0.66–3	.38
Gender, male	50/93 (54)	2.38	1.18–4.78	.01	2.1	0.93–4.64	.07
SAPS II							
≤34	25/78 (32)	1			1		
>34	43/69 (62)	3.5	1.77–6.92	.0003	3.6	1.66–7.7	.001
Δ RR							
>4	32/89 (36)	1			1		
4	36/58 (62)	2.91	1.47–5.78	.002	1.94	0.86–4.36	.1
pH after 1 hr							
>7.37	25/75 (33)	1			1		
≤7.37	43/72 (60)	2.96	1.51–5.8	.001	1.91	0.85–4.31	.11
Pa_{O_2}/F_{IO_2} after 1 hr							
>175	28/79 (35)	1			1		
≤175	40/68 (59)	2.92	1.49–5.72	.001	2.34	1.1–5.15	.03

OR, odds ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score; RR, respiratory rate; Δ RR, RR basal − RR after 1 hr.

[a]Chi-square test (analysis of maximum likelihood estimates). The outcome under study was generalized by using a dichotomous variable that could take value 1 in case of NPPV failure with endotracheal intubation and 0 in case of NPPV success with avoidance of intubation. Age and SAPS II were operationalized creating dichotomous variables based on median values of the distribution. The cutoff value of the Δ RR, pH after 1 hr, and Pa_{O_2}/F_{IO_2} after 1 hr were assessed with receiver operating characteristic curve analysis.

tinuous application of NPPV. The helmet was the interface used in most patients receiving NPPV for >72 hrs. The median duration of NPPV was 42 hrs, a finding similar to our prior studies in patients with hypoxemic ARF (6, 10).

Similar to prior studies (18, 27), NPPV failure was more likely in patients with higher SAPS II, a factor that probably contributed to increased mortality in intubated patients. The overall mortality rate in the present study (28%) was lower than that of previous reports (6, 9, 11, 30) and similar to that reported with conventional ventilation with low tidal volume (19). In agreement with the findings of prior randomized studies (5, 6, 10, 30), avoidance of intubation was associated with lower mortality rate. The high mortality rate (54%) observed in intubated patients raises the possibility that delaying intubation by 12–72 hrs might have somehow contributed to mortality. Although no deaths occurred during NPPV, we cannot completely exclude that delaying intubation, even under close observation, might have increased morbidity or mortality. This possibility was raised by the findings of a recent randomized study of patients with postextubation respiratory failure (31) that included only a few patients with ARDS. In our study, patients who achieved a Pa_{O_2}/F_{IO_2} <175 after 1 hr of NPPV and required intubation had a mortality rate (47.5%) similar to that reported by Ferguson and collaborators (28) (52.9%) for patients with persistent ARDS after 30 mins of controlled mechanical ventilation.

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In analyzing possible contributors to mortality, we found that most nonsurvivors (81%) developed sepsis or septic shock and progression of multiple organ failure after intubation. We are not aware of any study indicating that delayed intubation might increase the risk for infections. Furthermore, in agreement with our prior reports (9, 10) and the literature (reviewed in reference 2), avoidance of intubation was associated with a significant reduction in infectious complications, particularly ventilator-associated pneumonia ($p < .001$). Although our data cannot provide a reasonable assessment of the impact of delayed intubation on patients' outcome, we believe that a conservative approach should be taken until additional data from randomized studies can be obtained and in consideration that expert centers do not apply NPPV to ARDS patients in >30% of the cases.

For this reason, we suggest avoiding NPPV in ARDS patients with SAPS II ≥34 because of the high mortality observed in those who were eventually intubated (56%). In patients with SAPS ≤34, those with a Pao_2/Fio_2 >175 after 1 hr of NPPV will likely benefit from continuation of NPPV, whereas those with Pao_2/Fio_2 <175 should be closely monitored with a low threshold for intubation.

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