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Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study

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Abstract *Context*: In patients with hypoxemic acute respiratory failure (ARF), randomized studies have shown noninvasive positive pressure ventilation (NPPV) to be associated with lower rates of endotracheal intubation. In these patients, predictors of NPPV failure are not well characterized.
Objective: To investigate variables predictive of NPPV failure in patients with hypoxemic ARF.
Design: Prospective, multicenter cohort study.
Setting: Eight Intensive Care Units (ICU) in Europe and USA.
Patients: Of 5,847 patients admitted between October 1996 and December 1998, 2,770 met criteria for hypoxemic ARF. Of these, 2,416 were already intubated and 354 were eligible for the study.
Results: NPPV failed in 30 % (108/354) of patients. The highest intubation rate was observed in patients with ARDS (51 %) or community-acquired pneumonia (50 %). The lowest intubation rate was observed in patients with cardiogenic pulmonary edema (10 %) and pulmonary contusion (18 %). Multivariate analysis identified age > 40 years (OR 1.72, 95 % CI 0.92–3.23), a simplified acute physiologic score (SAPS II) ≥35 (OR 1.81, 95 % CI 1.07–3.06), the presence of ARDS or community-acquired pneumonia (OR 3.75, 95 % CI 2.25–6.24), and a PaO_2:FiO_2 ≤146 after 1 h of NPPV (OR 2.51, 95 % CI 1.45–4.35) as factors independently associated with failure of NPPV. Patients requiring intubation had a longer duration of ICU stay ($P < 0.001$), higher rates of ventilator-associated pneumonia and septic complications ($P < 0.001$), and a higher ICU mortality ($P < 0.001$).
Conclusions: In hypoxemic ARF, NPPV can be successful in selected populations. When patients have a higher severity score, an older age, ARDS or pneumonia, or fail to improve after 1 h of treatment, the risk of failure is higher.

Keywords Noninvasive positive pressure ventilation · Acute hypoxemic respiratory failure · Endotracheal intubation · Prospective, multicenter cohort study

Introduction

Noninvasive positive pressure ventilation (NPPV) is a safe and effective means to improve gas exchanges in selected patients with acute respiratory failure (ARF) of varied etiology [1]. Randomized studies in homogenous patient populations with ARF have provided supporting evidence for the early application of NPPV in hypercapnic ARF due to acute exacerbation of chronic obstructive pulmonary disease (COPD) [2, 3, 4, 5], and in hypoxemic ARF due to cardiogenic pulmonary edema [6, 7, 8, 9], severe community-acquired pneumonia [10], and following solid organ transplantation [11]. In these studies, the early application of NPPV in patients not yet meeting criteria for mechanical ventilation was associated with a significant reduction in the rate of endotracheal intubation. Compelling data indicate that avoidance of intubation reduces morbidity and mortality associated with mechanical ventilation [12]. The effectiveness of noninvasive ventilation was also investigated in patients with severe hypoxemic ARF meeting preselected criteria for mechanical ventilation and randomized to receive mechanical ventilation via a face mask or an endotracheal tube [12]. In this randomized study, mechanical ventilation delivered via a face mask was found to be equally effective to conventional ventilation in improving gas exchange, and intubation was avoided in 69 % of the patients [12]. A recent randomized study [13] found that hypoxemic patients without COPD were less likely to require intubation if randomized to NPPV.

Factors vital to the success of noninvasive ventilation include careful selection of patients, properly timed intervention, a comfortable, well-fitting interface, coaching and encouragement of patients, careful monitoring, and a skilled and motivated team [14]. For patients with hypercapnic ARF, reports of controlled and uncontrolled trials have described variables associated with an increased rate of intubation, including a higher severity of illness score [4, 15, 16] a higher $PaCO_2$ at study entry [16, 17], and failure to reduce $PaCO_2$ within 1–2 h of initiating noninvasive ventilation [17, 18]. In two studies, an inability to improve $PaCO_2$ was related to a leak in the nasal mask [15, 19], a factor that underscores the importance of selecting the proper interface to achieve best results with noninvasive ventilation.

Outcome predictors are important to identify patients who are less likely to improve with noninvasive ventilation, thus requiring closer observation and a readily available means of intubation. This is particularly important for patients with severe hypoxemia, where unnecessary delays in intubation may have serious consequences. Reported outcome predictors for noninvasive ventilation in patients with hypoxemic ARF are limited to a few studies with small numbers of patients. Predictors of response in older studies investigating continuous positive airway pressure (CPAP) delivered by face mask in hypoxemic ARF caused by a wide variety of lung pathologies, included the degree of hypoxemia at initiation of therapy [20, 21], and improvement in gas exchange and respiratory rate shortly after applying CPAP [22]. In a recent randomized study, Antonelli et al. [12] reported that among patients randomized to noninvasive ventilation those requiring intubation were older ($P = 0.006$), had a higher SAPS I ($P = 0.009$), and were less likely to improve PaO_2:FiO_2 ($P = 0.003$).

The aim of the present multicenter cohort study was to investigate prospectively outcome descriptors for noninvasive ventilation in a large population of patients with acute hypoxemic respiratory failure of varied etiologies.

Methods

Study design and patient selection

Between October 1996 and December 1998, we enrolled consecutive adult patients with hypoxemic ARF admitted to eight different intensive care units in Italy (Università Cattolica del Sacro Cuore and Università La Sapienza, Rome, Unità di Terapia Intensiva Respiratoria, Ospedale Maggiore di Crema, Ospedale Universitario Torrette Ancona, Servizio di Anestesia CTO Torino, Istituto ARTA, Trieste), Spain (M. Meseguer Hospital, Murcia), and the United States (University of Tennessee Medical Center, Memphis).

An ad hoc ethics committee approved the protocol, and all patients, or the next of kin, gave written, informed consent. The criteria for eligibility were acute respiratory distress including severe dyspnea at rest and all the following: a respiratory rate greater than 30 breaths/min, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) less than 200 while the patient was breathing oxygen through a Venturi mask; and active contraction of the accessory muscles of respiration or paradoxical abdominal motion.

Patients with any of the following were not included in the trial: a requirement for emergent intubation for cardiopulmonary resuscitation, respiratory arrest, severe hemodynamic instability, or encephalopathy; respiratory failure caused by neurological disease, acute exacerbation of COPD (on the basis of the clinical history, physical examination and chest radiograph), or status asthmaticus; more than two new organ failures (e.g., the simultaneous presence of renal and cardiovascular failures) [23]; brief ICU admissions (not exceeding 24 h) for post-operative monitoring or monitoring for other reasons; tracheostomy, facial deformities, or recent oral, esophageal, or gastric surgery; and the inclusion in other studies to compare the efficacy of NPPV versus conventional treatments. The simplified acute physiologic score (SAPS II) was calculated 24 h after admission to the ICU [24].

Patients had continuous electrocardiographic and arterial oxygen saturation monitoring (Biox 3700, Ohmeda, Boulder, Colo., USA). We used four types of mechanical ventilators: the Puritan Bennett 7200 (Puritan Bennett, Overland Park, Kan., USA), the Servo 900 C and Servo 300 Siemens (Siemens Elema, Uppsala, Sweden), and the Vision Respironics (Respironics, Pittsburgh, Pa., USA).

Noninvasive ventilation

During noninvasive ventilation, 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, N.J., USA) or double spring soft cushion (Benefit, Puritan Bennett, Overland Park, Kan., USA). The mask was secured with head straps avoiding a tight fit, and the head of the bed was kept elevated at a 45° angle. In most patients, a hydrocolloid sheet was applied over the nasal bridge. For patients with a nasogastric tube, a seal connector in the dome of the mask was used to minimize air leakage. After the mask was secured, pressure support was increased to obtain an exhaled tidal volume of 8–10 ml/kg, a respiratory rate of fewer than 25 breaths/min, the disappearance of accessory muscle activity (as evaluated by palpating the sternocleidomastoid muscle) [25], and patient comfort. CPAP was increased in increments of 2–3 cm of water until the FiO_2 requirement was 0.6 or less. Ventilator settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases. The patients were not sedated.

Duration of ventilation was standardized according to the protocol of Wysocki et al. [26] During the first 24 h, ventilation was continuously maintained until oxygenation and clinical status improved. Subsequently, each patient was evaluated daily while breathing supplemental oxygen without ventilatory support for 15 min. Noninvasive ventilation was reduced progressively in accordance with the degree of clinical improvement and was discontinued if the patient maintained a respiratory rate lower than 30 breaths/min and a PaO_2 greater than 75 mmHg, with a FiO_2 of 0.5 without ventilatory support.

Criteria for endotracheal intubation

Patients who failed noninvasive ventilation underwent endotracheal intubation with cuffed endotracheal tubes (internal diameter of 7.5–8.5 mm) and were mechanically ventilated. Predetermined criteria for endotracheal intubation [12] included failure to maintain a PaO_2 above 65 mmHg with a FiO_2 equal to or greater than 0.6; 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 more than 1 h despite fluid resuscitation); inability to correct dyspnea; or inability on the part of the patient to tolerate the face mask.

End points and definitions

The primary outcome variables were the need for endotracheal intubation and mechanical ventilation at any time during the study and the risk factors associated with failure of noninvasive ventilation. Secondary end points included complications not present on admission (such as ventilator-associated pneumonia or extra-pulmonary sepsis), duration of ventilatory assistance, length of the hospital stay, and ICU mortality.

Arterial blood gas levels were determined at baseline, at 1 h, and at 4-h intervals. Improvement in gas exchange was defined as ability to increase PaO_2:FiO_2 ratio above 200 or an increase in this ratio of more than 100 from baseline [12, 17]. Improvement in gas exchange was evaluated within 1 h (initial improvement) after study entry and over time (sustained improvement). Sustained improvement in gas exchange was defined as ability to maintain the defined improvement in PaO_2:FiO_2 until mechanical ventilation was discontinued, as confirmed by serial blood gas measurements.

Sepsis was defined as the systemic inflammatory response to an infectious process, with manifestations including tachycardia, tachypnea, hyperthermia or hypothermia and altered white-cell count [27]. Patients in whom clinical manifestation of pneumonia developed [28] underwent bronchoscopy with bronchoalveolar lavage. The methods and laboratory procedures followed consensus guidelines [29, 30]. Bacterial pneumonia was diagnosed when at least 100,000 colony-forming units of bacteria/ml were measured in bronchoalveolar lavage fluid [29]. Criteria for adult respiratory distress syndrome (ARDS) followed consensus guidelines [31]. Multiple organ failure was defined following previously described criteria [23].

Data analysis

Data were analyzed using the BMDP statistical package (BMPD statistical software, Los Angeles, Calif., USA, 1990). Results in the failure and successful group were evaluated with two-tailed chi-square test, unpaired *t*-test, or Kruskal-Wallis tests, as appropriate. Odds ratios (OR), confidence intervals and Pearson's chi-square test with Yates' correction or Fisher's exact test were calculated to identify which factors were most related to the failure of noninvasive ventilation. When confidence intervals, for ORs were not reliable, exact limits were calculated. A logistic regression was then performed to obtain an adjusted estimate of the ORs and to identify which factors were independently associated with failure of noninvasive ventilation. All variables which showed a P value below 0.25 in the univariate analysis were entered into the model [32]. 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 them in the final model and noting the change in the coefficient of the risk factors [32].

Results

Between October 1996 and December 1998, 5,847 patients were admitted to the ICUs of the eight participating centers. Three thousand and seventy-seven patients were not included: 2,253 because they required post-operative monitoring or monitoring for other reasons or because they did not need any form of mechanical ventilation and stayed for less than 24 h in the ICU, and 824 patients because they had acute exacerbation of COPD. Of the 2,770 patients with acute hypoxemic respiratory failure, 2,416 were admitted already intubated, while 354 entered the study and received NPPV.

Noninvasive ventilation was successful in avoiding intubation in 70 % (246/354) of patients, and the success rate was similar among all centers. The baseline characteristics of patients who avoided or required endotracheal intubation are shown in Table 1. At study entry, the two groups had similar PaO_2:FiO_2, $PaCO_2$, and pH and the number of patients with hypercapnia ($PaCO2 > 45$ mmHg) was not different in the two groups.

The group that required intubation, in comparison to the group that avoided intubation, had a higher number of patients with surgical admission ($P = 0.03$), and sepsis ($P < 0.001$).

Table 1 Baseline characteristics in patients that avoided or required intubation

Variable	Avoided intubation (n = 246)	Required intubation (n = 108)	P value
Age, year, median (range)	58 (16–94)	60 (13–86)	0.05[b]
Male, no. (%)	158 (64)	70 (65)	0.9[c]
SAPS II, mean (SD)	30 (10)	35 (10)	0.0001[d]
Underlying disease, no. (%)			
Systemic hypertension	38 (15)	16 (15)	0.50[c]
Cardiac ischemia	55 (22)	22 (20)	0.39[c]
Diabetes	10 (4)	11 (10)	0.05[c]
Immunodepression[a]	29 (12)	8 (7)	0.14[c]
None	114 (46)	51 (47)	0.48[c]
Reason for ICU admission, no. (%)			
Medical	160 (65)	58 (54)	0.03[c]
Surgical	25 (10)	23 (21)	0.005[c]
Trauma	61 (25)	27 (25)	0.53[c]
Patients with surgical intervention prior to ICU admission, no. (%)	91 (37)	38 (35)	0.80[c]
Sepsis present at the study entry, no. (%)	28 (11)	31 (29)	< 0.001[c]
Respiratory rate (breaths/min), median (range)	35 (30–48)	35 (30–52)	0.02[b]
pH, median (range)	7.4 (7.14–7.57)	7.4 (6.85–7.56)	0.7[b]
PaO2:FiO2 basal, mean (SD)	119 (35)	120 (40)	0.8[d]
PaCO2 basal, mean (SD)	41 (10)	41 (12)	0.6[d]
PaCO2 > 45 mmHg at baseline, no. (%)	43 (18)	22 (20)	0.6
PEEP, basal (mmHg), mean (SD)	7 (2)	7 (2)	0.6[d]
PaO2:FiO2 after 1 h, mean (SD)	212 (80)	184 (89)	0.003[d]

[a]Immunodepression includes hematological malignancies (ten patients), solid tumors (nine patients), and patients receiving immunosuppression after solid organ transplantation (18 patients)

[b]Kruskal-Wallis test unpooled t-test

[c]Pearson's chi-square test

[d]Fisher exact test

Timing and reasons for endotracheal intubation are shown in Fig. 1. The etiology of hypoxemic ARF in patients who avoided or required endotracheal intubation is shown in Fig. 2. Endotracheal intubation was required in 51% of the 86 patients with ARDS, in 54% of the 59 patients with ARDS of extrapulmonary etiology (OR 3.4, 95% CI 1.8–6.3, $P < 0.001$), and in 46% of the 27 patients with ARDS of pulmonary etiology (OR 2; 95% CI 0.9–4.9, $P = 0.09$). Endotracheal intubation was required in 50% of the 38 patients with community-acquired pneumonia (OR 2.07, 95% CI 1.3–5.4, $P = 0.005$). In patients with either ARDS or community-acquired pneumonia the intubation rate was not affected by the $PaCO_2$ value at study entry. The lowest intubation rate was observed in patients with cardiogenic pulmonary edema (CPE) (10%) and pulmonary contusion (18%). The changes in PaO_2:FiO_2 over time in patients who avoided or required intubation are shown in Fig. 3.

Continuous variables were categorized in quartiles and subsequently according to the associated probability of failure observed. Univariate analysis showed that the probability of failure increased in patients older than 40 years of age (19.5% of failures in patients ≤40 years old vs 35.3% in patients 41–59 years old, 34.0% in patients 60–69 years old, and 34.2% over 69 years); in patients with SAPS II score greater than 35 (20.4% of failures in patients with SAPS II ≤25, 25.8 for SAPS II 26–35, 45.1 for SAPS II 36–45, and 45% for SAPS II over 45); in patients with PaO2:FiO2 lower than 146 (48.9 for PaO2:FiO2 ≤146, 25.0 for PaO2:FiO2 147–186, 24.7 for PaO2:FiO2 187–235, 23.0 for PaO2:FiO2 > 235). These three variables have been categorized as shown in Table 2. The risk of failure also increased for: admission for a surgical or trauma reason, the presence of diabetes, and a base-line respiratory rate > 38 breaths/min. All these variables, as well as immunodepression and PaCO2 over 45 mmHg at the baseline, were entered in a logistic regression model: only age, SAPS II score equal to or more than 35, the presence of ARDS or community-acquired pneumonia, and a PaO2:FiO2 equal to or less than 146 after 1 h of treatment were independently associated with NPPV failure and were kept in the final logistic model (Table 2).

Outcome variables and complications in patients who avoided or required endotracheal intubation are shown in Table 3. Patients who required intubation had a longer duration of ICU stay ($P < 0.001$) and a higher rate of severe sepsis or septic shock ($P < 0.001$) (Ta-

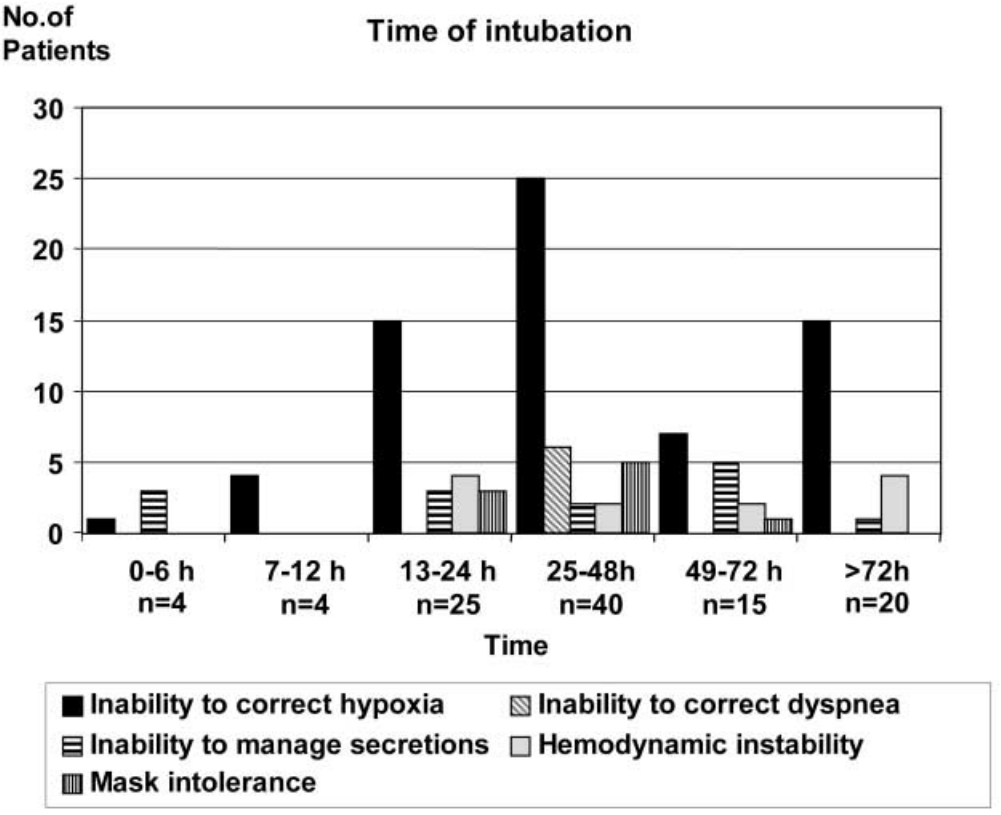

Fig. 1 Timing of endotracheal intubation. One hundred and eight (30 %) of the 354 patients required endotracheal intubation. Reasons for intubation were as follows: inability to correct hypoxia, 67 (62 %); inability to manage secretions, 14 (13 %); hemodynamic instability, 12 (11 %); mask intolerance, 9 (9 %); inability to correct dyspnea, 6 (5 %). The principal reason for failure of patients with community-acquired pneumonia, pulmonary ARDS, and extrapulmonary ARDS was the inability to correct hypoxemia [15 (79 %) patients with CAP, 25 (78 %) patients with extrapulmonary ARDS, and 11 (92 %) patients with pulmonary ARDS]. Seventy-three patients (68 %) were intubated within 48 h of initiating NPPV

ble 3). Ventilator-associated pneumonia was the leading cause of infection, and was diagnosed in 31 patients (30 in the group that required intubation), an average of 5 ± 3 days after study entry. A microbiological etiology of pneumonia was established in twenty-seven cases (87 %): 11 methicillin-resistant *Staphylococcus aureus*, eight *Pseudomonas aeruginosa*, four *Acinetobacter sp.,* two *Enterococcus*, one *S. maltophilia*, and one Nocardia (immunosuppressed patients). In four cases (one interstitial pneumonia), the causative agent was not identified.

Complications related to NPPV included nasal or facial skin necrosis (healed spontaneously within 1 week) in 34 (10 %) patients, conjunctivitis in seven (2 %) patients, and gastric distension in five (1 %) patients.

Sixty-four patients who required intubation (59 %), and 13 patients who avoided intubation (5 %) died in the ICU (OR 12, 95 % CI 5.9–26.7, $P < 0.001$). (Table 3). Univariate and multivariate analyses showed that patients requiring intubation had a significantly higher probability of staying in ICU for greater than 7 days, of developing complications, and of dying in ICU. Logistic regression analysis (adjusted for age, SAPS II, and ARDS etiology) showed that patients requiring intubation were four times more likely to stay in ICU for greater than 7 days, 17 times more likely to develop complications, and 27 times more likely to die in ICU (Table 4).

Discussion

In this study we found that noninvasive ventilation was frequently associated with a rapid and sustained improvement in gas exchange, and intubation was avoided in 70 % of patients. Multivariate analysis identified age > 40 years, a SAPS II ≥35, the presence of ARDS or community-acquired pneumonia, and a PaO_2:FiO_2 ≤146 after 1 h of NPPV as factors independently associated with failure of noninvasive ventilation.

According to Carlucci [33] who reported in a recent survey that NPPV can be used only in the 14 % of the patients with hypoxemic ARF, we could apply noninvasive ventilation to the 13 % of the 2,770 patients with hypoxemic ARF admitted to our ICUs. Similar to this study, avoidance of intubation was associated with a shorter duration of ICU stay ($P < 0.001$), a lower rate of septic complications ($P < 0.001$), and a lower mortality ($P < 0.001$).

NPPV, delivered mainly in the form of pressure support ventilation, was investigated in both uncontrolled [18, 34, 35, 36, 37, 38, 39] and controlled studies [5, 9, 10, 11, 12, 13, 40, 41, 42] involving patients with hypoxemic ARF.

The overall efficacy of noninvasive ventilation in avoiding intubation (70 %) is similar to the 73 % (range 69 %–79 %) rate reported in recent randomized studies

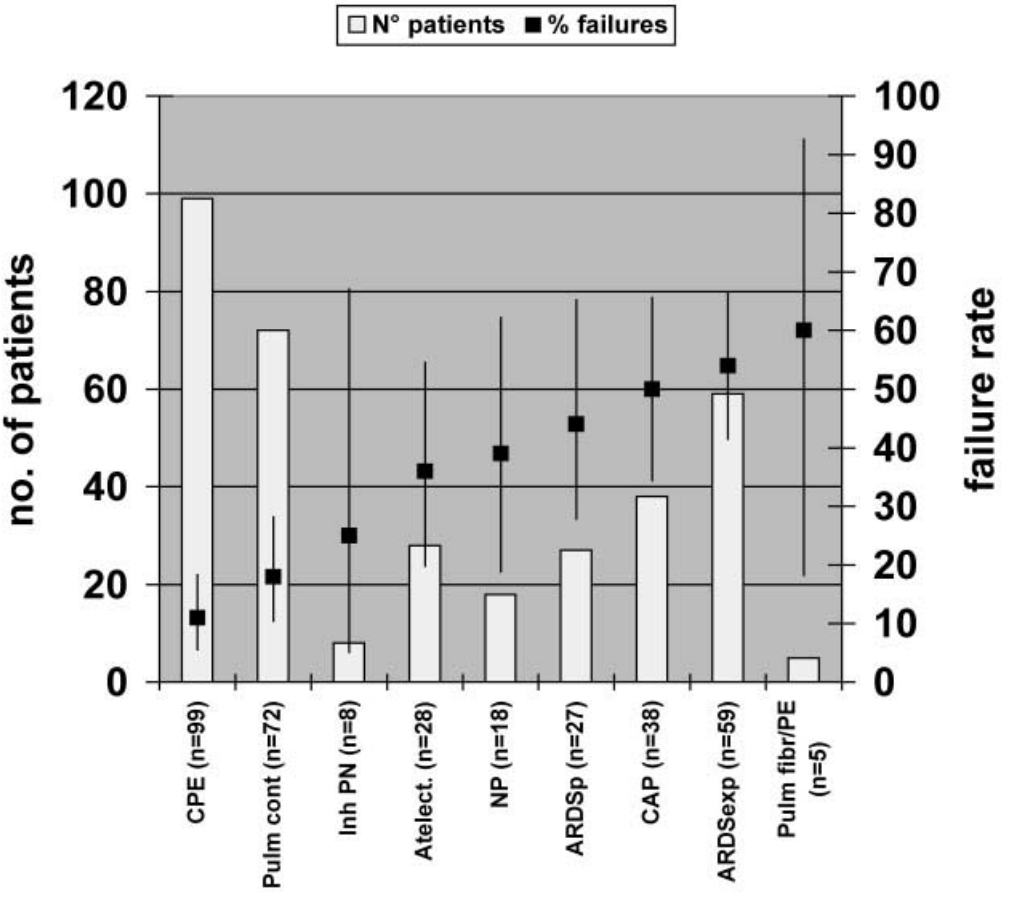

Fig. 2 Causes of acute respiratory failure and frequency of NPPV failure. *CPE* cardiogenic pulmonary edema, *Pulm Cont* pulmonary contusion, *Inh PN* inhalation pneumonia, *Atelect* atelectasis, *NP* nosocomial pneumonia, *ARDSp* pulmonary acute respiratory distress syndrome, *CAP* community-acquired pneumonia, *ARDSexp* extrapulmonary acute respiratory distress syndrome, *Pulm Fibr/PE* pulmonary fibrosis or pulmonary embolism. Causes of extra-pulmonary ARDS are listed for groups that required and avoided intubation, respectively: abdominal sepsis and pancreatitis 11 and 12; post-surgical sepsis 15 and 3; transfusion of more than 6 units of blood within the previous 24 h of ICU admission 6 and 11; and fat embolism 0 and 1. For each subgroup, the *column* represents the number of patients, the *dot* represents the percentages of patients requiring intubation, and the *line* represents the 95% confidence intervals

involving a heterogeneous patient population with a similar degree of hypoxemia at study entry [9, 10, 11, 12, 13]. In this study, the highest rate of intubation was observed in patients with ARDS (51%) and community-acquired pneumonia (50%), and these two conditions were identified by multivariate analysis as independent risk factors for failure of noninvasive ventilation. In contrast, the intubation rate was lower for patients with CPE (10%), pulmonary contusion (18%), and atelectasis (32%).

The present multicenter study included 86 patients with ARDS. We observed that the rate of intubation was similar among patients with ARDS of pulmonary (46%) or extra-pulmonary (54%) origin. A few uncontrolled studies [17, 34, 37, 43, 44] of the application of NPPV in patients with ARDS have previously been reported. In two recent controlled studies involving thirty-one patients with ARDS, the rate of intubation was 40% (6 of 15) for those randomized to noninvasive ventilation [11, 12]. In an uncontrolled study, Rocker et al. [37] reported an intubation rate of 34% in twelve episodes of ARDS. The ARDS mortality (35%) in this study is similar to the one of prior reports [11,12, 37]. In the two controlled studies [11, 12], the mortality rate for 15 ARDS patients randomized to conventional treatment was 40%. The findings of these studies invite a prudent approach to ARDS, and to limiting the application of NPPV to hemodynamically stable patients who can be closely monitored and where endotracheal intubation is promptly available. A randomized study is necessary to address the advantages and limitations of NPPV in patients with ARDS.

In the present study 19 (50%) of the 38 patients with severe community-acquired pneumonia required intubation. The response to NPPV in patients with pneumonia is not uniform [10, 15, 17, 45]. In a recent multicenter randomized trial of patients with severe community-acquired pneumonia and ARF, the rate of intubation was 21% in patients randomized to noninvasive ventilation and 50% in control ($P = 0.03$) [10]. Patients without COPD had a higher rate of intubation than patients with COPD (38.5% vs 0%). The percentage of failure was similar to that reported in this study, where only patients with acute hypoxemic respiratory failure were included.

In this study, the 99 patients with CPE had the lowest (10%) intubation rate, and a mortality rate of 18%.

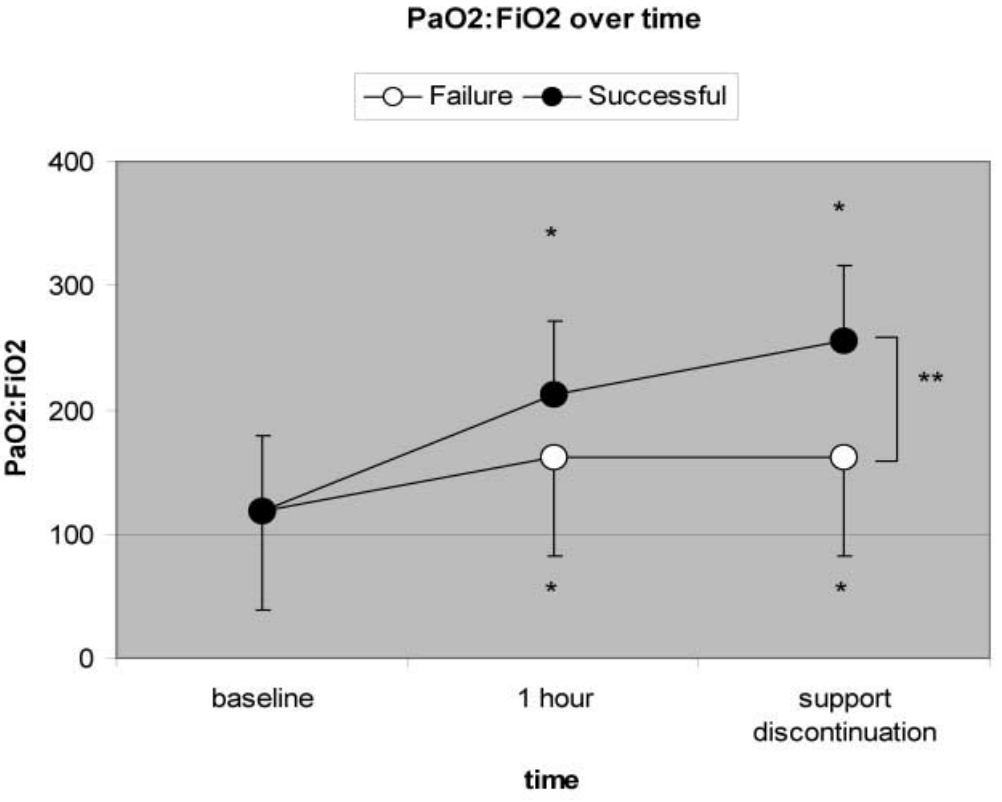

Fig. 3 Changes in PaO_2: FiO_2 over time. *$P < 0.003$ versus baseline, ** $P < 0.005$ successful versus failure 1 h after NPPV and at support discontinuation. An unpaired *t*-test was used for the statistical comparison. Discontinuation of support refers to the last arterial blood gas obtained prior to intubation (failure) or prior to the definitive removal of NPPV in patients who avoided intubation

Table 2 Univariate and multivariate analysis of the risk factors for failure of noninvasive ventilation

Variables	No. of failures/total (%)	Univariate analysis		Multivariate analysis	
		OR	95% CI	OR	95% CI
Reason for ICU admission					
Medical	58/218 (27)	1.00			
Surgical/trauma	50/136 (37)	1.96	1.11–3.45		
Age, years					
≤40	18/93 (19.4)	1.00			
> 40	90/261 (34.5)	2.19	1.19–4.06	1.72	0.92–3.23
SAPS II					
< 35	55/236 (23.3)	1.00		1.00	
≥35	53/118 (44.9)	2.68	1.63–4.42	1.81	1.07–3.06
Underlying disease					
None or none of the following	97/333 (29)	1.00			
Diabetes	11/21 (52)	2.47	1.06–5.74		
Etiology of respiratory failure					
None of the following	42/225 (18.6)	1.00		1.00	
ARDS, CAP	66/129 (51.1)	4.77	2.86–7.96	3.75	2.25–6.24
Respiratory rate at baseline, breaths/min					
≤38	79/285 (27.7)	1.00			
> 38	29/69 (42)	1.89	1.06–3.37		
PaO2:FiO2 after 1 h of NPPV					
> 146	64/264[a] (24.2)	1.00		1.00	
≤146	44/89 (49.4)	3.06	1.79–5.21	2.51	1.45–4.35
Sepsis on admission					
No	77/295 (26.1)	1.00			
Yes	31/59 (52.5)	3.13	1.70–5.78		

[a] For one patient PaO2:FiO2 value 1 h after NIV was missing

Table 3 Outcome variables, complications and mortality

Variable[d]	Avoided intubation (n = 246)		Required intubation (n = 108)		P value
Duration of NIV (h), median (range)	48	(1–216)	24	(1–192)	0.06[a]
Length of stay (days), median (range)	5	(3–31)	9	(1–72)	< 0.001[a]
No. of complications related to noninvasive ventilation (%)					
Nasal/facial skin necrosis	25	(10)	9	(8)	0.29[b]
Conjunctivitis	4	(2)	3	(3)	0.36[c]
Gastric distention	3	(1)	2	(2)	0.48[c]
No. of complications causing death in intensive care unit/total no. of complications (%)					
Ventricular fibrillation/cardiac arrest[d]	1/1	(0.4)	3/3	(3)	0.08[b]
Acute myocardial infarction	1/1	(0.4)	2/2	(2)	0.22[b]
Cardiogenic shock	5/6	(2)	8/8	(7)	0.19[b]
Pulmonary embolism	0/2	(1)	1/2	(1)	0.66[b]
Gastrointestinal bleeding	0/1	(0.4)	0/1	(1)	0.51[b]
Cerebral hemorrhage	0/0	(0)	0/1	(1)	0.30[b]
Ventilator-associated pneumonia	0/1	(0.4)	20/30	(28)	< 0.001[b]
Severe sepsis and septic shock with multiple organ failure after study entry[e]	6/8	(3)	50/70	(64.8)	< 0.001[b]
ICU Mortality, no. (%)[f]	13	(5.3)	64	(59.3)	< 0.001[b]
ICU Mortality by subgroups, no. of deaths/total no (%)					
Pulmonary ARDS	0/15	(0)	4/12	(33)	0.03[c]
Extra-pulmonary ARDS[g]	4/27	(15)	18/32	(56)	0.003[b]
Community-acquired pneumonia	0/19	(0)	10/19	(53)	< 0.001[b]
Nosocomial pneumonia	1/11	(9)	7/7	(100)	< 0.001[c]
Inhalation pneumonia	1/6	(16)	1/2	(50)	10.0[c]
Cardiogenic pulmonary edema	7/89	(8)	9/10	(90.0)	< 0.001[c]
Pulmonary embolism	0/2	(0)	2/2	(100)	0.33[c]
Mucous plugging and atelectasis	0/18	(0)	4/10	(40.0)	0.01[c]
Pulmonary fibrosis	0/0	(0)	1/1	(100)	–
Pulmonary contusion and multiple trauma	0/59	(0)	8/13	(64)	< 0.001[c]
Hospital mortality no (%)	20	(8.1)	69	(64)	< 0.001[b]

[a] Kruskal-Wallis test

[b] Chi-square test

[c] Fisher exact test

[d] One ventricular fibrillation in the group of failures occurred in a patient with atelectasis. Two cardiac arrests (both in the failure group) and 4 cardiogenic shock (2 in the failure group and 2 in the successful group) occurred during NIV. All the other cardiogenic shocks, acute myocardial infarctions, and ventricular fibrillations or cardiac arrests occurred after NIV failure or discontinuation

[e] Note that the number of septic complications occurring after the study entry included all the 20 pneumonia leading to severe sepsis and septic shock. Causes of severe sepsis and septic shock after the study entry not related to pneumonia by failure and successful group were: abdominal sepsis 10 and 4; urinary tract infection 2 and 1, CVC related infection 3 and 0; post-surgical infections 25 and 3

[f] Causes of death are reported for the group that required and avoided intubation, respectively: new pulmonary embolism 1 and 0; ventricular fibrillation or sudden cardiac arrest 3 and 1; cardiogenic shock or acute myocardial infarction 10 and 6; severe sepsis or septic shock with multiple organ dysfunction (MOF) 50 and 6. Twelve patients (five who required intubation, and seven who avoided intubation) died in the hospital, after ICU discharge. The reasons for death were not recorded

[g] Causes of extra pulmonary ARDS are listed by failure and successful groups, respectively and included: abdominal sepsis and pancreatitis 12 and 12; post-surgical sepsis 14 and 3; transfusion of more than 6 units of blood within the previous 24 h, 6 and 11; fat embolism 0 and 1

Randomized studies have proven the efficacy of mask CPAP and pressure support ventilation in patients with CPE [6, 7, 9].

In patients with CPE [41] bilevel pressure was found to be more effective than CPAP delivered by nasal mask in improving gas exchange, to have a similar rate (7%) of intubation, but was associated with an unexplained higher rate of acute myocardial infarction (71% vs 31%; $P < 0.05$). Sharon [40] et al. reported that high dose of intravenous nitrate was safer and better than BiPAP ventilation combined with conventional therapy in patients with CPE, but differences in the therapy delivered in the two treatment groups make it difficult to interpret these data. Rusterholtz et al. [38] reported on 26 patients treated with a combination of CPAP (5 cmH_2O) and PSV (20 H_2O). Intubation was required in five (19%) patients, and these had a significantly lower $PaCO_2$ (32 ± 2 mmHg vs 54.2 ± 15 mmHg) and higher creatine-kinase (CK) values related to acute myocardial infarction (4 of 5 in the failure group vs 2 of 21 in the success group) [38]. All those who developed acute myocardial infarction died.

Table 4 Risk of death, of complications, and longer ICU stay in patients who required or avoided intubation

Outcome	Outcome	Number/total (%)	Univariate analysis		Multivariate analysis[a]	
			OR[a]*	95% CI	OR[a]	95% CI
Mortality	Avoided intubation	13/246 (5.3)	1.0			
	Required intubation	64/108 (59.3)	26.1	12.7–54.6	27.7	13.4–57.4
Complications	Avoided intubation	34/246 (13.8)	1.0			
	Required intubation	81/108 (75.0)	18.7	10.2–34.4	17.4	9.5–31.6
ICU stay > 7 days	Avoided intubation	64/245 (26.1)	1.0			
	Required intubation	64/107 (59.8)	4.2	2.5–7.0	3.9	2.4–6.5

[a] ORs were adjusted through logistic regression modelling for predictors of death in univariate analysis, namely age, SAPS II, and etiology of ARDS

In a recent randomized trial on 37 patients with CPE the 19 patients who received noninvasive pressure support ventilation had a 5% of intubation rate in comparison to the 33% of the 18 assigned to conventional oxygen therapy ($P = 0.037$). and the resolution time of CPE was significantly shorter in the NPPV group ($P = 0.002$) [9]. In our study, 21 patients developed cardiac complications after study entry including acute myocardial infarction, ventricular fibrillation, cardiac arrest, and cardiogenic shock. Only six of these cardiac complications (two cardiac arrests and four cardiogenic shocks) occurred during NPPV. Base-line levels of creatine-kinase (CPK) were not predictive of failure; however, nineteen patients (13 required intubation and six avoided intubation) with CPE died with cardiogenic shock, new acute myocardial infarction, or ventricular fibrillation.

In the seventy-two patients with pulmonary contusion and multiple trauma, the intubation rate was 18%. Some previous studies have described the successful application of noninvasive ventilation in post-traumatic hypoxemic ARF [22, 35, 46, 47]. In 22 trauma patients, Gregoretti et al. [35] found that transfer from endotracheal tube to face mask during application of similar PEEP (5.8 ± 2.5 and 5.2 ± 2.2 cmH_2O) and PSV (13 ± 5 vs 12.8 ± 1.7 cmH_2O) resulted in a similar improvement in gas exchange and respiratory pattern.

In a study of patients with hypoxemic ARF meeting criteria for mechanical ventilation, Antonelli et al. [12] reported that seven trauma patients randomized to NPPV improved PaO_2:FiO_2, avoided intubation, and survived.

In the present study, 27 patients had atelectasis as a cause of hypoxemic ARF, and intubation was avoided in 69%. The successful application of mask CPAP for the treatment of established atelectasis has been reported in uncontrolled and controlled studies [21, 22, 48, 49].

As previously reported [4, 12, 26], patients with higher simplified acute physiologic scores had a higher rate of intubation and a worse outcome. In our study, a SAPS II ≥35 was an independent risk factor for NPPV failure, associated with a threefold increased risk for intubation. Antonelli et al. [12] previously observed that patients randomized to noninvasive ventilation and requiring intubation had a higher SAPS I score ($P = 0.009$), and found an association between a SAPS I score greater than 16 (that corresponds to a SAPS II of around 43) and NPPV failure.

In the present study, we have found that arterial blood gas findings at study entry had no predictive value, while the failure to achieve a PaO_2:FiO_2 equal to or higher than 146 after 1 h of noninvasive ventilation was identified as an independent risk factor for intubation. Most (62%) intubations were related to inability to correct gas exchange. This finding is similar to the one of a prior controlled study [12]. We have not confirmed the findings of Wysocki et al. [26] indicating that a $PaCO_2$ greater than 45 mmHg is associated with a lower rate of intubation. Similar to prior reports [4, 11, 12, 17, 26, 50], we have found that most intubations occurred within 48 h of initiating noninvasive ventilation.

In our study, patients who required intubation had a significantly higher rate of septic complications (64% vs 3%; $P < 0.001$). Pneumonia developed in 28% of intubated patients, while only one episode of pneumonia was detected in the 246 patients who avoided intubation. The findings of this study are in agreement with the published literature [4, 11, 12, 33, 50, 51] and underscore the inherent advantage of noninvasive ventilation in decreasing the risk for developing lower respiratory tract infections.

ICU mortality was significantly higher in patients who required intubation, and most deaths were associated with sepsis. Overall mortality rate in this study was 22%, similar to the one reported in our prior controlled studies in hypoxemic patients (20% and 28%) [11, 12].

This survey was conceived to identify some indicators of the risk of failure of noninvasive ventilation in hypoxemic ARF and not to select candidates for NPPV; we believe that the inference of our findings in everyday clinical practice should be done cautious-

ly and may need a specific study to validate the model.

In conclusion, in hypoxemic ARF, NPPV can be successful in selected populations, with 70% of patients avoiding intubation. When patients had an higher severity score, an older age, ARDS or pneumonia, or fail to improve after 1 h of treatment, the risk of failure was higher. Patients who avoided intubation had a shorter duration of ICU stay, a lower rate of septic complications, and improved survival rate.

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