Acute Respiratory Failure in Patients with Severe Community-acquired Pneumonia

A Prospective Randomized Evaluation of Noninvasive Ventilation

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In uncontrolled studies, noninvasive positive pressure ventilation (NPPV) was found useful in avoiding endotracheal intubation in patients with acute respiratory failure (ARF) caused by severe community-acquired pneumonia (CAP). We conducted a prospective, randomized study comparing standard treatment plus NPPV delivered through a face mask to standard treatment alone in patients with severe CAP and ARF. Patients fitting the American Thoracic Society criteria for severe CAP were included in presence of ARF (refractory hypoxemia and/or hypercapnia with acidosis). Exclusion criteria were: severe hemodynamic instability, requirement for emergent cardiopulmonary resuscitation, home mechanical ventilation or oxygen long-term supplementation, concomitant severe disease with a low expectation of life, inability to expectorate or contraindications to the use of the mask. Fifty-six consecutive patients (28 in each arm) were enrolled, and the two groups were similar at study entry. The use of NPPV was well tolerated, safe, and associated with a significant reduction in respiratory rate, need for endotracheal intubation (21% versus 50%; $p = 0.03$), and duration of intensive care unit (ICU) stay (1.8 $\pm$ 0.7 d versus 6 $\pm$ 1.8 d; $p = 0.04$). The two groups had a similar intensity of nursing care workload, time interval from study entry to endotracheal intubation, duration of hospitalization, and hospital mortality. Among patients with chronic obstructive pulmonary disease (COPD), those randomized to NPPV had a lower intensity of nursing care workload ($p = 0.04$) and improved 2-mo survival (88.9% versus 37.5%; $p = 0.05$). We conclude that in selected patients with ARF caused by severe CAP, NPPV was associated with a significant reduction in the rate of endotracheal intubation and duration of ICU stay. A 2-mo survival advantage was seen in patients with COPD. Confalonieri M, Potena A, Carbone G, Della Porta R, Tolley EA, Meduri GU. Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. AM J RESPIR CRIT CARE MED 1999;160:1585–1591.

Severe community-acquired pneumonia (CAP) requiring admission to an intensive care unit (ICU) is a distinct clinical entity from non-ICU-managed pneumonia in terms of clinical presentation, therapeutic intervention, and mortality (1, 2). Mortality of CAP requiring ICU admission ranges from 22 to 54% (2–4). Nearly 58 to 87% of patients with severe CAP develop respiratory failure and require mechanical ventilation. In several studies, the need for conventional ventilatory support was associated with a higher mortality (3–7).

Noninvasive positive pressure ventilation (NPPV) refers to the delivery of assisted mechanical ventilation without an invasive endotracheal airway (8). The theoretical advantages of this approach include avoiding the complications associated with endotracheal intubation, reducing the incidence of ventilator-associated pneumonia (9), improving patient comfort, preserving airway defense mechanisms, and preserving speech and swallowing without hampering effective cough and expectoration. Furthermore, experimental and clinical work has suggested that noninvasive application of positive pressure promotes effective removal of respiratory secretions by increasing collateral airflow to obstructed lung regions (10, 11).

Several uncontrolled studies described a favorable response to the application of noninvasive ventilation in patients with pneumonia and respiratory failure (12–14). Meduri and coworkers (12) reported on 41 patients with severe CAP (27 with chronic obstructive pulmonary disease [COPD]). With NPPV, more than 75% improved gas exchange, and 62% avoided intubation. Only three patients (7%) required intubation for an inability to clear secretions, and actual mortality (17%) was lower than predicted (36%) (12). Among 30 patients with acute respiratory failure (ARF) and receiving NPPV, Benhamou and coworkers (13) found no difference in response (60% success) in patients with (10 patients) or with-

(*Received in original form March 1, 1999 and in revised form May 21, 1999*)

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Am J Respir Crit Care Med Vol 160. pp 1585–1591, 1999
Internet address: www.atsjournals.org

out (20 patients) pneumonia. Confalonieri and coworkers (14) and Pollack and coworkers (15) reported a high (60 to 90%) success rate in treating 20 patients with nasal ventilation for pneumonia and respiratory failure. Contrary to these results, two smaller studies have reported that ARF caused by pneumonia was associated with a higher rate of NPPV failure in patients with (16) and without COPD (17).

For this reason, we conducted a multicenter, prospective, randomized trial to compare the efficacy of NPPV delivered through a face mask with the efficacy of standard medical treatment with supplemental oxygen administration in patients with severe CAP and ARF.

METHODS

Study Design and Patient Selection

We enrolled consecutive adult patients with severe CAP admitted to three intermediate respiratory ICUs (18) of the following Italian hospitals: Maggiore (Crema), Arcispedale (S. Anna di Ferrara), and Gradenigo (Torino). The patients were randomly assigned to receive either standard treatment with oxygen supplementation delivered by a Venturi mask or NPPV through a face mask. Computer-generated random assignments (software RND; Istituto Nazionale Ricerca sul Cancro, Genova, Italy) were concealed in sealed envelopes. The ethics committee of each hospital approved the protocol, and all patients or next of the kin gave written informed consent.

The criteria for eligibility were one or more of the American Thoracic Society (ATS) nonrespiratory criteria for severe CAP (1), and two or more of the following criteria for ARF: (*1*) acute respiratory distress including severe dyspnea at rest and a respiratory rate (RR) $>$ 35 breaths/min and/or active contraction of the accessory muscles of respiration or paradoxical abdominal motion; (*2*) $Pa_{O_2} < 68$ mm Hg while receiving a fraction of inspired oxygen ($F_{I_{O_2}}$) ≥ 0.4, or a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pa_{O_2}:$F_{I_{O_2}}$) < 250 while receiving an $F_{I_{O_2}} \geq 0.5$; (*3*) hypercapnia ($Pa_{CO_2} > 50$ mm Hg) with respiratory acidosis (pH < 7.33). The ATS nonrespiratory criteria for severe CAP included chest radiograph showing multilobar involvement at admission or 50% or greater increase in the size of the infiltrate within 48 h of admission; systolic blood pressure $\leq$ 90 mm Hg or diastolic blood pressure $\leq$ 60 mm Hg; necessity for vasopressors $>$ 4 h; or urine output $<$ 80 ml in 4 h (1). Patients with any of the following were excluded: a requirement for emergent intubation for cardiopulmonary resuscitation, respiratory arrest, severe hemodynamic instability, encephalopathy, severe neurologic disease, concomitant severe disease with an expectation of life less than 4 mo (e.g., advanced cancer), long-term oxygen therapy or home mechanical ventilation, contraindications to the use of the mask (tracheostomy or facial deformities), or inability to expectorate.

Medical management was similar in the two groups and included initial antibiotic administration following the ATS guidelines (macrolide plus third-generation cephalosporin with anti-*Pseudomonas* activity) (1) and later adjusted to the results of bacterial culture results and antibiogram (1). Oxygen administration was adjusted to achieve a level of arterial oxygen saturation (by oximetry) above 90%. Bronchodilators, chest physiotherapy, and corticosteroids were used at the discretion of the attending physician.

Noninvasive Ventilation

For patients assigned to NPPV, we followed a previously described methodology (8). The ventilator was connected with conventional tubing to a clear, full-face mask with an inflatable soft-cushion seal and a disposable foam spacer to reduce dead space (Gibeck, Upplands, Sweden). The initial ventilatory settings were continuous positive airway pressure (CPAP) 0 cm of water and pressure support ventilation (PSV) 5 to 10 cm H_2O. The mask was held on the patient's face until the patient was in full synchrony with the ventilator. The mask was then secured with head straps to avoid a tight fit, and the head of the bed was kept elevated at a 45° angle. PSV was then increased to obtain an exhaled tidal volume greater than 6 ml/kg, a respiratory rate of fewer than 25 breaths/min, the disappearance of accessory muscle activity, and patient comfort. CPAP level was then set at 2 cm H_2O and adjusted up to 8 cm H_2O to improve oxygenation if needed (19). Ventilator settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases. The patients were not sedated. We used four types of mechanical ventilators: Cesar (Thaema, Antony Cedex, France), Puritain Bennett 7200 (Puritain Bennett Co., Overland Park, KS), Vential (Saime, Savigny-le-Temple, France) and Servo 900C (Siemens Elema, Uppsala, Sweden). Patients had continuous electrocardiographic and arterial oxygen saturation monitoring (Biox 3700; Ohmeda, Boulder, CO).

In patients with a significant mask leak, we implemented a previously described sequential approach to improve the efficacy of NPPV that included one or more of the following: repositioning the mask and securing the headgear applying a hydrocolloid sheet to seal leaks reducing the amount of CPAP as tolerated reducing the amount of PSV as tolerated, and switching to a mask with nasal pillows (8). If these steps were unsuccessful in minimizing air leakage and ventilation was compromised, one of the following was tried: pressure-controlled ventilation mode with a time-cycling of 0.8 to 1 s or volume-control mode ventilation with a pressure limitation less than 40 cm H_2O (8). In patients with excessive secretions, inhaled bronchodilator therapy and chest physiotherapy were applied as needed and tolerated. Patients were monitored for the development of complications, such as facial skin necrosis or gastric distention.

Criteria for Endotracheal Intubation

Treatment of respiratory failure was defined as unsuccessful if the patient developed preselected and previously described objective criteria for endotracheal intubation (ETI) (20). Criteria for ETI included one major criterion or the persistence of two minor criteria after 1 h of treatment (20). Major criteria included respiratory arrest, respiratory pause with loss of consciousness, severe hemodynamic instability (heart rate $\leq$ 50 beats/min with loss of alertness, and/or systolic blood pressure $\leq$ 70 mm Hg), and psychomotor agitation making nursing care impossible and necessitating sedation (20). Minor criteria were a RR $>$ 35 breaths/min and above the value on admission, Pa_{O_2}:$F_{I_{O_2}} <$ 150, an increase in $Pa_{CO_2} > 20\%$ from prior arterial blood gas measurement, and change in mental status attributable to respiratory impairment (20). In patients randomized to NPPV and meeting gas exchange criteria for intubation, an attempt was made to adjust both mask and ventilator settings to correct gas exchange impairment before considering intubation. In patients randomized to NPPV, if a criterion for intubation developed after the withdrawal of ventilatory support, NPPV was reintroduced. If the criterion persisted after ventilation had been resumed, intubation was performed based on decision of both the investigator and the clinician primarily responsible for the patient. Patients submitted to endotracheal ventilation were transferred from the intermediate respiratory ICU to the ICU. The policy at the three hospitals permits patients to stay in the intermediate respiratory ICU for noninvasive ventilation and monitoring, whereas admission to ICU is reserved for those requiring intubation or invasive monitoring.

End Points and Definitions

The primary outcome variables were developing preselected objective criteria for ETI and the need for ETI and mechanical ventilation at any time during the study. Secondary end points were length of hospital stay, complications not present on admission (such as ventilator-associated pneumonia), duration of ventilatory assistance, duration of ICU and hospital stay, in-hospital survival, and 2-mo (from study entry) survival. Arterial blood gas levels were determined at baseline, at 2-h, 4-h, and 12-h intervals thereafter. The following data were obtained at study entry: Acute Physiology and Chronic Health Evaluation (APACHE) II score (21), presence of COPD, chest radiograph score (1 point for each involved lobe, range 1 to 5), results of diagnostic microbiological tests (sputum, blood, bronchoalveolar lavage [BAL], etc.), use of physiotherapy to facilitate expectoration, and dyspnea quantitated by a previously described visual analogic scale (22) from 0 (absence of breathlessness) to 10 (extreme breathlessness). The amount of daily nursing assistance was recorded on the first 3 d of the study following a visual analogic scale (23) ranging from 0 (no need of nursing care) to 10 (heavily time-consuming for nurse). Visual analogic scale for shortness of breath was obtained by

TABLE 1

DEMOGRAPHIC AND FINDINGS AT ENTRANCE

	Noninvasive Ventilation	Standard Treatment
Number	28	28
Age	66 ± 14 (min 30, max 86)	61 ± 21 (min 20, max 92)
Female:Male	5:23	11:17
APACHE II score	20 ± 5 (min 8, max 34)	18 ± 5 (min 9, max 27)
Patients with COPD	12	11
Respiratory rate, breaths/min	37 ± 5 (min 28, max 48)	36 ± 6 (min 18, max 45)
pH	7.34 ± 0.14 (min 6.85, max 7.51)	7.33 ± 0.12 (min 7.04, max 7.48)
Pa_{CO_2}, mm Hg	50 ± 21 (min 20, max 84)	47 ± 18 (min 24, max 88)
Pa_{O_2}:$F_{I_{O_2}}$	183 ± 36 (min 130, max 260)	167 ± 47 (min 78, max 257)
Heart rate	102 ± 20 (min 72, max 140)	116 ± 21 (min 74, max 160)
Systolic blood pressure, mm Hg	133 ± 30 (min 75, max 190)	140 ± 39 (min 80, max 220)
Dyastolic blood pressure, mm Hg	78 ± 16 (min 40, max 110)	81 ± 19 (min 50, max 120)
Dyspnea score	8.0 ± 1.4 (min 5, max 10)	8.7 ± 1.1 (min 7, max 10)
Chest radiograph score	2.4 ± 1.8	2.0 ± 1.2

asking the patients to point out on a board the degree of breathlessness experienced at the time, while the nursing care requirements were charted by a senior nurse. If indicated, bronchoscopy with BAL was performed to diagnose pneumonia, and in patients receiving NPPV, we followed the methodology originally described by Antonelli and coworkers (24). Methods and laboratory procedures followed consensus guidelines (25). Bacterial pneumonia was diagnosed when at least 10,000 colony-forming units of bacteria per milliliter were measured in BAL fluid.

Statistical Analysis

For variables measured once, *t* tests, Mann-Whitney U tests, or chi-square tests (or Fisher exact two-tailed tests) were used to compare noninvasive ventilation to standard treatment group. For continuous outcome variables, the effects of group and diagnosis were examined with 2-way analysis of variance (ANOVA). For continuous outcome variables measured repeatedly throughout the hospital stay, repeated measures ANOVA were used to examine the effects of group, diagnosis, and time. Multiple logistic regression analysis was used to identify independent predictors of hospital mortality. Unless indicated, data are reported as mean ± SE for NPPV and standard treatment group, respectively.

RESULTS

Between November 1996 and March 1998 102 adult patients with severe CAP and ARF were admitted to one of three intermediate respiratory ICUs. For each center, the number of patients with severe CAP screened for and recruited into the study are shown in parenthesis: Crema (42 and 24), Torino (22 and 13), and Ferrara (38 and 19). Reasons for excluding patients from the study included failure to meet entrance criteria in 42, and refusal to participate in four. Twenty-eight patients were randomly assigned to each group. The baseline characteristics of the two groups were similar according to age, blood gases, RR, and APACHE II score (Table 1). Two patients had a blood systolic pressure value ranging from 75 mm Hg to 90 mm Hg (1 NPPV group and 1 standard treatment). Patients with COPD were equally distributed in both groups (Table 1). A microbiological diagnosis of pneumonia (Table 2) was established in 32 patients (16 in each group). Nineteen of 24 patients without definitive microbiologic diagnosis were on antibiotics at the time of presentation to intermediate respiratory ICU. Ten of 11 BAL fluid quantitative cultures were positive, five in each group. In patients randomized to NPPV, four of the five diagnostic bronchoscopies were performed while patients received noninvasive ventilation (24). The medical treatments for pneumonia and of the underlying condition were similar in both groups. Eight patients in each group received physiotherapy to assist with expectoration. In patients randomized to NPPV, the initial (mean ± SD) ventilator settings were CPAP 4.9 ± 1.7 cm H_2O, PSV 14.8 ± 4.7 cm H_2O, and $F_{I_{O_2}}$ 0.3 ± 0.07. Patients randomized to NPPV had a rapid, significant, and sustained reduction in RR, whereas those randomized to standard treatment had no improvement in the first 24 h.

In the first 60 h of the study, 310 arterial blood gas analyses were obtained for patients receiving either supplemental by a Venturi mask, NPPV, or conventional ventilation. In the first 24 h of the study, the duration of mechanical ventilation delivered with either a face mask or an endotracheal tube was simi-

TABLE 2

MICROBIOLOGICAL ORIGIN OF PNEUMONIA

Cause of Pneumonia*	No. of Episodes
Streptococcus pneumoniae	7
Streptococcus spp.	2
Staphylococcus aureus	4
Mycoplasma pneumoniae	1
Legionella pneumophila	2
Chlamydia pneumoniae	2
Haemophilus influenzae	2
Moraxella catarrhalis	2
Escherichia coli	1
Klebsiella pneumoniae	2
Enterobacteriaceae	2
Pseudomonas spp.	2
Polymicrobial flora	3

* Microbiological diagnosis was established by BAL (10 patients), sputum (13 patients), blood (three patients), and serology (five patients).

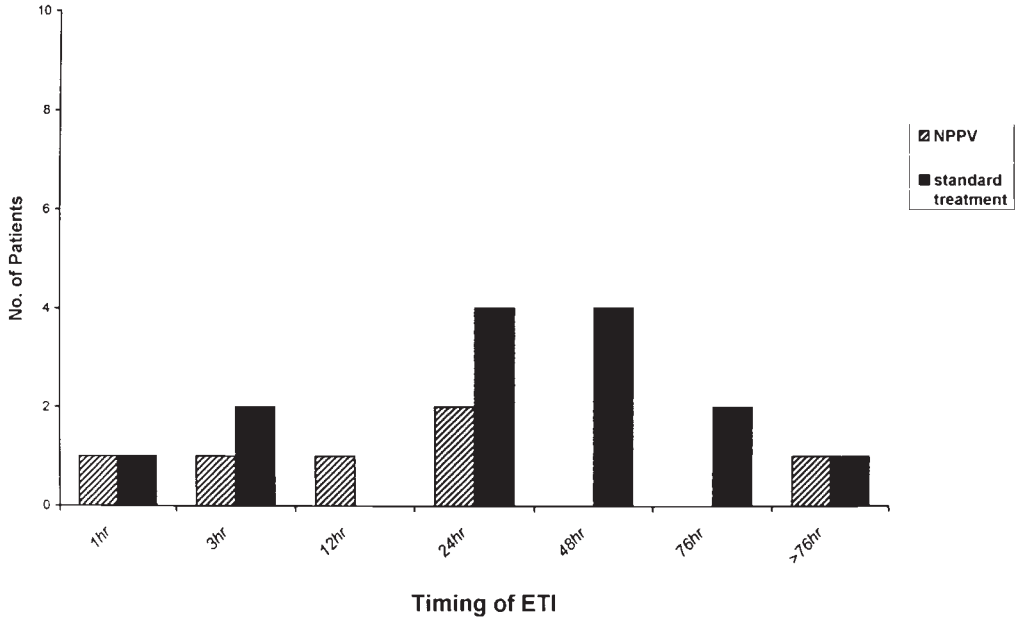

Figure 1. Time for endotracheal intubation in both groups of patients.

lar in the two groups (15 ± 1.7 h versus 11 ± 2.7 h; p = 0.3). In each group (NPPV and standard treatment), patients with and without COPD were analyzed separately, generating four subgroups. The Pa_{O_2}:$F_{I_{O_2}}$ slowly improved from baseline in all four subgroups (significant after 48 h), and without significant differences among subgroups over time. Among patients with COPD, the arterial pH (mean ± SE) improved more rapidly in those randomized to NPPV (2 h, from 7.28 ± 0.02 to 7.31 ± 0.03; p = 0.36) than in those randomized to standard treatment (2 h, from 7.27 ± 0.03 to 7.26 ± 0.03; p = 0.8). Nevertheless, mean pH data in patients randomized to standard treatment included those of three patients with time for intubation ⩽ 2 h because of worsening respiratory acidosis (2 h, pH respectively, 7.1, 7.25, 7.15). Over time, the two subgroups of COPD patients had a similar improvement in arterial pH (24 h, NPPV group 7.36 ± 0.03 versus standard treatment group 7.34 ± 0.07; p = 0.376) and Pa_{CO_2} (24 h, NPPV group 58.2 ± 10 versus standard treatment group 54.1 ± 6; p = 0.252). Hypercapnia (Pa_{CO_2} > 45 mm Hg) was present at admission in 25 patients and absent in 31. All 23 patients with COPD had hypercapnia with respiratory acidosis, and two of the 33 patients without COPD had hypercapnia.

Overall, 23 patients met preselected criteria for intubation, six (21%) in the NPPV group and 17 (61%) in the standard treatment group (p = 0.007). Twenty patients were intubated, six (21%) in the NPPV group and 14 (50%) in the standard treatment group (p = 0.03). No significant difference was observed in the intubation rate among patients treated with NPPV in the three centers (Crema 20%, Torino 24%, Ferrara 21%). Three COPD patients randomized to standard treatment received successful NPPV after meeting preselected criteria for intubation (at 2 h from admission, pH respectively, 7.24, 7.23, 7.23 and Pa_{CO_2}, respectively, 70, 101.8, 73.8 mm Hg). Endotracheal intubation was required in six of 19 (32%) hypercapnic patients versus 14 of 31 (45%) patients without hypercapnia (p = 0.100). Among the patients without COPD the two patients with hypercapnia avoided intubation, whereas intubation was required in 45% of those without hypercapnia (p = 0.46).

Mean time from study entry to endotracheal intubation (Figure 1) was 44 ± 24 h for patients randomized to NPPV (range, 1 to 140 h) and 42 ± 13 h for those randomized to standard treatment (range, 1 to 192 h). The reasons for meeting intubation criteria (NPPV and standard treatment groups, respectively) included worsening hypoxemia (2 and 8), worsening hypercarbia (0 and 6), severe hemodynamic instability (3 and 3), and secretion management (1 and 0). The main advantage of noninvasive ventilation relied in decreasing intubations for worsening hypoxemia (2 versus 13; p = 0.004). As shown in Table 3, patients randomized to NPPV, in comparison to patients randomized to standard treatment, had a similar intensity of nursing care and a shorter duration of ICU stay. The only complication associated with NPPV was one case of gastric distention that resolved with the application of intermittent nasogastric suctioning, and none of the patients developed facial skin necrosis. Complications associated with conventional mechanical ventilation included two cases of BAL-proven ventilator-associated pneumonia (one died during mechanical ventilation, and the other died after hospital discharge and within 2 mo of study entry), one case of otitis and mastoiditis, and one of pneumothorax. These complications occurred in patients originally randomized to standard treatment.

TABLE 3

OUTCOME VARIABLES IN THE TWO RANDOMIZATION GROUPS

	Noninvasive Ventilation (*n* = 28)	Standard Treatment (*n* = 28)	p Value
Met intubation criteria	6 (21%)	17 (61%)	0.007
Required intubation	6 (21%)	14 (50%)	0.03
Intensity of nursing care			
Day 1	7.9 ± 0.3	7.5 ± 0.5	NS
Days 1–3	6.6 ± 0.3	6.7 ± 0.7	NS
Duration of intubation	7 ± 3	10 ± 3	0.6
Duration of ICU stay, d	1.8 ± 0.7	6 ± 2	0.04
Duration of hospital stay, d	17 ± 2	18 ± 2	NS
Number of complications	1	4	NS
Hospital death	7	6	NS
2-mo survival	21	18	NS

TABLE 4

BASELINE AND OUTCOME VARIABLES IN PATIENTS WITH AND WITHOUT COPD

	Patients with COPD			Patients without COPD		
	Noninvasive Ventilation	Standard Treatment	p Value	Noninvasive Ventilation	Standard Treatment	p Value
Number	12	11		16	17	
Age	68.4 ± 4.8	73.0 ± 5.1	0.52	64.2 ± 4.2	53.3 ± 4.1	0.07
pH	7.28 ± 0.04	7.27 ± 0.06	0.13	7.39 ± 0.1	7.37 ± 0.1	0.57
Pa_{O_2}:$F_{I_{O_2}}$	194 ± 31	170 ± 42	0.64	165 ± 30	164 ± 52	0.94
Pa_{CO_2}	73 ± 7	68 ± 9	0.15	32 ± 7	34 ± 5	0.35
APACHE II score	20.1 ± 1.5	21.4 ± 1.5	0.55	19.9 ± 1.3	16.3 ± 1.2	0.05
Met intubation criteria	0 (0.0%)	6 (54.6%)	0.005	6 (37.5%)	8 (47.1%)	0.73
Avoided intubation	12 (100%)	5 (45.5%)	0.005	10 (62.5%)	9 (52.9%)	0.73
Nurse workload						
Day 1	7.3 ± 0.5	8.7 ± 0.5	0.06	8.5 ± 0.5	6.4 ± 0.5	0.005
Days 1–3	6.1 ± 0.6	8.1 ± 0.7	0.04	7.1 ± 0.7	5.5 ± 0.6	0.08
Duration of intubation, d	0	12.3 ± 3.9	0.00	6.8 ± 4.2	8.0 ± 3.4	0.41
Duration of use of MV, h	69 ± 36	220 ± 281	0.07	119 ± 105	195 ± 282	0.31
Duration of ICU stay, d	0.25 ± 2.1	7.6 ± 2.2	0.02	2.9 ± 1.8	4.8 ± 1.7	0.44
Duration of hospital stay, d	14.9 ± 3.4	22.5 ± 3.5	0.13	17.9 ± 2.9	15.1 ± 2.8	0.48
Hospital mortality	1 (8.3%)	2 (18.2%)	0.59	6 (37.5%)	4 (23.5%)	0.47
2-mo mortality	1/9 (11.1%)	5/8 (62.5%)	0.05	6/14 (42.9%)	5/15 (33.3%)	0.71

Definition of abbreviation: MV = mechanical ventilation (either noninvasive or invasive).

Eleven patients died in the ICU (10 prior to resolution of respiratory failure), two on the regular floor, and four after hospital discharge and within 2 mo of study entry. Nine patients died as a result of the original pneumonia, three from septic shock (two in the NPPV group), five from progression of multiple organ dysfunction syndrome (two in the NPPV group), and one from acute respiratory distress syndrome (ARDS) (NPPV group). One patient in the standard treatment group developed ventilator-associated pneumonia complicated by ARDS. One 85-yr-old patient with COPD randomized to NPPV was receiving only nocturnal ventilation when, 10 d after study entry, he died suddenly from a massive pulmonary embolism (postmortem exam confirmation). Mortality was associated with endotracheal intubation (RR = 4.043; 95% confidence interval 2.163 to 7.556). One patient in each group died after discharge from the intermediary respiratory ICU (cardiogenic pulmonary edema and ventricular fibrillation). Two months after study entry, mortality was unchanged for patients randomized to NPPV whereas four COPD patients originally randomized to standard treatment (three required intubation) died from relapse of pneumonia (three patients) or cardiac-related event (one patient).

Table 4 shows outcome variables in patients with and without COPD. Among patients with COPD, those randomized to NPPV required a lower intensity of nurse workload over 3 d and had a lower rate of endotracheal intubation, a shorter duration of ICU stay, and an improved 2-mo survival. In patients with COPD, higher APACHE II scores were associated with a significant ($p = 0.01$) increase in duration of hospitalization independent of treatment allocation. Among patients without COPD, those randomized to standard treatment were younger and had a lower APACHE II score at entrance. In these patients, a high APACHE II score was significantly associated with intubation requirement ($p = 0.004$) and hospital ($p = 0.04$) and 2-mo mortality ($p = 0.03$), whereas a high APACHE II score was not an independent predictor of outcome.

DISCUSSION

This is the first controlled randomized study evaluating early application of NPPV in patients with ARF caused by severe CAP. We have found that noninvasive ventilation was well tolerated, safe, did not compromise removal of respiratory secretions, and required an intensity of nursing care similar to standard treatment (with or without mechanical ventilation). Patients randomized to noninvasive ventilation had a significantly lower rate of endotracheal intubation (21% versus 50%; $p = 0.03$) and a shorter duration of ICU stay (1.8 ± 0.7 d versus 6 ± 1.8 d; $p = 0.04$). Both groups had similar characteristics at baseline with the exception of a trend toward a higher ratio female:male in those randomized to the standard treatment group. Gender, however, is not recognized as a negative prognostic factor in pneumonia (2).

A *posthoc* analysis showed that among COPD patients with similar severity of illness, those randomized to NPPV had a significant reduction in intubation rate, duration of intermediary respiratory ICU stay, and mortality at 2 mo from study entry.

Seventeen of the 28 (60%) patients randomized to standard treatment met preselected criteria for endotracheal intubation, a finding similar to the one reported in the literature for patients with severe CAP (2). In contrast, only six of 16 patients without COPD (37%) and none of 12 patients with COPD randomized to NPPV required endotracheal intubation, a percentage similar to that of a recent randomized trial (26). The advantage of noninvasive ventilation relied almost exclusively on reducing intubations to improve hypoxia or hypercapnia ($p = 0.004$). Among patients receiving NPPV only, one patient required intubation for inability to clear respiratory secretions, a finding in agreement with our previously reported experience (12, 27). In two uncontrolled studies involving 109 patients with ARF resulting from pneumonia (41 patients), acute bronchitic exacerbation of COPD (51 patients), or status asthmaticus (17 patients), we reported that among 24 intubations only four were indicated by the patient's inability to clear secretions (12, 27). Nevertheless, another group has reported a high failure rate with NPPV in patients with pneumonia (17).

Andersen and collaborators provided experimental and clinical evidence of the beneficial effects of positive pressure in facilitating removal of secretions (10, 11). In excised human lungs, they demonstrated that experimentally collapsed lung regions can be recruited with the application of positive pressure through collateral channels with pressures less than or

equal to those needed for reinflation through the ordinary bronchial route (10). Collateral reinflation also has a potential secretion-clearing effect, i.e., the pressure behind the obstruction rises and forces secretions centrally to larger bronchi where they are more easily removed (10). In a prospective randomized study of patients with postoperative atelectasis, the hourly application of 25 to 35 consecutive breaths of CPAP 15 cm H_2O by face mask was found superior to standard treatment in improving radiographic and physiologic manifestations of atelectasis (11). The results of these studies suggest that in nonsedated patients with intact upper airways and cough reflex, collateral ventilation may be an important "therapeutic tool" facilitating removal of secretions (10, 11).

In the present study, timing to endotracheal intubation was similar in both groups, and the rate of complications developing during intubation was not increased in patients failing NPPV and requiring intubation. Our findings contrast with the results of a recent randomized study evaluating bilevel positive pressure ventilation delivered through a nasal mask in patients (7 of 16 with pneumonia) with acute respiratory distress admitted to an emergency room department (28). In that study, the rate of endotracheal intubation was similar in both groups, whereas patients randomized to NPPV had a longer time interval (in hours) to intubation (mean $\pm$ SD, 26 $\pm$ 27 versus 4.8 $\pm$ 6.9; $p = 0.055$) and a higher mortality (25% versus 0%; $p = 0.123$). Although the risk of delaying intubation cannot be discounted, patients randomized to NPPV had a trend toward higher APACHE II scores than control subjects did (26 $\pm$ 14 versus 19 $\pm$ 8; $p = 0.4$), a factor that may have influenced success of noninvasive ventilation and final outcome (28).

We found that noninvasive ventilation was not associated with an increase in nurse workload, a finding in agreement with two prior randomized studies and one prospective controlled trial (22, 29, 30). The group's prior experience with noninvasive ventilation and the implementation of a simple protocol designed to meet patients' ventilatory needs while maintaining comfort was helpful in this regard.

A microbiological diagnosis of pneumonia was established in 32 (57%) patients, a result similar to the 50 to 69% diagnostic rate described in recent studies on severe CAP (31, 32). The lack of microbiological diagnosis in almost half of the patients is an obvious limitation of this study. In our study 22 of 24 patients without definitive microbiologic diagnosis were on antibiotics at the time of presentation to the respiratory intermediate ICU. The recent administration of antibiotics profoundly compromises the recovery of bacteria (especially gram-positive microorganisms), and the growth of most etiological agents of CAP can be suppressed by a single oral antibiotic dosage (33). We have previously reported a higher diagnostic rate for diagnosing ventilator-associated pneumonia in patients without the recent administration of new antibiotics (34).

In patients admitted with severe CAP, COPD is a frequent underlying disease (5, 33) but is not recognized as an independent risk factor for mortality (33). In prior randomized studies of patients with COPD and acute exacerbation, pneumonia was an exclusion criterion (20, 35). Similar to prior randomized studies (20, 26), we have found that patients with higher severity of illness score at ICU admission had a worse outcome irrespective of randomization. In one retrospective study of 69 COPD patients with ARF, only four of nine patients with pneumonia (no information was provided on the origin of pneumonia: community or nosocomial) improved with NPPV (16).

In a recent epidemiological survey, Guerin and coworkers (9) showed that noninvasive ventilation reduces the incidence of nosocomial pneumonia. Our findings are not comparable to those of Wysocki and coworkers (17) who found an advantage of NPPV in patients without COPD and with hypercarbia, because only two of our patients met these criteria. In our study, hypercapnia was not a marker for NPPV success. In a recent meta-analysis, pneumonia was not identified as a risk factor for noninvasive ventilation (36). In the present study, COPD patients in the two randomization groups had a similar APACHE II score, and those receiving NPPV had a significant reduction in intubation rate, duration of intermediary respiratory ICU stay, and mortality at 2 mo from study entry. The finding of improved long-term outcome is in agreement with prior historically matched controlled studies from our group and others (37, 38). Relapse of pneumonia was the leading cause of death after hospital discharge, and relapse occurred in previously intubated patients with COPD. Because antibiotic treatment was standardized, it is possible to assume that intubation itself or other factors associated with intubation may have impaired defense mechanisms and predisposed patients to relapse of pneumonia. Endotracheal intubation is known to alter local defense mechanisms, although the duration of this impairment has not been evaluated (39). Additional factors may include prolonged neurogenic weakness that reduces the capacity of the ventilatory pump and the ability to clear secretions in patients with COPD requiring conventional mechanical ventilation (40). Lastly, it must be remembered that the 2-mo survival advantage was observed with a *posthoc* analysis with all attendant weakness, and we cannot exclude a statistical aberration related to the small number of patients.

In conclusion, in selected patients with ARF caused by severe CAP, noninvasive ventilation was associated with a significant reduction in the rate of endotracheal intubation and duration of ICU stay. Among COPD patients with similar severity of illness, those randomized to noninvasive ventilation had a significant reduction in mortality 2 mo from study entry.

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