Noninvasive Pressure Support Ventilation in Patients With Acute Respiratory Failure*

A Randomized Comparison With Conventional Therapy

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The benefit of noninvasive pressure support ventilation (NIPSV) in avoiding the need for endotracheal intubation and reducing morbidity and mortality associated with endotracheal intubation was evaluated in 41 patients who presented with acute respiratory failure not related to chronic obstructive pulmonary disease (COPD). Patients were randomly assigned to receive conventional therapy (n=20) or conventional therapy plus NIPSV (n=21). NIPSV was delivered to the patient by a face mask connected to a ventilator (Puritan-Bennett 7200a) set in inspiratory pressure support (IPS) mode. The mean levels of IPS, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FIO_2) were respectively 15 ± 3 cm H_2O, 4 ± 2 cm H_2O, and $57 \pm 22\%$. The rate of endotracheal intubation (62 vs 70%, p=0.88), the length of ICU stay (17 ± 19 days vs 25 ± 23 days, p=0.16), and the mortality rate (33 vs 50%, p=0.46) were not different between patients treated with NIPSV and those treated conventionally. *Post hoc* analysis suggested that in patients with $PaCO_2$ >45 mm Hg (n=17), NIPSV was associated with a reduction in the rate of endotracheal intubation (36 vs 100%, p=0.02), in the length of ICU stay (13 ± 15 days vs 32 ± 30 days, p=0.04), and in the mortality rate (9 vs 66%, p=0.06). We conclude that NIPSV is of no benefit when used systematically in all forms of acute respiratory failure not related to COPD. A subgroup of patients, characterized by acute ventilatory failure and hypercapnia, may potentially benefit from this therapy and further studies are needed to focus on this aspect.

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ICU=intensive care unit; IPS=inspiratory pressure support; NIPSV=noninvasive pressure support ventilation; PEEP=positive end-expiratory pressure; SAPS=Simplified Acute Physiologic Score

Key words: acute respiratory failure, noninvasive ventilation, pressure support

Patients with acute respiratory failure often require endotracheal intubation and mechanical ventilation. Although endotracheal intubation is a routine maneuver in the ICU, it may cause complications, both during intubation and after extubation.[1] To reduce endotracheal intubation associated morbidity, noninvasive ventilation has been proposed in patients with chronic respiratory failure[2-4] and recently in patients with exacerbations of chronic respiratory failure.[5,6] Brochard et al[5] found that in patients with exacerbations of chronic obstructive pulmonary disease, the need for endotracheal intubation could be avoided in most of patients and that length of hospital stay could be reduced by the use of noninvasive pressure support ventilation (NIPSV) given by a special device (face mask inspiratory airway pressure [IPAP]). More recently a large randomized multicenter study[7] in patients with acute exacerbation of chronic obstructive pulmonary disease showed a 65% decrease in the need for endotracheal intubation and a reduction in the length of ICU stay and mortality rate. Patients with acute respiratory failure from other causes may also be successfully ventilated with NIPSV.[8,9] A nonrandomized study previously reported that 50% of patients with acute respiratory failure from various etiologies were successfully ventilated with NIPSV and did not require endotracheal intubation.[9] Pennock et al[8] reported a higher rate of success in patients with acute respiratory failure occurring after surgery. However, the real benefit of NIPSV to avoid the need for endotracheal intubation, to reduce morbidity and mortality associated with endotracheal intubation has not been prospectively evaluated in patients with acute respiratory failure. Therefore, we conducted a controlled prospective randomized study to determine whether the use of NIPSV would reduce the need for endotracheal intubation, the length of ICU stay, and the mortality rate in patients with acute respiratory failure.

Methods

Informed consent was obtained from the patient or next of kin as soon as possible after the patient was identified.

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Selection of Patients

The aim of the recruitment process was to enroll patients with severe respiratory failure and to randomly assign them to receive conventional therapy or conventional therapy plus NIPSV.

During the 27-month study period, all nonintubated patients admitted in the ICU who experienced respiratory distress were enrolled if they met at least two of the following criteria: respiratory rate of 25 breaths/min or more, arterial partial pressure of oxygen (PaO_2) below 60 mm Hg breathing room air or below 80 mm Hg with additional oxygen, arterial partial pressure of carbon dioxide ($PaCO_2$) of 50 mm Hg or more, and arterial pH of 7.38 or less.

Patients were excluded if the following occurred: (1) they had chronic respiratory insufficiency defined by a previous hospitalization for exacerbation and pulmonary function test showing a forced expiratory volume in 1 s (FEV_1) lower than 70% of the predicted value or a history of chronic bronchitis with hypercapnia and serum bicarbonate greater than 25 mM/L at the admission[7]; (2) respiratory failure was due to status asthmaticus; (3) respiratory failure was due to neurologic disease; (4) they had more than two organ failures[10] on admission; and (5) they had a recent history of otolaryngologic, facial, esophageal, gastric surgery, or trauma. Moreover, patients were not enrolled if endotracheal intubation was urgently required because of cardiac arrest, respiratory arrest, shock, or severe encephalopathy related to the respiratory distress.

Study Design

Randomization was done by block of eight using a table of random numbers[11] to assign the patient to either receive a conventional therapy or a conventional therapy plus NIPSV. The conventional therapy included medications related to the cause of the respiratory distress (antibiotics, diuretics, inotropics, *etc*) and oxygen supplementation via a nasal catheter to obtain a percutaneous oxygen saturation (Biox 3700, Ohmeda, Boulder, Colo) greater than 95%. Patients treated by NIPSV received the same medications in association with the systematic use of NIPSV. Before initiating NIPSV, when patients were likely not to have an empty stomach, a nasogastric tube was inserted for emptying the stomach. The nasogastric tube was then removed before initiating NIPSV to avoid leakage through the mask. In both groups, parenteral nutrition was administered during the first 48 h and until alimentation was possible by oral route or by nasogastric tube. NIPSV was delivered to the patient through a full-face mask, including a disposable soft foam cushion that molds the facial shapes covered by an external thermoplastic rigid part fixed to the patient with four rubber head straps (Cogia, Palaiseau, France). This mask was specially designed for noninvasive ventilation, to minimize air leakage, to reduce dead space, and to be well tolerated over long periods of ventilation. The mask was adjusted and connected to a ventilator (Puritan-Bennett 7200a) set in the inspiratory pressure support (IPS) mode. This mode of ventilatory assistance is now widely used in ventilated patients and has been described previously.[9] The length of NIPSV was determined in a standardized manner as follows: during the first 24 h, NIPSV was maintained continuously until clinical and oxygenation status improved. This was evaluated every day after 1 h of spontaneous breathing with oxygen supplementation and improvement was considered if respiratory rate was below or PaO_2 above the values on admission. Then NIPSV was administered discontinuously, several periods of 3 h in the day and of 6 h in the night, and the length was reduced progressively to at least 6 h/d. NIPSV was definitively withdrawn if respiratory rate remained below 25 breaths/min with a PaO_2 above 80 mm Hg and a $PaCO_2$ below 45 mm Hg without any ventilatory support. After special care provided for avoiding air leaks, the level of IPS was adjusted for each patient to obtain expired tidal volume measured by the ventilator between 7 to 10 mL/kg. Expirated tidal volume was measured by the ventilator cycle by cycle and we considered the mean of 10 consecutive measures. In addition, adequacy of the pressure supplied was suggested by disappearance of accessory respiratory muscle activity evaluated at bedside by palpating the activity of the sternocleidomastoid muscle.[12] The fraction of inspired oxygen (FIo_2) was adjusted to obtain a percutaneous oxygen saturation above 95%, and we used a slight level of positive end-expiratory pressure (PEEP) to increase the PaO_2/FIo_2 ratio and prevent atelectasis. Weaning from NIPSV was made progressively by reducing the length of NIPSV until 6 h/d. At this time, if respiratory rate remained below 25/min with a PaO_2 above 80 mm Hg without any ventilatory support, NIPSV was definitively withdrawn.

Assessment and End Point

The primary end-point of the study was to compare the rate of endotracheal intubation between patients treated with conventional therapy and those treated with conventional therapy plus NIPSV. The predetermined criteria for endotracheal intubation and mechanical ventilation were at least one of the following: (1) inability for the patient to clear tracheal secretions with frequent (more than twice) need for fiberoptic bronchoscopy; (2) severe encephalopathy; (3) increase in respiratory rate up to 20% by comparison with baseline; (4) deterioration in gas exchange defined by greater than 20% fall in PaO_2 or greater than 20% rise in $PaCO_2$ compared with baseline; and (5) circulatory shock defined by a sustained systolic blood pressure less than 80 mm Hg.

The secondary end points of this study were length of ICU stay and the rate of in-ICU death.

Physiologic Measurements

Systolic and diastolic blood pressure, heart rate, and respiratory rate were measured at study entry, at 30, 60, and 120 min, and then every 3 h. The pH, PaO_2, and $PaCO_2$ were measured (BMS3 Mk2, Radiometer, Copenhagen) at entry, at 120 min, and every day after at least 1 h of spontaneous breathing. Arterial blood gases in patients endotracheally intubated and mechanically ventilated were measured if necessary at discretion of the patient's attending physician. The neurologic status was assessed at entry by the Glasgow Coma Scale[13] and the degree of encephalopathy was scored[14] at the same time from 0 to 4: grade 0, no abnormality detected; grade 1, hypertonia or cogwheel rigidity without consciousness abnormality; grade 2, tremor or asterixis or logorrhea; grade 3, confusion or agitation; and grade 4, prostration or vigil coma. Radiologic lesions were documented on a chest radiography performed at study entry and scored as follows: the right and the left pulmonary areas were divided in three zones, and each zone was scored from 0 (no radiologic lesion) to 2 (dense radiologic lesion). Then scores of the six zones were summed (minimum, 0; maximum, 12). Severity of illness was assessed by the Simplified Acute Physiologic Score (SAPS).[15]

When endotracheal intubation was required, hemodynamics, gas exchanges, neurologic status, and encephalopathy were reevaluated just prior to endotracheal intubation.

For the purpose of this study, only data measured at study entry and just before endotracheal intubation were analyzed.

Statistical Analysis

On the basis of calculations of statistical power, a sample size of 40 patients would allow us to detect with a 95% probability and a power of 90%[16] a difference between a postulated 70% rate of endotracheal intubation in patients treated with conventional therapy and a 30% rate of endotracheal intubation in patients

Table 1—*Demographic Characteristics of Patients (n=41)**

Characteristics	Conventional Therapy (n=20)	NIPSV (n=21)	p Value
Age, yr	62±11	64±18	0.51
Male, %	12 (60)	12 (57)	0.90
SAPS	12±5	17±7	0.23
No. (%) of patients admitted in the ICU for respiratory distress	12 (60)	12 (57)	0.90
No. (%) of patients who developed respiratory distress during the course in ICU	8 (40)	9 (43)	0.90
Diagnosis at the time of ICU admission			
Surgical complication (%)	7 (35)	5 (24)	0.75
Pneumonia (%)	5 (25)	3 (14)	0.72
Cardiogenic pulmonary edema (%)	4 (20)	6 (29)	0.49
Drug abuse (%)	0 (0)	1 (5)	1
Multiple trauma (%)	1 (5)	1 (5)	1
Pancreatitis (%)	1 (5)	2 (9)	1
Acute renal failure (%)	2 (10)	1 (5)	1
Others (%)	0 (0)	2 (9)	0.25
Cause of the respiratory distress			
Pneumonia (%)	9 (45)	7 (33)	0.72
Cardiogenic pulmonary edema (%)	6 (30)	8 (38)	0.50
Laryngeal dyspnea (%)	1 (5)	3 (14)	0.72
Chest wall impairment (%)	3 (15)	2 (9)	1
Unknown (%)	1 (5)	1 (5)	1

*Continuous variables are expressed as mean ± SD and were compared with a Wilcoxon rank-sum test for nonpaired data. Dichotomus variables were compared with a χ^2 test with Yates' correction. A p value less than 0.05 was considered significant.

treated with NIPSV.

The rate of endotracheal intubation and mortality was compared by the χ^2 test with Yates' correction.[16] Continuous data such as baseline physiologic measurements and lengths of ICU stay were compared using a Wilcoxon rank-sum test for nonpaired data.[17] The means of several groups were compared using a multiple analysis of variance with Tukey's test.[18] All values are reported as mean ± standard deviation (SD); all p values are for two-tailed comparisons and were considered significant if <0.05. A software package (STATGRAPHICS, Statistical Graphics) was used for statistical analysis.

Results

Between July 16, 1990, and October 16, 1992, respiratory distress occurred in 116 nonintubated patients hospitalized in our ICU. Seventy-five (64%) were not enrolled in this study: 30 of them (40%) because of respiratory distress due to an acute exacerbation of chronic respiratory failure, 16 (21%) because of respiratory distress due to a neurologic disease, 16 (21%) because of more than two organ failures, 8 (10%) because of endotracheal intubation urgently required for cardiac arrest, 2 (3%) because of status asthmaticus, and 3 (4%) because of endotracheal intubation required for surgical procedure.

Fourty-one of the 116 patients (36%) were selected; 20 were randomly assigned to receive conventional therapy and 21 were assigned to receive conventional therapy plus NIPSV. Demographic characteristics of the patients, severity of the illness

Table 2—*Physiologic Measurements, Radiologic Score, Glasgow Coma Score, and Encephalopathic Score at Study Entry (n=41)**

	Conventional Therapy (n=20)	NIPSV (n=21)	p Value
Respiratory rate, breaths/min	35±8	35±8	0.93
Heart rate, beats/min	115±28	115±23	0.81
Systolic blood pressure, mm Hg	136±26	142±29	0.42
Body temperature, °C	37.7±0.9	37.4±0.6	0.21
Arterial pH	7.42±0.13	7.39±0.07	0.15
$PaCO_2$, mm Hg	42±14	44±13	0.38
$PaCO_2/FIO_2$, mm Hg	200±60	213±57	0.45
Radiologic score	5±3	4±3	0.10
Glasgow coma score	14±1	13±2	0.58
Encephalopathic score	2±2	1±1	0.68

*Variables are expressed as mean ± SD and were compared using a Wilcoxon rank-sum test for nonpaired data. A p value less than 0.05 was considered significant.

Table 3—*Patient's Outcome and Length of Stay in the ICU (n=41)**

	Conventional Therapy (n=20)	NIPSV (n=21)	p Value
Intubation and mechanical ventilation (%)	14 (70)	13 (62)	0.88
Length of ICU stay, days	25±23	17±19	0.16
No. deaths in ICU (%)	10 (50)	7 (33)	0.46

*Continuous variables are expressed as mean±SD and were compared with a Wilcoxon rank-sum test for nonpaired data. Dichotomus variables were compared with a χ^2 test with Yates' correction. A p value less than 0.05 was considered significant.

assessed by the SAPS,[15] and diagnosis related to the ICU admission and to the respiratory distress were identical in the two groups of patients (Table 1). At study entry, respiratory rate, gas exchanges, hemodynamic parameters, radiologic score, neurologic score, and encephalopathic score were also comparable in the two groups of patients (Table 2).

No difference in medical treatment was noted between the two groups of patients. For patients treated with NIPSV, the mean levels of IPS, PEEP, and FIo_2 were 15±3 cm H_2O, 4±2 cm H_2O, and 57±22%, respectively.

Endotracheal intubation was performed in 14 of the 20 patients (70%) treated conventionally and in 13 of the 21 patients (62%) treated with NIPSV (p=0.88) (Table 3). Physiologic and hemodynamic parameters, gas exchanges prior to endotracheal intubation, and reasons for endotracheal intubation were comparable in the two groups of patients (Table 4). The delay between study entry and endotracheal intubation was 17±25 h in the patients treated conventionally and 16±24 h (p=0.75) in those treated with NIPSV. Patients successfully ventilated with NIPSV (n=8) were ventilated 17±12 h over 2.5±1.3 days, those who failed (n=13) were ventilated 7.6±11.8 h over 1.5±1 days prior to endotracheal intubation.

The length of ICU stay was 25±23 days for patients treated conventionally and 17±19 days for patients treated with NIPSV (p=0.16). Death occurred in 10 of the 20 patients (50%) treated conventionally and in 7 of the 21 patients (33%) treated with NIPSV (p=0.46) (Table 3).

Because we found in a previous study[9] that patients with a $PaCO_2$ greater than 45 mm Hg had higher rate of success than patients with normal or low values of $PaCO_2$, we performed a subgroup analysis based on this criterion. Age, severity of the underlying disease assessed by the SAPS, diagnosis related to the admission in ICU and to the respiratory distress, hemodynamic parameters, and gas exchanges were comparable between hypercapnic patients treated conventionally (n=6) and those treated with NIPSV (n=11) (Table 5). Endotracheal intubation was performed in all of the 6 hypercapnic patients (100%) treated conventionally but only in 4 of the 11 hypercapnic patients (36%) treated with NIPSV (p=0.02). The

Table 4—*Physiologic Data Before Endotracheal Intubation, Time From Study Entry to Endotracheal Intubation, and Causes of Endotracheal Intubation**

	Conventional Therapy (n=14)	NIPSV (n=13)	p Value
Respiratory rate, breaths/min	35±8	30±10	0.12
Heart rate, beats/min	127±29	126±23	0.70
Systolic blood pressure, mm Hg	130±21	119±45	0.42
Body temperature, °C	37.7±1	37.6±0.9	0.84
Arterial pH	7.35±0.14	7.38±0.13	0.56
$PaCO_2$, mm Hg	49±16	49±18	0.95
PaO_2/FIo_2, mm Hg	170±77	191±94	0.68
Glasgow coma score	13±1	12±2	0.11
Encephalopathic score	2±1	2±2	0.89
Time from study entry to endotracheal intubation, h	17±25	16±24	0.75
Reasons for endotracheal intubation (%)			
Encephalopathy	4 (28)	5 (42)	0.96
Inability to clear tracheal secretions	2 (14)	2 (15)	1
Gas exchange deterioration	1 (7)	1 (8)	1
Increase in respiratory rate	1 (7)	1 (8)	1
Increase in respiratory rate and gas exchange deterioration	4 (28)	3 (23)	1
Shock	2 (14)	1 (8)	0.98

*Variables are expressed as mean±SD and were compared using a Wilcoxon rank-sum test for nonpaired data. Dichotomus variables were compared with a χ^2 test with Yates' correction. A p value less than 0.05 was considered significant.

Table 5—*Diagnosis at the Time of ICU Admission, Cause of the Respiratory Distress, and Physiologic Measurements and Outcomes in the Subgroup of Patients With an Initial $PaCO_2$ >45 mm Hg and in the Subgroup of Patients With an Initial $PaCO_2$ ≤45 mm Hg**

	$PaCO_2$ >45 mm Hg (n=17)			$PaCO_2$ ≤45 mm Hg (n=24)		
	Conventional Therapy (n=6)	NIPSV (n=11)	p Value	Conventional Therapy (n=14)	NIPSV (n=10)	p Value
Age, yr	65±11	59±20	0.62	60±11	68±16	0.19
SAPS	12±4	11±5	0.66	12±5	18±7†	0.03
Diagnosis at the time of ICU admission						
Surgical complication (%)	3 (50)	3 (27)	0.33	4 (28)	2 (20)	0.50
Pneumonia (%)	2 (33)	2 (18)	0.44	3 (21)	1 (10)	0.43
Cardiogenic pulmonary edema (%)	1 (17)	2 (18)	0.72	3 (21)	4 (40)	0.29
Drug abuse (%)	...	1 (9)	0.64	..	...	..
Multiple trauma (%)	...	...	...	1 (7)	1 (10)	0.83
Pancreatitis (%)	...	1 (9)	0.64	1 (7)	1 (10)	0.83
Acute renal failure (%)	...	1 (9)	0.64	2 (14)	...	0.32
Others (%)	...	1 (9)	0.64	...	1 (10)	0.41
Cause of the respiratory distress						
Pneumonia (%)	2 (33)	4 (36)	0.80	7 (50)	3 (30)	0.32
Cardiogenic pulmonary edema (%)	3 (50)	4 (36)	0.48	3 (21)	4 (40)	0.29
Laryngeal dyspnea (%)	1 (17)	2 (18)	0.72	...	1 (10)	0.41
Chest wall impairment (%)	...	1 (10)	0.64	3 (21)	1 (10)	0.43
Unknown (%)	...	...		1 (8)	1 (10)	0.83
Heart rate, beats/min	104±15	108±25	0.91	120±31	117±17	0.97
Systolic blood pressure, mm Hg	123±23	145±30	0.20	141±26	141±31	0.97
Respiratory rate, breaths/min	35±6	31±5	0.29	35±8	39±9	0.48
Arterial pH	7.32±0.09	7.37±0.05	0.38	7.46±0.08	7.41±0.09‡	0.15
$PaCO_2$, mm Hg	57±16	55±8	0.47	35±5‡	33±6‡	0.41
PaO_2/FIO_2, mm Hg	175±55	204±63	0.41	211±55	222±52	0.57
Intubation and mechanical ventilation (%)	6 (100)	4 (36)	0.02	8 (57)	9 (90)	0.19
Length of ICU stay, days	32±30	13±15	0.04	22±20	22±22	0.83
No deaths in ICU (%)	4 (66)	1 (9)	0.06	6 (43)	6 (60)	0.76

*Continuous variables are expressed as mean±SD and were compared with a Wilcoxon rank-sum test for nonpaired data. Dichotomus variables were compared with a χ^2 test with Yates' correction. Comparison between patients with an initial $PaCO_2$ >45 mm Hg and those with an initial $PaCO_2$ ≤45 mm Hg used an analysis of variance with a Tukey's test. A p value less than 0.05 was considered significant.

†p<0.05.

‡p<0.01 between patients with $PaCO_2$ ≤45 mm Hg and those with $PaCO_2$ >45 mm Hg.

length of ICU stay was significantly lower in hypercapnic patients treated with NIPSV (13±15 days vs 32±30 days, p=0.04) and death occurred in 4 of the 6 hypercapnic patients (66%) treated conventionally while only in 1 of the 11 hypercapnic patients (9%) treated with NIPSV (p=0.06) (Fig 1).

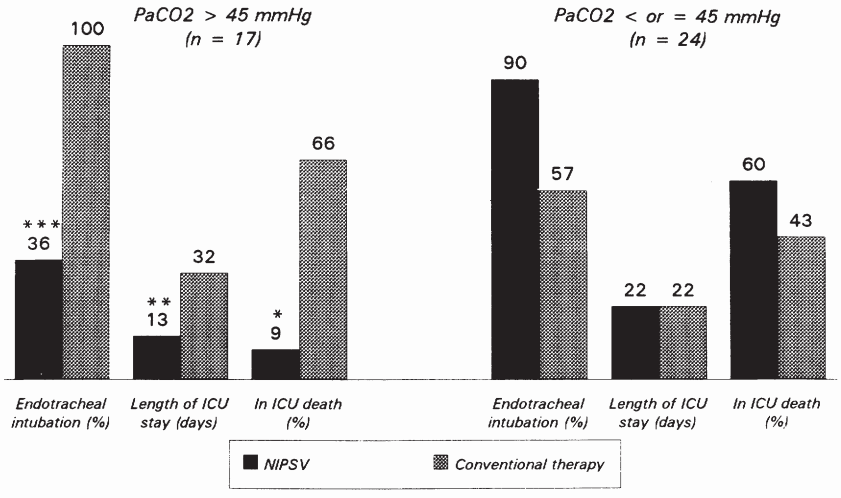

FIGURE 1. Percent of patients endotracheally intubated in the course in ICU, length of ICU stay, and in-ICU mortality rate between patients treated with NIPSV and those treated with conventional therapy in the subgroup of patients with an initial $PaCO_2$ >45 mm Hg (n=17) or ≤45 mm Hg (n=24). Three asterisks=p<0.02; two asterisks=p<0.04; and asterisk=p<0.06 between NIPSV and conventional therapy.

Conversely, in the subgroup of patients having an initial $PaCO_2$ of 45 mm Hg or below (n=24), no beneficial effect of NIPSV was noted (Table 5).

Discussion

The main finding of the present study is that in patients admitted to the ICU with acute respiratory failure not due to chronic obstructive pulmonary disease, the use of NIPSV did not significantly reduce the rate of endotracheal intubation, the length of ICU stay, and the mortality rate. In the subgroup of patients admitted with hypercapnic respiratory failure, NIPSV may have some beneficial effects. The design of the study, however, did not allow us to draw definitive conclusions in this group of patients.

Many patients admitted to the ICU with severe respiratory failure will ultimately require endotracheal intubation to improve oxygenation and avoid respiratory muscle fatigue.[19] However, these benefits must be weighed against the potential complications associated with these techniques.[1] To reduce the need for endotracheal intubation and the associated morbidity, noninvasive ventilatory support has been developed in patients presenting with various forms of acute respiratory failure.[5-9,20]

Significant beneficial effects have been shown in patients admitted to the ICU for acute exacerbation of chronic respiratory failure and for hypercapnic cardiogenic pulmonary edema.[5,7,20] In a previous study,[9] we found that IPS delivered from a ventilator through a face mask (NIPSV) reduced the need for endotracheal intubation with a success rate of 47% in patients presenting with acute respiratory failure from various etiologies. However, because of the absence of a control group in many studies, the real benefit of NIPSV in reducing the need for endotracheal intubation, the length of ICU stay, and the mortality is not known in such patients.

Several factors may have influenced the results toward a negative effect of NIPSV: (1) the severity of illness of the two groups; (2) the means by which the ventilatory support was delivered to the patient; and (3) the causes and mechanisms of respiratory failure and hypoxemic vs hypercapnic respiratory failure, in the population selected.

First, in the present study, using a Wilcoxon rank-sum test for nonpaired data and a poststratification analysis,[21] severity of the disease assessed by the SAPS did not significantly differ between patients treated conventionally and those treated with NIPSV. However, SAPS tended to be higher in patients treated with NIPSV (17 ± 7) than in those treated conventionally (12 ± 5). Moreover, 5 (24%) patients treated by NIPSV had a SAPS greater than 20 while there was only 1 (5%) with a SAPS greater than 20 of those treated conventionally (p=0.29). In a previous study,[22] we found that SAPS was higher in patients who failed to be ventilated with NIPSV (18 ± 7) by comparison with those successfully ventilated (11 ± 4, $p<0.05$). Moreover, in the same study, 8 of the 13 patients who failed to be ventilated with NIPSV had a SAPS greater than 16 ($p<0.02$). A high severity score suggest that patients did not have an easily reversible process causing the respiratory failure and in these situations NIPSV may be of no benefit. Thus, we cannot definitively exclude that the absence of benefit of NIPSV observed in the present study may be explained in part by a greater severity of patients treated with NIPSV.

Second, failure to ventilate nonintubated patients could be related to the means by which the ventilatory support was delivered to the patient. In our study, we used a ventilator (Puritan-Bennett 7200a) set in IPS mode. Because of the high sensitivity of the demand valve and the short time delay between the instigation of the inspiratory effort and the start of gas flow,[23] the ventilator we used was unlikely to explain the difference between our rate of success and those reported by others.[6,8] Moreover Meduri et al,[6] using a ventilator with a lower sensitivity of the demand valve and a higher time delay,[23] reported a higher rate of success.

In our study, pressure support was delivered to the patient by a face mask. Although the use of nasal mask can be better tolerated and can explain the higher rate of success reported by Pennock et al,[8] several of our patients did not cooperate, most of them were tachypneic and breathed via the mouth, a situation in which efficacy of nasal ventilation can be abolished.[24] Whether this difference could explain our results remains doubtful. Moreover, none of our patients failed to be ventilated with NIPSV because of nonaccommodation to the mask.

Third, the population selected in the present study was miscellaneous with respiratory failure from various causes not related to chronic respiratory insufficiency (Table 1). NIPSV probably acts preferentially by improving respiratory muscle strength[5] and may work predominantly in situations associated with respiratory muscle dysfunction. Previous studies found[6-9] that patients with acute respiratory failure occurring shortly after extubation were ventilated with NIPSV with a high rate of success. In the present study, only 8 (19%) patients were included because of postextubation respiratory distress. Four of these eight patients received NIPSV, and all were successfully ventilated, confirming the possible advantage of NIPSV in this situation. In accordance with previous findings,[22] NIPSV will probably be of poor benefit in patients with pneumonia. The high rate of failure of NIPSV for patients suffering from pneumonia may result from several factors, including inability to

handle secretions, high levels of ventilatory requirements, reduced lung compliance requiring higher levels of pressure than those used during noninvasive ventilation, and from inhomogeneous and often unilateral distribution of lesions. In the present study, respiratory distress was due to pneumonia in 16 patients (39%). Seven of these were randomly assigned to receive NIPSV; none was successfully ventilated and all required endotracheal intubation because of encephalopathy (n=3), deterioration in gas exchange (n=1), deterioration in respiratory rate and in gas exchange (n=2), and shock (n=1). By contrast, respiratory distress was not due to pneumonia in 25 other patients (61%) and 14 were randomly assigned to receive NIPSV; 8 were successfully ventilated with NIPSV (p=0.04).

NIPSV may be of benefit in hypercapnic respiratory failure related to respiratory muscle fatigue. In a previous study,[9] we found that $PaCO_2$ was significantly higher (57 ± 15 mm Hg) in patients successfully ventilated with NIPSV by comparison with those who failed (37 ± 17 mm Hg). In this study, 7 of the 9 patients (78%) with an initial $PaCO_2$ greater than 45 mm Hg were successfully ventilated with NIPSV by contrast with none of the 6 patients with an initial $PaCO_2$ lesser than 35 mm Hg ($p<0.02$). In the present study, poststratification based on $PaCO_2$ confirms these results (Table 5). Seventeen patients had a $PaCO_2$ greater than 45 mm Hg at study entry; 6 received conventional therapy and all were endotracheally intubated, 11 received conventional therapy plus NIPSV, and only 4 needed to be endotracheally intubated (p=0.02) suggesting a 64% reduction in the need of endotracheal intubation. The 6 hypercapnic patients treated conventionally did not appear to be statistically different than the 11 hypercapnic patients treated with NIPSV (Table 5) suggesting that the reduction in the need for endotracheal intubation in these patients could be due to the ventilatory support provided by NIPSV. These results are in agreement with the report of Pennock et al[8] in which hypercapnic patients (n=15) were noninvasively ventilated with an 80% rate of success. This analysis revealed that the reduction in the need for endotracheal intubation in hypercapnic patients was associated with a significant decrease in the length of ICU stay and in mortality. However, because of the small size of these two subgroups and because of the type of *post hoc* analysis, it is difficult to draw definitive conclusions from these data and the possibility of type 2 β-error cannot be excluded. These results mainly suggest, however, that these patients constitute a group on which further studies should focus. Of the six hypercapnic patients treated conventionally, four died (day 10, 21, 9, and 9 after initiation of mechanical ventilation) and two of these died of possible complications attributed to endotracheal intubation (1), and nosocomial pneumonia and anoxic cardiac arrest after self-extubation (1). Of the 11 hypercapnic patients treated with NIPSV, only 1 died of refractory cardiogenic shock. Again, because the subgroup of 17 patients with hypercapnic respiratory failure may not have been evenly distributed with regard to disease, the reduction in mortality with NIPSV need to be confirmed.

Finally, some considerations are needed about the sample size[25] we choose. A sample size of 40 patients would allow us to detect with a 95% probability and a power of 90%[16] a difference between a postulated 70% rate of endotracheal intubation in patients treated with conventional therapy and a 30% rate of endotracheal intubation in patients treated with NIPSV. Even if a higher sample size would allow us to detect a significant difference between the two groups, our results suggest that the difference observed in the rate of endotracheal intubation (70 vs 62%) would be of poor clinical relevance. By contrast, the large difference observed in the subgroup of hypercapnic patients in terms of avoiding the need for endotracheal intubation, of lowering the length of ICU stay, and of reducing the ICU mortality support further evaluation of NIPSV in these patients.

In conclusion, our study failed to show any beneficial effect of NIPSV in a heterogeneous population of patients with severe acute respiratory failure that was not due to COPD. In a subgroup of patients presenting with $PaCO_2$ greater than 45 mm Hg, NIPSV was associated with a significant reduction in the need for endotracheal intubation, the length of ICU stay, and tended to reduce the mortality. Larger studies, also addressing the possible added work imposed on the ICU staff,[26] need to be performed to determine whether NIPSV may be beneficial in subgroups of diseases such as hypercapnic respiratory failure unrelated to COPD.

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