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Noninvasive Positive-Pressure Ventilation To Treat Hypercapnic Coma Secondary to Respiratory Failure*

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Introduction: **Hypercapnic coma secondary to acute respiratory failure (ARF) is considered to be a contraindication to the use of treatment with noninvasive positive-pressure ventilation (NPPV). However, intubation exposes these patients to the risk of complications such as nosocomial pneumonia, sepsis, and even death.**

Patients and methods: **We performed a prospective, open, noncontrolled study to assess the outcomes of NPPV therapy in patients with a Glasgow coma scale (GCS) score of ≤ 8 points due to ARF. The primary goal of the study was to determine the success of NPPV therapy (defined as a response to therapy allowing the patient to avoid endotracheal intubation, and to survive a stay in the ICU and at least 24 h on a medical ward) in patients with hypercapnic coma, compared to those who started NPPV therapy while awake. The secondary goal of the study was to identify the variables that can predict a failure of NPPV therapy in these patients.**

Results: **A total of 76 coma patients (80%) responded to NPPV therapy, and 605 patients with GCS scores > 8 responded to therapy (70%; p = 0.04). A total of 25 coma patients died in the hospital (26.3%), and 287 noncoma patients died in the hospital (33.2%; p = 0.17). The variables related to the success of NPPV therapy were GCS score 1 h posttherapy (odds ratio [OR], 2.32; 95% confidence interval [CI], 1.53 to 3.53) and higher levels of multiorgan dysfunction, as measured by the maximum sequential organ failure assessment index score reached during NPPV therapy (OR, 0.72; 95% CI, 0.55 to 0.92).**

Conclusions: **We concluded that selected patients with hypercapnic coma secondary to ARF can be treated as successfully with NPPV as awake patients with ARF.**

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Key words: acute respiratory failure; bilevel positive airway pressure; COPD; hypercapnic coma; noninvasive ventilation

Abbreviations: APACHE = acute physiologic and chronic health evaluation; ARF = acute respiratory failure; DNI = do not intubate; EPAP = expiratory positive airway pressure; F_{IO_2} = fraction of inspired oxygen; GCS = Glasgow coma scale; IPAP = inspiratory positive airway pressure; NPPV = noninvasive positive-pressure ventilation; RR = respiratory rate; SAPS = simplified acute physiology score; SOFA = sequential organ failure assessment

In recent years, the use of therapy with noninvasive positive-pressure ventilation (NPPV) has become more widespread in ICUs for the treatment of acute respiratory failure (ARF).[1,2] In patients who experience acute exacerbations of COPD, NPPV therapy not only improves physiologic manifestations of respiratory failure, but also reduces the need for endotracheal intubation, the complications related to mechanical ventilation, the duration of hospitalization, and hospital mortality.[3–10] Furthermore, the treatment of these patients by NPPV may be more cost-effective than traditional therapies, including invasive mechanical ventilation.[11] Less evidence supports the use of NPPV to treat hypoxemic respiratory

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failure. The six randomized studies[12–17] thus far published on this application have not provided definitive results, mainly because they have included small numbers of patients with ARF of diverse etiologies.[18,19]

Of course, either acute hypoventilatory or hypoxemic respiratory failure can eventually lead to coma, which is usually related to increased $PaCO_2$ and other metabolic disturbances. Without exception, the randomized studies[3–19] evaluating the use of NPPV to treat ARF have used neurologic deterioration as an exclusion criterion, based on the concern that a depressed sensorium would predispose the patient to aspiration. In two review articles, the deterioration of consciousness was considered to be a contraindication to NPPV therapy[20] and a criterion for its exclusion.[21] An international consensus conference[22] considered the presence of severe encephalopathy with a Glasgow coma scale (GCS) score < 10 to be a contraindication for NPPV therapy. Ordinarily, these patients are intubated for airway protection. However, the need to exclude patients with coma from consideration for NPPV therapy has never been evaluated prospectively. Furthermore, we have observed that some patients who have declined intubation have successful outcomes using NPPV therapy despite their initial presentation while in a coma. This experience has led us to reexamine our experience with such patients. The objective of the present study was to evaluate prospectively the effectiveness and safety of NPPV when applied using bilevel positive airway pressure to patients with ARF and severe neurologic deterioration (GCS score ≤ 8) compared to those who present a score > 8. A second objective was to determine the variables that predict the lack of response to NPPV therapy in patients presenting with coma.

Materials and Methods

This prospective, observational study was carried out between January 1, 1997, and May 31, 2002, in patients who were admitted to the ICU with ARF and a severe deterioration of consciousness (GCS score ≤ 8). The study was approved by the ethics committee at our institution, and written consent was obtained from patients or their next of kin.

Patients Included

Consecutive patients presenting with ARF were treated with NPPV for the following standard indications: moderate-to-severe respiratory distress accompanied by tachypnea (for hypoventilatory causes, > 24 breaths/min; for hypoxemic causes, > 29 breaths/min) and acute or acute-on-chronic CO_2 retention ($PaCO_2$, > 45 mm Hg; pH < 7.35); or severe hypoxemia coma (PaO_2/fraction of inspired oxygen [FIO_2] ratio, < 200). Patients with coma (GCS score, ≤ 8) and CO_2 retention formed one group, and those without coma served as a comparison group.

Patients Excluded

Contraindications to the use of NPPV therapy were agonal breathing and apnea, recent facial, esophageal, or upper airway surgery, uncontrolled GI hemorrhaging, excessive airway secretions, or a facial deformity preventing the application of the mask. Hemodynamic instability that is responsive to treatment with fluid resuscitation and vasoactive drugs was not considered to be a contraindication to NPPV therapy. Patients were excluded if another etiology of coma, such as a hypoglycemic, neurologic, or pharmacologic etiology, was identified by means of clinical history and laboratory analysis. A CT scan of the head was obtained if the patients remained comatose despite normalization of pH and $PaCO_2$.

Ventilator, Ventilation Mode, and Interface

NPPV therapy was administered using bilevel positive airway ventilation (BiPAP ST-D or VISION Ventilator Support Systems; Respironics, Inc; Murrysville, PA) via a properly fitted face mask (Respironics). The head of the bed was raised to 45° in order to minimize the risk of pulmonary aspiration. The face mask was attached by means of head straps and was tightened to minimize leaks, although care was taken to avoid excessive tightening. Artificial skin was applied over the bridge of the nose in the majority of patients. Some leaking occurred around the nasogastric catheters, but it was minimized by placing the catheter in the position that minimized leaking and, when necessary, using tape or gauze to reduce leaks. We monitored inspiratory pressure and made certain that leaks were not large enough to reduce delivered pressures.

Noninvasive Ventilation Protocol

On admission to the ICU, a nasogastric tube was placed in all patients to minimize the risk of gastric distension and vomiting. The ventilator was set in the spontaneous/timed mode, with a minimum respiratory rate (RR) of 20 to 25 breaths/min. The initial inspiratory positive airway pressure (IPAP) was set at 12 cm H_2O. IPAP levels were raised by 2 to 3 cm H_2O every 4 h as tolerated in order to keep pH at > 7.3 but did not exceed 30 cm H_2O.

Expiratory positive airway pressure (EPAP) was begun at a level of 5 cm H_2O, although this could also be raised if needed to counterbalance the intrinsic positive end-expiratory pressure level or to treat hypoxemia, or it could be lowered to enhance patient comfort. FIO_2 was adjusted to maintain an arterial oxygen saturation of $> 92\%$ with an FIO_2 of $< 60\%$, if possible. Arterial blood gas samples were obtained from each patient before connection to the ventilator and at 1 h posttherapy. Subsequently, samples were obtained every 12 h or as clinically indicated.

All patients continued to receive mechanical ventilation until the GCS score rose to 15. When patients were being oxygenated adequately (*ie*, O_2 saturation, $> 95\%$; FIO_2, $< 40\%$ or equivalent) and the RR was ≤ 24 breaths/min, we decreased the levels of IPAP and EPAP by 3 cm H_2O and 2 cm H_2O each hour, respectively, until pressures of 12 cm H_2O and 5 cm H_2O, respectively, were reached. If oxygenation and RR remained stable, we discontinued NPPV therapy and observed. If the RR rose to > 30 breaths/min, oxygen saturation fell to $< 88\%$, or the patient became diaphoretic or manifested other evidence of excessive respiratory effort, we resumed NPPV therapy and intermittently discontinued it, as tolerated, until the patient could sustain unassisted breathing.

Criteria for Intubation

Patients who had not declined such a procedure were intubated endotracheally if any of the following conditions occurred: worsening respiratory distress despite NPPV therapy; respiratory arrest; unmanageable airway secretions; uncontrolled ventricular arrhythmias; hemodynamic instability that was unresponsive to therapy with fluid resuscitation and/or vasoactive drugs (with a maximum norepinephrine dose of 0.3 μg/kg/min); RR persistently > 40 breaths/min despite optimized interface and ventilation; failure of gas exchange to improve within the first 2 to 3 h of NPPV therapy; or lack of improvement in consciousness (*ie*, an increase of at least 2 points from the base GCS from the start of NPPV therapy). Patients who had declined intubation continued to receive NPPV therapy until they improved, declined further NPPV therapy, or died.

Effectiveness of the Technique

NPPV therapy was held to be successful when the patient avoided endotracheal intubation, completely recovered consciousness, was discharged from the ICU, and remained alive and conscious on a hospital ward for at least 24 h without requiring the resumption of NPPV therapy. Patients were considered to be intolerant to therapy if they were unable to cooperate with the technique, pulling the mask off and refusing to continue. Lack of response to NPPV therapy occurred if patients experienced a worsening of gas exchange or respiratory distress despite optimization of the technique, leading to intubation or death. Survivors were patients who were alive at hospital discharge.

Measurements

At the start of NPPV therapy, the following variables were also recorded: age; sex; indicators of severity with APACHE (acute physiologic and chronic health evaluation) II score and simplified acute physiologic score (SAPS) II; original location of the patient (*ie*, emergency department or hospital ward); underlying disease; and premorbid respiratory status. RR, heart rate, arterial BP, continuous arterial oxygen saturation, GCS score, temperature, and urine output were measured hourly. Also recorded were the total time of NPPV use in days and hours, as well as the ventilator parameters IPAP, EPAP, FIO_2, and air leakage.

In addition to the arterial blood gas samples, daily blood samples were also analyzed for levels of glucose, urea, creatinine, and hepatic enzymes, WBC count, and hemoglobin and platelet concentration. ICU patients underwent daily chest radiographs. During the patient's hospital stay, these additional variables also were recorded. The appearance of multiorgan failure syndrome was measured by the sequential organ failure assessment (SOFA) index,[23] with the failure score in each organ being recorded daily, along with the appearance of ventilation-related complications (eg, skin lesions, mucous dryness, vomiting, pulmonary aspiration, and discomfort). In addition, the stay in the ICU and in the hospital, hospital survival or mortality, and the mortality expected according to the SAPS II system were recorded.

Statistical Analysis

Continuous variables were expressed as the mean ± SD, and categoric variables were recorded as percentages. The relationship between two qualitative variables was tested using the χ^2 test or the Fisher exact test. The Kolmogorov-Smirnov test was used to identify variables with a normal distribution. In these cases, mean values were compared using the Student *t* test for independent data, while a paired *t* test was applied to compare the data of each patient before and after treatment. Variables without homogeneous variance and normal distribution were compared by nonparametric testing (Mann-Whitney). The relation between two qualitative variables was assessed by calculating Pearson correlation coefficients. All analyses were two-tailed, and significance was taken to be $p \leq 0.05$. Finally, multivariate analysis was performed with logistic regression. Only variables with $p \leq 0.10$ in univariate analysis were studied in the multivariate analysis. Statistical analysis was carried out using a statistical software package (SPSS, version 10.0; SPSS; Chicago, IL).

Results

During the period of the study, 2,865 ARF patients were admitted to the ICU, of whom 958 (33.4%) were treated with NPPV. Of these patients, 95 (10.1%) had GCS scores on ICU admission ≤ 8, and 863 had GCS scores > 8. The global success rate of NPPV therapy was slightly higher in coma patients than in patients with GCS scores > 8 (80.0% and 70.1%, respectively; $p = 0.0434$). Despite this, the hospital mortality rate was not significantly different between the two groups. The mortality rate of hypercapnic coma patients was 26.3%, compared to 33.2% for those patients who were not in a coma ($p = 0.1706$) [Table 1]. In the largest subgroup, patients with COPD, the success rate in those with severe encephalopathy was 86%, compared to 89% in other patients ($p = 0.5430$). Similarly, the hospital mortality rate was not significantly different between the groups (27% and 20%, respectively; $p = 0.2411$). On the other hand, coma patients with hypoxemic ARF caused by pneumonia or ARDS showed a lower NPPV success rate than those with higher levels of consciousness (25% vs 45%, respectively; $p = 0.299$), although the hospital mortality rates were similar (50% and 47%, respectively; $p = 1.000$).

Table 1—*Success and Hospital Mortality in Patients With and Without Coma at Start of NPPV Therapy

Variable	No Coma	Coma	p Value
Total	863 (100)	95 (100)	
Success	605 (70.1)	76 (80.0)	0.0434
Hospital mortality	287 (33.2)	25 (26.3)	0.1706
COPD	220 (25.5)	66 (69.5)	
Success	196 (89.0)	57 (86.3)	0.5430
Hospital mortality	45 (20.4)	18 (27.2)	0.2411
ACPE	189 (21.9)	10 (10.5)	
Success	140 (74.1)	8 (80.0)	1.000
Hospital mortality	63 (33.3)	2 (20.0)	0.503
Pneumonia-ARDS	194 (22.5)	8 (8.4)	
Success	89 (45.9)	2 (25.0)	0.299
Hospital mortality	91 (46.9)	4 (50.0)	1.000
Others	260 (30.1)	11 (11.6)	
Success	180 (69.2)	9 (81.8)	0.513
Hospital mortality	88 (33.8)	1 (9.1)	0.108

*Values given as No. (%), unless otherwise indicated. ACPE = acute cardiogenic pulmonary edema.

Characteristics of Comatose Patients

The group of comatose patients consisted of 46 men and 49 women. The mean age was 73 ± 9 years (men, 70 ± 12 years; women, 74 ± 12 years; age range, 42 to 88 years), the mean APACHE II score was 29 ± 7, and the mean SAPS II was 53 ± 13. The mean GCS score of these 95 patients on ICU admission was 6.5 ± 1.7. In 11.6% of cases, the GCS score was 3, in 40.1% of cases the score was 4 to 7, and in 45.3% of cases the score was 8. The etiology for ARF was COPD in 66 patients, pneumonia in 4 patients, ARDS in 4 patients (sepsis, 3 patients; acute pancreatitis, 1 patient), acute cardiogenic pulmonary edema in 10 patients, obesity hypoventilation syndrome in 5 patients, asthma in 2 patients, and kyphoscoliosis in 2 patients. There were also two postoperative patients (postthyroidectomy with vocal cord paralysis, one patient; postgastric ulcer surgery, one patient). In 25 patients (26.3%), there were specific do-not-intubate (DNI) orders. One ventilator (VISION; Respironics) was used in 57 patients (60%), and another ventilator (BiPAP ST-D; Respironics) was used in 38 patients (40%). After the first hour, the mean IPAP was 17 ± 2 cm H_2O, and the mean EPAP was 7 ± 1 cm H_2O.

Physiologic Measurements

At study entry, all comatose patients had severe respiratory failure. Most were hypercapnic, but some were hypoxemic initially, developed muscular fatigue, and became hypercapnic. The mean Pa_{O_2}/F_{IO_2} ratio on ICU admission was 139 ± 43, the mean Pa_{CO_2} was 99 ± 19 mm Hg (range, 60 to 166 mm Hg), and the mean pH was 7.13 ± 0.06 (range, 6.93 to 7.23). Physiologic parameters, with the exception of RR and systolic BP, improved significantly after 1 h of NPPV therapy (Table 2).

Table 2—*Evolution of Physiologic Variables in Patients Presenting With Coma**

Variable	NPPV Therapy		p Value
	At Start	After 1 h	
Pa_{O_2}/F_{IO_2} ratio	139 ± 43	189 ± 42	< 0.001
Arterial pH	7.13 ± 0.06	7.22 ± 0.05	< 0.001
Pa_{CO_2}, mm Hg	99 ± 18	81 ± 19	< 0.001
GCS	6.5 ± 1.7	10.5 ± 2.4	< 0.001
RR, breaths/min	27 ± 10	28 ± 6	0.652
HR, beats/min	109 ± 15	107 ± 14	0.036
BP, mm Hg			
Systolic	150 ± 24	153 ± 20	0.262
Diastolic	72 ± 14	69 ± 12	< 0.001

*Values given as mean ± SD, unless otherwise indicated. HR = heart rate.

Outcomes of Patients

The mean duration of NPPV therapy for the comatose patients was 2.0 ± 1.3 days, totaling 27 ± 19 h of NPPV treatment. Complete recovery of consciousness (GCS score, 15) was achieved in 81 patients (85.3%), within a mean time of 4.1 ± 2.4 h from the start of NPPV. In addition, there was a weak but statistically significant correlation ($r = 0.22$; $p = 0.048$) between the Pa_{CO_2} level on ICU admission and the time needed to recover consciousness (GCS score = 15).

A positive response to therapy (*ie*, success) was achieved in 76 of the comatose patients (80.0%). Thirteen patients (13.7%) were intubated, 10 because of shock that was unresponsive to therapy with fluids or vasoactive drugs and 3 for worsening respiratory failure. Six patients (6.3%), all of whom had DNI orders, died during NPPV therapy. The mean duration of stays in the ICU and hospital were 6.7 ± 16.8 days and 18.9 ± 19.9 days, respectively (Table 3). No patient was readmitted to the ICU after discharge to the ward. Ten patients (10.5%) died in the ICU (including the 6 who died while using NPPV), and 15 patients (15.8%) died while on hospital wards at least 24 h after ICU discharge, for a total of 25 deaths (Table 3). Of the 10 deaths that occurred in the ICU, 5 were caused by ARF and the others were caused by multiorgan failure. Of the 15 patients who died while on the ward, all had COPD, 11 died of ARF, 4 died of nosocomial infections, and 12 had DNI orders.

Table 3—*Patient Outcomes in Those Patients Who Responded Compared to Those Who Did Not Respond to NPPV Therapy**

Variable	Success (n = 76)	Failure (n = 19)	p Value
Multiorgan dysfunction			0.002
Failing organs			
2	40 (52.6)	4 (21.1)	
3	19 (25.0)	5 (26.3)	
4	14 (18.4)	5 (26.3)	
5	1 (1.3)	4 (21.1)	
6	2 (2.6)	1 (5.3)	
NPPV complications	21 (27.6)	8 (42.1)	0.200
Nasal ulceration	20 (26.3)	3 (15.8)	0.220
Ocular irritation/dry mucosa	12 (15.8)	3 (15.8)	1.000
Abdominal distension	2 (2.6)	3 (15.8)	0.053
Vomiting	0	3 (15.7)	0.007
Aspiration	0	1 (5.2)	0.200
ICU stay, d	3.7 ± 3.1	14.5 ± 36.6	0.034
Hospital stay, d	16.6 ± 12.6	29.0 ± 44.8	0.734
ICU mortality	0 (0)	10 (52.6)	< 0.0001
Hospital mortality	14 (18.4)	11 (57.9)	< 0.0001

*Values given as No. (%) or mean ± SD, unless otherwise indicated.

The time spent in the ICU was significantly longer for patients who did not respond to NPPV therapy than for those who responded to it, but the lengths of hospital stay were not significantly different (Table 3). Also, as would be expected, the hospital mortality rate was significantly higher among those patients who did not respond to NPPV therapy than among those who did (57.8% vs 18.4%, respectively; $p < 0.001$).

Complications

Complications attributable to NPPV were observed in 29 patients (30.5%) but did not lead to the lack of response to NPPV therapy (Table 3). The most frequent complication (affecting 23 patients [24.2%]) was skin ulceration on the nose or forehead. Gastric distension was observed in five patients, even though all patients had a nasogastric tube in place. In three of these patients, vomiting occurred, and one patient experienced pulmonary aspiration necessitating endotracheal intubation.

Factors Predicting Success of NPPV

A univariate analysis that was performed to identify factors that correlated with the response or lack of response to NPPV therapy demonstrated that neither gender nor age was related to a response to NPPV therapy (Table 4). Not surprisingly, lack of response was more likely among patients with higher acuity of illness and organ failure scores. GCS score, RR, pH, $Paco_2$, and Pao_2/Fio_2 ratio on ICU admission did not correlate with response to therapy, but, with the exception of RR, improvements in these variables within the first hour of NPPV therapy did correlate with a response to therapy (Table 4). A response to NPPV therapy was also significantly related to the etiology for ARF ($p = 0.013$), with the vast majority of patients who responded to NPPV therapy having COPD and two having severe asthma. Two asthmatic patients were men, were 55 and 60 years old, had pH values of 7.05 and 6.96, respectively, $Paco_2$ values of 98 and 110 mm Hg, respectively, GCS scores of 8 and 6, respectively, and durations of NPPV therapy of 8 and 6 h, respectively.

High rates of response to NPPV therapy also were achieved in patients with acute cardiac pulmonary edema and obesity hypoventilation syndrome, whereas those with pneumonia/ARDS had a high proportion of lack of response to therapy. DNI orders did not significantly influence the NPPV response rate, which was 74% when such orders were in place and 86% when they were not ($p = 0.560$). Likewise, the type of ventilator (BiPAP ST-D vs VISION) and the year of application were not associated with differences in outcome (Table 4).

Table 4—*Univariate Analysis of Factors Associated With NPPV Success or Failure in Patients With Coma

Variable	Success (n = 76)	Failure (n = 19)	p Value
Age, yr	73 ± 9	72 ± 11	0.465
APACHE II score	28 ± 6	32 ± 7	0.025
SAPS II	51 ± 11	63 ± 17	< 0.0001
Maximum SOFA score	7.9 ± 2.7	9.6 ± 3.1	0.019
GCS			
Admission	6.5 ± 1.8	6.1 ± 1.5	0.341
First hour	11.2 ± 2.0	7.9 ± 2.2	< 0.0001
RR			
Admission	27 ± 11	28 ± 9	0.686
First hour	27 ± 7	30 ± 5	0.144
pH			
Admission	7.13 ± 0.06	7.11 ± 0.08	0.631
First hour	7.23 ± 0.05	7.17 ± 0.05	< 0.0001
$Paco_2$, mm Hg			
Admission	98 ± 18	102 ± 25	0.513
First hour	78 ± 16	95 ± 25	< 0.0001
Pao_2/Fio_2 ratio			
Admission	138 ± 40	140 ± 50	0.907
First hour	195 ± 40	166 ± 42	0.008
15 h to recover GCS	4.0 ± 2.4	5.6 ± 2.7	0.166
NPPV			
d	2.2 ± 1.4	1.4 ± 0.9	0.017
h	23 ± 17	20 ± 26	0.062
Sessions	2.8 ± 2.2	1.4 ± 0.7	< 0.0001
IPAP, cm H_2O on admission	17 ± 2	17 ± 3	0.131
EPAP, cm H_2O on admission	7 ± 1	8 ± 1	0.116
Gender			0.151
Male	34	12	
Female	42	7	
Shock on admission	2 (2.6)	5 (26.3)	0.003
Type of ventilator			0.753
VISION	45 (78.9)	12 (21.1)	
BiPAP ST-D	31 (81.6)	7 (18.4)	
DNI, %	19 (25.0)	6 (31.6)	0.560

*Values given as mean ± SD or No. (%), unless otherwise indicated.

A multivariate analysis (Table 5) of factors that were significantly associated with response to therapy from the univariate analysis identified a higher GCS score 1 h after the initiation of NPPV therapy and

Table 5—*Variables Associated With NIV Failure and Hospital Mortality by Multivariate Analysis

Variable	β	OR	95% CI	p Value
NPPV success				
GCS in first hour	−0.8451	2.32	1.53–3.53	0.0001
SOFA maximum	0.3277	0.72	0.55–0.92	0.0111
Hospital mortality				
SOFA maximum	0.4242	0.65	0.51–0.83	0.0006
RR on admission	0.0962	0.90	0.84–0.97	0.0115
NPPV success	−1.8830	6.67	1.56–27.62	0.0101
DNI	1.5812	0.20	0.05–0.78	0.0210

*OR = odds ratio; CI = confidence interval.

less multiorgan dysfunction, as shown by a negative correlation with the maximum SOFA index score reached during NPPV.

Factors Predicting Hospital Survival in Comatose Patients Using NPPV

A separate univariate analysis (Table 6) demonstrated that hospital survival was significantly associated with lower ICU admission APACHE II score, SAPS II, and SOFA score, with less tachypnea at the start of NPPV, with the initiation of therapy taking in an emergency department rather than on an inpatient ward (84% vs 59%, respectively; $p = 0.007$), and the absence of DNI orders. Patients with DNI orders had a hospital mortality rate of 52%, as opposed to 24% when there were no such orders ($p = 0.001$). Also, patients who were treated during later years of the study, rather than during earlier years, had improved survival rates (Table 6). According to a multivariate analysis of factors that were significantly associated with survival from the univariate analysis, higher SOFA multiorgan dysfunction index scores, a higher RR on ICU admission, and DNI orders were associated with significant reductions in the likelihood of survival (all odds ratios, < 1), whereas a response to NPPV therapy was associated with a much greater likelihood of survival (as would be anticipated).

Table 6—*Variables Associated With Hospital Mortality

Variable	Survived (n = 70)	Died (n = 25)	p Value
Age, years	73 ± 9	73 ± 11	0.805
APACHE II score	28 ± 5	33 ± 9	0.015
SAPS II	50 ± 10	61 ± 18	0.013
Maximum SOFA score	7.5 ± 1.9	11.9 ± 4.8	< 0.0001
ECG			
Admission	6.5 ± 1.8	6.4 ± 1.6	0.934
First hour	10.6 ± 2.3	10.2 ± 2.8	0.451
15 h to recover GCS	4.1 ± 2.2	3.8 ± 3.2	0.592
pH			
Admission	7.13 ± 0.07	7.14 ± 0.06	0.603
First hour	7.22 ± 0.05	7.22 ± 0.05	0.822
$Paco_2$, mm Hg			
Admission	99 ± 18	100 ± 24	0.842
First hour	80 ± 18	84 ± 21	0.413
RR			
Admission	26 ± 11	32 ± 7	0.004
First hour	27 ± 7	30 ± 5	0.108
Pao_2/Fio_2			
Admission	139 ± 43	137 ± 44	0.816
First hour	193 ± 42	179 ± 41	0.153
IPAP, cm H_2O on admission	18 ± 2	17 ± 2	0.653
EPAP, cm H_2O on admission	7 ± 1	8 ± 1	0.071
NPPV			
d	2.1 ± 1.4	2.0 ± 1.1	0.692
h	27.5 ± 18.0	28.9 ± 22.4	0.774
Gender			0.377
Male	32	14	
Female	38	11	
Shock on admission	3 (4.3)	4 (16.0)	0.075
Ventilator type	43/27	14/11	0.634
VISION	43 (75.4)	14 (24.6)	
BiPAP ST-D	27 (71.1)	11 (28.9)	
DNI order	12 (17.1)	13 (52.0)	0.001
Complications	22 (31.4)	7 (28.0)	0.749

*Values given as mean ± SD or No. (%), unless otherwise indicated.

Discussion

This study shows that NPPV use in patients with acute severe respiratory insufficiency causing severe encephalopathy, and even coma, is associated with high response and hospital survival rates, improving gas exchange and consciousness with few serious side effects. These results are at odds with the conventional wisdom, considering that most previous trials of NPPV, including a number of randomized, controlled trials,[3–17] have deemed coma to be a contraindication to NPPV therapy. In addition, an international consensus conference in intensive care medicine[22] proposed that severe encephalopathy (*ie*, GCS score, < 10) should be considered a contraindication to NPPV therapy. Although there is no scientific basis for this recommendation, the rationale was that coma patients are at risk for pulmonary aspiration by virtue of their depressed sensorium and blunted cough mechanism.

Some earlier studies have found that higher levels of consciousness at the start and after the first hour of therapy correlate with a response to NPPV therapy.[24] Antón et al[25] evaluated 44 episodes of COPD exacerbation in 37 patients, and found that a better state of consciousness at initiation and greater improvement after the first hour of therapy predicted a response to NPPV therapy. Brochard et al[4] have made similar observations, reporting that an improvement in encephalopathy during the first 12 h of NPPV use is associated with a response to NPPV. However, only a few reports have previously described the use of NPPV in the context of hypercapnic coma. In one study,[26] 3 of 30 patients with ARF were in comas with a GCS score of 3, 2 patients were successfully treated with NPPV, and the other patients did not respond to therapy. A second report[27] described the restoration of full consciousness in an elderly patient with hypercapnic coma after treatment with NPPV for 61 h. More recently, a 92-year-old woman with COPD who was in a hypercapnic coma (pH 7.06; $Paco_2$, 185 mm Hg, GCS score, 3) was treated with NPPV via a face mask using bilevel airway pressure ventilation (inspiratory pressure, 30 cm H_2O; expiratory pressure, 5 cm H_2O). Her GCS

score was 15 after receiving ventilation for 10 h, and she was discharged home from the hospital after 15 days.[28] In a retrospective series[29] that used the iron lung negative-pressure ventilator to treat 150 patients with coma secondary to hypercapnic respiratory failure, the mean hospital admission APACHE II score was 31, $PaCO_2$ was 112 mm Hg, and arterial pH was 7.13. Despite the severity of illness on presentation, 70% of patients avoided intubation and survived the hospitalization.

In view of these initial favorable experiences using NPPV in patients with blunted levels of consciousness, we instituted the present NPPV protocol to prospectively treat and follow-up patients with ARF that was associated with severe encephalopathy or coma. Using this protocol, we have observed few complications, with most consisting of adverse mask-related side effects (*eg*, nasal ulceration) or gastric insufflation (Table 3). The most important complications were vomiting in three patients, one of whom aspirated and required intubation despite the presence of a nasogastric tube. This experience raises questions about the effectiveness of routine nasogastric tube insertion, and, as a consequence, we no longer routinely place nasogastric tubes in these patients.

Our overall NPPV therapy response rate, measured by the avoidance of endotracheal intubation and discharge alive from the ICU, was 80% in this seriously ill patient population. The rate was highest in patients with airway obstruction and lowest in those with pneumonia or ARDS. The response rate for COPD patients in our study (86.4%) compares favorably with the range of response rates (75 to 100%) reported previously in controlled trials.[4,6–9] The reported response rates for NPPV therapy in patients with pneumonia and/or ARDS have been variable, but usually are lower than those in COPD patients.[30]

One surprise in our study was that the overall NPPV success rate was actually higher in comatose patients than in noncomatose patients (80.0% vs 70.1%, respectively; $p = 0.043$). However, this was related to the proportionately greater percentage of patients with COPD (69.5% vs 25.5%, respectively) and the lower percentage of patients with pneumonia and ARDS (8.4% vs 22.5%, respectively) in the comatose vs noncomatose groups of patients. Because of the relatively high (and comparable) success rates in the COPD subgroups (upper 80% range) and the lower success rates in the pneumonia/ARDS subgroups, this unequal distribution of subgroups favored a higher overall success rate in the comatose group. Thus, it is most accurate to conclude that success rates were comparable between the comatose and noncomatose groups. The important inference from our study is that NPPV therapy can be applied to patients with severe encephalopathy and to comatose patients (GCS scores ≤ 8) without increasing failure or mortality rates relative to noncomatose patients with similar diagnoses.

The mean APACHE II score and SAPS II among our patients were remarkably high, higher than in most previous controlled trials.[4,6–9] Only the retrospective series of coma patients who were treated in the iron lung[29] included higher APACHE II scores, and even then only slightly. The very high acuity scores in our study are explained by the advanced age of the patients, and the severity of the neurologic and gas exchange derangements. In particular, a low mean pH (7.13) contributed to the high acuity scores, and such low pH values have been associated with lower success rates in prior studies.[10,24] Nonetheless, our success rate is comparable to that reported in some prior studies and is even better than others, despite having a lower mean pH.[24] The similarity of our results and those of the study of comatose COPD patients[29] who were treated with iron lungs is remarkable (success rate, 80% vs 70%, respectively). The two studies also obtained similar results for the number of hours of ventilation that was necessary for the patient to recover consciousness, the total number of hours of ventilation, and, above all, the hospital mortality rate (26% vs 24%, respectively). One case-control study[31] of COPD patients who were treated by noninvasive ventilation obtained similar success rates with the use of iron lungs and NPPV therapy.

Both the BiPAP ST-D and VISION ventilators (Respironics) were used in the current study. Although the VISION ventilator has an oxygen blender, graphic display, inspiratory time limit, and adjustable "rise time" that the BiPAP ST-D ventilator lacks, success rates were similar between the two devices. This may be related to the comatose state of the patients, which permitted excellent synchrony without sedation and negated the synchrony-enhancing features of the VISION ventilator. Also, most of our patients did not have severe hypoxemic respiratory failure, and the few who did were treated with the VISION ventilator. Of the eight patients with pneumonia, seven were treated with the VISION ventilator, including five patients who did not respond to therapy, whereas only one of the patients was treated with the BiPAP ST-D ventilator.

The improved survival rate over the last few years, because of patient selection and severity scores, did not change over time, and we believe that this was due to the increasing experience and enhanced skills of the doctors and nurses, as well as to improvements in ventilator and mask technology. The multivariate model identified the following two factors that were

significantly related to NPPV success: an increase in the GCS 1 h after starting NPPV therapy; and a lower multiorgan failure score, as measured by the maximum SOFA index. Some prior studies[32–34] have identified age and APACHE II score as predictors of NPPV success or failure, but these were not significant predictors in our study. However, other studies[24,25,35,36] have also failed to find a significant relationship between success rate and APACHE II score. Lack of response to NPPV therapy has also been associated with a lower initial pH in some studies,[4,24] but not in all.[32] In our study, initial pH, RR, $PaCO_2$, and PaO_2/FIO_2 ratio were unrelated to the success of therapy. However, when these variables were measured 1 h posttherapy, $PaCO_2$, pH, and PaO_2/FIO_2 ratio were higher in successful cases, whereas RR was lower, which is consistent with the findings of prior studies.[3,4,34,35]

Considering that death in the ICU or within the first 24 h after transfer to a regular hospital floor constituted NPPV failure, it is not surprising that predictors of mortality overlapped with predictors of NPPV failure in our study. For example, a higher SOFA index of multiorgan dysfunction was a strong predictor of both NPPV failure and mortality, which is consistent with the findings of prior studies.[37–39] At the initiation of therapy, RR and DNI status also predicted higher mortality rates. Not surprisingly, NPPV failure also was associated with a high risk of death. ICU and hospital mortality rates of NPPV-treated comatose patients presenting with ARF were 10% and 26%, respectively, and among COPD patients they were 4.5% and 27.3%, respectively. The hospital standardized mortality rate (the ratio between the mortality rate in our population and that predicted by the SAPS II system) was very low (0.49). While acknowledging that the uncontrolled nature of our study precludes firm conclusions being drawn about the effect of NPPV on survival, we believe that the low standardized mortality rate is highly suggestive of a survival benefit that is attributable to NPPV, which most likely is related to the avoidance of the complications of intubation.

The limitations of our study include its observational design and the lack of control subjects, which weaken the conclusions that we can draw. Also, many of our patients were very ill and may have died regardless of whether NPPV was used or not. Thus, the reliance on mortality rate alone as a way of assessing the effectiveness of the technique may be misleading, In addition, it is important to emphasize that these results were obtained in a center that was highly experienced to apply NPPV therapy. The results may not be so favorable in less experienced centers.

We conclude that patients with hypercapnic coma who are otherwise good candidates for NPPV therapy have outcomes after NPPV therapy that are as good as those of similar noncomatose patients. Patients with reversible causes for their ARF, such as COPD, asthma, or cardiogenic pulmonary edema, have the best outcomes, whereas those patients with ARDS or pneumonia are less likely to respond to therapy. Based on our findings, we think that coma should no longer be considered a contraindication to NPPV therapy. Rather, appropriate candidates for the NPPV modality who present while in a coma should be offered a trial of NPPV, with the expectation that intubation and mortality can be avoided in the majority of cases.

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