Noninvasive Ventilation during Persistent Weaning Failure
A Randomized Controlled Trial

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To assess the efficacy of noninvasive ventilation (NIV) in patients with persistent weaning failure, we conducted a prospective, randomized, controlled trial in 43 mechanically ventilated patients who had failed a weaning trial for 3 consecutive days. This trial was stopped after a planned interim analysis. Patients were randomly extubated, receiving NIV (n = 21), or remained intubated following a conventional-weaning approach consisting of daily weaning attempts (n = 22). Compared with the conventional-weaning group, the noninvasive-ventilation group had shorter periods of invasive ventilation (through tracheal intubation) (9.5 ± 8.3 vs. 20.1 ± 13.1 days, p = 0.003) and intensive care unit (ICU) (14.1 ± 9.2 vs. 25.0 ± 12.5 days, p = 0.002) and hospital stays (27.8 ± 14.6 vs. 40.8 ± 21.4 days, p = 0.026), less need for tracheotomy to withdraw ventilation (1, 5% vs. 13, 59%, p < 0.001), lower incidence of nosocomial pneumonia (5, 24% vs. 13, 59%, p = 0.042) and septic shock (2, 10% vs. 9, 41%, p = 0.045), and increased ICU (19, 90% vs. 13, 59%, p = 0.045) and 90-day survival (p = 0.044). The conventional-weaning approach was an independent risk factor of decreased ICU (odds ratio: 6.6; p = 0.035) and 90-day survival (odds ratio: 3.5; p = 0.018). Earlier extubation with NIV results in shorter mechanical ventilation and length of stay, less need for tracheotomy, lower incidence of complications, and improved survival in these patients.

Keywords: mechanical ventilation; noninvasive ventilation; persistent weaning failure; respiratory failure; weaning

Invasive mechanical ventilation is associated with an increased risk of nosocomial pneumonia and mortality (1–4). Prolonged mechanical ventilation, a major risk factor for nosocomial pneumonia (5, 6), may be a consequence of persistent weaning failure (7) and is associated with an increased morbidity and mortality, especially in patients with chronic respiratory failure (8).

Noninvasive ventilation (NIV) facilitates early extubation and improves the outcome of selected patients with an exacerbation of chronic obstructive pulmonary disease (COPD) and weaning failure (9). In patients with acute-on-chronic respiratory failure, failing one single weaning attempt, the use of NIV resulted in a mild reduction of the duration of endotracheal mechanical ventilation but no improvement in outcome (10). Despite this evidence, the efficacy of NIV in patients with persistent weaning failure, a frequent clinical situation in mechanically ventilated patients with chronic respiratory disorders, has not been assessed as yet.

We postulated that in patients with persistent weaning failure, earlier extubation, taking advantage of NIV, would reduce the period of invasive ventilation as the primary endpoint variable, hence decreasing the incidence of complications associated with prolonged mechanical ventilation and improving survival. Accordingly, we conducted a prospective, randomized clinical trial to assess the efficacy of this strategy compared with the conventional-weaning approach.

Some of the results of this study have been reported previously in abstract form (11).

METHODS

(For more details, *see* the online supplement.)

Patients

A prospective, randomized controlled study was conducted in two centers. Intubated patients who met criteria to proceed in the weaning attempt (*see* criteria in the online supplement) but had failed a spontaneous breathing trial for 3 consecutive days were considered eligible for the study. The exclusion criteria were (*1*) facial or cranial trauma or surgery, (*2*) recent gastric or esophageal surgery, (*3*) tracheotomy, (*4*) active upper gastrointestinal bleeding, (*5*) excessive amount of respiratory secretions, and (*6*) lack of co-operation. The study was approved by the Ethics Committee of the two institutions, and written informed consent was obtained in all cases.

Study Design

Weaning attempts consisted of once-daily spontaneous breathing trials with a T-piece. If no signs of spontaneous breathing trial failure appeared within 2 hours (*see* criteria in the online supplement), patients were extubated and were not eligible for the study. Alternatively, if signs of spontaneous breathing trial failure appeared during this period, patients were reconnected to the ventilator. Patients in whom the spontaneous breathing trial failed during 3 consecutive days were randomly allocated, using a computer-generated table for each center either for (*1*) extubation and NIV treatment (NIV group) or (*2*) reconnection to the ventilator and once-daily weaning attempts (conventional-weaning group).

NIV. NIV (BiPAP Vision; Respironics Inc., Murrysville, PA) using the S/T mode was continuously delivered immediately after extubation, at least during the first 24 hours after extubation. Then, NIV was gradually withdrawn if patients tolerated spontaneous breathing until they could permanently sustain spontaneous breathing. A face mask was used as the first choice, but a nasal mask was optionally used if patients did not tolerate the face mask.

Conventional weaning. Patients were reconnected to the ventilator and daily spontaneous breathing trials were performed until patients could be extubated (12, 13). When needed, low doses of sedatives or opioids were used between the spontaneous breathing trials to manage anxiety or pain and to avoid fighting against the ventilator. The weaning process was interrupted—and full sedation reinstituted—if complications that significantly worsened patients' clinical conditions occurred and resumed if these complications were solved.

Criteria for reintubation and for performing tracheotomy. Reintubation criteria were predefined: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation inadequately controlled by sedation, massive aspiration, persistent inability to remove respiratory secretions, heart rate below 50/minute with loss of alertness, and hemodynamic instability without response to fluids and vasoactive drugs. To avoid reintubation, NIV was initiated in the conventional-weaning group if other minor criteria of spontaneous breathing failure occurred (14). Tracheotomy was performed if patients were unable to clear or remove their secretions or if there was prolonged mechanical ventilation without positive evolution of the weaning process (15).

Data Collection and Definitions

Data from patients were recorded and patients' follow-up was extended to 90 days after randomization. Successful weaning was defined as the ability to sustain spontaneous breathing at least for 3 consecutive days. Extubation failure was defined as reintubation within 72 hours after extubation.

Clinical diagnosis of nosocomial pneumonia (16), septic shock (17), and multiple organ failure (18) were defined by criteria published previously (*see* criteria in the online supplement).

Statistical Analysis

Sample size estimation. The primary end-point variable was to decrease the duration of invasive ventilation, defined as positive pressure ventilation delivered through orotracheal intubation or tracheotomy, in the NIV group. Initial calculations revealed a required sample size of 42 subjects in each group, with the duration of invasive ventilation to be reduced by 6 days (9). We planned an interim analysis after inclusion of 50% of the estimated patients, using an α curtailment ($p < 0.005$) to correct the analysis.

Comparisons between the two groups. Qualitative or categorical variables were compared with the χ^2 test or Fisher's exact test. Quantitative continuous variables were compared using the unpaired Student's *t* test or the Mann–Whitney nonparametric test. The Kaplan–Meier estimate-of-survival curve was used to determine the cumulative probability of successful weaning and 90-day survival; curves between the two groups were compared using the log-rank test. The level of significance was set in all tests at 0.05 (all two-tailed).

Analyses of survival. Univariate and multivariate analyses of intensive care unit (ICU) survival were performed using logistic regression with a conditional stepwise forward model.

Univariate analyses of 90-day survival were performed with the Kaplan–Meier estimate-of-survival curve. Multivariate analyses of this type of survival were performed with Cox proportional hazard regression. To correct collinearity in all multivariate analyses, a conditional stepwise forward model was chosen ($p_{in} < 0.05$). Adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with survival.

RESULTS

Patients

The planned interim analysis after inclusion of 50% of the estimated patients revealed a significant reduction of the duration of invasive ventilation in the NIV group ($p = 0.003$). Therefore, the study was stopped, in such a way that 43 consecutive patients

were included during a 24-month period (Figure 1): 21 patients were allocated to the NIV group and 22 patients to the conventional-weaning group. General clinical characteristics of patients at randomization are summarized in Table 1. Thirty-three (77%) patients had chronic pulmonary disorders, including chronic obstructive pulmonary disease (n = 25), *sequelae* of pulmonary tuberculosis (n = 5), severe persistent asthma (n = 2), and widespread bronchiectasis (n = 1). Out of those, 19 were intubated due to an episode of exacerbation and 14 due to other causes. The remaining 10 patients (5 in each group) did not have chronic pulmonary disorders.

The physiologic parameters of patients on the day of randomization are summarized in Table 2. No significant differences during mechanical ventilation or during the spontaneous breathing trial between the two groups were shown in the breathing pattern, heart rate, blood pressure, and arterial blood gases.

Weaning Results and Length of Stay

Weaning results and length of stay are summarized in Table 3. Compared with the conventional-weaning group, the mean duration of invasive ventilation was reduced by 11 days ($p = 0.003$), the total period of ventilatory support by 9 days ($p = 0.012$), the ICU stay by 11 days ($p = 0.002$), and the hospital stay by 13 days ($p = 0.026$) in the NIV group. NIV was delivered in this group for a period of 3.5 ± 1.9 days (range, 1–9 days) and 43 ± 30 hours (range, 5–113 hours). The inspiratory and expiratory positive airways pressure ranged from 10 to 20 cm H_2O and from 4 to 5 cm H_2O, respectively. Four patients were ventilated with nasal masks because they tolerated nasal masks better than face masks. In the conventional-weaning group, the predominant modes of ventilatory support used were assist-control ventilation (n = 11 patients), pressure-support ventilation (n = 9), or both modalities (n = 2).

The probability of weaning success was significantly higher in the NIV group ($p = 0.002$), as shown in Figure 2. There were no significant differences in the incidence of reintubation between the two groups. In the conventional-weaning group, the use of NIV within 72 hours after extubation avoided reintubation in one patient. One patient from the NIV group and 13 patients from the conventional-weaning group needed tracheotomy to facilitate weaning, with differences that were significant ($p < 0.001$). In the whole population, tracheotomy was performed after 18 ± 4 days (range, 11–23 days) of mechanical ventilation.

Complications

The number of patients with serious complications diagnosed after entry into the study, as shown in Table 4, was higher in the conventional-weaning group ($p = 0.004$); and more specifically, the incidence of nosocomial pneumonia ($p = 0.042$) and of septic shock ($p = 0.045$) was higher in the conventional-weaning group. The incidence rate of nosocomial pneumonia was 29.4 and 25.1 cases per 1,000 invasive-ventilation days in the conventional-weaning and the NIV groups, respectively. Eight patients from the conventional-weaning group were never extubated because of the complications mentioned previously. These complications worsened their clinical condition and interrupted the weaning process. Mild to moderate nasal bridge ulceration occurred in six (29%) patients, respiratory secretions were difficult to eliminate in two (10%) patients, and gastric distension occurred in one (5%) patient from the NIV group.

Analyses of Survival

Compared with patients weaned conventionally, survival in the ICU ($p = 0.045$) was higher in the NIV group (Table 3). Likewise, the cumulative survival probability after 90 days of randomization,
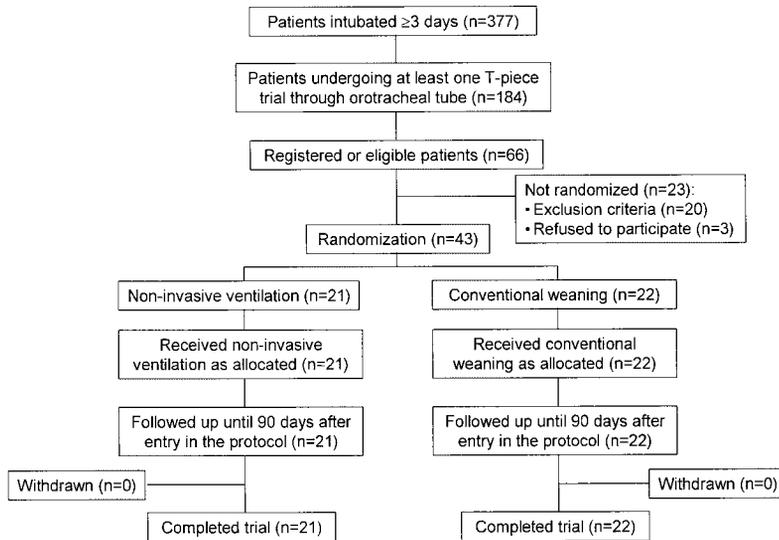
Figure 1. Trial profile.

as shown in Figure 3, was higher in the latter group (p = 0.044). The causes of death within 90 days of randomization are summarized in Table 3.

The univariate and multivariate analyses of survival are summarized in Table 5. Following a conventional-weaning approach was the only independent factor significantly associated with decreased ICU survival (p = 0.035). Likewise, the conventional-weaning approach (p = 0.018) together with advanced age ($>$ 70 years) (23 patients [76 $\pm$ 4 years] vs. 20 patients [65 $\pm$ 6 years]) and the development of hypercapnia (Pa_{CO_2} $>$ 45 mm Hg) (25 patients, Pa_{CO_2} 62 $\pm$ 11 mm Hg vs. 18 patients, Pa_{CO_2} 39 $\pm$ 4 mm Hg) during the spontaneous breathing trial at entry into the study (p = 0.003 both) were independent factors significantly associated with decreased 90-day survival.

DISCUSSION

In patients with persistent weaning failure, earlier extubation with NIV decreased the duration of ventilatory support, length of stay, incidence of nosocomial pneumonia and septic shock, and improved survival, compared with patients following a conventional-weaning approach.

The strongest evidence that NIV prevents endotracheal intubation and reduces complications and mortality is shown in patients with severe exacerbations of chronic obstructive pulmonary disease with hypercapnic respiratory failure and respiratory acidosis (14, 19–21). Moreover, in these patients with severe community-acquired pneumonia, NIV helped to avoid intubation and to improve survival (22). By contrast, significant debate still exists concerning the precise indications for NIV in patients

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS AT ENTRY INTO THE STUDY

	NIV Group (n = 21)	Conventional-Weaning Group (n = 22)	p Value
Age, yr	70.3 $\pm$ 7.5	71.0 $\pm$ 7.2	0.767
Sex, M/F	13/8	17/5	0.444
Current or former smoker, n (%)	13 (62)	17 (77)	0.444
Current or former alcohol abuse, n (%)	4 (19)	2 (9)	0.412
APACHE-II on admission	17.8 $\pm$ 4.6	18.5 $\pm$ 3.9	0.589
Duration of ICU stay, d	7.3 $\pm$ 2.8	7.5 $\pm$ 3.9	0.801
Duration of mechanical ventilation, d	7.1 $\pm$ 2.8	7.0 $\pm$ 3.4	0.959
Number of comorbidities per patient	1.8 $\pm$ 0.9	1.8 $\pm$ 0.9	0.894
White blood cells, $\times 10^9$/L	12.1 $\pm$ 4.3	12.4 $\pm$ 3.0	0.794
Hematocrit, L/L	0.38 $\pm$ 0.07	0.35 $\pm$ 0.05	0.170
Patients with chronic pulmonary disorders, n (%)	16 (76)	17 (77)	1.000
Causes of mechanical ventilation, n			0.545
Exacerbation of chronic pulmonary disorders	10	9	
Congestive heart failure	4	5	
Community-acquired pneumonia	2	4	
Hospital-acquired pneumonia	1	1	
Postoperative respiratory failure	–	2	
Acute lung injury	1	1	
Thoracic trauma	1	–	
Hemoptisis	1	–	
Cardiac arrest	1	–	

Definition of abbreviations: APACHE-II = acute physiology and chronic health evaluation-II score; ICU = intensive care unit; NIV = noninvasive ventilation.
Values are means $\pm$ SD.

TABLE 2. PHYSIOLOGIC PARAMETERS OF PATIENTS AT ENTRY INTO THE STUDY

	Mechanical Ventilation			Spontaneous Breathing Trial		
	NIV Group (n = 21)	Conventional-Weaning Group (n = 22)	p Value	NIV Group (n = 21)	Conventional-Weaning Group (n = 22)	p Value
f, min^{-1}	19.2 ± 5.6	17.4 ± 5.2	0.300	31.0 ± 5.2	28.7 ± 8.0	0.276
V$_T$, L	0.46 ± 0.13	0.50 ± 0.11	0.271	0.27 ± 0.08	0.32 ± 0.12	0.184
f/V$_T$ ratio	–	–	–	122 ± 42	108 ± 58	0.378
Heart rate, min^{-1}	97 ± 16	97 ± 12	0.840	109 ± 15	108 ± 17	0.791
Mean blood pressure, mm Hg	89 ± 13	85 ± 14	0.312	104 ± 20	97 ± 20	0.255
Arterial pH	7.42 ± 0.05	7.41 ± 0.05	0.740	7.37 ± 0.06	7.38 ± 0.07	0.708
Pa$_{CO_2}$, mm Hg	45.6 ± 10.6	47.0 ± 6.7	0.609	53.6 ± 16.2	51.9 ± 12.2	0.688
Pa$_{O_2}$, mm Hg	95 ± 30	86 ± 18	0.207	66 ± 21	70 ± 17	0.510
Pa$_{O_2}$/Fi$_{O_2}$	259 ± 81	226 ± 58	0.129	172 ± 57	171 ± 44	0.948

Definition of abbreviations: f/V$_T$ = respiratory frequency to V$_T$ ratio; NIV = noninvasive ventilation.

Values are means ± SD.

p Values denote differences among the two groups in all cases.

with acute nonhypercapnic respiratory failure. One study has demonstrated that NIV is an adequate alternative means to conventional invasive ventilation in such patients (23), and more recently, that it prevents endotracheal intubation in selected groups of patients with cardiogenic pulmonary edema (24), immunosuppression (25, 26), and acute respiratory failure after lung resection (27).

There is less evidence supporting the efficacy of NIV during weaning. Shortened weaning and avoidance of reintubation are promising uses of NIV (28). The application of NIV during weaning was performed in a selected group of patients with chronic obstructive pulmonary disease who failed a spontaneous breathing trial after early recovery from an acute exacerbation (9). In this randomized controlled trial, NIV facilitated extubation within 48 hours after intubation, decreasing the period of ventilatory support, the ICU stay, and the incidence of nosocomial

pneumonia, as well as increasing survival. Another randomized controlled trial in patients with acute-on-chronic respiratory failure after a single weaning trial failure (10) showed that NIV facilitated a modest reduction of the invasive-ventilation period, without significant changes in total duration of ventilation, ICU stay, incidence of complications, and survival. Conversely, a recent study showed no benefit from the addition of NIV to standard medical therapy in patients who develop postextubation respiratory distress (29).

The efficacy of NIV in patients with persistent weaning failure had not been assessed yet in randomized fashion. Persistent weaning failure is not an infrequent clinical situation in mechanically ventilated patients, especially those with chronic respiratory disorders. It is associated with prolonged mechanical ventilation (7) and increased morbidity and mortality (8), as shown by the more prolonged duration of mechanical ventilation and length

TABLE 3. WEANING RESULTS, LENGTH OF STAY, OUTCOME VARIABLES, AND CAUSES OF DEATH FOR THE NONINVASIVE VENTILATION AND THE CONVENTIONAL-WEANING GROUPS

	NIV Group (n = 21)	Conventional-Weaning Group (n = 22)	p Value
Duration of invasive ventilation, d	9.5 ± 8.3	20.1 ± 13.1	0.003
Total period of ventilatory support*, d	11.4 ± 8.0	20.1 ± 13.1	0.012
ICU stay, d	14.1 ± 9.2	25.0 ± 12.5	0.002
Hospital stay, d	27.8 ± 14.6	40.8 ± 21.4	0.026
Reintubation, n (%)	3 (14)	6 (27)	0.457
Main causes of reintubation, n			
Severe persistent hypoxemia	1	3	
Severe dyspnea	–	2	
Inability to manage secretions	2	–	
Hemodynamic instability	–	1	
Tracheotomy, n (%)	1 (5)	13 (59)	<0.001
ICU survival, n (%)	19 (90)	13 (59)	0.045
Causes of death within 90 d after entry in the study			
Septic shock/MOF	1	9	
Refractory hypoxemia	1	2	
Cardiac arrest	2	1	
Pneumothorax	–	1	
Stroke	1	–	
Pulmonary embolism	1	–	

Definition of abbreviations: ICU = intensive care unit; MOF = multiple organ failure; NIV = noninvasive ventilation.

Values are means ± SD.

*Computation of the total period of ventilatory support in the NIV group was done by the addition of the number of days when both noninvasive and invasive mechanical ventilation were received. In reintubated patients from both groups, the days without ventilatory support between extubation and reintubation were not computed as ventilation days.
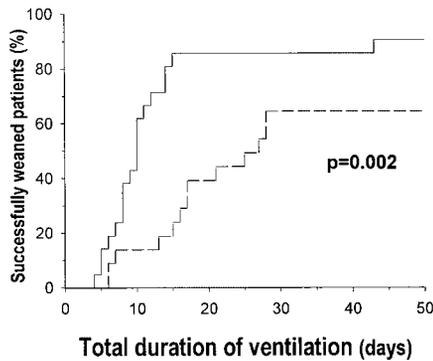
Figure 2. Kaplan–Meier curves for patients successfully weaned from mechanical ventilation, as defined. The first of the three days without ventilatory support, either invasive (*dashed lines*) or noninvasive (*solid lines*), was considered the end of the weaning process. The probability of weaning success was significantly higher for patients from the NIV group (*solid lines*) than in the conventional-weaning group (*dashed lines*) (log-rank test). Time denotes the period from intubation to final withdrawal of ventilatory support.

Figure 3. Kaplan–Meier curves for survivor patients within 90 days after entry into the protocol. In the overall population, the cumulative survival probability was significantly higher in the noninvasive (*solid lines*) ventilation group than in the conventional-weaning group (*dashed lines*) (log-rank test). Time denotes days after patients were entered in the study.

of stay in patients from the conventional-weaning group of the present study, compared with previous trials (9, 10). Accordingly, all measures to reduce the weaning period are welcome.
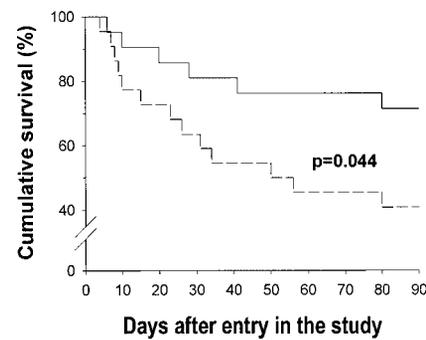
The present trial stopped after the planned interim analysis showed a significant reduction of the duration of invasive ventilation in the NIV group, in accordance with the predefined stopping rule. We chose this period instead of total duration of ventilation because intubation, and not ventilatory support, is the main determinant of increased risk of complications. This decision was reinforced by the decreased incidence of serious complications in this group, the need for tracheotomy, and the ICU stay, which were all related with poor outcome. The excellent tolerance of NIV without any sedation in this subset of patients and the potential hazards derived from the need for sedation in patients still intubated in the conventional-weaning group (30) were additional reasons for stopping the trial.

Because patients with unsuccessful weaning are likely to develop a rapid and shallow breathing pattern (31), the ability of NIV to improve hypoxemia and hypercapnia by correcting such an abnormal breathing pattern (32) might explain the benefits of NIV in these patients. Despite earlier extubation in the NIV group, the incidence of reintubation, a potentially hazardous complication associated with increased morbidity and mortality (33, 34), was approximately half of the conventional-weaning group, although these differences were not significant. Moreover, the use

of NIV resulted in a great reduction for the need to perform a tracheotomy to facilitate weaning. The presence of a tracheotomy for prolonged periods, even when patients are already breathing spontaneously, increases the period of artificial airway, and, therefore, susceptibility of patients to further acquire respiratory infections. In addition, these patients often need nasogastric intubation for enteral feeding. This is associated with increased incidence of gastroesophageal reflux and aspiration to the airways (35–37), a major risk factor for nosocomial pneumonia (5).

The time course of delivery may be relevant in the clinical efficacy of NIV. Similar to the study of Nava and coworkers (9), NIV in the present study was continuously delivered immediately after extubation for as much time as possible. Both studies showed marked improvement of outcome variables in patients who received NIV. By contrast, Girault and coworkers (10) used intermittent periods of NIV separated by scheduled periods of spontaneous breathing after extubation. This latter study did not show any significant differences in the incidence of complications and outcome among patients with and without NIV.

Prolonged invasive ventilation, as shown in the conventional-weaning group, is associated with a high incidence of nosocomial pneumonia (5, 6). It is of interest to note that the reported episodes of nosocomial pneumonia were late-onset (> 5 days of mechanical ventilation) (38). These types of pneumonia have higher mortality compared with early-onset ones. Consequently, the use of NIV to shorten the duration of invasive ventilation and to prevent late-onset pneumonias is of great benefit for the patient in terms of morbidity and mortality. In addition, and similar to other series of ventilated patients (9, 39, 40), the most frequent cause of death in this study was septic shock/multiple organ failure due to nosocomial pneumonia. A recent publication showed a slightly higher ICU mortality rate (above 50%) in patients ventilated for 20 days for clinical conditions similar to patients from our trial, not substantially different than our control group (41%) (41). Therefore, shortening such a prolonged period of invasive ventilation with the approach used in the NIV group without further complications in the majority of patients may explain the improved survival in this group. Moreover, the use of NIV was the only independent factor at the time of weaning to predict an increased ICU survival. Following this weaning approach may result in an important reduction in hospital costs as well because of the marked decrease of morbidity and the length of ICU and hospital stays. In addition, the use of NIV was also associated with improved outcome through a 90-day follow-up period. Other factors, such as ad-

TABLE 4. SERIOUS COMPLICATIONS DIAGNOSED IN THE INTENSIVE CARE UNIT AFTER ENTRY INTO THE STUDY

	NIV Group (n = 21)	Conventional-Weaning Group (n = 22)	p Value
Total number of patients	5	16	0.004
Nosocomial pneumonia	5	13	0.042
Catheter-related sepsis	–	2	–
Sacrum-infected ulcer	–	1	–
Urinary tract infection	–	1	–
Chest wall abscess	–	1	–
Gastrointestinal bleeding	1	–	–
Pneumothorax	–	1	–
Septic shock	2	9	0.045

Definition of abbreviation: NIV = noninvasive ventilation.

TABLE 5. UNIVARIATE AND MULTIVARIATE ANALYSES OF INTENSIVE CARE UNIT AND 90-DAY SURVIVAL

	Adjusted Odds Ratio	95% CI	p Value	Adjusted Odds Ratio	95% CI	p Value
Decreased ICU survival	Univariate analysis			Multivariate analysis		
Conventional-weaning approach	6.6	1.2–35.6	0.029	6.6	1.1–38.8	0.035
Age > 70 yr	5.8	1.1–31.3	0.041	–	–	NS
Decreased 90-d survival	Univariate analysis			Multivariate analysis		
Conventional-weaning approach	–	–	0.044	3.5	1.2–9.6	0.018
Age > 70 yr	–	–	0.012	5.1	1.7–15.0	0.003
Pa_{CO_2} during spontaneous breathing > 45 mm Hg	–	–	0.018	5.8	1.8–18.7	0.003

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; NS = not significant.

vanced age and the development of hypercapnia during the spontaneous breathing trial, were good predictors of decreased 90-day survival.

To our knowledge, this is the first study to identify the development of hypercapnia during a failed spontaneous breathing trial as a marker of poor prognosis. This factor appears to be an accurate indicator of clinical deterioration after recovery of a life-threatening episode of respiratory failure. The detection of hypercapnia during persistently failed weaning attempts should alert physicians to start measures, such as noninvasive ventilatory support, to avert the poor outcome associated with this arterial blood gas finding.

Two potential limitations have to be taken into account when analyzing the differences between the two groups. First, although not specifically monitored, patients from the conventional-weaning group received more sedation than those in the NIV group; this limitation is inherent to the design of the study and difficult to solve in future trials because intubated patients often need more sedation than patients receiving NIV (20). Second, the two groups followed different weaning regimens after inclusion in the study, i.e., the gradual withdrawal of NIV versus once-daily T-piece trials until patients tolerated spontaneous breathing. Another potential limitation of this type of open clinical trials is the difficulty for a correct blinding of the investigators that might lead to possible bias. Despite the fact that we predefined the criteria for all relevant interventions and clinical decisions to be made by the attending physicians, as well as the outcome variables, this bias could not be entirely controlled.

In conclusion, NIV is effective to shorten the period of invasive ventilation in patients with persistent weaning failure, and, in consequence, to decrease the incidence of nosocomially acquired infections, mortality, and other outcome parameters such as length of ICU and hospital stays.

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