Early Noninvasive Ventilation Averts Extubation Failure in Patients at Risk
A Randomized Trial

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Rationale: Respiratory failure after extubation and reintubation is associated with increased morbidity and mortality.

Objectives: To assess the efficacy of noninvasive ventilation in averting respiratory failure after extubation in patients at increased risk.

Methods: A prospective randomized controlled trial was conducted in 162 mechanically ventilated patients who tolerated a spontaneous breathing trial after recovery from the acute episode but had increased risk for respiratory failure after extubation. Patients were randomly allocated after extubation to receive noninvasive ventilation for 24 h (n = 79), or conventional management with oxygen therapy (control group, n = 83).

Measurements and Main Results: The primary end-point variable was the decrease in respiratory failure after extubation. In the noninvasive ventilation group, respiratory failure after extubation was less frequent (13, 16 vs. 27, 33%; p = 0.029) and the intensive care unit mortality was lower (2, 3 versus 12, 14%; p = 0.015). However, 90-d survival did not change significantly between groups. Separate analyses of patients without and with hypercapnia (arterial CO_2 tension greater than 45 mm Hg) during the spontaneous breathing trial showed that noninvasive ventilation improved intensive care unit mortality (0 vs. 4, 18%; p = 0.035) and 90-d survival (p = 0.006) in hypercapnic patients only; of them, 98% had chronic respiratory disorders.

Conclusions: The early use of noninvasive ventilation averted respiratory failure after extubation and decreased intensive care unit mortality among patients at increased risk. The beneficial effect of noninvasive ventilation in improving survival of hypercapnic patients with chronic respiratory disorders warrants a new prospective clinical trial.

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

Reintubation, which occurs in 6 to 23% cases within 48 to 72 h after planned extubation (1–3), is a relevant consequence of respiratory failure after extubation (4). The pathophysiology of respiratory failure after extubation includes upper airway obstruction, inadequate cough, excess respiratory secretions, encephalopathy, and cardiac dysfunction (3, 5–7). Among others, neurologic impairment, older age, severity of illness, cardiac failure, longer duration of ventilation before extubation, anemia,

and the use of continuous sedation have been identified as risk factors for extubation failure (1, 3, 8). Although the need for reintubation may be a marker of increased severity of illness, this is an independent risk factor for nosocomial pneumonia (9), and mortality and increased hospital stay (1). Therefore, in addition to an accurate prediction of extubation outcome, strategies for preventing the development of respiratory failure after extubation and subsequent reintubation are needed.

Noninvasive ventilation (NIV) was considered a promising therapy after extubation failure to avoid reintubation in an international consensus conference (10); this information was based on the findings of physiologic (11) and nonrandomized clinical studies (12). However, two randomized clinical trials have not shown benefits from NIV in avoiding reintubation in patients who have developed respiratory failure after extubation (4, 13). NIV has even been associated with higher mortality rates as compared with patients treated according to standard medical therapy (4), predominantly because the mortality rate among the patients who required reintubation and received NIV was higher than that of the reintubated patients from the control group. The time from extubation to reintubation, an independent risk factor for increased mortality in reintubated patients (14), was longer in patients who received NIV in this study (4).

NIV does not seem to be beneficial in avoiding reintubation when these patients have developed respiratory failure. However, a strategy based on the early use of NIV during the initial periods after extubation to avert respiratory failure after extubation in patients at risk for this complication needs to be tested. Therefore, we assessed the efficacy of this strategy compared with a conventional management in patients who underwent a planned extubation.

Some of the results of this study have been previously reported in the form of an abstract (15).

METHODS

See the online supplement for more details.

Patients

A prospective, randomized controlled study was conducted in two intensive care units (ICUs). Patients intubated for 48 h or more, who tolerated a spontaneous breathing trial after recovery from their disease, were considered eligible for the study if they had at least one of the following risk factors for respiratory failure after extubation: (*1*) age greater than 65 yr, (*2*) cardiac failure as the cause of intubation, or (*3*) increased severity, assessed by an Acute Physiology and Chronic Health Evaluation (APACHE)-II (16) score exceeding 12 on the day of extubation (1). Patients with tracheotomy were not screened for the study. Exclusion criteria were as follows: (*1*) facial or cranial trauma or surgery, (*2*) recent gastric or esophageal surgery, (*3*) active upper gastrointestinal bleeding, (*4*) excessive amount of respiratory secretions, (*5*) lack of cooperation, and (*6*) do-not-resuscitate order or any decision to limit therapeutic effort in the ICU. The Ethics Committee Hospital Clinic approved the study and written, informed consent was obtained.

Study Design

If no signs of spontaneous breathing failure appeared after 30 to 120 min of a T-piece trial (17), patients were extubated and randomly allocated, using opaque sealed envelopes for each ICU, either to (*1*) those who received NIV (NIV group) or (*2*) those who underwent conventional management (control group). Except for the specific interventions of this trial, patients were managed according to the clinical protocols of our institution.

NIV (BiPAP Vision; Respironics, Inc., Murraysville, PA) was continuously delivered immediately after extubation for a scheduled period of 24 h after extubation. Afterward, NIV was withdrawn and oxygen was administered by Venturi mask.

In the control group, patients received oxygen by Venturi mask after extubation.

Criteria for Reintubation and Definition of Respiratory Failure after Extubation

Immediate reintubation criteria were predefined, when any of the following major clinical events were present: 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 $50\ \text{min}^{-1}$ with loss of alertness, and severe hemodynamic instability without response to fluids and vasoactive drugs (17).

In addition to reintubation criteria, respiratory failure after extubation was defined as the presence and persistence, within 72 h of extubation, of at least two of the following: (*1*) respiratory acidosis (arterial pH of 7.35 or less with Pa_{CO_2} of 45 mm Hg or more); (*2*) arterial O_2 saturation by pulse oximetry less than 90% or Pa_{O_2} less than 60 mm Hg at an inspired O_2 fraction of 0.5 or more; (*3*) respiratory frequency exceeding $35\ \text{min}^{-1}$; (*4*) decreased consciousness, agitation, or diaphoresis; and (*5*) clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing, such as the use of respiratory accessory muscles, paradoxic motion of the abdomen, or retraction of the intercostal spaces (4).

Rescue therapy with NIV was used in patients from the two groups in the case of respiratory failure after extubation without the need for immediate reintubation. In the NIV group, rescue therapy consisted of reinstitution or continuation of NIV after 24 h of extubation. In addition to meeting criteria for immediate reintubation, when these patients showed deterioration of blood gases (arterial pH, Pa_{CO_2}, and Pa_{O_2}) or

tachypnea despite the use of NIV under optimal conditions, NIV was not prolonged for more than 4 h and then they were reintubated.

Data Collection and Definitions

All relevant data from the medical records and bedside flow charts of patients were reviewed at entry and at the end of the protocol, and patient follow-up was extended to 90 d after randomization. The causes of respiratory failure after extubation were assigned on the basis of adapted published definitions (14).

Diagnoses of hospital-acquired pneumonia (18, 19), purulent tracheobronchitis (20), septic shock (21), and multiple organ failure (22) were made on the basis of published criteria. Other relevant complications were recorded.

Statistical Analysis

Sample size estimation. The primary end-point variable was the decrease in respiratory failure after extubation in patients receiving NIV. We expected a 35% rate of respiratory failure after extubation in the control group, based on the incidence of respiratory failure after extubation during the preceding year in patients from our center meeting eligibility criteria, and a 20% absolute reduction in the NIV group. Initial calculations revealed a minimal sample size of 162 subjects.

Comparisons between the two groups. Qualitative or categorical variables were compared by χ^2 or Fisher's exact test, when appropriate. Quantitative continuous variables were compared by unpaired Student *t* test or Mann-Whitney nonparametric test, when appropriate. The Kaplan-Meier estimate-of-survival curve was used to determine the cumulative 90-d survival probability; survival curves between the two groups were compared by log-rank test. The analyses were in intention-to-treat, and the level of significance was set at 0.05.

Because hypercapnia ($Pa_{CO_2} > 45$ mm Hg) during the spontaneous breathing trial was identified as an independent predictor of decreased survival of patients with persistent weaning failure (17), we performed separate analyses of patients with and without hypercapnia.

RESULTS

Patients

We studied 162 consecutive patients from October 2001 to February 2004 (Figure 1): 79 were allocated to the NIV group and 83 to the control group. General clinical characteristics and

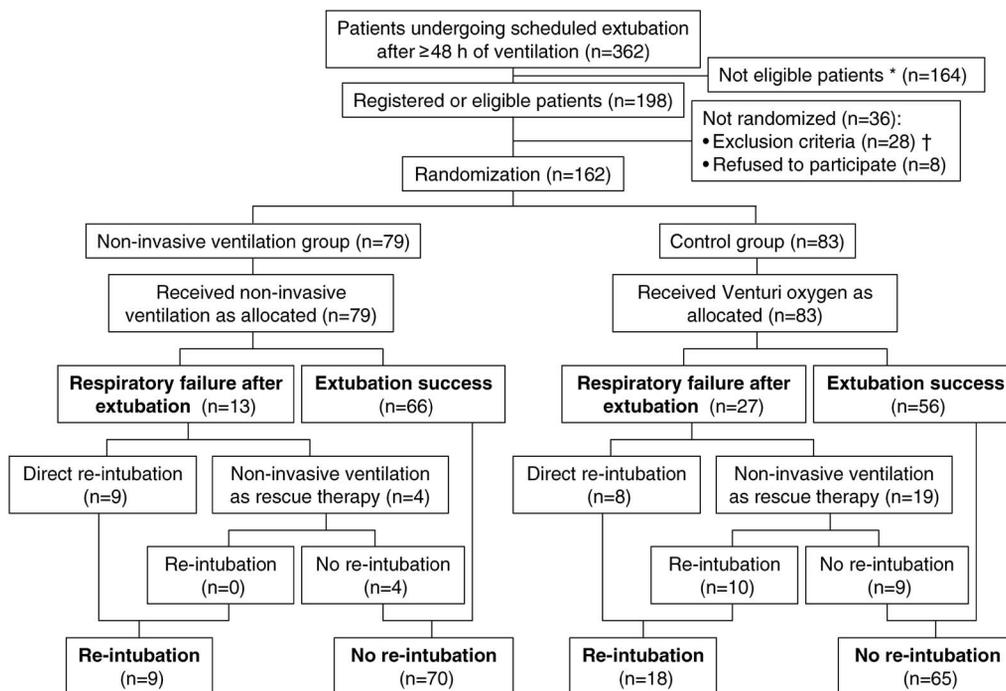*Figure 1.* Trial profile and primary outcomes of patients. *Patients deemed ineligible were those without risk factors for respiratory failure after extubation. †The main reasons for excluding patients were lack of cooperation (n = 18), previous decision to limit the therapeutic effort in the intensive care unit (n = 5), excessive amount of respiratory secretions (n = 3), and recent gastric (n = 1) and cranial (n = 1) surgery.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS ON ENTRY INTO STUDY

	NIV Group ($n = 79$)	Control Group ($n = 83$)	p Value
Age, yr	72 ± 10	70 ± 11	0.18
Sex, M/F	56/23	59/24	> 0.99
APACHE II on admission	22 ± 5	20 ± 6	0.11
APACHE II on entry into study	14 ± 3	13 ± 3	0.067
Duration of mechanical ventilation, d	6 ± 4	7 ± 5	0.65
Risk factors for respiratory failure after extubation on entry into study			
Age $\geqslant$ 65 yr, n (%)	67 (85%)	62 (75%)	0.16
APACHE II $\geqslant$ 12, n (%)	62 (78%)	56 (67%)	0.16
Cardiac failure at admission, n (%)	15 (19%)	11 (13%)	0.44
Underlying diseases			
Chronic respiratory disorders, n (%)*	41 (52%)	41 (49%)	0.87
Chronic heart disorders, n (%)†	26 (33%)	27 (33%)	> 0.99
Immunosuppression, n (%)‡	9 (11%)	8 (10%)	0.91
Diabetes mellitus, n (%)	18 (23%)	14 (17%)	0.45
Liver cirrhosis, n (%)	2 (3%)	5 (6%)	0.44
Neoplasm, n (%)	10 (13%)	8 (10%)	0.72
Chronic renal failure, n (%)	6 (8%)	8 (10%)	0.86
Causes of mechanical ventilation			0.72
Exacerbation of chronic respiratory disorders, n*	24	25	
Pneumonia, n	16	19	
Congestive heart failure, n	15	11	
Neurologic disease, n	8	10	
Sepsis, n	8	6	
Postoperative respiratory failure, n	5	6	
Other, n	3	6	

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II score; F = female; ICU = intensive care unit; M = male; NIV = noninvasive ventilation.

Plus–minus values represent means ± SD.

* Chronic respiratory disorders include chronic obstructive pulmonary disease, chronic bronchitis associated with dyspnea and current or former history of smoking in the absence of pulmonary function testing, sequelae of pulmonary tuberculosis, chest wall deformity or obesity associated with a restrictive ventilatory disorder, and bronchiectasis (*see* Table E1 in the online supplement for more details on these patients).

† Chronic heart disorders include coronary artery disease, hypertensive or valvular heart diseases, and dilated myocardial disease of any cause.

‡ Immunosuppression includes neutropenia after chemotherapy or bone marrow transplantation, drug-induced immunosuppression in solid organ transplantation or as a result of corticosteroid or cytotoxic therapy, and HIV–related disorders.

physiologic parameters of patients on entry into the study are summarized in Tables 1 and 2. The groups did not differ significantly at baseline.

NIV was delivered for a period of 19 ± 8 h (mean ± SD) in this group. The levels of inspiratory and expiratory positive airway pressure were 14 ± 2 and 5 ± 1 cm H_2O, respectively.

Respiratory failure after extubation, reintubation, length of stay, and complications. Compared with the control group, respiratory failure after extubation was less frequent (p = 0.029) in

the NIV group (*see* Table 3.). The main reduction of respiratory failure occurred within 1 d of extubation (Figure 2), whereas in the next 2 d, the incidence of respiratory failure was similar between groups. Thus, the mean time from extubation to respiratory failure was longer in the NIV group (p = 0.022). In patients who developed respiratory failure after extubation but did not require immediate reintubation, NIV as rescue therapy resulted in avoiding reintubation in 4 of 4 patients from the NIV group and 9 of 19 patients from the control group; the remaining 10

TABLE 2. PHYSIOLOGIC PARAMETERS OF PATIENTS ON ENTRY INTO STUDY

	Mechanical Ventilation			Spontaneous Breathing Trial		
	NIV Group ($n = 79$)	Control Group ($n = 83$)	p Value*	NIV Group ($n = 79$)	Control Group ($n = 83$)	p Value*
Respiratory frequency, min^{-1}	17 ± 4	17 ± 5	0.74	26 ± 7	25 ± 6	0.27
f/VT ratio	—	—	—	78 ± 39	72 ± 33	0.29
Heart rate, min^{-1}	82 ± 18	80 ± 22	0.53	90 ± 16	93 ± 17	0.38
Systolic blood pressure, mm Hg	133 ± 21	138 ± 24	0.20	154 ± 24	152 ± 26	0.54
Arterial pH	7.45 ± 0.06	7.46 ± 0.05	0.75	7.43 ± 0.05	7.44 ± 0.06	0.22
Pa_{CO_2}, mm Hg	41 ± 7	40 ± 7	0.45	44 ± 10	42 ± 9	0.15
Pa_{O_2}, mm Hg	104 ± 27	102 ± 21	0.68	88 ± 23	89 ± 22	0.68
$Pa_{O_2}/F_{I_{O_2}}$	278 ± 95	276 ± 94	0.88	227 ± 70	231 ± 65	0.67

Definition of abbreviations: $F_{I_{O_2}}$ = inspired fraction of oxygen; f/VT = respiratory frequency to tidal volume ratio; NIV = noninvasive ventilation.

Plus–minus values represent means ± SD.

* p values denote differences between the two groups in all cases.

TABLE 3. OUTCOME VARIABLES, LENGTH OF STAY, AND CAUSES OF DEATH FOR NONINVASIVE VENTILATION AND CONTROL GROUPS

	NIV Group (*n* = 79)	Control Group (*n* = 83)	p Value
Respiratory failure after extubation, n (%)	13 (16%)	27 (33%)	0.029
Time elapsed from extubation to respiratory failure after extubation, h after extubation	41 ± 19	25 ± 21	0.022
Reintubation, n (%)	9 (11%)	18 (22%)	0.12
Main causes of respiratory failure after extubation, n*			
Respiratory failure			
With hypercapnia	6	14	
Without hypercapnia	2	8	
Aspiration, excess respiratory secretions	1	3	
Cardiac failure	3	0	
Upper airway obstruction	1	1	
Encephalopathy	0	1	
ICU stay, d	11 ± 8	13 ± 11	0.14
Hospital stay, d	30 ± 23	29 ± 18	0.65
ICU mortality, n (%)	2 (3%)	12 (14%)	0.015
Hospital mortality, n (%)	13 (16%)	19 (23%)	0.41
Causes of death within 90 d of entry into study			
Shock/multiple organ failure	6	13	
Respiratory failure[†]	2	6	
Cardiac failure/cardiogenic shock	3	1	
Cardiac arrest	2	0	
Other	3	1	
Not determined[‡]	2	3	

Definition of abbreviations: ICU = intensive care unit; NIV = noninvasive ventilation.

Plus–minus values represent means ± SD.

* The causes of respiratory failure after extubation were assigned on the basis of published definitions (14).

[†] Death after progressive hypoxemia and/or hypercapnia without other major organ system failures.

[‡] For some patients who died after hospital discharge, the precise cause of death could not be determined.

patients from the control group needed reintubation. Hence, the reintubation rate was not significantly lower in the NIV group.

The ICU and hospital length of stay were similar among patients from the two groups.

The incidence of ICU-acquired infections for the NIV and the control groups were 18 (23%) and 27 (33%), respectively (p = 0.23). The most frequently recorded infections were pneumonia and purulent tracheobronchitis. Specific complications associated with NIV included nasal bridge damage in five patients (6%) and gastric distension in one patient (1%).

Analyses of Survival

Mortality in the ICU (p = 0.015) was lower in the NIV group (Table 3), but hospital mortality and 90-d survival (Figure 3) were not significantly different among patients from both groups in the overall population. The causes of death within 90 d of randomization are shown in Table 3.

In patients with hypercapnia during the spontaneous breathing trial, ICU mortality (p = 0.035) and hospital mortality (p = 0.003; Table 4), as well as 90-d survival (p = 0.006; Figure 3),

significantly improved in the NIV group. By contrast, for patients without hypercapnia, there were no changes in mortality or survival between the NIV and control groups.

The 90-d mortality rates for patients with and without hypercapnia (15, 31 vs. 27, 24%, respectively) were not significantly different. However, death due to respiratory failure was more frequent in hypercapnic patients (6, 12 vs. 2, 2%; p = 0.010). The remaining causes of death had no significantly different incidence among hypercapnic and nonhypercapnic patients.

In comparing patients who developed early and late respiratory failure after extubation (< or > 24 h after extubation, respectively), there was no trend to a different profile of mortality between these two subsets of patients.

DISCUSSION

NIV reduced the incidence of respiratory failure after extubation in patients at increased risk for this complication, confirmed by the higher rate of this complication in the control group, 33%, compared with a 25% rate in similar patients from a previous
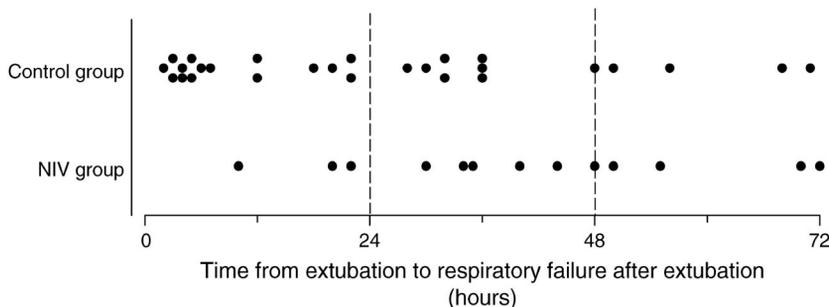

Figure 2. Time elapsed from extubation to the development of respiratory failure after extubation for the noninvasive ventilation (NIV) group and the control group.
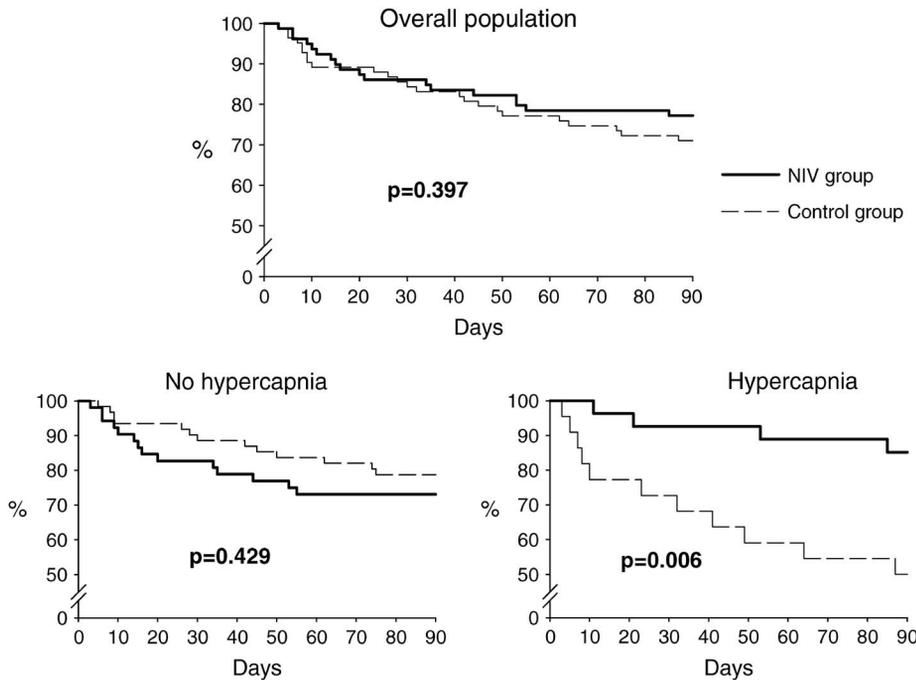
Figure 3. Kaplan-Meier survival curves for patients within 90 d of entry into the protocol. *Top*: Survival of the overall population. *Bottom*: Survival of the subset of patients without hypercapnia (*left*) and of the subset of patients with hypercapnia (*right*) who underwent the spontaneous breathing trial. The cumulative survival probability was significantly higher in the NIV group only in the subset of patients with hypercapnia (log-rank test). Time denotes days after patients were entered into the study.

study (4). Moreover, nine patients from the control group and four from the NIV group who did not require immediate reintubation escaped from reintubation after NIV was used as rescue therapy; thus, the differences between the two groups in terms of reintubation rate failed to be significant. Although reintubation after rescue therapy with NIV occurred later than direct reintubation, the time from extubation to reintubation did not influence mortality. Moreover, none of the 13 patients who escaped from reintubation after rescue therapy with NIV died in the hospital; this supports the use of NIV under these conditions.

The efficacy of NIV in averting respiratory failure after extubation contrasts with the lack of benefits previously reported in the treatment of patients who have developed this complication (4, 13). Several reasons may explain these differences. First, whereas the other studies applied NIV after patients had developed respiratory failure, we applied NIV immediately after extubation. Because longer time from extubation to reintubation is associated with worse outcome (14), and the delay in reintubation correlates with worse survival rates in patients who receive NIV (4), the early application of NIV seems crucial to avoid respiratory failure after extubation and, consequently, reintubation. Second, a significantly higher proportion of patients with chronic respiratory disorders, 51%, was included in the present study, whereas the previous trials reported that 10 to 11% of the enrolled patients had a diagnosis of chronic obstructive pulmonary disease (COPD) only (4, 13). Patients with COPD were even excluded from one trial (13) because evidence in the literature supported the beneficial effect of NIV for them, and therefore these authors always used NIV when patients with COPD presented respiratory failure after extubation. Third, we used in this study a ventilator specifically designed for NIV, as we did in previous trials (17, 23). This ventilator controls the levels of inspired oxygen, allows proper maintenance of positive pressure levels by means of effective compensation for leaks and a real-time assessment of mask pressure, and has a sensitive and rapid response flow-by trigger (24). By contrast, other studies used a ventilator with less performance (13) or did not choose a specific ventilator for the trial (4). Fourth, the long-time experience of our health care team involved in using NIV may have influenced the successful use of this technique, as reported (25). As in previous trials (17, 26), NIV was continuously applied after extubation. This is a key methodologic point in our study,

TABLE 4. OUTCOME VARIABLES AMONG PATIENTS WITH AND WITHOUT HYPERCAPNIA DURING SPONTANEOUS BREATHING TRIAL

	Patients with Hypercapnia			Patients without Hypercapnia		
	NIV Group (*n = 27*)	Control Group (*n = 22*)	p Value	NIV Group (*n = 52*)	Control Group (*n = 61*)	p Value
Pa_{CO_2} during spontaneous breathing trial, mm Hg	55 ± 7	53 ± 5	0.36	38 ± 5	37 ± 5	0.61
Patients with chronic respiratory disorders, n (%)*	27 (100%)	21 (95%)	—	14 (27%)	20 (33%)	—
Respiratory failure after extubation, n (%)	4 (15%)	9 (41%)	0.083	9 (17%)	18 (30%)	0.20
Reintubation, n (%)	3 (11%)	6 (27%)	0.27	6 (12%)	12 (20%)	0.36
ICU mortality, n (%)	0 (0%)	4 (18%)	0.035	2 (4%)	8 (13%)	0.11
Hospital mortality, n (%)	1 (4%)	9 (41%)	0.003	12 (23%)	10 (16%)	0.51

Definition of abbreviations: ICU = intensive care unit; NIV = noninvasive ventilation.
Plus–minus values represent means ± SD.
* Chronic respiratory disorders are defined in Table 1.

because the intermittent use of NIV for longer periods resulted in limited clinical efficacy (27).

Patients with severe hypercapnic respiratory failure secondary to exacerbations of COPD are among the best responders to NIV (28–30), even when they present other concomitant acute diseases such as community-acquired pneumonia (31) or cardiogenic pulmonary edema (32). We also found NIV to be more effective among patients with hypercapnia during the spontaneous breathing trial and chronic respiratory disorders. By contrast, the benefits of NIV in patients mainly without chronic respiratory disorders or hypercapnia are demonstrated only in the presence of life-threatening hypoxemia (23, 33), or in selected patients with cardiogenic pulmonary edema (34), and immunosuppression (35, 36).

Survival improved with the use of NIV in hypercapnic patients only; 98% of them had chronic respiratory disorders. Patients from the control group with hypercapnia had an important mortality, as shown in Table 4 and Figure 3. Respiratory failure was the most frequent cause of death in these patients. Because the benefits of NIV in averting respiratory failure occurred within the first day after extubation (Figure 2), the prevention of fatal respiratory failure during this period may have averted such poor outcome. By contrast, no differences in survival between the NIV group and the control group were shown in patients without hypercapnia; 30% of them had chronic respiratory disorders only. In these patients, shock/multiple organ failure was the most frequent cause of death and therefore we can expect NIV to be less effective in improving survival.

The association of hypercapnia during a spontaneous breathing trial and decreased survival has already been described in intubated patients with persistent weaning failure (17); in this study, 88% of hypercapnic patients had chronic respiratory disorders. Hypercapnia appears to be an accurate indicator of clinical deterioration after recovery from a life-threatening episode of respiratory failure. Alternatively, this may also reflect the presence of advanced chronic respiratory disease, as shown by the severe deterioration of their lung function. The detection of hypercapnia during weaning attempts should alert physicians to start measures, such as NIV after extubation, aimed at averting the poor outcome associated with this finding, regardless of whether the patients tolerate spontaneous breathing or not. This hypothesis should be tested in a future prospective, randomized, well-powered trial in this specific population. By contrast, there is no rationale for the systematic use of NIV after extubation because this strategy did not avoid reintubation in an unselected population of patients (37). In this study there was a great proportion of unplanned extubation, the main determinant of poor outcome.

Several limitations of this study must be taken into account. First, there is difficulty in achieving correct blinding of the investigators, attending physicians, and patients in this type of open clinical trial, which might lead to possible bias. Despite the fact that we predefined the criteria for all relevant interventions, clinical decisions, and outcome variables, this bias could not be entirely controlled. Second, a significant number of patients was not included because of lack of cooperation; this is inherent in this type of controlled clinical trial involving severely ill, awake patients, where several features need to be controlled. It does not exclude that these patients can benefit from receiving NIV in clinical practice, when such a degree of cooperation is not needed. Third, rescue therapy with NIV may have influenced the different outcomes between both groups, because more patients from the control group escaped reintubation.

In conclusion, the early use of NIV averted respiratory failure after extubation in patients at increased risk. The beneficial effects of NIV on survival appear to be restricted to patients with chronic respiratory disorders and hypercapnia during the spontaneous breathing trial. Extrapolation of these findings to all patients with hypercapnia warrants a new prospective clinical trial.

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