

ORIGINAL ARTICLE

Noninvasive Positive-Pressure Ventilation for Respiratory Failure after Extubation

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ABSTRACT

BACKGROUND

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The need for reintubation after extubation and discontinuation of mechanical ventilation is not uncommon and is associated with increased mortality. Noninvasive positive-pressure ventilation has been suggested as a promising therapy for patients with respiratory failure after extubation, but a single-center, randomized trial recently found no benefit. We conducted a multicenter, randomized trial to evaluate the effect of noninvasive positive-pressure ventilation on mortality in this clinical setting.

METHODS

Patients in 37 centers in eight countries who were electively extubated after at least 48 hours of mechanical ventilation and who had respiratory failure within the subsequent 48 hours were randomly assigned to either noninvasive positive-pressure ventilation by face mask or standard medical therapy.

RESULTS

A total of 221 patients with similar baseline characteristics had been randomly assigned to either noninvasive ventilation (114 patients) or standard medical therapy (107 patients) when the trial was stopped early, after an interim analysis. There was no difference between the noninvasive-ventilation group and the standard-therapy group in the need for reintubation (rate of reintubation, 48 percent in both groups; relative risk in the noninvasive-ventilation group, 0.99; 95 percent confidence interval, 0.76 to 1.30). The rate of death in the intensive care unit was higher in the noninvasive-ventilation group than in the standard-therapy group (25 percent vs. 14 percent; relative risk, 1.78; 95 percent confidence interval, 1.03 to 3.20; $P=0.048$), and the median time from respiratory failure to reintubation was longer in the noninvasive-ventilation group (12 hours vs. 2 hours 30 minutes, $P=0.02$).

CONCLUSIONS

Noninvasive positive-pressure ventilation does not prevent the need for reintubation or reduce mortality in unselected patients who have respiratory failure after extubation.

THE PROCESS OF DISCONTINUING mechanical ventilation must balance the risk of complications due to unnecessary delays in extubation with the risk of complications due to premature discontinuation and the need for reintubation.^{1,2} Evidence-based guidelines recommend a trial of spontaneous breathing to determine, in any given patient, whether mechanical ventilation can be successfully discontinued³; with this approach, the documented need for reintubation ranges from 13 to 19 percent.⁴⁻⁷

Patients who require reintubation have been noted to have a significantly higher mortality rate than those who are successfully extubated on the first attempt.^{8,9} The reasons for their increased risk of death may include both difficulties encountered during the reintubation period and the development of additional ventilator-related complications, such as pneumonia.¹⁰ The need for reintubation may also be a marker of increased severity of illness, but after adjustment for coexisting conditions and severity of illness, extubation failure is still an independent predictor of death.⁸ This suggests that, at least to some extent, the increased mortality seen in these patients may be reduced by treatments aimed at reducing either the need for reintubation or its subsequent complications.

Noninvasive positive-pressure ventilation has been deemed by a recent international consensus conference to be a promising therapy after failure of extubation.¹¹ This conference, which considered the findings of physiological and nonrandomized studies,^{12,13} called for randomized, controlled trials with clinical end points to examine the value of noninvasive ventilation as a means of averting the need for reintubation.¹¹ Subsequently, the results of one randomized, controlled trial, conducted while our study was being planned, were published. Keenan et al.¹⁴ reported no difference in either the rate of reintubation or mortality with the use of noninvasive positive-pressure ventilation as compared with standard medical therapy in patients who had respiratory failure within 48 hours after extubation. Their study was a relatively small, single-center trial that evaluated the rate of reintubation as a primary end point. The extent to which its results can be generalized has been questioned.¹⁵

We performed a large, multicenter, international study to determine whether noninvasive ventilation, as compared with standard medical therapy, would reduce the rate of death in the intensive care unit

among patients who have respiratory failure within 48 hours after elective extubation. We hypothesized that a reduction in mortality would be mediated through a decrease in the need for reintubation.

METHODS

The study protocol was approved by the institutional ethics review board at each of the participating centers (see the Appendix). Written informed consent was obtained from the patients or their surrogates at the time of their enrollment in the at-risk cohort.

SELECTION OF PATIENTS

Between November 1999 and May 2002, consecutive patients in the intensive care units of 37 centers in eight countries were enrolled in a cohort of patients at risk of requiring reintubation (the at-risk cohort). To be enrolled, the patients had to be older than 18 years of age, had to have undergone mechanical ventilation for more than 48 hours, and had to have been successfully extubated after the completion of a trial of spontaneous breathing. Exclusion criteria were the presence of a tracheostomy and the absence of informed consent.

In all the participating intensive care units, the following procedures were in place for the discontinuation of mechanical ventilation. Discontinuation was considered appropriate when all of the following criteria were met: the underlying cause of acute respiratory failure had improved; the patient was alert and able to communicate; the patient's core temperature was less than 38°C; there was no need for vasoactive drugs, with the exception of dopamine at doses lower than 5 µg per kilogram of body weight per minute; and the partial pressure of oxygen was greater than 60 mm Hg while the patient was breathing an inspired fraction of oxygen of 0.40 or less with a positive end-expiratory pressure of 5 cm of water or less. Discontinuation of mechanical ventilation was performed by means of one of the following techniques: a trial of spontaneous breathing (a single daily trial or multiple daily trials of spontaneous ventilation with the use of a T tube, continuous positive airway pressure, flow-by, or pressure support of 5 to 8 cm of water) for up to 120 minutes or a gradual reduction of pressure support in steps of 2 cm of water every 2 hours until a pressure of 7 cm of water was reached. Patients who successfully tolerated a trial of spontaneous

breathing (according to published criteria)²⁻⁴ were subsequently extubated.

After extubation, patients were observed for 48 hours for the onset of respiratory failure, as defined by the presence of two or more of the following: respiratory acidosis (defined as an arterial pH below 7.35 with a partial pressure of arterial carbon dioxide greater than 45 mm Hg), clinical signs suggestive of respiratory-muscle fatigue or increased respiratory effort (i.e., use of accessory muscles, intercostal indrawing, or paradoxical motion of the abdomen), a respiratory rate greater than 25 breaths per minute for two consecutive hours, and hypoxemia (defined as an arterial oxygen saturation of less than 90 percent or a partial pressure of arterial oxygen of less than 80 mm Hg with a fraction of inspired oxygen greater than 0.50).

Patients who met at least two of these criteria were randomly assigned to either standard medical therapy or noninvasive ventilation. The assignments were made with the use of a random-number table and opaque, sealed, numbered envelopes. Randomization was performed with variable block sizes and was stratified according to the study center and the presence or absence of chronic obstructive pulmonary disease.

STANDARD MEDICAL THERAPY

Patients assigned to the standard-therapy group received supplemental oxygen, respiratory physiotherapy, bronchodilators, and any other therapies as directed by the attending physician. These patients could be reintubated or crossed over to receive noninvasive ventilation if they met the prespecified criteria for reintubation (described below). In this group, the application of noninvasive ventilation was considered to indicate that standard medical therapy had failed.

NONINVASIVE VENTILATION

Patients assigned to the noninvasive-ventilation group received ventilation through a full facial mask from a ventilator located in the intensive care unit. Before ventilation was begun, the head of the patient's bed was positioned at a 45-degree angle. The initial ventilator mode was pressure support, set to achieve a tidal volume of more than 5 ml per kilogram of body weight and a respiratory rate of less than 25 breaths per minute. The fraction of inspired oxygen and the positive end-expiratory pressure were titrated to maintain the arterial oxygen saturation above 90 percent. The ventilator settings were

subsequently adjusted as needed for the patient's comfort (notably, if there was a decrease in the respiratory rate and heart rate), while an adequate arterial oxygen saturation and an arterial pH above 7.35 were maintained. The facial skin was assessed every four hours to prevent damage from the tightly fitting face mask used to deliver the ventilation.

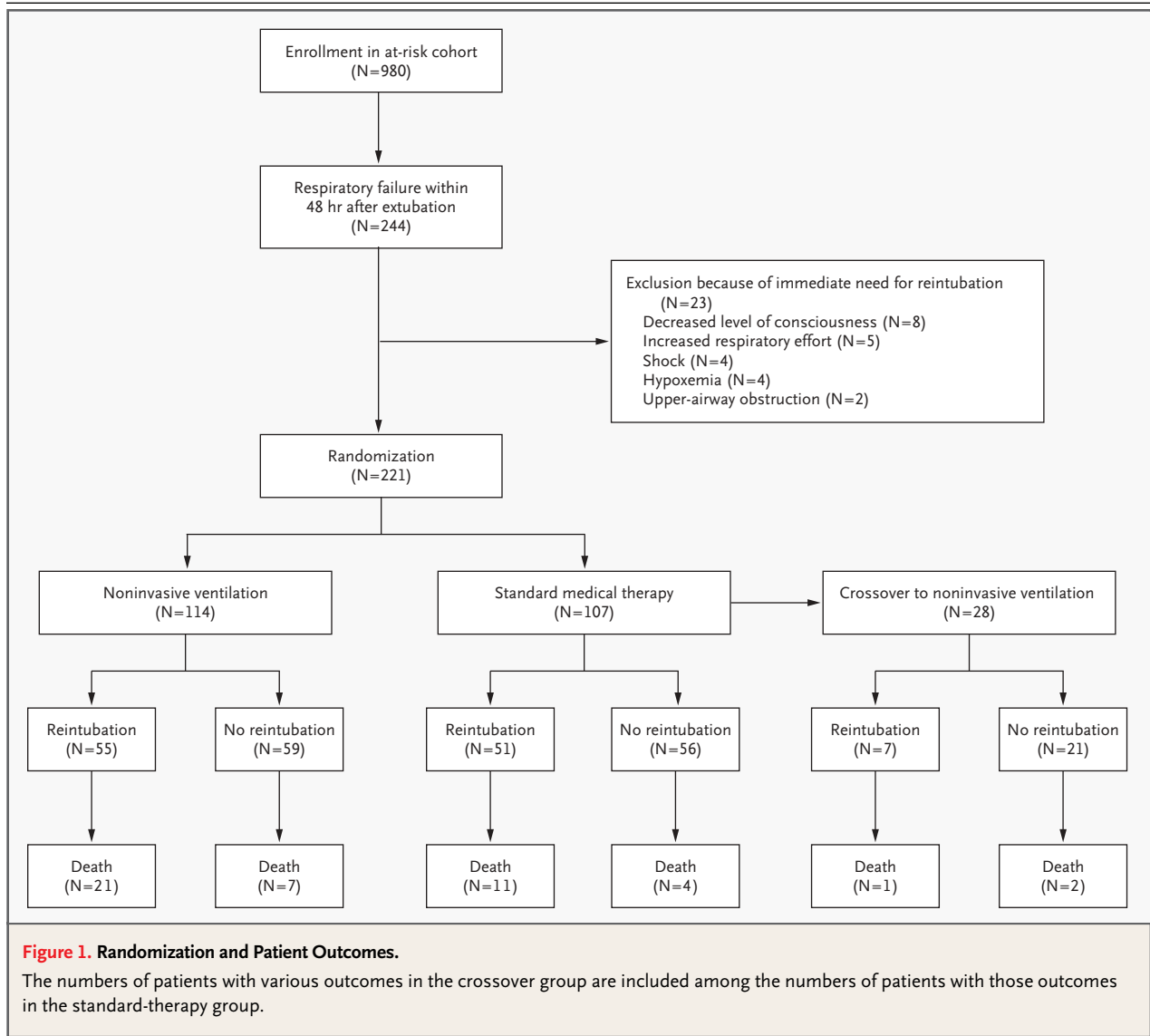
The patients in this group were encouraged to use noninvasive ventilation continuously for four-hour periods. The face mask could be removed, however, for 15-to-20-minute periods to allow the patient to drink fluids or receive nursing care. The decision regarding when to discontinue noninvasive ventilation was left to the attending physician. If respiratory failure subsequently developed, however, noninvasive ventilation was restarted.

CRITERIA FOR REINTUBATION

In both study groups, patients were reintubated if they met at least one of the following criteria, as judged after they had undergone the assigned treatment for at least 1 hour: lack of improvement in the pH or in the partial pressure of carbon dioxide; changes in mental status, rendering the patient unable to tolerate noninvasive ventilation; a decrease in the oxygen saturation to less than 85 percent, despite the use of a high fraction of inspired oxygen; lack of improvement in signs of respiratory-muscle fatigue; hypotension, with a systolic blood pressure below 90 mm Hg for more than 30 minutes despite adequate volume challenge, the use of vasopressors, or both; or copious secretions that could not be adequately cleared or that were associated with acidosis, hypoxemia, or changes in mental status. The final decision to reintubate was made by the treating physician, who recorded the single most relevant reason for reintubation from the list of six possible reasons.

DATA COLLECTION

At baseline, demographic data, the Simplified Acute Physiology Score II (which can range from 0 to 163 points, with higher scores indicating greater impairment), the reason for mechanical ventilation, the duration of mechanical ventilation before extubation, and the method of discontinuation of mechanical ventilation were recorded. Before extubation, the spontaneous tidal volume, the maximal negative inspiratory pressure, and the respiratory rate were measured, and the rapid shallow breathing index (the ratio of the respiratory rate [expressed in breaths per minute] to tidal volume [expressed in



liters], where a value greater than 105 breaths per minute per liter is associated with an increased risk of reintubation) was calculated. At the time of randomization, the respiratory rate, heart rate, arterial blood gas values, and oxygen saturation were recorded.

If needed, the time and reason for reintubation were recorded. Every patient was followed until discharge from the intensive care unit. The length of stay in the intensive care unit and the vital status at the time of discharge were recorded.

STATISTICAL ANALYSIS

We calculated that 194 patients would be required in each group to allow detection of a 13 percent ab-

solute reduction in the risk of death with the use of noninvasive ventilation (relative to a mortality rate of 33 percent in controls⁵) with a type I error of 5 percent and a power of 80 percent. One interim analysis by an independent data-monitoring board was planned after 200 patients had been recruited. The interim analysis was based on a comparison of the mortality in the two treatment groups with the use of a normal approximation for a two-sided test, according to the following rules: first, if noninvasive ventilation was associated with a reduction in mortality, the P value needed to stop the trial should be less than 0.029 (Pocock's value for one interim analysis)¹⁶; and second, if noninvasive ventilation was associated with an increase in mortality, the

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Non-invasive Ventilation (N=114)	Standard Medical Therapy (N=107)	P Value
Age — yr	61±17	58±19	0.25
Female sex — no. (%)	47 (41)	47 (44)	0.68
Simplified Acute Physiology Score II on admission†	37±13	36±10	0.77
Reason for initiation of mechanical ventilation			0.65
Acute respiratory failure — no. (%)			
Pneumonia	28 (25)	20 (19)	
Postoperative respiratory failure	20 (18)	23 (21)	
Sepsis	13 (11)	11 (10)	
Trauma	11 (10)	7 (7)	
Cardiac failure	8 (7)	12 (11)	
Acute respiratory distress syndrome	4 (4)	8 (7)	
Other	12 (11)	10 (9)	
Acute-on-chronic respiratory failure — no. (%)			
Chronic obstructive pulmonary disease	14 (12)	9 (8)	
Asthma	1 (1)	3 (3)	
Neuromuscular disease — no. (%)	3 (3)	4 (4)	

* Plus-minus values are means ±SD.

† The Simplified Acute Physiology Score II can range from 0 to 163 points. A higher score indicates greater impairment.

P value needed to stop the trial should be less than 0.05 (Pocock's recommended value).¹⁶ In the interim analysis, the observed mortality rate in the non-invasive-ventilation group was higher than that in the standard-therapy group, and the P value was less than 0.05 (P=0.048); the trial was therefore stopped according to the second rule. The analysis was performed on an intention-to-treat basis.

Continuous variables are presented as means ±SD or as medians and interquartile ranges. Comparison of continuous variables between the two groups was conducted with the use of Student's t-test for variables with a normal distribution and with the use of the Mann-Whitney U test for variables with a non-normal distribution. Results with respect to categorical variables are presented as proportions with 95 percent confidence intervals and were analyzed with the use of chi-square tests, except when small samples required the use of Fisher's exact test. All reported P values are two-sided.

RESULTS

A total of 980 patients who had been electively extubated after receiving ventilation for more than 48 hours were enrolled in the at-risk cohort. Respiratory failure developed within 48 hours after extubation in 244 of them (25 percent; 95 percent confidence interval, 22 to 28 percent). Twenty-three patients (four of whom died in the intensive care unit) did not undergo randomization because their clinical condition necessitated urgent reintubation. Therefore, 221 patients were randomly assigned to a study group — 114 to receive noninvasive ventilation and 107 to receive standard medical therapy (Fig. 1). The groups did not differ significantly at baseline, at the time of extubation, or at the time of randomization (Tables 1, 2, and 3).

PRIMARY OUTCOME

Mortality from all causes in the intensive care unit was higher in the noninvasive-ventilation group than in the standard-therapy group: 28 of the patients assigned to noninvasive ventilation died (25 percent; 95 percent confidence interval, 17 to 34 percent), as compared with 15 of those assigned to standard medical therapy (14 percent; 95 percent confidence interval, 8 to 23 percent; P=0.048). The absolute difference in mortality was thus 11 percentage points (95 percent confidence interval, 0 to 21 percentage points). This difference corresponds to a relative risk of death from all causes of 1.78 (95 percent confidence interval, 1.03 to 3.20) and a number needed to harm of 9 (95 percent confidence interval, 4.5 to 100) associated with noninvasive ventilation.

This difference appeared to be due to differences in the rate of death among the patients who required reintubation. Of the 55 patients in the noninvasive-ventilation group who required reintubation, 21 died (38 percent; 95 percent confidence interval, 26 to 52 percent); in comparison, 11 of the 51 patients in the standard-therapy group who required reintubation died (22 percent; 95 percent confidence interval, 12 to 36 percent; P=0.06).

SECONDARY OUTCOMES

There was no difference in the rate of reintubation between the two groups: reintubation was necessary in 55 of the patients assigned to noninvasive ventilation (48 percent; 95 percent confidence interval, 38 to 57 percent) and 51 of those assigned to stan-

dard medical therapy (48 percent; 95 percent confidence interval, 39 to 58 percent). The reasons for reintubation were similar in the two groups (Table 4). However, the interval between the development of respiratory failure and reintubation was significantly longer in the noninvasive-ventilation group (median, 12 hours; interquartile range, 2 hours 10 minutes to 28 hours) than in the standard-therapy group (median, 2 hours 30 minutes; interquartile range, 45 minutes to 16 hours 30 minutes; $P=0.02$).

In a post hoc analysis of the 23 patients with chronic obstructive pulmonary disease who were included in the study, we observed that the rate of reintubation was lower among those who had been assigned to noninvasive ventilation (7 of 14 [50 percent]) than among those who had been assigned to standard therapy (6 of 9 [67 percent], $P=0.67$), but the sample was too small to allow us to draw meaningful conclusions about this subgroup. Similarly, in a post hoc examination of the data from the patients who had respiratory acidosis after extubation, there was no significant difference between the study groups in the rate of reintubation, which was 52 percent (12 of 23 patients) in the noninvasive-ventilation group and 35 percent (6 of 17 patients) in the standard-therapy group ($P=0.29$).

The difference between the groups in the length of stay in the intensive care unit was also not significant. The median time was 18 days (interquartile range, 11 to 30) in the noninvasive-ventilation group and 18 days (interquartile range, 11 to 26) in the standard-therapy group ($P=0.59$).

Of the 114 patients assigned to noninvasive ventilation, 5 did not tolerate the procedure, and 2 of these 5 patients were reintubated. Of the 107 patients assigned to standard medical therapy, 28 (26 percent) received noninvasive ventilation as rescue therapy; of these 28 patients, 7 (25 percent; 95 percent confidence interval, 11 to 45 percent) subsequently required reintubation, and 3 died (Fig. 1).

DISCUSSION

The main finding of this study is that noninvasive ventilation did not reduce mortality or the need for reintubation among patients receiving mechanical ventilation who had respiratory failure after extubation. The mortality rate tended to be higher among the patients assigned to noninvasive ventilation than among those assigned to standard medical therapy, and the interval from the development of respiratory failure to reintubation was significantly long-

Table 2. Characteristics of the Patients at the Time of Extubation, According to Study Group.*

Characteristic	Non-invasive Ventilation (N=114)	Standard Medical Therapy (N=107)	P Value
Duration of mechanical ventilation — days			0.67
Median	7	8	
Interquartile range	4–12	4–13	
Tidal volume — ml/kg	6±2	6±2	0.76
Maximum inspiratory pressure — cm of water	33±15	32±15	0.72
Respiratory rate — breaths/min	24±7	23±7	0.20
Rapid shallow breathing index — breaths/min/liter†	62±31	58±30	0.33
Method of withdrawal from mechanical ventilation — no. (%)			0.99
Single daily trial of spontaneous breathing	61 (54)	54 (50)	
Multiple daily trials of spontaneous breathing	19 (17)	19 (18)	
Gradual reduction of pressure support	29 (25)	28 (26)	
Other	5 (4)	6 (6)	

* Plus-minus values are means ±SD.

† The rapid shallow breathing index is the ratio of the respiratory rate (expressed in breaths per minute) to the tidal volume (expressed in liters). A value greater than 105 breaths per minute per liter is associated with an increased risk of reintubation.

Table 3. Characteristics of the Patients at the Time of Randomization, According to Study Group.*

Characteristic	Non-invasive Ventilation (N=114)	Standard Medical Therapy (N=107)	P Value
Interval between extubation and respiratory failure (hr)			0.90
Median	9	9	
Interquartile range	3–21	2–21	
Respiratory rate (breaths/min)	29±7	29±6	0.70
Heart rate (beats/min)	98±24	95±24	0.36
pH	7.39±0.09	7.39±0.08	0.48
Partial pressure of arterial carbon dioxide (mm Hg)	47±18	45±16	0.37
Partial pressure of arterial oxygen (mm Hg)	73±29	79±29	0.11
Oxygen saturation (%)	93±6	93±5	0.88

* Plus-minus values are means ±SD.

er with noninvasive ventilation than with standard therapy.

Since the first report, in the late 1980s, of the use of noninvasive ventilation instead of intubation

Table 4. Reasons for Reintubation, as Defined in the Protocol Guidelines, According to Study Group.

Reason	Non-invasive Ventilation (N=55)	Standard Medical Therapy (N=51)	P Value
	no. (%)		
Lack of improvement in signs of muscle fatigue	25 (45)	23 (45)	0.97
Hypoxemia	9 (16)	15 (29)	0.11
Copious secretions	5 (9)	6 (12)	0.65
Lack of improvement in pH or partial pressure of carbon dioxide	8 (15)	3 (6)	0.13
Changes in mental status	4 (7)	2 (4)	0.45
Hypotension	4 (7)	2 (4)	0.45

in patients with acute respiratory failure,¹⁷ this technique has been used in a number of clinical situations. The majority of studies examining noninvasive ventilation have assessed its role in averting the need for primary endotracheal intubation in patients with acute respiratory failure.¹⁸⁻²² When the results of these studies were examined together in a recent meta-analysis, they showed that noninvasive ventilation is effective in reducing morbidity and mortality in patients with acute-on-chronic respiratory failure but that the benefit in patients with hypoxemic respiratory failure is less clear.²³ The use of noninvasive ventilation to avert the need for reintubation in patients with respiratory failure after extubation has been less extensively studied. Until very recently, the published literature addressing this question consisted entirely of physiological case series and nonrandomized studies.^{12,13,24-26} One randomized, controlled trial examining the use of noninvasive positive-pressure ventilation in patients with respiratory failure after extubation was conducted while we were planning this study and was recently published.¹⁴ In that trial, Keenan and colleagues enrolled 81 patients in a single-center study and, as in the current study, found that the use of noninvasive ventilation did not significantly alter the need for reintubation. These authors did not find differences between patients assigned to noninvasive ventilation and those assigned to standard therapy in the rate of death either in the intensive care unit or in the hospital overall, but their study was powered only to detect large differences in the rates of reintubation.¹⁴

There may be several reasons why noninvasive

ventilation was ineffective in preventing the need for reintubation in our study. First, the success of noninvasive ventilation could be dependent on the experience of the health care team using the technique. All the centers participating in this study, however, had incorporated noninvasive ventilation into their routine clinical practices at least one year before the start of the study. In addition, the findings in the study by Keenan et al.,¹⁴ in which a one-year training period was undertaken before the start of the trial, were similar to ours. Second, the timing of the initiation of noninvasive ventilation could be important. We chose to start noninvasive positive-pressure ventilation when respiratory failure first developed. The only trial of noninvasive positive-pressure ventilation after extubation in which the procedure was begun early, before the development of signs of respiratory failure, also failed to show positive results.²⁶ Finally, the composition of the study population may influence the results. It has been consistently shown that patients with chronic obstructive pulmonary disease benefit from noninvasive ventilation.²³ Only approximately 10 percent of our patients had chronic obstructive pulmonary disease (a proportion consistent with that reported in previous observational studies),^{27,28} and thus there may be a beneficial effect in these patients that was not detected in our study.

An important observation from our study was that the rate of death in the intensive care unit appeared to be greater among patients assigned to noninvasive ventilation than among those assigned to standard therapy. In a recent observational study conducted by our group, we found that patients with acute respiratory failure who were intubated after having first received noninvasive ventilation had a higher mortality rate than those who were intubated without having received noninvasive ventilation (48 percent vs. 31 percent, $P=0.01$).²⁸ In the current trial, the interval between the onset of respiratory failure and reintubation was significantly longer in the noninvasive-ventilation group than in the standard-therapy group. It is possible that this delay in reintubation was the reason for the significant increase in the risk of death in the former group, through a number of mechanisms such as cardiac ischemia, increased respiratory muscle fatigue, aspiration pneumonitis, and complications of emergency intubation.

We conclude that noninvasive ventilation is not effective in averting the need for reintubation in un-

selected patients in whom respiratory failure develops after extubation. In addition, noninvasive positive-pressure ventilation does not improve survival and may in fact be harmful. Although selected patients in specialized centers may benefit from this therapy, specific hypotheses need to be tested prospectively.

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APPENDIX

The following investigators participated in the study: *Argentina* — S. Bauque and S. Giannasi (Hospital Italiano de Buenos Aires), L. Bettini and A.R. Diez (Hospital Provincial del Centenario de Rosario), H.S. Canales (Hospital Interzonal General de Agudos General San Martín de la Plata de Mar del Plata), M.F. Costa and H. Solar (Hospital Profesor Posadas de Haedo), P.M. Desmery and A. Gómez (Sanatorio Mitre de Buenos Aires), P. Gómez and O. Yunk (Hospital Español de Buenos Aires), M. Grill and W. Vázquez (Hospital Español de Mendoza), E. Turchetto (Hospital Privado de la Comunidad de Mar del Plata), and R. Valentín (Centro de Estudios Médicos e Investigaciones Clínicas de Buenos Aires); *Brazil* — I.M. de Oliveira Rezende (Hospital Universitario São José, Belo Horizonte); *Colombia* — B. Gil (Clínica Medellín de Medellín), M. Granados (Fundación Valle de Lily de Cali); A. Guerra (Hospital General de Medellín and Clínica Soma de Medellín), and F. Molina (Clínica Universitaria Bolivariana de Medellín); *Saudi Arabia* — S. Haddad (King Fahad National Guard Hospital of Riyadh); *Spain* — A. Abella and M. Prieto (Hospital Universitario de Getafe, Madrid), J.M. Allegue and S. Rodríguez Fernández (Hospital Santa María del Rosell, Cartagena), S. Alonso and C. Boqué (Hospital Universitario Joan XXIII, Tarragona), A. Belenguer and T. Mut (Hospital General de Castellón), S. Benito and A. Claramunt (Hospital de Santa Creu i Sant Pau, Barcelona), J. Blanco (Hospital del Río Hortega, Valladolid), J.L. Buendía and J.A. Gómez Rubí (Hospital Virgen de la Arrixaca, El Palmar), R. Fernández Fernández and M.M. Fernández Fernández (Complejo Hospitalari de Parc Taulí, Sabadell), J. Gener and R. Tomás (Hospital Germans Trias i Pujol, Badalona), S. Macias and F. Martínez Soba (Hospital General de Segovia), and F. Esteban and I. Vallverdú (Hospital Universitari de Reus, Tarragona); *United States* — J. Houtchens and T. Liesching (Rhode Island Hospital, Brown University Medical School, Providence, R.I.), A. Pelaez and D. Vines (University of Texas Health Science Center, San Antonio), and N. Singh (New England Medical Center, Tufts University School of Medicine, Boston); *Venezuela* — M. Capdevielle (Hospital Universitario de Caracas), J.M. España (Hospital Universitario de Caracas), A. Medina (Hospital Militar), F. Pérez (Hospital de Clínicas de Caracas), and R.A. Zerpa (Hospital Militar).

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