# EFFECT OF A PROTECTIVE-VENTILATION STRATEGY ON MORTALITY IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

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## ABSTRACT

*Background*  In patients with the acute respiratory distress syndrome, massive alveolar collapse and cyclic lung reopening and overdistention during mechanical ventilation may perpetuate alveolar injury. We determined whether a ventilatory strategy designed to minimize such lung injuries could reduce not only pulmonary complications but also mortality at 28 days in patients with the acute respiratory distress syndrome.

*Methods*  We randomly assigned 53 patients with early acute respiratory distress syndrome (including 28 described previously), all of whom were receiving identical hemodynamic and general support, to conventional or protective mechanical ventilation. Conventional ventilation was based on the strategy of maintaining the lowest positive end-expiratory pressure (PEEP) for acceptable oxygenation, with a tidal volume of 12 ml per kilogram of body weight and normal arterial carbon dioxide levels (35 to 38 mm Hg). Protective ventilation involved end-expiratory pressures above the lower inflection point on the static pressure–volume curve, a tidal volume of less than 6 ml per kilogram, driving pressures of less than 20 cm of water above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes.

*Results*  After 28 days, 11 of 29 patients (38 percent) in the protective-ventilation group had died, as compared with 17 of 24 (71 percent) in the conventional-ventilation group (P<0.001). The rates of weaning from mechanical ventilation were 66 percent in the protective-ventilation group and 29 percent in the conventional-ventilation group (P=0.005); the rates of clinical barotrauma were 7 percent and 42 percent, respectively (P=0.02), despite the use of higher PEEP and mean airway pressures in the protective-ventilation group. The difference in survival to hospital discharge was not significant; 13 of 29 patients (45 percent) in the protective-ventilation group died in the hospital, as compared with 17 of 24 in the conventional-ventilation group (71 percent, P=0.37).

*Conclusions*  As compared with conventional ventilation, the protective strategy was associated with improved survival at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in patients with the acute respiratory distress syndrome. Protective ventilation was not associated with a higher rate of survival to hospital discharge. (N Engl J Med 1998;338:347-54.)
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MECHANICAL ventilation can damage the lungs.[1,2] Lesions at the alveolar–capillary interface,[3] alterations in permeability,[4] and edema[5-7] have repeatedly been shown to occur in animals subjected to adverse patterns of mechanical ventilation.

In clinical practice, however, the "mechanical stretch" caused by conventional ventilation has been found to be detrimental in only a few uncontrolled studies.[8-11] Large variations in the susceptibility of individual animal species[12] and the apparent success of mechanical ventilation based on a strategy of using the lowest positive end-expiratory pressure (PEEP) that results in acceptable oxygenation[13,14] suggest that the devastating effects observed in animals cannot be easily extrapolated to humans.

We recently demonstrated that mechanical lung protection can be provided in patients with the acute respiratory distress syndrome, resulting in better pulmonary function and higher rates of weaning from the ventilator.[15] Briefly, lung protection was based on a strategy of maintaining low inspiratory driving pressures (<20 cm of water above PEEP, with low tidal volumes and preferential use of limited airway pressure over regulation of arterial carbon dioxide levels), with the simultaneous circumvention of alveolar collapse through the use of high PEEP to keep end-expiratory pressures above the lower inflection point ($P_{FLEX}$) on the static pressure–volume curve of the respiratory system. The nearly maximal alveolar recruitment and aeration accomplished with this strategy were intended to minimize shear stresses in the lung tissue during inspiration.[15]

We have extended our earlier report[15] and evaluated the effect of mechanical lung protection on survival. We hypothesized that preventing the persistent collapse of recruitable units (alveolar units anatomically preserved but requiring high opening pressures for aeration) and reducing cyclic lung reopening and stretch during mechanical breaths would result in lower rates of pulmonary complications and mortal-

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ity at 28 days in patients with the acute respiratory distress syndrome.

## METHODS

### Study Population

Between December 1990 and July 1995, 53 patients with the acute respiratory distress syndrome were prospectively enrolled in the trial (including 28 described previously[15]). The hemodynamic data in 48 of the patients during the first seven days of the study have been reported elsewhere.[16] The study was conducted in two intensive care units in Brazil: one in São Paulo and one in Porto Alegre. The protocol was approved by the hospitals' medical-ethics committees, and informed consent was obtained from each patient or the patient's next of kin.

Each year during the study period, a total of about 60 patients with the acute respiratory distress syndrome were admitted to the two intensive care units. The criteria for enrollment were an underlying disease process known to be associated with the acute respiratory distress syndrome along with a lung-injury score[17] of 2.5 or higher (range, 0 [normal] to 4 [most severe]) plus a pulmonary arterial wedge pressure of less than 16 mm Hg. Confirmation that the tip of the pulmonary arterial catheter was in the area of the lung zone where capillary vessels were patent, transmitting left atrial pressures backward, was assessed with two mechanical maneuvers.[5,18] The exclusion criteria (listed in decreasing order of frequency) were previous lung or neuromuscular disease, mechanical ventilation for more than one week, uncontrolled terminal disease, previous barotrauma (pneumothorax, pneumomediastinum, or subcutaneous emphysema), previous lung biopsy or resection, an age of more than 70 years or less than 14 years, uncontrollable and progressive acidosis, signs of intracranial hypertension, and documented coronary insufficiency. The primary diagnoses at enrollment are shown in Table 1.

### Stabilizing Procedures and Randomization

After enrollment, all patients underwent a standardized regimen of ventilatory–hemodynamic procedures for at least 30 minutes (control period), during which time their initial clinical condition was evaluated and stabilized. This regimen consisted of volume-controlled ventilation (tidal volume, 10 ml per kilogram of body weight), a square-wave inspiratory flow of 50 liters per minute, a respiratory rate of 15 cycles per minute, an inspiratory pause of 0.4 second, an inspiratory oxygen fraction of 1.0, PEEP of 5 cm of water or the minimal value necessary to maintain an arterial oxygen saturation of more than 85 percent, 5 percent albumin administered intravenously until the pulmonary arterial wedge pressure was higher than 9 mm Hg, dobutamine administered intravenously in a fixed dose of 5 $\mu$g per kilogram per minute, and norepinephrine administered intravenously whenever the mean arterial pressure remained lower than 60 mm Hg (the minimal dose that kept the pressure at or above 60 mm Hg).

After the patient's condition had been stabilized, respiratory, hemodynamic, and laboratory measurements were performed. These data were used for a base-line comparison of the two groups and for calculating the risk of death according to the severity of illness (Table 1). The physiologic data for Acute Physiology and Chronic Health Evaluation (APACHE) II[21] scores were collected during the 24-hour period starting at this time. The worst values during this interval, including the control-period measurements, were recorded, except for blood gas and heart-rate values. To avoid the overestimating effects of subsequent permissive hypercapnia on these variables (since respiratory acidosis and tachycardia usually increase the APACHE score), only the control-period measurements of blood gas and heart rate were considered (adjusted APACHE II score).

Subsequently, a bedside procedure was performed to calculate the inspiratory and static pressure–volume curve without disconnecting the ventilator, as described previously.[15,22] A well-defined

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE STUDY GROUPS.*

| CHARACTERISTIC | PROTECTIVE VENTILATION (N=29) | CONVENTIONAL VENTILATION (N=24) |
|---|---|---|
| Age (yr) | 33±13 | 36±14 |
| Duration of mechanical ventilation before entry (days) | 1.9±1.8 | 2.2±2.6 |
| Extrapulmonary organ failure | 2.6±1.3 | 2.7±1.5 |
| APACHE II† | | |
|   Standard score | 28±7 | 27±6 |
|   Standard risk of death (%) | 65±18 | 60±19 |
|   Adjusted score | 24±7 | 24±6 |
|   Adjusted risk of death (%) | 54±23 | 52±21 |
| Critical-care score | 19±6 | 17±6 |
| Lung-injury score | 3.4±0.4 | 3.2±0.4 |
| Ventilator score | 87±12 | 84±14 |
| Respiratory tract infection (%) | 52 | 63 |
| Sepsis (%) | 86 | 79 |
| PaO$_2$:FiO$_2$ | 112±51 | 134±67 |
| P$_{FLEX}$ | 14.7±3.9 | 14.0±3.7 |
| Static compliance (ml/cm of water) | 28.2±8.3 | 30.0±6.5 |
| Primary diagnosis (no.) | | |
|   Leptospirosis | 4 | 4 |
|   Bacterial pneumonia | 1 | 3 |
|   Aspirative pneumonia | 4 | 0 |
|   Atypical pneumonia | 2 | 4 |
|   Pneumocystis pneumonia | 4 | 1 |
|   Puerperal sepsis and disseminated intravascular coagulation | 4 | 2 |
|   Systemic lupus erythematosus and sepsis or pneumonia | 2 | 2 |
|   Acute pancreatitis | 1 | 1 |
|   Soft-tissue infection with sepsis | 1 | 3 |
|   Abdominal sepsis | 1 | 2 |
|   Intracranial hemorrhage | 1 | 0 |
|   Pulmonary contusion | 1 | 0 |
|   Near-drowning | 2 | 0 |
|   Disseminated tuberculosis | 1 | 0 |
|   Immune alveolar hemorrhage | 0 | 1 |
|   Polytransfusion | 0 | 1 |

*There were no statistically significant differences between the two groups for any of the variables. Fisher's exact test was used for categorical variables, the two-tailed t-test with unequal variance for continuous variables, and the Mann–Whitney rank-sum test for ordinal variables. Extrapulmonary organ failure, respiratory tract infection, and sepsis have been defined previously.[15] The critical-care score is described by Yeung et al.,[19] the lung-injury score by Murray et al.,[17] and the ventilator score by Smith and Gordon.[20] Whereas the Acute Physiology and Chronic Health Evaluation (APACHE) II score (range, 0 to 72) and the critical-care score (range, 0 to 71) are systemic indexes of the severity of illness, the lung-injury score (range, 0 to 4) and the ventilator score (range, 3 to 170) indicate the degree of impairment in lung function. For all scores, higher values indicate greater severity. Plus–minus values are means ±SD. PaO$_2$:FiO$_2$ denotes the ratio of arterial oxygen tension to the fraction of inspired oxygen, and P$_{FLEX}$ the end-expiratory pressure above the lower inflection point on the static pressure–volume curve.

†The standard APACHE II score was based on the worst physiologic values during the 24-hour period just before the control period. The adjusted APACHE II score was calculated in the same way, except for arterial-blood gas and heart rate, which were based exclusively on measurements made during the control period (before permissive hypercapnia).

$P_{FLEX}$ (corresponding to an upward shift in the slope of the curve and signaling an increment in lung compliance) could be determined for 49 patients, but the corresponding value was used to adjust PEEP only in the group assigned to protective mechanical ventilation. Since this was the only curve calculated during the protocol, PEEP was then kept constant in this group until the inspiratory oxygen fraction was less than 0.4.[15] After determining the pressure–volume curve, we randomly assigned the patients to one of the two groups. Randomization was performed with sealed envelopes and a 1:1 assignment scheme.

### General Ventilatory Support

Protective or conventional mechanical ventilation was rigorously maintained until the patient was extubated or died. Each patient was connected to a closed system for aspirating tracheal secretions; the patient remained connected to the ventilator during aspiration, minimizing temporary drops in airway pressure. In both groups, the target partial pressure of arterial oxygen was 80 mm Hg, and the PEEP level was never set below 5 cm of water, even during weaning from the ventilator. The weaning procedure was the same in the two groups: a gradual decrease in the level of pressure support.[15] Patients received ventilation exclusively through endotracheal tubes.

### Conventional Approach

We sought to maintain an arterial carbon dioxide level of 35 to 38 mm Hg, independent of airway pressures, and an inspiratory oxygen fraction of less than 0.6 with adequate systemic oxygen delivery. To optimize this compromise, we used a stepwise algorithm for PEEP increments.[15,16] Other ventilatory settings were as follows: tidal volume, 12 ml per kilogram (volume-cycled assisted or controlled ventilation); square-wave inspiratory flow rate, 50 to 80 liters per minute (adjusted to avoid auto-PEEP, or abnormal gas trapping leading to an elevated end-respiratory pressure); inspiratory pause, 0.4 second; and backup respiratory rate, 10 to 24 cycles per minute (depending on the value for arterial carbon dioxide). In addition to the administration of sedative drugs to keep the patients comfortable, additional doses of sedatives were given to prevent patient-triggered respiratory rates higher than 24 cycles per minute or arterial carbon dioxide values lower than 25 mm Hg.

### Protective Approach

The protective approach was intended to prevent alveolar collapse and overdistention, regardless of arterial carbon dioxide levels, and to maintain an "open lung" independently of hemodynamic conditions. The tidal volume was maintained at a level lower than 6 ml per kilogram, with a respiratory rate of less than 30 cycles per minute, even during pressure support. Permissive hypercapnia and continuous infusions of fentanyl and diazepam were used to prevent discomfort and signs of increased respiratory drive. Initial arterial carbon dioxide levels of up to 80 mm Hg were allowed, and slow intravenous sodium bicarbonate infusions (≤50 mmol per hour) were permitted if the arterial pH was less than 7.2.

Driving pressures ($P_{PLAT}$−PEEP, with $P_{PLAT}$ defined as the plateau pressure after the inspiratory pause) and peak airway pressures were kept below 20 and 40 cm of water, respectively. Only pressure-limited modes of ventilation (pressure-controlled inverse-ratio ventilation [ratio of inspiration to expiration, >1] and pressure-support ventilation, both generating constant airway pressure during inspiration) or combined modes (volume-ensured pressure-support ventilation, in which a constant inspiratory pressure is targeted at the same time that a minimal tidal volume is guaranteed[23]) were used, according to a stepwise algorithm.[15]

PEEP was preset at 2 cm of water above $P_{FLEX}$. When auto-PEEP (defined as the difference between alveolar pressures at end expiration and airway pressures) was present, the total PEEP (external PEEP plus auto-PEEP) was considered and adjusted to equal $P_{FLEX}$ plus 2 cm of water. Finally, if a sharp $P_{FLEX}$ could not be determined on the pressure–volume curve, an empirical total-PEEP value of 16 cm of water was used.[15] Recruiting maneuvers — aimed at reaerating alveolar units requiring very high opening pressures — were frequently used, especially after inadvertent disconnections from the ventilator. Continuous positive airway pressures of 35 to 40 cm of water were applied for 40 seconds, followed by a careful return to previous PEEP levels. Finally, pressure-controlled inverse-ratio ventilation was used whenever the inspiratory oxygen fraction was higher than 0.5, in order to decrease minute-volume requirements.[24]

### General Support

All patients were monitored with the Swan–Ganz catheter, and a stepwise algorithm for hemodynamic optimization[15,16] was used. Measurements of plasma lactate and mixed venous saturation were used to correct imbalances between oxygen transport and demand. The pulmonary-artery wedge pressure never exceeded 15 mm Hg. Procedures for nutritional support, treatment of infections, and renal dialysis (when needed) were the same in both groups.[15,16] Corticosteroids were given only to patients with *Pneumocystis carinii* pneumonia. No patients received immunotherapy. The protocol for sedation was the same for both groups, with only two sedatives prescribed (fentanyl and diazepam) and only one neuromuscular paralyzing drug (pancuronium). Although larger doses (up to 9 mg per day) were used in the protective-ventilation group, continuous infusions of fentanyl were used in both groups to keep the patients comfortable. All patients received ranitidine (50 mg intravenously every eight hours) as prophylaxis against bleeding.

### Statistical Analysis

The primary end point was survival at 28 days. The effect of the protective approach was analyzed with a Cox proportional-hazards model, with the base-line adjusted APACHE II score (adjusted risk of death) included as a covariate.

After the first block of 28 patients had been enrolled, a beneficial effect of the protective approach on pulmonary function became evident,[15] and we were concerned about the possibility of subjecting the patients to an unnecessary continuation of the protocol.[25] Therefore, we performed an interim analysis after each new block of five patients. We estimated that a maximal sample of 58 patients was required, assuming a type I error of 5 percent, a statistical power of 85 percent, and a survival rate in the protective-ventilation group that would be 2.4 times that in the conventional-ventilation group, according to our initial results.[15]

To counterbalance the increased chance of prematurely stopping the study because of a type I error, we used the conservative correction for multiplicity proposed by Peto et al.[26] and Geller and Pocock,[27] with a nominal significance level of ≤0.001 for an interim analysis, if the study was stopped early, and a significance level of ≤0.04 for the final analysis, if the study was completed.[27]

The secondary end points were survival to hospital discharge, occurrence of clinically detectable barotrauma, and weaning rate adjusted for APACHE II score (Cox model). Bonferroni's adjustment for multiple comparisons was performed for each secondary end point. All other statistical tests are described below. All P values (two-tailed) were calculated with the BMDP software package (BMDP Statistical Software, version 7.0, Los Angeles).

## RESULTS

The study was stopped during the fifth interim analysis, after 53 patients had been enrolled, because of a significant survival difference between the groups (Tables 2 and 3 and Fig. 1). After 28 days, 11 of 29 patients (38 percent) in the protective-ventilation group had died, as compared with 17 of 24 (71 percent) in the conventional-ventilation group (P<0.001). The results were similar when the groups

**TABLE 2.** STUDY OUTCOMES ACCORDING TO THE INTENTION-TO-TREAT ANALYSIS.

| OUTCOME | PROTECTIVE VENTILATION (N=29) | CONVENTIONAL VENTILATION (N=24) | P VALUE | |
|---|---|---|---|---|
| | | | ISOLATED COMPARISONS | COMPARISONS CORRECTED FOR MULTIPLE TESTING* |
| Primary end point — no. (%) | | | | |
| Mortality at 28 days | 11 (38) | 17 (71) | <0.001† | <0.001 |
| Secondary end points — no. (%) | | | | |
| In-hospital death | 13 (45) | 17 (71) | 0.09‡ | 0.37 |
| Barotrauma | 2 (7)§ | 10 (42)¶ | 0.004‡ | 0.02 |
| Weaning at 28 days | 19 (66) | 7 (29) | 0.001† | 0.005 |
| Other outcomes | | | | |
| Death in the intensive care unit — no. (%) | 11 (38) | 17 (71) | 0.03‡ | |
| Death after weaning — no. | 4 | 0 | >0.10‡ | |
| Nosocomial pneumonia — no. | 17 | 11 | >0.10‡ | |
| Use of paralyzing agents for >24 hr — no. | 17 | 8 | 0.10‡ | |
| Neuropathy after extubation — no. | 2 | 0 | >0.10‡ | |
| Dialysis required — no. | 7 | 5 | >0.10‡ | |
| Packed red cells infused — ml/patient/day | 230 | 309 | 0.25‖ | |
| Cause of in-hospital death — no.** | | | | |
| Progressive respiratory failure | 1 | 6 | | |
| Refractory septic shock | 6 | 7 | | |
| Accidental extubation | 2 | 1 | | |
| Gastric hemorrhage | 2 | 1 | | |
| Cerebral nocardiosis | 1 | 0 | | |
| Accidental hemothorax | 1 | 0 | | |
| Ventricular fibrillation | 0 | 1 | | |
| Intracranial hemorrhage | 0 | 1 | | |

*Bonferroni's correction was used.

†A Cox proportional-hazards model adjusted for the base-line APACHE II score (adjusted risk of death) was used.

‡A two-tailed Fisher's exact test was used.

§Both patients had pneumothorax.

¶Five patients had pneumothorax, two had pneumomediastinum, four had subcutaneous emphysema, and two had bronchopleural fistulae.

‖A two-tailed t-test with unequal variance was used.

**Four patients died after extubation: one each from refractory septic shock, gastric hemorrhage, cerebral nocardiosis, and accidental hemothorax.

were stratified according to the initial severity of illness or the center where the patient was treated.

The difference in weaning rates mirrored the results for survival, with 19 of 29 patients (66 percent) in the protective-ventilation group successfully weaned from the ventilator, as compared with 7 of 24 (29 percent) in the conventional-ventilation group (P=0.005 after adjustment for multiple comparisons). The rate of clinical barotrauma was also significantly lower in the protective-ventilation group than in the conventional-ventilation group (7 percent vs. 42 percent, P=0.02 after adjustment for multiple comparisons). The difference in survival to hospital discharge was not significant; 13 of 29 patients in the protective-ventilation group (45 percent) died in the hospital, as compared with 17 of 24 patients in the conventional-ventilation group

(71 percent, P=0.37 after adjustment for multiple comparisons).

Within the first 28 days, the most frequent causes of death were refractory septic shock and progressive respiratory failure (Table 2).[15] Fourteen episodes of accidental extubation (usually during repositioning of the patient) occurred in nine patients in the protective-ventilation group, as compared with 10 episodes in seven patients in the conventional-ventilation group. In two of the patients in the protective-ventilation group and one in the conventional-ventilation group, irreversible cardiac events followed these episodes. Although successfully extubated (at ≥48 hours), four patients in the protective-ventilation group died before hospital discharge: one from massive hemothorax with arterial rupture during attempts at central venous cannulation (on day 7), one from

**TABLE 3.** BASE-LINE FACTORS INFLUENCING THE RELATIVE RISK OF DEATH AT 28 DAYS.

| FACTOR | RELATIVE RISK (95% CI)* | P VALUE |
|---|---|---|
| Univariate analysis† | | |
| Age | 1.01 (0.98–1.04) | 0.43 |
| Lung-injury score | 0.58 (0.22–1.51) | 0.27 |
| Duration of mechanical ventilation | 0.97 (0.82–1.15) | 0.77 |
| Sepsis | 1.37 (0.47–3.94) | 0.55 |
| No. of organ failures | 1.12 (0.84–1.48) | 0.45 |
| APACHE II‡ | | |
| Adjusted score | 1.07 (1.02–1.13) | 0.008 |
| Adjusted risk of death | 1.02 (1.01–1.04) | 0.006 |
| Standard score | 1.07 (1.01–1.13) | 0.02 |
| Standard risk of death | 1.03 (1.01–1.05) | 0.01 |
| Group assignment | 0.35 (0.16–0.75) | 0.006 |
| Multivariate analysis | | |
| APACHE II adjusted risk of death‡ | 1.04 (1.02–1.06) | <0.001 |
| Group assignment | 0.19 (0.08–0.47) | <0.001 |

*The relative risks associated with the listed factors are expressed as follows: age, the risk associated with each additional year; lung-injury score, the risk associated with each increment in the score; duration of mechanical ventilation, the risk associated with each additional day; sepsis, the risk associated with its presence as compared with its absence; number of organ failures, the risk associated with each additional failure; APACHE II standard and adjusted scores, the risk associated with each increment in the score; APACHE II standard and adjusted risk of death, the risk associated with each 1 percent increment; and group assignment, the risk associated with assignment to the protective-ventilation group as compared with the conventional-ventilation group. CI denotes confidence interval.

†Other variables included in the univariate analysis were the end-expiratory pressure above the lower inflection point on the static pressure–volume curve, static compliance, ratio of arterial oxygen tension to the fraction of inspired oxygen, pulmonary shunt, presence of fungi in secretions, respiratory tract infection at entry, and critical-care score. None were significantly related to survival.

‡Adjusted scores on APACHE II were based on the worst physiologic values during the 24-hour period just before the control period, except for arterial-blood gas and heart rate, which were based exclusively on measurements made during the control period (before permissive hypercapnia). Data obtained during permissive hypercapnia were included in the calculation of standard scores.

diffuse gastrointestinal bleeding (on day 23), one from intracerebral nocardiosis with brain edema (on day 11), and one from a new episode of nosocomial pneumonia followed by refractory septic shock (on day 68). Except for the episode of arterial rupture, no iatrogenic event related to central lines occurred after study entry.

The values for the respiratory variables measured during the first week of the study are shown in Table 4. The objectives of ventilatory support were achieved in 48 of the 53 patients. Although the mean respiratory values suggest good adherence to the protocol, there were minor protocol violations in the care of four patients in the protective-ventilation group and one patient in the conventional-ventilation group. In the patient in the conventional-ventilation group, a tidal volume of 7 ml per kilogram was inadvertently used for 12 hours. Among the violations in the protective-ventilation group, there was an inadvertent use of a tidal volume higher than 7 ml per kilo-

gram during a period of eight hours, a PEEP prematurely reduced in disregard of the protocol, use of antibiotics in disregard of the protocol, and a previous pneumothorax detected during a careful review of radiographs. The exclusion of these five patients from the analysis of mortality had little effect on the mortality rate associated with the protective-ventilation approach (relative risk of death, 0.14 [95 percent confidence interval, 0.05 to 0.38], as compared with 0.19 [95 percent confidence interval, 0.08 to 0.47]). The protective-ventilation approach had significant benefits with regard to oxygenation and lung compliance.
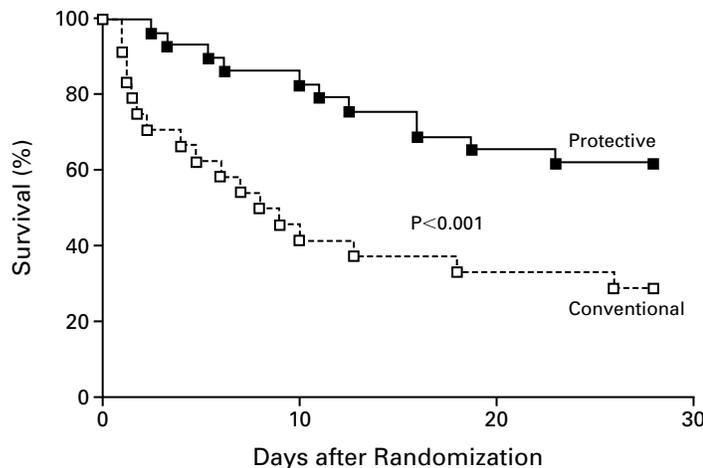
Table 3 shows the results of univariate and multivariate analyses of mortality at 28 days according to base-line factors (data collected during the control period before randomization). The APACHE II scores and the ventilatory treatment were the only significant factors. These were the two covariates that had been included a priori in the final multivariate Cox regression model.

## DISCUSSION

We found that in a group of patients with severe acute respiratory distress syndrome, the protective approach to mechanical ventilation improved the survival rate at 28 days and the weaning rate but not the rate of survival to hospital discharge. The incidence of barotrauma was significantly lower in the protective-ventilation group than in the conventional-ventilation group, despite the use of higher PEEP levels and higher mean airway pressures.

The complexity of the procedures in this study precluded the use of a protocol in which the investigators were unaware of the treatment assignments. Nevertheless, we believe that the stringent algorithms used for infectious problems, hemodynamic values, nutrition, sedation, dialysis, and general care[15] were sufficient to minimize additional bias due to differences in the management of nonrespiratory problems. We demonstrated in a previous analysis that we were able to accomplish the planned hemodynamic goals in most patients in both groups.[16] Finally, it is difficult to ascribe the better outcome in the protective-ventilation group to uncontrolled or unrecognized factors, since our staff was much more used to the conventional approach. In fact, a greater number of fatal iatrogenic accidents occurred in the protective-ventilation group than in the conventional-ventilation group. Considering the small size of the study, the conservative nature of Bonferroni's statistical adjustment,[27] and the severity of base-line disease in the patients (which was responsible for many of the late deaths), the failure to detect a significant difference in survival to hospital discharge was not surprising.

Despite the use of an appropriate rule for early termination of the study during all interim analyses,[26,27]

**Figure 1.** Actuarial 28-Day Survival among 53 Patients with the Acute Respiratory Distress Syndrome Assigned to Protective or Conventional Mechanical Ventilation.

The data are based on an intention-to-treat analysis. The P value indicates the effect of ventilatory treatment as estimated by the Cox regression model, with the risk of death associated with the adjusted base-line score on APACHE II included as a covariate.

the estimates of relative risk shown in Table 3 may be imprecise. The corrections proposed for multiple sequential analysis can properly control the overall type I error, but they cannot prevent associated distortions of the magnitude of the treatment effect caused by early termination or the small sample.[28]

Since the effect of the protective-ventilation strategy on survival was observed in the context of many concomitant maneuvers (permissive hypercapnia, lower peak and driving pressures, higher PEEP, a tidal volume of less than 6 ml per kilogram, and so forth), we performed a pooled "retrospective" analysis to determine the key combination of ventilatory variables responsible for the ventilatory treatment effect on mortality at 28 days (data not shown). When the treatment assignment was removed from the Cox mortality model, there were three significant prognostic factors: the APACHE II score, the mean PEEP used during the first 36 hours (with a protective effect indicated by a coefficient of $-0.15$), and the driving pressures ($P_{PLAT}-$PEEP) during the first 36 hours (with a deleterious effect of high driving pressures indicated by a coefficient of 0.06). All other respiratory variables were of secondary importance. Higher PEEP values (preferentially above the $P_{FLEX}$ value) and lower driving pressures were independently associated with better survival. High initial PEEP values appeared to be beneficial, even when the $P_{PLAT}$ value increased, as long as the driving pressure did not change disproportionately.

The strong protective effect associated with a high PEEP value is consistent with recent experimental data,[7,29-33] and the benefit seems to be more pronounced than the deleterious effect of high distending pressures.[7,29,30] Had we not used high PEEP levels ($>P_{FLEX}$), the results might have been very different, with the isolated reduction in $P_{PLAT}$ potentially causing reabsorption atelectasis, loss of alveolar surface, and hypoxemia in some patients.

Recent evidence suggests that the minimization of ventilator-induced lung injury may have important systemic benefits, decreasing the release of proinflammatory mediators,[34-36] the dissemination of infections,[37-39] and possible complications related to air embolism.[40,41] In addition to preventing progressive respiratory failure, the protective-ventilation approach may be associated with these mechanisms.

Despite the use of higher PEEP values (up to 24 cm of water) and higher mean airway pressures, there was a lower incidence of barotrauma in the protective-ventilation group. The protective-ventilation approach may thus not only improve pulmonary function and oxygenation but also reduce clinically apparent alveolar damage. Another study suggested a protective effect of PEEP against clinical barotrauma.[42] The paucity of data in favor of this concept may be explained by the correlation normally found between PEEP and peak pressures.[43,44] In our study, however, the use of high PEEP levels did not necessarily result in high peak or plateau pressures.

**TABLE 4.** RESPIRATORY VALUES DURING THE FIRST WEEK OF MECHANICAL VENTILATION.*

| VARIABLE | CONTROL PERIOD | FIRST HOUR | FIRST 36 HOURS | DAY 2 TO DAY 7 |
|---|---|---|---|---|
| | | mean ±SE | | |
| PEEP (cm of water) | | | | |
|   Protective ventilation | 6.2±0.6 | 16.3±0.7† | 16.4±0.4† | 13.2±0.4‡ |
|   Conventional ventilation | 6.2±0.5 | 6.9±0.8 | 8.7±0.4 | 9.3±0.5 |
| Plateau pressure (cm of water) | | | | |
|   Protective ventilation | 32.5±1.5 | 31.8±1.4 | 30.1±0.7† | 23.9±0.7† |
|   Conventional ventilation | 29.5±1.5 | 34.4±1.9 | 36.8±0.9 | 37.8±1.2 |
| Peak pressure (cm of water) | | | | |
|   Protective ventilation | 40.1±1.5 | 32.2±1.4† | 30.5±0.7† | 24.0±0.7† |
|   Conventional ventilation | 38.2±2.1 | 44.2±2.6 | 46.0±1.1 | 45.5±1.5 |
| Mean airway pressure (cm of water) | | | | |
|   Protective ventilation | 14.1±0.7 | 24.2±1.2† | 23.5±0.6† | 17.0±0.6 |
|   Conventional ventilation | 13.4±0.8 | 15.7±1.1 | 17.9±0.6 | 18.7±0.8 |
| Tidal volume (ml) | | | | |
|   Protective ventilation | 661±15 | 362±11† | 348±6† | 387±7† |
|   Conventional ventilation | 646±24 | 763±26 | 768±13 | 738±17 |
| Minute volume (liters/min) | | | | |
|   Protective ventilation | 10.9±0.4 | 7.0±0.4† | 6.8±0.2† | 8.3±0.2† |
|   Conventional ventilation | 10.8±0.5 | 12.1±0.6 | 13.1±0.3 | 13.9±0.4 |
| $PaCO_2$ (mm Hg) | | | | |
|   Protective ventilation | 38.1±1.6 | 58.2±3.3† | 55.0±1.2† | 50.8±1.1† |
|   Conventional ventilation | 37.9±1.4 | 35.7±1.7 | 33.2±0.6 | 35.0±0.7 |
| Arterial pH | | | | |
|   Protective ventilation | 7.32±0.02 | 7.19±0.02† | 7.25±0.01† | 7.35±0.01 |
|   Conventional ventilation | 7.34±0.02 | 7.37±0.02 | 7.40±0.01 | 7.41±0.01 |
| $PaO_2$:$FiO_2$ (mm Hg) | | | | |
|   Protective ventilation | 112±10 | 198±16† | 220±7† | 239±6† |
|   Conventional ventilation | 134±14 | 139±12 | 135±6 | 146±7 |
| Static compliance (ml/cm of water) | | | | |
|   Protective ventilation | 28.5±1.6 | 28.4±2.0 | 33.8±1.3‡ | 39.7±1.3† |
|   Conventional ventilation | 30.0±1.3 | 30.5±1.3 | 30.1±0.7 | 29.1±1.0 |

*The values are means of the average values for all measurements in each patient, with all 53 patients included (intention-to-treat analysis). At least three measurements of all respiratory variables, along with blood-gas and hemodynamic variables, were performed each day. PEEP denotes positive end-expiratory pressure, $PaCO_2$ partial pressure of carbon dioxide, and $PaO_2$:$FiO_2$ the ratio of arterial oxygen tension to the fraction of inspired oxygen. P values are for the comparison between the two groups during the specified interval, with adjustment for differences in the incremental area under the curve.[15]

†P<0.001.

‡P<0.01.

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