

EVALUATION OF A VENTILATION STRATEGY TO PREVENT BAROTRAUMA IN PATIENTS AT HIGH RISK FOR ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Background A strategy of mechanical ventilation that limits airway pressure and tidal volume while permitting hypercapnia has been recommended for patients with the acute respiratory distress syndrome. The goal is to reduce lung injury due to overdistention. However, the efficacy of this approach has not been established.

Methods Within 24 hours of intubation, patients at high risk for the acute respiratory distress syndrome were randomly assigned to either pressure- and volume-limited ventilation (limited-ventilation group), with the peak inspiratory pressure maintained at 30 cm of water or less and the tidal volume at 8 ml per kilogram of body weight or less, or to conventional ventilation (control group), with the peak inspiratory pressure allowed to rise as high as 50 cm of water and the tidal volume at 10 to 15 ml per kilogram. All other ventilatory variables were similar in the two groups.

Results A total of 120 patients with similar clinical features underwent randomization (60 in each group). The patients in the limited-ventilation and control groups were exposed to different mean (\pm SD) tidal volumes (7.2 ± 0.8 vs. 10.8 ± 1.0 ml per kilogram, respectively; $P < 0.001$) and peak inspiratory pressures (23.6 ± 5.8 vs. 34.0 ± 11.0 cm of water, $P < 0.001$). Mortality was 50 percent in the limited-ventilation group and 47 percent in the control group (relative risk, 1.07; 95 percent confidence interval, 0.72 to 1.57; $P = 0.72$). In the limited-ventilation group, permissive hypercapnia (arterial carbon dioxide tension, >50 mm Hg) was more common (52 percent vs. 28 percent, $P = 0.009$), more marked (54.4 ± 18.8 vs. 45.7 ± 9.8 mm Hg, $P = 0.002$), and more prolonged (146 ± 265 vs. 25 ± 22 hours, $P = 0.017$) than in the control group. The incidence of barotrauma, the highest multiple-organ-dysfunction score, and the number of episodes of organ failure were similar in the two groups; however, the numbers of patients who required paralytic agents (23 vs. 13, $P = 0.05$) and dialysis for renal failure (13 vs. 5, $P = 0.04$) were greater in the limited-ventilation group than in the control group.

Conclusions In patients at high risk for the acute respiratory distress syndrome, a strategy of mechanical ventilation that limits peak inspiratory pressure and tidal volume does not appear to reduce mortality and may increase morbidity. (N Engl J Med 1998; 338:355-61.)

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A STRATEGY of mechanical ventilation that places limits on airway pressure and tidal volume has been recommended for patients with the acute respiratory distress syndrome.¹⁻⁴ This recommendation is based on the observation that mechanical ventilation, although life-sustaining, can cause marked lung injury in both animals⁵⁻⁹ and humans¹⁰ if lung overdistention occurs. Patients with the acute respiratory distress syndrome are particularly prone to overdistention, especially when conventional tidal volumes are used (10 to 15 ml per kilogram of body weight), because the number of lung units available for ventilation is markedly reduced as a result of fluid accumulation, consolidation, and atelectasis.^{11,12} Ventilation strategies that limit airway pressure and volume often result in hypercapnia and respiratory acidosis, which can be deleterious.^{3,4} Nonetheless, observational studies have reported reduced mortality when patients with the acute respiratory distress syndrome undergo ventilation at decreased pressure and tidal volume.^{13,14} A randomized study found a trend toward reduced morbidity when lower tidal volumes were routinely used in patients receiving mechanical ventilation.¹⁵ More recently, mortality was lower when lower tidal volumes and airway pressures were used in a randomized trial comparing two ventilation techniques, but it is difficult to be certain of the part that pressure and volume limitation played, because end-expiratory pressure was also modified and a procedure to re-expand the lung after the ventilator was disconnected was used.^{16,17}

In 1993 a consensus conference made recommendations for the use of mechanical ventilation in a variety of illnesses.^{1,2} It was recommended that, under conditions in which lung overdistention was likely to occur, airway pressures be limited by reducing tidal

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volumes and accepting the attendant increase in arterial carbon dioxide levels. We undertook this study to determine whether a strategy of mechanical ventilation that placed specific limits on peak inspiratory pressure and tidal volume in patients at high risk for the acute respiratory distress syndrome would affect in-hospital mortality.

METHODS

Selection of Patients

With the approval of the institutional review boards and after obtaining informed consent, we enrolled patients at eight tertiary care centers. Inclusion criteria were as follows: age, more than 18 years; duration of intubation, 24 hours or less; high risk for the acute respiratory distress syndrome (indicated by one or more risk factors, defined in Appendix 2); and a ratio of arterial oxygen tension (PaO_2) to the fraction of inspired oxygen (FiO_2) below 250 at a positive end-expiratory pressure (PEEP) of 5 cm of water. Patients who met the definition for sepsis or burns were eligible regardless of the ratio of PaO_2 to FiO_2 . Exclusion criteria were the expectation on the part of the attending physician that mechanical ventilation would be required for less than 48 hours; 2 hours or more of exposure to peak inspiratory pressures above 30 cm of water before randomization; little chance of survival, as determined by the attending physician; cardiogenic pulmonary edema, previous heart failure, or cor pulmonale; a high risk of cardiac arrhythmias or myocardial ischemia (indicated by the occurrence of ventricular fibrillation, ventricular tachycardia, unstable angina, or myocardial infarction within the preceding month); a known intracranial abnormality; pregnancy; and enrollment in another interventional study.

Study Intervention

Patients were randomly assigned (by means of computer-generated random-number tables, with stratification according to center) to a strategy of ventilation that limited pressure and volume (limited-ventilation group) or to conventional ventilation (control group). The experimental ventilation strategy limited peak inspiratory pressure to no more than 30 cm of water and tidal volume to no more than 8 ml per kilogram. For the control group, peak inspiratory pressure could be as high as 50 cm of water and tidal volume was maintained at 10 to 15 ml per kilogram. Ideal body weight was used to calculate tidal volume. In both groups, an assist-control mode of ventilation with a decelerating wave-form flow pattern was used; pressure control could be substituted if the threshold for peak inspiratory pressure was consistently reached.

For both groups, PEEP in the range of 5 to 20 cm of water was adjusted in increments of 2.5 cm of water to maintain the FiO_2 at 0.5 or less with arterial oxygen saturation of 89 to 93 percent. Respiratory rates were adjusted (5 to 35 breaths per minute) in an attempt to maintain arterial carbon dioxide tension at 35 to 45 mm Hg (hypercapnia was accepted if this target could not be achieved within the ventilatory limits). Severe respiratory acidosis ($\text{pH} < 7.0$) was managed with sodium bicarbonate at a dosage of 2 mmol per kilogram every four hours (up to a maximum of three doses). For the limited-ventilation group, if the pH remained below 7.0, the peak pressure was increased by increments of 2 cm of water (maximum, 40 cm) until the pH reached 7.0 or higher. Adjustments to the inspiratory flow rates and inverse-ratio ventilation, sedation, and paralytic drugs were used at the discretion of the attending physician. To avoid excessive doses of paralytic drugs, patients receiving them had the dosage adjusted daily with use of a peripheral-nerve stimulator.

Patients were withdrawn from the protocol if any of the following conditions, defined a priori, occurred: refractory acidosis, defined as a pH below 7.0, despite the interventions described above; uncontrolled barotrauma, indicated by persistent pneumothorax despite the insertion of three chest tubes on the involved side; or

refractory hypoxemia, defined as a ratio of PaO_2 to FiO_2 below 60, with the fraction of inspired oxygen at 1.0 for at least one hour, despite the adjustment of PEEP and use of paralytic drugs.

Base-line demographic variables, including the Acute Physiology and Chronic Health Evaluation (APACHE) II score,¹⁸ were recorded before randomization. Ventilatory and hemodynamic data were recorded every 8 hours, and multiple-organ-dysfunction scores (with higher scores indicating greater dysfunction)¹⁹ and data from chest radiography were collected daily until successful extubation (defined as a period of more than 48 hours without mechanical ventilation). The oxygen index was also calculated every eight hours, according to the following formula: $(\text{FiO}_2 \times \text{mean airway pressure in centimeters of water} \times 100) \div \text{PaO}_2$ in millimeters of mercury.

Outcome Measures

The primary outcome was in-hospital mortality. Investigators at each study site classified the primary cause of deaths in the intensive care units as respiratory failure (due to profound hypoxemia), multiple-organ failure (three or more organs), sepsis, cardiac arrhythmia, or withdrawal of life support from a patient because of an irreversible chronic condition. Secondary outcomes included barotrauma (indicated by the appearance of pneumothorax, pneumomediastinum, pneumoperitoneum, or pneumopericardium on the chest radiograph), the highest total multiple-organ-dysfunction score, dysfunction of individual organs (defined as an individual organ-dysfunction score of 3 or more [maximum, 4]),¹⁹ clinically relevant arrhythmia, the need for dialysis (defined as any form of dialysis or ultrafiltration to treat renal failure that developed during the study), and the duration of mechanical ventilation, the stay in the intensive care unit, and the hospital stay.

A data and safety monitoring committee consisting of three independent specialists in intensive care reviewed all charts to evaluate the safety of both ventilation protocols with respect to mortality and all secondary-outcome data. This committee met twice (at six and nine months) and reported back to the executive committee, which, in turn, reported to the institutional review boards.

Statistical Analysis

Data are presented as means \pm SD. A comparison of survival between the groups was performed with Kaplan-Meier curves and the log-rank test. All other measures expressed as means or proportions were compared with t-tests for continuous data and chi-square tests for proportions. All tests of statistical significance were two-sided. We did not correct for multiple testing. An intention-to-treat analysis was used.

RESULTS

From July 1995 to September 1996, 120 patients were enrolled. Base-line characteristics and risk factors are presented in Tables 1 and 2, respectively. Fourteen patients met the a priori criteria for discontinuation of the assigned protocol: two who had refractory acidosis (both in the limited-ventilation group), two who had uncontrolled barotrauma (both in the control group), six who had refractory hypoxemia (three in each group), and four for miscellaneous reasons. These patients were included in all analyses.

The mean ventilatory variables on days 1, 3, and 7 are presented in Table 3; the differences in the mean peak inspiratory pressure, tidal volume, plateau pressure, and respiratory rate between the groups were statistically significant, whereas those in PEEP, FiO_2 , and minute ventilation were not. More patients in the limited-ventilation group than the con-

TABLE 1. BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	LIMITED-VENTILATION GROUP (N = 60)	CONTROL GROUP (N = 60)
Age — yr	59±17	58±19
Female sex — no. (%)	13 (22)	23 (38)
APACHE II score	22.4±7.3	21.5±9.5
PaO ₂ :FiO ₂	123±47	145±72†
Oxygen index	10.5±6.1	9.9±7.6
Multiple-organ-dysfunction score	6.8±3.6	7.0±3.8
No. of organs with failure‡	1.4±1.0	1.3±1.2
Risk factors for ARDS — no. (%) of patients		
1	34 (57)	40 (67)
2	22 (37)	15 (25)
3	4 (7)	5 (8)

*Plus-minus values are means ±SD. APACHE denotes Acute Physiology and Chronic Health Evaluation, PaO₂ arterial oxygen tension, FiO₂ fraction of inspired oxygen, and ARDS acute respiratory distress syndrome. The oxygen index was calculated as follows: (FiO₂ × mean airway pressure in centimeters of water × 100) ÷ PaO₂ in millimeters of mercury.

†P<0.05 for the comparison with the limited-ventilation group.

‡An organ failure was defined as a multiple-organ-dysfunction score of ≥3 (maximum, 4) for that system.

TABLE 2. DISTRIBUTION OF RISK FACTORS FOR THE ACUTE RESPIRATORY DISTRESS SYNDROME.

RISK FACTOR*	LIMITED-VENTILATION GROUP (N = 60)	CONTROL GROUP (N = 60)
	no. of patients	
Pneumonia	21	29
Sepsis	26	21
Gastric aspiration	14	6
Shock	9	10
Acute pancreatitis	3	5
Multiple transfusions	3	3
Inhalation injury	2	4
Burn	3	2
Multiple fractures	3	2
Pulmonary contusion	4	1
Drug overdose	2	2

*The risk factors are defined in Appendix 2.

TABLE 3. MEAN VENTILATORY VARIABLES ON DAYS 1, 3, AND 7.*

VARIABLE	DAY 1		DAY 3		DAY 7	
	LIMITED-VENTILATION GROUP (N = 60)	CONTROL GROUP (N = 60)	LIMITED-VENTILATION GROUP (N = 51)	CONTROL GROUP (N = 49)	LIMITED-VENTILATION GROUP (N = 30)	CONTROL GROUP (N = 35)
Tidal volume (ml/kg)	7.0±0.7	10.7±1.4†	7.2±0.8	10.8±1.0†	6.8±0.6	10.1±1.4†
Peak inspiratory pressure (cm of water)	24.2±5.2	32.1±9.5†	23.6±5.8	34.0±11.0†	24.3±4.4	33.5±11.3†
Plateau airway pressure (cm of water)	22.3±5.4	26.8±6.7‡	22.2±3.9	28.5±7.2‡	20.0±4.7	28.6±7.2‡
PEEP (cm of water)	8.6±3.0	7.2±3.3§	8.7±3.6	8.4±3.8	9.6±3.9	8.0±3.6
FiO ₂	0.57±0.20	0.51±0.18	0.47±0.14	0.47±0.17	0.44±0.10	0.45±0.18
Respiratory rate (breaths/min)	22.1±6.2	15.6±5.0†	23.1±6.3	17.0±6.0†	24.9±6.5	19.2±4.7†
Minute ventilation (liters/min)	11.1±3.0	11.7±3.8	11.3±3.2	11.8±4.2	11.6±2.8	12.3±4.0

*Variables are means ±SD for the second reading on the day specified. PEEP denotes positive end-expiratory pressure, and FiO₂ fraction of inspired oxygen. The numbers of patients shown for the various days are those who were still alive.

†P<0.001 for the comparison with the limited-ventilation group.

‡P<0.01 for the comparison with the limited-ventilation group.

§P<0.02 for the comparison with the limited-ventilation group.

trol group underwent dialysis (13 vs. 5, P=0.04) or received paralytic drugs (23 vs. 13, P=0.05).

In-hospital mortality and secondary end points are presented in Table 4. No significant difference in mortality was observed between the groups. Figure 1 shows the Kaplan–Meier survival analysis for the two groups. This was true for mortality adjusted for the APACHE II score (relative risk of death in the limited-ventilation group as compared with the control group, 1.04; 95 percent confidence interval, 0.48 to 2.23) as

well as unadjusted mortality. Five patients died after discharge from the intensive care unit (two in the limited-ventilation group and three in the control group).

Table 5 summarizes the incidence, degree, and duration of hypercapnia in the two groups. The baseline oxygen index was similar in the groups (Table 1). The mean oxygen index was lower for the survivors than for the patients who died (base-line index, 8.7±5.9 vs. 11.8±7.5 [P=0.02]; mean index for the entire ventilation period, 5.8±2.4 vs. 12.8±9.8

TABLE 4. MAIN OUTCOME VARIABLES.*

VARIABLE	LIMITED-VENTILATION	CONTROL GROUP	P VALUE
	GROUP (N = 60)	(N = 60)	
Barotrauma — no. of patients (%)	6 (10)	4 (7)	0.74
Maximal multiple-organ-dysfunction score	10.7±4.8	10.6±5.1	0.96
No. of organs with failure†	2.3±1.4	2.1±1.5	0.63
Arrhythmias — no. of patients (%)‡	17 (28)	20 (33)	0.55
Ventricular arrhythmias — no. of patients (%)§	1 (2)	2 (3)	1.0
Dialysis required — no. of patients (%)¶	13 (22)	5 (8)	0.04
Paralytic drugs received — no. of patients (%)	23 (38)	13 (22)	0.05
Duration of mechanical ventilation — days	16.6±39.2	9.7±10.5	0.20
ICU stay — days	19.9±39.1	13.7±15.8	0.26
Hospital stay — days	33.7±47.8	27.4±26.5	0.38
Death — no. of patients (%)	30 (50)	28 (47)	0.72
Cause of death in ICU — no. of patients**			
Respiratory failure	0	3	
Multiorgan failure	18	11	
Sepsis	7	8	
Cardiac arrhythmia	0	1	
Withdrawal of life support	3	2	

*Plus-minus values are means ±SD. ICU denotes intensive care unit.

†An organ failure was defined as a multiple-organ-dysfunction score of ≥ 3 (maximum, 4) for that system. Six systems were assessed.

‡Arrhythmias were defined as a new onset of atrial fibrillation, atrial flutter, supraventricular tachycardia, sinus bradycardia (heart rate < 60 beats per minute), complete heart block, asystole, ventricular tachycardia (5 consecutive beats of a wide-complex tachyarrhythmia at a rate above 120 beats per minute), or ventricular fibrillation.

§Ventricular arrhythmias included both ventricular tachycardia and ventricular fibrillation.

¶Dialysis denotes any form of dialysis or ultrafiltration for the treatment of renal failure that developed during the study. The numbers and percentages represent patients undergoing dialysis or ultrafiltration while in the ICU, except for those who required such treatment before admission.

||Receipt of paralytic drugs was defined as the use of neuromuscular blocking drugs after randomization, excluding the use of such drugs to facilitate short procedures.

**The causes listed are primary causes of death. Five patients died outside the ICU (two in the limited-ventilation group and three in the control group).

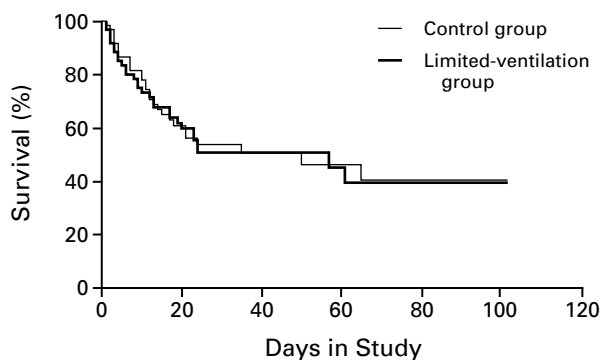


Figure 1. Kaplan-Meier Survival Analysis for the Patients Undergoing Ventilation with Limits on Pressure and Volume (Limited-Ventilation Group) and Those Undergoing Conventional Ventilation (Control Group).

[$P < 0.001$]; and mean maximal index, 12.0 ± 8.3 vs. 24.4 ± 17.9 [$P < 0.001$]).

DISCUSSION

The primary finding of this study was that hospital mortality was not reduced by a strategy of mechanical ventilation that limited both tidal volume and peak inspiratory pressures in patients who had at least one major risk factor for the acute respiratory distress syndrome. The aim of our early randomization procedure and our exclusion of patients who had previously been exposed to peak inspiratory pressures above 30 cm of water was to eliminate those who might have had ventilator-induced lung injury before randomization.

Other investigators have evaluated the role of lung-protection measures during mechanical ventilation. Gattinoni et al. reported a 52 percent mortality rate among 43 patients who underwent mechanical ventilation with “lung rest” (pressure limitation and low frequency) in conjunction with

TABLE 5. HYPERCAPNIA IN THE TREATMENT GROUPS.

VARIABLE*	LIMITED-VENTILATION GROUP (N = 60)	CONTROL GROUP (N = 60)	P VALUE
Maximal PaCO ₂ — mm Hg			0.002
Mean ±SD	54.4±18.8	45.7±9.8	
Range	28–116	29–72	
Arterial pH			0.036
Mean	7.29	7.34	
Range	6.99–7.49	7.08–7.51	
Hypercapnia — no. of patients (%)	31 (52)	17 (28)	0.009
Duration of hypercapnia — hr	146±265	25±22	0.017

*Maximal PaCO₂ denotes the mean maximal partial pressure of arterial carbon dioxide. The arterial pH is the mean value at the time of the maximal PaCO₂. Hypercapnia is defined as a PaCO₂ greater than 50 mm Hg; the table shows the number of patients in each group who had hypercapnia on one or more occasions. The duration of hypercapnia is the total mean (±SD) duration of hypercapnia as assessed by blood gas measurements every eight hours.

extracorporeal carbon dioxide removal,¹³ as compared with an expected mortality of more than 90 percent.²⁰ Hickling et al. reported that mortality among 50 patients with the acute respiratory distress syndrome was 16 percent when pressure and volume limitation was combined with permissive hypercapnia, as compared with a rate of 40 percent expected on the basis of the APACHE II score.¹⁴ However, neither study included concurrent controls, and a subsequent controlled trial of extracorporeal carbon dioxide removal with lung rest revealed no benefit in terms of mortality among patients with the acute respiratory distress syndrome.²¹ Amato and colleagues recently randomly assigned 28 patients with the acute respiratory distress syndrome to undergo ventilation according to an “open lung approach,” with limits on pressure and volume, or to a control group in which conventional ventilatory measures were used to maintain a relatively low arterial carbon dioxide level of 25 to 38 mm Hg.¹⁶ They found better evolution of lung function among the patients assigned to pressure and volume limitation (indicated by compliance and the ratio of PaO₂ to FiO₂) but no difference in mortality. When the study was expanded to include 48 patients, a difference in 28-day mortality favored the lung-protection group (approximately 38 percent vs. 65 percent).¹⁷ That study demonstrated that the particular ventilation strategy used can affect morbidity and mortality. Part of the observed difference in mortality may have been related to the control strategy (death due to respiratory failure was common in the control group), which allowed unlimited airway pressures in order to maintain the specified carbon dioxide level. In our control group, we elected to limit peak inspiratory pressure to 50 cm of water, since this was representative of conventional treatment in the study institutions. In addition, hoping to avoid unnecessary deaths from respiratory failure, we included criteria for the

withdrawal of patients from the study if they had profound hypoxemia, acidosis, or barotrauma.

There are a number of possible explanations for the lack of efficacy of the pressure- and volume-limited ventilation strategy used in our study. First, the limits on peak inspiratory pressures and tidal volumes in the control group may have been sufficient to protect the lungs. Second, some important component of lung protection may not have been evaluated. Third, the study population may have been too heterogeneous for us to detect a difference in mortality. And fourth, the beneficial effects of pressure and volume limitation may have been offset by the harmful effects of hypercapnia.

When the participants in the consensus conference made their recommendations regarding mechanical ventilation in patients with the acute respiratory distress syndrome, they emphasized that high airway pressures were a matter of concern and, in particular, that plateau pressures in excess of 35 cm of water should be avoided (unless there was decreased chest-wall compliance).^{1,2} We limited peak inspiratory pressure (rather than plateau pressure) in this study, for three reasons: peak inspiratory pressure was already routinely measured and used in all the centers; our perception was that peak inspiratory pressure was more commonly limited by clinicians than plateau pressure, perhaps as a result of previous reports; and a limit of 30 cm of water on inspiratory pressure would ensure that plateau pressures were maintained well below 30 to 35 cm of water in all patients in the limited-ventilation group. We also found that most patients in the control group (despite receiving ventilation at tidal volumes of 10 to 15 ml per kilogram) had a plateau pressure below 35 cm of water, which is considered safe; this is in accord with our finding that the incidence of barotrauma was similar in the two groups and was very low in comparison with published rates.²²

Since most patients in the control group had plateau pressures that did not exceed a value that would be anticipated to cause overdistention (i.e., the pressures remained at or below 35 cm of water), the results of our study should not be interpreted to imply that there is no role for pressure and volume limitation in patients receiving mechanical ventilation. This strategy may have an important role in patients with more severe lung injury or in those exposed to higher end-expiratory pressures. It is not the peak inspiratory pressure or the plateau pressure that clinicians should be concerned about but, rather, transpulmonary pressure (alveolar minus pleural pressure), since it is this factor that determines alveolar distention.²³ Normal lung tissue becomes maximally distended at a transpulmonary pressure of 30 to 35 cm of water. If pleural pressure is assumed to be close to 0 cm of water, then plateau pressures (a surrogate measure of alveolar pressure) in excess of 30 to 35 cm of water would cause overdistention.²⁴ However, when the plateau pressure exceeds 35 cm of water, lung overdistention may not occur if pleural pressure is also elevated, as when there is reduced chest-wall or abdominal compliance. In such circumstances, limits on pressure and volume may promote collapse of unstable lung units, resulting in unnecessary hypoxemia and hypercapnia.

In addition to the problem of overinflation, there is a large body of evidence demonstrating that underinflation or inadequate end-expiratory pressures also result in damage to injured or surfactant-depleted lungs.^{25,26} Our goal was not to test all aspects of lung protection but, rather, to address the specific role of pressure and volume limitation in a well-defined population. Therefore, the amount of PEEP was similar in our two groups. It is possible that inadequate lung recruitment is a critical factor leading to ventilator-induced lung injury; this might explain the difference between our observations and those reported by Amato et al., who not only limited pressure and volume but also attempted to keep the lung open.^{16,17}

The mortality among patients with acute respiratory distress syndrome depends on a variety of factors, including age and severity of illness.²⁷ Our study included patients of any age over 18 years who had acute lung injury as a result of a variety of illnesses (Table 2). It is possible that the benefits of pressure and volume limitation in a subgroup of patients with acute lung injury may not be clear when such a large, heterogeneous population is studied. Nonetheless, the specific subgroups that might benefit from this strategy are currently not known.

Permissive hypercapnia was more common in the group assigned to ventilation with pressure and volume limits. There are numerous possible adverse side effects of permissive hypercapnia, most of which remain speculative.³ We attempted to evaluate some of

the adverse effects of pressure and volume limitation (and potentially of permissive hypercapnia) by assessing the multiple-organ-dysfunction score, which quantifies dysfunction in six organ systems.¹⁹ There was no significant difference between the two groups with respect to the maximal multiple-organ-dysfunction score or the total number of organs with failure. However, the need for dialysis was greater in the limited-ventilation group than in the control group. Since we did not have a priori criteria for the institution of dialysis, this observation needs to be interpreted with caution. A variety of factors (such as lower pH due to respiratory acidosis) could have resulted in the use of dialysis more often in the limited-ventilation group. It is also possible that permissive hypercapnia had a direct role, since carbon dioxide has known vasoactive properties that may have impaired renal blood flow, leading, in turn, to the need for dialysis.²⁸ In the group assigned to ventilation with pressure and volume limitation, we also found an increased use of paralytic agents and a trend toward more days of ventilation and longer stays in the intensive care unit and the hospital; all these factors may be related. Since the protocol did not specify when to use paralytic agents, these observations must be interpreted with caution.

During the design of this study, we hypothesized that patients in the limited-ventilation group would have lower ratios of PaO₂ to FiO₂ and more lung infiltrates than the control patients with the same degree of lung injury, because of the lower mean airway pressures. Therefore, we used the oxygen index (which controls for mean airway pressure), a valuable tool in neonates that has had limited use in adults.^{29,30} The oxygen index may prove to be valuable for comparing the effects of lung injury on gas exchange among various methods of ventilation.

Over the past decade, practice patterns with regard to pressure and volume during mechanical ventilation have changed, but with little evidence of benefit.³¹⁻³³ The results of this study suggest that an approach to mechanical ventilation that limits both peak inspiratory pressure (to 30 cm of water or less) and tidal volume (to 8 ml or less per kilogram) in patients such as ours does not decrease mortality and may be associated with harm. It cannot be concluded that pressure and volume limitation has no role. Indeed there may be a need for such a strategy in patients prone to lung overdistention (as evidenced by an elevated transpulmonary pressure, for example). In addition, other forms of lung protection, such as the prevention of underinflation and changes in body position, as well as other therapies, may have important roles in protecting the lungs and in reducing mortality. Clinicians should proceed with caution when using pressure- and volume-limited ventilation as a routine measure in patients with respiratory failure.

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APPENDIX 1

The members of the Pressure- and Volume-Limited Ventilation Strategy Group Steering Committee, in addition to the authors, were Mr. Rod MacDonald (respiratory-therapy coordinator), Ms. Barb Hooper, Mr. Andrew Cheeatowa, Dr. Ben Guslits (Henry Ford Hospital, Detroit), Ms. Merrilee Loewen, Ms. Kusun Sharma, Ms. Marg Oddi, Mr. Mike Aubin, Ms. Diane McRae, Mr. Grant Mawhinney, and Dr. Jesus Villar (Canary Islands, Spain). The Safety Committee included Dr. Brian Kavanaugh, Dr. Patricia Cruchly, Dr. Richard Cooper, Dr. Patrick Hanly, and Dr. David Wong.

APPENDIX 2

Definitions of Risk Factors

The risk factors for the acute respiratory distress syndrome were defined as follows:

1. Sepsis — two or more of the following five factors: (1) core temperature >38.5°C or <36°C, (2) white-cell count >12,000 per cubic millimeter or <3500 per cubic millimeter or >20 percent immature forms, (3) one blood culture positive for a common pathogen, (4) a strongly suspected site of infection from which a known pathogen was cultured, and (5) gross pus in a closed space; plus one or more of the following three factors: (1) systemic arterial hypotension for at least two hours (systolic blood pressure <85 mm Hg or >40 mm Hg below the base-line value or need for inotropic agents to maintain systolic blood pressure >85 mm Hg), (2) systemic vascular resistance less than 800 dyn·sec·cm⁻⁵ (if a pulmonary arterial catheter is present), and (3) unexplained metabolic acidosis (base deficit >5 mmol per liter).
2. Gastric aspiration — inhalation of gastric contents, witnessed or documented by suctioning of gastric contents from the endotracheal tube.
3. Pulmonary contusion — a localized infiltrate appearing on chest radiography within six hours of blunt chest trauma, in association with overlying ecchymosis or rib fractures.
4. Multiple transfusions — infusion of at least 10 units of whole blood or packed red cells within a 12-hour period.
5. Multiple fractures — fractures of two or more major long bones, an unstable pelvic fracture, or one major long-bone fracture and a major pelvic fracture.
6. Pneumonia — presence of an infiltrate on chest radiography, plus any three of the following four factors: (1) purulent endotracheal aspirate, (2) known pathogens on Gram's staining or culture of sputum or blood, (3) temperature >38.5°C or <36°C, and (4) white-cell count >12,000 per cubic millimeter or <3500 per cubic millimeter or >20 percent immature forms.
7. Inhalation injury — hypoxemia within three days of smoke inhalation or inhalation of a chemical lung irritant.
8. Burn — involvement of >25 percent of the body-surface area in a second- or third-degree burn.
9. Acute pancreatitis — severe abdominal pain, nausea, and vomiting with a serum amylase level >3 times the local upper limit of normal.
10. Drug overdose.
11. Shock — systemic arterial hypotension lasting two hours or more (systolic blood pressure <85 mm Hg or >40 mm Hg below the base-line value or need for inotropic drugs to maintain systolic blood pressure >85 mm Hg).

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