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VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

ABSTRACT

Background Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome. We therefore conducted a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients.

Methods Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter, randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 ml per kilogram of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 ml per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less. The first primary outcome was death before a patient was discharged home and was breathing without assistance. The second primary outcome was the number of days without ventilator use from day 1 to day 28.

Results The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent, $P=0.007$), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean [±SD], 12±11 vs. 10±11; $P=0.007$). The mean tidal volumes on days 1 to 3 were 6.2±0.8 and 11.8±0.8 ml per kilogram of predicted body weight ($P<0.001$), respectively, and the mean plateau pressures were 25±6 and 33±8 cm of water ($P<0.001$), respectively.

Conclusions In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use. (N Engl J Med 2000;342:1301-8.)

THE mortality rate from acute lung injury and the acute respiratory distress syndrome[1] is approximately 40 to 50 percent.[2-4] Although substantial progress has been made in elucidating the mechanisms of acute lung injury,[5] there has been little progress in developing effective treatments.

Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight.[6] These volumes are larger than those in normal subjects at rest (range, 7 to 8 ml per kilogram), but they are frequently necessary to achieve normal values for the partial pressure of arterial carbon dioxide and pH. Since atelectasis and edema reduce aerated lung volumes in patients with acute lung injury and the acute respiratory distress syndrome,[7,8] inspiratory airway pressures are often high, suggesting the presence of excessive distention, or "stretch," of the aerated lung. In animals, ventilation with the use of large tidal volumes caused the disruption of pulmonary epithelium and endothelium, lung inflammation, atelectasis, hypoxemia, and the release of inflammatory mediators.[9-14] The release of inflammatory mediators could increase lung inflammation and cause injury to other organs.[10,15] Thus, the traditional approach to mechanical ventilation may exacerbate or perpetuate lung injury in patients with acute lung injury and the acute respiratory distress syndrome and increase the risk of nonpulmonary organ or system failure.

The writing committee (Roy G. Brower, M.D., Johns Hopkins University, Baltimore; Michael A. Matthay, M.D., University of California, San Francisco; Alan Morris, M.D., LDS Hospital, Salt Lake City; David Schoenfeld, Ph.D., and B. Taylor Thompson, M.D., Massachusetts General Hospital, Boston; and Arthur Wheeler, M.D., Vanderbilt University, Nashville) assumes responsibility for the overall content and integrity of the manuscript. Address reprint requests to Dr. Brower at the Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, 600 N. Wolfe St., Baltimore, MD 21287.

*Members of the Acute Respiratory Distress Syndrome (ARDS) Network are listed in the Appendix.

The use of lower tidal volumes during ventilation in patients with acute lung injury and the acute respiratory distress syndrome may reduce injurious lung stretch and the release of inflammatory mediators.[16-18] However, this approach may cause respiratory acidosis[16,17] and decrease arterial oxygenation[19,20] and may therefore require changes in the priority of some objectives in the care of these patients. With the traditional approach, the attainment of normal partial pressure of arterial carbon dioxide and pH is given a higher priority than is protection of the lung from excessive stretch. With an approach that involves lower tidal volumes, the reverse is true. Uncontrolled studies suggested that the use of a lower tidal volume would reduce mortality in patients with acute lung injury and the acute respiratory distress syndrome,[17] but the results of four randomized trials of lung-protecting ventilation strategies have been conflicting.[21-24] The present trial was conducted to determine whether the use of a lower tidal volume with mechanical ventilation would improve important clinical outcomes in such patients.

METHODS

Patients

Patients were recruited from March 1996 through March 1999 at the 10 university centers of the Acute Respiratory Distress Syndrome Network of the National Heart, Lung, and Blood Institute (the centers are listed in the Appendix). The protocol was approved by the institutional review board at each hospital, and informed consent was obtained from the patients or surrogates at all but one hospital, where this requirement was waived. A complete description of the methods is available on the World Wide Web (at www.ardsnet.org) or from the National Auxiliary Publications Service (NAPS).*

Patients who were intubated and receiving mechanical ventilation were eligible for the study if they had an acute decrease in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen to 300 or less (indicating the onset of hypoxemia; values were adjusted for altitude in Denver and Salt Lake City), bilateral pulmonary infiltrates on a chest radiograph consistent with the presence of edema, and no clinical evidence of left atrial hypertension or (if measured) a pulmonary-capillary wedge pressure of 18 mm Hg or less.[1] Patients were excluded if 36 hours had elapsed since they met the first three criteria; they were younger than 18 years of age; they had participated in other trials within 30 days before the first three criteria were met; they were pregnant; they had increased intracranial pressure, neuromuscular disease that could impair spontaneous breathing, sickle cell disease, or severe chronic respiratory disease; they weighed more than 1 kg per centimeter of height; they had burns over more than 30 percent of their body-surface area; they had other conditions with an estimated 6-month mortality rate of more than 50 percent; they had undergone bone marrow or lung transplantation; they had chronic liver disease (as defined by Child–Pugh class C)[25]; or their attending physician refused or was unwilling to agree to the use of full life support.

A centralized interactive voice system was used for randomization. Patients were randomly assigned to receive mechanical ventilation involving either traditional tidal volumes or lower tidal volumes.

*See NAPS document no. 05542 for 15 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpk., West Hempstead, NY 11552.

Ventilator Procedures

The volume-assist–control mode was used for the ventilator until the patient was weaned from the device or for 28 days after randomization on day 0. Because normal lung volumes are predicted on the basis of sex and height,[26,27] a predicted body weight was calculated for each patient from these data.[28] The predicted body weight of male patients was calculated as equal to $50 + 0.91(\text{centimeters of height} - 152.4)$; that of female patients was calculated as equal to $45.5 + 0.91(\text{centimeters of height} - 152.4)$. In the group treated with traditional tidal volumes, the initial tidal volume was 12 ml per kilogram of predicted body weight. This was subsequently reduced stepwise by 1 ml per kilogram of predicted body weight if necessary to maintain the airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) at a level of 50 cm of water or less. The minimal tidal volume was 4 ml per kilogram of predicted body weight. If the plateau pressure dropped below 45 cm of water, the tidal volume was increased in steps of 1 ml per kilogram of predicted body weight until the plateau pressure was at least 45 cm of water or the tidal volume was 12 ml per kilogram of predicted body weight.

In the group treated with lower tidal volumes, the tidal volume was reduced to 6 ml per kilogram of predicted body weight within four hours after randomization and was subsequently reduced stepwise by 1 ml per kilogram of predicted body weight if necessary to maintain plateau pressure at a level of no more than 30 cm of water. The minimal tidal volume was 4 ml per kilogram of predicted body weight. If plateau pressure dropped below 25 cm of water, tidal volume was increased in steps of 1 ml per kilogram of predicted body weight until the plateau pressure was at least 25 cm of water or the tidal volume was 6 ml per kilogram of predicted body weight. For patients with severe dyspnea, the tidal volume could be increased to 7 to 8 ml per kilogram of predicted body weight if the plateau pressure remained 30 cm of water or less.

Plateau pressures were measured with a half-second inspiratory pause at four-hour intervals and after changes in the tidal volume or positive end-expiratory pressure. Plateau pressures of more than 50 cm of water in the patients in the group treated with traditional tidal volumes and of more than 30 cm of water in patients in the group treated with lower tidal volumes were allowed if the tidal volume was 4 ml per kilogram of predicted body weight or if arterial pH was less than 7.15.

All other objectives and ventilation procedures, including weaning, were identical in the two study groups (Table 1). If a patient became able to breathe without assistance but subsequently required additional mechanical ventilation within a period of 28 days, the same tidal-volume protocol was resumed.

Organ or System Failure

Patients were monitored daily for 28 days for signs of the failure of nonpulmonary organs and systems.[29] Circulatory failure was defined as a systolic blood pressure of 90 mm Hg or less or the need for treatment with any vasopressor; coagulation failure as a platelet count of 80,000 per cubic millimeter or less; hepatic failure as a serum bilirubin concentration of at least 2 mg per deciliter (34 μmol per liter); and renal failure as a serum creatinine concentration of at least 2 mg per deciliter (177 μmol per liter). We calculated the number of days without organ or system failure by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death. Organs and systems were considered failure-free after patients were discharged from the hospital.

Plasma Interleukin-6 Concentrations

Blood samples were obtained from 204 of the first 234 patients on day 0 and on day 3 for measurement of plasma interleukin-6 by immunoassay (R & D Systems, Minneapolis).[30] Blood samples were stored in sterile EDTA-treated glass tubes.

Data Collection

Data on demographic, physiologic, and radiographic characteristics, coexisting conditions, and medications were recorded with-

TABLE 1. SUMMARY OF VENTILATOR PROCEDURES.*

VARIABLE	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	GROUP RECEIVING LOWER TIDAL VOLUMES
Ventilator mode	Volume assist–control	Volume assist–control
Initial tidal volume (ml/kg of predicted body weight)†	12	6
Plateau pressure (cm of water)	≤50	≤30
Ventilator rate setting needed to achieve a pH goal of 7.3 to 7.45 (breaths/min)	6–35	6–35
Ratio of the duration of inspiration to the duration of expiration	1:1–1:3	1:1–1:3
Oxygenation goal	PaO_2, 55–80 mm Hg, or SpO_2, 88–95%	PaO_2, 55–80 mm Hg, or SpO_2, 88–95%
Allowable combinations of FiO_2 and PEEP (cm of water)‡	0.3 and 5 0.4 and 5 0.4 and 8 0.5 and 8 0.5 and 10 0.6 and 10 0.7 and 10 0.7 and 12 0.7 and 14 0.8 and 14 0.9 and 14 0.9 and 16 0.9 and 18 1.0 and 18 1.0 and 20 1.0 and 22 1.0 and 24	0.3 and 5 0.4 and 5 0.4 and 8 0.5 and 8 0.5 and 10 0.6 and 10 0.7 and 10 0.7 and 12 0.7 and 14 0.8 and 14 0.9 and 14 0.9 and 16 0.9 and 18 1.0 and 18 1.0 and 20 1.0 and 22 1.0 and 24
Weaning	By pressure support; required by protocol when $FiO_2 \leq 0.4$	By pressure support; required by protocol when $FiO_2 \leq 0.4$

*PaO_2 denotes partial pressure of arterial oxygen, SpO_2 oxyhemoglobin saturation measured by pulse oximetry, FiO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

†Subsequent adjustments in tidal volume were made to maintain a plateau pressure of ≤50 cm of water in the group receiving traditional tidal volumes and ≤30 cm of water in the group receiving lower tidal volumes.

‡Further increases in PEEP, to 34 cm of water, were allowed but were not required.

in four hours before the ventilator settings were changed on day 0. Physiologic and radiographic data, medication use, and use of other investigational treatments were recorded between 6 and 10 a.m. on days 1, 2, 3, 4, 7, 14, 21, and 28. Data were transmitted weekly to the network coordinating center. Patients were followed until day 180 or until they were breathing on their own at home.

Assessment of Compliance

Randomly selected ventilator and blood gas variables were analyzed for compatibility with the protocol. Quarterly reports of these data from each of the 10 centers were used by investigators to assess compliance.

Statistical Analysis

The first primary outcome was death before a patient was discharged home and was breathing without assistance. Patients who were in other types of health care facilities at 180 days were considered to have been discharged from the hospital and to be breathing without assistance. The second primary outcome was ventilator-free days, defined as the number of days from day 1 to day 28 on which a patient breathed without assistance, if the period of unassisted breathing lasted at least 48 consecutive hours. A difference in ventilator-free days could reflect a difference in mortality, ventilator days among survivors, or both. Other outcomes were the number of days without organ or system failure and the occurrence of barotrauma, defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Interim analyses were conducted by an independent data and safety monitoring board after the enrollment of each successive group of approximately 200 patients. Stopping boundaries (with a two-sided α level of 0.05) were designed to allow early termination of the study if the use of lower tidal volumes was found to be either efficacious[31] or ineffective.[32]

The comparison of traditional with lower tidal volumes was one of two trials conducted simultaneously in the same patients in a factorial experimental design. Ketoconazole was compared with placebo in the first 234 patients, and lisofylline was compared with placebo in the last 194 patients; no drugs were assessed in the middle 433 patients.

We used Student's t-test or Fisher's exact test to compare baseline variables. We used analysis of covariance to compare log-transformed plasma interleukin-6 values. We used Wilcoxon's test to compare the day 0 and day 3 plasma interleukin-6 concentrations, ventilator-free days, and organ-failure–free days, which had skewed distributions. We used the 180-day cumulative incidence of mortality to compare the proportion of patients in each group who died before being discharged home and breathing without assistance,[33] after stratification for other experimental interventions: treatment with ketoconazole, the ketoconazole placebo, lisofylline, the lisofylline placebo, or no other agent. We used a chi-square test to determine whether there was an interaction between the study group and the other experimental interventions with respect to the mean (±SE) mortality rates at 180 days. All P values are two-sided.

RESULTS

The trial was stopped after the fourth interim analysis because the use of lower tidal volumes was found to be efficacious (P=0.005 for the difference in mortality between groups; P value for the stopping boundary, 0.023). The base-line characteristics of the 861 patients who were enrolled were similar, except that minute ventilation was slightly but significantly higher (P=0.01) in the group treated with lower tidal volumes (Table 2).

The tidal volumes and plateau pressures were significantly lower on days 1, 3, and 7 in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (Table 3). The mean (±SD) tidal volumes on days 1 to 3 were 6.2±0.8 and 11.8±0.8 ml per kilogram of predicted body weight (P<0.001), respectively, and the mean plateau pressures were 25±6 and 33±8 cm of water (P<0.001), respectively. The partial pressure of arterial oxygen was similar in the two groups at all three times, but the positive end-expiratory pressure and fraction of inspired oxygen were significantly higher and the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen was significantly lower in the group treated with lower tidal volumes on days 1 and 3. On day 7, positive end-expiratory pressure and the fraction of inspired oxygen were significantly higher in the group treated with traditional tidal volumes. The respiratory rate was significantly higher in the group treated with lower tidal volumes on days 1 and 3, but minute ventilation was similar in the two groups on these days. The partial pressure of arterial carbon dioxide was significantly higher on days 1, 3, and 7 and arterial pH was significantly lower on days 1 and 3 in the group treated with lower tidal volumes.

The probability of survival and of being discharged home and breathing without assistance during the first 180 days after randomization is shown in Figure 1. The mortality rate was 39.8 percent in the group treated with traditional tidal volumes and 31.0 percent in the group treated with lower tidal volumes (P=0.007; 95 percent confidence interval for the difference between groups, 2.4 to 15.3 percent). The interaction between the study group and stratification for other experimental interventions was not significant (P=0.16).

Data were available to calculate the static compliance of the respiratory system at base line in 517 patients (Fig. 2). The interaction between the quartile of static compliance at base line and the study group with respect to the risk of death was not significant (P=0.49).

The number of ventilator-free days was significantly higher in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (Table 4). The median duration of ventilation was 8 days among patients in both groups who were discharged from the hospital after weaning and 10.5 and 10 days, respectively, among those who died in the group treated with lower tidal volumes and the group treated with traditional tidal volumes. The number of days without nonpulmonary organ or system failure was significantly higher in the group treated with lower tidal volumes (P=0.006). This group had more days without circulatory failure (mean [±SD], 19±10 vs. 17±11 days; P=0.004), coagulation failure (21±10 vs. 19±11 days, P=0.004), and renal failure (20±11 vs. 18±11 days, P=0.005) than did the group treated with traditional tidal volumes. The

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	GROUP RECEIVING LOWER TIDAL VOLUMES (N=432)	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES (N=429)
Age (yr)	51±17	52±18
Female sex (%)	40	41
Race or ethnic group (%)		
White	75	71
Black	16	19
Hispanic	5	7
Other or unknown	4	3
APACHE III score†	81±28	84±28
PaO_2:FiO_2	138±64	134±58‡
PaO_2:FiO_2 ≤200 (%)	82	85
Tidal volume (ml)§	676±119	665±125
Minute ventilation (liters/min)	13.4±4.3¶	12.7±4.3
No. of nonpulmonary organ or system failures‖	1.8±1.1	1.8±1.0
Lung injury (%)		
Pneumonia	33	36
Sepsis	27	26
Aspiration	15	14
Trauma	13	9
Other causes	10	11
Multiple transfusions	2	3

*Plus–minus values are means ±SD. Because of rounding, not all percentages total 100. PaO_2 denotes partial pressure of arterial oxygen, and FiO_2 fraction of inspired oxygen.

†APACHE III denotes Acute Physiology, Age, and Chronic Health Evaluation. Scores can range from 0 to 299, with higher scores indicating more severe illness.[34]

‡Data were missing for one patient.

§Data were available for 300 patients in the group treated with lower tidal volumes and for 290 patients in the group treated with traditional tidal volumes.

¶P=0.01.

‖Organ and system failures were defined as described in the Methods section.

TABLE 3. RESPIRATORY VALUES DURING THE FIRST SEVEN DAYS OF TREATMENT IN PATIENTS WITH ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.*

VARIABLE	DAY 1		DAY 3		DAY 7	
	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES
Tidal volume (ml/kg of predicted body weight)	6.2±0.9	11.8±0.8	6.2±1.1	11.8±0.8	6.5±1.4	11.4±1.4
No. of patients	387	405	294	307	181	179
Plateau pressure (cm of water)	25±7	33±9	26±7	34±9	26±7	37±9
No. of patients	384	399	294	307	168	173
Peak inspiratory pressure (cm of water)	32±8	39±10	33±9	40±10	33±9	44±10
No. of patients	382	401	295	308	178	177
Mean airway pressure (cm of water)	17±13	17±12	17±14	19±17	17±14	20±10
No. of patients	369	385	288	301	176	173
Respiratory rate (breaths/min)	29±7	16±6	30±7	17±7	30±7	20±7
No. of patients	389	406	296	308	185	181
Minute ventilation (liters/min)	12.9±3.6	12.6±4.5	13.4±3.5	13.4±4.8	13.7±3.8	14.9±5.3
No. of patients	387	401	296	307	182	177
FiO_2	0.56±0.19	0.51±0.17	0.54±0.18	0.51±0.18	0.50±0.17	0.54±0.20
No. of patients	390	406	296	308	185	181
PEEP (cm of water)	9.4±3.6	8.6±3.6	9.2±3.6	8.6±4.2	8.1±3.4	9.1±4.2
No. of patients	390	406	296	308	185	181
PaO_2:FiO_2	158±73	176±76	160±68	177±81	165±71	164±88
No. of patients	350	369	284	297	148	160
PaO_2 (mm Hg)	76±23	77±19	74±22	76±23	73±17	75±21
No. of patients	350	369	284	297	148	160
$PaCO_2$ (mm Hg)	40±10	35±8	43±12	36±9	44±12	40±10
No. of patients	351	369	285	297	147	160
Arterial pH	7.38±0.08	7.41±0.07	7.38±0.08	7.41±0.07	7.40±0.07	7.41±0.08
No. of patients	351	369	285	297	148	160

*Plus–minus values are means (±SD) of the values recorded between 6 and 10 a.m. on days 1, 3, and 7 after enrollment. The numbers of patients refers to those who were receiving ventilation and for whom data were available. FiO_2 denotes fraction of inspired oxygen, PEEP positive end-expiratory pressure, PaO_2 partial pressure of arterial oxygen, and $PaCO_2$ partial pressure of arterial carbon dioxide. All differences between study groups were significant on each day ($P<0.05$) except for mean airway pressure on days 1, 3, and 7; the PaO_2:FiO_2 on day 7; minute ventilation on days 1 and 3; pH on day 7; and PaO_2 on days 1, 3, and 7.

incidence of barotrauma after randomization was similar in the two groups.

There were no significant differences between groups in the percentages of days on which neuromuscular-blocking drugs were used among patients who were discharged home and breathing without assistance (6±14 percent in the group treated with lower tidal volumes and 6±15 percent in the group treated with traditional tidal volumes) or among those who died (20±32 percent and 16±28 percent, respectively), or in the percentages of days on which sedatives were used among patients who were discharged home and breathing without assistance (65±26 percent and 65±24 percent, respectively) or those who died (73±24 percent and 71±28 percent, respectively). Investigational treatments for acute lung injury and the acute respiratory distress syndrome that were not included in the factorial design of the experimental interventions were given to 15 patients in the group treated with lower tidal volumes and 12 patients in the group treated with traditional tidal volumes. These included prone positioning in 14 and 9 patients, respectively.

The mean log-transformed plasma interleukin-6 values decreased from 2.5±0.7 pg per milliliter on day 0 to 2.3±0.7 pg per milliliter on day 3 in the group treated with traditional tidal volumes and from 2.5±0.7 pg per milliliter to 2.0±0.5 pg per milliliter in the group treated with lower tidal volumes. The decrease was greater in the group treated with lower tidal volumes ($P<0.001$), and the day 3 plasma interleukin-6 concentrations were also lower in this group ($P=0.002$).

DISCUSSION

In this large study of patients with acute lung injury and the acute respiratory distress syndrome, mortality was reduced by 22 percent and the number of ventilator-free days was greater in the group treated with lower tidal volumes than in the group treated

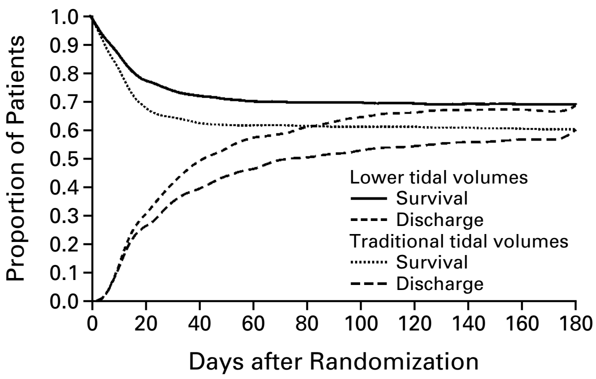

Figure 1. Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.

The status at 180 days or at the end of the study was known for all but nine patients. Data on these 9 patients and on 22 additional patients who were hospitalized at the time of the fourth interim analysis were censored.

TABLE 4. MAIN OUTCOME VARIABLES.*

VARIABLE	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	P VALUE
Death before discharge home and breathing without assistance (%)	31.0	39.8	0.007
Breathing without assistance by day 28 (%)	65.7	55.0	<0.001
No. of ventilator-free days, days 1 to 28	12±11	10±11	0.007
Barotrauma, days 1 to 28 (%)	10	11	0.43
No. of days without failure of nonpulmonary organs or systems, days 1 to 28	15±11	12±11	0.006

*Plus–minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.

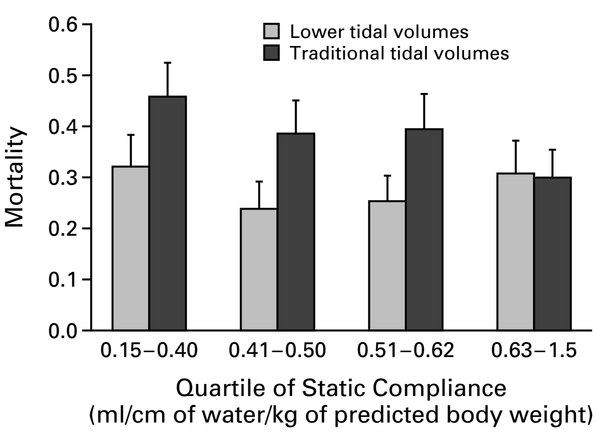

Figure 2. Mean (+SE) Mortality Rate among 257 Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome Who Were Assigned to Receive Traditional Tidal Volumes and 260 Such Patients Who Were Assigned to Receive Lower Tidal Volumes, According to the Quartile of Static Compliance of the Respiratory System before Randomization.

The interaction between the study group and the quartile of static compliance at base line was not significant (P=0.49).

with traditional tidal volumes. These results are consistent with the results of experiments in animals[9-14] and observational studies in humans.[16,17]

These benefits occurred despite the higher requirements for positive end-expiratory pressure and fraction of inspired oxygen and the lower ratio of partial pressure of arterial oxygen to fraction of inspired oxygen in the group treated with lower tidal volumes on days 1 and 3. These results, coupled with the greater reductions in plasma interleukin-6 concentrations, suggest that the group treated with lower tidal volumes had less lung inflammation.[35] The greater reductions in plasma interleukin-6 concentrations may also reflect a reduced systemic inflammatory response to lung injury, which could contribute to the higher number of days without organ or system failure and the lower mortality in the group treated with lower tidal volumes.[15]

Several factors could explain the difference in results between our trial and other trials of ventilation using lower tidal volumes in patients with acute lung injury and the acute respiratory distress syndrome.[22-24] First, our study had a greater difference in tidal volumes between groups. In one earlier trial, the traditional tidal volume was equivalent to approximately 12.2 ml per kilogram of predicted body weight and the lower tidal volume was equivalent to approximately 8.1 ml per kilogram of predicted body weight.[23] In a second study, the traditional and lower tidal volumes were approximately 10.3 and 7.1 ml per kilogram of dry body weight (calculated as the measured weight minus the estimated weight gain from fluid retention), respectively.[22] In the present trial, measured weight exceeded predicted body weight by approximately 20 percent. Assuming a similar difference, and assuming that half the difference was dry weight in excess of predicted body weight, tidal volumes in the second trial would have been approximately 11.3 and 7.8 ml per kilogram of predicted body weight. Therefore, the traditional tidal volume of 11.8 ml per kilogram of predicted body weight in our study was similar to the values in the previous two trials.

However, the tidal volume of 6.2 ml per kilogram of predicted body weight in the group receiving lower tidal volumes was lower than the values in the previous two trials.

If one assumes that measured weights also exceeded predicted body weights by 20 percent in the earlier trials, the tidal volumes in the traditional groups were approximately 10.2 and 9.4 ml per kilogram of measured weight, respectively, as compared with 9.9 ml per kilogram of measured weight in our study. Therefore, the tidal volumes in the traditional groups in each of the three trials were consistent with traditional recommendations.[6,36]

A second possible explanation for the different results is that the previous trials were designed to detect larger differences in mortality between groups.[22-24] Hence, they lacked the statistical power to demonstrate the moderate effects of lower tidal volumes that we found.

A third difference in the trials was in the treatment of acidosis. Increases in the ventilator rate were required and bicarbonate infusions were allowed to correct mild-to-moderate acidosis in our study, which resulted in smaller differences in the partial pressure of arterial carbon dioxide and pH between the study groups than in the previous trials.[22-24] The deleterious effects of acidosis in the previous studies may have counteracted a protective effect of the lower tidal volumes.

In addition to being caused by excessive stretch, lung injury may also result from repeated opening and closing of small airways or from excessive stress at margins between aerated and atelectatic regions of the lungs.[37] These types of lung injury may be prevented by the use of a higher positive end-expiratory pressure.[10,13,37,38] A slightly higher positive end-expiratory pressure was necessary in the group treated with lower tidal volumes during the first few days to maintain arterial oxygenation at a level similar to that in the group treated with traditional tidal volumes, but positive end-expiratory pressure was not increased as a means of protecting the lungs.

In a recent trial in 53 patients with acute respiratory distress syndrome, 28-day mortality was significantly lower with a ventilation strategy that used a higher positive end-expiratory pressure combined with limited peak inspiratory pressure than with a strategy of traditional ventilation.[21] These results suggest that both increased positive end-expiratory pressure and reduced inspiratory stretch could have beneficial effects.

Stretch-induced lung injury may not occur if lung compliance is not greatly reduced. However, the benefit of ventilation with a lower tidal volume was independent of the static compliance of the respiratory system at base line, suggesting that the lower tidal volume was advantageous regardless of lung compliance. Variations in chest-wall compliance, which contributes to compliance of the respiratory system and is reduced in many patients with acute lung injury and the acute respiratory distress syndrome,[39] may have obscured a true interaction between tidal volume and base-line lung compliance.

Barotrauma occurred with similar frequency in the two study groups, a finding consistent with the results of other studies in which the incidence of barotrauma was independent of airway pressures.[22-24,40,41] The most common manifestation of barotrauma was pneumothorax, which could have been the result of invasive procedures. Pneumothorax is not a sensitive or specific marker of stretch-induced injury with the tidal volumes used in this study.

The similarity in the number of days of ventilator use among the survivors in both groups suggests that the higher number of ventilator-free days in the group treated with lower tidal volumes resulted from reduced mortality rather than from a reduced number of days of ventilation among the survivors. However, the comparison of the number of days of ventilator use among the survivors could be misleading.[42] Some patients who would have survived in the group treated with traditional tidal volumes might have needed the ventilator on fewer days had they been in the group treated with lower tidal volumes. This beneficial effect would have been obscured if prolonged ventilation was required before recovery among patients who otherwise would have died in the group treated with traditional tidal volumes. For similar reasons, it is also difficult to compare the number of days with organ or system failure among the survivors in the two study groups.

We found that treatment with a ventilation approach designed to protect the lungs from excessive stretch resulted in improvements in several important clinical outcomes in patients with acute lung injury and the acute respiratory distress syndrome. On the basis of these results, high priority should be given to preventing excessive lung stretch during adjustments to mechanical ventilation, and this lower-tidal-volume protocol should be used in patients with acute lung injury and the acute respiratory distress syndrome.

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APPENDIX

In addition to the members of the Writing Committee, the members of the National Heart, Lung, and Blood Institute ARDS Network were as follows: **Network Participants:** *Cleveland Clinic Foundation* — H.P. Wiedemann, A.C. Arroliga, C.J. Fisher, Jr., J.J. Komara, Jr., P. Perez-Trepichio;

Denver Health Medical Center — P.E. Parsons, R. Wolkin; *Denver Veterans Affairs Medical Center* — C. Welsh; *Duke University Medical Center* — W.J. Fulkerson, Jr., N. MacIntyre, L. Mallatratt, M. Sebastian, R. McConnell, C. Wilcox, J. Govert; *Johns Hopkins University* — D. Thompson; *LDS Hospital* — T. Clemmer, R. Davis, J. Orme, Jr., L. Weaver, C. Grissom, M. Eskelson; *McKay–Dee Hospital* — M. Young, V. Gooder, K. McBride, C. Lawton, J. d'Hulst; *MetroHealth Medical Center of Cleveland* — J.R. Peerless, C. Smith, J. Brownlee; *Rose Medical Center* — W. Pluss; *San Francisco General Hospital Medical Center* — R. Kallet, J.M. Luce; *Jefferson Medical College* — J. Gottlieb, M. Elmer, A. Girod, P. Park; *University of California, San Francisco* — B. Daniel, M. Gropper; *University of Colorado Health Sciences Center* — E. Abraham, F. Piedalue, J. Glodowski, J. Lockrem, R. McIntyre, K. Reid, C. Stevens, D. Kalous; *University of Maryland* — H.J. Silverman, C. Shanholtz, W. Corral; *University of Michigan* — G.B. Toews, D. Arnoldi, R.H. Bartlett, R. Dechert, C. Watts; *University of Pennsylvania* — P.N. Lanken, H. Anderson III, B. Finkel, C.W. Hanson; *University of Utah Hospital* — R. Barton, M. Mone; *University of Washington–Harborview Medical Center* — L.D. Hudson, C. Lee, G. Carter, R.V. Maier, K.P. Steinberg; *Vanderbilt University* — G. Bernard, M. Stroud, B. Swindell, L. Stone, L. Collins, S. Mogan; **Clinical Coordinating Center:** *Massachusetts General Hospital* and *Harvard Medical School* — M. Ancukiewicz, D. Hayden, F. Molay, N. Ringwood, G. Wenzlow, A.S. Kazeroonian; **National Heart, Lung, and Blood Institute Staff:** D.B. Gail, C.H. Bosken, P. Randall, M. Waclawiw; **Data and Safety Monitoring Board:** R.G. Spragg, J. Boyett, J. Kelley, K. Leeper, M. Gray Secundy, A. Slutsky; **Protocol Review Committee:** T.M. Hyers, S.S. Emerson, J.G.N. Garcia, J.J. Marini, S.K. Pingleton, M.D. Shasby, W.J. Sibbald.

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