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Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients

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Links

Abstract

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Abstract

Objective: To assess the safety and potential efficacy of a mechanical ventilation strategy designed to reduce stretch-induced lung injury in acute respiratory distress syndrome.

Design: Prospective, randomized, controlled clinical trial.

Setting: Eight intensive care units in four teaching hospitals.

Patients: Fifty-two patients with acute respiratory distress syndrome.

Interventions: Traditional tidal volume patients: tidal volume 10-12 mL/kg ideal body weight, reduced if inspiratory plateau pressure was >55 cm H_2 O (7.3 kPa). Small tidal volume patients: tidal volume 5-8 mL/kg ideal body weight, to keep plateau pressure < 30 cm H_2 O (4.0 kPa).

Measurements and Main Results: Mean tidal volumes during the first 5 days in traditional and small tidal volume patients were 10.2 and 7.3 mL/kg, respectively ($p < .001$), with mean plateau pressure = 30.6 and 24.9 cmH_2O (3.3 kPa), respectively ($p < .001$). There were no significant differences in requirements for positive end-expiratory pressure or FIO_2, fluid intakes/outputs, requirements for vasopressors, sedatives, or neuromuscular blocking agents, percentage of patients that achieved unassisted breathing, ventilator days, or mortality.

Conclusions: The reduced tidal volume strategy used in this study was safe. Failure to observe beneficial effects of small tidal volume ventilation treatment in important clinical outcome variables may have occurred because a) the sample size was too small to discern small treatment effects; b) the differences in tidal volumes and plateau pressures were modest; or c) reduced tidal volume ventilation is not beneficial. (Crit Care Med 1999; 27:1492-1498)

Key Words: acute respiratory distress syndrome (ARDS); acute lung injury; tidal volume; permissive hypercapnia; mechanical ventilation; plateau pressure

Mortality from acute respiratory distress syndrome (ARDS) remains high despite advances in treatments for the conditions that cause or are associated with this disorder [1,2]. Animal studies have shown that mechanical ventilation (MV) may cause acute lung injury from overdistention of lung tissue [3-9]. This could occur in ARDS patients receiving traditional techniques of MV, which would exacerbate or perpetuate respiratory failure. It has been suggested that recovery from ARDS could improve if gas exchange were maintained without overdistending the lung [10-12].

Low mortality rates were reported in ARDS patients who received MV with small tidal volumes to prevent stretch-induced lung injury [13,14]. However, without concurrent control groups, these studies did not allow direct comparisons of mortality with small tidal volume ventilation (STV) vs. traditional tidal volume ventilation (TTV). This comparison is necessary because there may be adverse effects of STV. In dogs and humans [15-17], ventilation with smaller volumes was associated with higher intrapulmonary shunt and alveolar-arterial PO_2 gradients, perhaps from atelectasis. Thus, STV may require higher FIO_2 or positive end-expiratory pressure (PEEP) to maintain arterial oxygenation. Patients may experience acute respiratory acidosis with STV. This could decrease contractility of the heart or diaphragm or alter systemic vascular tone and the distribution of systemic blood flow [18-21]. STV and acidosis also may contribute to dyspnea and agitation, increasing requirements for sedatives and neuromuscular blocking agents. Despite the limitations of the earlier studies of STV and concerns for potential adverse effects, many clinicians have adopted its use in clinical practice [22].

A primary purpose of this phase II study was to assess for adverse effects and potential benefits of STV. This information is necessary to establish the safety of STV and to design further studies to establish its value. Effects on pulmonary gas exchange were assessed by comparing levels of PEEP and FIO_2 required to maintain the same levels of arterial oxygenation. If the predominant effect of STV is greater intrapulmonary shunt, then requirements for oxygenation support should increase. If the predominant effect of STV is reduced lung injury, then requirements for high FIO_2 and PEEP should decrease. Effects of STV on dyspnea and agitation were assessed by comparing requirements for medications used for sedation and neuromuscular blockade. Effects on circulation were assessed by comparing fluid balances (intakes and outputs) and requirements for vasopressors. Finally, to aid in the design of future trials, data were collected regarding time to reversal of respiratory failure (RRF, achievement of >or=to48 hrs of unassisted breathing) and percent mortality.

MATERIALS AND METHODS

Patients. Patients were recruited from the hospitals and intensive care units listed in Table 1. The protocol was approved by the institutional review board of each hospital. Informed consent was obtained from patients when they were competent or from surrogates.

Hospital/ICU	No. of TTV/STV Patients
Johns Hopkins Hospital	
Medical ICU	8/7
Surgical ICU	4/4
Oncology	1/1
Hopkins Bayview Medical Center	
Medical ICU	5/3
University of Maryland Medical Center	
Medical ICU	3/1
Surgical ICU	0/2
Oncology	4/5
Baltimore Veterans Administration Hospital	
Medical ICU	2/2
Total	26/26

ICU, intensive care unit; TTV, traditional tidal volume ventilation; STV, small tidal volume ventilation.

Table 1. Patient recruitment

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Patients were eligible if all of the following inclusion criteria occurred within the same 24-hr interval: a) $PaO_{2/FIO2}$ <or=to 200 torr; b) bilateral alveolar or interstitial radiographic infiltrates, not attributable to atelectasis or effusions (all radiographs were interpreted by a member of the study team before enrollment); c) no suspicion of congestive heart failure (when a right heart catheter was in place, pulmonary artery wedge pressure <or=to 18 torr (2.4 kPa) was required); and d) receiving positive pressure ventilation via an endotracheal tube. Patients were enrolled within 24 hrs of the time when the eligibility criteria were first met.

Patients were excluded for any of the following conditions: a) age < 18 yrs; b) pregnancy; c) acute neurologic disease for which hypercapnia would be contraindicated; d) anticipated life expectancy from co-morbid conditions < 3 months; e) severe chronic obstructive or restrictive respiratory disease; f) history of sickle cell (hemoglobin SS or hemoglobin SC) disease; or g) lobectomy or pneumonectomy during the current hospitalization.

Randomization. Randomization was stratified by intensive care unit, with equal numbers of patients in each treatment group in variable-sized blocks. All members of the study team and clinical staffs were masked to the study group assignment sequence and block size.

Ventilator Management. The rules for ventilator management are summarized in Table 2. Acceptable ranges were specified for some patient and ventilator variables. When a variable fell within an acceptable range, changes in treatment were allowed but not required.

Table 2. Ventilator management

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The initial ventilator mode was volume-assist/control. Ventilator set rate was adjusted from 6-30 breaths/min to achieve target $PaCO_2$ of 30-45 torr (4.0-6.0 kPa) if possible. If a patient's intrinsic respiratory rate exceeded 30 breaths/min, synchronized intermittent mandatory ventilation mode with <or=to5 cm H_2 O (0.6 kPa) pressure support was required. The maximum ventilator rate of 30 breaths/min was used to minimize air trapping and to improve protocol control of lung volume and airway pressures.

Measurements of inspiratory plateau pressure (Pplat) were required twice daily and immediately after each change in tidal volume (Vt) or PEEP. Pplat measurements were obtained with a 0.5-sec end-inspiratory pause, when patients were relaxed and not coughing or moving.

Initial Vt in TTV patients was 10-12 mL/kg ideal body weight (IBW), which represented a consensus of the current practices of the intensivists in the participating intensive care units. IBW in kilograms was calculated from the following equations [23]: male IBW = 50 + 2.3 (height [inches] - 60); female IBW = 45.5 + 2.3 (height [inches] - 60). Vt remained at this level in TTV patients unless Pplat was >45-55 cm H_2O (6.0-7.3 kPa). If this limit was exceeded in TTV patients, Vt was reduced in increments of 0.5 mL/kg IBW until Pplat was <45-55 cm H_2O (6.0-7.3 kPa). In STV patients, the initial Vt was 8 mL/kg IBW. If necessary, Vt was reduced further in STV patients in increments of 0.5 mL/kg IBW at intervals of 3-6 hrs to achieve Pplat of <or=to30 cm H_2O (4.0 kPa). Thereafter, further reductions in Vt of 0.5 mL/kg were made only if Pplat exceeded 30 cm H_2O (4.0 kPa). The lower limit for Vt in both TTV and STV patients was 5 mL/kg.

Arterial oxygenation was monitored continuously in most patients by pulse oximetry. The target range for oxygen saturation (SpO_2) was 86% to 94%. If pulse oximetry was not available or clinicians preferred to use arterial PO_2 to guide therapy, the acceptable range for oxygenation was 55 <or=to PaO_2 <or=to 75 torr (7.3-10 kPa). When in use, SpO_2 was recorded at least once per hour. When SpO ($_2$) was not available, PaO_2 was measured when clinically indicated. Oxygenation was controlled in both treatment groups according to the same protocol procedures that allowed only specific combinations of PEEP and FIO_2 (Table 2). When oxygenation deviated from the target range, either PEEP or FIO_2 was increased or decreased according to the PEEP/FIO_2 scheme until SpO_2 or PaO_2 returned to the target range. PEEP > 20 cm H_2O (2.7 kPa) was allowed but not required if PaO ($_2$) was <55 torr (7.3 kPa) or SpO_2 was <86% with FIO_2 of 1.0. PEEP < 5 cm H_2O (0.7 kPa) and FIO_2 < 0.5 were allowed but not required if oxygenation exceeded the target range on those settings.

Acid-base balance was managed in both groups according to the following rules: a) adjust ventilator set rate to achieve $PaCO_2$ of 30-45 torr (4.0-6.0 kPa) if possible (without exceeding a ventilator set rate of 30 breaths/min); b) if pH was <7.30, administration of sodium bicarbonate was permissible; and c) if pH was <7.20, intravenous sodium bicarbonate was required at >or=to10 mEq/hr. Measurements of arterial pH were obtained when clinically indicated.

During the protocol initiation phase, ventilator changes were made by one of the investigators in conjunction with the intensive care unit staff. This phase lasted [similar]60-180 mins, until Vt was 10-12 mL/kg IBW (TTV group) or <or=to8 mL/kg IBW (STV group), PEEP and FIO_2 were compatible with the PEEP/FIO_2 scheme, inspiratory time was less than or equal to expiratory time, and SpO_2 (or PaO_2), $PaCO_2$, Pplat, and pH were within their respective target ranges. After these initial protocol ventilator changes, subsequent ventilator adjustments were made by the intensive care unit clinical staffs according to a protocol order set. Study procedures were continued for 28 days or until a patient achieved RRF or died. Members of the study team monitored each patient's progress to maintain compliance with study procedures.

Weaning from positive pressure ventilation was allowed and encouraged when oxygenation was within the acceptable range on PEEP of 5 cm H_2O (0.7 kPa) and FIO_2 of <or=to50%. The weaning method was not controlled.

Data Collection. Demographic, physiologic, and chronic health data were recorded before initial ventilator changes. Thereafter, physiologic data were recorded daily until death or RRF. For frequently measured variables such as FIO_2 and PaO_2, mean values were calculated for each patient-day (daily-mean). All doses of medications used for sedation, neuromuscular blockade, and vasopressors (Neo-Synephrine, norepinephrine, epinephrine, and dopamine >or=to 5 [micro sign]g/kg/min) were recorded daily. Twenty-four-hour totals for fluid intakes and outputs were recorded for each day a patient received MV. Each barotrauma event (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, and pneumatoceles > 2 cm in diameter) was recorded for all patients.

Protocol Compliance. Compliance with study procedures was assessed by retrospective review of clinical records. For each patient, two dates/times during MV before weaning were generated randomly by computer. At each of these times, the most recently recorded values of Pplat, PaO_2, SpO_2, PCO_2, ventilator mode, Vt, and PEEP/FIO_2 were assessed for consistency with the study rules.

Study Design and Statistics. The effects of TTV vs. STV treatment on oxygenation were assessed by analyzing trends over time in requirements for oxygenation support with PEEP and FIO_2. Because SpO_2 or PaO_2 were maintained in the same target ranges throughout each patient's course, increasing or decreasing PEEP and FIO_2 requirements over

time represented worsening or improving gas exchange, respectively. Treatment group effects on gas exchange, if any, were anticipated to occur within several days. Moreover, the number of patients who died or achieved spontaneous ventilation was substantial after 5 days (33% of all patients enrolled). Therefore, slopes of the relationships of FIO_2 vs. time and of PEEP vs. time were calculated for each patient from linear regressions of the daily-mean FIO_2 and PEEP values from day 0 (day of enrollment) through day 5 (or through day 2, 3, or 4 for patients who died or achieved unassisted breathing before day 5). If lung injury decreased and gas exchange improved with STV, these slopes would be lower in STV patients. In contrast, if the predominant effect of STV was worse shunt, these slopes would be greater. Differences in these slopes between treatment groups were assessed by multiple linear regression, adjusting for effects of age, Acute Physiology and Chronic Health Evaluation (APACHE) III score [24], Murray lung injury score [25], gender, race, cause of ARDS (pneumonia, sepsis, aspiration, or pancreatitis), and type of intensive care unit (medical, surgical, or oncology).

The effects of TTV vs. STV treatment on circulation were assessed by comparing requirements for intravenous fluids and vasopressors. Total fluid intakes and outputs were compared between groups by unpaired t-tests. To compare the use of vasopressors, a value was calculated for each patient representing the mean number of different vasopressors used per MV day through protocol day 5. These values were compared between treatment groups by a permutation test that accounted for ordered outcomes.

To analyze differences in the use of sedatives, a value was calculated for each patient representing the number of different medication classes (benzodiazepines, narcotics, and haloperidol) used per MV day through day 5. These values were compared between treatment groups by a nonparametric linear rank permutation test that accounted for ordered outcomes [26]. Because benzodiazepines were used most commonly for sedation, use of these medications was analyzed further. Each patient's 5-day total doses of lorazepam and midazolam were converted to diazepam equivalents by multiplying by 4 and 2, respectively [27]. Each patient's total 5-day diazepam equivalent dose per kilogram IBW was divided by the number of days the patient was alive and on MV. These values were compared between treatment groups by unpaired t-test. To analyze the use of neuromuscular blocking agents, a fraction was calculated for each patient representing the proportion of MV days through protocol day 5 on which pancuronium, vecuronium, or atracurium was used. Treatment group differences in these fractions were compared by a nonparametric linear rank permutation test that accounted for ordered outcomes [26]. The use of neuromuscular blocking agents was analyzed further by converting each patient's 5-day total doses of vecuronium and atracurium to pancuronium equivalents by multiplying by 0.5 and 0.08, respectively [28]. For each patient, a single 5-day pancuronium equivalent dose per kilogram IBW was divided by the number of days the patient was alive and on MV. These values were compared between treatment groups by unpaired t-test.

The effects of TTV vs. STV treatment on the proportion of patients who died before hospital discharge were assessed by logistic regression, adjusting for the effects of age, APACHE III score, Murray lung injury score, gender, race, cause of ARDS, and type of intensive care unit.

A sample size was calculated based on estimations of treatments' effects on RRF. Because RRF is a dichotomous variable and is affected in each patient by many factors in addition to ventilator treatment, a larger sample is probably necessary to demonstrate treatment effects on RRF than on variables such as oxygenation. The proportion of TTV and STV patients who would achieve RRF was estimated to be 35% and 65%, respectively, consistent with previous studies [13,14,29-32]. The study was designed to have 90% power to detect this difference with a two-sided hypothesis test with type I error of 5%. With these assumptions, 65 patients would be required in each arm to complete the trial.

A sequential design allowed analyses of safety data and RRF after completion of the protocol by groups of 26 patients. Stopping boundaries were designed to stop the trial at an interim analysis for STV superiority or for futility (if it appeared very unlikely that superiority could be demonstrated with additional enrollment).

All values are expressed as mean +/- SEM unless indicated otherwise. Differences in continuous measurements between treatment groups were assessed for statistical significance using unpaired t-tests. All p values reported are two-sided. Statistical significance was inferred at $p < .05$. All statistical analyses were conducted using SPSS for Windows software, version 7.0 (SPSS, Chicago, IL) and Stat Xact for Windows, version 3 (Cytel Software, Cambridge, MA).

RESULTS

Fifty-two patients were enrolled between May 2, 1994, and March 1, 1996. Patient characteristics at enrollment are shown in Table 3. An administrative decision was made to stop the trial to allow participation in another ARDS study. The decision was made after the second interim analysis, when it was apparent that there were sufficient data to

address the questions regarding STV effects on gas exchange, circulation, and sedation and that it was unlikely that beneficial treatment effects on RRF could be demonstrated if the trial were to continue.

	TTV	STV
Age (yrs)	49.8 (14.4)	46.9 (17.1)
Female/male (%)	58/42	31/69
Race (%)		
White, non-Hispanic	54	62
Black	46	31
Asian	0	7
APACHE III score	84.6 (27.1)	90.6 (26.4)
LIS	2.7 (0.5)	2.8 (0.5)
Conditions causing ARDS		
Pneumonia	17	11
Sepsis	6	6
Aspiration	2	6
Pancreatitis	1	3
Co-morbid conditions		
AIDS	2	2
BMT	2	4
Cancer	2	3
Pa_{O_2}/Fi_{O_2}	150 (69)	129 (51)

TTV and STV, traditional and small tidal volume treatment groups, respectively; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; AIDS, acquired immunodeficiency syndrome; BMT, bone marrow transplantation; LIS, lung injury score (25).

Numbers in parentheses are SD values. Pa_{O_2}/Fi_{O_2} ratios are the first values obtained after protocol ventilator procedures were initiated.

Table 3. Patient characteristics

Mean daily-mean Vt (mL/kg IBW) and Pplat for TTV and STV patients for each of the first 5 days after enrollment are shown in Figure 1. Mean daily-mean Vt values in TTV and STV patients during the first 5 days were 621 +/- 8 and 462 +/- 10 mL, 10.2 +/- 0.1 mL/kg and 7.3 +/- 0.1 mL/kg IBW, respectively ($p < .001$). Mean daily-mean TTV and STV Pplat values during this interval were 30.6 +/- 0.8 cm H_2O (4.1 +/- 0.1 kPa) and 24.9 +/- 0.8 cm H_2O (3.3 +/- .10 kPa), respectively ($p < .001$). The highest daily-mean $PaCO_2$ values for each patient from the day of enrollment through day 5 are shown in Figure 2. The mean highest daily-mean $PaCO_2$ values in TTV and STV patients during the first 5 days were 40.1 +/- 1.6 and 50.3 +/- 3.5 torr (5.3 +/- 0.2 and 6.7 +/- 0.5 kPa), respectively ($p = .01$). These corresponded to daily-mean pH values in TTV and STV patients of 7.38 +/- 0.02 and 7.34 +/- 0.02, respectively ($p = .12$).

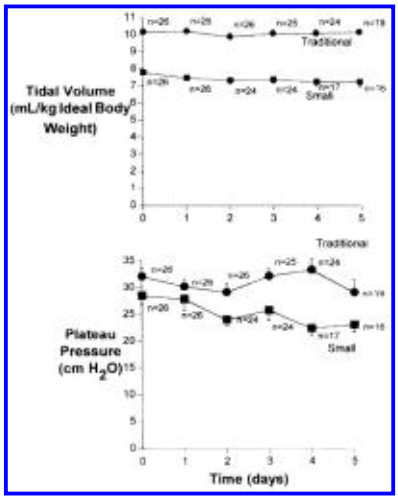

Figure 1. Tidal volumes (top) and plateau pressures (bottom) in traditional tidal volume ventilation (circles) and small tidal volume ventilation (squares) patients. Values shown are mean +/- SEM of the daily-mean for all patients remaining on mechanical ventilation during the first 5 days after randomization. n, number of patients remaining on mechanical ventilation.

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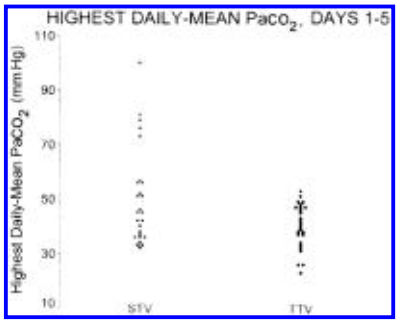

Figure 2. Highest daily-mean $PaCO_2$ values for each patient from enrollment through day 5. TTV, traditional tidal volume ventilation; STV, small tidal volume ventilation.

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Effects of STV on Requirements for FIO_2 and PEEP. Mean daily-mean PO_2 values for the TTV and STV treatment groups for the first 5 days after enrollment were 83.2 +/- 1.9 and 79.8 +/- 2.2 torr (11.1 +/- 0.3 and 10.6 +/- 0.3 kPa), respectively (p = .25). These exceeded the upper limit of the target range (75 torr, 10 kPa) primarily because decreases in PEEP or FIO_2 were not required when PEEP was <or=to5 and FIO_2 was <or=to0.50.

Mean daily-mean PEEP and FIO_2 values through day 5 are shown in Figure 3. The mean slopes of FIO_2 vs. time for TTV and STV patients were -0.02 +/- 0.01 and -0.02 +/- 0.01, respectively. The mean slopes of PEEP vs. time for TTV and STV patients were -0.28 +/- 0.21 and -0.54 +/- 0.25, respectively. There was no predictive value of TTV vs. STV treatment on either the FIO_2 or the PEEP slope after adjusting for the effects of age, APACHE III score, Murray lung injury score, cause of ARDS, intensive care unit type, race, or gender. Thus, STV treatment was not associated with either improvements or deteriorations in requirements for oxygenation support. Age alone had significant predictive value for PEEP requirements (p = .01). None of the factors in the model had predictive value for FIO_2 requirements.

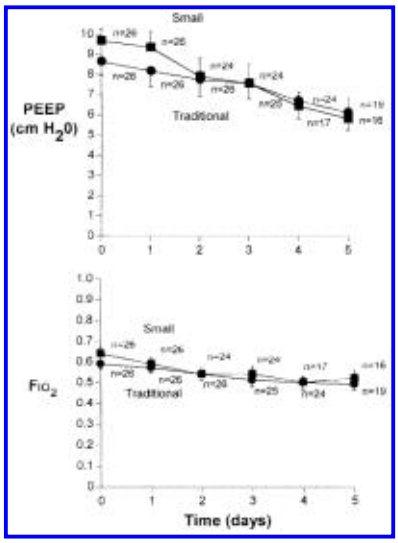

Figure 3. Positive end-expiratory pressure (PEEP, top) and FIO_2 (bottom) for traditional tidal volume ventilation (circles) and small tidal volume ventilation (squares) patients during the first 5 days after randomization. Values shown are mean +/- SEM of the daily-mean values during the first 5 days after randomization. n, number of patients remaining on mechanical ventilation.

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Effects of STV on Circulation. Mean daily total fluid intakes for all patients alive and on MV during the first 5 days after randomization were 3821 +/- 283 and 3842 +/- 270 mL

in the TTV and STV groups, respectively (not significant). Mean total fluid outputs were 3230 +/- 224 and 3132 +/- 289 mL, respectively (not significant). The mean net intake-output/day were 708 +/- 350 and 592 +/- 323 mL in the TTV and STV groups, respectively (p = .80). The mean numbers of vasopressors used per patient ventilator day through day 5 were 0.40 +/- 0.13 and 0.47 +/- 0.13 in the TTV and STV groups, respectively (not significant).

Use of Neuromuscular Blockers and Sedatives. The mean proportion of ventilator days through day 5 on which a neuromuscular blocker was used was 0.16 +/- 0.06 and 0.31 +/- 0.07 in TTV and STV patients, respectively (p = .13). The mean pancuronium equivalent doses during the first 5 days after enrollment in TTV and STV patients were 0.16 +/- 0.08 and 0.20 +/- 0.07 mg/kg/day, respectively (p = .69). The mean number of sedative medication classes administered per patient ventilator day through day 5 was 1.23 +/- 0.13 and 1.37 +/- 0.16 in the TTV and STV groups, respectively (p = .70). The mean diazepam equivalent doses in the TTV and STV groups were 0.13 +/- 0.03 and 0.26 +/- 0.09 mg/kg/day, respectively (p = .17).

Reversal of Respiratory Failure, Mortality, and Barotrauma. In both the TTV and STV groups, 15 of 26 patients (58%) achieved RRF (Figure 4). None of these patients returned to positive pressure ventilation before discharge or death. Of the patients who achieved RRF, the mean number of days on positive pressure ventilation were 11.9 +/- 1.9 and 11.3 +/- 2.2 days for TTV and STV patients, respectively (not significant). The mean number of days from the first day that weaning from MV was allowed (when FIO_2 was <or=to0.50 and PEEP was <or=to5) to RRF was 5.2 +/- 1.1 and 5.1 +/- 1.0 in the TTV and STV groups, respectively (p = .94).

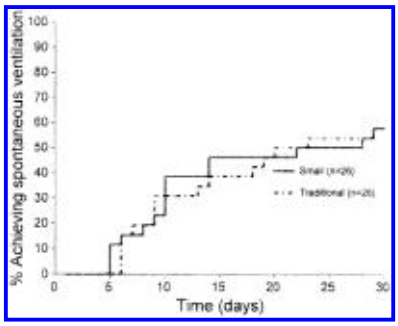

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Figure 4. Time to achieve spontaneous ventilation (breathing through T-piece or after extubation for >or=to48 hours). Small, small tidal volume ventilation; Traditional, traditional tidal volume ventilation.

Mortality before hospital discharge was 46% in the TTV group and 50% in the STV group. By logistic regression, treatment group was not predictive of mortality after adjustment for age, APACHE III score, Murray lung injury score, gender, race, cause of ARDS, and type of intensive care unit (p = .61). Only the APACHE III score had significant predictive value (p = .01) for mortality.

There was one barotrauma event in TTV patients and one in STV patients during the first 5 days after enrollment. One additional barotrauma event occurred between days 5 and 28 in the STV group.

Protocol Compliance. Percentages of ventilator and patient variables that were within protocol-specified ranges at the randomly selected times are shown in Table 4. Compliance with protocol rules controlling Vt, $PEEP/FIO_2$, and mode exceeded 95% in both treatment groups. Moreover, protocol targets for Pplat were achieved 96%-100% of the time. Targets for PaO_2, $PaCO_2$, and SpO_2 were achieved at rates of 69%-87%. There were no significant differences between groups. Weaning was initiated in only one patient (TTV) before PEEP was <or=to5 and FIO_2 was <or=to0.50.

Variable	All	TTV	STV
Pa_{O_2}	73	69	77
Sp_{O_2}	84	82	86
Pa_{CO_2}	87	83	90
Pplat	96	100	92
Mode	99	100	98
PEEP/F_{IO_2}	94	92	96
Tidal volume	98	96	100

TTV, traditional tidal volume ventilation; STV, small tidal volume ventilation; Sp_{O_2}, oxygen saturation; Pplat, plateau pressure; PEEP, positive end-expiratory pressure.

Numbers represent percentages of the randomly selected values on all patients that were consistent with the protocol rules.

Table 4. Random assessments: Percentage compliance with protocol

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DISCUSSION

The primary purpose of this randomized, controlled phase II trial was to assess the safety and potential beneficial effects of a ventilator strategy similar to the approach used in the previous uncontrolled series [13,14], in which mortality in ARDS patients was considerably lower than in historical controls. In this study, STV patients did not require greater PEEP and FIO_2 during the first 5 days of treatment, suggesting that gas exchange did not deteriorate with STV. There were no differences between the STV and TTV groups in fluid intake or output or requirements for vasopressors, suggesting that circulation was not impaired. The use of medications for sedation and neuromuscular blockade were similar in the TTV and STV groups. Together, these data suggest that STV was safe. However, there were no encouraging trends with STV in the proportion of patients who achieved RRF, time to RRF, or mortality before hospital discharge. There are several possible reasons why beneficial effects of STV were not observed in this study or in two recently reported similar clinical trials of STV in patients with or at risk for ARDS [33-35]. First, the between-group differences in Vt and Pplat were not as large as in the animal studies, in which stretch-induced lung injury occurred during relatively short experiments [3-9]. The TTV Vt target was chosen to represent a recent consensus of ventilator management practices in our intensive care units, not to purposely increase airway pressures and lung stretch. With mean TTV Vt at enrollment of 620 mL, mean PEEP of [similar]9 cm H_2 O (1.2 kPa), and respiratory system compliance of [similar]29 mL/cm H ($_2$) O (mL/3.9 kPa), it follows that the mean Pplat for TTV patients was just slightly >30 cm H_2 O (4 kPa). The STV strategy required reducing Vt to maintain Pplat of <or=to30 cm H_2 O (4 kPa). Therefore, many STV Pplats were within [similar]5 cm H_2 O (0.7 kPa) of this target. Thus, daily-mean Pplat values were separated by only [similar]6-7 cm H_2 O (0.8-0.9 kPa) during the first 5 days.

Beneficial effects of STV might occur if there were greater differences in Vt and Pplat between the TTV and STV groups. However, larger TTV Vt and Pplat values might not accurately reflect MV strategies currently in use, and smaller STV Vt and Pplat values might not accurately reflect the approach used in the previous reports [13,14]. Greater between-group differences in Pplat also could be achieved by restricting enrollment to patients with very low respiratory system compliance. However, this would prevent early use of STV in patients with milder injury, which could be important to prevent additional lung injury. Therefore, patients were enrolled in this trial within 24 hrs of ARDS onset.

A second possible explanation for the apparent absence of beneficial STV effects is that the trial was small and lacked sufficient power to detect small or even moderate differences between treatment groups. Moreover, inequities between treatment groups are more likely to obscure treatment effects in a small trial. APACHE III scores tended to be higher, $PaO_{2/FIO2}$ values tended to be lower (Table 3), and requirements for PEEP and FIO_2 were slightly greater on the day of enrollment in STV patients (Figure 2).

Because the trial was stopped for administrative reasons, a true treatment effect might have been missed. However, in the absence of any difference in the RRF end point after 52 patients, the probability that RRF could be demonstrated to be significantly better with STV was very small, even if the trial had continued to its maximum planned enrollment. Moreover, STV was not associated with reductions in requirements for PEEP or FIO_2. These variables reflect lung injury more directly than RRF, ventilator days, and mortality, which are more likely to be affected by co-morbid conditions. It is possible that STV could have modest beneficial effects on lung injury, ventilator days, RRF, and mortality but that this trial was too small to detect small differences.

A third possible explanation for the apparent lack of beneficial effects from STV in this trial is that overdistention may not be an important cause of lung injury in ARDS.

Although acute lung injury occurred in animal studies when high airway pressures and lung volumes were used, it was attenuated when higher PEEP values were added [5,9,36-38]. This suggests that cyclic opening and closing of unstable airways may be a more important cause of lung injury than stretch. Ventilation-associated lung injury in ARDS may be reduced by applying higher PEEP values than are necessary to achieve oxygenation goals [35-41]. In the present study, the levels of PEEP used to support oxygenation were lower than those recommended to prevent ventilation-associated lung injury, and the levels were similar in both treatment groups (Figure 3).

A fourth possible explanation for the lack of beneficial effects of STV treatment is that respiratory rates were allowed to increase to higher levels in the STV patients. Beneficial reductions in exposure to stretch during each inspiration may have been counteracted by effects of more frequent inspirations over time.

A fifth possible explanation for the absence of effects of STV treatment is that beneficial effects were counteracted by deleterious effects. For example, improved oxygenation from reduced stretch injury may have been counteracted by atelectasis. In STV patients with the smallest tidal volumes, hypercapnia and acidosis may have caused organ or system dysfunction that was not recognized.

A secondary objective of this study was to determine if ventilator management could be rigorously controlled in a clinical environment in which MV administration is strongly affected by clinician preferences [22]. In addition to tidal volume, most other ventilator settings can directly or indirectly affect lung stretch or other potential causes of lung injury. Tight control of ventilator management may increase the probability of observing the effects of STV, if any are present. In this trial, high rates of compliance with ventilator management rules and the key patient variable, Pplat, were achieved. Further improvements in compliance with protocol rules or achievement of protocol objectives would probably require greater monitoring of patient progress and improved education for clinical personnel. Decision support tools, such as computer-based programs that explain trial rules, may ensure better execution of technically difficult trials such as this [42].

In summary, the STV strategy used in this trial appeared to be as safe as TTV, but there were no beneficial effects of STV on gas exchange, RRF, ventilator days, or mortality. Beneficial effects may occur with STV if Vt is reduced more aggressively to further reduce lung stretch or if STV is used only in the most severe cases of ARDS, in which stretch-induced lung injury is most likely. However, additional trials would be necessary to assess the effects of these interventions on important clinical outcomes.

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