Influence of Low Tidal Volume Ventilation on Time to Extubation in Cardiac Surgical Patients

Sugantha Sundar, M.D.,* Victor Novack, M.D., Ph.D.,† Karinne Jervis, M.D.,‡ S. Patrick Bender, M.D.,‡ Adam Lerner, M.D.,§ Peter Panzica, M.D.,§ Feroze Mahmood, M.D.,§ Atul Malhotra, M.D.,‖ Daniel Talmor, M.D., M.P.H.#

ABSTRACT

Background: Low tidal volumes have been associated with improved outcomes in patients with established acute lung injury. The role of low tidal volume ventilation in patients without lung injury is still unresolved. We hypothesized that such a strategy in patients undergoing elective surgery would reduce ventilator-associated lung injury and that this improvement would lead to a shortened time to extubation

Methods: A single-center randomized controlled trial was undertaken in 149 patients undergoing elective cardiac surgery. Ventilation with 6 *versus* 10 ml/kg tidal volume was compared. Ventilator settings were applied immediately after anesthesia induction and continued throughout surgery and the subsequent intensive care unit stay. The primary endpoint of the study was time to extubation. Secondary endpoints included the proportion of patients extubated at 6 h and indices of lung mechanics and gas exchange as well as patient clinical outcomes.

Results: Median ventilation time was not significantly different in the low tidal volume group; a median (interquartile range) of 450 (264–1,044) min was achieved compared with 643 (417–1,032) min in the control group ($P = 0.10$). However, a higher proportion of patients in the low tidal volume group was free of any ventilation at 6 h: 37.3% compared with 20.3% in the control group ($P = 0.02$). In addition, fewer patients in the low tidal volume group required reintubation (1.3 *vs.* 9.5%; $P = 0.03$).

Conclusions: Although reduction of tidal volume in mechanically ventilated patients undergoing elective cardiac surgery did not significantly shorten time to extubation, several improvements were observed in secondary outcomes. When these data are combined with a lack of observed complications, a strategy of reduced tidal volume could still be beneficial in this patient population.

What We Already Know about This Topic

- Low tidal volume ventilation is beneficial for patients with acute respiratory distress syndrome.
- However, optimal mechanical ventilation for patients at risk of acute respiratory distress syndrome is controversial.

What This Article Tells Us That Is New

- In a randomized controlled trial of 149 patients undergoing elective cardiac surgery, low tidal volume ventilation strategy resulted in lower incidence of mechanical ventilation at 6 h from intubation and a lower reintubation rate after surgery.

LOW tidal volumes are clearly beneficial for patients with established acute respiratory distress syndrome/acute lung injury (ARDS/ALI).[1–3] However, the optimal mechanical ventilation of patients at risk of ARDS/ALI re-

* Assistant Professor, † Fellow, ‡ Assistant Professor, # Associate Professor, Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, Harvard Medical School, Boston, Massachusetts. § Lecturer, Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Cambridge, Massachusetts, Clinical Research Center, Soroka Medical Center, Beer-Sheva, Israel. ‖ Associate Professor, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts, Harvard Medical School, Cambridge, Massachusetts.

Received from the Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, and Harvard Medical School, Cambridge, Massachusetts. Submitted for publication March 3, 2010. Accepted for publication January 6, 2011. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Talmor: Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, 1 Deaconess Road, CC-470, Boston, Massachusetts 02215. dtalmor@bidmc.harvard.edu. Anesthesiology 2011; 114:1102–10

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 7A.

◆ This article is accompanied by an Editorial View. Please see: Wrigge H, Pelosi P: Tidal volume in patients with normal lungs during general anesthesia: Lower the better? ANESTHESIOLOGY 2011; 114:1011–3.

mains unclear. In theory, lung overdistention could contribute to lung injury among predisposed individuals, leading to prolongation of mechanical ventilation.

Gajic *et al.*[4] conducted a retrospective analysis of patients who did not have ARDS when mechanical ventilation was initiated. They observed that high tidal volume was an independent risk factor for ALI among patients with relatively normal gas exchange. The authors[4] concluded that strong consideration should be given to limiting large tidal volume, not only among patients with established ALI, but also for at-risk patients. Subsequent retrospective analyses have confirmed these findings.[5,6] However, other researchers[7] have suggested that low tidal volume may be unnecessary in non-ALI cases and that it may lead unnecessarily to patient discomfort, increased work during breathing, high sedation requirements, autopositive end-expiratory pressure (PEEP; high respiratory rate), hypercapnia (low respiratory rate), and atelectasis. Thus, despite biologic plausibility and considerable retrospective data to support limiting tidal volume in all ventilated patients, equipoise remains regarding optimal tidal volume in non-ALI patients. Although various groups of surgical patients, but especially cardiac surgical patients, have been observed,[8–20] these investigations have focused primarily on surrogate outcomes measures, leaving a lack of clarity regarding optimal perioperative ventilator strategy.

Therefore, we performed a randomized controlled trial comparing ventilation with 6 *versus* 10 ml/kg tidal volume for patients undergoing elective cardiac surgery. We hypothesized that using a low tidal volume ventilator strategy would reduce ventilator-associated lung injury and that this improvement would reduce time to extubation.

Materials and Methods

Setting and Patients

The trial (NCT00538161) was performed in the operating rooms and cardiac surgical intensive care unit (ICU) of Beth Israel Deaconess Medical Center (Boston, Massachusetts). The protocol was approved by the institutional review board. Informed consent was obtained from patients or from their nearest relatives. No commercial entities providing equipment or devices had a role in any aspect of this study.

Patients undergoing elective cardiac surgery were eligible for study enrollment. Exclusion criteria included emergent, nonscheduled surgery, cardiogenic shock (preoperative inotropic or intra-aortic balloon support), preexisting pulmonary disease (significant obstructive or restrictive lung disease), active infection (treated with antibiotics), and the need for single lung ventilation during the procedure.

The Society of Thoracic Surgeons database was used to collect demographic and clinical data and to calculate expected mortality rates.[21] Data were collected on ventilator settings, variables of gas exchange, lung mechanics, and secondary outcome variables (hospital mortality, length of hospital stay, duration of mechanical ventilation) by observers blinded to patient allocation.

Experimental Protocol

A block randomization scheme was used to allocate patients to one of two experimental groups. Study ventilator settings were applied immediately after induction of general anesthesia and continued throughout surgery and the subsequent ICU stay.

Low Tidal Volume Group. Tidal volume was set to 6 ml/kg using predicted body weight.

For male patients, predicted body weight was calculated as follows: kg = 50 + 2.3 (height, in − 60); for female patients: kg = 45.5 + 2.3 (height, in − 60). PEEP and inspired oxygen fraction (FIO_2) levels were set according to a sliding scale as described by Acute Respiratory Distress Syndrome Network investigators.[1]

Control Group. Tidal volume was set to 10 ml/kg predicted body weight. PEEP and FIO_2 levels were set using the same sliding scale. In both groups, respiratory rates were adjusted to maintain a PCO_2 of 40–55 mmHg and a pH higher than 7.25.

Anesthetic management of patients in both study groups was similar, consisting of anesthetic induction with propofol, fentanyl, and pancuronium. Anesthesia was maintained with isoflurane, fentanyl, and repeat doses of pancuronium, as required. In both study groups, ventilation was stopped during the period of cardiopulmonary bypass. At the end of bypass, lungs were manually reinflated under direct observation using a continuous positive airway pressure of 20 cm H_2O. Patients were then returned to allocated ventilator settings. In the ICU, all patients were placed on assist-control ventilation and continued on study ventilation parameters until such time as they were deemed ready for extubation by the ICU team, which included a nurse practitioner, a respiratory therapist, and the bedside nurse. Readiness criteria included awake status (Riker Sedation-Agitation Scale score of 3 or 4), hemodynamic stability (minimal doses of nitroglycerin or phenylephrine), and adequate gas exchange ($PaCO_2$ >100 mmHg; FIO_2 = 0.4; PEEP = 5 cm H_2O). Patients were then placed in protocol sequence; they were placed on pressure support ventilation, assessed using the rapid shallow breathing index on PEEP, receiving pressure support levels of 5 cm H_2O, followed by a spontaneous breathing trial of 30 min. Patients who passed this sequence were then extubated. If a patient failed either the rapid shallow breathing index or spontaneous breathing trial, he or she was returned to pressure support ventilation. On failure of pressure support ventilation, the patient was returned to controlled mechanical ventilation using the assigned study settings. Although anesthesia and ICU teams were not blinded to ventilator settings, they were not part of the study team. Decisions on the need for reintubation or any other intervention were made by these teams based on their clinical assessments. The study team took no part in clinical care of study subjects.

Therapies other than mechanical ventilation were managed by primary anesthesia and ICU teams. These teams

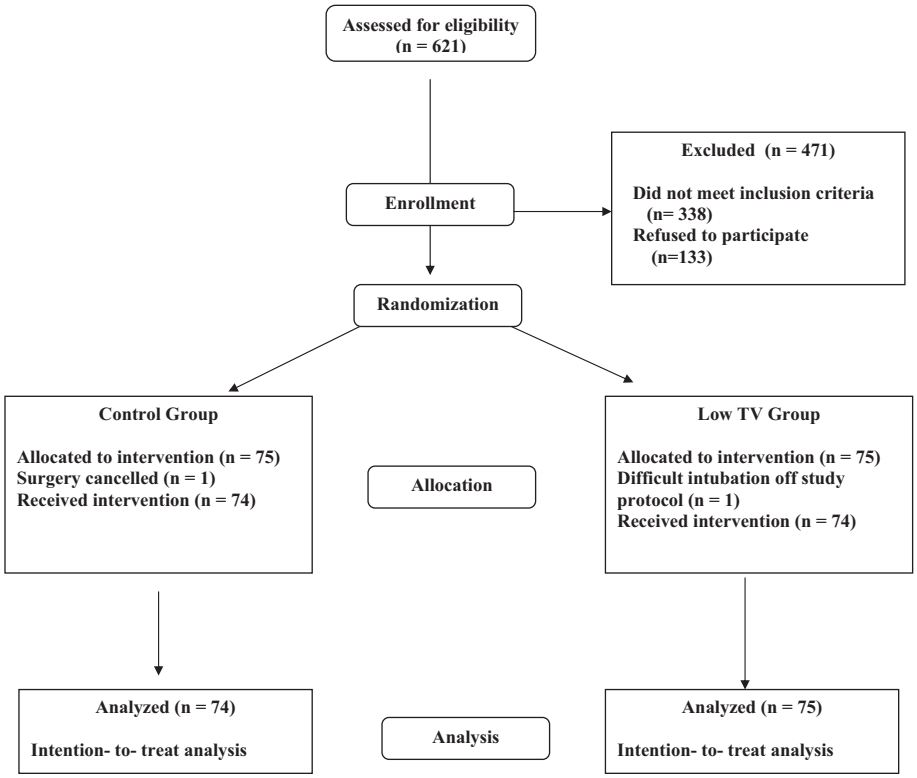

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of study enrollment. Analysis was done on an intention-to-treat basis.

made use of extensive protocols to guide hemodynamic resuscitation, sedation, and use of ventilator bundles to prevent complications. These care standards were rigorously applied to both study groups.

Statistical Analysis

The primary endpoint of the study was time to extubation, which was defined as total time of intubation including reintubation. Secondary endpoints included the proportion of

Table 1. Patient Characteristics at Baseline

Characteristics	Control (n = 74)	Low Tidal Volume (n = 75)	*P* Value
Men, No. (%)	56 (75.7)	50 (66.7)	0.23
Age, yr	66.5 ± 11.0	66.0 ± 11.7	0.78
Body weight, kg	85.1 ± 19.1	87.0 ± 20.0	0.65
Height, cm	170.3 ± 9.6	170.9 ± 10.3	0.72
Body mass index, kg/m^2	29.3 ± 5.3	29.6 ± 5.6	0.71
Ejection fraction <40%, No. (%)	6 (10.0)	6 (10.0)	0.95
Comorbidities, No. (%)	—	—	—
Myocardial infarction	26 (35.1)	24 (32.0)	0.69
Congestive heart failure	14 (19.4)	11 (14.7)	0.44
Diabetes	29 (39.2)	24 (32.0)	0.36
Dyslipidemia	58 (78.4)	61 (81.3)	0.65
Hypertension	58 (78.4)	60 (80.0)	0.81
Stroke	13 (17.6)	10 (13.3)	0.47
Peripheral vascular disease	13 (17.6)	11 (14.7)	0.63
Smoking	20 (27.0)	19 (25.3)	0.81
Current smoking	6 (8.1)	7 (9.3)	0.79
Chronic obstructive pulmonary disease	6 (8.1)	7 (9.3)	0.79
Society of Thoracic Surgeons mortality score, %	2.87 ± 2.97	2.72 ± 3.31	0.80

Chi-square testing was used to analyze categorical variables appearing as No. (%). Student *t* test was used for continuous variables appearing as mean ± SD. Mann–Whitney U test was used for continuous variables with not normal distribution appearing as median (interquartile range).

Table 2. Surgical Characteristics

Characteristics	Control (n = 74)	Low Tidal Volume (n = 75)	*P* Value
Surgery type, No. (%)	—	—	—
CABG	31 (41.9)	40 (53.3)	0.26
Valve repair/replacement	16 (21.6)	18 (24.0)	—
CABG + valve	22 (29.7)	14 (18.7)	—
Aortic surgery	5 (6.8)	2 (2.7)	—
Other	0 (0.0)	1 (1.3)	—
Surgery sequence, No. (%)	—	—	—
First cardiovascular surgery	68 (91.9)	68 (90.7)	0.96
First re-op cardiovascular surgery	5 (6.8)	6 (8.0)	—
Second re-op cardiovascular surgery	1 (1.4)	1 (1.3)	—
Cardiopulmonary bypass time, mean ± SD, min	102 ± 34	101 ± 38	0.97
Operative complications, No. (%)	—	—	—
Perioperative bleeding	2 (2.7)	2 (2.7)	0.99
Postoperative new renal failure	2 (3.3)	—	0.50
Complete heart block	7 (9.5)	—	0.01
Cardiac arrest	2 (2.7)	1 (1.7)	0.55
Atrial fibrillation	15 (20.3)	13 (17.3)	0.65
Neurological complications	2 (2.7)	2 (2.7)	0.99
Preoperative PRBC transfusion, No. (%)	5 (6.8)	4 (5.3)	0.74
Intraoperative blood products, No. (%)	29 (39.2)	25 (33.3)	0.46
PRBC	22 (29.7)	24 (32.0)	0.76
Fresh frozen plasma	7 (9.5)	6 (8.0)	0.75
Platelets	8 (10.8)	9 (12.0)	0.82
Postoperative blood products, No. (%)	33 (44.6)	26 (34.6)	0.29
PRBC	32 (43.2)	26 (34.6)	0.28
Fresh frozen plasma	6 (8.1)	3 (4.0)	0.33
Platelets	5 (6.8)	3 (4.0)	0.49
Total anesthetic drug use (operating room + ICU), mean ± SD	—	—	—
Fentanyl, μg	1,346 ± 386	1,278 ± 356	0.26
Pancuronium, mg	18 ± 4	17 ± 4	0.12
Propofol, mg	124 ± 93	139 ± 94	0.62

Chi-square testing was used to analyze categorical variables appearing as No. (%). Student *t* test was used for continuous variables appearing as mean ± SD. Mann–Whitney U test was used for continuous variables with not normal distribution appearing as median (interquartile range).

CABG = coronary artery bypass grafting; ICU = intensive care unit; PRBC = packed red blood cells.

patients extubated at 6 h, indices of lung mechanics and gas exchange (respiratory system compliance, $PaCO_2$-FIO_2 ratio), and patient outcomes (prolonged intubation, length of ICU/hospital stay, patient mortality at 28 days). Before trial initiation, preliminary data from our institution suggested a mean time to extubation after surgery of 1,200 min. To determine an appropriate sample size, we assumed that a low tidal volume strategy would lead to a 20% reduction in this time for the intervention group. Using this preliminary data, an SD of 400 min was calculated with 90% power to detect a 20% reduction in time to extubation. A two-tailed α of 0.05 required a sample size of 60 subjects per study group with an adjustment for nonparametric distribution. We assumed no loss to follow-up. Because time to extubation is not expected to be a normally distributed variable, calculations were based on the nonparametric Mann–Whitney U test. After the enrollment of 120 subjects, the independent Data and Safety Monitoring Board recommended enrollment of an additional 30 subjects. The Data and Safety Monitoring Board's consideration was that stopping the trial at the pre-specified endpoint would lead to equivocal results and that a more ethical approach would be to add patients in an attempt to reach a definitive answer regarding the study's hypothesis. The Data and Safety Monitoring Board dictated that an α-spending function be used to take into account this first look at the data.

Data on continuous variables with normal distribution were presented as mean ± SD; for nonnormally distributed variables, median (interquartile range) was used. Categorical data are shown as No. (%). Differences in categorical variables were assessed using chi-square tests and Cochran-Mantel-Haenszel tests for general associations and trends. Student *t* tests and Mann–Whitney U tests (non-normally distributed variables) were applied to continuous variables. Time to extubation was visualized using Kaplan-Meier curves, where extubation was an event, and observations were censored at 50 h.

To preserve the overall α level at 0.05, a *P* value below 0.049 (two-sided) in the final analysis of the primary outcome was considered statistically significant. For physio-

Table 3. Ventilation Parameters for Intubated Patients, Mean ± SD

Ventilation Parameters	Baseline (Postintubation)			ICU Admission		
	Control	Low TV	*P* Value	Control	Low TV	*P* Value
Tidal volume, cc^3	651 ± 99	400 ± 96	<0.001	651 ± 99	412 ± 92	<0.001
Respiratory rate, min^{-1}	12.6 ± 2.0	17.6 ± 3.4	<0.001	12.6 ± 2.0	17.1 ± 3.1	<0.001
PEEP, cm H_2O	4.9 ± 0.5	5.0 ± 0.8	0.71	5 ± 0	5.3 ± 1.1	0.05
FIO_2, %	100 ± 0	100 ± 0	1.00	100 ± 0	99 ± 0.1	0.16
Tidal volume/pBW, cc/kg	10.0 ± 0.5	6.2 ± 0.9	<0.001	10.0 ± 0.5	6.3 ± 0.9	<0.001
PaO_2/FIO_2 ratio	394 ± 76	378 ± 61	0.18	278 ± 94	251 ± 122	0.13
Plateau pressure, cm H_2O	—	—	—	19.2 ± 4.5	18.0 ± 4.1	0.015
Minute ventilation, L	8.1 ± 1.1	7.2 ± 1.6	<0.001	8.1 ± 1.1	7.0 ± 1.4	<0.001
Respiratory compliance, ml/cm H_2O	—	—	—	32.1 ± 7.8	30.2 ± 8.1	0.23

Student *t* test was used to analyze continuous (mean ± SD) variables.

* Data presented on patients with synchronized intermittent mandatory ventilation (SIMV) or assist control ventilation (AC; control, n = 39; low tidal volume [TV], n = 36). † Data presented on patients with SIMV or AC (control, n = 23; low TV, n = 22). ‡ Data presented on patients with SIMV or AC (control, n = 16; low TV, n = 20).

ICU = intensive care unit; pBW = predicted body weight; PEEP = positive end expiratory pressure.

logic variables, we adjusted the significance criterion to accommodate multiple comparisons. Using the Bonferroni correction, we considered a *P* value below 0.008 statistically significant for each parameter tested over time (six time points). For all other analyses, a *P* value of less than 0.05 (two-sided) was considered statistically significant. Statistical analyses were performed using SPSS (version 18; SPSS Inc., Chicago, IL).

Results

The current study was performed from September 2007 to July 2009. Six hundred and twenty-one patients were assessed for study eligibility and 149 patients were enrolled (fig. 1). One patient in the low tidal volume group had an unexpectedly difficult intubation followed by profound hypoxemia and did not receive ventilation per study protocols. A second patient in the low tidal volume group required unplanned single lung ventilation during surgery. At the end of surgery, this subject was returned to study-allocated ventilation settings. These patients are included in the analysis on an intention-to-treat basis.

Subject characteristics were well matched at baseline (table 1). It is noteworthy that the mean ± SD Society of Thoracic Surgeons predicted mortality score was 2.87 ± 2.97 in the control group and 2.72 ± 3.31 ($P = 0.80$) in the low tidal volume group, indicating a patient population at mild to moderate risk. There were no significant differences between study groups in terms of types of surgery or operative complications, except for a higher incidence of complete heart block in the control group (table 2; 9.5 *vs.* 0%; $P = 0.01$). Total doses of propofol, fentanyl, and pancuronium administered in the operating room and ICU are presented in table 2. These measures were not significantly different between the two study groups.

Ventilator parameters are presented in table 3. At baseline, all but 1 patient had a $PaCO_2$-to-FIO_2 ratio greater than 200. By design, tidal volumes were significantly lower in the low tidal volume group at all time points, indicating good adherence to the study protocol. Although $PaCO_2$ was significantly lower in the low tidal volume group immediately after cardiopulmonary bypass, it was not significantly different in the ICU (fig. 2). PCO_2 was significantly higher in the low tidal volume group at intubation, immediately after cardiopulmonary bypass and until 4 h after ICU admission (fig. 2).

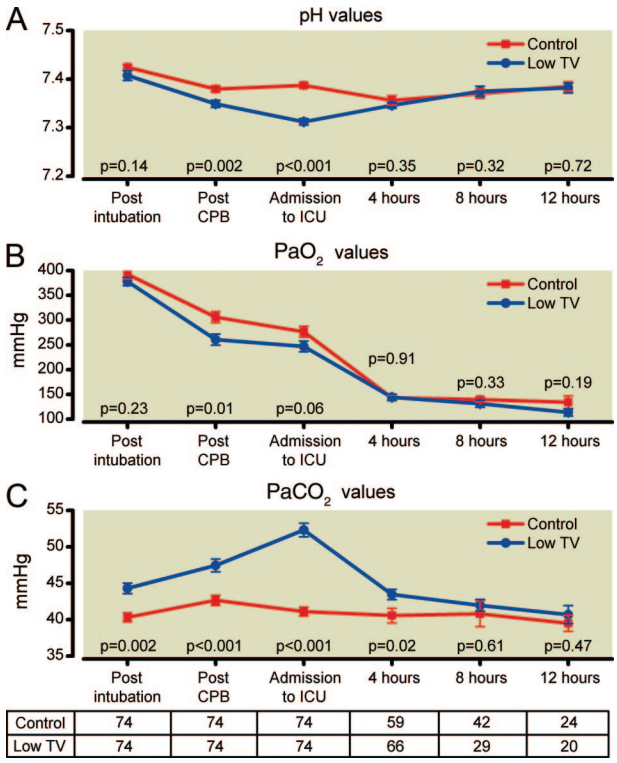

Fig. 2. pH (Panel A), PaO_2 (Panel B) and $PaCO_2$ (Panel C) for intubated patients in the low tidal volume (TV) and control groups. Time is shown from intubation. *Vertical bars* represent SEM. CPB = cardiopulmonary bypass; ICU = intensive care unit.

Table 3. Continued

4 h			8 h			12 h		
Control	Low TV	*P* Value	Control	Low TV	*P* Value	Control	Low TV	*P* Value
624 ± 110	432 ± 133	<0.001*	609 ± 97	419 ± 82	<0.001†	567 ± 110	411 ± 107	0.001‡
13.7 ± 3.0	21.2 ± 6.5	<0.001*	14.3 ± 3.1	21.5 ± 4.1	<0.001†	15.1 ± 3.9	21.9 ± 4.1	<0.001‡
5.6 ± 1.6	6.0 ± 1.9	0.24	5.6 ± 1.5	5.9 ± 1.8	0.47	5.2 ± 0.8	5.8 ± 1.8	0.16
51 ± 12	52 ± 11	0.93	47 ± 5	48 ± 7	0.29	44 ± 5	48 ± 9	0.05
9.8 ± 1.1	6.7 ± 1.7	<0.001*	10.1 ± 0.7	6.8 ± 1.3	<0.001†	9.9 ± 1.1	6.8 ± 1.6	<0.001‡
298 ± 96	285 ± 99	0.59	306 ± 83	274 ± 105	0.20	306 ± 80	253 ± 79	0.26
19.7 ± 4.1	17.0 ± 4.0	0.014*	20.8 ± 3.4	17.9 ± 4.5	0.03†	20.4 ± 4.5	19.7 ± 3.6	0.65‡
8.4 ± 1.8	9.2 ± 3.6	0.21*	8.7 ± 2.3	8.9 ± 2.3	0.75†	8.4 ± 1.8	8.7 ± 2.1	0.658‡
32.9 ± 8.1	29.4 ± 11.2	0.25*	31.8 ± 8.1	27.4 ± 10.8	0.19†	—	—	—

Median total ventilation time was not significantly shorter in the low tidal volume group when compared with controls (7.5 *vs.* 10.7 h; $P = 0.10$; table 4). Overall, at 6 h from intubation, 37.3% of patients in the low tidal volume group were free of any ventilation compared with 20.3% in the control group ($P = 0.02$; table 4). By 8 h from ICU admission, 53.3% of patients in the low tidal volume group and 31.1% of controls were extubated ($P = 0.006$). Kaplan-Meier analysis (fig. 3) demonstrates that, by 16 h, the curves describing time to extubation between the two study groups converged, as would be expected in patients undergoing elective surgery. Patients in the control group had a significantly higher rate of reintubation (9.5 *vs.* 1.3%; $P = 0.03$).

Length of ICU stay was not significantly different between the low tidal volume and control groups (31.3 *vs.* 34.5 h; $P = 0.35$; table 4). Although hospital length of stay was shortened in the low tidal volume group (5.0 *vs.* 5.5 days; $P = 0.16$; table 4), this difference did not reach statistical significance.

We examined the relationship between perioperative blood transfusion and the duration of mechanical ventilation. Transfusion rates before, during, and after surgery were similar in the two study groups (table 2). Patients who were transfused before surgery did not differ from other subjects with regard to total ventilation time. The 54 subjects who required transfusion during cardiac surgery did, however, have a longer median (interquartile range) total ventilation time when compared with those who were not transfused (969 [533–1,369] *vs.* 450 [255–692]min; $P < 0.001$). Because the proportion of patients requiring transfusion either before or during cardiac surgery was similar between study groups, adjustment for the need of the transfusion is not expected to alter the results of this randomized trial.

Discussion

In this study, although we found that using low tidal volume ventilation for patients undergoing elective cardiac surgery

Table 4. Clinical Outcomes

Outcomes	Control (n = 74)	Low Tidal Volume (n = 75)	*P* Value
Total ventilation time, min, median (IQR)	643 (417–1,032)	450 (264–1,044)	0.10
Ventilation, No. (%)	—	—	—
<6 h	15 (20.3)	28 (37.3)	0.02
<12 h	40 (54.1)	48 (64.0)	0.22
<24 h	66 (89.2)	66 (88.1)	0.82
Length of stay, median (IQR)	—	—	—
Intensive care unit, h	34.5 (26.0–94.6)	31.3 (26.0–68.0)	0.35
Postoperative hospital, days	5.5 (4.0–7.0)	5.0 (4.0–6.0)	0.16
Reintubation, No. (%)	7 (9.5)	1 (1.3)	0.03
Reason for reintubation, No. (%)	—	—	—
Arrhythmia	2	1	—
Respiratory failure	3	0	—
Pancreatitis	1	0	—
Bleeding	1	0	—
28-day mortality, No. (%)	2 (1.7)	1 (1.3)	0.62

Chi-square testing was used to analyze categorical variables appearing as No. (%). The Mann–Whitney U test was used for continuous variables with not normal distribution appearing as median (interquartile range [IQR]).

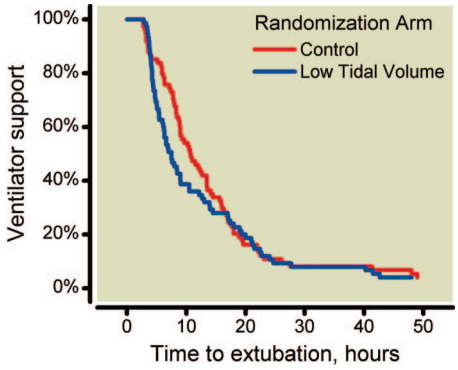

Fig. 3. Kaplan-Meier analysis of time to extubation. At 16 h, the curves describing time to extubation between the two study groups converge.

did not shorten the time to extubation, there were statistically significant differences in secondary outcomes. Specifically, significantly more patients were extubated and breathing without assistance at 6–8 h after surgery in the low tidal volume group. This study group also had reduced need for postoperative reintubation. Although the primary outcomes of this study showed no change with low tidal volume ventilation, secondary outcomes suggest that this ventilation strategy may still confer patient benefits. These advantages were obtained at no cost in increased complications.

Substantial preclinical data suggest that ventilation with large tidal volumes and high airway pressures may lead to ventilator-induced lung injury.[22] This finding has been consistent among patients with healthy *versus* previously injured lungs. Ventilation with low tidal volumes in patients with ARDS/ALI is now the standard of care.[1,2,23–26] However, patients with ALI represent a minority of ventilated ICU patients and an even smaller fraction of those ventilated in the operating room. It has been suggested that other patients may also benefit from low tidal volumes.[27,28] This hypothesis, however, has not been adequately tested. Several retrospective studies have demonstrated that ventilation with high tidal volumes may lead to ALI, presumably secondary to ventilator-induced lung injury.[4–6] A number of studies have examined biochemical markers of lung injury among patients undergoing anesthesia for major surgery, mainly cardiac surgery. These patient groups were appropriate models of short-term ventilation in patients who, although without preexisting lung injury, are at risk of ALI. The results of these studies have been mixed, with some investigators showing increases in serum and bronchoalveolar lavage markers of injury[10,13–16,19] whereas others have not.[11,12,17,18] There have been remarkably few trials examining clinical outcomes associated with low tidal volume ventilation strategies in otherwise healthy populations. In 1990, Lee *et al.*[29] randomly assigned 103 surgical ICU patients to ventilation with 6 *vs.* 12 ml/kg tidal volume. Although those authors[29] found trends towards fewer pulmonary infections, shortened ventilator times, and reduced length of ICU stay, the only statistically significant result was decreased oxygenation in the low tidal volume group. A subsequent study of 25 patients undergoing coronary artery bypass grafting reported improved lung compliance when patients were randomly assigned to 6 ml/kg tidal volume rather than 12 ml/kg.[9] Recently, Determann *et al.*[20] reported the results of a larger randomized controlled trial. In that trial, 150 patient without ARDS/ALI were allocated to 6 *versus* 10 ml/kg tidal volume. Researchers[20] demonstrated a statistically significant reduction in circulating plasma IL-6 levels in the low tidal volume group. In addition, it is noteworthy that this study was stopped early as a result of an increased incidence of ALI in the higher tidal volume group. Our study extends and expands on this work by reporting the influence of tidal volume limitation on clinically relevant outcomes in elective cardiac surgery. However, we were unable to demonstrate a statistically significant impact of low tidal volume ventilation on time to extubation in cardiac surgical patients.

Our study has several limitations. It was a single-center study with a small group of investigators. The teams caring for the patients in the ICU were not blinded to patient allocation. Lack of blinding may lead to changes in care during the experimental arm of a trial, which is systematically different from the control arm based on either conscious or subconscious influences on decisions. These factors may influence clinical outcomes and study results. Although we recognize the importance of blinding, we are aware of no major mechanical ventilation study that has effectively accomplished it. Even when attempts at blinding have been made, it is obvious to the caregivers who is in which group based on blood gases, physical examination, imaging, *etc.* Therefore, to avoid subtle differences in patient care during the experimental *versus* control arm of the investigation, we carefully and to the best of our ability protocolized care in all nonventilator aspects of patient management. That is, we included study protocols for sedation, weaning, fluid resuscitation, blood transfusion, nutrition, glucose control, antibiotic therapy, and so forth. It is for this reason that we are reasonably confident that patient care did not differ in any systematic way between the two experimental groups. We have reviewed available data regarding blood transfusions and sedation use and found these to be balanced between groups; however, we did not systematically assess compliance with the other protocols as they are well established in our institution. We are unable to detect any subtle differences in patient care between study groups. We doubt that clinical outcomes were impacted by undetected differences in clinical management. In addition, the structure of our cardiac ICU is such that the decision to extubate is made by clinical nurse practitioners, bedside nurses, and respiratory therapists based on predefined criteria rather than cardiac surgeons or investigators. Thus, important decisions regarding patient care were largely out of the hands of potentially biased individuals. However, the generalizability of our conclusions should be further tested in a larger randomized controlled trial.

Finally, the primary endpoint of our study was time to extubation. We chose not to use cytokine levels in the plasma as a marker of lung injury. This decision was made because previous studies using this outcome have shown mixed results. In addition, this outcome is difficult to interpret in the setting of cardiac surgery. Thus, many have questioned the clinical relevance of cytokine levels in isolation (*i.e.*, without corroborative clinical outcome measures). We chose time to extubation rather than more robust outcomes, such as ventilator-induced lung injury as indicated by the clinical manifestation of ARDS/ALI or mortality. Mortality in cardiac surgical patients is expected to be below 2%, with a similarly low incidence of ARDS/ALI, making detection of intervention effects on mortality dependent on high volume patient enrollment. Although an alternative strategy would be to design such a study around composite outcomes, the clinical relevance of such an approach has been called into question.[30,31]

The physiologic rationale for limiting tidal volume in the absence of lung injury deserves some discussion. For example, if large tidal volumes themselves could cause lung injury, then one would predict that exercising athletes would be subject to similar risk. There are several lines of logic that might suggest a strategy to limit tidal volume may be useful outside the setting of ARDS/ALI. First, in contrast to exercising athletes, evidence of systemic inflammation is known to occur in the operating room and after cardiac bypass.[32] As a result, there may be several factors predisposing patients to lung injury in the postoperative setting, providing a rationale for limiting ventilator-induced lung stress. Second, some evidence suggests that ARDS/ALI can go unrecognized in many patients. For example, gradual increases in FIO_2 in response to pulse oximetry can occur without a full appreciation for the fact that the PaO_2/FiO_2 ratio has fallen below 300 mmHg. Similarly, several studies have suggested that subtle bilateral infiltrates can be underappreciated on portable ICU films.[33] Thus, treatment for ARDS/ALI may be delayed or may not occur unless tidal volumes are empirically lowered.[34] Third, classic physiology studies have estimated shear forces at junctions of normal and abnormal lung.[35] Such forces can be well in excess of any applied pressure, suggesting that parenchymal heterogeneity may be a major contributor to risk of ventilator-induced lung injury. Indeed, in the setting of cardiac surgery, left lower lobe collapse and atelectasis is highly prevalent, emphasizing that parenchymal heterogeneity is likely present in the majority of postoperative cardiac surgery patients. Thus, there exists a strong biologic basis for the notion that limiting tidal volume may be advantageous beyond the setting of ALI.

In conclusion, reduction of tidal volume in mechanically ventilated patients undergoing elective cardiac surgery does not shorten time to extubation. Observed improvements in secondary outcomes (*e.g.*, extubation at 6 and 8 h after surgery, reduced rates of reintubation) suggest that further study in a larger cohort of patients is needed. Similar studies in other groups of ventilated patients who do not have ARDS/ALI should also be considered.

References

1. 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. N Engl J Med 2000; 342:1301–8
2. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–54
3. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS, Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med 1998; 338:355–61
4. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004; 32:1817–24
5. Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A: Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 2005; 31:922–6
6. Jia X, Malhotra A, Saeed M, Mark RG, Talmor D: Risk factors for ARDS in patients receiving mechanical ventilation for > 48 h. Chest 2008; 133:853–61
7. Kallet RH, Campbell AR, Dicker RA, Katz JA, Mackersie RC: Effects of tidal volume on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome. Crit Care Med 2006; 34:8–14
8. Altemeier WA, Matute-Bello G, Frevert CW, Kawata Y, Kajikawa O, Martin TR, Glenny RW: Mechanical ventilation with moderate tidal volumes synergistically increases lung cytokine response to systemic endotoxin. Am J Physiol Lung Cell Mol Physiol 2004; 287:L533–42
9. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M: Protective ventilation attenuates postoperative pulmonary dysfunction in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000; 14:514–8
10. Choi G, Wolthuis EK, Bresser P, Levi M, van der Poll T, Dzoljic M, Vroom MB, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. ANESTHESIOLOGY 2006; 105:689–95
11. Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N: Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. Intensive Care Med 2004; 30:620–6
12. Meier T, Lange A, Papenberg H, Ziemann M, Fentrop C, Uhlig U, Schmucker P, Uhlig S, Stamme C: Pulmonary cytokine responses during mechanical ventilation of noninjured lungs with and without end-expiratory pressure. Anesth Analg 2008; 107:1265–75
13. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray JP: Protective ventilation influences systemic inflammation after esophagectomy: A randomized controlled study. ANESTHESIOLOGY 2006; 105:911–9
14. Reis Miranda D, Gommers D, Struijs A, Dekker R, Mekel J, Feelders R, Lachmann B, Bogers AJ: Ventilation according to the open lung concept attenuates pulmonary inflammatory

response in cardiac surgery. Eur J Cardiothorac Surg 2005; 28:889–95

15. Wolthuis EK, Choi G, Dessing MC, Bresser P, Lutter R, Dzoljic M, van der Poll T, Vroom MB, Hollmann M, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. ANESTHESIOLOGY 2008; 108:46–54
16. Wrigge H, Uhlig U, Baumgarten G, Menzenbach J, Zinserling J, Ernst M, Drömann D, Welz A, Uhlig S, Putensen C: Mechanical ventilation strategies and inflammatory responses to cardiac surgery: A prospective randomized clinical trial. Intensive Care Med 2005; 31:1379–87
17. Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M, Uhlig S, Putensen C: The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg 2004; 98:775–81
18. Wrigge H, Zinserling J, Stüber F, von Spiegel T, Hering R, Wetegrove S, Hoeft A, Putensen C: Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. ANESTHESIOLOGY 2000; 93:1413–7
19. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, Ranieri VM: Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial. J Thorac Cardiovasc Surg 2005; 130:378–83
20. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, Hofstra JJ, de Graaff MJ, Korevaar JC, Schultz MJ:Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: A preventive randomized controlled trial. Crit Care 2010; 14:R1
21. Ichikado K, Suga M, Muranaka H, Gushima Y, Miyakawa H, Tsubamoto M, Johkoh T, Hirata N, Yoshinaga T, Kinoshita Y, Yamashita Y, Sasaki Y: Prediction of prognosis for acute respiratory distress syndrome with thin-section CT: Validation in 44 cases. Radiology 2006; 238:321–9
22. Slutsky AS: Lung injury caused by mechanical ventilation. Chest 1999; 116(1 suppl):9S–15S
23. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S: Prospective, randomized, controlled clinical trial comparing traditional *versus* reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 1999; 27:1492–8
24. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS: Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med 1998; 338:355–61
25. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. Crit Care Med 2006; 34:1311–8
26. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E, Clémenti E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 1998; 158:1831–8
27. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? ANESTHESIOLOGY 2007; 106:1226–31
28. Bonetto C, Terragni P, Ranieri VM: Does high tidal volume generate ALI/ARDS in healthy lungs? Intensive Care Med 2005; 31:893–5
29. Lee PC, Helsmoortel CM, Cohn SM, Fink MP: Are low tidal volumes safe? Chest 1990; 97:430–4
30. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, Johnson MG, Williams AR, Cutshall SM, Mundy LM, Rizza RA, McMahon MM: Intensive intraoperative insulin therapy *versus* conventional glucose management during cardiac surgery: A randomized trial. Ann Intern Med 2007; 146:233–43
31. Tomlinson G, Detsky AS: Composite end points in randomized trials: There is no free lunch. JAMA 2010; 303:267–8
32. Suleiman MS, Zacharowski K, Angelini GD: Inflammatory response and cardioprotection during open-heart surgery: The importance of anaesthetics. Br J Pharmacol 2008; 153: 21–33
33. Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA: Interobserver variability in applying a radiographic definition for ARDS. Chest 1999; 116:1347–53
34. Rubenfeld GD, Cooper C, Carter G, Thompson BT, Hudson LD: Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med 2004; 32: 1289–93
35. Mead J, Takishima T, Leith D: Stress distribution in lungs: A model of pulmonary elasticity. J Appl Physiol 1970; 28:596–608