ORIGINAL CLINICAL RESEARCH REPORT

Low Tidal Volumes Are Associated With Slightly Improved Oxygenation in Patients Having Cardiac Surgery: A Cohort Analysis

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BACKGROUND: Mechanical ventilation with low tidal volumes appears to provide benefit in patients having noncardiac surgery; however, whether it is beneficial in patients having cardiac surgery is unclear.

METHODS: We retrospectively examined patients having elective cardiac surgery requiring cardiopulmonary bypass through a median sternotomy approach who received mechanical ventilation with a single lumen endotracheal tube from January 2010 to mid-August 2016. Time-weighted average tidal volume (milliliter per kilogram predicted body weight [PBW]) during the duration of surgery excluding cardiopulmonary bypass was analyzed. The association between tidal volumes and postoperative oxygenation (measured by arterial partial pressure of oxygen (Pao_2)/fraction of inspired oxygen ratio [Pao_2/Fio_2]), impaired oxygenation (Pao_2/Fio_2 <300), and clinical outcomes were examined.

RESULTS: Of 9359 cardiac surgical patients, larger tidal volumes were associated with slightly worse postoperative oxygenation. Postoperative Pao_2/Fio_2 decreased an estimated 1.05% per 1 mL/kg PBW increase in tidal volume (97.5% confidence interval [CI], −1.74 to −0.37; P_{Bon} = .0005). An increase in intraoperative tidal volumes was also associated with increased odds of impaired oxygenation (odds ratio [OR; 97.5% CI]: 1.08 [1.02–1.14] per 1 mL/kg PBW increase in tidal volume; P_{Bon} = .0029), slightly longer intubation time (5% per 1 mL/kg increase in tidal volume (hazard ratio [98.33% CI], 0.95 [0.93–0.98] per 1 mL/kg PBW; P_{Bon} < .0001), and increased mortality (OR [98.33% CI], 1.34 [1.06–1.70] per 1 mL/kg PBW increase in tidal volume; P_{Holm} = .0144). An increase in intraoperative tidal volumes was also associated with acute postoperative respiratory failure (OR [98.33% CI], 1.16 [1.03–1.32] per 1 mL/kg PBW increase in tidal volume; P_{Holm} = .0146), but not other pulmonary complications.

CONCLUSIONS: Lower time-weighted average intraoperative tidal volumes were associated with a very modest improvement in postoperative oxygenation in patients having cardiac surgery. (Anesth Analg 2020;130:1396–406)

KEY POINTS

- **Question:** Is mechanical ventilation with low tidal volumes beneficial for cardiac surgical patients?
- **Findings:** Smaller intraoperative tidal volumes were associated with slightly improved postoperative oxygenation and a reduction in acute postoperative respiratory failure, but not other pulmonary complications.
- **Meaning:** Mechanical ventilation with small tidal volumes was associated with a very modest improvement in postoperative oxygenation and minor improvement in clinical pulmonary complications.

GLOSSARY

ARDS = acute respiratory distress syndrome; **ARE OR** = average relative effect odds ratio; **CI** = confidence interval; **EF** = ejection fraction; **Fio_2** = fraction of inspired oxygen; **HR** = hazard ratio; **ICU** = intensive care unit; ***ICD*** = *International Classification of Disease*; **LOS** = length of stay; **OR**

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= odds ratio; **Pao_2** = arterial partial pressure of oxygen; **PBW** = predicted body weight; **PEEP** = positive end-expiratory pressure; **STROBE** = Strengthening the Reporting of Observational Studies

Mechanical ventilation with low tidal volumes reduces mortality in patients suffering from acute lung injury and acute respiratory distress syndrome (ARDS).[1] In noncardiac surgery patients, mechanical ventilation with low tidal volumes appears to be beneficial,[2,3] though conflicting data exist.[4,5] The benefit of mechanical ventilation with low tidal volumes in patients having cardiac surgery, however, is unclear.

Limited reports investigated the benefit of low tidal volume ventilation specifically in cardiac surgical patients. A recent meta-analysis demonstrated reduced pulmonary complications when noncardiac and cardiac surgical patients received low tidal volume ventilation[6]; however, subgroup analysis found no benefit in cardiac surgical patients and only subclinical outcomes, such as inflammatory markers and pulmonary function, were assessed.[6] One systematic review that examined cardiac and noncardiac surgical patients found intraoperative tidal volume <10 mL/kg predicted body weight (PBW) decreased pneumonia and the need for postoperative mechanical ventilatory support.[7] One clinical trial reported that protective ventilation with tidal volumes of 6 mL/kg PBW reduced the number of patients requiring mechanical ventilation at 6 hours after cardiac surgery, though time to extubation, the primary outcome, was not reduced.[8] A large observational investigation in patients having cardiac surgery reported an approximately 2-fold increase in prolonged ventilatory support, kidney injury, and hemodynamic instability when large tidal volumes (>12 mL/kg) were given[9]; however, tidal volumes were measured on arrival to the intensive care unit (ICU), rather than during surgery, and, tidal volumes of 6–8 mL/kg PBW (recommended for protective ventilation[1]) were not examined. Further evidence examining the benefit of low tidal volumes in cardiac surgical patients is needed.

Determining whether mechanical ventilation with low tidal volumes provides clinical benefit in cardiac surgical patients is challenging because procedure-related pulmonary complications may obscure complications related to a (relatively) brief duration of mechanical ventilation with large tidal volumes. Therefore, a cause-specific primary outcome, postoperative oxygenation, was selected. The purpose of this investigation was thus to determine whether intraoperative ventilation with lower tidal volumes was associated with improved oxygenation, assessed by the postoperative arterial partial pressure of oxygen/fraction of inspired oxygen (Pao_2/Fio_2) ratio, in patients having cardiac surgery. We also examined the association between intraoperative tidal volumes and postoperative pulmonary complications, duration of mechanical ventilation, hospital length of stay, and mortality after cardiac surgery.

METHODS

With the approval of the Cleveland Clinic Institutional Review Board, who waived the requirement for written informed consent, this retrospective observational single-center cohort investigation used data from the Cleveland Clinic Automated Record Keeper System (electronic intraoperative anesthesia record), Perioperative Health Documentation System, institutional Society of Thoracic Surgeons database, and patient's medical record. All patients aged 18–89 years who had elective cardiac surgery requiring cardiopulmonary bypass through a median sternotomy at the Cleveland Clinic Main Campus from January 2010 to mid-August 2016 and received mechanical ventilation with a single lumen endotracheal tube were included. We excluded patients (1) who were transferred from ICU to operating room; (2) who required intraoperative deep hypothermia (lowest core temperature <30°C during surgery); (3) with known respiratory disease requiring chronic oxygen therapy at home; (4) with preoperative oxygen saturation <90% and/or partial pressure of oxygen in arterial blood of <60 mm Hg based on arterial blood gas before induction of anesthesia; (5) with preoperative endocarditis; (6) undergoing transplantation of the heart, lungs, or both; (7) requiring mechanical circulatory support (left ventricular assist device, extracorporeal membrane oxygenation) during surgery or within 6 hours postoperatively; (8) undergoing descending aorta replacement surgery; (9) experiencing postoperative phrenic nerve injury.

Of 11,936 adult patients (18–89 years), 2577 (22%) patients did not meet inclusion and met exclusion criteria. Thus 9359 subjects were considered for analysis (Figure 1). This report adheres to Strengthening the Reporting of Observational Studies (STROBE) guidelines.

Management of Intraoperative Ventilation

During surgery, the mode of ventilation, fraction of inspired oxygen, use of positive end-expiratory pressure (PEEP), tidal volume, and respiratory rate were at the discretion of the attending anesthesiologist. Tidal volumes were recorded in the electronic automated anesthesia record every 15 minutes from endotracheal intubation until surgery completion. Patients were not ventilated during cardiopulmonary bypass. Intraoperative (pre- and postcardiopulmonary bypass) time-weighted average tidal volume per kilogram PBW was calculated. Distribution of

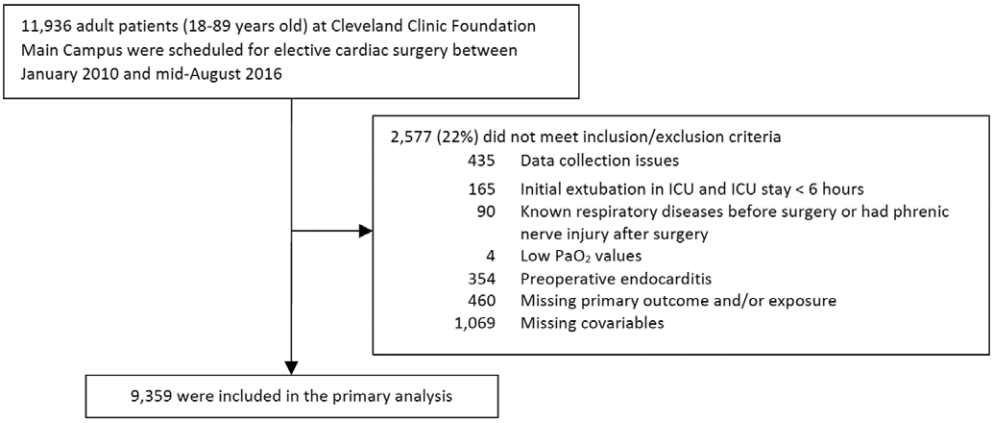

Figure 1. Patient flow diagram of available cardiac surgical cases between January 2010 and mid-August 2016 at Cleveland Clinic Foundation Main Campus. ICU indicates intensive care unit; Pao_2, arterial partial pressure of oxygen.

intraoperative time-weighted average tidal volumes is shown in Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/C989.

Management of Postoperative Ventilation

Postoperative mechanical ventilation was protocolized and managed by ICU respiratory therapists. The protocol for initial ventilation settings on ICU admission dictated pressure control-synchronized intermittent mandatory ventilation with PEEP 5–10 cm H_2O, tidal volumes 6–8 mL/kg PBW, and Fio_2 0.6. Respiratory rate was adjusted to pH >7.30. PBW was calculated as follows:[1] males, PBW = 50 kg + 0.91 kg × (height [cm] – 152.4); females, PBW = 45.5 kg + 0.91 kg × (height [cm] – 152.4). Although mechanical ventilation parameters were standardized on admission to the ICU, actual tidal volume data from ICU admission until extubation were not available.

End Points

The exposure of interest was the time-weighted average tidal volume (milliliter per kilogram PBW) over the duration of surgery, excluding time on cardiopulmonary bypass. Time-weighted average tidal volume takes into account fluctuating tidal volumes irregularly spaced throughout the surgery. We initially planned to examine the influence of secondary exposure variables including (1) PEEP and (2) driving pressure (ΔP; airway plateau pressure – PEEP) during surgery; however, this analysis was precluded by a large number of missing variables. Thus only tidal volumes measured in milliliter per kilogram PBW were examined in the primary analysis. Two sensitivity subanalyses included PEEP.

The primary outcomes were (1) a measure of postoperative oxygenation, the Pao_2/Fio_2 ratio, assessed with arterial blood gas analysis after ICU arrival before tracheal extubation, and (2) impaired oxygenation, defined as Pao_2/Fio_2 ratio <300 mm Hg. For patients who were extubated within 6 hours after ICU arrival, the Pao_2/Fio_2 ratio was calculated from an arterial blood gas measured immediately before initiation of a spontaneous breathing trial. At this time point, patients received mechanical ventilation with an Fio_2 of 0.4 and PEEP of 8 cm H_2O; thus, an accurate Pao_2/Fio_2 ratio could be calculated. For patients who were not extubated within 6 hours, the Pao_2/Fio_2 ratio was calculated from an arterial blood gas measured closest to 6 hours after ICU arrival while still on mechanical ventilatory support. Limiting the time period for arterial blood gas measurement to <6 hours after ICU arrival allowed the performance of routine postoperative procedures (eg, electrocardiogram, chest radiograph) while stabilizing the postoperative respiratory status on standardized ICU ventilator settings. Impaired oxygenation was defined as Pao_2/Fio_2 ratio <300 mm Hg. This cutpoint was selected because of the clinical significance of Pao_2/Fio_2 ratio <300 mm Hg (American-European Consensus Conference on ARDS used Pao_2/Fio_2 ratio <300 mm Hg to define acute lung injury,[10] and the updated Berlin definition used this Pao_2/Fio_2 ratio to define mild ARDS[11]).

Our secondary outcomes included time to initial extubation, hospital length of stay, and a composite of in-hospital mortality and postoperative pulmonary complications. Time to initial extubation was defined as the time between ICU arrival and initial postoperative extubation. Criteria for extubation and hospital discharge are described in Supplemental Digital Content, Appendix 2, http://links.lww.com/AA/C989. A composite of mortality and postoperative pulmonary complications were comprised of 5 components: (1) in-hospital mortality, defined as death from any cause during the same admission of surgery; (2) respiratory complications, including ventilator-associated pneumonia, postprocedural aspiration pneumonia, and other respiratory complications related to mechanical ventilation; (3) acute postoperative respiratory failure, including acute respiratory failure following trauma and surgery and acute respiratory

failure related to surgery; (4) ARDS; and (5) reintubation, defined as respiratory failure after initial tracheal extubation requiring reintubation. Complications (2), (3), and (4) described previously were assessed by *International Classification of Disease (ICD)-9* and *ICD-10* billing codes listed in Supplemental Digital Content, Appendix 2, http://links.lww.com/AA/C989.

With the exception of aortic cross-clamp time, intraoperative mechanical ventilation, and postoperative Pao_2/Fio_2 ratio measurements, all regression models were adjusted for the variables in Tables 1 and 2.

Statistical Analysis

Primary Analyses. Bonferroni correction was used to adjust for testing multiple primary hypotheses; thus, the significance criterion was $P_{Bon} < .025$ for each primary analysis (ie, 0.05/2 analyses = 0.025).

Multivariable gamma regression using the log link was used to assess if time-weighted average tidal volume (milliliter per kilogram PBW) was independently associated with Pao_2/Fio_2 ratio after surgery. Gamma regression enables us to analyze right-skewed, nonnegative continuous outcomes, without transforming the data. Thus, we can draw inferences on the covariate-adjusted estimated arithmetic mean change in the outcome on the original scale. Normal, log-linear, and gamma regression using the identity link were also explored; gamma regression using the log link resulted in the best fit. Estimated percent mean change in Pao_2/Fio_2 ratio per 1 mL/kg PBW increase in time-weighted average tidal volume is presented, with a corresponding Bonferroni-adjusted 97.5% Wald confidence interval (CI) and *P* value. Residuals were examined to ensure there were no gross deviations from regression assumptions.

Multivariable logistic regression was used to assess the relationship between time-weighted average tidal volumes and odds of impaired oxygenation, defined as $Pao_2/Fio_2 < 300$. A covariate-adjusted odds ratio (OR) for odds of hypoxia per 1 mL/kg PBW increase in time-weighted average tidal volume is reported, along with its Bonferroni-adjusted 97.5% CI and *P* value.

SAS software version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses.

Secondary Analyses. We also evaluated if tidal volumes were associated with time to extubation, length of hospital stay, and a composite of in-hospital mortality and postoperative pulmonary complications. Bonferroni correction was used to adjust for testing multiple secondary analyses, thus the significance criterion will be $P_{Bon} < .0167$ for each analysis (ie, 0.05/3 analyses = 0.0167).

Time to Initial Extubation. A multivariable Cox proportional hazards regression model was used to evaluate the relationship between intraoperative tidal volumes and time to initial extubation. To avoid survival bias due to in-hospital mortality, we analyzed extubation for patients who died before the event as "nonevents" in the Cox models, with time to initial extubation censored at the longest observed duration of intubation time. The proportional hazards assumption of the Cox model was evaluated by testing the log (time to initial extubation) and tidal volume interaction term in the Cox model.

Hospital Length of Stay. A multivariable Cox proportional hazards regression model was used to evaluate the relationship between intraoperative tidal volume and hospital length of stay. Again, we analyzed the event (discharge) for patients who died before the discharge as "nonevents" in the Cox models, with hospital length of stay censored at the longest observed duration of hospital stay. The proportional hazards assumption of the Cox model was evaluated by testing the log (length of stay) and tidal volume interaction term in the Cox model.

Composite of Adverse Events. A composite outcome was used to examine the relationship between tidal volume and adverse postoperative pulmonary events and mortality. A multivariate multivariable "distinct effects" generalized estimating equations model with an unstructured working correlation was used to estimate an average relative effect (average relative risk generalized) OR across 5 components and test if the estimate was equal to one given incidences varied across components.[12,13] We assessed heterogeneity of tidal volume effect across the components by testing the interaction term between tidal volume and the components; $P < .05$ indicated a difference of effect across components. Holm-Bonferroni step-down procedure for multiple testing adjustment[14] was utilized to adjust the component-specific *P* values. The associations between tidal volume and each component are reported in addition to the average relative effect.

Sensitivity Analyses. Two sensitivity analyses were performed to account for the effect of PEEP on the association between tidal volume and the primary outcome. (1) A sensitivity analysis was performed in patients with PEEP data (N = 7167 [77%]) that examined the association between tidal volume and primary outcome with adjustment for PEEP and variables listed in Tables 1 and 2. (2) In a second sensitivity analysis, all patients were included (N = 9359); PEEP = 0 cm H_2O was assumed if PEEP measurement was unavailable.

Sample Size/Power Consideration. We expected to have approximately 10,000 patients meeting all study criteria. To conservatively plan sample size for a study that incorporated linear regression between a continuous

Table 1. Summary Statistics of Baseline Characteristics

		Tertiles of Time-Weighted Average Tidal Volume (mL/kg PBW)			
	Total (N = 9359)	First (N = 3119)	Second (N = 3120)	Third (N = 3120)	*P*
Time-weighted average tidal volume (mL/kg PBW)	8.1 ± 1.3	6.8 ± 0.5	7.9 ± 0.3	9.5 ± 0.9	<.001[a]
Demographic variables					
Age	64.2 ± 13.2	64.4 ± 13.7	64.1 ± 12.9	64.0 ± 12.9	.34[a]
Female	3080 (32.9)	516 (16.5)	876 (28.1)	1688 (54.1)	<.001[b]
Race					.072[b]
Caucasian	8651 (92.4)	2884 (92.5)	2894 (92.8)	2873 (92.1)	
African American	340 (3.6)	100 (3.2)	105 (3.4)	135 (4.3)	
Others	368 (3.9)	135 (4.3)	121 (3.9)	112 (3.6)	
Body mass index (kg/m^2)	28.9 ± 6.0	26.3 ± 4.4	28.4 ± 5.0	32.1 ± 6.9	<.001[a]
Smoking status					.70[b]
Never	6825 (73)	2290 (73)	2256 (72)	2279 (73)	
Quit	1581 (17)	518 (17)	558 (18)	505 (16)	
Current	953 (10)	311 (10)	306 (10)	336 (11)	
Medical history					
Congestive heart failure	1887 (20.2)	608 (19.5)	608 (19.5)	671 (21.5)	.072[b]
Myocardial infarction	1565 (16.7)	509 (16.3)	507 (16.3)	549 (17.6)	.28[b]
Hypertension	7718 (82.5)	2484 (79.6)	2562 (82.1)	2672 (85.6)	<.001[b]
Atrial fibrillation or flutter	2155 (23.0)	761 (24.4)	717 (23.0)	677 (21.7)	.040[b]
Pulmonary hypertension	1374 (14.7)	430 (13.8)	419 (13.4)	525 (16.8)	<.001[b]
Stroke	685 (7.3)	233 (7.5)	222 (7.1)	230 (7.4)	.86[b]
Chronic obstructive pulmonary disease	1958 (20.9)	613 (19.7)	621 (19.9)	724 (23.2)	<.001[b]
Renal disease/renal failure on dialysis	149 (1.6)	38 (1.2)	58 (1.9)	53 (1.7)	.11[b]
Diabetes mellitus	2340 (25.0)	597 (19.1)	735 (23.6)	1008 (32.3)	<.001[b]
Cardiovascular surgical history					
Previous cardiac surgery	2088 (22.3)	641 (20.6)	726 (23.3)	721 (23.1)	.015[b]
Carotid surgery	425 (4.5)	121 (3.9)	143 (4.6)	161 (5.2)	.052[b]
Major noncarotid vascular surgery	116 (1.2)	43 (1.4)	34 (1.1)	39 (1.3)	.59[b]
Preoperative medications					
Steroids	280 (3.0)	102 (3.3)	88 (2.8)	90 (2.9)	.53[b]
Inhalation or oral bronchodilator	868 (9.3)	264 (8.5)	264 (8.5)	340 (10.9)	<.001[b]
Preoperative laboratory values					
Hematocrit (%)	41.0 [38.0, 43.5]	41.6 [38.5, 44.0]	41.2 [38.4, 43.7]	40.1 [37.1, 43.0]	<.001[c]
Creatinine (mg/dL)	1.00 [0.80, 1.1]	1.00 [0.90, 1.2]	1.00 [0.80, 1.2]	0.90 [0.80, 1.1]	<.001[c]
Preoperative echocardiography results					
EF					.045[c]
Normal (EF > 55%)	6128 (65)	2084 (67)	2053 (66)	1991 (64)	
Mild dysfunction (45 < EF ≤ 55%)	2058 (22)	651 (21)	694 (22)	713 (23)	
Moderate dysfunction (40 < EF ≤ 45%)	378 (4.0)	122 (3.9)	120 (3.9)	136 (4.4)	
Moderate-severe dysfunction (35 < EF ≤ 40%)	289 (3.1)	91 (2.9)	93 (3.0)	105 (3.4)	
Severe dysfunction (EF ≤ 35%)	506 (5.4)	171 (5.5)	160 (5.1)	175 (5.6)	

Statistics are presented as mean ± standard deviation, median [P25, P75], median (min, max), or N (column %).
Abbreviations: EF, ejection fraction; PBW, predicted body weight.
[a]Analysis of variance.
[b]Pearson χ^2 test.
[c]Kruskal-Wallis test.

exposure and a continuous outcome, conservative assumptions of variability for the outcome and exposure variables were utilized. We thus conservatively assumed a standard deviation of 100 for Pao_2/Fio_2 ratio and a standard deviation of 1 mL/kg for time-weighted average of tidal volume. We had >90% power at a significance level of .025 to detect a minimal clinically meaningful slope coefficient of 20 for 1 unit decrease in time-weighted average of tidal volume during surgery.

RESULTS

Time-weighted average tidal volume (milliliter per kilogram PBW) is presented as 3 equal tertiles in Table 1 to provide a summary of the bivariate relationships between tidal volume and a priori confounding variables; all regression models, however, use continuous tidal volume, not tertiles. With the exception of aortic cross-clamp time, intraoperative mechanical ventilation, and postoperative Pao_2/Fio_2 ratio measurements, all regression models were adjusted for each variable listed in Tables 1 and 2. A scatterplot of the relationship between time-weighted average tidal volume and Pao_2/Fio_2 ratio is shown in Supplemental Digital Content, Appendix 3, http://links.lww.com/AA/C989.

Table 2. Summary Statistics of Perioperative Variables

Preoperative echocardiography results					
Ejection fraction (%)	59 [55, 64]	59 [55, 63]	59 [55, 64]	60 [55, 64]	.88[a]
Mitral insufficiency					.19[a]
None	3929 (42)	1302 (42)	1366 (44)	1261 (40)	
Trivial	431 (4.6)	49 (1.6)	158 (5.1)	224 (7.2)	
Mild	1869 (20)	600 (19)	599 (19)	670 (21)	
Moderate	1086 (12)	358 (11)	325 (10)	403 (13)	
Severe	2044 (22)	810 (26)	672 (22)	562 (18)	
Surgery-related variables					
Staff anesthesiologist[b]					<.001[c]
Types of surgery					
Coronary artery bypass grafting	3539 (37.8)	1128 (36.2)	1212 (38.8)	1199 (38.4)	.063[c]
Aortic valve repair or replacement	7260 (77.6)	2398 (76.9)	2423 (77.7)	2439 (78.2)	.47[c]
Mitral valve repair	2124 (22.7)	840 (26.9)	686 (22.0)	598 (19.2)	<.001[c]
Mitral valve replacement	1163 (12.4)	367 (11.8)	368 (11.8)	428 (13.7)	.028[c]
Tricuspid valve repair	1068 (11.4)	393 (12.6)	336 (10.8)	339 (10.9)	.038[c]
Tricuspid valve replacement	58 (0.62)	17 (0.55)	19 (0.61)	22 (0.71)	.72[c]
Aortic surgery	1669 (17.8)	562 (18.0)	589 (18.9)	518 (16.6)	.060[c]
Myectomy	750 (8.0)	244 (7.8)	226 (7.2)	280 (9.0)	.037[c]
Maze procedure	1054 (11.3)	399 (12.8)	331 (10.6)	324 (10.4)	.004[c]
Duration of surgery (min)	352 [292, 426]	349 [289, 426]	357 [297, 430]	349 [290, 423]	.016[a]
Duration of cardiopulmonary bypass (min)	88 [65, 115]	87 [64, 115]	89 [67, 117]	87 [64, 114]	.091[a]
Duration of aortic cross-clamp (min)[d]	69 [50, 93]	69 [50, 93]	70 [51, 95]	69 [50, 92]	.25[a]
Duration of intraoperative mechanical ventilation (min)[d]	254 [210 312]	253 [208, 310]	257 [212, 314]	252 [211, 311]	.036[a]
Time from ICU admission to postoperative Pao_2/Fio_2 ratio measurements (min)[d]	262 [173, 316]	252 [160, 311]	260 [173, 315]	269 [187, 320]	<.001[a]
Intraoperative fluid balance					
Crystalloid (mL)	3000 [2400, 3700]	3000 [2400, 3750]	3000 [2400, 3600]	3000 [2300, 3600]	.003[a]
Colloid (mL)	250 [0, 500]	0 [0, 500]	250 [0, 500]	250 [0, 500]	<.001[a]
Blood products transfusion					
Red blood cell (mL)	0 (0, 6300)	0 (0, 6300)	0 (0, 3500)	0 (0, 10,500)	<.001[a]
Platelets (mL)	0 (0, 1750)	0 (0, 1250)	0 (0, 1500)	0 (0, 1750)	.10[a]
Fresh frozen plasma (mL)	0 (0, 5100)	0 (0, 3600)	0 (0, 3600)	0 (0, 5100)	.72[a]
Cryoprecipitate (mL)	0 (0, 800)	0 (0, 600)	0 (0, 600)	0 (0, 800)	.88[a]

Statistics are presented as mean ± standard deviation, median [P25, P75], median (min, max), or N (column %).

Abbreviations: Fio_2, fraction of inspired oxygen; ICU, intensive care unit; Pao_2, arterial partial pressure of oxygen.

[a]Kruskal-Wallis test.

[b]N = 44 staff anesthesiologists were represented in the sample. After collapsing anesthesiologists who participated in 10 or fewer surgeries, N = 33 unique levels were included in all multivariable regression models.

[c]Pearson χ^2 test.

[d]Data not available for all subjects. Missing values: duration of aortic cross-clamp = 239, duration of intraoperative mechanical ventilation = 1, duration of postoperative Pao_2/Fio_2 ratio measurements = 50.

Primary Outcomes

Intraoperative tidal volume was associated with Pao_2/Fio_2 ratio after surgery. Mean postoperative Pao_2/Fio_2 decreased an estimated 1.05% per 1 mL/kg PBW increase in time-weighted average tidal volume (97.5% CI, −1.74 to −0.37; P_{Bon} = .0005, which is less than the Bonferroni-adjusted significance criterion of .025), holding all confounders constant. For example, mean postoperative Pao_2/Fio_2 in our sample is 348 mm Hg; if time-weighted average intraoperative tidal volume increased 2 mL/kg PBW, mean postoperative Pao_2/Fio_2 ratio would decrease to 341 mm Hg, all else equal.

Tidal volume size was associated with impaired oxygenation. Odds of impaired oxygenation increased an estimated 1.08 (97.5% CI, 1.02–1.14; P_{Bon} = 0.0029, which is less than the Bonferroni-adjusted significance criterion of .025) times per 1 mL/kg PBW increase in time-weighted average tidal volume. Odds of impaired oxygenation would be an estimated 17% higher for an average patient receiving a time-weighted average intraoperative tidal volume 2 mL/kg higher than a comparable patient.

Secondary Outcomes

Time to Initial Extubation. A multivariable Cox model was used to produce an adjusted hazard ratio (HR) and test for an association between time to initial extubation and tidal volume. Larger time-weighted average tidal volumes were associated with prolonged intubation. Time to tracheal extubation increased an estimated 5% per 1 mL/kg PBW increase in tidal volume (HR [98.33% CI], 0.95 [0.93–0.98] per 1 mL/kg PBW, P_{Bon} < .0001, which is less than the Bonferroni-adjusted significance level 0.0167), holding other covariates constant. An increase of 2 mL/kg PBW intraoperative tidal volume is associated with an estimated 9.4% decrease in expected extubation per hour of intubation. There was no evidence that the proportional hazards assumption was violated (time × time-weighted average tidal volume interaction P = .75).

Hospital Length of Stay. A multivariable Cox model was used to produce an adjusted HR and test for an association between hospital length of stay and tidal volumes. Time-weighted average intraoperative tidal volume was not associated with length of stay (HR [98.33% CI], 1.01 [0.98–1.04] per mL/kg; P = .52). There was no evidence that the proportional hazards assumption was violated (time × time-weighted average tidal volume interaction P = .90).

Composite of Adverse Events. In Table 3, prevalences among the components varied from 0.5% (in-hospital mortality) to 4.1% (reintubation). Therefore, a covariable-adjusted average relative effect OR—which estimates then averages the effect across 5 components—was estimated for the composite outcome. With the average relative effect, the estimate is not driven by components with higher frequencies, but accounts for correlation among components, and enables estimation of component-specific "distinct effects." There was evidence for heterogeneity of tidal volume effect across components (χ^2_5 = 21.45; P = .0007). Thus, component-specific ORs (98.33% CIs) and Holm-adjusted P values along with composite average relative effect OR are presented. After controlling for confounding and adjusting for multiple testing, we found an association between time-weighted average tidal volume and in-hospital mortality and acute postoperative respiratory failure. The odds of in-hospital mortality increased an estimated 1.34 (98.33% CI, 1.06–1.70; P_{Holm} = .0144) times per 1 mL/kg PBW increase in tidal volume after holding confounders constant. Causes of postoperative in-hospital mortality are presented in Supplemental Digital Content, Appendix 4, http://links.lww.com/AA/C989. The odds of acute postoperative respiratory failure increased an estimated 1.16 (98.33% CI, 1.03–1.32; P_{Holm} = .0146) times per 1 mL/kg PBW increase in tidal volume after holding confounders constant. The composite outcomes and components are shown in Figure 2 and Table 3.

Sensitivity Analyses

In our first sensitivity analysis limited to patients with PEEP data, intraoperative tidal volume was associated with Pao_2/Fio_2 ratio and impaired oxygenation after adjusting for confounding variables. Median [Q1, Q3]

Table 3. Summary of Findings

	Overall (N = 9359)	Tertiles of Time-Weighted Average Tidal Volume, mL/kg PBW			Estimate (CI)	P
		First (N = 3119)	Second (N = 3120)	Third (N = 3120)		
Time-weighted average tidal volume, mL/kg PBW	8.1 ± 1.3	6.8 ± 0.5	7.9 ± 0.3	9.5 ± 0.9		
Primary						
Pao_2/Fio_2 ratio	348 ± 96	360 ± 96	347 ± 93	337 ± 100	−1.05% (−1.74% to −0.37%)[a]	.0005[b]
Postoperative impaired oxygenation	2865 (31)	791 (28)	952 (33)	1122 (39)	1.08 (1.02–1.14)[a]	.0029[b]
Secondary						
Time to initial extubation, hours to extubation alive	6 [4, 11]	5 [3, 10]	6 [3, 11]	6 [4, 13]	0.95 (0.93–0.98)[c]	<.0001[e]
LOS, days to discharge alive	7 [5, 9]	7 [5, 9]	7 [5, 9]	7 [6, 9]	1.01 (0.98–1.04)[c]	>.99[e]
Adverse events composite						
Components						
In-hospital mortality	49 (0.5)	13 (0.4)	10 (0.3)	26 (0.8)	1.34 (1.06–1.70)[c]	.0144[d]
Acute postoperative respiratory failure	274 (2.9)	71 (2.3)	97 (3.1)	106 (3.4)	1.16 (1.03–1.32)[c]	.0146[d]
Reintubation	380 (4.1)	115 (3.7)	117 (3.8)	148 (4.7)	1.11 (0.99–1.25)[c]	.0722[d]
ARDS	221 (2.4)	72 (2.3)	74 (2.4)	75 (2.4)	0.96 (0.84–1.09)[c]	.4370[d]
Respiratory complications	315 (3.4)	110 (3.5)	104 (3.3)	101 (3.4)	0.93 (0.83–1.05)[c]	.3087[d]
ARE OR	1239 (2.7)	381 (2.4)	402 (2.6)	456 (2.9)	1.09 (1.00–1.20)[c]	.0578[e]

Time-weighted average tidal volume: mean ± standard deviation of time-weighted average tidal volume (mL/kg PBW) overall and by tertile. Primary outcomes: Pao_2/Fio_2 ratio – mean ± standard deviation Pao_2/Fio_2 overall and by tertile are presented along the multivariable Gamma (log link) regression estimate (97.5% CI) for percent change in arithmetic mean Pao_2/Fio_2 per 1 mL/kg increase in time-weighted average tidal volume. Postoperative impaired oxygenation: N (prevalence) overall and by tertile are presented with multivariable OR (97.5% CI) for odds of impaired oxygenation (Pao_2/Fio_2 < 300) per 1 mL/kg increase in time-weighted average tidal volume. Secondary outcomes: Time to initial extubation – median [Q1, Q3] hours for time to initial extubation overall and by tertile with adjusted hazard ratio via Cox proportional hazards (98.33% CI) comparing the rate of time to initial extubation per 1 mL/kg PBW increase in tidal volume. LOS – median [Q1, Q3] days for LOS overall and by tertile with adjusted hazard ratio via Cox proportional hazards (98.33% CI) comparing the rate of LOS per 1 mL/kg increase in tidal volume. Adverse events composite: Components: N (prevalence) overall and by tertile with adjusted OR (98.33% CI) for odds of component per 1 mL/kg increase in tidal volume and Holm-adjusted P values. Composite: Multivariate N (prevalence) overall and by tertile with adjusted generalized estimating equations estimated average relative risk OR (98.33% CI) per 1 mL/kg increase in tidal volume.

Abbreviations: ARDS, acute respiratory distress syndrome; ARE OR, average relative effect odds ratio; estimates then averages time-weighted average tidal volume (per mL/kg PBW) effect across the 5 distinct components; CI, confidence interval; LOS, postoperative hospital length of stay until discharge alive; Pao_2/Fio_2, arterial partial pressure of oxygen/fraction of inspired oxygen; PBW, predicted body weight; Q1, first quartile; Q3, third quartile.

[a]Regression estimate (97.5% CI).

[b]Bonferroni significance criterion: P < .025.

[c]Regression estimate (98.33% CI).

[d]Holm-adjusted P value; Bonferroni significance criterion: P < .0167.

[e]Bonferroni significance criterion: P < .0167.

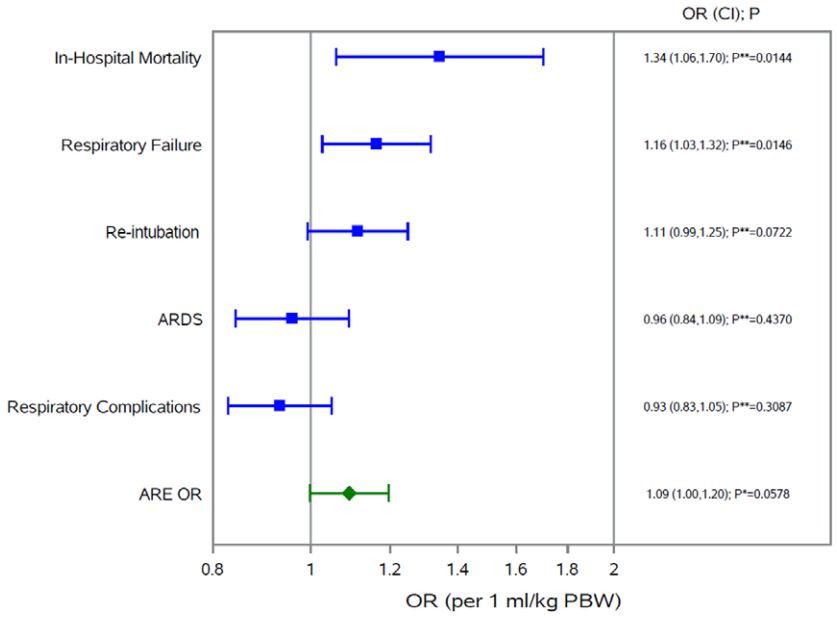

Figure 2. Forest plot for composite outcome and components. Covariable-adjusted ORs (98.33% CIs); multiple testing adjusted *P* values of intraoperative tidal volume (mL/kg) and the individual components of the adverse postoperative pulmonary outcomes and in-hospital mortality components (blue) and the overall ARE OR for the composite (green). After adjustment for confounding and Holm-adjustment for multiple testing, we found an association between time-weighted average tidal volume (per 1 mL/kg PBW) and in-hospital mortality and acute postoperative respiratory failure. The odds of in-hospital mortality increased an estimated 34% (98.33% CI, 6–70; *P*** = .0144) per 1 mL/kg PBW increase in time-weighted average tidal volume. The odds of acute postoperative respiratory failure increased an estimated 16% (98.33% CI, 3–32; *P*** = .0146) per 1 mL/kg PBW increase in time-weighted average tidal volume. *P** = Bonferroni-adjusted *P* value (adjusted for testing 3 secondary outcomes); *P*** = Holm-adjusted *P* values (adjusted for testing the 5 components individually due to the heterogeneity of effects among the components of the composite – component × time-weighted average tidal volume interaction *P* = .0007). ARDS indicates acute respiratory distress syndrome; ARE OR, average relative effect odds ratio, estimates then averages time-weighted average tidal volume (per mL/kg PBW) effect across the 5 distinct components; CI, confidence interval; OR, odds ratio; PBW, predicted body weight.

time-weighted average PEEP in 7167 patients was 5.0 [4.3, 5.0]. Mean postoperative Pao_2/Fio_2 decreased an estimated 1.09% per 1 mL/kg PBW increase in time-weighted average tidal volume (97.5% CI, –1.76 to –0.43; P_{Bon} = .0013, which is less than the Bonferroni-adjusted significance criterion of .025), holding all confounders constant. The odds of impaired oxygenation increased an estimated 1.09 (97.5% CI, 1.02–1.16; *P* = .0023, which is less than the Bonferroni-adjusted significance criterion of .025) times per 1 mL/kg PBW increase in time-weighted average tidal volume. The second sensitivity analysis (missing PEEP data were considered to be PEEP = 0) demonstrated that intraoperative tidal volume was associated with Pao_2/Fio_2 ratio and impaired oxygenation. Median [Q1, Q3] time-weighted average PEEP in 9359 patients was 5.0 [2.3, 5.0] after setting missing values to 0. Mean postoperative Pao_2/Fio_2 decreased an estimated 1.02% per 1 mL/kg PBW increase in time-weighted average tidal volume (97.5% CI, –1.61 to –0.44, P_{Bon} = .0007, which is less than the Bonferroni-adjusted significance criterion of .025), holding all confounders constant. The odds of impaired oxygenation increased an estimated 1.07 (97.5% CI, 1.01–1.13, P_{Bon} = .0057, which is less than the Bonferroni-adjusted significance criterion of 0.025) times per 1 mL/kg PBW increase in time-weighted average tidal volume.

DISCUSSION

Our investigation found an association between higher intraoperative tidal volumes and worse postoperative oxygenation, though the decrease in Pao_2/Fio_2 ratio with increasing tidal volume was modest. Patients ventilated with higher tidal volume experienced a slightly longer duration of mechanical ventilation and higher in-hospital mortality. Of several postoperative pulmonary complications, only 1 category, namely acute postoperative respiratory failure, increased when larger tidal volumes were given. Hospital length of stay and other respiratory complications were not associated with larger tidal volumes.

Detecting adverse effects from mechanical ventilation with large tidal volumes in patients having cardiac surgery is difficult because pulmonary complications consequent to the intrathoracic procedure and the need for mechanical ventilation for nonpulmonary reasons are common. We considered that common postoperative pulmonary complications may overwhelm an effect from relatively brief intraoperative use of large tidal volumes. Certainly, about 30% of cardiac surgery patients experience postoperative atelectasis diagnosed by chest radiograph,[15,16] and an even higher incidence (75%–100%) when computed tomography is used for diagnosis.[17,18] Postoperative pleural effusions are also common, occurring in 40%–56% of patients after surgery.[17,19,20] Other postoperative pulmonary complications directly result from intrathoracic surgical trauma, lung manipulation and injury, atelectasis, pleural spaces opening, complications of blood transfusion, fluid overload, prolonged ventilation for hemodynamic instability or

cardiogenic failure, and other events.[21–23] These complications could easily overwhelm the detection of lung injury from mechanical ventilation.

To identify lung injury related to mechanical ventilation, an important and cause-specific outcome, the Pao_2/Fio_2, ratio was measured early after surgery, to provide a sensitive measure of lung function while avoiding competing risks of other postoperative complications (eg, atelectasis, pleural effusions, prolonged ventilation), which typically occur later in the postoperative period. A cause-specific outcome is more sensitive to change, less likely to lead to spurious conclusions by random variations in categories of outcomes that are not affected by treatment, and less influenced by confounding.[24] Further, the Pao_2/Fio_2 ratio is an important measure of oxygenation and more specific for lung injury from mechanical ventilation. The Pao_2/Fio_2 ratio provides an important measure of pulmonary function and is considered diagnostic criteria for multiple pulmonary complications, including ARDS and acute lung injury,[25] severity of pulmonary contusion after blunt chest trauma,[26] and risk for postoperative mortality.[27] Others have found that lower postoperative Pao_2/Fio_2 ratios were associated with pulmonary complications and postoperative mortality in patients underwent major noncardiac surgery and not extubated in the operation room.[3] Our investigation also examined impaired oxygenation, defined as Pao_2/Fio_2 <300 (normal 500), as a coprimary outcome. Important postoperative complications, including mortality, were assessed as secondary outcomes.

Every milliliter per kilogram increase in tidal volume slightly reduced the Pao_2/Fio_2 ratio. Impaired oxygenation increased as tidal volumes increased, occurring in 28% of patients in the lowest tertile of tidal volumes, compared with 39% in the highest tertile. Even though the impact of intraoperative tidal volumes on postoperative oxygenation was modest, our results suggest that mechanical ventilation with small tidal volumes provides some benefit on postoperative lung function with minimal risk, and is reasonable to consider, especially in patients who may require more prolonged mechanical ventilator support after surgery. It is possible that the brief duration of mechanical ventilation during cardiac surgery limited further lung injury. Others reported similar benefits on Pao_2/Fio_2 ratio in noncardiac surgery.[28] These results contrast with a few randomized trials that did not find differences in the Pao_2/Fio_2 ratio between low and high tidal volume groups after noncardiac[29] and cardiac surgery,[30–32] though only a small number of patients were enrolled.

Our study demonstrated that patients ventilated with higher tidal volumes had a slightly longer duration of mechanical ventilatory support. Previous reports similarly demonstrated an effect on intubation time.[8] Although, the duration of mechanical ventilatory support is influenced by other patient factors (eg, postoperative hemodynamic instability) and logistical factors (respiratory therapist availability, etc). These competing risks may have reduced the impact of tidal volume size. Certainly, the Pao_2/Fio_2 ratio, our primary outcome, is less affected by these factors.

Smaller tidal volumes were not associated with shorter hospital length of stay or reduced incidence of ARDS, reintubation or respiratory complications. These results contrast with a prospective clinical trial in noncardiac surgery patients where smaller tidal volumes resulted in a 60% reduction in pulmonary and extrapulmonary complications and a 70% reduction in reintubation or requirement for noninvasive ventilation and prolonged length of hospital stay.[2] In contrast, our report includes cardiac surgery patients, rather than high-risk major abdominal surgery patients where direct surgical intervention in the chest is avoided.

In-hospital mortality was higher in patients who received larger tidal volumes. The odds of in-hospital mortality increased by 34% per 1 mL/kg increase in tidal volume. An explanation for this association is unclear; however, this small number of affected patients provides somewhat fragile results. In addition, our data demonstrate an association, not causation. We speculate that patients who died may have suffered from concomitant and unrelated pulmonary dysfunction and received more aggressive ventilation with larger tidal volumes in response to worse oxygenation, rather than the alternative.

Although our usual clinical practice targets tidal volumes between 6 and 8 mL/kg PBW, larger tidal volumes were common, perhaps because tidal volumes are often calculated using actual body weight, rather than PBW. Obese and female patients are at higher risk for "overventilation" with higher tidal volumes[9,33] because of a greater difference between actual body weight and PBW. Other studies reported that higher body weight and female sex were risk factors of pulmonary complications after surgery[34,35] and this increased risk may also be related to the administration of larger tidal volume. Our results demonstrate that overventilation and "volutrauma" is common, underlining the need for calculation of PBW for the administration of tidal volumes based on patient height.

There are limitations of the current study. First, this investigation is subject to risks inherent to its retrospective design including the possibility of unmeasured confounding variables and the ability to detect an association without proving causation. Certainly, larger tidal volumes may have been given

to patients with worse lung function and poor oxygenation. A large number of patients were excluded because of missing covariables; however, post hoc analysis found no difference in the association to the primary outcome in this subgroup. Though the primary analysis did not include PEEP, PEEP was examined in the sensitivity analysis with consistent results. Our investigation evaluated only intraoperative tidal volumes because postoperative mechanical ventilation parameters were unavailable, though mechanical ventilatory support after ICU admission followed an institutional standardized protocol. In contrast, intraoperative mechanical ventilation is highly influenced by the primary anesthesia care team. We thus adjusted for the primary anesthesiologists in our analyses.

In summary, our results demonstrate a modest improvement in postoperative lung function when lower tidal volumes were administered during cardiac surgery. Tidal volumes of 6 mL/kg PBW were associated with an improved Pao_2/Fio_2 ratio, reduced incidence of impaired oxygenation, and reduction of one of several clinical pulmonary complications. Our results suggest that mechanical ventilation with small tidal volumes provides some benefit on postoperative lung function with minimal risk, and is reasonable for patients undergoing cardiac surgery.

DISCLOSURES

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