# Management of One-lung Ventilation

## *Impact of Tidal Volume on Complications after Thoracic Surgery*

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## ABSTRACT

**Background:** The use of lung-protective ventilation (LPV) strategies may minimize iatrogenic lung injury in surgical patients. However, the identification of an ideal LPV strategy, particularly during one-lung ventilation (OLV), remains elusive. This study examines the role of ventilator management during OLV and its impact on clinical outcomes.

**Methods:** Data were retrospectively collected from the hospital electronic medical record and the Society of Thoracic Surgery database for subjects undergoing thoracic surgery with OLV between 2012 and 2014. Mean tidal volume ($V_T$) during two-lung ventilation and OLV and ventilator driving pressure ($\Delta P$) (plateau pressure – positive end-expiratory pressure [PEEP]) were analyzed for the 1,019 cases that met the inclusion criteria. Associations between ventilator parameters and clinical outcomes were examined by multivariate linear regression.

**Results:** After the initiation of OLV, 73.3, 43.3, 18.8, and 7.2% of patients received $V_T$ greater than 5, 6, 7, and 8 ml/kg predicted body weight, respectively. One hundred and eighty-four primary and 288 secondary outcome events were recorded. In multivariate logistic regression modeling, $V_T$ was inversely related to the incidence of respiratory complications (odds ratio, 0.837; 95% CI, 0.729 to 0.958), while $\Delta P$ predicted the development of major morbidity when modeled with $V_T$ (odds ratio, 1.034; 95% CI, 1.001 to 1.068).

**Conclusions:** Low $V_T$ *per se* (*i.e.*, in the absence of sufficient PEEP) has not been unambiguously demonstrated to be beneficial. The authors found that a large proportion of patients continue to receive high $V_T$ during OLV and that $V_T$ was inversely related to the incidence of respiratory complications and major postoperative morbidity. While low (physiologically appropriate) $V_T$ is an important component of an LPV strategy for surgical patients during OLV, current evidence suggests that, without adequate PEEP, low $V_T$ does not prevent postoperative respiratory complications. Thus, use of physiologic $V_T$ may represent a necessary, but not independently sufficient, component of LPV. **(Anesthesiology 2016; 124:00-00)**

MECHANICAL ventilation is a necessary supportive therapy for critically ill patients and those undergoing major surgeries. However, phasic lung expansion under positive pressure subjects the lungs to a variety of potentially injurious stimuli, which can ultimately result in clinically significant ventilator-induced lung injury (VILI). Historically, approaches to intraoperative mechanical ventilation focused primarily on preventing intraoperative atelectasis and thus endorsed the use of high tidal volumes ($V_T$s).[1] More recent experimental and clinical studies have demonstrated that a high $V_T$ approach to ventilator management can be injurious. The demonstration that high $V_T$ ventilation resulted in significantly higher mortality in patients with acute respiratory distress syndrome (ARDS)[2] led to the concept of "protective" ventilation strategies—that is, limiting alveolar overdistension through the application of smaller physiologic $V_T$, and this approach represents the standard of care for critically ill patients with lung injury. Subsequent studies of high $V_T$ ventilation in surgical patients at risk for lung injury confirm that a similar approach may decrease systemic and pulmonary inflammation[3,4] and improve postoperative pulmonary function[3,5] and clinical outcomes including pulmonary complications[6] and hospital stay.[6]

### What We Already Know about This Topic

- Low tidal volume is an important component of protective ventilation and may minimize lung injury during surgery, but the optimal combination of tidal volume and positive end-expiratory pressure (especially during one-lung ventilation) is unknown.

### What This Article Tells Us That Is New

- Analysis from 1,019 patients undergoing one-lung ventilation indicated that low tidal volume in the presence of low positive end-expiratory pressure is associated with increased pulmonary complications. This suggests that low tidal volume during one-lung ventilation is protective only when accompanied by adequate positive end-expiratory pressure.

Patients undergoing thoracic surgery may be at increased risk for complications as a result of preexisting disease

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processes, the nature of the planned surgery, loss of functional lung parenchyma (pulmonary resection), and the detrimental effects of mechanical ventilation, particularly one-lung ventilation (OLV). Thus, these patients could potentially derive even greater benefit from the application of protective ventilation principles. Despite significant advances in our understanding of protective ventilation in patients subjected to two-lung ventilation (TLV), considerably less evidence is available to guide management of OLV, a technique commonly used to optimize operating conditions for thoracic surgery. In this study, we hypothesized that large $V_T$s and higher driving pressures during OLV are associated with an increased risk of postoperative pulmonary complications and overall morbidity after thoracic surgery.

## Materials and Methods

This study was approved by the University of Virginia Institutional Review Board for Health Sciences Research. Data were retrospectively collected from the hospital electronic medical record and the Society of Thoracic Surgeons (STS) database for all patients undergoing thoracic surgery with OLV between January 1, 2012, and June 30, 2014. Cases were excluded for the following reasons: age less than 18 yr and incomplete height and/or weight data. A total of 1,232 cases met the initial inclusion criteria. Additionally, we excluded cases due to reoperation, incomplete data, or erroneous duplication of case records. The final study cohort consisted of 1,019 cases. Patient demographics and characteristics included age, sex, height, weight, and medical diagnoses. Ventilator parameters recorded during TLV and OLV included $V_T$s, PEEP, plateau ventilator pressures ($P_{plat}$), inspired oxygen fraction, expiratory carbon dioxide, and respiratory rate. Ventilation parameters for TLV were recorded for a 5-min epoch beginning 10 min before initiation of OLV. For OLV, the 5-min epoch began 10 min after the initiation of OLV. Standard practice during the study period included initiation of OLV well before chest wall incision. Thus, the transition from TLV to OLV in the current study generally reflects a transition to OLV well before opening of the pleura. Also, since the 5-min epoch started 10 min after the initiation of OLV, the nonventilated lung can be considered to be at least partially collapsed. $V_T$ was calculated on the basis of actual body weight (ABW) and predicted body weight (PBW). PBW was calculated as follows: PBW for males = 50 kg + 2.3 kg × (Height [in] − 60); PBW for females = 45.5 kg + 2.3 kg × (Height [in] − 60).

The STS database was used to obtain information for risk prediction based on previously published thoracic surgery risk models[7–9] and for specific information on postoperative outcomes. Definitions of risk predictors and specific outcome events are as specified by the STS (STS GTSD Version 2.3, updated January 2015) and are available *via* the following link: http://www.sts.org/sites/default/files/documents/STSThoracicDataSpecsV2_3.pdf (accessed March 21, 2016). The candidate risk predictor—major preoperative morbidity—was defined to include any patient with a preoperative diagnosis of coronary artery disease, congestive heart failure, peripheral vascular disease, and/or diabetes mellitus.

The primary outcome was respiratory complications, including tracheostomy, empyema requiring treatment, pneumonia, reintubation, initial ventilator support greater than 48 h, ARDS, bronchopleural fistula, pulmonary embolism, air leak greater than 5 days, atelectasis requiring bronchoscopy, and respiratory failure. The secondary complication was overall postoperative morbidity, including all respiratory complications listed above and major nonrespiratory complications such as unexpected return to the operating room, atrial or ventricular dysrhythmias requiring treatment, myocardial infarction, sepsis, renal failure, central neurologic event, unexpected intensive care unit admission, and anastomotic leak.

Driving pressure ($\Delta P$) and static compliance ($C_s$) were defined and calculated as follows: $\Delta P = P_{plat} - PEEP$; $C_s = V_T/(P_{plat} - PEEP)$.

### Statistical Analysis

Summary and descriptive statistics were obtained for all clinical data. $V_T$ during TLV and OLV were calculated relative to ABW and PBW.

Categorical variables were compared using chi-square tests, and continuous variables were compared across patient groups using means and the two-sample *t* test. Changes within patients from TLV to OLV were compared using paired *t* tests for continuous variables and McNemar test for discrete variables. Associations between continuous variables were assessed using Pearson correlation.

The association of primary and secondary outcomes with patient and surgical characteristics was assessed using multivariate logistic regression. The regression models were constructed with variables identified *a priori*, based on previous studies,[7–9] as significant predictors of adverse outcomes after major thoracic surgeries. Since there were fewer primary than secondary outcome events, adherence to the statistical rule allowing 10 outcome events per predictor mandated a reduced set of predictors in the primary outcome models.[10] Forced expiratory volume 1-s ($FEV_1$) data were missing in 37.4% of cohort patients. Since spirometric testing data, including $FEV_1$, are more likely to be available in patients with advanced lung disease and/or in those undergoing major pulmonary resection surgery, the absence of such data may itself represent a meaningful predictor. To control for potential confounding, we added a "$FEV_1$ missing" indicator variable and replaced the missing $FEV_1$ data with zeros. This approach leaves the $FEV_1$ coefficient identical to the condition in which data were restricted to only patients with nonmissing $FEV_1$ and separately models risk for those patients with missing $FEV_1$ data.

Area under the receiver operating characteristic curve was used to evaluate the regression models' sensitivity and

specificity for predicting outcome. Differences were considered significant at *P* values less than 0.05. All statistical analyses were performed in R (version 3.1.3; R Foundation for Statistical Computing, Austria. Available at: https://www.R-project.org/. Accessed March 21, 2016.).

## Results

Baseline patient characteristics and procedural frequencies are shown in table 1. Figure 1 depicts the derivation of the final study cohort. Table 2 depicts ventilation parameters during TLV and OLV periods. Mean $V_T$ during TLV was 6.0 ml/kg ABW and 7.3 ml/kg PBW. After initiation of OLV, the mean $V_T$ decreased from 6.0 to 4.9 ml/kg ABW ($P < 0.001$) and from 7.3 to 5.9 ml/kg PBW ($P < 0.001$). $P_{plat}$ increased from 17.7 to 21.7 cm $H_2O$ ($P < 0.001$), end-tidal carbon dioxide increased from 37.4 to 39.5 mmHg ($P < 0.001$), and the frequency of cases utilizing PEEP greater than or equal to 5 cm $H_2O$ increased from 32.5 to 46.6% ($P < 0.001$). Static compliance decreased during this transition from 35.6 to 23.2 ml/cm $H_2O$ ($P < 0.001$).

Mean PEEP values during OLV for the cohort was 4.2 cm $H_2O$ (SD, 1.6 cm $H_2O$), and this did not significantly differ between patients who developed complications (4.2 cm $H_2O$) and those who did not (4.2 cm $H_2O$).

As a function of ABW, 42.4% of this cohort received $V_T$ greater than 5 ml/kg during OLV, 19.4% received greater than 6 ml/kg, 6.6% greater than 7 ml/kg, and 2.3% greater than 8 ml/kg. As a function of PBW, the percentage of patients receiving $V_T$ greater than 5, 6, 7, and 8 ml/kg during OLV were 73.3, 43.3, 18.8, and 7.2%, respectively (data not shown).

The frequency and types of major morbidities are shown in table 3. Multivariate logistic regression models for the primary and secondary outcomes are shown in table 4. Generally, the patient and procedural risk predictors were consistent with previously published models in the surgical literature. Risk predictors for the primary outcome included Zubrod score, preoperative $FEV_1$, thoracotomy incision, and segmentectomy/lobectomy procedures. Significant predictors for the secondary outcome include patient age, Zubrod score, induction chemotherapy and/or radiation, $FEV_1$, thoracotomy incision, esophageal surgery, segmentectomy and lobectomy procedures, and blood product transfusion.

$V_T$ was inversely related to the incidence of the primary outcome—respiratory complications (odds ratio [OR], 0.837; 97.5% CI, 0.729 to 0.958). Thus, an increase in $V_T$ of 1 ml/kg PBW was associated with approximately a 16% reduction in the risk of respiratory complications. The relationship between $V_T$ and major morbidity was qualitatively similar and approached, but did not reach, statistical significance ($P = 0.08$). The inverse relationship between $V_T$ and the primary outcome was also seen in model 2 (OR, 0.854; 97.5% CI, 0.748 to 0.973), which excluded ΔP and included PEEP, although PEEP itself was not predictive for development of either outcome. Ventilator ΔP was identified as a risk factor for the development of the secondary outcome (OR, 1.034; 97.5% CI, 1.001 to 1.068) in model 1. Each unit of driving pressure (1 cm $H_2O$) was associated with a 3.4% increase in the risk of major morbidity. When modeled without $V_T$ (model 3), the effect of ΔP approached,

**Table 1.** Baseline Patient and Procedural Characteristics

| | N = 1,019, n (%), Median (IQR) |
|---|---|
| Age at surgery | 63 (54–71) |
| Female sex | 481 (47.2) |
| BMI (kg/m$^2$) | 26.6 (23–30) |
| Zubrod score | 1 (1–1) |
| ASA status | 3 (2–3) |
| Renal dysfunction | 22 (2.2) |
| Current smoker | 205 (20.1) |
| Induction chemotherapy or radiation | 141 (13.8) |
| Preoperative steroid therapy | 66 (6.5) |
| $FEV_1$ (% predicted) | 78 (59–93) |
| Major preoperative morbidity | 336 (33.0) |
| Blood product transfusion | 46 (4.5) |
| VATS | 616 (60.5) |
| Thoracotomy | 325 (31.9) |
| Other approach | 78 (7.7) |
| Wedge resection | 167 (16.4) |
| Bilobectomy/pneumonectomy | 33 (3.2) |
| Esophageal procedure | 145 (14.2) |
| Lung transplantation | 25 (2.5) |
| Pleura/diaphragm/mediastinal/chest wall | 219 (21.5) |
| Segmentectomy/lobectomy | 285 (28.0) |
| Other thoracic procedure | 145 (14.2) |

Baseline patient and procedural characteristics are shown as percentages of the total cohort or as median values.

ASA = American Society of Anesthesiologists; BMI = body mass index; $FEV_1$ = forced expiratory volume in 1 s; IQR = interquartile range; VATS = video-assisted thoracoscopic surgery.

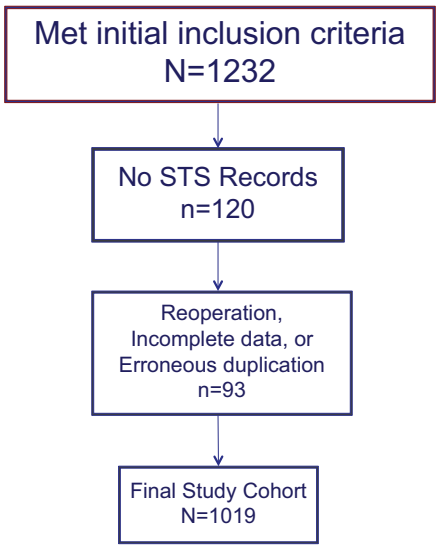


**Fig. 1.** Derivation of the study cohort. STS = Society of Thoracic Surgeons.

**Table 2.** Characteristics of Ventilation during TLV and OLV

| Ventilator Variable | TLV, Mean (SD) | OLV, Mean (SD) | *P* Value |
|---|---|---|---|
| Tidal volume (ml) | 458.8 (110.8) | 370.9 (87.8) | < 0.001 |
| Tidal volume (ml/kg PBW) | 7.3 (1.9) | 5.9 (1.5) | < 0.001 |
| Tidal volume (ml/kg ABW) | 6.0 (1.7) | 4.9 (1.4) | < 0.001 |
| End-tidal carbon dioxide (mmHg) | 37.4 (5.0) | 39.5 (6.0) | < 0.001 |
| PEEP (cm $H_2O$) | 3.8 (1.6) | 4.2 (1.6) | < 0.001 |
| Percentage with PEEP > 5 | 32.5 (1.5) | 46.6 (1.6) | < 0.001 |
| Peak pressure (cm $H_2O$) | 21.0 (6.2) | 26.1 (6.8) | < 0.001 |
| Plateau pressure (cm $H_2O$) | 17.7 (5.2) | 21.7 (5.8) | < 0.001 |
| Driving pressure (cm $H_2O$) | 13.9 (5.0) | 17.5 (5.7) | < 0.001 |
| Static compliance (ml/cm $H_2O$) | 35.6 (18.0) | 23.2 (8.5) | < 0.001 |

Values displayed are means and SD for depicted ventilation variables during two-lung ventilation (TLV) and one-lung ventilation (OLV) periods. Means of ventilation characteristics were compared using the paired *t* test with the exception of percentage with positive end-expiratory pressure (PEEP) > 5, which were compared with the McNemar test.

ABW = actual body weight; PBW = predicted body weight.

but did not reach, significance ($P = 0.084$). Receiver operating characteristic curve analysis of the models for the primary and secondary outcomes (model 1) yielded area under the curve of 0.78 and 0.79, respectively, indicating moderate ability to predict complications.

Derivation of the study cohort and exclusions are shown in figure 1. Static compliance during OLV and delivered $V_T$ were significantly ($P < 0.001$) but not strongly correlated (fig. 2), yielding a correlation coefficient of 0.467. To assess whether the relationship between low $V_T$ and increased risk of primary and secondary outcome events was independent of compliance, multivariate models were recalculated including compliance. Compliance was not itself significantly predictive of outcomes and did not affect the association of either $V_T$ with the primary outcome or ΔP with the secondary outcome (data not shown). The correlation between driving pressure and $V_T$ ($r = 0.126$) is depicted in figure 3. The relationships between $V_T$ or ΔP and the log odds of developing respiratory complications or major postoperative complications are depicted in figures 4 and 5.

**Table 3.** Frequency of Complications and Outcomes

| | Frequency (% of Cases) |
|---|---|
| Tracheostomy | 18 (1.8) |
| Empyema requiring treatment | 12 (1.2) |
| Pneumonia | 40 (3.9) |
| Reintubation | 50 (4.9) |
| Initial ventilator support > 48 h | 12 (1.2) |
| ARDS | 12 (1.2) |
| Bronchopleural fistula | 1 (0.1) |
| Pulmonary embolus | 8 (0.8) |
| Air leak > 5 days | 60 (5.9) |
| Atelectasis requiring bronchoscopy | 105 (10.3) |
| Respiratory failure | 54 (5.3) |
| Unexpected return to operating room | 35 (3.4) |
| Atrial arrhythmia requiring treatment | 115 (11.3) |
| Ventricular arrhythmia requiring treatment | 4 (0.4) |
| Myocardial infarction | 11 (1.1) |
| Anastomotic failure requiring treatment | 8 (0.8) |
| Sepsis | 20 (2.0) |
| Central neurologic event | 3 (0.3) |
| Renal failure | 12 (1.2) |
| Unexpected ICU admission | 78 (7.7) |
| Mortality within 30 days | 18 (1.6) |
| Primary outcome | 184 (18.1) |
| Secondary outcome | 288 (28.3) |

The frequency of complications within the studied cohort, both observed as a number of each complication and as a percentage of the cohort.

ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

## Discussion

In this study cohort, we found that, during OLV, patients received higher $V_T$ when calculated on the basis of PBW as compared to ABW. In multivariate logistic regression models, $V_T$ was inversely related to the incidence of the primary outcome—respiratory complications. After controlling for other candidate risk predictors, the odds of developing respiratory complications after thoracic surgery were lower in patients ventilated with higher $V_T$. Ventilator ΔP was identified as a risk factor for the development of major morbid complications in a regression model inclusive of $V_T$. However, when modeled without $V_T$, the effect of ΔP approached, but did not reach, statistical significance.

### *Protective Ventilation in TLV and OLV*

Studies of general surgery patients at high risk for postoperative respiratory complications have reported that lung-protective ventilation (LPV) strategies (lower $V_T$s and higher PEEP) improve clinical outcomes in patients with preoperatively healthy lungs.[5,6] However, these studies have been criticized for the use of a control group with high $V_T$s without the use of PEEP (zero end-expiratory pressure [ZEEP]). Although these studies may contribute to the identification of a protective ventilation strategy, they do not permit the elucidation of specific factors ($V_T$, PEEP, airway pressure, driving pressure, and transpulmonary pressure) responsible for the observed clinical effect. More recent trials have

**Table 4.** Multivariate Logistic Regression Models for Respiratory Complications and Major Morbidity

| | Multivariate Model for Respiratory Complications | | | Multivariate Model for Major Morbidity | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| Intercept | 0.247 | 0.046–1.260 | 0.097 | **0.059** | **0.010–0.331** | **0.002** |
| Age (per year) | 1.007 | 0.991–1.023 | 0.417 | **1.024** | **1.010–1.040** | **0.001** |
| ASA status (per unit) | | | | 1.172 | 0.810–1,703 | 0.403 |
| Blood product transfusion (any *vs.* none) | | | | **2.599** | **1.235–5.618** | **0.013** |
| Body mass index (per 1 kg/m$^2$) | | | | 0.996 | 0.967–1.026 | 0.806 |
| Preoperative renal dysfunction | 1.686 | 0.501–5.172 | 0.374 | 0.999 | 0.314–2.976 | 0.999 |
| Preoperative steroid therapy | 1.575 | 0.743–3.222 | 0.223 | 0.981 | 0.467–1.987 | 0.959 |
| Zubrod score (per unit) | **1.663** | **1.323–2.098** | **< 0.001** | **1.341** | **1.069–1.684** | **0.011** |
| Current cigarette smoker (*vs.* none) | 1.169 | 0.744–1.813 | 0.229 | 1.198 | 0.793–1.798 | 0.387 |
| $FEV_1$ (per 1% increase in % predicted) | **0.980** | **0.969–0.991** | **< 0.001** | **0.983** | **0.973–0.993** | **< 0.001** |
| Patient missing $FEV_1$ data (*vs.* available $FEV_1$ data) | **0.236** | **0.089–0.629** | **0.004** | **0.332** | **0.137–0.805** | **0.015** |
| Female sex (*vs.* male) | 1.026 | 0.691–1.522 | 0.898 | 0.724 | 0.511–1.025 | 0.069 |
| Induction chemotherapy and/or radiation | 1.044 | 0.604–1.767 | 0.874 | 1.369 | 0.862–2.162 | 0.180 |
| Major preoperative comorbidity | 1.174 | 0.788–1.743 | 0.427 | 1.251 | 0.874–1.789 | 0.220 |
| Segmentectomy or lobectomy (*vs.* wedge resection) | **5.584** | **2.914–11.450** | **< 0.001** | **4.832** | **2.767–8.755** | **< 0.001** |
| Bilobectomy or pneumonectomy (*vs.* wedge resection) | 2.076 | 0.674–6.186 | 0.193 | 1.647 | 0.591–4.460 | 0.331 |
| Procedure of pleura, diaphragm, mediastinum, chest wall (*vs.* wedge resection) | 0.511 | 0.207–1.269 | 0.144 | 0.642 | 0.306–1.353 | 0.242 |
| Major esophageal procedure (*vs.* wedge resection) | 1.986 | 0.803–5.068 | 0.143 | **2.871** | **1.346–6.254** | **0.007** |
| Other incisional approach (*vs.* VATS) | 1.022 | 0.508–1.982 | 0.950 | 1.489 | 0.815–2.690 | 0.190 |
| Thoracotomy (*vs.* VATS) | **2.008** | **1.255–3.225** | **0.004** | **1.901** | **1.260–2.874** | **0.002** |
| Lung transplantation (*vs.* wedge resection) | 1.884 | 0.556–6.477 | 0.310 | 2.152 | 0.626–7.714 | 0.229 |
| Other thoracic surgical procedure (*vs.* wedge resection) | 0.581 | 0.224–1.460 | 0.252 | 0.674 | 0.309–1.438 | 0.311 |
| Model 1 | | | | | | |
| $V_T$ during OLV (per 1 ml/kg PBW) | **0.837** | **0.729–0.958** | **0.010** | 0.898 | 0.795–1.012 | 0.080 |
| Ventilator driving pressure ($P_{plat}$ – PEEP; per 1 cm $H_2O$) | 1.021 | 0.987–1.055 | 0.229 | **1.034** | **1.001–1.068** | **0.044** |
| Model 2 (all variables in model 1 except driving pressure) | | | | | | |
| PEEP during OLV (per 1 cm $H_2O$) | 0.988 | 0.879–1.109 | 0.834 | 0.948 | 0.852, 1.054 | 0.323 |
| $V_T$ during OLV (per 1 ml/kg PBW) | **0.854** | **0.748–0.973** | **0.019** | 0.915 | 0.812–1.029 | 0.139 |
| Model 3 (all variables in model 1 except $V_T$ during OLV) | | | | | | |
| Ventilator driving pressure ($P_{plat}$ – PEEP; per 1 cm $H_2O$) | 1.010 | 0.977–1.043 | 0.563 | 1.0285 | 0.996–1.062 | 0.084 |

Bold entries indicate risk predictors shown to be statistically significant with regard to prediction of outcome events.

ASA = American Society of Anesthesiologists; $FEV_1$ = forced expiratory volume in 1 s; OLV = one-lung ventilation; OR = odds ratio; PBW = predicted body weight; PEEP = positive end-expiratory pressure; $P_{plat}$ = plateau pressure; VATS = video-assisted thoracoscopic surgery; $V_T$ = tidal volume.

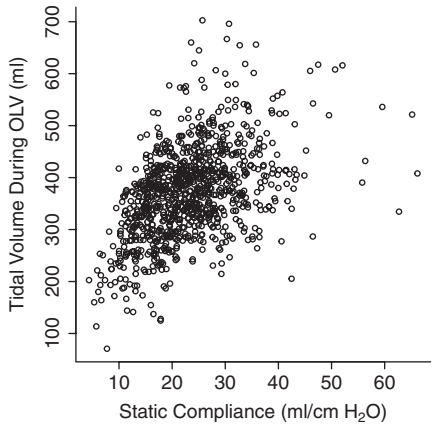


**Fig. 2.** The relationship between calculated static compliance during one-lung ventilation (OLV) and delivered tidal volume. Median tidal volume during a 5-min epoch 10 min after the start of OLV for each case is plotted against calculated static compliance for the same period.

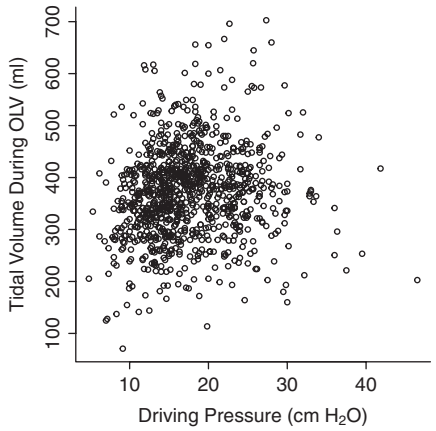


**Fig. 3.** The relationship between calculated driving pressure during one-lung ventilation (OLV) and delivered tidal volume. Median tidal volume during a 5-min epoch 10 min after the start of OLV for each case is plotted against driving pressure for the same period.

evaluated the role of $V_T$ and PEEP in lung protection *via* controlled modification of a single ventilator variable. Treschan *et al.*[11] demonstrated no differences in postoperative lung function in upper abdominal surgery patients ventilated with a high ($V_T$ 12 ml/kg PBW) or low ($V_T$ 6 ml/kg PBW) $V_T$ strategy that included comparable levels of PEEP (5 cm $H_2O$) in both groups.

In thoracic surgery patients, OLV contributes to the development of lung injury and the development of serious complications. Very little data exist to specifically support a particular approach to management of OLV with regard to clinical outcomes. Some but not all[12] prospective studies examining putative protective OLV (reduced $V_T$ and moderate PEEP) have demonstrated a reduction in pulmonary[13] or systemic inflammation,[3] extravascular lung water,[14,15] or pulmonary complications.[13,16] A retrospective study following institution of a protective ventilation protocol incorporating reduced $V_T$, increased PEEP, limited ventilator pressures, and recruitment maneuvers during OLV for lung cancer surgery is also consistent with a reduced risk of acute lung injury.[17] In retrospective reviews of pneumonectomy, $V_T$s,[17,18] ventilation pressures,[19,20] and duration of OLV[19] have been identified as risk factors for the development of lung injury.

It is important to note that the results of the current study complement rather than contradict those of recent high-quality prospective trials. No studies have yet unambiguously demonstrated a specific advantage of low $V_T$ ventilation in the absence of other ventilatory strategies (PEEP, airway pressure limitation, and recruitment maneuvers), and it is not yet clear which ventilator parameters, if any, are most likely to predict adverse outcomes. That a low $V_T$ regimen *per se* is not inherently protective is supported by a high-quality study of surgical patients, which demonstrated no difference in postoperative pulmonary function between high and low $V_T$ regimens, both with equivalent moderate levels of PEEP[11]; a large retrospective study of surgical patients, which demonstrated an association between low intraoperative $V_T$ with minimal PEEP and the subsequent risk of mortality[21]; and the results of the present study, in which we found a similar inverse relationship between $V_T$ during OLV and the risk of complications after thoracic surgery. In our study cohort, as in the study by Levin *et al.*,[21] patients received low PEEP (4.2 cm $H_2O$), which may have been insufficient to stabilize alveoli, reduce alveolar strain, and prevent atelectasis. While atelectasis is a significant consideration in all anesthetized surgical patients, it may be of greater importance during OLV, due to the use of higher inspiratory oxygen fractions (absorption atelectasis) and the greater potential for dependent lung compression (compression atelectasis). Without adequate PEEP, low $V_T$ during OLV may predispose to atelectasis and thus contribute to an increased risk of morbidity. Perioperative atelectasis results in a profoundly injurious inflammatory state and has been extensively reviewed.[22] The presence of nonlobar atelectasis appears to act as a "stress concentrator" and can even cause inflammation and alveolar injury in adjacent healthy lung parenchyma.[23] Furthermore, the presence of atelectatic regions may promote bacterial translocation[24] and increase the risk of pneumonia.[24–26]

That atelectasis contributes to the increased risk of morbidity in surgical patients ventilated with both low $V_T$ and low PEEP is supported by studies that demonstrate that the addition of significant PEEP is required to promote lung protection, improve lung function, and reduce the risk of postoperative complications during both TLV[5,6] and OLV.[3,13,16] The administration of either high PEEP[27] or low $V_T$[11] as a sole variable between groups has not been shown to be protective. The synergistic interaction between $V_T$ and PEEP has been described in experimental models that demonstrate an interdependence between these variables.[28,29] Moreover, although the use of all studied ventilation regimens resulted in substantial release of cytokines in an animal model of lung injury, the

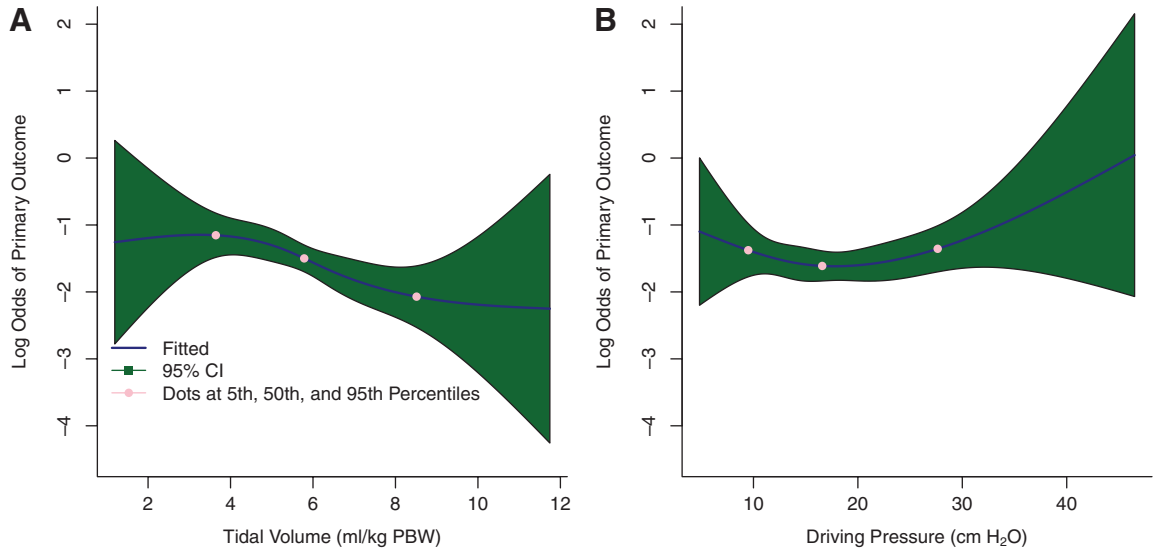


**Fig. 4.** Log odds of primary outcome *versus* tidal volume and driving pressure. The logarithm of the odds of developing the primary outcome (respiratory complications) is plotted against the (*A*) tidal volume and (*B*) driving pressure during one-lung ventilation. PBW = predicted body weight.

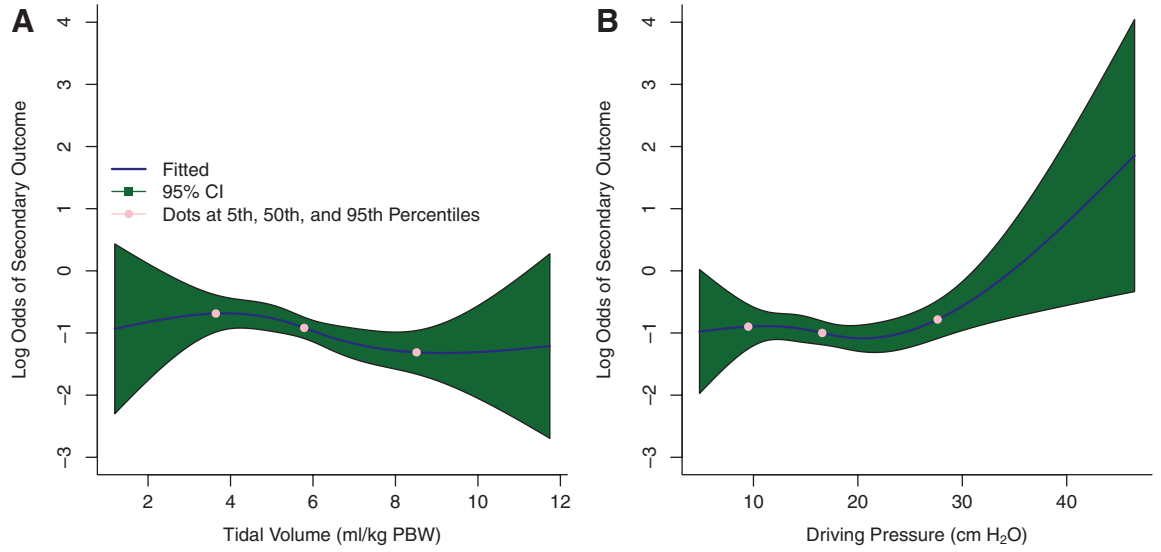


**Fig. 5.** Log odds of secondary outcome *versus* tidal volume and driving pressure. The logarithm of the odds of developing the secondary outcome (major morbidity) is plotted against the (*A*) tidal volume and (*B*) driving pressure during one-lung ventilation. PBW = predicted body weight.

combination of low $V_T$ and ZEEP resulted in a much higher mortality relative to groups that received either higher $V_T$ or PEEP,[30] suggesting that the nature, and perhaps severity, of lung injury resulting from atelectasis *versus* overdistension may be qualitatively different. The ideal amount of PEEP and the ideal approach to titrating PEEP in surgical patients have not yet been elucidated. However, the use of pulmonary mechanical parameters to identify intratidal recruitment during TLV suggests that 5 cm $H_2O$ PEEP may be insufficient to prevent this injurious process.[31] Likewise, titrating PEEP on the basis of static compliance during OLV resulted in the selection of a much higher PEEP (10 cm $H_2O$) than is conventionally used by most practitioners.[32] Collectively, these studies indicate that an effective LPV strategy results from the use of a physiologic (low) $V_T$ and sufficient PEEP to minimize both overdistension and atelectasis and suggest that the level of PEEP utilized in the current OLV study cohort and that of a previously reported TLV cohort[21] were insufficient to prevent the pathophysiologic processes and sequelae of atelectasis and tidal recruitment/derecruitment.

An alternative explanation for the results of both studies is that unidentified patient factors, which may lead anesthesia care providers to use lower $V_T$, might be independently linked to adverse outcomes. That the use of lower $V_T$ in their cohort might be caused by reduced compliance and higher airway pressures was excluded by Levin *et al.*[21] based

on their inclusion of compliance and inspiratory pressure in the multivariate model. Our results paralleled those of Levin *et al.* $V_T$ and static compliance ($V_T/P_{plat}$ – PEEP) were significantly ($P < 0.001$) but not strongly correlated ($r = 0.467$). However, inclusion of compliance in regression models for both the primary and secondary outcomes did not alter the primary findings. This indicates that, despite a correlation between $V_T$ and compliance, a low $V_T$ is an independent risk factor for the development of these adverse outcomes.

### Practice Patterns of OLV

In the present study examining single tertiary center practice patterns of OLV for thoracic surgery, we found that relative to current recommendations,[33] practitioners continue to use high $V_T$ and low levels of PEEP. Moreover, high patient body mass index was associated with the use of larger $V_T$ upon normalization to PBW. After normalization to PBW, 73.3, 43.3, 18.8, and 7.2% of patients in the cohort were ventilated with $V_T$ greater than 5, 6, 7, and 8 ml/kg, respectively. These findings mirror those of large database studies of surgical patients, which demonstrated that patients of short stature, high body mass index, and female sex received higher $V_T$ than the general population when normalized to predicted or ideal body weight.[21,34] This occurs presumably because anesthesia ventilators in general do not receive input regarding patient height or weight and because the selection of $V_T$ by the anesthesia care provider tends to inadequately compensate for the discrepancy between ABW and PBW. Mean PEEP levels during OLV in our cohort were 4.2 cm $H_2O$ and did not significantly differ between patients with and without major postoperative morbidity. During OLV, fewer than half (47%) of the patient cohort received PEEP greater than or equal to 5 cm $H_2O$.

### Pathophysiologic Determinants of VILI

It is important to point out that much of the contradictory results in studies of VILI in critically ill and surgical patients may arise from the imprecision inherent in the studied ventilator variables. Neither $V_T$ nor PEEP data contain information inherently important from a pathophysiologic standpoint. That is, the pathophysiologic effect of a delivered positive pressure tidal breath, if any, derives from the generated transpulmonary pressure ($P_L$) and its subsequent impact on tissue deformation (stress and strain). Dynamic alveolar strain ($V_T$/functional residual capacity) defines the degree of alveolar tissue deformation between inspiration and expiration. Dynamic but not static alveolar strain is injurious in healthy pigs ventilated at total lung capacity[35] and appears to be the more important determinant of VILI.[36]

Although ΔP has been identified as a risk factor for the development of ARDS in a general surgical population, it has not been previously studied in thoracic surgery.[37] In a large retrospective study of ARDS patients, Amato *et al.*[38] identified ΔP but not $V_T$ as the ventilation variable that best stratified risk of mortality. Using double-stratification analysis, these authors were able to identify ΔP as the only ventilator variable that predicted mortality in ARDS. Thus, ΔP may serve as a surrogate for dynamic alveolar strain. PEEP is important to the extent that it reduces ΔP and dynamic strain. That PEEP stabilizes the alveolus and can be used to reduce dynamic strain is well established from animal[28] and clinical models.[35,36] The effect of ΔP on major morbidity after OLV is not yet entirely clear. While ΔP predicts major morbidity after thoracic surgery with OLV in a model including $V_T$, the effect of ΔP in a model without $V_T$ approaches, but does not reach, statistical significance.

### Limitations

There are several limitations to this study. First, as a consequence of its retrospective design, the relationship between $V_T$, driving pressure, and subsequent complications cannot yet be construed as causal. Second, in an effort to reduce the risk of inaccurate sampling of anesthetic/ventilator data (due to undocumented termination of OLV), we evaluated brief periods (5-min epochs) early during both TLV and OLV. This approach was mandated by the absence of a clearly documented OLV end-time in approximately 40% of these cases. We believe that this approach is likely to result in a sampling of ventilator management data most representative of overall OLV since standard OLV management at our institution is established early during this period and early sampling of OLV data is most likely to avoid the undocumented reinstitution of TLV. Also, this is a single-center study and as such may not be reflective of practice patterns at other institutions.

Finally, in this study as in that of Amato *et al.*,[38] statistical analysis of ΔP and $V_T$ is limited by the mechanistic linkage between these variables. Although the correlation between these variables in the current study is low, there is nonetheless a concern about physiologic interdependence. That is, for a given respiratory system compliance, ΔP should be proportional to $V_T$. Thus, one would expect a qualitatively similar relationship between both variables and the studied outcome measures. However, we found that, while $V_T$ was inversely related to the primary outcome, ΔP predicted major morbidity after thoracic surgery with OLV in a regression model including $V_T$ and approached, but did not reach, statistical significance in a model without $V_T$. One explanation for this discrepancy relates to the variation in ΔP resulting from a given $V_T$ based on the "size" of functional lung parenchyma in a manner analogous to that of the "baby lung" concept in ARDS.[39] Significant variation in nature and severity of lung diseases and resultant effects on functional lung volume and elastance is expected in a large cohort of thoracic surgical patients. Severely diseased lungs, particularly those with restrictive disease, would be expected to exhibit a larger ΔP for a given $V_T$, while normal lungs would be expected to exhibit a lesser increase in ΔP. A larger $V_T$ delivered to normal lung parenchyma (with a resultant lower ΔP relative to that of a diseased lung) could conceivably contribute to a reduced likelihood of atelectasis development, while a

low $V_T$ in such a patient would be more likely to promote atelectasis and related morbidity. The discrepant ability of $V_T$ and ΔP to predict postoperative morbidity in this cohort might then be explained by a differential potential of a given $V_T$ to cause overdistension or contribute to atelectasis based on functional lung volume and respiratory system elastance. Additionally, since composite outcome measures used in this study are not likely to reflect a single pathophysiologic mechanism, it is also possible that lower $V_T$ and higher ΔP might differentially promote distinct pathophysiologic pathways—atelectasis *versus* overdistension. Such a possibility is supported by experimental evidence that while high $V_T$ with ZEEP produces a similar cytokine response, low $V_T$ with ZEEP results in higher mortality.[30]

## Conclusions

Mechanical ventilation has the potential to adversely affect outcomes in surgical patients. These risks clearly extend to patients subjected to OLV. Protective ventilation with low $V_T$ and PEEP has been recommended by a number of experts,[33,40,41] but no standardized guidelines exist. While it is clear that a high $V_T$ regimen without PEEP is injurious, especially in high-risk patients and surgeries, low $V_T$ without adequate PEEP may also be injurious.[21,30] It is important for the practitioner to note that we are not advocating the use of high or supraphysiologic $V_T$. High-quality prospective data strongly support the use of LPV in TLV and, to a lesser extent, in OLV. While the ideal LPV regimen is yet to be completely elucidated, the current evidence strongly indicates that protection from iatrogenic lung injury follows from the concomitant use of both physiologic (low) $V_T$ and sufficient PEEP to prevent overdistension, atelectasis, and tidal recruitment/derecruitment phenomena. Ultimately, advances in our understanding of protective ventilation during OLV are likely to derive from well-designed randomized trials controlling for variables of inherent pathophysiologic significance. The control of $P_L$, ΔP, and alveolar strain in such trials of protective ventilation will be important for the identification of optimal ventilation strategies.

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## Competing Interests

The authors declare no competing interests.

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