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A Lower Tidal Volume Regimen during One-lung Ventilation for Lung Resection Surgery Is Not Associated with Reduced Postoperative Pulmonary Complications

Douglas A. Colquhoun, M.B.Ch.B., M.Sc., M.P.H., Aleda M. Leis, M.S., Amy M. Shanks, Ph.D., Michael R. Mathis, M.D., Bhiken I. Naik, M.B.B.Ch., Marcel E. Durieux, M.D., Ph.D., Sachin Kheterpal, M.D., M.B.A., Nathan L. Pace, M.D., M.Stat., Wanda M. Popescu, M.D., Robert B. Schonberger, M.D., M.H.S., Benjamin D. Kozower, M.D., M.P.H., Dustin M. Walters, M.D., Justin D. Blasberg, M.D, M.P.H., Andrew C. Chang, M.D., Michael F. Aziz, M.D., Izumi Harukuni, M.D., Brandon H. Tieu, M.D., F.A.C.S., Randal S. Blank, M.D., Ph.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Lower tidal volume ventilation with moderate positive end-expiratory pressure (PEEP) compared with higher tidal volumes with low PEEP is associated with fewer pulmonary complications in adult respiratory distress syndrome and in abdominal surgery with two-lung ventilation.
- Fewer studies have assessed optimal ventilation strategies for thoracic surgery with one-lung ventilation. Optimal lung protective strategies for one-lung ventilation are undefined.

What This Article Tells Us That Is New

- This five-center retrospective observational study evaluated records from 3,232 thoracic surgical patients who underwent one-lung ventilation for pneumonectomies, bilobectomies, single lobectomies, segmentectomies, or wedge resections.
- Patients with tidal volumes 5 ml/kg or lower and PEEP greater than 5 cm H_2O did not have significantly different 30-day adverse pulmonary outcomes compared with patients not ventilated with this strategy.
- Higher mechanical ventilation driving pressures were not associated with composite 30-day adverse pulmonary outcome.
- The protective ventilation regimen tested was not associated with decreased pulmonary complications.

ABSTRACT

Background: Protective ventilation may improve outcomes after major surgery. However, in the context of one-lung ventilation, such a strategy is incompletely defined. The authors hypothesized that a putative one-lung protective ventilation regimen would be independently associated with decreased odds of pulmonary complications after thoracic surgery.

Methods: The authors merged Society of Thoracic Surgeons Database and Multicenter Perioperative Outcomes Group intraoperative data for lung resection procedures using one-lung ventilation across five institutions from 2012 to 2016. They defined one-lung protective ventilation as the combination of both median tidal volume 5 ml/kg or lower predicted body weight and positive end-expiratory pressure 5 cm H_2O or greater. The primary outcome was a composite of 30-day major postoperative pulmonary complications.

Results: A total of 3,232 cases were available for analysis. Tidal volumes decreased modestly during the study period (6.7 to 6.0 ml/kg; $P < 0.001$), and positive end-expiratory pressure increased from 4 to 5 cm H_2O ($P < 0.001$). Despite increasing adoption of a "protective ventilation" strategy (5.7% in 2012 *vs.* 17.9% in 2016), the prevalence of pulmonary complications did not change significantly (11.4 to 15.7%; $P = 0.147$). In a propensity score matched cohort (381 matched pairs), protective ventilation (mean tidal volume 6.4 *vs.* 4.4 ml/kg) was not associated with a reduction in pulmonary complications (adjusted odds ratio, 0.86; 95% CI, 0.56 to 1.32). In an unmatched cohort, the authors were unable to define a specific alternative combination of positive end-expiratory pressure and tidal volume that was associated with decreased risk of pulmonary complications.

Conclusions: In this multicenter retrospective observational analysis of patients undergoing one-lung ventilation during thoracic surgery, the authors did not detect an independent association between a low tidal volume lung-protective ventilation regimen and a composite of postoperative pulmonary complications.

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Postoperative pulmonary complications are common and highly morbid, particularly in thoracic surgery patients.[1] Previous reports have demonstrated that protective ventilation can improve postoperative pulmonary function and reduce the incidence of complications, but the precise definition of protective ventilation remains elusive. Prospective studies of protective ventilation in surgical patients have often compared groups that differ on the basis of multiple ventilatory variables. These fixed ventilation "bundles" are typically comprised of tidal volume (V_T) and positive end-expiratory pressure (PEEP), with or without alveolar recruitment maneuvers.[2–7] The optimal combination of V_T and PEEP to minimize postoperative pulmonary complications has not yet been defined.

Definitions of protective one-lung ventilation emerge from expert opinion, translation of evidence from two-lung ventilation in general surgical patients, and a small number of clinical trials.[2,6–10] Perioperative studies of protective

ventilation typically compare lower V_T and moderate PEEP against higher V_T and minimal PEEP.[5–7] Recent work has demonstrated that lower V_T in the absence of adequate PEEP may be detrimental to patient outcomes.[11,12] While the specific impact of V_T is unclear, emerging evidence appears to implicate airway driving pressure, rather than V_T or PEEP, as a potential determinant of postoperative pulmonary complication risk.[13,14]

The Society of Thoracic Surgeons (Chicago, Illinois) General Thoracic Surgery Database is a well-established, validated national clinical outcomes registry used for peer-reviewed publications and quality improvement.[15,16] We sought to leverage this database in combination with the Multicenter Perioperative Outcomes Group (Ann Arbor, Michigan) database—a repository of machine-captured intraoperative physiologic data including ventilator parameters—to evaluate the association between intraoperative ventilation practices during one-lung ventilation and patient outcomes.

The primary aim of this study was to examine the relationship among V_T, PEEP, and use of a recommended protective ventilation strategy during one-lung ventilation with the subsequent development of pulmonary complications in patients undergoing thoracic surgery. The secondary aims were (1) to identify an optimal combination of V_T and PEEP that minimized postoperative pulmonary complications when adjusted for known risk factors and (2) to determine whether increased airway pressures during ventilation were associated with adverse outcomes. This study expands upon previous work we and others have reported examining the association between ventilation exposures and postoperative clinical outcomes.[5–7,12] Advances in the field attributable to this study derive from several factors including the integration of Multicenter Perioperative Outcomes Group and Society of Thoracic Surgeons thoracic surgical databases to produce a large relatively homogeneous multicenter cohort of lung resection patients and the subsequent detailed study of the individual and combinatorial associations between ventilation variables and clinically relevant outcome measures.

Materials and Methods

Approvals

The Multicenter Perioperative Outcomes Group (MPOG) at the University of Michigan obtained institutional review board (IRB) approval for this observational cohort study (University of Michigan, Ann Arbor, Michigan, IRB MED HUM00024166, HUM00033894). Each participating site additionally obtained IRB approval for submission of a limited data set to the Multicenter Perioperative Outcomes Group database. The requirement for written informed consent was waived by the IRB at participating centers. This site IRB approval includes provision for submission of Society of Thoracic Surgeons registry data to the Multicenter Perioperative Outcomes Group from each center. In keeping with the Multicenter Perioperative Outcomes Group bylaws, this study protocol was presented to the Multicenter Perioperative Outcomes Group Perioperative Clinical Research Committee and was approved on March 28, 2017. After data acquisition, an unanticipated imbalance between the protective *versus* nonprotective cohorts was discovered. We revised the protocol twice to address this as well as unmeasured confounding caused by excess population heterogeneity. The plan for statistical analysis was revised, circulated, and approved by the Perioperative Clinical Research Committee on July 11, 2018, and January 29, 2020. After approval, a data analysis and statistical plan was written and filed with a private entity (Multicenter Perioperative Outcomes Group Perioperative Clinical Research Committee) before data were accessed or revised analysis conducted (Supplemental Digital Content 1, http://links.lww.com/ALN/C543). During the peer review process, additional changes as requested by editors were incorporated. Final methods are presented below. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist in developing this manuscript.

Data Source and Study Inclusion and Exclusion Criteria

The Multicenter Perioperative Outcomes Group database, as well as methods for data entry, validation, and quality assurance, have been previously described[17] and have been used for multiple published observational studies.[18,19] Multicenter Perioperative Outcomes Group data are drawn from cases documented in the Electronic Health Record at participating sites. These data are extracted; standardized; joined to additional laboratory, billing, and diagnosis coding data; and de-identified with the exception of date of service, producing a limited dataset.

Five large academic medical centers that submit Society of Thoracic Surgeons General Thoracic Surgery Database and Multicenter Perioperative Outcomes Group data were included in this study. The General Thoracic Surgery

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version. Elements of this work, as preliminary analyses, have been presented at the International Anesthesia Research Society Annual Meeting 2018 in Chicago, Illinois, April 28 to May 1, 2018; and Anesthesiology 2018 in San Francisco, California, October 13 to 17, 2018.

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Database is managed by each site and uses standard definitions and data elements captured by the data collection form (https://www.sts.org/registries-research-center/sts-national-database/general-thoracic-surgery-database/data-collection; accessed February 10, 2020).

Data are gathered and aggregated by trained data managers who review medical records of patients undergoing surgical procedures by participating thoracic surgeons at each institution to capture demographics, comorbidities, details of preoperative evaluation, intraoperative course, and postoperative outcomes. The Society of Thoracic Surgeons training manual is the common reference for all data managers who receive annual training at the Advances in Quality Outcomes Seminar hosted by the Society of Thoracic Surgeons (https://www.sts.org/meetings/calendar-of-events/advances-quality-outcomes-data-managers-meeting-0; accessed February 10, 2020). These data are externally and independently audited and are known to be greater than 95% accurate.[20]

General Thoracic Surgery Database records were linked to Multicenter Perioperative Outcomes Group records using patient-level identifiers at each participating site. These identifiers were removed before data upload to the Multicenter Perioperative Outcomes Group Coordinating Center (University of Michigan, Ann Arbor, Michigan). At the Coordinating Center, the patient-matched records from both databases were linked using case start date and time.

Patients undergoing one-lung ventilation between January 1, 2012, and December 31, 2016, for pneumonectomy, bilobectomy, lobectomy, segmentectomy, or wedge resection/metastasectomy with available General Thoracic Surgery Database and Multicenter Perioperative Outcomes Group records were included. We had originally intended to include procedures through May 31, 2017, but data were not available across all sites for this time period, and thus the study period was restricted to December 31, 2016. Time of one-lung ventilation initiation and termination (where available) was defined based on use of a structured data element in the anesthesia record. Cases were excluded if one-lung ventilation was used for less than 15 min, if either height or weight data were unavailable, if lung transplantation was performed, or if surgery represented a reoperation within 30 days of a previous included surgery.

Protective Ventilation and Other Respiratory Parameter Exposure Variables

Values of V_T, PEEP, airway pressures (mean, peak [P_{MAX}] and plateau pressures), end tidal-carbon dioxide, fraction of inspired oxygen, respiratory rate, and calculated modified driving pressure (P_{MAX} – PEEP) were derived for use in this study. These variables are stored in the Multicenter Perioperative Outcomes Group database at 1-min intervals. Consistent with our previous work, we used a sampling methodology for evaluation of ventilation parameters.[18,19] We calculated the median value for the time period 5 to 15 min after the time-stamped documentation of initiation of one-lung ventilation for each case.

Criteria for protective ventilation were based upon expert opinion and guidelines for optimal practice during one-lung ventilation.[8–10] Cases were considered to have been conducted with protective ventilation only if both of the following criteria were met: median V_T was less than or equal to 5 ml/kg predicted body weight, and median PEEP was greater than or equal to 5 cm H_2O. Ventilation variables were subsequently expressed and analyzed as means of the individual case median values.

Modified driving pressure was used as a surrogate of driving pressure in this investigation, since plateau airway pressure data, required for the calculation of driving pressure, were not available from all participating institutions. This modification of driving pressure has been previously reported.[21]

Patient and Procedure Variables

In construction of the statistical models used in this manuscript, we included data from the Multicenter Perioperative Outcomes Group database and General Thoracic Surgery Database (appendix 1).

Data from the Multicenter Perioperative Outcomes Group database are institution, presence of blood product transfusion (as a binary variable), fluid balance (volume of input [crystalloids + colloids + blood products] – volume of fluid output [urine + gastric tube output + estimated blood loss + chest tube] as documented on the anesthetic record), and American Society of Anesthesiologists (ASA; Schaumburg, Illinois) physical status.

Data from the General Thoracic Surgery Database are forced expiratory volume in 1 s (FEV_1), presence of missing FEV_1 data, preoperative renal dysfunction, preoperative steroid therapy, Zubrod Performance Classification score, current smoking status, preoperative chemotherapy and/or radiation, and major preoperative comorbidity (defined as coronary artery disease, congestive heart failure, peripheral vascular disease, or diabetes). Procedure type was categorized as pneumonectomy, bilobectomy, lobectomy, segmentectomy, or wedge resection/metastasectomy (which acted as the reference value in our models). Additionally, we classified surgical approach as thoracotomy or video-assisted thoracoscopic surgery (which acted as the reference value in our models).

Demographic variables for age, sex, and body mass index were preferentially extracted from the General Thoracic Surgery Database; however, if not available or invalid, they were derived from the Multicenter Perioperative Outcomes Group database.

Outcomes of Interest

The primary outcome was a composite of major postoperative pulmonary complications drawn from the General

Thoracic Surgery Database. Pulmonary complications were defined as one or more of the following: initial ventilator support greater than 48 h, reintubation, pneumonia, atelectasis requiring bronchoscopy, acute respiratory distress syndrome (ARDS), air leak greater than 5 days, bronchopleural fistula, respiratory failure, tracheostomy, pulmonary embolism, or empyema requiring treatment. Two progressively more comprehensive secondary outcomes were (1) major morbidity—pulmonary complications (as defined above) *or* one or more of the following: unexpected return to the operating room (during same hospital stay), atrial or ventricular dysrhythmias requiring treatment, myocardial infarction, sepsis, renal failure, central neurologic event, unexpected intensive care unit admission, or anastomotic leak; and (2) major morbidity (defined above) and/or mortality. All outcomes were drawn from the General Thoracic Surgery Database record and followed the definitions at time of data entry (https://www.sts.org/registries-research-center/sts-national-database/general-thoracic-surgery-database/data-collection; accessed February 10, 2020).

Statistical Analysis

A complete case analysis was conducted. Data were presented as mean ± SD or frequencies with percentages. Univariate comparisons between groups were assessed using Pearson chi-square or Fisher exact tests for categorical data and Student's *t* or Mann–Whitney U tests for continuous variables, as appropriate. Absolute standardized difference percentages are reported.

The final statistical analysis plan included the use of propensity score matching to adjust for differences between the protective and nonprotective ventilation groups. A nonparsimonious regression model was used to estimate each participant's propensity to receive the protective ventilation exposure. The propensity score model contained age, sex, body mass index, FEV_1, presence of missing FEV_1 data, ASA physical status, preoperative renal dysfunction, preoperative steroid therapy, Zubrod score, current smoking status, preoperative chemotherapy and/or radiation, institution, and major preoperative comorbidity. Protective ventilation patients were propensity score–matched 1:1 to those not receiving protective ventilation using the "onetomanymtch" greedy matching algorithm.[22] Residual covariate imbalance after the match was assessed by computing standardized differences. Variables with an absolute standardized difference less than 10% were considered a strong match. Within the matched cohort, univariate differences between those with and without protective ventilation were assessed using McNemar test for categorical variables and paired *t* tests or Wilcoxon signed-rank tests for continuous variables, as appropriate.

Before regression models were constructed, all variables under consideration for model inclusion were assessed for collinearity using the condition index. If the condition index was greater than 30, a Pearson's correlation matrix was developed. Those variable pairs with a correlation of greater than or equal to 0.70 were combined into a single concept, or the variable with the larger univariate effect size was selected for inclusion. All other variables were considered fit for model entry.

To evaluate the primary aim in the matched cohort, a conditional logistic regression model was used to assess the relationship between protective ventilation status and outcome with the covariates of blood product transfusion, fluid balance, surgical procedure (wedge resection, segmentectomy, lobectomy, bilobectomy, pneumonectomy), and surgical approach (video-assisted thoracoscopic surgery *vs.* open). Measures of effect for model covariates were reported as conditional adjusted odds ratios with 95% CIs. The model predictive capability was reported using the area under the receiver operating characteristic curve c-statistic. Any covariate found to be statistically significant was considered an independent predictor of the outcome of interest. These models were also constructed for the secondary outcomes (morbidity; morbidity and mortality).

The full study cohort was used for analysis of optimal V_T and PEEP combinations and examination for any relationship between airway pressures and outcome. Traditional logistic regression models were used for these analyses. Measures of effect for model covariates were reported for logistic regression as adjusted odds ratios with 95% CIs. Any covariate found to be statistically significant after adjustment was considered an independent predictor of the outcome of interest.

To assess if an alternative combination of V_T and PEEP was associated with a lower risk of pulmonary complications, a matrix of adjusted odds ratios was constructed with the reference category of V_T between 4 and 6 ml/kg predicted body weight and PEEP between 4 and 6 cm H_2O.

To assess if modified driving pressure was associated with primary or secondary outcomes, three multivariable logistic regression models were constructed, adjusted for the covariates specified above. A similar analysis was conducted for P_{MAX}.

All analyses were conducted using SAS 9.4 (SAS Institute, USA) and SPSS 24 (IBM Corp., USA). Two-tailed hypothesis testing was conducted, and a *P* value of 0.05 was considered statistically significant for all analyses. Additional information regarding aim-specific analyses can be found in appendix 2.

Power Analysis

An *a priori* sample size calculation was performed using a two-sided Z test with unpooled variance. A sample size of 1,315 unmatched cases in each group (total study N = 2,630) provided 90% power at an alpha = 0.05 to detect a 5% difference (deemed to represent a clinically significant difference) in the rate of pulmonary complications, assuming a 22% rate of events in the nonprotective ventilation group.

Results

Study Populations and Outcomes Experienced

Of 3,721 cases that were eligible for analysis, 489 were excluded for missing data required for model construction. A total of 3,232 cases from five institutions were available for the final analysis (fig. 1). Baseline cohort characteristics are shown in table 1. It should be noted that some cases from one institution have been previously reported (693 cases from 2012 to 2014; 194 cases that are included in the current matched cohort).[12]

In the unmatched cohort, a primary pulmonary complication outcome occurred in 427 (13.2%) of cases; secondary outcomes—major morbidity and major morbidity and/or mortality—occurred in 659 (20.4%) and 676 (20.9%) cases, respectively (table 2). In 2012, mean ± SD V_T was 6.7 ± 1.61 ml/kg; in 2016, mean ± SD V_T was 6.0 ± 1.25 ml/kg ($P < 0.0001$), while mean ± SD PEEP was 4 ± 2 cm H_2O in 2012 and 5 ± 2 cm H_2O in 2016 ($P < 0.0001$; table 1; fig. 2). The proportion of cases meeting the definition of lung-protective ventilation was 5.7% in 2012 and 17.9% ($P < 0.001$) in 2016 (fig. 2). The prevalence of the primary outcome and major morbidity did not change significantly during the study period (pulmonary complications: 11.4 to 15.7%, $P = 0.147$; major morbidity: 18.5 to 22.9%, $P = 0.088$). However, there was a significant increase in secondary outcome of major morbidity and/or mortality from 2012 to 2016 (18.6 to 23.8%, $P = 0.039$; Supplemental Digital Content 2 [http://links.lww.com/ALN/C544] and 3 [http://links.lww.com/ALN/C545]).

Primary Aim: Relationship between Protective Ventilation and Outcome

Propensity score matching addressed differences between the baseline characteristics of the protective and nonprotective ventilation populations (table 1). Of the 388 cases that met the protective ventilation definition, 381 (98.2%) were propensity score–matched to nonprotective ventilation cases, resulting in a primary aim study population of 762 patients. In our conditional logistic regression model, protective ventilation was not found to be associated with differential risk of pulmonary complications (adjusted odds ratio, 0.86; 95% CI, 0.56 to 1.32; $P = 0.480$), major morbidity (adjusted odds ratio, 0.81; 95% CI, 0.55 to 1.19; $P = 0.283$), or morbidity and mortality (adjusted odds ratio, 0.81; 95% CI, 0.55 to 1.19; $P = 0.281$).

Secondary Aim: Exploration of an Alternative Definition of Lung-protective Ventilation

Given the lack of association between this definition of protective ventilation and outcome, we attempted to derive an alternative definition of protective ventilation associated with lower risk for pulmonary complications. We used a matrix of odds ratios to determine if an alternative combination of V_T and PEEP was associated with a lower risk of pulmonary complications. We did not find a combination of these parameters that predicted a lower risk of pulmonary complications compared to the reference definition (data not shown). When V_T or PEEP was analyzed in isolation as categorical ranges—per 1 ml/kg for V_T and 1 cm H_2O for PEEP—we found no significant relationship with predicted probability of pulmonary complications (Supplemental Digital Content 4 [http://links.lww.com/ALN/C546] and 5 [http://links.lww.com/ALN/C547]).

Secondary Aim: Relationship between Airway Pressures and Patient Outcome

Consistent with previous work, modified airway driving pressure was used as a proxy for airway driving pressure. Using the subjects for which both values were available, we plotted the relationship between them (Supplemental Digital Content 6, http://links.lww.com/ALN/C548). The correlation between modified airway driving pressure and airway driving pressure was 0.87 (95% CI, 0.86 to 0.88; $P < 0.001$). In multivariable regression models, neither modified airway driving pressure nor P_{MAX} was associated with a significant increase in the odds of pulmonary complications for each 5 cm H_2O increase in pressure (modified airway driving pressure: adjusted odds ratio, 0.93; 95% CI, 0.84 to 1.04; $P = 0.145$; $P_{MAX:}$ adjusted odds ratio, 0.94; 95% CI, 0.85 to 1.05; $P = 0.304$; Supplemental Digital Content 7, http://links.lww.com/ALN/C549; fig. 3).

Discussion

In this study, we examined the relationship between ventilation variables, including V_T, PEEP, and airway pressures, and the subsequent development of postoperative complications in patients undergoing one-lung ventilation for thoracic surgery. We draw several conclusions. First, use of recommended ventilation parameters increased during the study period. Second, this definition of protective ventilation was not independently associated with a lower prevalence of pulmonary complications. Third, the development of postoperative complications was not associated with either modified driving pressure or P_{MAX}.

Association of a Conventional Definition of Protective Ventilation and Outcome

The use of a conventional definition of protective one-lung ventilation was not associated with a difference in the prevalence of pulmonary complications (primary outcome), major morbidity or major morbidity and/or mortality (secondary outcomes) between protective and nonprotective ventilation subcohorts after propensity score adjustment for population differences. Our study demonstrates a practice trend of increasing use of recommended protective ventilation parameters consistent with that from previous

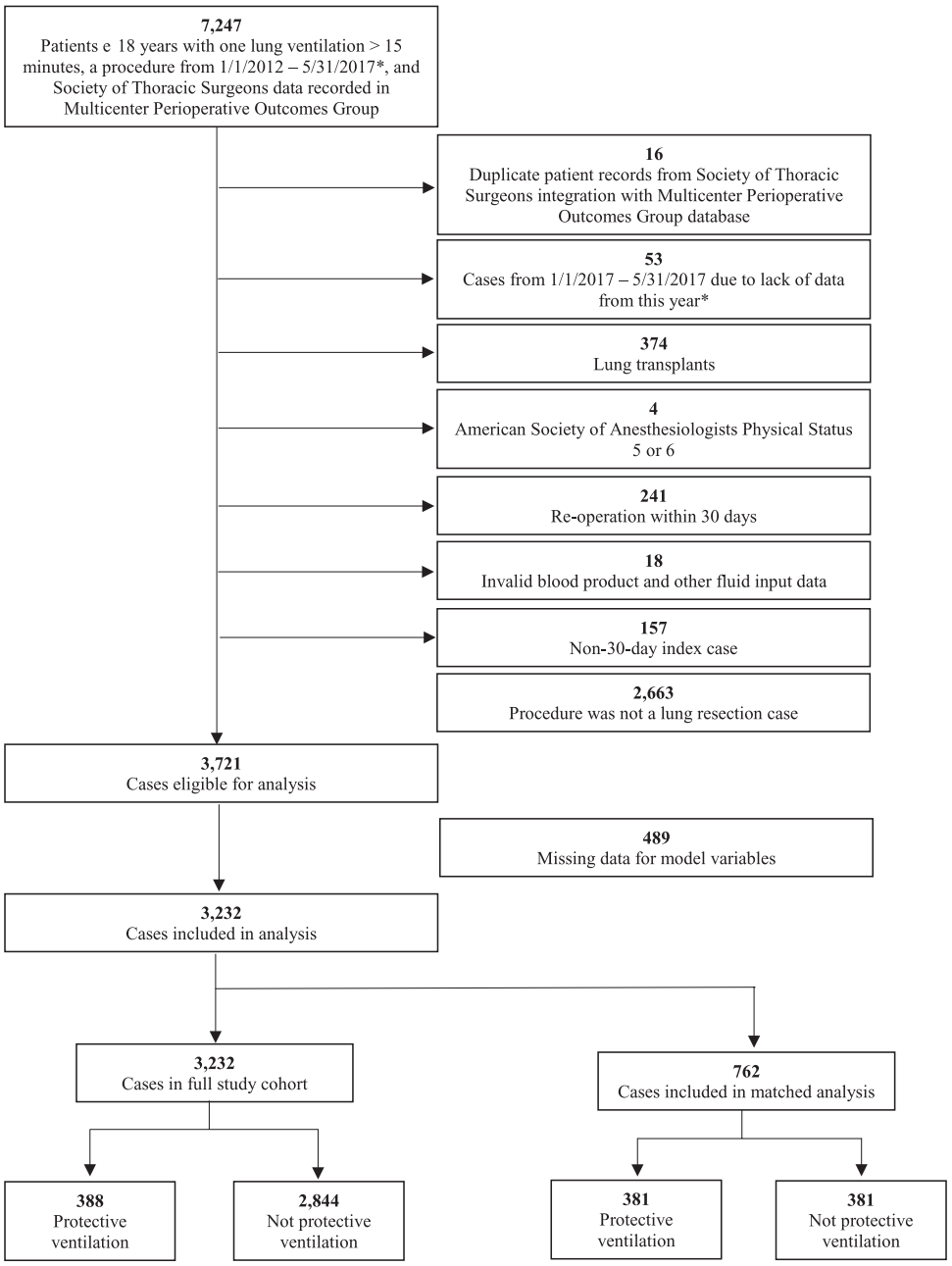

Fig. 1. Flow of patients through study.

reports.[18,19,23] Despite the decrease in V_T (6.7 to 6.0 ml/kg predicted body weight), and an increase in use of protective ventilation, the prevalence of pulmonary complications and major morbidity did not change significantly during the study period. However, there was a significant increase in the prevalence of major morbidity and/or mortality from 2012 to 2016 (18.6 to 23.8%, $P = 0.039$; Supplemental Digital Content 2 [http://links.lww.com/ALN/C544] and 3 [http://links.lww.com/ALN/C545]).

Our chosen target values for V_T (5 ml/kg predicted body weight) and PEEP (5 cm H_2O) in the definition of protective one-lung ventilation are based on published expert opinion.[8–10] Although these parameters are generally considered to be "protective," the former reflects a supraphysiologic V_T, and the latter (PEEP) may be insufficient to maintain an open lung state that prevents atelectasis and atelectrauma during one-lung ventilation.[24,25] The notion that low V_T in the setting of low PEEP is not intrinsically

Table 1. Patient Characteristics and Demographics for the Full Study Cohort Population and the Matched Study Population

	Full Study Cohort Population				Matched Population			
	No Protective Ventilation (n = 2,844)	Protective Ventilation (n = 388)	Absolute Standardized Difference (%)	*P* Value	No Protective Ventilation (n = 381)	Protective Ventilation (n = 381)	Absolute Standardized Difference (%)	*P* Value
Demographics								
Age	62.6 ± 12.4	62 ± 13.6	5.2	0.351	61.6 ± 13.8	62.3 ± 13.3	5	0.491
Female sex	1,577 (55.5)	138 (35.6)	40.7	< 0.001	140 (36.8)	136 (35.7)	2.2	0.763
Body mass index	28.5 ± 6.5	27.6 ± 6.8	13.2	0.014	28 ± 5.7	27.6 ± 6.7	6.7	0.354
ASA physical status III or higher	2,217 (78.0)	308 (79.4)	3.5	0.523	307 (80.6)	301 (79.0)	3.9	0.589
Comorbidities								
COPD	671 (23.6)	90 (23.2)	1	0.857	90 (23.6)	88 (23.1)	1.2	0.862
Congestive heart failure*	81 (4.7)	22 (7.1)	10.2	0.121	16 (5.1)	19 (6.3)	4.8	0.548
Coronary artery disease	427 (15.0)	67 (17.3)	6.1	0.247	66 (17.3)	66 (17.3)	0	0.999
Cerebrovascular history			5.9	0.304			5.8	0.421
Transient ischemic attack	74 (2.6)	12 (3.1)			12 (3.2)	12 (3.2)		
Cerebrovascular accident	65 (2.3)	12 (3.1)			8 (2.1)	12 (3.2)		
Diabetes	449 (15.8)	60 (15.5)	0.9	0.870	57 (15.0)	60 (15.8)	2.2	0.763
Dialysis	14 (0.5)	3 (0.8)	3.5	0.545	3 (0.8)	3 (0.8)	0	0.999
Hypertension	1,547 (54.4)	193 (49.7)	9.3	0.085	213 (55.9)	191 (50.1)	11.6	0.111
Peripheral vascular disease*	101 (5.8)	14 (4.5)	6	0.309	19 (6.1)	14 (4.6)	6.6	0.413
Previous cardiothoracic surgery	420 (14.8)	66 (17.0)	6.1	0.247	61 (16.0)	64 (16.8)	2.1	0.770
Pulmonary hypertension	24 (0.8)	5 (1.3)	22.2	< 0.001	0 (0.0)	4 (1.1)	2.6	N/A
Smoking			8.9	0.100			4.8	0.506
Never smoked	757 (26.6)	115 (29.6)			118 (31.0)	111 (29.1)		
Past smoker (> 1 month)	1,565 (55.0)	213 (54.9)			209 (54.9)	211 (55.4)		
Current smoker	522 (18.4)	60 (15.5)			54 (14.2)	59 (15.5)		
Major preoperative comorbidity	817 (28.7)	109 (28.1)	1.4	0.795	113 (29.7)	108 (28.4)	2.9	0.690
Chemotherapy and/or radiation within 6 months	131 (4.6)	20 (5.2)	2.5	0.631	22 (5.8)	20 (5.3)	2.3	0.751
Renal dysfunction	100 (3.5)	13 (3.4)	0.9	0.868	7 (1.8)	13 (3.4)	9.9	0.174
FEV_1 (% predicted)	77.0 ± 31.7	73.7 ± 33.0	10.6	0.048	74.5 ± 32.8	74.6 ± 32.1	0.1	0.986
Missing FEV_1	268 (9.4)	45 (11.6)	7.1	0.206	40 (10.5)	40 (10.5)	0	0.999
Zubrod scale								
0	1,270 (44.7)	174 (44.9)	6.5	0.257	182 (47.8)	174 (45.7)	2.8	0.699
1	1,374 (48.3)	177 (45.6)			169 (44.4)	176 (46.2)		
2	168 (5.9)	29 (7.5)			27 (7.1)	29 (7.6)		
3	27 (1.0)	2 (0.5)			2 (0.5)	2 (0.5)		
4	5 (0.2)	6 (1.6)			1 (0.3)	0 (0.0)		
Intraoperative factors								
Blood product use*	55 (1.9)	4 (1.0)	7.5	0.117	7 (1.8)	4 (1.1)	6.6	0.363
Fluid balance	1,311 ± 797.5	1185.9 ± 816.6	15.5	0.004	1145.1 ± 757.7	1197.8 ± 816	6.7	0.356
Surgical duration	162.8 ± 97.5	165.3 ± 102.5	2.52	0.636	173.3 ± 106.9	165.6 ± 102	7.759	0.309
Anesthesia duration	247.9 ± 106.4	252.6 ± 111.1	4.3	0.420	261.4 ± 117.1	252.8 ± 110.8	7.51	0.300
Surgical type								
Segmentectomy	135 (4.8)	21 (5.4)	3	0.566	14 (3.7)	21 (5.5)	8.8	0.226
Lobectomy	1,405 (49.4)	167 (43.0)	12.8	0.019	188 (49.3)	167 (43.8)	11.1	0.128
Bilobectomy	93 (3.3)	16 (4.1)	4.5	0.423	17 (4.5)	16 (4.2)	1.3	0.859
Pneumonectomy	84 (3.0)	7 (1.8)	7.5	0.125	10 (2.6)	6 (1.6)	7.3	0.313
Wedge resection	1,127 (39.6)	177 (45.6)	12.1	0.024	152 (39.9)	171 (44.9)	10.1	0.164
Surgical approach			3.4	0.537			8.1	0.243
Thoracotomy	805 (28.3)	104 (26.8)			116 (30.5)	102 (26.8)		
Video-assisted thoracoscopic surgery	2,039 (71.7)	284 (73.2)			268 (70.0)	279 (73.2)		
Median physiologic factors for first 5–15 min after start of one-lung ventilation								
Respiratory Rate	12 ± 2.7	14 ± 3.1	63.2	<0.001	12 ± 2.6	14 ± 3.3	57.6	< 0.001
FIO_2 %	89 ± 12.5	89 ± 13.5	2.1	0.704	89 ± 12.5	88 ± 13.6	4	0.588
Mean inspiratory pressure	11 ± 2.4	11 ± 2.2	9.2	0.103	10 ± 2.3	10 ± 2.2	0.9	0.914
Peak inspiratory pressure	24 ± 5.3	23 ± 5.7	31.9	<0.001	24 ± 5.1	23 ± 5.5	30.4	< 0.001
Plateau pressure	21 ± 5	21 ± 5.7	18.6	0.025	21 ± 5	21 ± 5.4	22.4	0.049
$ETCO_2$	35 ± 5.3	39 ± 5.8	61.9	<0.001	37 ± 5.1	39 ± 5.7	46.3	< 0.001
Tidal volume/predicted body weight (ml/kg)	6.7 ± 1.4	4.4 ± 0.5	217.4	<0.001	6.4 ± 1.2	4.4 ± 0.5	208.4	< 0.001
PEEP (cm H_2O)	5 ± 1.7	6 ± 1.1	67.7	<0.001	5 ± 1.8	6 ± 1.1	65.4	< 0.001
Modified driving pressure	17 ± 12.5	15 ± 5.1	42.6	<0.001	17 ± 12.5	15 ± 5.4	47	< 0.001

Data are presented as frequency (percentage) or mean ± SD, as appropriate. Full study cohort comparisons were calculated using *t* tests or Mann–Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical variables, as appropriate. Matched population comparisons were calculated using paired *t* tests or Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables, as appropriate. There were no standardized differences greater than 10% for matched factors.

*Data are presented as percentage of nonmissing data.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; $ETCO_2$, end-tidal carbon dioxide; FEV_1, forced expiratory volume in 1 s; FIO_2, fraction of inspired oxygen; N/A, not applicable; PEEP, positive end-expiratory pressure.

Table 2. Experienced Postoperative Outcomes, in the Full Study Cohort and Matched Cohort

	Full Study Cohort			Matched Cohort		
	No Protective Ventilation (n = 2,844)	Protective Ventilation (n = 388)	*P* Value	No Protective Ventilation (n = 381)	Protective Ventilation (n = 381)	*P* Value
Postoperative outcomes						
30-Day pulmonary complications	362 (12.7)	65 (16.8)	0.028	59 (15.5)	64 (16.8)	0.615
30-Day major morbidity	565 (19.9)	94 (24.2)	0.046	86 (22.6)	93 (24.4)	0.544
30-Day major morbidity and/or mortality	578 (20.3)	98 (25.3)	0.025	89 (23.4)	96 (25.2)	0.550
Pulmonary complications						
ARDS	9 (0.3)	2 (0.5)	0.632	0 (0.0)	2 (0.5)	N/A
Air leak > 5 days	178 (6.3)	27 (7.0)	0.596	24 (6.3)	27 (7.1)	0.662
Atelectasis	77 (2.7)	22 (5.7)	0.002	19 (5.0)	21 (5.5)	0.739
Bronchopleural fistula	2 (0.1)	0 (0.0)	0.999	0 (0.0)	0 (0.0)	N/A
Pneumonia	62 (2.2)	11 (2.8)	0.415	11 (2.9)	10 (2.6)	0.827
Pneumothorax	60 (2.1)	10 (2.6)	0.553	18 (4.7)	10 (2.6)	0.131
Other pulmonary event	34 (1.2)	8 (2.1)	0.158	5 (1.3)	8 (2.1)	0.405
Pulmonary embolism	12 (0.4)	4 (1.0)	0.116	3 (0.8)	4 (1.1)	0.706
Respiratory failure	40 (1.4)	9 (2.3)	0.180	4 (1.1)	8 (2.1)	0.248
Tracheostomy	14 (0.5)	2 (0.5)	0.999	1 (0.3)	1 (0.3)	0.999
Ventilator support > 48 h	7 (0.3)	1 (0.3)	0.999	1 (0.3)	0 (0.0)	N/A
Morbidity complications						
Return to operating room	0 (0.0)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	N/A
Atrial arrhythmia	241 (8.5)	39 (10.1)	0.300	31 (8.1)	39 (10.2)	0.302
Ventricular arrhythmia	9 (0.3)	0 (0.0)	0.611	5 (1.3)	0 (0.0)	N/A
Myocardial infarction	12 (0.4)	2 (0.5)	0.681	4 (1.1)	2 (0.5)	0.414
Sepsis	9 (0.3)	1 (0.3)	0.999	1 (0.3)	1 (0.3)	0.999
Renal failure	9 (0.3)	3 (0.8)	0.167	1 (0.3)	2 (0.5)	0.564
Central neurologic event	8 (0.3)	1 (0.3)	0.999	2 (0.5)	1 (0.3)	0.564
Unexpected ICU admission	66 (2.3)	11 (2.8)	0.533	11 (2.9)	11 (2.9)	0.999
Anastomic leak	0 (0.0)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	N/A
Any morbidity	303 (10.7)	50 (12.9)	0.186	42 (11.0)	49 (12.9)	0.425
Mortality complications						
30-Day mortality	27 (1.0)	6 (1.6)	0.277	3 (0.8)	5 (1.3)	0.480

Data are presented as frequency (percentage). Prematch population comparisons calculated using chi-square or Fisher exact tests for categorical variables, as appropriate. Matched population comparisons were calculated using McNemar tests for categorical variables.

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; N/A, not applicable.

protective is supported by the previously demonstrated inverse relationship[11,12] or lack of relationship[26] between V_T and the risk of adverse outcomes in both two- and one-lung ventilation surgical settings.

These findings are consistent with results of trials that have evaluated putative protective regimens, combining lower V_T and higher levels of PEEP compared to conventional regimens combining supraphysiologic V_T with minimal PEEP.[2,4–7] Such protective regimens may minimize both volutrauma and atelectrauma by limiting distending stress and volume loss/atelectasis, respectively, and have been demonstrated to decrease airway driving pressure and mechanical energy delivery.[27,28] In a meta-analysis of multiple protective ventilation trials, protective ventilation differed from conventional ventilation most markedly on the basis of PEEP (greater than sixfold difference), whereas "protective" V_T was only 32% lower than that of the conventional groups.[29] Thus, the primary difference between protective and conventional ventilation may be the use of an open lung strategy, which includes sufficient PEEP to minimize volume loss, atelectasis, and the risk of atelectrauma rather than lower V_T *per se*. This view is further supported by recent trials that demonstrated no outcome improvements in patients randomized to receive lower V_T.[30,31]

In our analysis, the primary outcome is a composite of 11 distinct postoperative pulmonary complications, rather than a single outcome more directly related to lung injury (*e.g.*, ARDS). It should be noted that the individual outcome events contributing to a composite outcome vary greatly on the basis of severity (*i.e.*, ARDS *vs.* atelectasis) and frequency (range, 0.3 to 3.1%). Despite its multicenter design and relatively large sample size, our study did not have sufficient power to determine if specific outcome events were associated with different V_T and PEEP combinations.

Relationship of Driving Pressure and Outcome

Previous studies have demonstrated an association between airway driving pressure and complications in patients

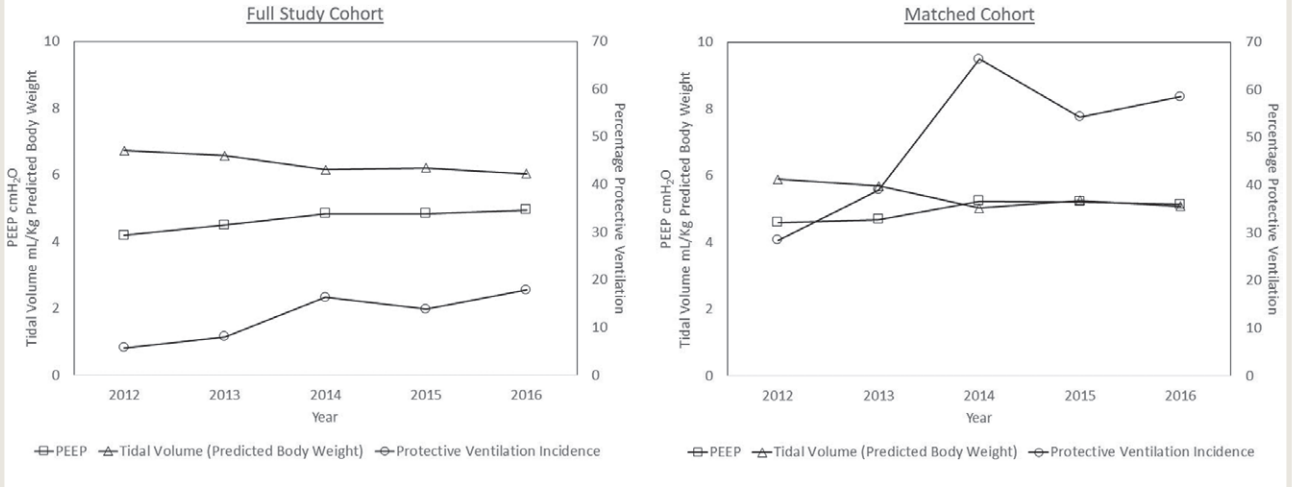

Fig. 2. Mean positive end-expiratory pressure (PEEP) in centimeters of water, mean tidal volume milliliters per kilogram of weight by predicted body weight, and percentage of cases meeting protective ventilation criteria over time by study year.

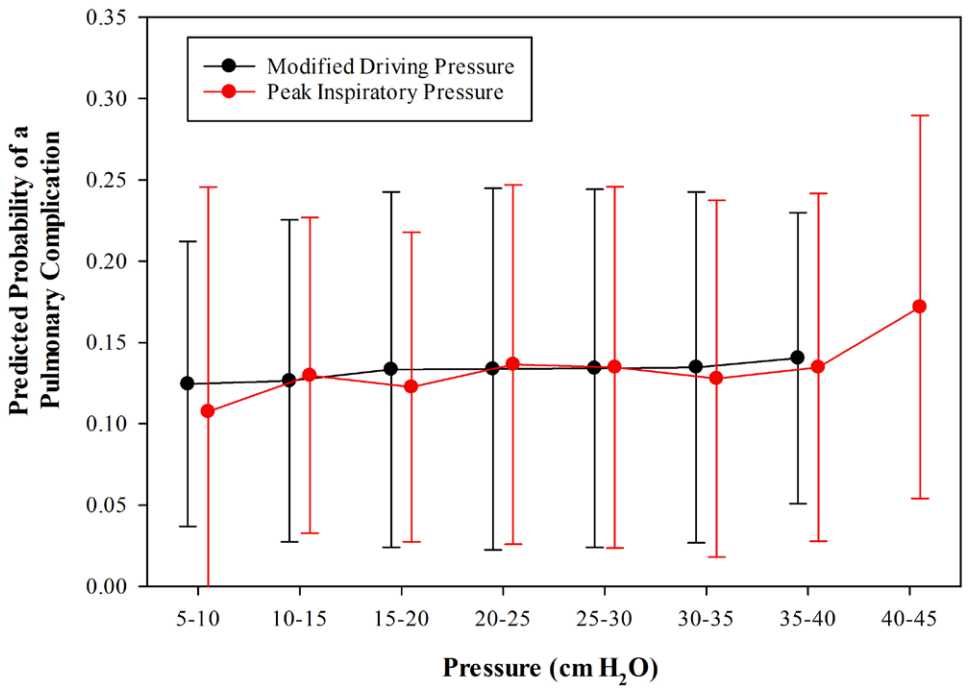

Fig. 3. Mean and 95% CI predictive probability of pulmonary complications by modified driving pressure and peak inspiratory pressure (centimeters of water). Pressure was analyzed in five-unit increments.

ventilated for ARDS and surgery, although very little information is available for procedures involving one-lung ventilation.[13,14] In the current study, we found that neither modified driving pressure nor P_{MAX} was associated with significantly increased odds of pulmonary complications when analyzed as continuous variables in fixed-effects logistic regression models controlling for other risk predictors. These findings are not consistent with those of previous studies.[12,13]

The current study differs with regard to the use of a surrogate measure, modified driving pressure (P_{MAX} – PEEP).

Despite being shown to predict ARDS in a large cohort of general surgical patients, its specific utility as a predictor of pulmonary complications in a thoracic surgical population receiving one-lung ventilation is not yet established.[21] Despite its very close correlation with driving pressure (0.87; 95% CI, 0.86 to 0.88; $P < 0.001$), it is conceivable that this modification is less useful than driving pressure as a surrogate marker of dynamic strain. It is also conceivable that the dramatic elevation of lung elastance associated with one-lung ventilation in the lateral position could confound the relationship between airway driving pressure and dynamic strain.[32] Finally, it is also possible that the contribution to the overall postoperative pulmonary complication rate from specific pulmonary complications emerging from elevated dynamic strain (*e.g.*, ARDS) is dwarfed by complications from other injurious processes (*e.g.*, atelectasis).

Park *et al.* recently reported a randomized trial of thoracic surgical patients who were randomized to receive one-lung ventilation (V_T, 6 ml/kg) with either fixed PEEP 5 cm H_2O or an individualized PEEP based on an increment trial to the lowest driving pressure.[14] In this study, PEEP titration was associated with a reduction in the incidence of pulmonary complications from 12.2 to 5.5%. However, both the delivered PEEP (5 *vs.* 3 cm H_2O) and resultant driving pressure (10 *vs.* 9 cm H_2O) differences between groups were small. The contribution of driving pressure, if any, to the observed findings remains unclear.

Limitations

Although intraoperative ventilation exposures from the Multicenter Perioperative Outcomes Group database are detailed and accurate, available data are limited by relative practice homogeneity in ventilation management during the study period. While V_T differences between groups are similar to those seen in modern protective ventilation trials,[29] the smaller difference in PEEP between the protective and nonprotective groups may be insufficient to elicit detectable differences in outcome.

Although recruitment maneuvers have been advocated by some authors as a component of protective ventilation,[8,9] they were not included in our definition for two reasons. First, recruitment maneuvers cannot be accurately derived from physiologic data with one-minute temporal resolution. Second, there are no evidence-based standardized criteria for their use. Recruitment maneuvers represent a heterogeneous group of practices. Further, they neither constitute a universal feature of protective ventilation nor are required for the outcome benefits[5–7] or necessarily to maintain an open lung state avoiding atelectasis.[25,33] Further, they may have the potential to cause harm,[34,35] and recent guidelines for protective one-lung ventilation do not unambiguously support their use.[10] While our study did not include them and is unable to account for them, the possibility that recruitment maneuvers contribute to the variance in patient outcome remains and may need to be addressed in future work.

We were not able to assess changes in ventilation management that may have occurred during the course of the anesthetic in response to hypoxemia because our sampling methodology focused on the start of one-lung ventilation. We have previously demonstrated that the ventilator data from this early period very closely match those used for the entire period of one-lung ventilation.[19] Furthermore, hypoxemia typically occurs early in the one-lung ventilation period and is thought to be a very infrequent occurrence in modern thoracic anesthesia practice.[36]

Finally, included data were derived from five academic medical centers, which exhibited variation in the prevalence of complications. The integration of both the Multicenter Perioperative Outcomes Group database and the General Thoracic Surgery Database allowed us to combine the advantages of the automatically gathered, detailed, annotated dataset from Multicenter Perioperative Outcomes Group with the highly accurate and validated outcome data derived from the General Thoracic Surgery Database. Limitations of the latter database derive from the fact that participation is voluntary. As participants are typically general thoracic surgeons, results may not be generalizable to those of other surgeons or institutions performing similar procedures. Our approach leverages the advantages and strengths of each data source, which improves the validity and generalizability of our findings.

Conclusions

This multicenter study demonstrates an increase in adoption of a ventilation regimen including V_T less than or equal to 5 ml/kg predicted body weight in combination with PEEP greater than 5 cm H_2O during one-lung ventilation. However, this lower V_T regimen was not associated with reduced odds of major pulmonary complications. Furthermore, in this study cohort, neither increasing P_{MAX} or modified airway driving pressure was associated with increased odds of major pulmonary complications.

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Competing Interests

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Correspondence

Address correspondence to Dr. Blank: Department of Anesthesiology, University of Virginia, Box 800710 Health System, Charlottesville, Virginia 22908-0710. rsb8p@hscmail.mcc.virginia.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix 1: List of Variables Used in the Analysis from the Multicenter Perioperative Outcomes Group (MPOG) and Society of Thoracic Surgeons (STS) Databases

MPOG Database	STS Database
MPOG_Patient_ID	Race
MPOG_Case_ID_String	Smoking status
MPOG_Institution_ID	Reoperation
Date of surgery	Hypertension
Case times	Steroid use
Age	Congestive heart failure
Sex	Coronary artery disease
ASA class	Peripheral vascular disorders
Height	Previous cardiothoracic surgery
Weight	Current chemotherapy status
BMI	Thoracic radiation therapy and timing
WHO BMI classification	Cerebrovascular history
Predicted body weight	Pulmonary hypertension
Presence of existing airway	Diabetes and type of control
Bronchial blocker used	Dialysis
Primary anesthesia CPT code	Chronic obstructive pulmonary disease
Anesthesia and surgical duration	Interstitial fibrosis
Fluid totals	Smoking status
Total crystalloid equivalents given	FEV_1 percent predicted
Tidal volume	Zubrod scale
Respiratory rate	Primary surgical CPT code
Positive end-expiratory pressure	Intraoperative blood transfusion
Peak inspiratory pressure	Postoperative destination
Plateau airway pressure	30-day postoperative status
Mean inspiratory pressure	30-day postoperative morbidity
Spo_2	Postop complication - anastomic leak
Fio_2	Postop complication - unexpected ICU admission
$ETco_2$	Postop complication - central neurological event
One-lung and two-lung ventilation start and stop times	Postop complication - renal failure
Blood product use	Postop complication - sepsis
	Postop complication - MI
	Postop complication - Atrial arrhythmia
	Postop complication - ventricular arrhythmia
	Postop complication - return to OR
	Postop complication - respiratory failure
	Postop complication - atelectasis
	Postop complication - air leak > 5 days
	Postop complication - pulmonary embolism
	Postop complication - bronchopleural fistula
	Postop complication - ARDS
	Postop complication - tracheostomy
	Postop complication - empyema
	Postop complication - pneumonia
	Postop complication - DVT
	Postop complication - pneumothorax
	Postop complication - ileus
	Postop complication - surgical site infection
	Postop complication - sepsis
	Postop complication - other infection
	Postop complication - delirium
	Postop complication - other pulmonary event
	Postop complication - discharge status
	Postop complication - 30-day readmission
	Postop complication - ventilator support > 48 h
	Unanticipated surgical conversion
	Unanticipated surgical conversion type

ARDS, acute respiratory distress syndrome; ASA, American Society of Anesthesiologists; BMI, body mass index; CPT, current procedural terminology; DVT, deep vein thrombosis; $ETco_2$, end-tidal carbon dioxide; FEV1, forced expiratory volume in 1 s; Fio_2, fraction of inspired oxygen; ICU, intensive care unit; MI, myocardial infarction; OR, operating room; Spo_2, oxygen saturation measured by pulse oximetry; WHO, World Health Organization.

Appendix 2: Aim-specific Statistical Analysis

Aim 1: Assessment of the Relationship of Ventilator Parameters, Adherence to Suggested Lung-protective Strategy, and Patient Outcome

The matched cohort was used for this analysis. Univariate comparisons between lung-protective ventilation group status and the rate of each outcome were computed using McNemar test. A Cochran-Armitage test for trend was used to determine if there was an increase in documented use of lung-protective ventilation over time, where time is defined in quarters.

Aim 2: Derivation of a Recommended Tidal volume and Driving Pressure

The full study cohort was used for this analysis. To determine the most beneficial combination of positive end-expiratory pressure (PEEP) and tidal volume (Vt) to reduce pulmonary complications, a matrix of adjusted odds ratios was constructed with the reference category of PEEP between 4 and 6 cm H_2O and Vt between 4 and 6 ml/kg predicted body weight. The logistic regression model was adjusted for age, gender, body mass index, forced expiratory volume in 1 s (FEV_1), presence of missing FEV data, American Society of Anesthesiologists (ASA) status, preoperative renal dysfunction, preoperative steroid therapy, Zubrod score, current smoking status, preoperative chemotherapy and/or radiation, major preoperative comorbidity, institution, presence of blood product transfusion, fluid balance, segmentectomy (*vs.* wedge resection), lobectomy (*vs.* wedge resection), bilobectomy (*vs.* wedge resection) or pneumonectomy (*vs.* wedge resection), and thoracotomy (*vs.* video-assisted thoracoscopic surgery).

Aim 3: Assessment of the Relationship between Driving Pressure and Outcome

The full study cohort was used in this analysis. Two multivariable logistic regression models were constructed as above to evaluate the impact of ventilator parameters on the primary outcome of pulmonary complications. In addition to the previously mentioned covariates, model 1 contained the variable for modified airway driving pressure (per 1 cm H_2O). Model 2 contained the variable P_{MAX}. If modified airway driving pressure or P_{MAX} were statistically significant after adjusting for other significant predictors, they were considered independent predictors of pulmonary complications. Similar models were constructed for the secondary outcomes. Nonlinear trends were not assessed.

Aim 4: Assessment of Risk Groups for High Driving Pressures

The full study cohort was used in this analysis. To determine whether patients known to be at higher risk for receiving high V_T/kg predicted body weight were more

likely to be subjected to ventilator regimens associated with higher levels of modified airway driving pressure, three bivariable linear regression models were constructed for the dependent variable of modified airway driving pressure. The first model contained the fixed effect of body mass index, the second model contained the fixed effect of height (cm), and the third model contained the fixed effect of gender.

Next, three nonparsimonious logistic regression models were constructed to evaluate whether patients known to be at higher risk for receiving high V_T were at higher risk of postoperative pulmonary complications. The covariates of body mass index and sex were removed from the model previously specified, to be entered separately. The first model contained the additional fixed effect of body mass index, the second model contained the additional fixed effect of height, and the third model contained the additional fixed effect of gender. A similar set of models was be constructed for all secondary outcomes. If the additional fixed effect for each model was found to be statistically significant, that characteristic was considered an independent predictor of the outcome of interest. If all three were independent predictors, then those at high risk for receiving high V_T were said to be at higher risk for postoperative complications.

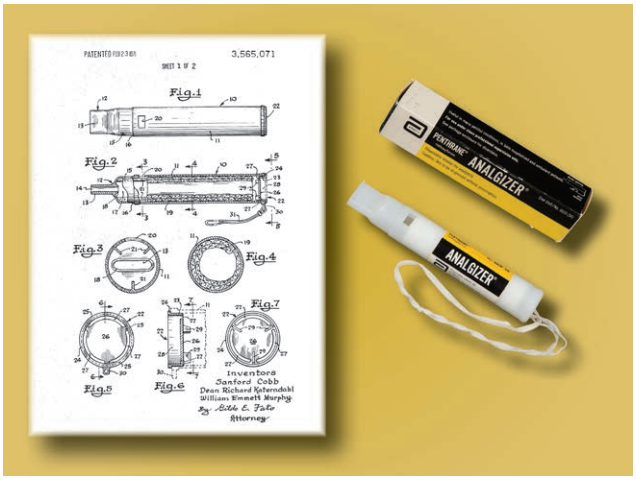
Appendix 3: Group Collaborators

Patrick J. McCormick, M.D., M.Eng., Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

William Peterson, M.D., Department of Anesthesiology, Sparrow Health System, Lansing, Michigan.

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From Cigar to Green Whistle: The Unfinished Tale of the Methoxyflurane Inhaler



Methoxyflurane, or Penthrane, a fluorinated hydrocarbon, was hailed as a nontoxic alternative to halothane. Although hallowed for its potency and inflammability, halothane could induce hepatitis and arrhythmias. Penthrane gained a superior reputation for hemodynamic stability and analgesia that endured, even at subanesthetic doses. Thus, in spite of a 1966 report that 17% of methoxyflurane recipients in one hospital had developed high-output nephropathy, the disposable Analgizer (*right*), designed for self-administration of the vapor for pain relief, was introduced in 1968. A rolled polypropylene wick within the device's polyethylene cylinder (*left*) held the volatile agent. Lovingly called "the cigar" at one Canadian hospital, the Analgizer, with its inhalational mouthpiece, was used for obstetric labor, perioperative pain, and burn dressing changes. However, after new studies correlated cases of renal failure with methoxyflurane's metabolic byproducts, the Analgizer was withdrawn from the market in 1974. Even so, "the cigar" was reincarnated in Australia as "the green whistle," or Penthrox, the very next year. "The whistle" used a lower dose and an activated charcoal chamber to adsorb gas exhaled through its bidirectional mouthpiece. Since its birth, Penthrox has thrived in prehospital and military settings, emergency departments, and procedural suites throughout Australia and New Zealand. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.)

Jane S. Moon, M.D., University of California, Los Angeles, California, and Melissa L. Coleman, M.D., Penn State College of Medicine, Hershey, Pennsylvania.