PCRC Proposal Cover Sheet

Management of one lung ventilation during lung resection surgery – impact on postoperative complications

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| **Title of Study or Project:** | Management of one lung ventilation during lung resection surgery – impact on postoperative complications |
| **Primary Institution:** | University of Virginia |
| **Principal Investigator:** | Randal S. Blank, M.D., Ph.D. |
| **Co-Investigators:** | Michael R. Mathis, M.D., Douglas A. Colquhoun, M.B. Ch.B., M.Sc., Amy M. Shanks, Ph.D, Bhiken I. Naik, M.D., Aleda M. Leis, M.S., Marcel E. Durieux, M.D., Benjamin D. Kozower, M.D., M.P.H., Dustin M. Walters, M.D., Sachin Kheterpal M.D., M.B.A., Nathan L. Pace, M.D., M.Stat., Wanda M. Popescu, M.D., Robert B. Schonberger, Justin D. Blasberg, M.D., Ph.D., Andrew C. Chang, M.D., Michael F. Aziz, M.D., Izumi Harukuni, M.D., Brandon H., Tieu, M.D., F.A.C.S., Linda W. Martin, M.D., Ph.D. |
| **Type of Study:** | ☒ Retrospective Observational Outcomes Study |
| **Hypothesis:** | We hypothesize that 1) management of one lung ventilation (1LV) affects the development of postoperative complications, 2) in the presence of low levels of PEEP, low VT do not predict a decrease in complication rate, 3) ventilatory correlates of dynamic alveolar strain – notably Pplat and/or P (Pplat-PEEP) are more predictive of postoperative complications than is VT, 4) that patients known to be at higher risk for receiving high VT/kg PBW – patients with high BMI, short stature, and female gender are more likely to be subjected to ventilator regimens associated with higher levels of P, and consequently 5) that after adjustment for other risk predictors, these patients are at higher risk for postoperative complications. |
| **Number of Patients/Participants:** | Anesthetic cases utilizing 1LV for lung resection between January 1st 2012 and July 1st 2017. |
| **Power Analysis:** | N/A |
| **Proposed statistical test/analysis:** | Multiple tests as described in Methods |
| **Resources (Brief summary of resources for data collection, personnel, financial):** | Multiple investigators at included sites |

Proposal for Clinical Research – MPOG Group Application

Title of Proposal

Management of one lung ventilation during lung resection surgery – impact on postoperative complications

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**Introduction**

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 volumes1. More recently, a variety of observational and experimental studies have endorsed the concept that this approach to ventilator management can be profoundly injurious. Mechanical ventilation can induce pulmonary and distant organ injury through a number of overlapping effects including alveolar overdistension (volutrauma), cyclic opening and collapse of alveoli (atelectrauma), and the release of mediators (biotrauma) which have the potential to adversely affect other organ systems. The demonstration that high tidal volume (conventional) ventilation resulted in significantly higher mortality in patients ventilated for respiratory failure due to ARDS2, led to the concept of “protective” ventilation strategies – that is limiting alveolar overdistension through the application of smaller physiologic tidal volumes. Subsequent studies of high tidal volume ventilation critically ill patients without preexisting lung injury3-7 and in surgical patients at risk for lung injury confirm that a similar approach may decrease systemic and pulmonary inflammation8-10, improve postoperative pulmonary function8,11 and clinical outcomes including pulmonary complications12,13 and hospital stay 12.

 Prominent studies of general surgery patients at high risk for postoperative respiratory complications have reported ventilatory strategies which improve clinical outcomes in patients with preoperatively healthy lungs. However, these studies have been criticized for the use of a control group which may not reflect modern clinical practice, that is; high tidal volumes without the use of PEEP (ZEEP). Although these studies may contribute to the identification of a protective ventilation strategy, they do not permit the elucidation of specific factors (VT, PEEP, airway pressure) responsible for the observed clinical effect. More recent trials have evaluated the role of VT and PEEP in lung protection via controlled modification of a single ventilator variable. Treschan and colleagues14 demonstrated no differences in postoperative lung function in upper abdominal surgery patients ventilated with a high (VT 12 ml/kg PBW) or low (VT 6 ml/kg PBW) VT strategy that included comparable levels of PEEP (5 cm H2O) in both groups. In retrospective database studies of surgical patients, low VT were associated with a significantly increased odds of mortality after general surgery15 and respiratory complications after thoracic surgery16. Thus, in patients receiving 2LV for elective surgery, low VT per se has not been demonstrated to be protective.

 Patients presenting for lung resection surgery may be at elevated risk for complications as a result of preexisting disease processes, the nature of the planned surgery, loss of functional lung parenchyma (for pulmonary resection procedures), and the detrimental effects of mechanical ventilation, particularly one lung ventilation (1LV). 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 (2LV), considerably less evidence is available to guide management of 1LV, a technique commonly used to optimize operating conditions for a variety of surgical procedures within the thorax. Of the limited studies in this area, most have focused on surrogate markers of lung injury and inflammation. Very little data exists to specifically support a particular approach to management of 1LV with regard to clinical outcomes. Most, but not all17,18 prospective studies examining putative protective 1LV (reduced VT, moderate PEEP), have demonstrated a reduction in pulmonary19 or systemic inflammation8, extravascular lung water20, or pulmonary complications19. A retrospective study following institution of a protective ventilation regimen incorporating reduced VT, increased PEEP, limited ventilator pressures, and recruitment maneuvers during 1LV for lung cancer surgery is also consistent with a reduced risk of acute lung injury21. Tidal volumes during 1LV22 have been identified as a risk factor for respiratory failure after pneumonectomy (although they were not actually measured during this period). In retrospective reviews of pneumonectomy, tidal volumes21-23, ventilation pressures24,25 and duration of 1LV24 have been identified as risk factors for the development of lung injury. Small prospective trials in esophagectomy patients have demonstrated attenuation of systemic inflammation and improvements in postoperative pulmonary gas exchange 8 and a reduction in the incidence of pulmonary complications19 in patients randomized to receive lower VT ventilation with PEEP. The results of protective ventilation trials in human 26 and animal models 27 generally support the use of lower tidal volumes as well. Yang and colleagues26 found a significantly lower incidence of postoperative pulmonary dysfunction in lung resection patients randomized to a protective strategy (FIO2 0.5, VT 6 ml/kg, 5 cm H2O PEEP) versus conventional ventilation (FIO2 1.0, VT 10 ml/kg, ZEEP). These results are consistent with an animal study which convincingly demonstrated a dramatic increase in extravascular lung water (EVLW) after pneumonectomy in animals ventilated with high VT (12 ml/kg) versus those ventilated with low VT 6 ml/kg27 and a clinical study which found reduced EVLW in thoracic surgery patients receiving VT 4 ml/kg versus those who received higher VT20. It is important to note however, that studies have not yet unambiguously demonstrated a specific advantage of low VT ventilation in the absence of other ventilatory strategies (PEEP, recruitment maneuvers) and/or independently of other potentially important ventilation parameters (airway, plateau, driving, and transpulmonary pressures) and it is not yet clear which ventilator parameters, if any, are most likely to predict adverse outcomes and hence which ventilator modifications are most likely to improve outcomes.

 Protective ventilation with low VT and moderate PEEP levels has been recommended by experts28,29 but no standardized guidelines exist. Systematic adoption of putative protective ventilator management for 1LV may be hindered by the lack of large trials demonstrating outcome improvements, the unintentional delivery of inappropriately large tidal volumes due to high default ventilator settings or a high body mass to ideal body mass ratio30, and by a yet incomplete understanding of the ventilator factors actually responsible for injurious ventilation.

 It is thus important to note out that much of the contradictory results regarding protective or injurious ventilation in studies of VILI in critically ill and surgical patients may arise from the imprecision inherent in the studied ventilator variables. Neither VT 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 (PL) and its subsequent impact of tissue deformation (stress and strain). Dynamic alveolar strain (VT/FRC) defines the degree of alveolar tissue deformation between inspiration and expiration, but cannot be measured without knowing the starting lung volume (FRC or end expiratory lung volume (EELV)). Indeed dynamic but not static alveolar strain is injurious in healthy pigs ventilated at total lung capacity31 and appears to be the more important determinant of VILI32. Of interest, airway pressure release ventilation (APRV), a ventilation mode shown to reduce alveolar strain33 also prevents the development of VILI in an experimental animal model34. Gattinoni and colleagues35 have made a compelling argument that studies of VILI should control pathophysiologically important variables – namely PL, or failing that, PPLAT, which is a better surrogate of PL than is VT. This physiologic argument appears to be supported by an observational study of ARDS patients who were ventilated using standardized “ARDSnet” strategy. Computed tomography was used to assess lung aeration associated with injurious ventilation and PPLAT greater than 25 cm H2O was identified as a threshold value associated with injurious ventilation.36

 Driving pressure (peak inspiratory pressure minus PEEP) has also been identified as a risk factor for the development of ARDS in a general surgical population37. Peak inspiratory ventilator pressure has been identified as a potential risk factor for postpneumonectomy pulmonary edema25 and acute lung injury after pulmonary resection24. In a large retrospective study of ARDS patients from previously published trials, Amato et al.38 identified driving pressure (P=VT/Crs) but not VT as the ventilation variable which best stratified risk of mortality. Using multilevel mediation analysis, these authors were able to partition subcohorts of patients by matching patient exposures to a single ventilator variable such as PEEP, while varying the other variables - P and Pplat. This statistical approach allowed them to identify P as the only ventilator variable which predicted mortality.

 In light of our recently enhanced understanding of the biomechanics of VILI and resulting interplay of forces acting upon the alveoli during mechanical ventilation, the following tentative conclusions appear to be justified. First, although high VT may be injurious, particularly when accompanied by low PEEP levels, the primary determinant of VILI appears appears to be the level of tidal alveolar tissue deformation – or dynamic strain. Secondly, it then follows that no absolute level of VT or PEEP is inherently injurious or “protective”. This assertion is well supported by prospective clinical trials14,17, retrospective clinical studies15 and elegant studies in animal models31,39. Third, discrepancies in the results of published studies are likely to be explained by a) whether administered PEEP and/or recruitment maneuvers were sufficient to eliminate atelectasis and prevent tidal derecruitment and b) whether the combination of administered VT and PEEP and the resultant generation of a transpulmonary pressure resulted in pathologic levels of tidal alveolar tissue deformation (strain). Moderate levels of PEEP (5 cm H2O) may not be sufficient to prevent tidal decruitment in ventilated surgical patients40 and high VT in the absence of sufficient PEEP can induce cyclic alveolar recruitment and derecruitment41, a process known to induce inflammatory alveolar changes42,43.

 We hypothesize that 1) management of mechanical ventilation during thoracic surgery affects the development of postoperative complications, 2) in the presence of low levels of PEEP, low VT do not predict a decrease in complication rate, 3) ventilatory correlates of dynamic alveolar strain – notably modified P (mP; peak inspiratory pressure (PIP)-PEEP) are more predictive of postoperative complications than is VT, 4) that patients known to be at higher risk for receiving high VT/kg PBW – patients with high BMI, short stature, and female gender are more likely to be subjected to ventilator regimens associated with higher levels of mP, and consequently 5) that after adjustment for other risk predictors, these patients are at higher risk for postoperative complications.

**Materials and Methods**

**Specific Aims**

**1) To assess the relationship between ventilator parameters – VT, PEEP, and airway pressure (including mP) and the development of postoperative complications. This aim will include the following sub aims:**

**1a) To determine whether the use of a putative LPV strategy conforming to expert recommendations for 1LV (defined as a VT ≤ 5 mL/kg PBW and PEEP ≥ 5 cm H2O) predicts improvements in postoperative respiratory complications.**

**1b) To determine whether the use of a putative LPV strategy conforming to expert recommendations for 1LV (defined as a VT ≤ 5 mL/kg PBW and PEEP ≥ 5 cm H2O) predicts improvements in postoperative morbidity.**

**1c) To determine whether the documented increase in adherence to LPV recommendations over the study period (if repeated in current study) has led to discernible improvements in clinical outcomes.**

**2) To assess the interaction between ventilator parameters (particularly VT and PEEP) to determine a “best” combination of VT and PEEP during 1LV.**

**3) To determine whether ventilatory correlates of dynamic alveolar strain – notably PIP and/or mP (PIP-PEEP) are predictive of postoperative complications.**

**4a) To determine whether patients known to be at higher risk for receiving high VT/kg PBW – patients with high BMI, short stature, and female gender - are more likely to be subjected to ventilator regimens associated with higher levels of mP, and consequently,**

**4b) Whether, after adjustment for other risk predictors, these patients are at higher risk for postoperative complications.**

 The MPOG database will be utilized for this study. The MPOG database contains de-identified perioperative data relevant to this study. Institutional Review Board approval has already been obtained for MPOG projects involving the University of Michigan, Ann Arbor, Michigan. Additional institutional review board (IRB) approval will be sought and attained for all contributing centers to be supplying Society of Thoracic Surgeons (STS) Database data. Centers to be included pending final confirmation and IRB approval are: University of Michigan Health System, University of Virginia Health System, Washington University School of Medicine, University of Colorado, Yale University, and the University of Vermont (Fletcher Allen Health Care). Procedures performed between the dates of January 1st 2012 and July 1st 2017 will be reviewed.

 Utilizing MPOG Concepts, subjects meeting inclusion criteria in whom 1LV is administered will be identified. Demographic, preoperative, anesthetic and surgical data to be collected includes: age, gender, race, height, weight, BMI, ASA physical status, MPOG patient identifier, MPOG institution identifier, provider, provider status (attending alone, supervised resident, supervised CRNA), year of service, postoperative destination (PACU vs. ICU), preoperative comorbidities (particularly pulmonary diseases which might influence choice of ventilation parameters (e.g. COPD, interstitial lung disease)), planned and performed surgical procedure(s) (surgical procedure CPT code), set tidal volume (if any) and delivered tidal volume during 2LV and 1LV, respiratory rate, PEEP, peak and plateau airway pressures, ventilator mode setting, inspired oxygen fraction (FIO2), oxygen saturation (SpO2), the duration of anesthesia, surgery, 2LV, and 1LV. We will also collect data on the method of lung isolation as the use of bronchial blockers may be associated with the intentional use of lower ventilation pressures and the use of continuous positive airway pressure (CPAP) delivered to the non-ventilated lung during 1LV as this may augment oxygenation and potentially lessen inflammatory stress. End-tidal carbon dioxide data will be collected in an effort to determine whether permissive hypercapnea accompanies the use of lower tidal volume ventilation. Finally, data on fluid administration and fluid balance will also be collected. Predicted body weight (PBW) will be calculated as follows: PBW for males = 50kg + 2.3kg \* (Height (in) - 60); PBW for females = 45.5kg + 2.3kg \*(Height (in) - 60)); BMI will be calculated (weight in kg/ height in m2); along with VT in cc/kg of PBW.

The STS database will be used on an institutional basis to obtain information for candidate risk predictors based on previously published thoracic surgery risk models16,44-46 and for postoperative outcome data. 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](https://email.healthsystem.virginia.edu/owa/redir.aspx?SURL=n1f9gpJ0UUI2df8bXsvDKBx47ovoigC9HJEpjwAtkSBus3rP_mHSCGgAdAB0AHAAOgAvAC8AdwB3AHcALgBzAHQAcwAuAG8AcgBnAC8AcwBpAHQAZQBzAC8AZABlAGYAYQB1AGwAdAAvAGYAaQBsAGUAcwAvAGQAbwBjAHUAbQBlAG4AdABzAC8AUwBUAFMAVABoAG8AcgBhAGMAaQBjAEQAYQB0AGEAUwBwAGUAYwBzAFYAMgBfADMALgBwAGQAZgA.&URL=http%3a%2f%2fwww.sts.org%2fsites%2fdefault%2ffiles%2fdocuments%2fSTSThoracicDataSpecsV2_3.pdf)

Outcome data from the STS database include the following: unexpected return to OR, postoperative events, reoperation for bleeding, postoperative air leak greater than 5 days, atelectasis requiring bronchoscopy, pleural effusion requiring drainage, pneumonia, ARDS, respiratory failure, bronchopleural fistula, pulmonary embolus, pneumothorax, initial ventilator support > 48 hours, reintubation, tracheostomy, other pulmonary event, atrial fibrillation, ventricular arrhythmia requiring treatment, myocardial infarction, deep venous thrombosis requiring treatment, gastric outlet obstruction, ileus, anastomotic leak, empyema, wound infection, surgical site infection, sepsis, other infection requiring antibiotics, central neurological event, delirium, renal failure, unexpected admission to the ICU, discharge status, readmission within 30 days, and status at 30 days (mortality).

The primary outcome is postoperative respiratory complications, defined as any one or more of the following: tracheostomy, empyema requiring treatment, pneumonia, reintubation, initial ventilator support greater than 48 hours, ARDS, bronchopleural fistula, pulmonary embolism, air leak greater than 5 days, atelectasis requiring bronchoscopy, and respiratory failure. The two secondary outcomes include a) major morbidity - any or all of the following: respiratory complications (as above), unexpected return to the OR, atrial or ventricular dysrhythmias requiring treatment, myocardial infarction, sepsis, renal failure, central neurologic event, unexpected ICU admission, anastomotic leak and b) the composite outcome - any of the major morbidities above and/or mortality.

Driving pressure (P), modified driving pressure (mP), static (Cs) and dynamic compliance (Cdyn) are defined and will be calculated as follows: P=Pplat-PEEP; mP= PIP – PEEP; Cs=VT/ (Pplat-PEEP), Cdyn=VT/(PIP-PEEP), respectively. As above, the calculation of P requires Pplat data, which are not currently available from all participating MPOG institutions. Consequently, it is anticipated that mP will be used as the primary driving pressure covariate throughout the study.

The **initial period of 2LV** will encompass the 10 minute epoch beginning 10 minutes before the initiation of 1LV. The duration of 1LV will include the period from the recorded time of 1LV initiation to the first re-iniitation of 2LV. **Initial ventilator settings during 1LV** will be derived for the 10 minute epoch beginning 5 minutes after the onset of 1LV. If more than one period of is reported per case, we will examine only the first time period greater than 10 minutes in duration. Cases employing 1LV for less than 15 minutes will not be included in the analysis.

Inclusion Criteria

 Subjects/cases will be included if they meet the following criteria: subjects are of age 18 years or greater, height and weight data are available, cases employ 1LV for at least 15 minutes, and include any of the following primary surgical procedures – wedge resection or metastasectomy of lung tissue, lung segmentectomy, lobectomy, bilobectomy, or pneumonectomyas defined by the following CPT codes: Any included procedure must occur at least 10 times in the dataset.

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|   | Primary CPT | Descriptor | N |
| Seg/Lobe | 32663 | Thoracoscopy, surgical; with lobectomy | 824 |
| 32480 | Removal of lung, single lobe (lobectomy) | 448 |
| 32669 | Thoracoscopy with removal of a single lung segment (segmentectomy) | 90 |
| 32486 | Removal of lung, sleeve lobectomy | 57 |
| 32484 | Removal of lung, single segment (segmentectomy) | 35 |
| Pneum/BiLobe | 32482 | Removal of lung, two lobes (bilobectomy) | 71 |
| 32440 | Removal of lung, total pneumonectomy | 65 |
| 32670 | Thoracoscopy with removal of two lobes (bilobectomy) | 18 |
| 32488 | Removal of lung, completion pneumonectomy | 11 |
| Wedge | 32666 | Thoracoscopy with therapeutic wedge resection (eg mass or nodule, initial, unilateral | 670 |
| 32607 | Thoracoscopy, diagnostic; with biopsy(s) of lung infiltrate(s) (eg wedge), unilateral | 300 |
| 32505 | Thoracotomy with therapeutic wedge resection (eg mass nodule) initial | 77 |
| 32608 | Thoracoscopy, diagnostic; with biopsy(s) of lung nodule(s) or mass(es) (eg incisional), unilateral | 65 |
| 32096 | Thoracotomy with biopsy(s) lung infiltrate(s) (eg wedge), unilateral | 26 |

**Exclusion Criteria**

The following subjects and cases will excluded from analysis: subjects less than 18 years of age, cases employing 1LV for less than 15 minutes and those for which patient height and weight data are not available.

**Statistical Analysis**

Descriptive statistics for all relevant clinical data will be computed as frequencies and percentages for categorical variables and means and standard deviations for continuous variables between lung protection ventilation used (LPV) and non-LPV groups. Continuous data elements will be checked for normality using exploratory data techniques such as histograms and Q-Q plots, and all variables deemed to be non-parametric will be reported as medians, 25th and 75th percentiles. Categorical data will be analyzed using Pearson Chi-square or Fischer’s exact test as appropriate. Continuous data elements will be analyzed using a student’s t test or Mann-Whitney U as appropriate. Standardized differences will be reported for all univariate comparisons. In addition, we will examine the univariate associations between LPV use (yes/no) and 30-day combined respiratory complications, 30-day mortality, and 30-day combined morbidity and mortality. To determine whether the documented increase in adherence to LPV recommendations over the study period (if repeated in current study) has led to discernible improvements in clinical outcomes, a Cochran-Armitage test for trend will be computed for each strata of use of LPV and outcome rate for each quarter of the study period. This analysis will be performed on the entire study cohort.

A sample size calculation was performed using a two-sided Z test with un-pooled variance. A sample size of 1315 cases in each group (total study N = 2630) provides 90% power at an alpha = 0.05 to detect a 5% difference in the primary outcome measure, assuming a 22% rate of events in the non-LPV group.

LPV cases will be 1:1 propensity-score greedy matched to non-lung protective ventilation cases. The logistic regression model to create the propensity scores will have the outcome of LPV and the independent variables of age, gender, BMI, ASA status, preoperative renal dysfunction, preoperative steroid therapy, Zubrod score, current smoking status, forced expiratory volume in 1 second (FEV1), presence of missing FEV data, induction chemotherapy and/or radiation, major preoperative comorbidity, and institution as fixed effects. Standardized differences will be reported for all matched variables, and a standardized difference <10% will be considered an adequate match. The matched cohort will then be used for all analyses unless otherwise noted.

Before any regression models are constructed, all variables under consideration for model inclusion will be checked for collinearity using Pearson correlations and variance inflation factor. Those variables deemed to be collinear (defined as a correlation of >= 0.70 or variance inflation factor > 10) will be either combined into a single variable or selected for removal. All variables that are not considered to be collinear will be allowed to enter the models.

For all conditional fixed effects logistic regression models, the goodness for fit will be reported using pseudo r-squared. Measures of effect for model covariates will be reported as adjusted odds ratios with 95% confidence intervals. Any covariate found to be statistically significant following adjustment within the model will be considered an independent predictor of the outcome of interest.

All analyses will be conducted using SAS 9.4 (SAS Institute, Cary, NC) and SPSS 24 (IBM Corp.). A p-value of 0.05 will be considered statistically significant for all analyses.

**Aim 1a: The use of a putative LPV strategy conforming to expert recommendations for 1LV (defined as a VT ≤ 5 mL/kg PBW and PEEP ≥ 5 cm H2O) predicts improvements in postoperative respiratory complications**

The aim will first be tested using a McNemar test between use of LPV (yes/no) and the outcome of postoperative respiratory complications. If this association is statistically significant, a conditional fixed effects logistic regression model will be constructed where the dependent variable will be postoperative respiratory complications and the use of LPV covariate, as well as the following intraoperative fixed effects (variables identified as risk predictors in published studies of adverse outcomes after major thoracic surgeries44-46): presence of blood product transfusion, fluid balance, or lung resection type ((vs. wedge resection or metastesectomy) - segmentectomy, lobectomy, bilobectomy or pneumonectomy), thoracotomy (vs. VATS), use of bronchial blocker (vs. double lumen tube), and any variables deemed a poor match based on a standardized difference >= 10%. Additionally, as sample size allows, age, sex, institution, and other clinically relevant variables will be included in the model. If use of LPV is found to be a statistically significant predictor of the primary outcome after adjusting for clinically relevant intraoperative covariates, it will be considered an independent predictor of postoperative respiratory complications.

**Aim 1b) The use of a putative LPV strategy conforming to expert recommendations for 1LV (defined as a VT ≤ 5 mL/kg PBW and PEEP ≥ 5 cm H2O) predicts improvements in postoperative morbidity**

Aim 1b will be tested as in Aim 1a, with the outcome of major morbidity in place of postoperative respiratory complications. If use of LPV is found to be a statistically significant predictor of the outcome after adjusting for clinically relevant covariates, it will be considered an independent predictor of major morbidity.

**Aim 2: To assess the relationship between ventilator parameters – VT, PEEP, and airway pressure (including mP) - and the development of postoperative complications.**

To attempt to determine the “best” combination of VT and PEEP during 1LV, a response surface regression plot will be constructed. First, the risk of having a primary outcome event will be calculated for the matched cohort with a fixed-effects conditional logistic regression model containing the following covariates: presence of presence of blood product transfusion, fluid balance, or lung resection type ((vs. wedge resection or metastasectomy) - segmentectomy, lobectomy, bilobectomy or pneumonectomy)), thoracotomy (vs. VATS), use of bronchial blocker (vs. double lumen tube), and any variables deemed a poor match based on a standardized difference >= 10%. Additionally, as sample size allows, age, sex, institution, and other clinically relevant variables will be included in the model. Next, the response surface will be constructed using VT and PEEP as the horizontal axes and the predicted risk as the vertical axis. The lowest point on the response surface will correspond to the levels of VT and PEEP where the outcome risk is the lowest. Similar response surface plots will be constructed for all secondary outcomes. Additional data visualization of the response surface will be presented using heat maps, as below:





The response-surface driven LPV (RS-LPV) definition will then be: VT ≤ VT value corresponding to the lowest point on the response surface and PEEP ≥ PEEP value corresponding to the lowest point on the response surface. Patients who meet both criteria will be considered to have received RS-LPV.



If a lowest point is able to be determined and represents a clinically reasonable practice, five fixed-effects conditional logistic regression models will be constructed to evaluate the impact of ventilator parameters on the primary outcome of postoperative respiratory complications, adjusting for variables identified as significant risk predictors in published studies of adverse outcomes after major thoracic surgeries as sample size allows 44-46.. The following fixed effects will be included in all models: presence of blood product transfusion, fluid balance, or lung resection type ((vs. wedge resection or metastasectomy) - segmentectomy, lobectomy, bilobectomy or pneumonectomy)), thoracotomy (vs. VATS), use of bronchial blocker (vs. double lumen tube), and any variables deemed a poor match based on a standardized difference >= 10%. Additionally, as sample size allows, age, sex, institution, and other clinically relevant variables will be included in the model. In addition to the above, model 1 will contain VT during 1LV (per 1 ml/kg PBW) and modified airway driving pressure (mP; PIP-PEEP; per 1 cm H2O), as well as an interaction term between VT and mP. Model 2 will contain all the variables in model 1 with the exception of PEEP during 1LV (per 1 cm H2O) as a replacement for mP, and an interaction term between VT and PEEP. The third model will contain all variables from model 1, with the exception of VT during 1LV. The fourth model will contain the RS-LPV variable as a fixed effect. The fifth model will include a three-way interaction term between VT, PEEP, and mP, as well as the fixed effects for these variables. For all models with interaction terms, if the interaction term is non-significant it will be removed and the fixed effects of the variables from the interaction will remain in the model. If VT, PEEP, and/or mP are statistically significant after adjusting for other significant predictors, they will be considered independent predictors of postoperative respiratory complications.

A similar set of models will be constructed to determine if VT, PEEP, and/or mP are independent predictors of the secondary outcomes of 30-day postoperative morbidity and 30-day postoperative mortality.

**Aim 3: To determine whether ventilatory correlates of dynamic alveolar strain – PIP and/or mP are predictive of postoperative complications**

Three fixed-effects conditional logistic regression models will be constructed on the matched cohort to evaluate the impact of ventilator parameters on the primary outcome of postoperative respiratory complications, adjusting for variables identified as significant risk predictors in published studies of adverse outcomes after major thoracic surgeries as sample size allows 43-45. The following fixed effects will be included in all models: presence of blood product transfusion, fluid balance, or lung resection type ((vs. wedge resection or metastasectomy) - segmentectomy, lobectomy, bilobectomy or pneumonectomy)), thoracotomy (vs. VATS), use of bronchial blocker (vs. double lumen tube), and any variables deemed a poor match based on a standardized difference >= 10%. Additionally, as sample size allows, age, sex, institution, and other clinically relevant variables will be included in the model. In addition to the above, model 1 will contain mP (per 1 cm H2O). Model 2 will contain all of the variables above and PIP. If mP or PIP are statistically significant after adjusting for other significant predictors, they will be considered independent predictors of postoperative respiratory complications.

A similar set of models will be constructed to determine if PIP and/or mP are independent predictors of the secondary outcomes of 30-day postoperative morbidity and 30-day postoperative mortality.

**Aim 4a: To determine whether patients known to be at higher risk for receiving high VT/kg PBW – patients with high BMI (BMI > 30), short stature (height < 165cm), and female gender - are more likely to be subjected to ventilator regimens associated with higher levels of mP.**

To determine whether patients known to be at higher risk for receiving high VT/kg PBW are more likely to be subjected to ventilator regimens associated with higher levels of mP, three GEE linear regression models will be constructed using the matched cohort for the dependent variable (mP) and fixed effect of institution. The first model will contain the fixed effect of BMI, the second model will contain the fixed effect of height, and the third model will contain the fixed effect of gender.

**Aim 4b: To determine whether, after adjustment for other risk predictors, patients at higher risk for receiving high VT/kg PBW (high BMI, short stature, female gender) are also at higher risk for postoperative complications.**

Three fixed effects conditional logistic regression models will be constructed on the matched cohort to evaluate whether patients known to be at higher risk for receiving high VT are at higher risk of the primary outcome of postoperative respiratory complications, adjusting for variables identified as significant risk predictors in published studies of adverse outcomes after major thoracic surgeries as sample size allows 43-45. The following fixed effects will be included in the model: presence of blood product transfusion, fluid balance, or lung resection type ((vs. wedge resection or metastasectomy) - segmentectomy, lobectomy, bilobectomy or pneumonectomy)), thoracotomy (vs. VATS), use of bronchial blocker (vs. double lumen tube), and any variables deemed a poor match based on a standardized difference >= 10%. Additionally, as sample size allows, age, sex, institution, and other clinically relevant variables will be included in the model. In addition to the above, the first model will contain the fixed effect of BMI, the second model will contain the fixed effect of height, and the third model will contain the fixed effect of gender.

A similar set of models will be constructed for all secondary outcomes.

If the additional fixed effect for each model is found to be statistically significant, that characteristic will be considered an independent predictor of the outcome of interest. If all three are independent predictors, then those at high risk for receiving high VT will be said to be at higher risk for postoperative complications.

***References***

***1.*** *Bendixen HH, Hedley-Whyte J, Laver MB. Impaired Oxygenation in Surgical Patients during General Anesthesia with Controlled Ventilation. A Concept of Atelectasis. The New England journal of medicine. Nov 7 1963;269:991-996.*

***2.*** *Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. The New England journal of medicine. May 4 2000;342(18):1301-1308.*

***3.*** *Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med. Sep 2004;32(9):1817-1824.*

***4.*** *Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med. Jul 2005;31(7):922-926.*

***5.*** *Jia X, Malhotra A, Saeed M, Mark RG, Talmor D. Risk factors for ARDS in patients receiving mechanical ventilation for > 48 h. Chest. Apr 2008;133(4):853-861.*

***6.*** *McKay A, Gottschalk A, Ploppa A, Durieux ME, Groves DS. Systemic lidocaine decreased the perioperative opioid analgesic requirements but failed to reduce discharge time after ambulatory surgery. Anesth Analg. Dec 2009;109(6):1805-1808.*

***7.*** *Choi G, Wolthuis EK, Bresser P, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. Anesthesiology. Oct 2006;105(4):689-695.*

***8.*** *Michelet P, D'Journo XB, Roch A, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology. Nov 2006;105(5):911-919.*

***9.*** *Yon JH, Choi GJ, Kang H, Park JM, Yang HS. Intraoperative systemic lidocaine for pre-emptive analgesics in subtotal gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. Canadian journal of surgery. Journal canadien de chirurgie. Jun 2014;57(3):175-182.*

***10.*** *Zupancich E, Paparella D, Turani F, et al. Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial. The Journal of thoracic and cardiovascular surgery. Aug 2005;130(2):378-383.*

***11.*** *Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. Jun 2013;118(6):1307-1321.*

***12.*** *Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. The New England journal of medicine. Aug 1 2013;369(5):428-437.*

***13.*** *Mathews TJ, Churchhouse AM, Housden T, Dunning J. Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? Interactive cardiovascular and thoracic surgery. Feb 2012;14(2):194-199.*

***14.*** *Treschan TA, Kaisers W, Schaefer MS, et al. Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function. Br J Anaesth. Aug 2012;109(2):263-271.*

***15.*** *Levin MA, McCormick PJ, Lin HM, Hosseinian L, Fischer GW. Low intraoperative tidal volume ventilation with minimal PEEP is associated with increased mortality. Br J Anaesth. Jul 2014;113(1):97-108.*

***16.*** *Blank RS, Colquhoun DA, Durieux ME, et al. Management of One-lung Ventilation: Impact of Tidal Volume on Complications after Thoracic Surgery. Anesthesiology. Jun 2016;124(6):1286-1295.*

***17.*** *Maslow AD, Stafford TS, Davignon KR, Ng T. A randomized comparison of different ventilator strategies during thoracotomy for pulmonary resection. The Journal of thoracic and cardiovascular surgery. Jul 2013;146(1):38-44.*

***18.*** *Ahn HJ, Kim JA, Yang M, Shim WS, Park KJ, Lee JJ. Comparison between conventional and protective one-lung ventilation for ventilator-assisted thoracic surgery. Anaesthesia and intensive care. Sep 2012;40(5):780-788.*

***19.*** *Shen Y, Zhong M, Wu W, et al. The impact of tidal volume on pulmonary complications following minimally invasive esophagectomy: a randomized and controlled study. The Journal of thoracic and cardiovascular surgery. Nov 2013;146(5):1267-1273; discussion 1273-1264.*

***20.*** *Qutub H, El-Tahan MR, Mowafi HA, El Ghoneimy YF, Regal MA, Al Saflan AA. Effect of tidal volume on extravascular lung water content during one-lung ventilation for video-assisted thoracoscopic surgery: a randomised, controlled trial. European journal of anaesthesiology. Sep 2014;31(9):466-473.*

***21.*** *Licker M, Diaper J, Villiger Y, et al. Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Crit Care. 2009;13(2):R41.*

***22.*** *Fernandez-Perez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology. Jul 2006;105(1):14-18.*

***23.*** *Marret E, Miled F, Bazelly B, et al. Risk and protective factors for major complications after pneumonectomy for lung cancer. Interactive cardiovascular and thoracic surgery. Jun 2010;10(6):936-939.*

***24.*** *Licker M, de Perrot M, Spiliopoulos A, et al. Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg. Dec 2003;97(6):1558-1565.*

***25.*** *van der Werff YD, van der Houwen HK, Heijmans PJ, et al. Postpneumonectomy pulmonary edema. A retrospective analysis of incidence and possible risk factors. Chest. May 1997;111(5):1278-1284.*

***26.*** *Yang M, Ahn HJ, Kim K, et al. Does a protective ventilation strategy reduce the risk of pulmonary complications after lung cancer surgery?: a randomized controlled trial. Chest. Mar 2011;139(3):530-537.*

***27.*** *Kuzkov VV, Suborov EV, Kirov MY, et al. Extravascular lung water after pneumonectomy and one-lung ventilation in sheep. Crit Care Med. Jun 2007;35(6):1550-1559.*

***28.*** *Slinger P, Kilpatrick B. Perioperative lung protection strategies in cardiothoracic anesthesia: are they useful? Anesthesiol Clin. Dec 2012;30(4):607-628.*

***29.*** *Grichnik KP, Shaw A. Update on one-lung ventilation: the use of continuous positive airway pressure ventilation and positive end-expiratory pressure ventilation--clinical application. Current opinion in anaesthesiology. Feb 2009;22(1):23-30.*

***30.*** *Fernandez-Bustamante A, Wood CL, Tran ZV, Moine P. Intraoperative ventilation: incidence and risk factors for receiving large tidal volumes during general anesthesia. BMC Anesthesiol. 2011;11:22.*

***31.*** *Protti A, Andreis DT, Monti M, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? Crit Care Med. Apr 2013;41(4):1046-1055.*

***32.*** *Protti A, Votta E, Gattinoni L. Which is the most important strain in the pathogenesis of ventilator-induced lung injury: dynamic or static? Current opinion in critical care. Feb 2014;20(1):33-38.*

***33.*** *Kollisch-Singule M, Emr B, Smith B, et al. Airway pressure release ventilation reduces conducting airway micro-strain in lung injury. J Am Coll Surg. Nov 2014;219(5):968-976.*

***34.*** *Emr B, Gatto LA, Roy S, et al. Airway pressure release ventilation prevents ventilator-induced lung injury in normal lungs. JAMA surgery. Nov 2013;148(11):1005-1012.*

***35.*** *Gattinoni L, Carlesso E, Cadringher P, Valenza F, Vagginelli F, Chiumello D. Physical and biological triggers of ventilator-induced lung injury and its prevention. The European respiratory journal. Supplement. Nov 2003;47:15s-25s.*

***36.*** *Terragni PP, Filippini C, Slutsky AS, et al. Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. Anesthesiology. Oct 2013;119(4):880-889.*

***37.*** *Blum JM, Stentz MJ, Dechert R, et al. Preoperative and intraoperative predictors of postoperative acute respiratory distress syndrome in a general surgical population. Anesthesiology. Jan 2013;118(1):19-29.*

***38.*** *Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. The New England journal of medicine. Feb 19 2015;372(8):747-755.*

***39.*** *Halter JM, Steinberg JM, Gatto LA, et al. Effect of positive end-expiratory pressure and tidal volume on lung injury induced by alveolar instability. Crit Care. 2007;11(1):R20.*

***40.*** *Wirth S, Baur M, Spaeth J, Guttmann J, Schumann S. Intraoperative positive end-expiratory pressure evaluation using the intratidal compliance-volume profile. Br J Anaesth. Mar 2015;114(3):483-490.*

***41.*** *Kozian A, Schilling T, Rocken C, Breitling C, Hachenberg T, Hedenstierna G. Increased alveolar damage after mechanical ventilation in a porcine model of thoracic surgery. J Cardiothorac Vasc Anesth. Aug 2010;24(4):617-623.*

***42.*** *Chu EK, Whitehead T, Slutsky AS. Effects of cyclic opening and closing at low- and high-volume ventilation on bronchoalveolar lavage cytokines. Crit Care Med. Jan 2004;32(1):168-174.*

***43.*** *Bellani G, Messa C, Guerra L, et al. Lungs of patients with acute respiratory distress syndrome show diffuse inflammation in normally aerated regions: a [18F]-fluoro-2-deoxy-D-glucose PET/CT study. Crit Care Med. Jul 2009;37(7):2216-2222.*

***44.*** *Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg. Sep 2010;90(3):875-881; discussion 881-873.*

***45.*** *Shapiro M, Swanson SJ, Wright CD, et al. Predictors of major morbidity and mortality after pneumonectomy utilizing the Society for Thoracic Surgeons General Thoracic Surgery Database. Ann Thorac Surg. Sep 2010;90(3):927-934; discussion 934-925.*

***46.*** *Wright CD, Gaissert HA, Grab JD, O'Brien SM, Peterson ED, Allen MS. Predictors of prolonged length of stay after lobectomy for lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk-adjustment model. Ann Thorac Surg. Jun 2008;85(6):1857-1865; discussion 1865.*

|  |  |  |  |
| --- | --- | --- | --- |
| Demographic data | Standardized View/Table | View/Concept | MPOG Concept ID |
|  |  |  |  |
|  | Case ID | General Case Information -> MPOG\_Case\_ID | V |  |
|  | Institution ID | \*\* Institution ID \*\* | T |  |
|  | Age | Patient Demographics -> AIMS\_Patient\_Age\_Years | V |  |
|  | Sex | Patient Demographics -> AIMS\_Sex | V |  |
|  | Race | Patient Demographics -> MPOG\_Race\_Concept\_ID |  |  |
|  | ASA status | ASA Class -> ASA\_Class | V |  |
|  | Height | Patient Anthropometrics -> MPOG\_Height\_cm | V |  |
|  | Weight | Patient Anthropometrics -> MPOG\_Weight\_kg | V |  |
|  | BMI | Patient Anthropometrics -> MPOG\_Body\_Mass\_Index |  |  |
|  | Comorbidites | \*\*\* From ICD9 Billing Data \*\*\* | C |  |
|  | Zubrod score |  |  |  |
|  | Induction chemotherapy and/or radiation |  |  |  |
|  | Renal Dysfunction |  |  |  |
|  | Forced expiratory volume (FEV1) |  |  |  |
|  | Steroid Therapy |  |  |  |
|  |  |  |  |
| Procedure Data  |  |  |  |
|  |  |  |  |
|  | Surgery CPT codes | Charge\_Capture -> Primary\_Surgery\_Code | V |  |
|  | Anesthesia CPT Codes | Charge\_Capture -> Primary\_Anesthesia\_Code | V |  |
|  | Bronchial blocker use |  |  |  |
|  | Year of Service | Derived from Case Times -> Anesthesia\_Start\_DT | V |  |
|  | Planned Surgical Procedure | General Case Information -> AIMS\_Scheduled\_Procedure\_Text | V |  |
|  | Performed Surgical Procedure | General Case Information -> AIMS\_Actual\_Procedure\_Text | V |  |
|  | Duration of Anesthesia | Case Times -> Case\_Duration\_Anesthesia\_min | V |  |
|  | Duration of Surgery | Case Times -> Case\_Duration\_Surgery\_min | V |  |
|  | Provider Status | \*\*\* Need to link Anesthetist\_Primary to status \*\*\* | T | 6000 / 6004 / 6005 / 6010 / 6014 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Primary Attending Provider | Case Providers -> Attending\_Primary | V |  |
|  |  |  |  |  |
| Intraop Data |  |  |  |
|  |  |  |  |
|  | Set Tidal Volume | Physiologic Observations | T | 3192 |
|  | Measured Tidal Volume | Physiologic Observations | T | 3190 |
|  | Respiratory Rate – Gas Analyzer | Physiologic Observations | T | 3230 |
| 1.
 | Respiratory Rate – Ventilator - Set | Physiologic Observations | T | 3198 |
|  | PEEP – Set | Physiologic Observations | T | 3212 |
|  | PEEP – Measured | Physiologic Observations | T | 3210 |
|  | Peak Inspiratory Pressure | Physiologic Observations | T | 3185 |
|  | Plateau Airway Pressure | Physiologic Observations | T | 3186 |
|  | Ventilator Mode Setting (if available) | Physiologic Observations | T | 3182 |
|  | Inspired O2 Fraction – Gas Analyzer | Physiologic Observations | T | 3240 |
|  | Inspired O2 Fraction – Ventilator | Physiologic Observations | T | 3200 |
|  | Thoracic - Single lung ventilation (1LV Start) | Intraoperative Events, Interventions, and Observations | T | 50501 |
|  | Thoracic - Single lung ventilation side detail (Alternative 1LV Start) | Intraoperative Events, Interventions, and Observations | T | 50502 |
|  | Thoracic - bronchial cuff inflation detail | Intraoperative Events, Interventions, and Observations | T | 50641 |
|  | Thoracic - bronchial cuff inflated or deflated (Alternative 1LV Start) | Intraoperative Events, Interventions, and Observations | T | 50640 |
|  | Thoracic - Two lung ventilation (TLV Start/Restart) | Intraoperative Events, Interventions, and Observations | T | 50500 |
|  | Blood product use | Intraoperative Blood Products In |  | 10490/10492/10493/10494/10495/10496  |
|  |  |  |  |
| Postoperative |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Post Operative Destination | \*\* Unknown \*\*\* | T |  |
|  | Mortality |  |  |  |
|  | Anastomotic leak |  |  |  |
|  | Unexpected ICU admission |  |  |  |
|  | Central Neurologic event |  |  |  |
|  | Renal failure |  |  |  |
|  | Sepsis |  |  |  |
|  | Myocardial Infarction |  |  |  |
|  | Atrial or ventricular dysrhythmias requiring treatment |  |  |  |
|  | Unexpected return to OR |  |  |  |
|  | Respiratory failure |  |  |  |
|  | Atelectasiss requiring bronchoscopy |  |  |  |
|  | Air leak > 5 days |  |  |  |
|  | Pulmonary embolism |  |  |  |
|  | Bronchopleural fistula |  |  |  |
|  | ARDS |  |  |  |
|  | Tracheostomy |  |  |  |
|  | Empyema requiring treatment |  |  |  |
|  | Pneumonia |  |  |  |
|  | Reintubation |  |  |  |
|  | Initial ventilator support > 48 hours  |  |  |  |