Cleveland Clinic

Ventilation Strategy during General Anesthesia for Orthopedic Surgery

Alparslan Turan, M.D and Colleagues

Version 1, September 6, 2017
Version 2, December 18, 2017
Version 3, March 5, 2018
Version 4, March 20, 2018
Version 5, August 13, 2018
Version 6, April 30, 2019
Version 7, August 20, 2020

Collaboration between the Departments of OUTCOMES RESEARCH, General Anesthesiology, and Orthopedic Surgery.

Summary of changes

Version 7 (August 20, 2020)

Explanation about the meaning of the primary outcome was added in measurement and data collection (page 10): The diagnostic criteria of acute lung injury (ALI) has traditionally relied on clinical findings and PaO_2/F_IO_2 ratio[14]. PaO_2/F_IO_2 ratio describes the severity of lung injury (e.g. PaO_2/F_IO_2 ≤300 for ALI and ≤200 for acute respiratory distress syndrome). Recently, SaO_2/F_IO_2 has been accepted as a surrogate for PaO_2/ FiO_2 ratio on the diagnosis of adults with acute lung injury and ARDS.[15,16,17] Noticeable, previous work demonstrated that a PaO2/FiO2 decrease of 10% from baseline was clinically meaningful of lung injury. [18, 19, 20] Therefore, we decide to use SaO_2/F_IO_2 ratio because: 1) it avoids invasive blood sampling, 2) there is evidence that $SaO2/F_IO_2$ is a reliable substitute for PaO_2/F_IO_2 with good sensitivity and specificity in diagnosing lung injury, including ALI and ARDS,[17,21,22] and 3) a 10% difference on SaO_2/F_IO_2 between groups may be indicative of differences the level of lung injury induced by the ventilatory strategy.

Version 6 (April 30, 2019)

- Exploratory objective has been added: estimated blood loss and perioperative transfusions *(Objectives and Hypotheses section, page 5 and page 11.*

Version 5, August 13, 2018

- Exploratory objective has been added: time from extubation to first oxygen saturation on ambient air breathing *(Objectives and Hypotheses section, page 5 and page 11)*
- Tidal volume will be calculated according predicted body weight and not ideal body weight *(Study procedures section, page 7)*
- Patients excluded from the study will be register*: (Measurements and Data collection section, page 9)*
- Respiratory parameters related to intubation and extubation procedures will be excluded from the analysis. *(Measurements and Data collection section, page 9)*
- We restricted our primary outcome, the time-weighted average SaO_2/FIO_2 ratio in the post-anesthesia care unit (PACU) to the first postoperative hour. (*Measurements and Data collection section, page 9*)

- The secondary outcome will be the oxygenation in ward, defined as the overall of SaO_2/F_IO_2 instead the time-weighted average (TWA) SaO_2/F_IO_2 (*Measurements and Data collection section, page 11*)
- We eliminated pulmonary collapse and hypoxemia from the composite of serious postoperative pulmonary complications. (*Measurements and Data collection section,* Table 4, page 10)

Version 4, March 20, 2018.

- Minors were excluded

Version 3, March 5, 2018.

- The protocol was revised as research project instead of quality improvement project.
- An Information Sheet as an alternative to written consent with a drop out option (last paragraph) was added.

Version 2, December 18, 2017

- A paragraph explaining why this project is eligible for waiver informed consent was added (page 8)

Background

Anesthesia and mechanical ventilation cause pathophysiological respiratory and ventilatory changes that can lead to pulmonary complications. Postoperative pulmonary complications are common after anesthesia, and cause substantial morbidity and mortality[1] that worsen clinical outcomes. Pulmonary complications also augment the cost of a surgery 2-12-fold.[2] The Cleveland Clinic Perioperative Health Documentation System database indicates that postoperative pulmonary complications occur after 5-10% of all surgeries, and that those complications are associated with in-hospital mortality, prolonged hospitalization, 30-day readmission, and higher overall cost.[3,4] Because they cause so much morbidity and impose such a substantial burden on health-care systems, pulmonary complications have become a key quality and safety metric for United States hospitals.[5]

The twin — and potentially contradictory — goals of mechanical ventilation are adequate gas exchange and prevention of iatrogenic lung injury. Two key ventilator settings are tidal volume and positive end-expiratory pressure (PEEP). Traditionally generous tidal volumes (i.e., 10-12 ml/kg of predicted body weight – PBW) were routine as high volumes prevents atelectasis and improve oxygenation. But relatively recently, restricted tidal volumes (i.e., 4-8 ml/kg PBW) were proven beneficial in critical care patients with acute respiratory distress syndrome/acute lung injury who were ventilated for days.[1] Restricted tidal volumes have since been inconsistently adapted for operating room use — despite lack of evidence that lower volumes reduce pulmonary risk or improve outcomes in surgical patients who rarely have serious pre-existing lung disease and are usually ventilated for only a few hours.

Restricted intraoperative tidal volumes improve breathing mechanics and reduce the risk of postoperative reintubation after cardiac surgery.[6] Lower tidal volumes also prevent alveolar inflammation and coagulation in healthy surgical patients.[7] On the other hand, low tidal volumes promote atelectasis which is an important cause of postoperative lung injury, and promotes pneumonia and respiratory failure. It remains unknown whether restricted tidal volumes are preferable during surgery, or whether lower volumes might actually worsen outcomes.

There is similarly ongoing debate about the optimal level of intraoperative PEEP. Generous PEEP reduces atelectasis, but also increases intrathoracic pressure and thus promotes hypotension and a consequent reduction in coronary blood flow.[8] Generous PEEP reduces lung injury in patients with acute respiratory distress syndrome. The IMPROVE study by *Futier et al*. is the most recent and largest relevant trial.[9] In this multicenter randomized trial of 400 patients, protective lung ventilation (tidal volume 6-8 ml/kg PBW and 6-8 cm H_2O PEEP) was compared with conventional ventilation (tidal volume 10-12 ml/kg PBW and no PEEP) in patients having major abdominal surgery who were at intermediate-to-high risk of postoperative complications. There were fewer

pulmonary and extra-pulmonary complications in patients assigned to protective ventilation.

In contrast, the PROVHILO trial compared the effects of high (12 cm H_2O) vs low (<2 cm H_2O) PEEP during open abdominal surgery and found no difference in postop pulmonary complications. Furthermore, patients assigned to high PEEP had more intraoperative hypotension requiring treatment.[10] The PROVHILO results are consistent with a systematic review by *Briel et al*. that included 2,299 patient from three trials (ALVEOLI, LOVS, and EXPRESS) in which PEEP did not influence in-hospital mortality in non-ARDS patients, leading the authors to conclude that high PEEP may be harmful in patients without ARDS.[11] Because existing results conflict, there is no consensus whatsoever on the optimal level of PEEP during elective surgery.

A consequence of limited and conflicting literature about optimal ventilation strategy is that ventilator settings in our institution vary widely amongst practitioners and patients. For example, between 2007-2016 at the Main Campus, 18% of patients were ventilated with tidal volumes exceeding 10 mL/kg PBW. Patients presenting for orthopedic surgeries are typically elderly, and often debilitated. Comorbidities are common, including cardiac and pulmonary disease, thus putting orthopedic patients at special risk for postoperative pulmonary complications. Curiously, no substantive trials of ventilator management in orthopedic patients have been published.

As part of developing a care pathway for Cleveland Clinic orthopedic surgical patients, we thus propose a research project to evaluate commonly used ventilator settings. Both the anesthesia and surgical teams have agreed to the proposed project, and representatives are designated co-investigators. While the results will presumably be published, our primary goal is to test the potential clinical consequences of switching to a standardized ventilation strategy in this unique patient population. We will use a non-randomized alternating intervention cohort approach, restricted to the physically distinct orthopedic surgery unit (H operating rooms 32-37) on the Main Campus.

Objectives and Hypotheses

Our objective is to determine the optimal intraoperative ventilation strategy among the chosen tidal volume and PEEP levels, and standardize it in an enhanced recovery pathway for orthopedic surgical patients. In particular, we propose to determine which combination of intraoperative tidal volume and positive end-expiratory pressure is best for patients having elective orthopedic surgery.

Primary objective:

Evaluate the effects of various ventilation strategies, tidal volume at 6 versus 10 ml/kg of PBW and PEEP at 5 versus 8 cmH_20, on oxygenation in the postoperative care unit, defined by the SaO_2/F_IO_2 ratio, a validated measure of acute lung injury.[12]

Secondary objective:

To evaluate the effects of various ventilation strategies on:

1. A composite of serious postoperative pulmonary complications;
2. Oxygenation in surgical wards, defined by the SaO_2/F_IO_2 ratio;
3. Postoperative duration of hospitalization.

Exploratory objective:

1. Time from extubation to first oxygen saturation on ambient air breathing
2. Intraoperative estimated blood loss and perioperative transfusions.

Methods

We propose a non-randomized alternating intervention cohort study in which all orthopedic surgery operating rooms will alternate amongst four designated ventilation settings which include two tidal volumes and two PEEP levels (**Table 1**). At the end of the four-week sequence, the entire sequence will be repeated 26 times over a 2-year period. Thus, ventilator settings will not be randomized on a per-patient basis, or even among study weeks.

Ventilation parameters will be designated at the beginning of each study week. However, clinicians will be free to adjust to whatever ventilation settings they believe is optimal in individual patients to ensure oxygenation and patient safety. We anticipate that approximately 2,500 patients will be included in the study.

Subject selection

This research study will be restricted to the operating rooms 32-37 which are primarily used for orthopedic surgery. The participating cohort will thus exactly represent those who will benefit from the proposed enhanced recovery pathway. Operating rooms 32-37 constitute a physically distinct unit that is normally staffed by a small group of anesthesiologists and surgeons. Typically, about 150-200 cases with general anesthesia are performed each month in these operating rooms.

We request a waived consent because: 1) obtaining individual consent would be nearly impossible for the number of patients required; 2) the interventions we propose are well within national and local standards-of-care and used routinely at the Cleveland Clinic; 3) the interventions are low risk; 4) clinicians are free to modify ventilation parameters as they see fit in individual patients. From a practical perspective, this unfunded research project will not be feasible except as an alternating intervention trial with waived consent.

Inclusion criteria:

1. Patient age ≥ 18 years old;
2. Surgery in orthopedic operating rooms 32-37;
3. General anesthesia with endotracheal intubation.

Exclusion criteria:

1. Non-orthopedic procedures;
2. Intubation before induction of anesthesia.

Study procedures

Four combinations of PEEP and tidal volume (Vt) will be used in patients having orthopedic surgery with general anesthesia, endotracheal intubation, and mechanical ventilation. Designated tidal volumes and PEEP levels were selected on the basis of previous studies[12] and after discussion with Clinic orthopedic anesthesiologists. All are well within the range of ventilator setting commonly used in orthopedic patients at the Clinic. The following suggested ventilatory parameters will be suggested during each study month:

Table 1. Tidal volume and PEEP settings

Week	Tidal volume (ml /predicted body weight)	PEEP (cm H_2O)
1	6	5
2	6	8
3	10	5
4	10	8

As usual, predicted body weight (PBW) will be used to determine tidal volume, and charts will be provided in each orthopedic operating room. To calculate PBW we'll use the formula which was used by ARDS network trial[39] as following:

Male 50 + 0.91(centimeters of height – 152.4);

Female 45.5 + 0.91(centimeters of height – 152.4).

Inspired oxygen concentration will be at least 50%, per Clinic routine. However, enough oxygen will always be given to maintain oxygen saturation (as determined by pulse oximetry) ≥ 95%. The respiratory rate will be adjusted to maintain an end-tidal partial carbon dioxide partial pressure between 35 and 45 mmHg, with a default inspired-to-expired ratio of 1:2.

Recruitment maneuvers are designed to re-expand atelectasis and are considered good clinical practice. Typically, a recruitment maneuver would be to maintain a constant airway pressure of 40-45 cmH_2O for 40 seconds[13]. Clinicians will be asked to perform a recruitment maneuver after induction of anesthesia at a F_IO_2 of 50%, and shortly before extubation. Intraoperative driving pressure Driving pressure, plateau pressure minus positive end-expiratory pressure (Pplat – PEEP), will be kept less than 15 cmH_2O by adjusting tidal volume and PEEP as necessary.

There will be no other restriction on anesthetic management. Clinicians will thus be free to use any combination of drugs they care to for general anesthesia. There will also be no restriction on peripheral nerve blocks or postoperative analgesic management.

Measurements and Data collection

All data will be obtained from the Cleveland Clinic Perioperative Health Documentation System (PHDS) and the Clinic's Electronic Medical Record (EMR). Demographic and morphometric characteristics will be recorded including age, sex, race, weight, height, and body mass index. We will also consider risk factors which may increase chance of pulmonary complications including American Society of Anesthesiologists physical status, preoperative comorbidities, smoking history.

Types of surgery will be characterized from ICD-9 codes using AHRQ Clinical Classifications Software. Routine anesthetic variables recorded in PHDS include use of regional anesthesia, patient position, anesthetic agent, tidal volume, PEEP, ventilation frequency, minute volume, airway pressures, inspired oxygen fraction, expired carbon dioxide partial pressure, SaO_2, blood pressure, transfused blood products, iv fluid types and volumes given during surgery, vasoactive medication needs, and duration of surgery.

We will register in redcap database all patients excluded from the study due to:

- Patients decision
- Anesthesiology decision
- Surgeon decision

Other Respiratory parameters related to intubation and extubation procedures will be excluded from the analysis. Thus we will exclude the tidal volume and PEEP values within 15 minutes from the after intubation and before extubation.

Baseline Patient/Surgery Characteristics

1. Age
2. Gender
3. Race
4. BMI
5. ASA status
6. Charlson score
7. Smoking status
8. Medical history
    a. Obstructive sleep apnea
    b. COPD
    c. Asthma
9. Intraoperative risk factors:
    a. Duration of surgery
    b. Total dose of muscle relaxants
    c. Intraoperative crystalloids
    d. Intraoperative blood products transfused
10. Surgery characteristics:
    a. Surgery type
    b. Anesthesia type
11. Mechanical ventilation parameters:
    a. PEEP
    b. Tidal volume

Primary outcome

The primary outcome will be time-weighted average SaO_2/FIO_2 ratio in the post-anesthesia care unit (PACU) during the first postoperative hour. SaO_2 is monitored continuously in the PACU by pulse oximetry. F_IO_2 will be estimated from the type of device and the oxygen flow rate, using the following conversion table (**Table 3**). We will assume that the F_IO_2 remains at the same level until the time of next record.

The diagnostic criteria of acute lung injury (ALI) has traditionally relied on clinical findings and PaO_2/F_IO_2 ratio[14]. PaO_2/F_IO_2 ratio describes the severity of lung injury (e.g. PaO_2/F_IO_2 ≤300 for ALI and ≤200 for acute respiratory distress syndrome). Recently, SaO_2/F_IO_2 has been accepted as a surrogate for PaO_2/ FiO_2 ratio on the diagnosis of adults with acute lung injury and ARDS.[15,16,17] Noticeable, previous work demonstrated that a PaO2/FiO2 decrease of 10% from baseline was clinically meaningful of lung injury. [18, 19, 20] Therefore, we decide to use SaO_2/F_IO_2 ratio because: 1) it avoids invasive blood sampling, 2) there is evidence that SaO2/F_IO_2 is a reliable substitute for PaO_2/F_IO_2 with good sensitivity and specificity in diagnosing lung injury, including ALI and ARDS,[17,21,22] and 3) a 10% difference on SaO_2/F_IO_2 between groups may be indicative of differences the level of lung injury induced by the ventilatory strategy.

Table 3. Estimation of F_IO_2

Method	O_2 flow (l/min)	Estimated FiO2 (%)
Nasel cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

Secondary Outcomes

1. Composite of serious postoperative pulmonary complications

Postoperative diagnoses will be collected from electronic medical records of patients. Individual chart reviews (blinded to ventilation management) will confirm that terms of the composite are met will be performed. Our composite of postoperative pulmonary complications is defined as the presence of at least one of the following ICD-10 codes (**Table 4**) that were not present on admission:

Table 4. Secondary Outcome: Composite of Pulmonary complications (ICD-10 codes)

Respiratory complications	997.31….J95851 997.32…..J9589 997.39…..J95859, J9588, J9589
Pulmonary infection, Pneumonia	481…….J13, J181 482…….J150 483…….J157, J160, J168 484…….B250 485…….J180 486…….J189
Respiratory failure and distress	518.3…….J82 518.51…….J95821, J9600 518.52…….J952, J953 518.53…….J95822, J9620 518.81…….J9600, J9690 518.84…….J9620
Tracheitis and Bronchitis	466……...J209 464…….J040
Pulmonary edema	518.4…….J810
Pneumothorax and air leak	512…….J930, 512.84……J9382
Pleural effusion	511.9……..J918
Atelectasis	518.0……..J9811, J9819
ARDS	518.5…….. J80 518.82…… J80
Acute COPD exacerbation Acute asthma exacerbation	491.21……J441 493.92……J45901
Other continuous invasive mechanical ventilation	xxxxxx……Z99.11
Re-intubation	Defined by: Re-intubation surrogate search • Intubation note • Propofol bolus >100 mg • Etomidate • Muscle relaxant
Transfusion-related acute lung injury	518.7……..J9584
Pulmonary embolism Respiratory acidosis	415.1……..I2699 276.2……..E872

2. Oxygenation in ward, defined as SaO_2/F_IO_2 ratio

Oxygen administration and SaO_2 are normally recorded at 4-hour intervals on surgical wards. The overall of SaO_2/F_IO_2 will be compared among different ventilation strategies.

3. Length of postoperative hospital stay

Exploratory outcome:

- Time from extubation to first oxygen saturation on ambient air breathing.
- As exploratory outcome, the time between extubation and the first saturation while breathing ambient air, can be related to underlying oxygen deficits and postoperative pulmonary complications.[23,24]

Data analysis

Control for confounding variables

Given that this study will not be randomized, we will control for observed potential confounding variable (**Table 5**) using the inverse propensity score weighting method. To estimate the propensity score, we will first fit a multinomial logistic regression model with the four treatments of different ventilation strategies as outcome. For each patient, the probability of receiving each treatment given the observed confounding variables is estimated and the weight is calculated as inverse of the propensity score. To be conservative, we stabilized the weights further by truncating at 99^{th} percentile. The success of the control for confounding will be assessed by pairwise comparisons among four groups on potential confounders using absolute standardized difference (ASD), defined as the absolute difference in means or proportions divided by the pooled standard deviation. Any confounding variables with an ASD > 0.10 will be adjusted for in all analyses.

Table 5. List of potential confounders

Demographics	Age
	Sex
	Race
Baseline characteristics	BMI
	ASA status
	Charlson score
	Smoking status
Comorbidity	Obstructive sleep apnea
	COPD
	Asthma
Intraoperative risk factors	Duration of surgery
	Total dose of muscle relaxants
	Intraoperative crystalloids
	Intraoperative blood products transfused

Primary analysis

Linear regression will be used to assess the effect of tidal volume (2 levels), PEEP (2 levels) and their interaction on the time-weighted average SaO_2/F_IO_2ratio during first postoperative hour in PACU, including propensity score weights and adjusting for unbalanced confounders as appropriate. If interaction effect is not significant (P>0.10), treatment effect estimates will be summarized using mean difference comparing tidal volume of 10 vs. 8 and PEEP of 8 vs. 5. If interaction is significant, the effects of each intervention will be assessed within levels of the other intervention. Moreover, we will use time-weighted average SaO_2/F_IO_2 value as outcomes and assess the effect of ventilation on it as a sensitivity analysis. With an overall alpha of 0.05 for the primary analysis, the significance criterion will be 0.25 for each treatment effect without significant interaction (i.e. 0.05/2, Bonferroni correction) before adjusting for interim analysis.

Secondary analysis

We will use logistic regression model to assess the effect of tidal volume level, PEEP level and their interaction on the binary outcome of postoperative pulmonary complication. The effect on the lowest SaO_2/F_IO_2 at ward will be assessed using linear regression. Finally, we will evaluate the length of hospital stay using a Cox proportional hazard regression model. The length of stay will be analyzed as time from operation to live discharge from hospital, where patients who died before hospital discharge will be considered as never having the event and will be assigned a censoring time using the observed longest duration among those discharged alive.

Interim analyses

At each quarter of the maximum enrollment, we will conduct an interim analysis to assess for efficacy and futility of tidal volume and PEEP and SaO_2/F_IO_2. The interim analysis will use the gamma spending function with parameters -4 for alpha (efficacy) and -1 for beta (futility). Boundaries for efficacy (futility in parentheses) at each stage are P<0.0008 (P>0.9056), P<0.0024 (P>0.4969), P<0.0072 (P>0.1249), and P<0.0215 (P>0.0215), respectively.

Sample size estimation

Based on literature and a preliminary query of PHDS database and Epic EMR system, we assume that the mean TWA SaO_2/F_IO_2 is 330 with a standard deviation of 100. After accounting for 3 interim analyses and 1 final analysis, a maximum N=2,500 in total patients (i.e., 625 for each of the 4 groups for assessing each main effect) will be needed to have 90% power at the 0.025 significance level to detect main effects of 15 or more in PaO_2/F_IO_2 for tidal volume and PEEP (high versus low).

The table below provides the probability of stopping the study for possible true underlying treatment effects: Null (no effect), Alternative (20 increase in SaO_2/F_IO_2), half-way between the null and alternative, and 1.5 times the alternative effect. For example, if the alternative hypothesis were true, the cumulative probability of crossing either efficacy or futility boundary at the 1^{st}, 2^{nd}, 3^{rd} and 4^{th} looks would be 0.086, 0.392, 0.778 and 1 respectively.

Table 1. Expected Cumulative Stopping Probabilities.

Effect	Expected Stopping Stage	Stopping Probabilities			
		Stage 1	Stage 2	Stage 3	Stage 4
Null	2.47	0.095	0.538	0.898	1.000
½ Null, Alt	2.96	0.069	0.315	0.652	1.000
Alternative	2.74	0.086	0.392	0.778	1.000
Alt X 1.5	1.89	0.295	0.830	0.987	1.000

Human Subjects

The project we propose is primarily for research and cost reduction, although the results may be interesting enough to publish. Specifically, we seek to determine which combination of tidal volume and PEEP should be specified in the enhanced recovery pathway being developed for orthopedic surgical patients.

We will use a non-randomized alternating treatment design in which various tidal volumes and PEEP levels will be used for successive weeks in a designated physically distinct surgical unit. The two tidal volumes and two PEEP levels we propose to use are generally thought to be safe in perioperative use, and are well within the range of current practice at the Clinic. The protocol includes safeguards to prevent excessive peak airway pressure and assure adequate ventilation. *Importantly, clinicians will be free to provide whatever ventilation they believe might be necessary in individual patients*. An Information Sheet will be used as alternative to written consent.

Significance

Postoperative pulmonary complications are common, occurring in about 5% of surgical patients. Pulmonary complications increase morbidity, mortality, length of hospital stay, and healthcare costs. Because so many orthopedic surgeries are performed at the Cleveland Clinic, reducing PACU time and pulmonary complications will improve clinical outcomes and reduce healthcare costs. Our research project will provide strong clinical evidence for selecting an optimal ventilation strategy for an enhanced care pathway in patients having elective orthopedic surgeries with mechanical ventilation.

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