Study protocol

Impact of COVID on patterns and predictors of lung protective ventilation in a large Canadian health authority

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This protocol has been compiled in accordance with sections 6.1 and 6.2 of the Guidance notes for new applications for ethical review by the Fraser Health research ethics board

1. Introduction and background

Postoperative pulmonary complications (PPCs) affect 5 to 33% of patients undergoing non-cardiothoracic surgery, and are a major cause of postoperative morbidity and mortality (1-4). PPCs include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, aspiration pneumonitis, and acute respiratory distress syndrome (ARDS) (5). In addition, patients who develop PPCs have more admissions to the intensive care unit (ICU), an increased length of hospital stay (LOS), and increased 30-day mortality rate of up to 20%[1]. One proven method of reducing PCC's is to use intraoperative lung protective ventilation (LPV), with a number needed to treat of 24 for post-operative pneumonia and 38 for post-operative ventilatory support in a Cochrane systematic review including over 1000 patients (6). LPV comprises using a tidal volume of 6-8 mL/kg ideal body weight (IBW) and positive end-expiratory pressure (PEEP) of 5 cm H_2O for initial ventilator settings (7).

For the past two decades, adoption of a similar strategy of ventilation in the intensive care unit for patients with acute respiratory distress syndrome have yielded decreased mortality (8-10). However, uptake of LPV usage in the operating room has been slower, with less than 50% compliance (11, 12). Factors that influence compliance in some centers include extremes of patient IBW, unoptimized default ventilator settings, and clinician misconceptions surrounding LPV guidelines (12-14). While adherence to LPV was higher for COVID positive patients during the start of the COVID pandemic with evidence for lower mortality in the intensive care unit (15, 16), it is unknown whether an increase in overall LPV compliance occurred outside of COVID positive patients, and if so, whether such a shift in practice was sustained. In addition, most studies querying LPV compliance occurred in centers outside of Canada (12-14), with differences in medical education and practice patterns compared to Canadian centers. To fill these gaps in the literature, we therefore aim to explore patterns of LPV compliance in a large Canadian health authority in a retrospective manner, and to elucidate predictors influencing LPV compliance. We will also explore trends of LPV compliance throughout the COVID pandemic, into the post-pandemic era.

2. Purpose and Justification

The purpose of this study is to investigate patterns of LPV compliance, elucidate predictors of LPV compliance, and gauge the effects of COVID on LPV compliance in Fraser Health Authority. Although the use of nonprotective ventilation has decreased over time, a large proportion of patients continue to be ventilated with high tidal volumes and little PEEP(13, 17, 18). While the use of LPV strategies has been improved, patients that are short-stature, obese, or female have an increased tendency to be ventilated with larger tidal volumes in non-Canadian studies (11, 19). Contributing to this shortfall may be lack of patient height documentation as well as lack of awareness by providers regarding the significant impact of height (rather than patient weight) in determining LPV ventilation parameters. Compliance with LPV has been shown to be increased following implementing education about LPV, feedback regarding developmental performance, departmental LPV policies, and modification of default ventilator

settings (12, 14, 19). Therefore, identifying patterns and predictors of LPV compliance in a Canadian context through our study may help inform the design of educational efforts and systemic changes to tackle areas of deficiency.

3. Research question

Primary research question: In patients undergoing general anesthesia with an endotracheal tube for non-cardiac surgery, what is the compliance rate to LPV in Fraser Health Authority, and predictors of such compliance?

Secondary research questions: What are time trends and shifts in LPV compliance from the pre-COVID to the post-COVID era? Are these trends sustained into the "new normal" era?

4. Research objectives and hypothesis

The objectives for this study are to:

1. Identify rates of compliance with LPV guidelines in the Fraser Health Authority in the Province of British Columbia, Canada. Compliance with ventilation guidelines is defined as meeting two criteria. The first is that their average tidal volume is 6-8 mL/kg IBW and the second is that the average positive end expiratory pressure (PEEP) is at least 5 cm H2O. Patients ventilated according to one or neither of the above criteria will not be considered to have been ventilated according to the guidelines.
2. To elucidate predictors of compliance with LPV practice among providers. These predictors may help inform the design of educational efforts and systemic changes to tackle areas of deficiency.
3. To elucidate time trends and shifts in LPV compliance from the pre-COVID pandemic to post-pandemic era.
4. To evaluate whether time trends and shifts in LPV compliance through the pandemic are sustained.

The primary hypothesis is that not all patients will be ventilated according to the recommended LPV strategy. We further hypothesize that patient height will be a major predictor in determining compliance to LPV, as our clinical experience suggests that while IBW used to set tidal volumes is calculated based on height, many anesthesiologists set tidal volumes by actual weight rather than IBW. Therefore, this practice by may result in tidal volumes outside of a patient's acceptable tidal volume as would be recommended by LPV guidelines. Our other hypothesized predictors to LPV compliance include predictors that indicate respiratory dysfunction (e.g. severe COPD, CHF) or severe illness (American Society of Anesthesiologists [ASA] classification, sepsis), as anesthesiologists may be more cognizant of the need for LPV in these patients. Lastly, we hypothesize that the COVID pandemic will introduce a shift towards increased LPV compliance, but this shift may not be sustained in the post-pandemic era as precautions waned.

5. Methods

Study design

Our study is a retrospective cohort study investigating the correlation between hypothesized predictors of LPV compliance and actual LPV practice in a large multi-center health authority. The study population is all patients who underwent who underwent a general anesthetic for any procedure at a Fraser Health Authority hospital from January 2014 – December 2023. See Section 7 for more details regarding inclusion and exclusion criteria.

Sampling and sample description

We aim to use convenience sampling by including all patients who meet eligibility criteria. All procedures conducted under general anesthesia within the Fraser Health Authority with an endotracheal tube for over 30 minutes and within the date range specified that meet the inclusion criteria are eligible for inclusion in this study. This is a multicentre study and includes all hospitals within the Fraser Health Authority using Centricity Perioperative Anesthesia (CPA) system, which collects intraoperative data. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) is an outcomes-based program to measure and improve the quality of surgical care by tracking patient data preoperatively through 30-days postoperatively; NSQIP data will be used for perioperative variables such as comorbidities. . Procedures must be followed by NSQIP and currently within the CPA database to be included in our study (see inclusion and exclusion criteria). Based on historical data and the surgical volume contributing to the Fraser Health CPA system we expect there to be approximately 100,000 cases.

Inclusion and exclusion criteria

Inclusion criteria for this retrospective study include any patient that is over the age of 18 and underwent general anesthesia with endotracheal tube placement for a procedure lasting ≥30 minutes. Patients must be included in the NSQIP database and linked to their anesthetic dataset within CPA by either their name, date of birth, medical record number (MRN, i.e. RC number), Personal Health Number (PHN), and/or date of surgery. Exclusion criteria for this retrospective study include: any patient that underwent cardiac or thoracic surgery or received an anesthetic that did not utilize an endotracheal tube, ASA 6 (organ donor), Hyperthermic intraperitoneal chemotherapy, transplant cases, surgical procedure related to an occurrence or complication of prior procedure during the same admission/within 30 days, multiple National Surgical Quality Improvement Program (NSQIP) assessed cases within 30 days only for same patient, cases in CPA that are unable to be linked to NSQIP data or vice versa.

6. Data collection

Data sources

Predictors and demographic data: The American College of Surgeons National Surgical Quality Improvement Program is a validated, risk adjusted, outcome-based program that measures the

quality of surgical care internationally and in Canada. NSQIP data contains pre-operative, intra-operative and 30-day postoperative variables derived from operative reports, medical records and patient interviews to provide a comprehensive reflection of 30-day surgical outcomes. Data uses standard definitions and is provided in real-time to participating hospitals(20). The data extracted from this source are listed below (see *Data collection* section).

Intraoperative data: Centricity Perioperative Anesthesia (CPA), an Anesthesia Information Management System (AIMS), is an electronic record used by anesthesiologists to automate data capture from the operating room. Information is collected using physiologic monitoring devices and includes clinical interventions such as placement of intraoperative monitors, derived measurements and pharmacologic interventions. The data obtained is automatically collected, reliable and can be stored and subsequently used for analysis, typically for quality assurance and research purposes. CPA at our institution includes only the basic component of an automated anesthesia record, rather than information from the pre-operative, post-operative and ancillary areas in the hospital available at other centers. Therefore, to obtain these data, data obtained from CPA must be linked to patients' NSQIP data using with their name, date of birth, medical record number (MRN, i.e. RC number), Personal Health Number (PHN), and/or date of surgery.

Data collection procedures

This is a retrospective study sampling data from all patients who underwent general anesthesia for non-cardiac surgery at a Fraser Health Authority institution from January 2014 – December 2023 meeting our inclusion criteria. This dataset includes clinical and administrative data from all hospitals within the Fraser Health medical system using CPA. There will be no prospective recruitment or sampling of patients, and thus a waiver of consent will not be requested in accordance with article 3.7A of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Predictors and demographic data: Data will be obtained from the NSQIP database include patient characteristics such as age, medical record number, sex, age, weight, height, procedure, inpatient status, hospital where procedure occurred, elective surgery status, principal anesthesia technique, surgical specialty, attending staff surgeon, diabetes mellitus, current smoker within 1 year, dyspnea, functional heath status, ventilator dependent, history of severe chronic obstructive pulmonary disease (COPD), ascites w/in 30 days prior to surgery, congestive heart failure within 30 days prior to surgery, hypertension requiring medication, acute renal failure, currently requiring or on dialysis, disseminated cancer, open wound with or without infection, steroid/immunosuppressant use for chronic condition, >10% loss of body weight in the 6 months prior to surgery, bleeding disorder, preoperative transfusions (packed red blood cells within 72 hrs prior to surgery start time), sepsis (SIRS/sepsis/septic shock within 48h postoperatively), emergency case, duration of surgical procedure (in minutes), ASA classification, postoperative pneumonia, postoperative unplanned intubation, postoperative ventilation > 48 hours, intraoperative or postoperative transfusion, death within 30 days of the procedure, and hospital length of stay from surgery to discharge. Preoperative bloodwork values include serum sodium, serum sodium date, BUN, BUN date, serum creatinine, serum creatinine date, albumin, albumin date, total bilirubin, total bilirubin date, AST/SGOT, AST/SGOT date, alkaline phosphatase, alkaline phosphatase date, WBC, WBC date, hematocrit, hematocrit date, platelet count, platelet

count date, INR, INR date, PTT, PTT date. Post-operative complications will also be obtained from the NSQIP database. These include respiratory complications (pneumonia, re-intubation, ventilator use present either before or after surgery) and if the patient died within 30 days post-operatively.

Physiologic and therapy data: Data obtained from the CPA data warehouse will include all data from the anesthesia monitor (e.g., heart rate, oxygen saturation, and MAP) and ventilator (e.g.: tidal volume, end tidal carbon dioxide (EtCO2), and end tidal inhalational gas concentrations) as well as any data entered manually (medications, procedures). The primary variables of interest include respiratory rate, set and exhaled tidal volume, peak pressure, PEEP, non-invasive and invasive blood pressures including systolic, diastolic and mean arterial pressures, heart rate, inspired oxygen, oxygen saturation, and end-tidal CO2 and volatile gas measurements. All data will be extracted as averages during "total surgical monitoring time" (see Appendix for details). FiO2 values will be restricted to values between 21-100% and SpO2 values will be restricted to values between 70-100% prior to calculating averages. PEEP data will be limited to values between 0-15 mmHg. If data is missing at a given timestamp it will be excluded from the analysis. Measured average tidal volume will be compared to LPV tidal volume based on IBW as calculated by the patient's height. Patients will be deemed to have been ventilated according to a lung protective strategy if their average tidal volume was 6-8 mL/kg IBW and their average PEEP throughout the case was as least 5 cm H2O. Date of surgery will also be extracted to facilitate plotting of the Shewhart chart, and determination of pre-COVID/COVID era status (see section 7 Statistical Plan). Time of surgery start will be extracted to determination of night/weekend shift status.

Measures

Baseline demographics for all study patients include age, sex, height, weight, smoking status in the last year, and ASA classification. Data relating to the surgery includes the date of surgery, hospital admission date, hospital discharge date, if the surgery was elective or emergency, a common procedural code used to identify the type of surgery, and duration of the procedure.

To determine "compliance to LPV", the response variable of our prediction model, tidal volume per unit of body weight in kilograms will be calculated and compared to the guidelines. Average PEEP will be calculated in cm H2O and compared to the guidelines. The average tidal volume will be calculated in mL throughout each case. IBWs will be calculated using height according to the Devine formula[29]:

Ideal body weight (IBW) (men) = 50 kg + 2.3 kg x (height (inches) – 60)
Ideal body weight (IBW) (women) = 45.5 kg + 2.3 kg x (height (inches) – 60)

7. Statistical plan

Software

Microsoft Excel (Microsoft Corporation, Redmond, WA), R Console (R Foundation for Statistical Computing, Vienna, Austria), Anaconda Navigator Distribution (python), and SAS Base 9.4 statistical analysis software will be used for analysis.

Part I: Patterns of compliance to LPV and relationship with default ventilator settings

- Descriptive statistics for proportion compliance to LPV will be calculated for the entire dataset
- Among the non-compliance cases, the % attributable to the following will be calculated. This analysis is useful for determining areas of intervention/education required:
    - Low PEEP
    - Inappropriate (both too high or too low) tidal volume
    - Too low tidal volume
    - Too high tidal volume
    - Both low PEEP and inappropriate tidal volume
- Using the entire data set, for tidal volumes from 400-600mL, we will plot the % of patients in whom that tidal volume satisfies LPV criteria. This will inform any required change to the default tidal volume ventilator setting to maximize the number of patients satisfying LPV criteria if the tidal volume setting were left unchanged.
- We will model improvements in LPV compliance if the default PEEP setting on anesthesia machines were changed from PEEP = off to PEEP = 5.

Part II: Investigation of time trends to compliance

A Shewhart control chart (p chart) of LPV compliance each month will be presented to investigate time trends of LPV compliance as correlated to the COVID pandemic, and to identify special-cause variation in LPV compliance throughout the pandemic. The following rules to look for trends and shifts will be employed (5):

- 1 point is outside the control limits.
- 2 out of 3 consecutive points are more than 2 sigmas from the center line in the same direction.
- 4 out of 5 consecutive points are more than 1 sigma from the center line in the same direction.
- 8/9 points on the same size of the center line.
- 6 consecutive points are steadily increasing or decreasing.
- 14 consecutive points are alternating up and down.
- 15 consecutive points are within 1 sigma of the center line.
- 8 consecutive points on either side of the center line with not within 1 sigma.

Part III: Predictors of compliance to LPV

- Our list of hypothesized predictors to LPV use include:
    - Age
    - sex
    - height
    - obesity (body mass index > 30)
    - elective/emergency
    - ASA Class
    - sepsis
    - functional health status
    - anesthesia duration
    - dyspnea
    - severe COPD
    - CHF
    - smoker
    - surgical specialty
    - ventilatory dependent
    - Pre-COVID era vs. COVID era
    - Night or weekend shift (1)
    - Hospital site
    - Use of neuromuscular blockade
    - Presence of epidural anesthesia
    - Inpatient vs. outpatients
    - Laparoscopic surgery
    - Transfusion of blood products
    - Dialysis
    - Ascites
    - NB: We considered before January 2020 as the pre-COVID era, and after June 2020 as the COVID era. The former cutoff was chosen as January 2020 contained the first COVID case in BC. The latter cutoff was chosen as it constitutes three months after March 2020, when the World Health Organization announced COVID's pandemic status, and BC announced a state of emergency with the start of isolation policies. We hypothesized that any impact of the COVID pandemic on LPV compliance patterns would unlikely to have occurred prior COVID's arrival in BC, but would likely be in full swing three months after initiation of widespread social isolation, a very palpable event in society.
    - NB2: parameters such as oxygen saturation, end-tidal carbon dioxide, and peak inspiratory pressures may be affected by use of LPV, and therefore will not be included as candidate predictors due to high likelihood of reverse causation (2). Mode of ventilation has been shown to correlate with LPV compliance(2), but this is unfortunately not recorded in our dataset.
- To screen for inclusion in the multivariate logistic regression model, the association of each hypothesized predictor to LPV use will be first explored using bivariate analyses.

Chi squared test will be used for categorical hypothesized predictors (or Fisher's exact test if a covariate pattern results in < 5 cases). Bivariate logistic regression (including only the predictor and LPV) will be used for continuous hypothesized predictors.

- We will use a multivariate logistic regression model to determine the independent predictors of LPV use. Predictors with a $p < 0.2$ in the bivariate analysis will be incorporated into model construction. A conservatively high cut-off for the p-value was chosen to minimize type II error (exclusion of a predictor that would have become significant if adjusted for other predictors in the multivariate model). For the same reason, we will not adjust the p-value for multiple comparisons during the predictor screening phase.
- For face validity, we will include age, sex, height, obesity status, night or weekend shift, hospital site, laparoscopic surgery, and pre-COVID era vs. COVID era in the model regardless of bivariate analysis results.
- We will add candidate predictors that passed the bivariate phase in a forward selection method, minimizing the Akaike Information Criterion (3), which rewards improved goodness of fit while simultaneously penalizes over-fitting.
- Pairwise interaction among included terms will be investigated via adding an interaction term for each pair, and comparing the model with and without the interaction term via a likelihood ratio test. A $p < 0.05$ will result in inclusion of that interaction term. As before, to minimize type II error, the p value will not be adjusted for multiple comparison at this stage.
- Finally, the odds ratio of each predictor for LPV use in the final model will be presented with and without Bon Ferroni adjustment for multiple comparisons. A separate result will be presented for interactions, if any are detected.

Sensitivity analyses, subgroup analyses, and other supplemental analyses

- Part I: none planned
- Part II:
    - Subgroup analysis for: academic hospital sites, laparoscopic surgery.
    - Subgroup analysis for patients who would not have met LPV criteria if ventilated by default ventilator settings for tidal volume. This analysis explores whether clinicians became more likely to adjust the ventilator settings intentionally to achieve LPV.
- Part III:
    - We will adjust the date cut-offs for pre-COVID era vs. COVID era based on Shewhart chart results of Part II (i.e. the dates that the Shewhart chart indicated shifts in practice pattern)
    - Subgroup analysis for academic hospital sites only.

8. Ethical considerations

This data set includes clinical and administrative data from all hospitals within the Fraser Health medical system using CPA. There will be no prospective recruitment or sampling of patients, and thus a waiver of consent will not be requested in accordance with article 3.7A of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

9. Data management plan

Access to medical records (A.2)

CPA is an AIMS database within FHA that stores details on intra-operative patient management. CPA is accessed through a dedicated subset of database views stored in a Microsoft SQL Server 2012 controlled by the Fraser Health Authority. After REB approval, this data will be queried by Dr. Perseus Missirlis and data analysts within FHA.

Type of data to be collected (A.3)

From CPA, all data for patients that have undergone surgical procedures will be accessed. Data describing the previously mentioned monitoring data will be collected. All relevant NSQIP variables (as described above) will be collected. Due to the size of the data, NSQIP data may be provided as a database flat file. Only data linked to CPA based on the inclusion and exclusion criteria of this study this file will be used for the analysis and the flat file will be destroyed after data linking has occurred.

Number of records required (A.4)

All records will be included that meet the inclusion criteria in Section 7. We expect this to be approximately 100,000 cases.

Personal information (A.5)

The following identifiable information will be required during data collection and/or analysis:

CPA database: MRN, PHN, sex, date of birth, date and time of surgery.

NSQIP: MRN, PHN, age at time of surgery, sex, date of birth, date and time of surgery

Risks associated with disclosure of data (A.7)

Disclosure may expose patients and their families to risk of identifying them as having undergone a general anesthetic and surgery at an FHA hospital.

Protecting identity of participants (A.8)

For analysis, patients will be identified using a unique study code (see below). Study data for analysis will be password protected and kept on M: drive in the FHA corporate intranet. Additionally, de-identified data will only be transferred using the Fraser Health secure file sharing tool 'Cerberus'.

Unique Study Code

Participating patients will be assigned a random number once variables of interest have been collected and linked between the 2 datasets.

UBC REBs require the use of a unique study code not derived from or related to the information about the individual i.e. name, SIN, PHN, hospital number, DOB, or unique characteristic.

Access to study data (A.9)

Only Dr. Perseus Missirlis and Fraser Health data analysts will have access to the key and raw data, which will be kept on password-protected file on an FHA computer. The data linking will be performed with the assistance of an FHA data analyst on an FHA corporate computer. Other investigators and the FHA statistician will only have access to the data file (on FHA or Cerberus secure drives), once it has been stripped of all identifying information for the purposes of statistical analysis and manuscript preparation.

Data storage (A.10)

Study documents containing identifiable information will be stored as files that are both password protected and encrypted on the principal investigator's corporate FHA account. De-identified information for the purposes of statistical analysis and manuscript preparation will be stored in FHA encrypted network drives.

Confidentiality and security (A.11)

Original files, which contain identifiers, will be password protected on an FHA computer only accessible by the principal investigator. Access to the de-identified data file will be limited to the research team by their FHA log-in credentials.

End of study procedures (A.12)

Research data will be kept for 5 years post-publication as outlined in the UBC study data retention guidelines. Any data required to be submitted along with a manuscript as a requirement for publication in a peer-reviewed scientific journal will be de-identified as per the de-identification protocol outlined above.

Once the project's data has reached its effective lifespan, hard copies will be securely destroyed using the on-site FHA approved secure document shredding service, while digital data will be deleted and wiped from the servers as per standard 85 of the UBC information security policy.

Data Transfer (A.13)

No data transfer anticipated outside of Fraser Health and UBC or its affiliated hospitals is planned.

Data Linkage (A.14)

Data linking and anonymization: Data linking between the NSQIP database and the CPA database will be done utilizing a similar technique used in a recently REB-approved study (H18-03578). In brief, the patients will be matched with their name, date of birth, medical record number (MRN, i.e. RC number), Personal Health Number (PHN), and/or date of surgery. This will be performed by the principal investigator or a Fraser Health data analyst on a corporate Fraser Health computer only. Date of surgery, PHN, medical record number, sex, date of birth and date of surgery may be confirmed internally with data from the Fraser Health Authority Meditech or Surgical Information Systems to reconcile data linkage errors between CPA and NSQIP. Once linked, each record's identifying information (name, date of birth, MRN, PHN, date of surgery) will be deleted from the research dataset.

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11. Appendix

Total surgical monitoring time – defined as:

1. Duration between **'Surgical Incision'** and **'Surgery End'** event texts (annotated by anesthesiologist in CPA) if:
    a. both event texts were logged
    b. duration between these 2 event texts is > 10 minutes (this is to omit those cases where anesthesiologist forgot to change the observed time when logging the events)
    c. surgical incision time in CPA is within 15 min of Meditech surgery start time
2. If the above conditions are not met, then data will be extracted based on volatile anesthetic gas thresholds as surrogate start and end times for surgery. Data is extracted once the end tidal volatile gas % exceeds and then drop below the 0.3 MAC threshold of a 40 year old[30]:
    a. End-tidal sevoflurane % >= 0.5
    b. End-tidal desflurane % >= 2.0
    c. End-tidal isoflurane % >= 0.35