Title

An observational study to determine the feasibility and validity of esophageal and transpulmonary pressure measurements during one-lung ventilation

Specific aim

- To investigate feasibility and validity of measurements of esophageal and transpulmonary pressure in patients undergoing one-lung ventilation

Background and rationale

Postoperative pulmonary complications (PPC) increase hospitalization, mortality and health care costs.[1] Improved patient outcome with avoidance of high tidal volumes and application of positive end-expiratory pressure (PEEP)[2,3] indicate that intraoperative lung injury through mechanical stress or atelectasis greatly contributes to the development of PPC.

PPC occur in up to 30% of patients undergoing non-cardiac intrathoracic surgery with one-lung ventilation (OLV).[4] During OLV, the ventilated single lung is vulnerable to mechanical stress due to a decrease in total lung volume, and limitation of inspiratory pressure can reduce PPC.[5] Ventilation guided by transpulmonary pressure (P_L), which is defined as the difference between intra-alveolar and intrapleural pressure, facilitates assessment and further limitation of mechanical stress, as well as adjustment of adequate PEEP to avoid atelectasis.[6,7] In the clinical setting, intra-alveolar pressure can be determined from airway pressure at end-inspiratory or end-expiratory hold, while intrapleural pressure is estimated from esophageal pressure (P_{es}).

Previous investigations have described postural changes in P_L and P_{es} when switching from the standing to supine and lateral position in spontaneously breathing patients.[8,9] These investigations proposed corrections for P_{es} measurements due to the weight of the mediastinum in relationship to the esophageal catheter.[9] It remains unclear how lateral positioning with OLV, e.g. during intrathoracic surgery, affect measurements of P_{es}. Furthermore, it is unclear to what extend P_{es} reflects intrapleural pressure within the dependent part of the single ventilated lung, which is vulnerable to atelectasis and might therefore benefit from P_L-guided PEEP titration.

In this study, we aim to describe the changes in P_{es} and P_L associated with OLV and lateral positioning. Additionally, we aim to estimate adjustments accounting for 1. differences in P_{es} in lateral position between two-lung and one-lung ventilation and 2. the difference between P_{es} and intrapleural pressure of the dependent lung areas of the single ventilated lung

Measurements

Measurement of esophageal pressure

P_{es} will be measured using an orogastric tube equipped with an additional balloon catheter (AVEA Ventilator Nasogastric Pressure Monitoring Tube Set; CareFusion, USA*).* In brief, the catheter is placed after induction of anesthesia with the balloon at 40 cm from the mouth in the patients esophagus. Positioning is confirmed and adjusted by observation of cardiac artefacts in the esophageal pressure curve and by artefacts caused by compression of the patient's thorax. Airway and P_{es} waveforms will be recorded and stored on a dedicated laptop computer.

Measurements of airway opening / closing pressure

- *Electrical Impedance Tomography*

Lung aeration will be assessed using Electrical Impedance Tomography (EIT) (*ENLIGHT 1800, Timpel, Sao Paolo, Brazil*). In brief, a 16-electrode silicone belt is equipped around the patient's thorax at the level of the 5th intercostal space. Closing pressure of dependent lung areas will be estimated during a static, decremental PEEP trial with continuous EIT recording[10]: patients will be ventilated in volume-controlled mode as to institutional standard (typically 6ml/kg PBW). After positioning of the patient in the lateral position and initiation of OLV within clinical routine, a recruitment maneuver using CPAP of 40 cm H2O for 30 seconds will be conducted. Volume-controlled ventilation will then be resumed, and PEEP will be decreased from 20 to 0 cm H2O by steps of 3 cm H2O every 2-3 min. Corresponding P_{es} waves and airway pressures will be continuously recorded during the trial. End-expiratory closing pressure of dependent lung areas will be defined as the PEEP at which lung collapse occurs, which will be determined by visualization of EIT images during the trial, and ultimately by a decrease in localized aeration and localized compliance ("pixel compliance") through post-hoc analyses of the stored EIT recordings.[11,12]

Assuming that P_L at lung collapse of the dependent lung areas approaches zero and end-expiratory P_L can be calculated as P_L=PEEP-P_{PL}, P_{PL} at lung collapse of the dependent lung should be equal to the PEEP at lung collapse.

The decision to conduct the PEEP trial will be at the discretion of the attending anesthesiologist. An inspiratory plateau airway pressure higher than 60 cm H2O, a reduction of SpO2 below 85%,

a mean arterial pressure lower than 60 mmHg, or a sudden change in cardiac rhythm will be used as criteria for interrupting the decremental PEEP titration maneuver.

- *Pressure-volume curves*

Airway opening pressure will be estimated from the lower inflection point, derived from routinely measured pressure-volume curves.[13–15]

Determination of corrections for P_{es}-derived PL during OLV and lateral positioning

1. *Adjustment for esophageal pressure differences between two and one-lung ventilation in the lateral position*

Due to the position of the esophagus in relation to surrounding structures of the mediastinum, esophageal pressure measurements depend on patient positioning. When changing from the standing to the supine position, postural artifacts need to be accounted for. For example, the weight of the heart increases esophageal pressure by about 5 cmH2O.[9] Since it is unknown to which extend OLV exerts changes in esophageal pressure, we will calculate differences in esophageal pressure in the lateral position between two- and one-lung ventilation.

2. *Adjustment for differences between esophageal and intrapleural pressure of the dependent lung areas during one-lung ventilation in the lateral position.*

In the lateral position with OLV, esophageal pressure is expected to reflect intrapleural pressure of the upper (i.e. non-dependent) areas of the ventilated lung, comparable to ventral areas in the supine position. However, the lower (i.e. dependent) areas of the ventilated lung are expected to be subject to atelectasis formation (comparable to the dorsal areas in the supine position) and might benefit the most from P_L-guided PEEP titration. Thus, we will assess the esophageal pressure at which lung collapse of the dependent lung areas occurs (see above).

The *correction factor* c for the esophageal pressure-derived intrapleural pressure will be calculated as the difference in airway pressure at lung collapse (i.e. closing pressure, defined either as the PEEP derived from EIT-guided PEEP trial, or the pressure at the lower inflection point from pressure-volume curves) and the corresponding esophageal pressure P_{es}: $c = P_{closing} - P_{es,}$ which equals the P_{es}- derived P_L at lung collapse.

Study protocol

Figure 1 provides an overview of study procedures (see below). Patients will be equipped with the EIT belt before induction of anesthesia, and a one-minute EIT recording during spontaneous breathing will be conducted. Anesthesia will be induced as to institutional standards and upon the discretion of the attending anesthesiologist. Typically, propofol (2 mg/kg), fentanyl (0.5-1.5 yg/kg) and rocuronium (0.6 mg/kg) are used and the double-lumen endotracheal tube will be placed with endoscopic verification of the correct positioning. Then, an orogastric tube will be passed, as is routinely done for these procedures. For this study, the orogastric tube will contain an additional esophageal balloon.

After placement of the catheter, esophageal pressure, transpulmonary pressure and closing pressure from pressure-volume curves will be assessed ("*baseline*"). Subsequently, the patient is positioned in the lateral position and a second measurement series is conducted ("*lateral*"). OLV will then be initiated and a third measurement ("*OLV*") is made. During this measurement, EIT-guided assessment of closing pressure during a decremental PEEP trial will be conducted, as described above. Constant and adequate muscle paralysis throughout the measurements will be confirmed through quantitative neuromuscular monitoring. After completion of the third measurement, the EIT belt is opened and removed from the surgical field to avoid interference. Finally, when surgery is finished, before reversal of neuromuscular blockade and extubation, two-lung-ventilation will be re-established, a recruitment maneuver will be conducted and the patient will be repositioned in the supine position. Finally, a final measurement is conducted.

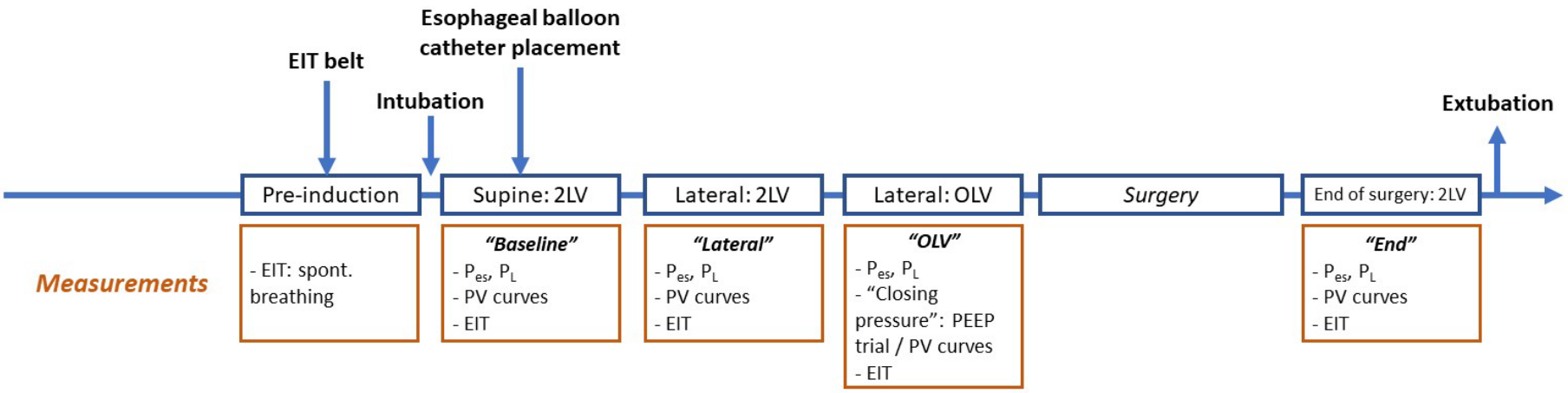

Figure 1 Study diagram. 2LV: Two-lung ventilation; OLV: One-lung ventilation; EIT: Electrical Impedance Tomography; Pes: Esophageal pressure; PL: Transpulmonary pressure; PV curve: pressure-volume curve

Study subjects

We will include adult patients undergoing non-cardiac, intrathoracic surgery with general anesthesia and one-lung ventilation. Exclusion criteria will be the

- Inability to give written informed consent
- Pregnancy
- Structural lung disease, COPD, active Asthma
- Active respiratory infections
- Prior lung resection
- Prior esophageal or gastric surgery
- Esophageal varices
- Patients under effective anticoagulation
- Pacemaker or internal cardioverter/defibrillator (ICD)

Statistical analysis and sample size estimation

The primary hypothesis will be that esophageal pressure changes from the supine to the lateral position, and from the lateral position to one-lung ventilation. The co-primary hypothesis will be that in lateral position with OLV, there is a difference ("correction factor") between PL derived from esophageal pressure and the closing pressure of the dependent lung areas. Our secondary hypothesis will be that the "correction factor" differs depending on whether the right or left lung is down and subject to OLV due to anatomical differences (e.g. positioning of the heart). Comparison of esophageal pressure between *baseline, lateral* and *OLV* will be made using repeated measures ANOVA (Sidak post-hoc test). Comparison to the "Post" measurement will only be made within an exploratory analysis to avoid alpha inflation due to multiple comparisons. All calculations will be made with alpha set to 0.05.

In a previous investigations in patients undergoing general anesthesia with mechanical ventilation, we found esophageal pressure to be 16.2 ±3.8 cmH2O after intubation in the supine position. We consider a 20% change in esophageal pressure when changing from the supine to the lateral position to be relevant. Therefore, we would need 8 patients to achieve a 90% power for detecting this difference (paired t-test, alpha 0.05). To adjust for multiple comparison (supine to lateral to OLV), we plan to include ***25 patients*** (3*8 + 1 patient to account for failed measurements) into this study.

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