Titration of intraoperative positive end-expiratory pressure to optimize gas exchange in patients undergoing robotic-assisted laparoscopic prostatectomy

Project summary

Optimal intraoperative positive end expiratory pressure (PEEP) improves patient outcomes. The pulse-oximetry has been used to determine the lung opening and closing pressures. We hypothesize that optimal PEEP can be obtained by titration of intraoperative PEEP level and FiO_2 with guide of SpO_2. Our secondary hypothesis is that maintenance of intraoperative optimal PEEP improves intraoperative oxygenation and reduces incidences of postoperative hypoxemia. We tested our hypothesis in patients undergoing robotic-assisted laparoscopic prostatectomy.

Forty-six males undergoing elective robotic assisted laparoscopic prostatectomy were randomly assigned to either optimal PEEP (Group O, n=23) or control with fixed PEEP of 5 cmH2O (Group C, n=23). Optimal PEEP, defined as the PEEP with lowest FiO2 or 0.21 to maintain SpO2≥ 95%, was obtained in both groups after placing the patients in Trendelenburg position and peritoneal insufflation. Patients in Group O maintained the optimal PEEP and in Group C maintained PEEP of 5cmH2O intraoperatively. Both groups were extubated in a sitting position once the extubation criteria met. The primary outcome was the partial arterial oxygen pressure (PaO2)/inspiratory oxygen fraction (FiO2) prior to extubation. Secondary outcome was the incidence of postoperative hypoxemia (SpO2 < 92% on room-air after extubation) in post-operative care unit.

General information

Protocol title: Titration of intraoperative positive end-expiratory pressure to optimize gas exchange in patients undergoing robotic-assisted laparoscopic prostatectomy

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Rationale & background information

Optimal intraoperative positive end expiratory pressure (PEEP) has been demonstrated to improve patient outcomes[1, 2]. However, the optimal PEEP is not only very different among individuals, but individual's optimal PEEP is affected by positioning, muscle paralysis, and several other factors[3, 4]. The common application of a fixed PEEP often leads to either lung overinflation or atelectasis. Therefore, optimal PEEP should be individualized and adjusted dynamically according to patients' needs[5]. Several techniques have been used to determine the optimal PEEP[6-10]. For example, electrical impedance tomography (EIT) can be performed at the bedside[5, 11, 12].

However, the application of this technique requires special training, increases the workload of the care team, and the cost-efficiency of this procedure remains to be determined. Chest CT is the gold standard technique for the assessment of lung inflation [13]. However, it is not feasible for use at the bedside, it exposes patients to X-rays, and its cost-effectiveness is not favorable. Transpulmonary pressure is another alternative that can be used at the bedside and is potentially cost-effective[14]. However, it requires special training and additional equipment in order to measure transpulmonary pressure. Development of new methods which can be used intraoperatively, cost-effective and user-friendly is an urgent demand.

Recently, Ferrando et al. reported that optimal PEEP can be obtained via titration of PEEP by administering a minimal fraction of inspiratory oxygen (FiO2) with the guidance of pulse oximetry (SpO2) and measurements of transpulmonary pressure in anesthetized patients[15]. We hypothesized that optimal PEEP could be obtained by titration of intraoperative PEEP levels and FiO2 with SpO2 guidance. Our secondary hypothesis was that maintenance of intraoperative optimal PEEP derived via this method improves intraoperative oxygenation and reduces the incidence of postoperative hypoxemia. We tested our hypothesis in patients undergoing robotic-assisted laparoscopic prostatectomy (RALP).

Study goals and objectives

Goals: To determine the optimal intraoperative PEEP in patients undergoing robotic-assisted laparoscopic prostatectomy by titration of intraoperative PEEP level and FiO2 with guide of SpO2 and determine the effect of optimal intra-operative PEEP on intraoperative and post-operative oxygenation.

Outcome:

Primary outcome: the partial arterial oxygen pressure (PaO2)/inspiratory oxygen fraction (FiO2) prior to extubation.

Secondary outcome: the incidence of postoperative hypoxemia (SpO2 < 92% on room-air after extubation) in post-operative care unit.

Study design

Type: a single center, randomized clinical study.

Inclusion and exclusion criteria: adult patients aged 18 years or older who were scheduled for elective robotic-assisted laparoscopic prostatectomy under general anaesthesia and who presented with ASA physical status of I-III were recruited for this study. Patients with acute or chronic respiratory disorders, including chronic obstructive pulmonary disease (COPD), asthma, pulmonary hypertension, neuromuscular disease, and/or preoperative SpO2<95% on room air were excluded.

Methodology

After tracheal intubation, mechanical ventilation was conducted with pressure-regulated volume-controlled ventilation using an operating room ventilator (Flow-I, Maquet Inc., Heidelberg, Germany). The ventilation was set at a tidal volume 6 mL kg-1, was initiated with an FiO2 of 1.0 to 0.21, a PEEP of 18 cmH2O, and a respiratory rate of 12-15 beats min-1 in order to keep the end-tidal CO2 partial pressure between 35-45 mmHg. After placement in the Trendelenburg position and peritoneal insufflation, all patients received the first recruitment maneuver (RM1) of 40 cmH2O for 15 seconds followed by PEEP at 18 cmH2O, similar to a previous study demonstrating that the maximal optimal PEEP was not greater than 18 cmH2O3. If the peak inspiratory pressure was >40 cmH2O at a PEEP of 18 cmH2O, the participant's study would be terminated. The target SpO2 was 95-96%.

The PEEP titration process is shown in Supplementary Fig.1. If the SpO2 was at 95-96% with a FiO2 of 0.21 and a PEEP of 18 cmH2O, the optimal PEEP was 18 cmH2O; this was kept constant throughout the procedure until extubation. If the SpO2 was greater than 96%, the PEEP was reduced by 2 cmH2O step-wise, with each step lasting for 5 min until SpO2 dropped below 95%. Then, PEEP was increased up to 18 cmH2O in reverse order in the same stepwise manner until the intended SpO2 was reached and remained at a steady saturation of 95-96%. At a PEEP of 18 cmH2O, if the SpO2 was lower than 95%, the FiO2 was incrementally increased by 0.05 per step; each step lasted for 5 minutes in order to achieve an SpO2 of 95-96%. If PEEP was increased to 18 cmH2O and FiO2 was measured at 1.0 (while the SpO2 remained lower than 95%), the study was terminated. The PEEP level at the minimal FiO2 necessary to maintain a SpO2 of 95-96% was considered the optimal PEEP. Once the optimal PEEP was achieved, patients randomized to Group C received a PEEP of 5 cmH2O intraoperatively or were maintained within Group O, thus maintaining optimal PEEP until extubation. Patients in both groups were extubated in the post anaesthesia care unit (PACU) in the sitting position once they met the criteria for extubation according to the judgment of their medical care team.

For both groups, intraoperative pulmonary dynamic compliance (Cdyn), PEEP, FiO2 (i.e., real-time FiO2 obtained from the gas analyzer within the anaesthesia machine), driving pressure, and plateau pressure were recorded continuously. Intermittent blood gas analysis was performed in order to verify the accuracy of the SpO2 readings and to calculate the alveolar-arterial gradient [P(A-a)O2], while the respiratory rate was adjusted in order to maintain the PaCO2 in the range of 35–45 mmHg. In the PACU, vital signs and arterial blood gas analysis were recorded at 5, 10, and 30 minutes after extubation, and supplementary O2 was provided to the patients via nasal cannula if the SpO2 was below 92%. The titration process is summarized in Figure 1.

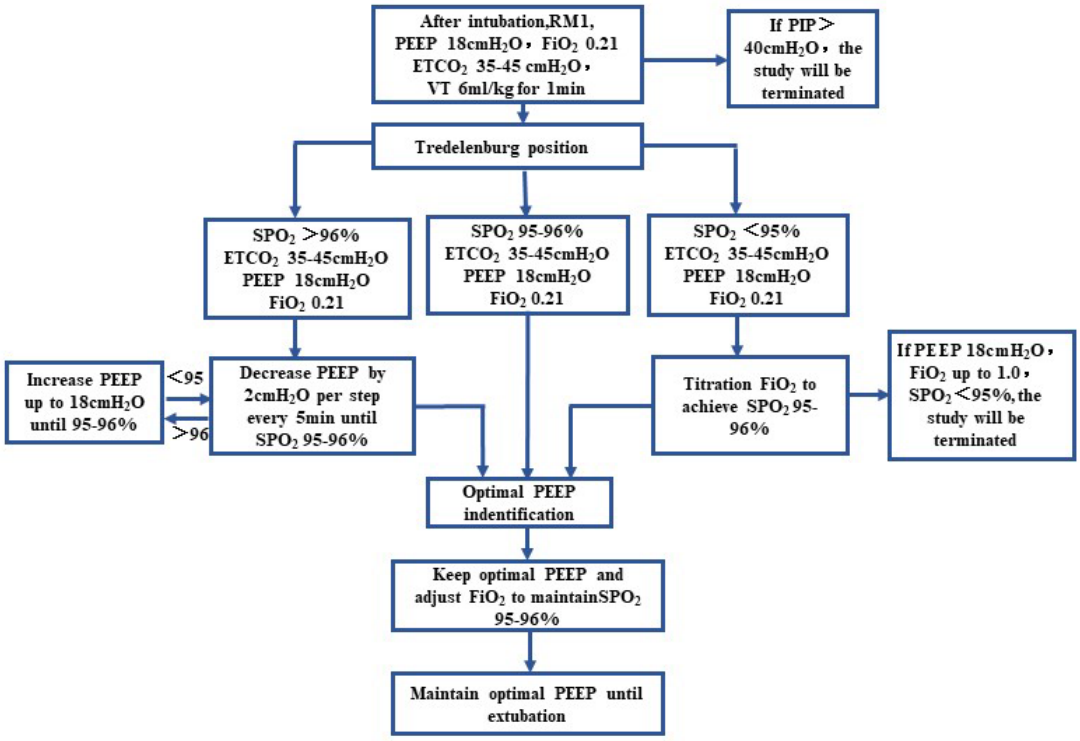

Figure1. Titration process of optimal PEEP. RM: recruitment maneuver; PIP: peak inspiratory pressure.

Safety considerations

The first concern is that high PEEP, up to 20cmH2O, is above the PEEP value of routine clinical practice. High PEEP may lead to decrease in venous blood return and hypotension. However, optimal PEEP ranging from 6 up to 23 cmH2O did not show any negative effect in patients undergoing laparoscopy in the supine position. We anticipate that the optimal PEEP of up to 20 cmH2O in patients in this study will not cause harm. In addition, hypotension will be treated per usual, thus not restricting the care team's treatment of hypotension. If the care team encounters hypotension that does not respond to the usual therapies, the study will be terminated and routine care will be resumed. The second concern is lung overstress. Previous studies have shown that PEEP up to 23cmH2O for patents in supine position did not result in clinically relevant lung injury. Another concern is high PEEP, up to 20cmH2O, may cause high peak pressure which may lead to lung overstress, even pneumothorax. In practice, the peak airway pressure obtained with bag mask ventilation can easily exceed 40 cmH2O. Without a pressure manometer attached to a bag mask ventilation system, it is impossible to know how much pressure is applied but when a manometer is used pressures exceeding 40 cmH2O pressure in adults are common. Pneumothorax has only been reported occurring in association with recruitment maneuver when peak airway pressure was above 55 cmH2O.

O2 saturation 95-96% may be lower than the patient's baseline SpO2. However, an SpO2 of 95-96% is within normal limits. On other hand, multiple studies have shown

that hyperoxemia can cause harm. Therefore, we believe that maintaining SpO2 no less than 95% is safe.

Simple size calculation

Intraoperative PaO_2/FiO_2 was reported as 55.7±10.9 kPa before extubation in patients undergoing RALP[4]; we assumed that there were 10 kPa differences between the two groups, with a variance of 10.9 kPa, a statistical power of 80%, and a two-sided α significance level of 0.05. A sample size of 18 patients in each arm was required to test our hypothesis. Considering a dropout rate of 30%, a total of 24 patients for each group (for a total of 48 patients) were enrolled.

Randomization

Randomization was performed using a minimization randomization method as previously described[16].The randomization was performed via MinimPy2 software (version2.0, OSDN, Columbus, OH, USA). Randomization was performed the day before surgery by a research team member who was blinded to the trial condition. The data were managed and analyzed by an independent researcher (PL).

Follow-up

The date collection was over before the patient leaving the operating room.

Data management and statistical analysis

For both groups, intraoperative pulmonary dynamic compliance (Cdyn), PEEP, FiO2 (i.e., real-time FiO2 obtained from the gas analyzer within the anaesthesia machine), driving pressure, and plateau pressure were recorded continuously. Intermittent blood gas analysis was performed in order to verify the accuracy of the SpO2 readings and to calculate the alveolar-arterial gradient [P(A-a)O2], while the respiratory rate was adjusted in order to maintain the PaCO2 in the range of 35–45 mmHg. In the PACU, vital signs and arterial blood gas analysis were recorded at 5, 10, and 30 minutes after extubation, and supplementary O2 was provided to the patients via nasal cannula if the SpO2 was below 92%.

Statistical analyses

Continuous variables were presented as means ± SD or medians with IQR according to whether the distribution was normal, while categorical variables were presented as counts and percentages. The χ^2-test was used to compare differences in patient characteristics between the two groups. The unpaired *t* tests were used to compare differences in oxygen indices, driving pressure, and Cdyn at different time points.

Repeated-measures analysis of variance (ANOVA) was used to compare differences in PaO_2/FiO_2, driving pressure, and Cdyn under mechanical ventilation prior to extubation. Differences in vital parameters, vasoactive medication dosage, and incidence of complications were tested via unpaired *t* tests, and the Wilcoxon Man-Whitney test was used when the data were not normally distributed. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS)software (version 24, IBM, Armonk, NY, USA) and GraphPad Prism 8.0 software (GraphPad Inc., San Diego, CA, USA). Statistical significance was set at $P < 0.05$.

Quality assurance

Data and Safety Monitoring Committee.

Expected outcomes of the study

Individualized optimal PEEP can be achieved with equipment available for anaesthesia by titration of PEEP and FiO_2 guided by SpO_2. Maintaining intraoperative optimal PEEP improves intraoperative oxygenation and reduces the incidence of postoperative hypoxemia in patients likely to require high intraoperative PEEP.

Dissemination of results and publication policy

None.

Duration of the project

2021/06-2021/8	Project demonstration, designing and expert discussion
2021/09	Ethical declaration and approval
2021/09-2021/10	Date collection
2020/10	Date analysis

Problems anticipated

None.

Project management

LLG conducted data analysis and manuscript preparation, drafted and finalized the manuscript; LY participated in study design, data analysis and manuscript preparation. LLP participated in protocol optimization, data retrieval and data analysis. YC participated in protocol optimization and manuscript preparation. JZ participated study design, data collection and analysis, manuscript preparation and finalization.

Ethics
This clinical trial was performed in Fudan university Shanghai Cancer Center and approved by the Ethics Committee (IRB2010225-11). This study was registered at the ClinicalTrial.gov and written informed consents were obtained from all participating subjects before enrollment.

Informed consent forms
Written informed consents were obtained from all participating subjects before enrollment.

Budget
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Collaboration with other scientists or research institutions
None.

Links to other projects
None.

Curriculum Vitae of investigators
None.

Other research activities of the investigators
None.

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None.

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