Official Title: **Intraoperative Positive End-Expiratory Pressure Setting Guided by Esophageal Pressure Measurement in Patients Undergoing Laparoscopic Gynecologic Surgery**

Brief Title: **Intraoperative PEEP Setting During Laparoscopic Gynecologic Surgery**

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Introduction

Nowadays, laparoscopic surgery has been substantially performed worldwide. It is considered as minimally invasive procedure with numerous advantages compared with open surgery including less postoperative pain, faster recovery, shorter length of hospital stay and less overall medical cost[1]. The creation of pneumoperitoneum (PP) during laparoscopic surgery, however, can have significant effects on the respiratory system. The rise in intraabdominal pressure (IAP) causes cephalic displacement and stiffness of the diaphragm resulting in a decrease in the compliance of the respiratory system (C_{RS}) and of the chest wall (C_{CW})[2-4] as well as an increase in pleural pressure (P_{pl}) likely due to thoracoabdominal transmission of IAP. Combine with a decrease in respiratory muscle tone following general anesthesia[5], the vital capacity and the functional residual capacity (FRC) are declined[2]. There also atelectasis formation resulted from airway closure (compressive atelectasis) and absorption of gas trapped distal to occluded airways (absorption atelectasis)[6]. All of these changes potentially lead to an increase in dead space ventilation as well as shunt and subsequently impair oxygenation[5]. This pathophysiology may put patients at risk of postoperative pulmonary complications (PPCs) such as respiratory infection, respiratory failure, reintubation or prolonged mechanical ventilation and possibly increase mortality[7, 8].

Therefore, intraoperative mechanical ventilation has an important role in respiratory management during laparoscopic surgery[9]. Setting of positive end-expiratory pressure

(PEEP) has been shown to attenuate the derangement of respiratory mechanics and the impairment in oxygenation caused by PP[10-15]. In addition, the application of PEEP as a part of intraoperative protective mechanical ventilation may be associated with a decrease in PPCs following laparoscopic surgery[16]. Nevertheless, there is no consensus on the optimal PEEP level and the best method to set PEEP during laparoscopic surgery[9]. In patients with acute respiratory distress syndrome (ARDS), Talmor et al[17] demonstrated that mechanical ventilation with PEEP set according to P_{pl} measured by using esophageal balloon catheter significantly had beneficial effects in terms of oxygenation, C_{RS} and possible mortality. With PEEP set according to this method, the transpulmonary pressure (P_{TP}), which is the difference between the pressure inside alveoli or PEEP and the pressure outside or P_{pl}, is constantly maintained positive during expiration. Consequently, it helps to prevent the formation of atelectasis as well as to recruit the collapsed alveoli and, thus, to improve oxygenation. To date, there is limited data regarding the use of esophageal balloon catheter to set PEEP in mechanically ventilated patients undergoing laparoscopic surgery. Therefore, the aim of this study is to determine whether PEEP titration guided by P_{pl} measurement during laparoscopic surgery would improve pulmonary function in term of oxygenation as well as other parameters such as compliance and alveolar dead space.

Material and Method

Patient population

This randomized controlled trial includes patients with age of equal or more than 18 years old undergoing laparoscopic gynecologic surgery with anticipated surgical duration of more than 2 hours. Patients with the American Society of Anesthesiologists (ASA) physical status of equal or more than 3, those with significant cardiovascular or respiratory diseases, those with significant pathological lesion in pharynx and esophagus that preclude placement of esophageal balloon catheter, those with contraindications for PEEP titration such as increased intracranial pressure or unstable hemodynamic, those with arrhythmias, those who refuse to provide written informed consent, and those undergoing surgery with duration of less than 2 hours are excluded from the study. Informed consent is obtained from all included patients.

Study protocol

Prior to induction of general anesthesia, standard monitoring including non-invasive blood pressure measurement, pulse oxymetry, electrocardiogram, capnometry and peripheral nerve stimulator (TOF-Watch, Organon, Ireland), which is applied to the temporal branch of facial nerve and recorded response of the orbicularis oculi, as well as non-invasive cardiac output measurement with the pulse wave transit time technology (Vismo, Nihon Kohden, Janpan) are applied to all patients. General anesthesia is induced with 1.5-2 mg/kg of propofol, 2 mcg/kg of fentanyl and 0.6 mg/kg of rocuronium and then trachea is intubated with proper size of endotracheal cuff tube. After induction and intubation, arterial catheter is inserted at radial artery for repeated arterial blood gas sampling. Anesthesia is maintained with 1 minimal alveolar concentration (MAC) of

desflurane and supplemental doses of morphine and rocuronium as required. Train-of-four (TOF) stimulation with peripheral nerve stimulator is kept between 1 and 2 twitches to facilitate relaxation. In case of hemodynamic instability, fluid as well as inotropes and vasopressors are administered according to discretion of anesthesia staff. The surgery is initially started in the lithotomy position and then in the 45-degree Trendelenburg position at the initiation of PP. PP is created by intraabdominal insufflation of carbon dioxide (CO_2) and IAP is maintained at 12 to 15 mm Hg during PP. At the end of the surgery, reversal of paralysis with 0.2 mg of sugammadex is administered and extubation is carried out after fulfilled criteria of extubation and TOF ratio monitoring of more than 90%. All patients are then transferred to the recovery room and monitored for 1.5 hours prior to transfer to ward.

For management of mechanical ventilation, all patients are ventilated by an anesthetic machine (Aespire View, Datex-Ohmeda Inc., Wisconsin, USA) with preset tidal volume of 8 mL/kg of predicted body weight, inspiratory to expiratory time ratio of 1:2 with 45% inspiratory pause, respiratory rate adjusted to maintain end-tidal carbon dioxide ($EtCO_2$) between 35 and 45 mm Hg, fraction of inspired oxygen (FiO_2) of 0.40 in one liter per minute of the mixture of oxygen and air which can be adjusted to maintain peripheral oxygen saturation (SpO_2) of equal or more than 95% and PEEP set according to the study groups. All included patients are randomly allocated into 2 groups, the control group (Group C) and the intervention group (Group E), by computer-generated block-of-four randomization. In the Group E, the 5-French, latex-free adult esophageal balloon catheter (CooperSurgical Inc., Connecticut, USA) is inserted after induction and intubation and connected to the pressure transducer system (TruWave, Edwards

Lifesciences, Irvine, USA). The proper position of the catheter is in the lower one third of the esophagus, which is determined by rising in pressure during positive pressure ventilation plus presence of cardiac oscillation recognized on the pressure tracing[18-20]. The esophageal pressure (P_{eso}) is measured and used as a surrogate of P_{pl}[19-21]. PEEP is titrated to maintain P_{TP} during expiration, which is equal to PEEP minus P_{eso} during expiration, between 0 and 5 cm H_2O. The conversion factor of 1.36 is used to convert mm Hg to cm H_2O. In the group C, the esophageal balloon catheter is inserted as in the group E for measuring P_{eso} but patients are ventilated with fixed PEEP of 5 cm H_2O throughout the operation.

Data collection

In all patients, demographic data including age, weight, height, body mass index (BMI), the ASA physical status, comorbid diseases, diagnosis, operation, duration of the operation are recorded. After induction and intubation and insertion of the esophageal balloon catheter, hemodynamic parameters including blood pressure, heart rate, cardiac index and stroke volume index; respiratory mechanics including peak inspiratory pressure, plateau pressure (P_{plat}), PEEP, P_{eso} during inspiration and expiration, and tidal volume; and gas exchange parameters including partial pressure of arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$), pH, FiO_2, SpO_2 and $EtCO_2$ are recorded as baseline T0 parameters. After initiation of PP and position in 45-degree Trendelenburg position, PEEP is set according to patient's group allocation. Hemodynamic parameters, respiratory mechanics, gas exchange parameters and IAP are recorded at 15 minutes and at one hour after setting of PEEP as T1 and T2 parameters, respectively. Thirty minutes after arrival in the recovery room, hemodynamic and gas exchange parameters are

recorded again as T3 parameters. The C_{RS} is calculated from tidal volume in mL divided by difference between P_{plat} and PEEP in cm H_2O and the alveolar dead space to tidal volume ratio (V_D/V_T) is calculated using the formula reported by Hardman et al[22]. Adverse respiratory events defined as requirement of oxygen supplement after discharge from the recovery room, episodes of desaturation (SpO_2 of less than 90%), now-onset respiratory infection, new infiltration on chest radiograph, or respiratory failure are followed up in all patients for 72 hours postoperatively or until discharge from hospital. Length of hospital stay as well as other adverse events are also recorded.

Statistical analysis

The primary endpoint of the study is to determine the difference in oxygenation that is PaO_2 between the Group E and the Group C. Spadaro et al[15] reported PaO_2 of 127.5±30 mm Hg during PP in patients undergoing laparoscopic abdominal surgery with application of PEEP of 5 cm H_2O. Meanwhile, PaO_2 was reported as high as 142.5±30 mm Hg[15] to 190.2±11.9 mm Hg[12] during PP with application of PEEP of 10 cm H_2O. Given that PaO_2 in the Group C is equal to that reported by Spadaro et al[15] and estimated 20% higher PaO2 in the Group E is clinically relevant, with a power of 0.8 and a significance level of 0.05, sample size of 22 subjects per group is required. The secondary endpoints are the difference in C_{RS} and V_D/V_T between the two groups, changes in hemodynamic parameters with application of PEEP, proportion of thoracoabdominal transmission of IAP as well as adverse respiratory events and length of hospital stay in the two groups.

Categorical variables are reported as number with percentage and compared between the groups using the chi-squared test or the Fisher's exact test as appropriated.

Continuous variables are tested for normal distribution with the Kolmogorov–Smirnov test and reported as mean with standard variation (SD) or median with interquartile range (IQR) and compared between the groups using the unpaired Student's t-test or the Mann Whitney U test as appropriated. The changes in parameters within the group are analyzed using the repeated-measure analysis of variance (ANOVA). For all analyses, a two-tailed test is performed and a *p* value of less than 0.05 is considered statistical significance. The statistical analysis is carried out using the IBM SPSS Statistics 21 (IBM Corporation, New York, USA).

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Siriraj Institutional Review Board

Certificate of Approval

COA no. Si 401/2017

Protocol Title(English) : Intraoperative Positive End-Expiratory Pressure Setting Guided By Esophageal Pressure Measurement in Patients Undergoing Laparoscopic Gynecologic Surgery

Protocol Title(Thai) : การตั้งค่าแรงดันบวกที่จุดสิ้นสุดการหายใจโดยวิธีการวัดความดันภายในหลอดอาหารในผู้ป่วยที่เข้ารับการผ่าตัดส่องกล้องทางนรีเวช

Protocol number : 253/2560(EC3)

Principal Investigator/Affiliation: Dr.Annop Piriyapatsom, M.D. / Department of Anesthesiology
Faculty of Medicine Siriraj Hospital, Mahidol University

Research site : Faculty of Medicine Siriraj Hospital

Approval includes :

1. SIRB submission form
2. Participant information sheet
3. Informed consent form
4. Case Record Form
5. Curriculum vitae

Approval date : July 20, 2017
Expired date : July 19, 2018

This is to certify that Siriraj Institutional Review Board is in full compliance with international guidelines for human research protection such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

(Prof. Chairat Shayakul, M.D.)
Chairperson

27 JUL 2017
date

(Prof.Dr. Prasit Watanapa, M.D., Ph.D.)
Dean of Faculty of Medicine Siriraj Hospital

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1. Conduct the research as approved by the SIRB and will not make any changes in the research without prior SIRB review and approval, except when necessary to eliminate apparent immediate hazards to participants.
2. Use only the forms bearing the 'SIRB APPROVED STAMP' in the research.
3. Conduct the informed consent process without coercion or undue influence, and give sufficient opportunity to consider participation. One copy of the consent and/or assent form must be given to the subject after it is signed.
4. Promptly report to the SIRB of any new information that may affect the safety and well-being of the subjects.
5. Report to the SIRB all serious adverse events, unanticipated problems, protocol deviation and/or violation in accordance with the SIRB policy and operating procedures.
6. Provide the progress report to the SIRB as a Continuing Review 30 days prior to the COA expiration for at least once a year from the approval date unless otherwise indicated. The Continuing Review must be used to renew approval prior to the expired date.
7. Provide the Final Report as a close-out within 30 days after the research is complete.

Non-compliance may result in the suspension or termination of the study.