Opinion

Lung-Protective Ventilation Strategy in Surgical Patients: Optimal Setting of Positive End-Expiratory Pressure?

Fu-Shan Xue, Xu Liao, Rui-Ping Li, and Xin-Long Cui

More than 230 million of patients undergoing general anesthesia for major surgery require mechanical ventilation annually worldwide (1). It has been reported that 5-10% of all surgical patients and about 30-40% of those undergoing thoracic or abdominal surgery develop postoperative pulmonary complications (PPCs), such as atelectasis, pneumonia, respiratory failure, acute respiratory distress syndrome, pleural effusion, etc (2). The improved perioperative management in the past decade has significantly decreased case-fatality rate of surgical patients, but the frequency of PPCs has still remained relatively constant due to the increased number and complexity of the operations performed and the increased acuity and age of patients. It has been shown that PPCs are major causes of postoperative morbidity and mortality, and are associated with considerable costs in hospital cares (3). Thus, PPCs are important clinical problems in modern practice and the prevention of PPCs has become a measure of quality of care (4).

Mechanical ventilation is an essential supportive strategy during general anesthesia, but increasing evidence shows that inadequate ventilator settings can aggravate and even initiate lung injury in surgical patients with healthy lungs, the so-called ventilator-associated lung injury (VALI) (5). VALI results from overdistention of nondependent lung tissue causing excessive cyclic strain of alveolar cells, and repetitive opening and closing of dependent lung tissue resulting in cyclic cell stress due to the extreme forces exposed to lung cells at the interfaces between open and closed alveoli (6). Based on results from acute respiratory distress syndrome and critically ill patients, there is a growing trend to favor lung protective ventilatory strategies with low tidal volume (V_T), positive end-expiratory pressures (PEEP) and repeated recruitment maneuvers for surgical patients requiring mechanical ventilation (4-6).

With regard to optimal PEEP setting of lung-protective ventilation for surgical patients, however, two recent studies provided the inconsistent results. In *The Lancet*, an international multicentre randomized controlled trial (PROVHILO trial) by The PROVE Network Investigators comparing the ventilation strategies in the patients at risk of PPCs after open abdominal surgery showed that compared with a strategy with a low level of PEEP (≤2 cm H_2O) without recruitment manoeuvres, a strategy with a high level of PEEP (12 cm H_2O) and recruitment manoeuvres did not protect against PPCs. Thus, the PROVHILO trial concluded that an intraoperative lung-protective ventilation strategy should include a low V_T and low PEEP (≤2 cm H_2O) (7). However, in a retrospective single-centre study of 29,343 patients receiving mechanical ventilation and undergoing general noncardiac surgeries under general anesthesia, Levin and his colleagues (8) showed that use of V_T in the range applied in the PROVHILO trial published by *The Lancet* (7) and minimum levels of PEEP (median=4 cm H_2O) were associated with an increase in 30-day mortality and prolongation of hospital stay.

Actually, the findings of Levin et al. also are significantly different from the conclusions of two recent comprehensive analyses done by Coppola et al. (9) and Futier et al. (6) regarding the current randomized controlled clinical trials comparing protective versus conventional ventilation strategies during general anesthesia in surgical patients. The conclusions of these two reviews are that lung-protective ventilation strategy (low V_T with PEEP and/or recruitment maneuvers) is beneficial in abdominal surgery (lower inflammatory response and better outcome). During thoracic and cardiac surgery, lung-protective ventilation strategy has also been associated with a reduced inflammatory response.

After carefully reading this retrospective study by Levin et al. and previously published randomized controlled clinical trials, we agree with Levin and his colleagues that use of a low level PEEP without recruitment manoeuvres is one of the possible causes for their worse postoperative outcomes (8), because the use of low V_T ventilation with low levels of PEEP can promote loss of lung aeration and atelectasis formation (4). Moreover, this study is a retrospective analysis using observational designs, which potentially introduces a number of confounding variables that a nonrandomized study may not have removed completely. In our view, several important issues in this study may have confounded interpretation of the results.

Firstly, health status, types of surgery and comorbidities are the most important determinants for postoperative morbidity and mortality (10). In the study by Levin et al., patients' age, American Society of Anesthesiologists (ASA) physical status, All Patient Refined- Diagnosis Related Group (APR- DRG) severity of illness (SOI) and risk of mortality (ROM) scores and types of surgery were significantly different among patients with various ventilation strategies. In our opinion, no matter how refined the adjustment is for differences in health status, surgery burden and relevant comorbidities, it is never possible to ensure a complete adjustment for differences among patients with different ventilation strategies, even if propensity score matching is used. Most importantly, some of independent risk factors related to postoperative morbidity and mortality were not included in data analysis. For example, preoperative anemia is common among noncardiac surgery patients, and low preoperative and postoperative hemoglobin levels are associated independently with increased perioperative mortality, increased postoperative pneumonia, and prolonged hospital length of stay (11, 12). In addition, Levin et al. did not include serum albumin level in patients' demographic data. It has been shown that a low serum albumin level is an important predictor of pulmonary complications after major noncardiac surgery (13). According to the guideline of the American College of Physicians on risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery, serum albumin should be measured in all patients who are clinically suspected of having hypoalbuminemia and in those with one or more risk factors for PPCs (14).

Secondly, in the study by Levin et al., anesthetic agent, ventilation mode (volume control versus pressure control), ventilator settings, and fraction of inspired oxygen were chosen at the discretion of the attending anesthetist. Consequently, we cannot exclude the possibility that anesthetists would have selected anesthetic and ventilation strategies based on baseline characteristics and pre-existing comorbidities of surgical patients. Furthermore, we are not provided with details of anesthetic and intraoperative managements. Actually, intraoperative hypoxemia, blood loss, transfusion, hypotension, tachycardia and hypertension have been associated independently with postoperative morbidity and mortality of noncardiac surgical patients (15, 16).

Thirdly, the postoperative morbidity and mortality are actually results of many perioperative factors and their interaction (10). To differentiate the effect of one factor on the postoperative adverse outcomes, all of the other factors have to be standardized and controlled in the study design. It is impossible for the retrospective study using an observational method to achieve this target. Thus, in the study by Levin et al., association between postoperative outcomes and low V_T ventilation with minimal PEEP did not prove causality, though propensity score- matched analysis was used to adjust and reduce the influences of confounding variables on study endpoints. We argue that when making decisions about use of a treatment such as low V_T ventilation with PEEP to decrease postoperative morbidity and mortality of surgical patients, we should rely on a large body of robust evidence of efficacy and safety. This high-level evidence comes from the randomized controlled clinical trials with a large number of subjects and their meta-analysis, rather than any study employing an observational design (17).

Finally, it must be pointed out that inclusion of only two arms comparing ventilation strategies with high and low PEEP (7) may be a limitation of the PROVHILO trial's design. Due to lack of a control arm using conventional ventilation strategy without PEEP, this study can not prove the conclusion that an intraoperative protective ventilation strategy should include a low V_T and low PEEP (≤2 cm H_2O), without recruitment manoeuvres. In the available literatures, there is actually robust evidence that improved functional or physiological and clinical postoperative outcomes have been obtained with a protective ventilation strategy with low V_T (6-8 ml/kg of predicted body weight), moderate PEEP (6- 8 cm H_2O), and recruitment maneuvers in patients undergoing abdominal surgery (4). However, more clinical data and evidence are still needed before making any recommendation for mechanical ventilation in patients undergoing thoracic surgery (9). To prevent PPCs and improve surgical outcomes, moreover, we believe that an integrated strategy of perioperative management including intraoperative use of lung-protective ventilation, adequate fluid administration and optimized pain management should be considered (6, 18).

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Citation: Fu-Shan Xue, Xu Liao, Rui-Ping Li, Xin-Long Cui. Lung-protective ventilation strategy in surgical patients: optimal setting of positive end-expiratory pressure? *J Anesth Perioper Med* 2015; 2: 45-7.

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