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Perioperative Acute Lung Injury: Reviewing the Role of Anesthetic Management

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Introduction

Postoperative pulmonary complications can develop after major surgery such as cardiac, thoracic or vascular surgery. Despite either the various types of lung injury (Table 1), or the different severity of the pulmonary impairment, respiratory complications have a significant impact on the clinical outcome [1,2]. The respiratory failure associated with the acute lung injury (ALI) and/or the acute respiratory distress syndrome (ARDS) (Table 2), is one of the most important contributors to postoperative mortality. Lung injury can result from many different insults affecting the lung throughout the perioperative period. Some of these insults are strictly connected with the patients' preoperative clinical conditions; others depend on intraoperative risk factors. The interaction between predisposing risk factors and aggressive surgical and/or anesthesiological management can lead to lung damage and postoperative complications. Although anesthesia has been implicated in the impairment of lung function, there is no evidence that the type of anesthesia used significantly influences intraoperative oxygenation [3].

Despite the advancements in both the surgical techniques and the perioperative management, the incidence of postoperative ALI is still quite remarkable. Postoperative ALI occurs in about 0, 2-5% of the surgical patients (pts) submitted to major surgery. The occurrence of postoperative ALI is conditionated by the type of surgery ranging from 2-4% after thoracotomy for lung resection to <0, 5% after cardiac surgery [4,5]. Although its mortality rate has been progressively decreased in the last decade, ALI remains one of the most important causes of death of the critically ill pts with a mortality rate ranging from 40-50% of the cases [6].

A primary form of ALI that complicates surgery in the immediate postoperative period should be distinguished from a secondary ALI, usually delayed and showing an onset from 3 to 12 days after surgery. Whereas the primary ALI strictly depends on the systemic inflammatory response induced by the surgical events, the secondary ALI is triggered by several postoperative complications including sepsis, pulmonary embolism, gastric content aspiration, and pneumonia [7].

Intraoperative risk factors

Inflammatory response

Major lung surgery is generally associated with a systemic inflammatory response induced by surgical trauma (as in lung resection) or by lung manipulation and collapse (as during cardiopulmonary bypass (CBP)) [8,9]. Thus, the type of surgery performed is important in the development of postoperative ALI. Intraoperative factors that can increase the risk of postoperative pulmonary injury depend not only on direct manipulation during surgery, but also on the pulmonary manifestations of the systemic inflammatory response. Inflammatory markers cause damage to both the alveolar and microvascular endothelium, and this damage alter the integrity of the alveolar-capillary barrier, impairing gas exchange and causing extravascular fluid accumulation [7]. This pulmonary damage results in an increase in the extravascular lung water (EVLW), which is one of the hallmarks of ALI [10]. The main predictors of ALI in thoracic surgery include pneumonectomy, fluid overload and single-lung ventilation [3,5,7]. Cardiac surgery patients are susceptible to ALI primarily because of cardiopulmonary bypass (CBP) and its consequent systemic inflammatory response [11]. After both cardiac and major vascular surgery, pulmonary function can be impaired because of lung injury. Hypovolemic hypotension (requiring high volume fluid replacement), intraoperative bleeding, and ischemia/reperfusion injuries are common risk factors for postoperative lung injury. Intraoperative bleeding and massive blood replacement can also cause lung injury and lead to transfusion related lung injury (TRALI) [12,13].

Anesthesia

The anesthesiological management of patients who undergo either thoracic surgery or major cardiovascular surgery has been investigated to determine the impact of anesthetic drugs on the lung and their eventual effect on respiratory function. Atelectasis generally occurs in the basal portion of the lung in anesthetized patients. Under general anesthesia and mechanical ventilation, the basal portions of the lungs commonly collapse because of a high inspiratory oxygen fraction or the reduction in functional residual capacity induced by most anesthetics. In addition, loss of surfactant can worsen intraoperative pulmonary function. The loss of muscular tone induced by paralytic drugs decreases lung expansion [14]. Most studies are performed in patients undergoing OLV. Some reports suggest that volatile anesthetics inhibit hypoxic vasoconstriction, leading to intraoperative hypoxemia because of an increase in intrapulmonary shunting [15-17]. The ventilated lung suffers from a redistribution of blood perfusion and, consequently, a ventilation/perfusion mismatch. The ventilation/perfusion mismatch results in a decreased arterial oxygen tension. Administration of inhaled anesthesia seems to impair arterial oxygenation, whereas, the administration of most of the intravenous anesthetic agents does not. Despite these experimental studies, there is little evidence available regarding the effects of anesthetics on pulmonary function or lung injury. More recent studies have demonstrated that the type of the anesthesia used does not significantly impact intraoperative oxygenation [7]. The hypoxic effects induced by volatile anesthetics more likely depend on the hemodynamic impairment caused by myocardial depressant action (low cardiac output, systemic hypotension, and tachycardia). General

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anesthesia, whether inhaled or intravenous, does not represent a significant risk factor in the development of lung injury during major surgery. The association between general anesthesia and epidural analgesia has been investigated during OLV [18]. The majority of these studies have demonstrated that epidural anesthesia does not affect intraoperative oxygenation [3]. The use of epidural analgesia, in conjunction with volatile anesthetics, allows for the use of reduced concentrations of volatile anesthetics; this reduced concentration requirement results in improved pulmonary oxygenation.

Positive-pressure ventilation

The role of intraoperative positive pressure ventilation in the development of postoperative ALI has been debated for years. Intraoperative mechanical ventilation should provide either the best arterial oxygenation or the fewest pulmonary complications (such as barotrauma, volutrauma, absorption atelectasis and oxidative damage). In fact, the protective intraoperative positive-pressure ventilation has become mandatory [3,5,7]. Pressure-controlled ventilation, small tidal volumes (TV) and the lowest possible FiO2 are considered optimal strategies to provide adequate oxygenation as well as reduced the chance of lung injury [5,7]. Several studies have demonstrated that small TV significantly reduces the lungs' inflammatory response. In addition, the use of a 6-8 ml/Kg TV protects the lung from the mechanical insults of the ventilation, contributes to reducing the extravascular water accumulation and provides adequate arterial oxygenation [3].

Aggressive positive pressure ventilation has been recognized as one of the most important risk factors of postoperative ALI. Hyperinflation and cyclic stretching of the lungs, which occurs when the alveoli are exposed to prolonged high dose oxygen, may be the main causes of lung injury [7,19]. The tissue damage leads to a local inflammatory reaction with the production of radical oxygen intermediates and other inflammatory markers that cause a pulmonary edema via disruption of the alveolar-capillary barrier. A protein-rich fluid then accumulates in the interstitial space, worsening the condition of the respiratory unit and causing gas-exchange disturbance [5,7]. The ventilated lung, especially when the patient is in the lateral position, is exposed to the mechanical injury of the positive pressure ventilation, whereas, the non-ventilated lung may be injured by surgical manipulation as well as affected by a reduction in surfactant production with consequent atelectasis [3,5]. Ventilator-associated lung injury (VALI) is generally due to an inadequate ventilation pattern. The role of protective ventilation to limit lung injury due to the ventilator has become increasingly recognized in recent years. Although, the injurious effects of a long-term aggressive MV have been clearly recognized, actually it has not been well understood yet if the short-term MV during surgery can significantly damage a healthy lung [20-22]. According to the literature, the employment of a low TV ventilatory pattern seems to be protective in those pts without pre-existing lung injury, who must be submitted to long-term mechanical ventilation [21,23]. Others trials suggest that also the pts submitted to short-term mechanical ventilation during surgery may benefit from such ventilatory strategy [22]. Although the idea of a protective ventilatory strategy that prevents the mechanical ventilation-induced lung injury is both suggestive and full of interest, the lack of prospective and randomized controlled trial (RCT) is not helpful to clarify its effective role in the surgical population. Actually there is not yet strong evidence that the use of low-TV ventilation is more protective than conventional ventilatory pattern in the surgical pts [23]. In a prospective randomized trial, Wrigge et al. reported that the employment of a protective ventilatory strategy with low TV didn't significantly reduce the systemic inflammatory response in healthy cardiac surgery pts submitted to CPB [24].

In the recent years literature has largely emphasized the protective role of a low TV ventilatory pattern in surgical pts without pre-existing lung injury, because of its capability to reduce the plasmatic levels of the inflammatory mediators [25]. Determann et al. in a recent RCT has reported the positive effect of low TV ventilation in a cohort of pts not previously suffering from lung injury; among the investigated population there were also surgical pts submitted to elective surgery. The authors suggest that the lack of information about the effects of the mechanical ventilation on the surgical pts is due to the short duration of the mechanical ventilation during surgery [26].

One-lung ventilation

One-lung ventilation (OLV) is another important predictor of postoperative ALI [1,3,5,7,27]. One-lung ventilation is required in most thoracic surgical procedures, such as lung resection, aortic surgery, cardiac surgery and esophageal resection. Although OLV is not mandatory for all of the operations in which it is performed, its employment is particularly helpful to facilitate the surgical approach. Thoracic surgery and OLV are actually considered strong predictors for postoperative ALI [5]. During OLV, because only one of the lungs is ventilated but both are perfused, ventilation/perfusion mismatch and intrapulmonary shunting occur, causing hypoxemia [3,5,7]. In the past years, intraoperative hypoxemia has been treated with either increasing oxygen administration (FiO2 up to 80-100%), either with high TV ventilatory pattern. As previously reported, according to the recent literature, a ventilatory strategy based on small TV, adequate PEEP level and low FiO2, is actually considered the best treatment for the pts submitted to OLV in order to reduce the risk of postoperative ALI. Some predictors of intraoperative hypoxemia during OLV have been identified, even if their role remains unclear. Knowledge of the preoperative ventilation-perfusion ratio could be extremely important to identify patients at a high risk for the development of postoperative pulmonary complications and to assess the best intraoperative strategy to prevent ALI [7].

In a retrospective and prospective study, Slinger reported the surprising correlation between the preoperative forced expiratory volume in 1 (FeV1) value and intraoperative hypoxemia. Slinger demonstrated that patients with the lowest preoperative FeV1 measurements (FeV1 < 1) had the best intraoperative oxygenation [5,28]. This unexpected result could be explained by considering that the air trapping caused by the pulmonary obstruction may generate a positive end expiratory pressure (PEEP) in the alveoli of the ventilated lung, thereby improving the intraoperative oxygenation [7,19]. Other studies have failed to demonstrate any predictive value of the preoperative functionality tests. In contrast, the preoperative arterial blood gas analysis of the arterial oxygen tension seems to be well correlated with intraoperative oxygenation [7]. Other significant predictors of intraoperative hypoxemia during OLV are as follows: the site of the operation (left-thoracotomy is associated with better oxygenation because of the difference in size of the two lungs), the lateral position (because of the effects of gravity on the ventilation-perfusion regimen of the dependent lung) and the preoperative perfusion difference between the two lungs [5,7]. Oxygen saturation depends on the balance between ventilation and perfusion throughout the two lungs; there should be less perfusion in the less ventilated lung

and more perfusion in the more ventilated lung for the oxygenation to be adequate.

Fluid administration

An excess of fluid intake has been reported as one of the predisposing factors to develop perioperative ALI [7]. Contrarily, however, the administration of large quantities of fluid over the first 24 postoperative hours seems more correlated with postoperative ALI. Thus, a balanced fluid intake could be protective, especially in patients undergoing large pulmonary resection such as pneumonectomy [29].

Patients' Predisposing Factors

In addition to the surgical risk, patients' preoperative conditions play an important role in the development of postoperative ALI. Preoperative chronic obstructive pulmonary disease (COPD), severe respiratory failure, diabetes mellitus, gastroesophageal reflux disease and alcohol abuse are considered strong predictors of postoperative lung injury. Despite some evidences of a protective role of diabetes mellitus for the development of postoperative ALI exist in literature; other recent investigations identify this pathology as a strong predictor for postoperative ALI. [30]. Chronic alcohol consumption has been shown to be one of the most important risk factors in ALI.

Interestingly, among predisposing factors, genetic factors have also been proposed as playing a role in making patients more prone to develop ALI. In recent studies some genes contributing to an ALI phenotype [31] have been identified, in particular genes encoding for angiotensin-converting enzyme (ACE), surfactant protein B, heat-shock protein 70, pre-B-cell colony enhancing factor, myosin light-chain kinase and macrophage migration inhibitory factor seem to be involved. Such evidence was reported both in thoracic and esophageal surgery [32-34].

Prevention of intraoperative lung injury

Considering the incidence of postoperative ALI (approximately 2.6%) and the postoperative mortality rate (40-50%), the social and economic effects of this pathology cannot be ignored. Among the postoperative pulmonary complications, ALI and its more severe form, ARDS, are associated with higher than expected mortality rates and prolonged lengths of hospital stay. Therefore, measures that either reduce the perioperative risk or help to assess the proper intraoperative management should be strongly encouraged [1].

Preoperative evaluation: The individual predisposing risk factors should be adequately identified and treated to reduce the incidence of postoperative ALI. According to the literature pts submitted to high-risk surgery are prone to develop postoperative acute lung injury when presenting preoperative predisposing risk factors for ALI. The identification of these high-risk pts gives the opportunity to provide an adequate preoperative prevention either a proper intraoperative strategy to reduce the incidence of the postoperative ALI. Despite several risk-prediction models for postoperative ALI have been proposed, the most of them present limitations in the preoperative assessment of the risk of postoperative ALI. More recently a new score system for the assessment of postoperative ALI in the pts undergoing major surgery (SLIP= surgical lung injury prediction) has been proposed. Despite significant limitations, this prediction model is able to stratify the surgical pts into three levels of risk for developing postoperative ALI (low, intermediate and high risk) providing a valid predictive score [35].

Among the strategies used to prevent intraoperative hypoxemia, working to improve the patients' preoperative clinical conditions has been the most widely adopted [1,3,7]. Avoidance of alcohol, improvement in the nutritional status and increasing the patients' functional respiratory performance are all very important preventive strategies [1,7]. Patients that abuse alcohol are at high risk for postoperative ALI [36,37]. Alteration of the immune system, malnutrition and other comorbidities associated with alcohol abuse lead to an increased risk of infection with major surgery. In addition, the chronic consumption of high doses of ethanol reduces the production of the surfactant, which alters the alveolar surface [38].

Preoperative physiotherapy has been proposed as a possible strategy to provide an adequate lung expansion and to reduce atelectasis, even if its effectiveness is still debated. COPD patients could benefit either from preoperative inspiratory muscle training or from optimization of the medical therapy [1]. The use of bronchodilator drugs and removal of airway secretions should be considered in high-risk patients.

Hypoxemia: When intraoperative hypoxemia occurs, the anesthesiologist must recognize the cause and treat it as soon as possible. Different measures to prevent intraoperative hypoxemia have been proposed. An increase in the FiO2 most rapidly reduces hypoxemia. An increased oxygen concentration to the non-dependent lung (FiO2 up to 50-100%) improves the arterial oxygen saturation. Meanwhile, the anesthesiologist either finds the primary cause of the hypoxemia or optimizes the ventilation strategy. While the use of high oxygen inspiration fraction (FiO2) has been widely accepted for years as a beneficial maneuver to prevent post-thoracotomy hypoxia, the concept that a lower FiO2 is adequate and may prevent post-thoracotomy lung injury has been recently advocated in the management of high-risk patients undergoing thoracic surgery. The lowest FiO2 that provides a satisfactory peripheral saturation (SaO2 $\geq$ 90%) is considered the best treatment to reduce oxidative damage and to prevent absorption atelectasis [3,5,7]. Thus, the use of high FiO2 is now only acceptable for a short period during surgery. One of the most frequent causes of intraoperative hypoxemia is an incorrect positioning of the double-lumen endotracheal tube (DLT). A recent retrospective analysis of patients undergoing OLV has reported that in 3% of the cases, intraoperative hypoxemia was correlated to a DLT malposition [39]. Although the loss of separation between the two lungs does not immediately lead to inadequate oxygenation, surgical manipulation of the operated lung can further displace the tube, worsening the arterial oxygenation. The position of the DLT should always be checked with a fiber optic bronchoscope, which allows the tube to be repositioned during the direct visualization of the airways [40]. The correct use of the double-lumen endotracheal tube, which that allows adequate separation of the two lungs during OLV, has been recognized as an important safety strategy to improve oxygenation by correcting intrapulmonary shunting. Once the DLT has been checked, another important strategy to treat hypoxemia is the expansion of the non-ventilated lung. The application of a continuous positive pressure (CPAP) to the non-ventilated lung after recruitment maneuvers has been recently proposed as an efficacious strategy to treat hypoxemia [41]. Once the recruitment maneuvers allow the collapsed lung to expand, low levels of CPAP (5-10 cm/H2O) are sufficient to ensure that the lung remains inflated and the alveoli open [3,42]. The CPAP strategy seems more comfortable for the thoracic surgeon, who can operate on a continuously expanded but immobile lung, rather than a cyclically and irregularly inflated organ. It is important that when the recruitment maneuvers are employed to improve oxygenation, the ventilation pattern should be adjusted to maintain the benefits obtained from the lung expansion; in these clinical settings, either the

increase of the TV or the application of moderate levels of PEEP could ameliorate the arterial oxygenation.

Some studies have reported the beneficial use of nitrous oxide (NO) during OLV [3,43,44]. The aim of the administration of this gas is to restore an adequate ventilation/perfusion balance between the two separated lungs. Because NO provides a vasodilation of the pulmonary vessels, it increases both the perfusion and reduces the intrapulmonary shunt when it is inhaled by the ventilated lung [3,43,45].

Ventilation Strategies

Because high-risk patients can develop intraoperative hypoxemia and ALI can occur during major surgery, an adequate ventilation pattern must be applied to achieve the best arterial oxygenation and to reduce potential lung injury [46-48]. The use of high TV has long been advocated to increase arterial oxygenation, by providing lung expansion or reducing the incidence of intraoperative atelectasis. Despite the beneficial effects of this ventilation setting, the potential lung damage caused by the resulting pulmonary hyperinflation should be considered. Some studies have reported that a more intense inflammatory response can occur when large TV's are employed [49]; however, these studies have also demonstrated that the use of high TV ventilation is not the only cause of lung injury [50,51]. When ventilation impacts either a previously damaged lung or reaches a critical setting perioperative ALI can more easily occur [3,7]. In fact, a ventilation pattern characterized by small TV is becoming more popular. Despite the fact that a small TV can cause atelectasis, several studies have not reported any difference in the arterial oxygenation between the high TV ventilation pattern and the small TV ventilation setting.

According to the second-hit hypothesis, some different studies have reported that an aggressive MV can induce a postoperative acute lung injury acting on a preexisting local inflammatory response. The primary insult (first hit) makes the lung to be predisposed to the MV's injury (second hit). Major surgery and firstly cardiac surgery when CPB is employed, usually provide an intense systemic inflammatory response that make the lung prone to the injurious effects of an aggressive MV [24] Despite the lack of strong evidences, the intraoperative use of a protective MV during major surgery could be considered.

Positive end expiratory pressure

The application of a positive end-expiratory pressure (PEEP) to the ventilation pattern has been considered in high-risk patients and in the treatment of ALI [52]. Because the application of a PEEP maintains the alveoli open at the end of the expiration, its use can be helpful either to provide better oxygenation or to limit the formation of intraoperative atelectasis [53,54]. Considering that atelectasis is one of the causes of intraoperative hypoxemia, PEEP is observed as one of the most important strategies to prevent desaturation. Intraoperative atelectasis frequently occurs in mechanically ventilated patients under general anesthesia. Even though PEEP is commonly used to ameliorate the gas-exchanges during positive pressure ventilation, especially when OLV is required, its effectiveness is still debated. Recent studies have reported that PEEP does not always improve oxygenation; some patients can benefit from the application of PEEP, while others do not receive any benefit from its use. Although the benefits of positive end-expiratory pressure have been recognized, the full effects of the PEEP are still not completely clarified. It seems that the patients who respond to recruitment maneuvers benefit the most from the application of PEEP. While several studies have demonstrated the effectiveness of PEEP combined with small TV in patients undergoing major surgery, the correct level of PEEP is not well defined. Since the intrinsic PEEP in these patients can vary significantly, especially when high TV's are employed [55], the adequate level of PEEP should be individually assessed. Generally PEEP levels between 5 and 10 cm/H2O are sufficient to improve oxygenation and prevent intraoperative hypoxemia [56,57]. The combination of PEEP with a small TV ventilation pattern seems to be the best way to ventilate high-risk patients undergoing major surgery and the patients suffering from ALI and/or ARDS.

The best ventilation strategy should provide the best arterial oxygenation while limiting tissue damage and intraoperative lung injury. Different ventilation strategies have been proposed to achieve either the best oxygenation or to reduce the lung damage. The use of high TV (10-12 ml/Kg) has been proposed as a valid tool to prevent intraoperative hypoxemia [5,7]. However, this strategy can potentially injure the lung due to hyperinflation. Although the use of high TV has long been considered the best ventilation strategy, the potential damage of the lung induced by high TV has been recently recognized. Low TV (6-8 ml/Kg) and high PEEP levels have been shown to reduce the lung inflammatory response and to decrease the risk of lung injury. Several studies have reported the protective role of recruitment maneuvers to open the lung, followed by a ventilation strategy that combines low TV and high PEEP levels to keep alveoli open [46,47,49].

Discussion

General anesthesia and mechanical ventilation can cause lung injury and postoperative pulmonary complications by different mechanisms. Atelectasis, impaired gas-exchanges, local inflammation with alteration of the alveolar-endothelium barrier and mechanical ventilation-induced tissue damage can all occur during anesthesia. The employments of either a high oxygen fraction or an aggressive ventilation pattern are both considered significant risk factors for the development of perioperative lung injury. The type of surgery and the patients' preoperative clinical conditions are recognized as important predictors of either lung tissue damage or respiratory dysfunction. Despite several studies that have demonstrated the protective role of low TV mechanical ventilation pattern to prevent intraoperative hypoxemia and lung injury, the effectiveness of these strategies remains still controversial. Recruitment maneuvers have been proposed as the best strategy to open the lung, thereby preventing both atelectasis and lung collapse. In addition, the application of an adequate level of PEEP, after the recruitment maneuvers have been performed, positively affects the respiratory function. The adequate level of PEEP should be individually addressed because many perioperative factors, such as the intrinsic PEEP level, can alter the ventilation effects. The mechanical ventilation-induced lung damage more frequently occurs in patients undergoing OLV. Therefore, OLV is an important predictor of perioperative ALI. In the operative setting, the occurrence of hypoxemia is generally the first sign of impaired lung function. As suggested by many authors, hypoxemia requires either immediate treatment or a proper diagnosis to prevent further lung damage.

An adequate postoperative treatment of the patients, who develop hypoxemia, has been recognized as mandatory to reduce the lung injury and the postoperative mortality. Postoperative physiotherapy can be helpful to provide lung expansion and to achieve an adequate airways' cleaning from secretion [58]. Maneuvers to increase the respiratory function, including early mobilization, stimulation of an active cough, inspiratory exercises can also be a valid easily provides either an adequate lung expansion or a valid airways toilette [59]. Preoperative non invasive ventilation (NIV) can be preventively performed in the

patients with moderate to severe respiratory failure; these patients can benefit from NIV to ameliorate either the respiratory gas-exchanges or to improve the respiratory reserve. NIV can also be extremely helpful to treat the most severe form of postoperative hypoxemia [60].

It should be considered that, despite either the severity either the clinical outcome of the postoperative ALI, some cases of ALI are self-limiting, or further investigations on the pathophysiological mechanisms involved are needed. The unexpected spontaneous resolution of these episodes of ALI suggests the implication of a sort of endogenous modulating system that is actually still unknown. In this contest the role of the adenosine has been recently evaluated. Some studies have reported the possible positive effects of the adenosine in protecting the lung from the results of MV [5,61]. Different investigations have reported that the extracellular accumulation of the adenosine is able to attenuate the lung injury in experimental models. Because it is supposed that this activity is genetically mediated, it could represent a chance for the future of the prevention and treatment of postoperative ALI.

Conclusion

Despite several perioperative strategies have been proposed and some of them have been satisfactorily employed in the high-risk patients submitted to major surgery, the adequate prevention of the postoperative ALI is still far to be well assessed. However, due to his/her pivotal position in the perioperative management, the anesthesiologist plays a crucial role in the preventive strategy. In fact, either the accurate patients' selection either the proper preoperative optimization of the clinical conditions performed by the anesthesiologist can significantly reduce the rate of the pulmonary complications. Also, an adequate intraoperative treatment can contribute to reduce the lung injury and the postoperative mortality.

Considering the clinical impact of the pulmonary complications in surgical patients, preventive strategies should be absolutely enhanced. Further research is therefore needed to better understand the role of anesthetic management in preventing the perioperative acute lung injury.

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