

REVIEW

Protective lung ventilation during general anesthesia: is there any evidence?

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Introduction

In acute respiratory distress syndrome (ARDS) several studies have shown that mechanical ventilation with high tidal volume (V_T) and low levels of positive end-expiratory pressure (PEEP) can promote ventilator-induced lung injury (VILI), thus increasing morbidity and mortality [1]. An open lung strategy, combining the use of low V_T with adequate PEEP levels and recruitment maneuvers, has thus been recommended in ARDS patients [2]–[4]. In patients without ARDS admitted to intensive care units (ICUs), who required mechanical ventilation for at least 12 hours, the use of a high V_T significantly increased the inflammatory response [5], [6]. In contrast to critically ill patients, during general anesthesia, mechanical ventilation is required only for a few hours, thus the beneficial effects of lung-protective ventilation remain questionable. Moreover, there are limited data from few randomized controlled trials with only small cohorts of enrolled patients.

Two recent meta-analyses that enrolled patients from ICUs and the operating room (OR) showed that lung-protective ventilation was associated with lower mortality and postoperative complications [2], [7]. However, there are no recommendations regarding optimal ventilatory strategies in patients without lung injury during general anesthesia.

In the present article, we provide a comprehensive picture of the current literature on lung-protective ventilation during general anesthesia in patients without ARDS, focusing on the applications of this strategy in patients undergoing abdominal, thoracic and cardiac surgery.

How mechanical ventilation is applied in the operating room

Although the protective ventilation approach may be beneficial in a broader population with and without ARDS, the use of high V_T without PEEP is still common during general anesthesia. A large French multicenter observational study, in which more than 2,900 patients undergoing general anesthesia were enrolled, showed that 18 % of patients were ventilated with a V_T greater than 10 ml/kg body weight and 81 % without PEEP [8]. Moreover, a recruitment maneuver was applied in only 7 % of patients.

Similarly a 5-year observational study, in which 45,575 patients were enrolled, reported that although use of a V_T less than 10 ml/kg and PEEP levels greater than 5 cmH₂O increased progressively over time, 16–18 % of patients continued to receive a V_T greater than 10 ml/kg without application of PEEP [9]. The presence of obesity and a short height were the main risk factors for receiving a large V_T during prolonged anesthesia [10].

Rationale for lung-protective ventilation during general anesthesia

General anesthesia affects lung function primarily because of the loss of muscle tone, which promotes a reduction in lung volume, an alteration in ventilation-perfusion ratio and the onset of lung atelectasis. The development of atelectasis is very common and occurs in more than 90 % of subjects undergoing general anesthesia [11], [12]. Atelectasis is mainly due to three basic mechanisms [13], [14]:

- compression atelectasis
- absorption atelectasis
- loss of surfactant atelectasis.

Compression atelectasis is caused by the alterations in chest wall mechanics induced by general anesthesia *per se* and by several other mechanisms, such as the patient's position (head-down), the body mass index, the age of

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patient and the type of surgery (abdominal surgery or laparoscopy), which increase intra-abdominal pressure (IAP), thus decreasing chest compliance and functional residual capacity (FRC), with the consequent development of intraoperative atelectasis, intrapulmonary shunting and hypoxemia. Other factors related to surgery can contribute to the reduction in pulmonary inflation and to the development of atelectasis, such as a prolonged recumbent position intraoperatively, residual pain that reduces cough effectiveness, and postoperative diaphragmatic dysfunction that can persist for up to one week [15], [16]. If the FRC is reduced below closing capacity, airway closure will occur; consequently the lung bases will be well perfused, but underventilated due to airway closure and alveolar collapse. This phenomenon increases ventilation-perfusion mismatch and promotes further atelectasis generation and hypoxemia.

Absorption atelectasis can be caused by exposure to high inspired fraction of oxygen (FiO_2) levels. When oxygen is absorbed from the alveolar gas into the capillary in distal occluded alveolar areas or where the ventilation-perfusion ratio is low or high FiO_2 levels are delivered, reabsorption of gas is promoted and generates atelectasis [11].

Loss of surfactant atelectasis arises from alterations in surfactant induced by effects of general anesthesia on healthy lungs [17].

The presence of atelectasis is an important factor in the pathogenesis of postoperative pulmonary complications, such as hypoxemia, pulmonary infections and local inflammatory response [18]. Postoperative pulmonary complications in the first hours after surgery are mainly due to atelectasis in the dependent regions of the lungs. Lung atelectasis may also promote the development of VILI by lung overdistension and by cyclic opening and closing of lung units at the boundary between the normally inflated and collapsed lung units. On the basis of several studies of mechanical ventilation in ARDS patients, the same mechanisms of injury could be applied to mechanically ventilated patients during general anesthesia with healthy lungs. The use of recruitment maneuvers associated with adequate levels of PEEP could open and keep open previously collapsed lung regions. In addition, the use of a low-moderate V_T could avoid overstress-overdistension of lung units.

Protective versus conventional lung ventilation strategies during general anesthesia

In Table 1, we provide a synopsis of randomized controlled trials (RCT) comparing protective *versus* conventional lung ventilation strategies during general anesthesia over time, in specific surgical settings showing the main outcomes explored in these studies. In Figure 1, we show the numbers of RCTs that we considered, divided according to the type of surgery.

Abdominal surgery

Postoperative pulmonary complications remain a significant problem after surgery. They occur in 5–10 % of all surgical patients and 9–40 % of those undergoing abdominal surgery experience postoperative pulmonary complications [19], which increase morbidity and mortality [19], [20]. Among the postoperative pulmonary complications, lung atelectasis is one of the principle mechanisms for the development of VILI, pneumonia and postoperative respiratory failure.

In this context, Wrigge and colleagues investigated in two studies the effect of different ventilatory strategies on the release of inflammatory mediators in patients undergoing elective surgery [21], [22]. In the first study, 39 patients scheduled for extra-thoracic surgery (abdominal, vascular, bone and other) were randomized to one of three mechanical ventilation strategies: 1) V_T of 15 ml/kg ideal body weight without PEEP; 2) V_T of 6 ml/kg without PEEP; and 3) V_T of 6 ml/kg with PEEP 10 cmH₂O. Plasma levels of interleukin (IL)-6, IL-10 and tumor necrosis factor (TNF)- α were measured after one hour of mechanical ventilation [21]. In the second study, 64 patients undergoing general anesthesia were randomized to receive mechanical ventilation with a V_T of 12–15 ml/kg ideal body weight without PEEP, or with V_T of 6 ml/kg and PEEP levels of 10 cmH₂O. Local and systemic inflammatory biomarkers, including IL-8, IL-1, IL-6, IL-10, TNF- α and IL-12, were determined after 3 hours of mechanical ventilation [22]. Both studies were unable to find any significant differences in terms of inflammatory mediators and the authors concluded that, in contrast to patients with acute lung injury in whom there is a systemic inflammatory reaction during major surgery, in uninjured normal lungs short term mechanical ventilation alone with high V_T levels did not increase pulmonary or systemic inflammation related to surgery [21], [22]. No differences in biomarkers of lung epithelial injury were observed after 5 hours in a later study, which compared ventilation with V_T 12 ml/kg ideal body weight without PEEP versus V_T 6 ml/kg and PEEP 10 cmH₂O [23].

To explore the effect of a high compared to a low V_T for similar PEEP levels, Treschan et al. randomized patients to receive a V_T of 12 ml/kg body weight versus 6 ml/kg with a PEEP of 5 cmH₂O [24]. Except for the intraoperative oxygenation, which was higher in the high V_T group, there was no significant difference in forced vital capacity and forced expiratory volume in one second between groups, for up to five days after the surgery.

Different from the previous studies, Weingarten et al. evaluated an open lung strategy in which low V_T ventilation was associated with PEEP plus a recruitment maneuver in order to minimize atelectasis and shear stress in the lung parenchyma [25]. This open lung

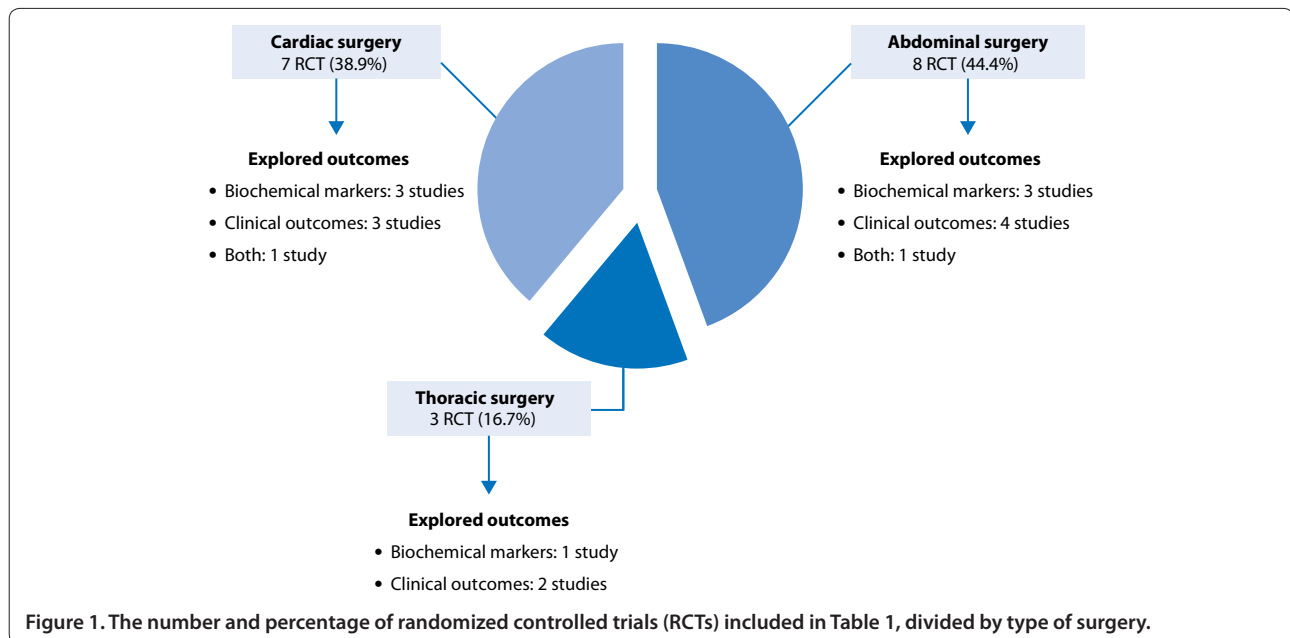
Table 1 Synopsis of randomized controlled trials comparing protective versus conventional lung ventilation strategy during general anesthesia. Studies are grouped according to specific surgical settings: abdominal, thoracic and cardiac surgery

	First author [ref]	Year	N° pts	Ventilatory strategy						Outcomes
				V_T (ml/kg)		PEEP (cmH ₂ O)		Recruitment maneuver (Yes/No)		
				Case	Control	Case	Control	Case	Control	
Abdominal	Wrigge [21]	2000	39	66 6	15	0 10	0	No	No	Systemic IL-6, IL-10, TNF- α : similar
	Wrigge [22]	2004	30	6	12–15	10	0	No	No	Systemic/pulmonary IL-8-1-6-10-12, TNF- α : similar
	Determann [23]	2008	40	6	12	10	0	No	No	Lung epithelial injury biomarkers: similar
	Weingarten [25]	2010	40	6	10	12	0	Yes	No	Intraoperative PaO ₂ , Lung mechanics: better Systemic IL-8, IL-6: similar
	Treschan [24]	2012	101	6	12	5	5	No	No	Postoperative dynamic spirometry: similar
	Severgnini [26]	2013	56	7	9	10	0	Yes	No	Clinical Pulmonary Infection Score: lower Postoperative respiratory function: better
	Futier [27]	2013	400	6-8	10–12	6–8	0	Yes	No	Pulmonary/extrapulmonary complications: lower Hospital stay: shorter
Thoracic	PROVHILO [28]	–	900	< 8	< 8	12	≤ 2	Yes	No	Postoperative pulmonary complications
	Schilling [33]	2005	32	5	10	0	0	No	No	Pulmonary TNF- α , IL-8, IL-10: lower TNF- α
	Michelet [36]	2006	52	5	9	5	0	No	No	Systemic IL-1 β , IL-6, IL-8: lower Oxygenation: better Postoperative MV length: shorter
	Yang [35]	2011	100	6	10	5	0	No	No	Oxygenation: better Postoperative pulmonary complications: lower
Cardiac	Chaney [49]	2000	25	6	12	5	5	No	No	Postoperative lung mechanics: better
	Koner [42]	2004	44	6 10	10	5 5	0	No	No	Systemic IL-6, TNF- α : similar Hospital LOS: similar Postoperative pulmonary function: similar
	Zupancich [44]	2005	40	8	10–12	10	2–3	No	No	Pulmonary and systemic IL-6, IL-8: lower
	Reis [47]	2005	62	4–6	6–8	10	5	Yes	No	Systemic IL-8, IL-10: lower Systemic IL-6, TNF- α , IFN- γ : similar
	Reis [48]	2005	69	4–6	6–8	10	5	Yes	No	Postoperative hypoxemia: lower Postoperative FRC: better
	Wrigge [41]	2005	44	6	12	9*	7*	No	No	Systemic TNF- α , IL-6-8-2-4-10: similar Pulmonary TNF- α , IL-6-8-2-4-10: lower TNF- α
	Sundar [43]	2011	149	6	10	5*	4.9*	No	No	Time to extubation: similar Extubation at 6–8 h after surgery: better Reintubation: lower

Case: lung-protective ventilation group; Control: conventional ventilation strategy group. Outcome results always refer to the case group. In the Thoracic surgery section, ventilatory parameters refer to one-lung ventilation. *PEEP levels set according to ARDSnetwork strategy. V_T : tidal volume; PEEP: positive end-expiratory pressure; MV: mechanical ventilation; FRC: functional residual capacity; IL: interleukin; TNF: tumor necrosis factor; IFN: interferon; pts: patients; PaO₂: partial pressure of oxygen in arterial blood; LOS: length of stay.

strategy, consisting of a V_T of 6 ml/kg predicted body weight with PEEP 12 cmH₂O and recruitment maneuvers, significantly improved only intraoperative oxygenation with no difference in the inflammatory response or length of hospital stay compared to a V_T of 10 ml/kg without PEEP [25]. These first studies seem to suggest that a protective ventilator strategy does not have any role in patients without lung injury [21]–[25]. However, these studies demonstrated that this mode of ventilation

is feasible in open abdominal surgery with no adverse effects [23], [25]. In contrast to the previous studies, Severgnini et al., comparing a lung protective mechanical ventilation consisting of a V_T of 7 ml/kg ideal body weight with PEEP levels of 10 cmH₂O and recruitment maneuvers versus a V_T of 9 ml/kg without PEEP, showed beneficial effects of the lung-protective strategy during general anesthesia lasting more than 2 hours [26]. The lung-protective strategy improved postoperative



respiratory function in terms of dynamic spirometry, oxygenation, and pulmonary complications for up to 5 days after surgery, without increasing the incidence of intraoperative complications. Although there was no significant difference in the hospital length of stay between groups, 20 % of the patients in the lung-protective group, compared with 40 % in the control group, were still in hospital on postoperative day 14 [26].

A recent multicenter randomized clinical trial in which lung-protective ventilation with a V_T of 6–8 ml/kg predicted body weight, PEEP 6–8 cmH₂O and recruitment maneuvers repeated every 30 minutes was compared with non-protective ventilation with V_T 10–12 ml/kg without PEEP, found that the lung-protective ventilation significantly reduced major pulmonary and extrapulmonary complications from 27.5 % to 10.5 % [27]. The lung-protective strategy also significantly reduced the proportion of patients who required postoperative ventilator assistance from 17 % to 5 % and the hospital length of stay.

Compared to the earlier studies [22]–[25], these two recent trials found a beneficial effect of a lung-protective strategy probably because of the large number of enrolled patients, the homogeneity of the selected population of patients undergoing open abdominal surgery with an expected duration of at least 2 hours, the standardization of fluid management, and the clinically relevant outcomes explored (not only lung inflammatory mediators) in the postoperative period.

These results demonstrate that in patients undergoing abdominal surgery a multifaceted open lung protective strategy can prevent the intraoperative alveolar opening

and closing and overdistension of lung areas that lead to VILI and pulmonary complications. Currently, we are waiting for the results of the PROVHILO study, a worldwide multicenter RCT in which patients scheduled for abdominal surgery are being enrolled. In this study, all patients are ventilated with protective tidal volumes (in both groups, $V_T < 8$ ml/kg predicted body weight) and randomly assigned to a lung-protective strategy with use of recruitment maneuvers and PEEP levels of 12 cmH₂O or a conventional strategy without recruitment maneuvers and PEEP between 0 and 2 cmH₂O [28]. If the results of this study confirm those of the last two trials [27], [26], lung-protective strategies will be more widely applied in patients undergoing abdominal surgery [28].

Thoracic surgery

During thoracic surgery, one-lung ventilation is an established procedure that could increase the risk of promoting VILI compared to double lung ventilation, because of greater reduction in lung volume and greater degree of alveolar collapse in dependent lung regions. Two retrospective studies of patients who had undergone elective pneumonectomy found that larger intraoperative V_T and higher inspiratory airway pressure were associated with the development of pulmonary edema and respiratory failure [29], [30]. Despite this, conventional mechanical ventilation in these patients consists of V_T between 8–12 ml/kg to prevent lung atelectasis with zero or low levels of PEEP to avoid shunt aggravation by redistribution of blood flow to non-ventilated regions [31], [32]. However this approach is not an evidence-based guideline.

Schilling et al., in a randomized study in patients scheduled for open thoracic surgery undergoing one-lung ventilation, showed that mechanical ventilation with V_T of 5 ml/kg ideal body weight compared to 10 ml/kg significantly decreased the pulmonary inflammatory response up to 2 hours postoperatively [33]. Subsequently, Licker et al. retrospectively evaluated the implementation of a lung-protective ventilation strategy in lung cancer resection combining a low V_T (< 8 ml/kg) with PEEP 4–10 cmH₂O and recruitment maneuvers *versus* a conventional V_T target ventilation of 9–12 ml/kg during two-lung ventilation and 8–10 ml/kg during one-lung ventilation without recruitment maneuvers and PEEP applied at the discretion of the anesthetist [34]. The lung-protective strategy significantly reduced the incidence of atelectasis (from 8.8 % to 5 %), postoperative acute lung injury (from 3.7 % to 0.9 %), ICU admission (from 9.4 % to 2.5 %) and length of hospital stay (from 14.5 ± 3.3 to 11.8 ± 4.1 days). These data were confirmed in a randomized study during elective lobectomy in which patients were ventilated with a high V_T of 10 ml/kg without PEEP compared to a low V_T of 6 ml/kg with 5 cmH₂O of PEEP and pressure controlled ventilation [35]. The lung-protective ventilation was associated with a lower incidence of lung infiltration or atelectasis (2 versus 10) and of cases of hypoxemia (1 versus 8).

During esophagectomy, a procedure requiring a prolonged period of one-lung ventilation, Michelet et al. demonstrated in an RCT that lung-protective ventilation (V_T 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during one-lung ventilation and PEEP 5 cmH₂O throughout the operative time) could prevent alterations in lung function and reduce the inflammatory response in patients without previous lung disease compared to conventional ventilation strategy (V_T 9 ml/kg during two- and one-lung ventilation without PEEP) [36].

The majority of studies so far have demonstrated that, during thoracic surgery, traditional intraoperative ventilatory settings seem to be harmful. An intraoperative open lung approach based on small V_T , moderate-high PEEP and recruitment maneuvers may be beneficial but further randomized clinical trials are necessary to generate clinical evidence.

Cardiac surgery

In cardiac surgery, use of cardiopulmonary bypass (CPB), contact of the blood with artificial surfaces and ischemia/reperfusion of the heart and lungs are associated with a pulmonary and systemic inflammatory response, with activation of elements of the complement cascade, neutrophils and pro-inflammatory cytokines [37]–[39]. This systemic inflammatory response syndrome can be mild to severe in 10 to 35 % of cases and may induce an acute lung injury, which generally resolves within

24 hours. This clinical event contributes to increased morbidity and mortality [40]. In this context, injurious mechanical ventilation could aggravate the primary inflammatory response described above (first hit), representing a second hit. Moreover, during CPB, the lungs are not ventilated and either rest at low values of continuous positive pressure [41] or are completely disconnected from the ventilator [42]–[44]. Traditionally, ventilator settings in cardiac surgery patients included large V_T (10–15 ml/kg) in order to minimize atelectasis and minimal levels of PEEP to reduce hemodynamic consequences. Following the results of clinical trials in ARDS patients [45], [46], there has been increased interest in protective lung ventilatory strategies during cardiac anesthesia and several trials have tried to demonstrate the role of protective lung ventilation in this context.

Koner et al. found no differences in plasma levels of IL-6 and TNF- α 2 hours after the end of CPB among patients randomized to receive protective ventilation (V_T 6 ml/kg ideal body weight, PEEP 5 cmH₂O) or conventional V_T ventilation (V_T 10 ml/kg) with and without PEEP levels at 5 cmH₂O [42]. There were no differences among groups in the explored clinical outcomes, including total intraoperative fluid balance, intubation time and hospital length of stay [42].

Wrigge et al. measured pulmonary and plasma levels of different cytokines and chemokines (IL-2, IL-4, IL-6, IL-8, IL-10, TNF- α and interferon- γ) in patients ventilated with high or with low tidal volumes (V_T 12 ml/kg *versus* V_T 6 ml/kg ideal body weight). They observed higher values of TNF- α after 6 hours of ventilation with high V_T , with no differences in other inflammatory mediators [41].

However, a significantly reduced inflammatory response, in terms of pulmonary and systemic mediator levels (IL-6 and IL-8) was observed when applying a moderate PEEP level strategy (V_T 8 ml/kg with PEEP 10 cmH₂O) compared to a low PEEP and high V_T strategy (10–12 ml/kg with PEEP 2–3 cmH₂O) [44]. In comparison to previous studies [41], [42], this study evaluated a greater difference in PEEP levels and a longer duration of mechanical ventilation [44].

Reis et al. investigated the effect of open lung ventilation, consisting of low V_T (4–6 ml/kg) with moderate-high PEEP levels (10 cmH₂O) and recruitment maneuvers, on inflammatory mediators. In this study, they compared an early (immediately after intubation) and a late (at the end of CPB) application of the same open lung strategy, with conventional ventilation (V_T 6–8 ml/kg, PEEP 5 cmH₂O). Both the open lung approaches significantly decreased IL-8 and IL-10 levels after CPB [47]. Subsequently, the same authors showed that the early open lung approach significantly attenuated the reduction in postoperative FRC, for up to 5 days after surgery,

and reduced the incidence of hypoxemic events during the first 3 days after extubation [48]. Ventilation and weaning times were similar among groups. This positive effect on postoperative FRC could be related to the prevention of additional lung injury caused by mechanical ventilation. Chaney et al. similarly reported better dynamic and static lung compliance and less shunt in patients ventilated with low compared to high V_T (6 versus 12 ml/kg) [49].

Recently Sundar and colleagues observed that a larger number of patients were extubated after 8 hours (53 % versus 31 %) when ventilated with a low V_T of 6 ml/kg ideal body weight compared to V_T 10 ml/kg with similar PEEP levels. Furthermore, a lower postoperative reintubation rate was observed. However, global time to extubation was similar between groups, as were ICU length of stay and 28-day mortality [43].

There is, therefore, a small amount of evidence from small studies in support of lung-protective ventilation in cardiac surgery patients [50]. However, the presence of several confounding factors, not related to mechanical ventilation, which could contribute to the development of a systemic inflammatory response and postoperative pulmonary complications, may have influenced the main outcome results. Hence, further studies with larger cohorts of patients are needed to confirm the still weak evidence in favor of lung-protective ventilation in cardiac anesthesia.

Conclusions

Mechanical ventilation is necessary for patients during general anesthesia. Although mechanical ventilation is considered a safe procedure, it can generate pulmonary stress and strain, promoting lung injury. There is increasing evidence that lung-protective ventilation may be beneficial in abdominal surgery (lower inflammatory response and better outcome). During thoracic and cardiac surgery, lung protective ventilation has only been associated with a reduced inflammatory response.

Lung-protective ventilation should be considered in the presence of pulmonary disease, prolonged anesthesia, in high-risk patients or for high-risk surgery. Although lung-protective ventilation may be beneficial for the lung, it may impair the cardiovascular system, reducing venous return and cardiac output and requiring the use of fluids and vasopressors. Thus, the risks and benefits of lung-protective ventilation need to be balanced in each individual patient.

List of abbreviations used

ARDS: acute respiratory distress syndrome; FiO_2 : inspired fraction of oxygen; FRC: functional residual capacity; IAP: intra-abdominal pressure; IFN: interferon; IL: interleukin; LOS: length of stay; MV: mechanical ventilation; OR: operating room; PEEP: positive end-expiratory pressure; PaO_2 : partial pressure of oxygen in arterial blood; pts: patients; RCT: randomized controlled trials; TNF: tumor necrosis factor; VILI: ventilator-induced lung injury; V_T : tidal volume.

Competing interests

The authors declare that they have no competing interests.

Declarations

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