David S. Warner, M.D., Editor

Intraoperative Protective Mechanical Ventilation for Prevention of Postoperative Pulmonary Complications

A Comprehensive Review of the Role of Tidal Volume, Positive End-expiratory Pressure, and Lung Recruitment Maneuvers

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ABSTRACT

Postoperative pulmonary complications are associated with increased morbidity, length of hospital stay, and mortality after major surgery. Intraoperative lung-protective mechanical ventilation has the potential to reduce the incidence of postoperative pulmonary complications. This review discusses the relevant literature on definition and methods to predict the occurrence of postoperative pulmonary complication, the pathophysiology of ventilator-induced lung injury with emphasis on the noninjured lung, and protective ventilation strategies, including the respective roles of tidal volumes, positive end-expiratory pressure, and recruitment maneuvers. The authors propose an algorithm for protective intraoperative mechanical ventilation based on evidence from recent randomized controlled trials. **(ANESTHESIOLOGY 2015; 123:692-713)**

POSTOPERATIVE pulmonary complications (PPCs) can have an important impact on the morbidity and mortality of patients who need major surgery.[1] Approximately 5% of patients undergoing general surgery will develop a PPC, and one of the five patients who developed a PPC will die within 30 days of surgery.[1] Furthermore, the number of PPCs is strongly associated with postoperative length of stay and short-term and long-term mortality.[1,2]

There is growing evidence that intraoperative lung-protective mechanical ventilation using low tidal volumes, with or without high levels of positive end-expiratory pressure (PEEP), and recruitment maneuvers prevents PPCs compared with mechanical ventilation with high tidal volumes and low levels of PEEP without recruitment maneuvers.[3–6]

In the current article, we review the definition of and methods to predict PPCs, the pathophysiology of ventilator-induced lung injury (VILI) with emphasis on the noninjured lung, and ventilation strategies to minimize PPCs. To identify the most recent evidence from the literature on randomized controlled trials (RCTs) addressing intraoperative mechanical ventilation and nonclinical as well as clinical postoperative outcome measures, we conducted a MEDLINE review

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Table 1. Risk Factors for Postoperative Pulmonary Complications

Patient Characteristics	Preoperative Testing	Surgery	Anesthetic Management
Age	Low albumin	Open thoracic surgery	General anesthesia
Male sex	Low Spo_2 (≤95%)	Cardiac surgery	High respiratory driving pressure (≥13 cm H_2O)
ASA class ≥3	Anemia (Hb <10 g/dl)	Open upper abdominal surgery	High inspiratory oxygen fraction
Previous respiratory infection		Major vascular surgery	High volume of crystalloid administration
Functional dependency		Neurosurgery	Erythrocyte transfusion
Congestive heart failure		Urology	Residual neuromuscular blockade
COPD		Duration of surgery >2 h	Nasogastric tube use
Smoking		Emergent surgery	
Renal failure			
Gastroesophageal reflux disease			
Weight loss			

Respiratory driving pressure is defined as inspiratory plateau airway pressure *minus* positive end-expiratory pressure.

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; Hb = hemoglobin concentration; SpO_2 = oxygen saturation as measured by pulse oximetry.

using the following search terms: "lower tidal volume" OR "low tidal volume" OR "protective ventilation" OR "recruitment maneuvers" OR "PEEP" OR "positive end expiratory pressure." Retrieved articles, and cross-referenced studies from those articles, were screened for pertinent information.

Definition and Prediction of PPCs

Summary of Current Definitions

Postoperative pulmonary complications are usually presented as a composite, which then includes possible fatal and nonfatal respiratory events of new onset occurring in the postoperative period. Currently, there is no agreement about which of these events should be considered as PPC, for example, respiratory failure, lung injury, pneumonia, prolonged or unplanned mechanical ventilation or intubation, hypoxemia, atelectasis, bronchospasm, pleural effusion, pneumothorax, ventilatory depression, and aspiration pneumonitis.[7,8] From a clinical standpoint, it is worthwhile to present PPCs as a composite because any of these events alone or their associations has a significant impact on the postoperative outcome,[1] using different definitions. However, it is clear that these events can have different pathophysiologic mechanisms. For this reason, some studies have focused on single events, mainly respiratory failure[9] and pneumonia.[10]

Postoperative pulmonary complications, to be considered as such, must be related to anesthesia and/or surgery. Furthermore, the time frame must be well defined. Usually, an event is only considered as PPC if it develops within 5 to 7 days after surgery.[8,11]

Prediction of PPCs

Prediction of PPCs, or any of the single postoperative respiratory events that is part of that composite, can be useful to plan perioperative strategies aiming at their prevention and also to reduce health system costs.[12] First, the risk factors associated with the development of PPCs must be identified. In 2006, the American College of Physicians published a systematic review of the literature listing a number of risk factors for PPCs according to their respective levels of evidence.[13] In recent years, that list has been expanded to include other factors found to increase the risk of PPCs. Table 1 depicts the risk factors associated with PPCs according to the current literature. Approximately 50% of the risk factors for PPCs are attributable to the patient's health conditions, whereas the other 50% are related to the surgical procedure and the anesthetic management itself.[1]

Based on risk factors, different scores have been developed that have the potential to predict the occurrence of PPCs,[6,14–16] as shown in table 2. However, their applicability may be limited because they were derived from restricted settings,[16] retrospective databases,[15] or only validated for specific PPCs.[6,14] The Assess Respiratory RIsk in Surgical Patients in CATalonia (ARISCAT) study was conducted in a general surgical population of Catalonia, Spain.[1] After a multivariate analysis, a score based on seven risk factors was developed and underwent internal validation, showing a clinically relevant predictive capability (*c*-statistic, 0.90). Recently, the ARISCAT score was externally validated in a large European surgical sample (the Prospective Evaluation of a RIsk Score for Postoperative Pulmonary COmPlications in Europe study).[2] Although differences in the performance of the ARISCAT score have been observed between European geographic areas, the score was able to discriminate three levels of PPCs risk (low, intermediate, and high). Thus, at present, the ARISCAT score may represent the most valuable tool for predicting PPCs across different countries and surgical populations.

Putative Mechanisms of VILI

The coexistence of closed, recruitable, and already overdistended alveolar regions makes the lung vulnerable to detrimental effects of mechanical stress and strain induced by

Table 2. Scores for Prediction of PPCs

References Published	Study Design	Patient Population	Patients, No.	Score Acronym	Scoring System		Cutoff	Quality of Prediction
Prediction of general PPCs								
Canet *et al.* [1]	Prospective, multicenter, observational cohort study	Adult patients undergoing non-obstetric surgical procedures under general, neuraxial, or regional anesthesia	2,464 overall; 1,624 derivation; 837 validation; 3 patients with missing data for two parameters relevant for the score (Spo_2 + respiratory infection during last month)	ARISCAT	Age: 51–80	3	Level/point/rate of PPC: low/<26/1.6%; medium/26–44/13.3%; high/≥45/42.1% (validation subsample)	Derivation cohort: AUC: 0.89
					>80	16		
					Spo_2%: 91–95	8		
					<90	24		
					Respiratory infection during last month	17		
					Preoperative anemia (Hb <10 g/dl)	11		
					Surgical incision			
					Peripheral	1	PPC: respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, aspiration pneumonitis	Validation cohort: AUC: 0.84
					Upper abdominal	15		
					Intrathoracic	24		
					Duration of surgery, h ≤2	1		
					>2–3	16		
					>3	23		
					Emergency procedure	8		
Mazo *et al.*[2] (validation of ARISCAT score from the study by Canet *et al.*[1] in a larger, international, multicenter cohort)	Prospective, multicenter, observational cohort study	Adult patients undergoing non-obstetric surgical procedures under general, neuraxial, or plexus block anesthesia	5,099	ARISCAT	See above		Level/point/predicted/observed rate of PPC: low/<26/0.87%/3.39%; medium/26–44/7.82%/12.96; high/≥45/38.13%/38.01%	AUC: 0.80

(*Continued*)

Table 2. Continued

References Published	Study Design	Patient Population	Patients, No.	Score Acronym	Scoring System		Cutoff	Quality of Prediction
Prediction of selected PPCs								
Johnson *et al.*[14] (reevaluated in a broader cohort from the study by Arozullah *et al.*[9])	Prospective, multicenter, observational cohort study	Adult patients undergoing major general or vascular procedures performed under general, spinal, or epidural anesthesia	90,055 derivation; 89,948 validation	Respiratory failure Risk Index	Type of surgery		Level/point/predicted/observed probability of PRF: low/<8/0.2%/0.08%; medium/8–12/1.0%/0.84%; high/>12/6.6%/6.75%	Derivation cohort: AUC: 0.856
					Integumentary	1		
					Respiratory and hemic	3		
					Heart	2		
					Aneurysm	2		
					Mouth, palate	7		
					Stomach, intestines	2		
					Endocrine	2		
					Predisposing factors			
					Male sex	1		
					Age 40–65	2		
					Age >65	2		
					ASA class 3	3		
					ASA class 4–5	5		
					Work RVU 10–17	2		
					Work RVU >17	4		
					Emergency	2		
					Sepsis	2		
					History of severe COPD	2		
					Ascites	2	PRF: mechanical ventilation for >48 h or unplanned reintubation	Validation cohort: AUC: 0.863
					Dyspnea	1		
					Impaired sensorium	1		
					>2 alcoholic drinks/d in 2 wk	1		
					Bleeding disorders	1		
					Weight loss >10%	1		
					Acute renal failure	2		
					Congestive heart failure	1		
					Smoker	1		
					Stroke	1		
					Wound class other than clean	1		
					Preoperative albumin <3.5	1		
					Creatinine >1.5	2		
					Preoperative bilirubin >1.0	1		
					White blood count <2.5/>10	1		
					Preoperative serum sodium >145	2		
					Platelet count <150	1		
					SGOT >40	1		
					Hematocrit <38	1		

(*Continued*)

Table 2. Continued

References Published	Study Design	Patient Population	Patients, No.	Score Acronym	Scoring System		Cutoff	Quality of Prediction
Brueckmann *et al.*[15]	Retrospective, single-center, observational cohort study	Cases with a surgical procedure if the adult patient was intubated at the beginning and extubated at the end of the procedure	33,769 overall; 16,885 derivation; 16,884 validation	Score for Prediction of Postoperative Respiratory Complications	ASA score ≥3	3	Score values/probability of reintubation: 0/0.12%; 1–3/0.45%; 4–6/1.64%; 7–11/5.86% (validation subsample)	Derivation cohort: AUC: 0.81 Validation cohort: AUC: 0.81
					Emergency procedure	3		
					High-risk service	2		
					Congestive heart failure	2		
					Chronic pulmonary disease	1		
Prediction of ALI/ARDS								
Gajic *et al.*[6] (similar to the study by Trillo-Alvarez *et al.*[17] but used a larger, multicenter cohort)	Prospective, multicenter, observational cohort study	Adult patients with one or more ALI risk factors, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery	5,584 overall; 2,500 derivation; 3,084 validation	Lung Injury Prediction Score	Predisposing conditions		>4; cutoff for development of ALI/ARDS	Combined: AUC: 0.80; sensitivity: 0.69; specificity: 0.78
					Shock	2		
					Aspiration	2		
					Sepsis	1		
					Pneumonia	1.5		
					High-risk surgery			
					Orthopedic spine	1		
					Acute abdomen	2		
					Cardiac	2.5		
					Aortic vascular	3.5		
					If emergency surgery	+1.5		
					High-risk trauma			
					Traumatic brain injury	2		
					Smoke inhalation	2		
					Near drowning	2		
					Lung contusion	1.5		
					Multiple fractures	1.5		
					Risk modifiers			
					Alcohol abuse	1		
					Obesity (BMI >30)	1		
					Hypoalbuminemia	1		
					Chemotherapy	1		
					F_{IO_2} >0.35 (>4 l/min)	2		
					Tachypnea (RR >30)	1.5		
					Sp_{O_2} <95%	1		
					Acidosis (pH <7.35)	1.5		
					Diabetes mellitus	–1, if septic		

(*Continued*)

Table 2. Continued

References Published	Study Design	Patient Population	Patients, No.	Score Acronym	Scoring System		Cutoff	Quality of Prediction
Kor *et al.*[16] (similar to the study by Kor *et al.*[18], but used a larger, multicenter cohort; secondary analysis of the study by Gajic *et al.*[6])	Secondary analysis of a prospective, multicenter cohort study	Adult patients presenting with one or more ALI risk factors, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery and undergoing a surgical procedure	1,562	Surgical Lung Injury Prediction 2	Surgical procedure		≥19; cutoff for development of ARDS	AUC: 0.84; Sensitivity: 0.82; Specificity: 0.75
					High-risk cardiac surgery	7		
					High-risk aortic vascular surgery	11		
					Emergency surgery	10		
					Baseline health status			
					Sepsis	10		
					Cirrhosis	20		
					Admission source other than home 9			
					Physiologic markers of acute illness			
					Respiratory rate 20–29	7		
					Respiratory rate ≥30	14		
					FIO_2 >35%	13		
					SpO_2 <95%	5		

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ARISCAT = Assess Respiratory RIsk in Surgical Patients in CATalonia; ASA = American Society of Anesthesiologists classification; AUC = area under the curve; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FIO_2 = fraction of inspired oxygen; Hb = hemoglobin; PPC = postoperative pulmonary complication; PRF = postoperative respiratory failure; RR = respiratory rate; RVU = relative value units (a measure of surgical complexity); SGOT = serum glutamic-oxaloacetic transaminase; SpO_2 = oxygen saturation as measured by pulse oximetry.

mechanical ventilation.[19,20] The physical forces in some alveolar regions may exceed the elastic properties of the lungs although gross measurements of airway pressures or lung mechanics as usually monitored under anesthesia still suggest mechanical ventilation is in a "safe" zone.[21,22] Several mechanisms have been postulated to describe the development of VILI.[23] Increased airway pressure (barotrauma) or the application of high tidal volumes (volutrauma) may cause damage or disruption of alveolar epithelial cells, by generating transpulmonary pressures (stress) that exceed the elastic properties of the lung parenchyma above its resting volume (strain).[24,25] It has been demonstrated that the duration of mechanical stress defined as the stress *versus* time product affects the development of pulmonary inflammatory response.[26] Although high stress *versus* time product increased the gene expression of biological markers associated with inflammation and alveolar epithelial cell injury and low stress *versus* time product increased the molecular markers of endothelial cell damage, balanced stress *versus* time product as defined by an inspiratory to expiratory time ratio of 1:1 was associated with attenuated lung damage.[26] Especially in the presence of atelectasis, mechanical ventilation may cause damage by repetitive collapse and reopening of alveolar units, a phenomenon known as atelectrauma.[27] All three mechanisms, namely barotrauma, volutrauma, and atelectrauma, may affect alveolar as well as vascular epithelial and endothelial cells[28,29] and promote extracellular matrix fragmentation.[30,31]

The extracellular matrix of the lung parenchyma seems to be particularly sensitive to stress from mechanical ventilation, as illustrated in figure 1. Initially, the proteoglycans on the endothelial side and between the endothelial and epithelial lines undergo damage dependent on tidal volume,[30] as well as breathing pattern.[31] The mechanical fragmentation of the extracellular matrix promotes interstitial edema and activation of metalloproteinases, further damaging the extracellular matrix itself. In a second step, fragments of the extracellular matrix can promote the activation of inflammatory mediators.[32,33] Furthermore, the damage of the extracellular matrix induced by mechanical ventilation might be exacerbated by fluid load,[34] which is not uncommon during general anesthesia. However, fluid overload seems to minimize the inflammatory response, likely by dilution of extracellular matrix fragments or changes in their structure, thereby down-regulating the local inflammatory response.[34] This suggests that (1) injurious mechanical ventilation makes the lung more susceptible to further insults; and (2) in previously healthy lungs, VILI can be induced without early increase in inflammatory mediators.

At the cellular level, physical stimuli are transformed into chemical signals, for example, proinflammatory and antiinflammatory mediators by means of direct cell injury or indirect activation of cellular signaling pathways. This process is known as "mechanotransduction."[35] Some mediators may promote local effects such as proapoptotic or profibrotic actions, whereas others act as homing molecules recruiting

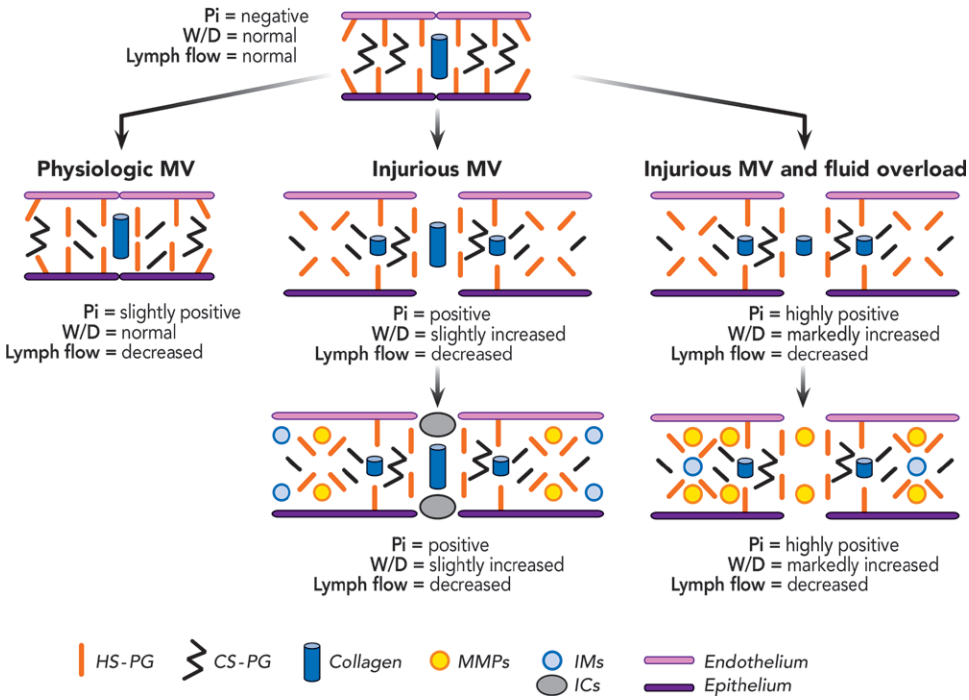

Fig. 1. Alterations of the extracellular matrix in lungs during mechanical ventilation and fluid administration. CS-PG = chondroitin sulfate proteoglycans; HS-PG = heparan sulphate proteoglycans; ICs = inflammatory cells; IMs = inflammatory mediators; MMPs = metalloproteases; MV = mechanical ventilation; Pi = interstitial pressure; W/D = wet/dry ratio.

local and remote immune cell populations (*e.g.*, neutrophils and macrophages).[36] These local effects as well as their immunological consequences are summarized by the term "biotrauma."[37]

Besides the extracellular matrix, both the endothelial and the epithelial compartments of the alveolar–capillary unit are affected by stress and strain originating from mechanical ventilation. In the endothelium, high stress can lead to direct cell breaks, resulting in capillary stress failure.[38,39] Furthermore, mechanical stress as well as inflammatory stimuli (*i.e.*, tumor necrosis factor-α) may trigger contractions of the cytoskeleton,[40] resulting in disruption of adherence junctions,[41] which increase the endothelial permeability and contribute to edema formation. Similar to the pulmonary endothelium, mechanical stress and strain increase the permeability of the alveolar epithelium,[42] a phenomenon found during ventilation at high[43] as well as low[44] lung volumes. In addition, low lung volume ventilation can lead to repetitive collapse and reopening of lung, affecting the epithelium of small airways, yielding plasma membrane disruption,[45] and epithelial necrosis and sloughing.[46]

Alveolar fluid clearance is essential to maintain intraalveolar fluid homeostasis, which is usually compromised during VILI. Whereas ventilation with high tidal volumes directly decreases Na^+/K^+-adenosine triphosphatase activity,[47] ventilation at low lung volumes may indirectly impair fluid clearance due to hypoxia following increased alveolar collapse.[48]

Impairment of barrier function of the endothelium and epithelium, as well as of fluid clearance, leads to the development of interstitial and alveolar edema, which subsequently causes surfactant dysfunction, and impairs lungs elastic and resistive properties.[49] Dysfunction of the surfactant system makes the lung susceptible to alveolar collapse contributing to deterioration of lung mechanics and impairing pulmonary host defense.[50]

Although most evidence of gross structural alterations of endothelium and epithelium induced by mechanical ventilation originates from *in vitro* investigations of cultured cells or *in vivo* investigations in acute lung injury models,[51] ventilation applying clinically relevant settings in noninjured lungs can affect the alveolar–capillary barrier function, especially in the presence of independent inflammatory triggers, making mechanical ventilation a powerful hit in the presence of systemic inflammation.[29]

Due to the disturbed integrity of the alveolar–capillary barrier function and consecutive systemic translocation of pathogens or inflammatory mediators, VILI may lead to a systemic inflammatory response affecting not only the lungs but the distal organs as well.[52]

Lung inhomogeneity, for example, due to atelectasis formation, is a major contributing factor to the development of VILI. However, most experimental evidence is derived from the acute lung injury models. Although their basic pathogenetic mechanisms may be similar, the magnitude and time course of atelectasis formation in acute lung injury may be very different from those of atelectasis occurring during anesthesia and relatively short-term intraoperative mechanical ventilation. Resorption of

alveolar gas[53,54] and compression of lung structures[55–58] may lead to atelectasis during short-term mechanical ventilation in noninjured lungs, whereby the former might play a more important role.

In a porcine model of experimental pneumonia, both exogenous surfactant administration and ventilation according to the open lung approach attenuated bacterial growth and systemic translocation by minimizing alveolar collapse and atelectasis formation.[59] In a similar model of experimental pneumonia in mechanically ventilated piglets, bacterial translocation was lowest with individually tailored PEEP levels, whereas low and high PEEP promoted bacterial translocation.[60]

In isolated nonperfused mouse lungs, both an "open lung approach" (tidal volume 6 ml/kg, recruitment maneuvers, and PEEP of 14 to 16 cm H_2O) and a "lung rest strategy" (tidal volume of 6 ml/kg, PEEP of 8 to 10 cm H_2O, and no recruitment maneuvers) were associated with reduced pulmonary inflammatory response and improved respiratory mechanics compared with injurious mechanical ventilation (tidal volume of 20 ml/kg and PEEP of 0 cm H_2O).[61] Interestingly, the "lung rest strategy" was associated with less apoptosis but more ultrastructural cell damage, most likely due to increased activation of mitogen-activated protein kinase pathways as compared with the "open lung strategy."[61]

In healthy mice, mechanical ventilation with a tidal volume of 8 ml/kg and PEEP of 4 cm H_2O induced a reversible increase in plasma and lung tissue cytokines as well as increased leukocyte influx, but the integrity of the lung tissue was preserved.[62] In another investigation, even least-injurious ventilator settings were able to induce VILI in the absence of a previous pulmonary insult in mice.[63] Of note, the deleterious effects of mechanical ventilation in noninjured lungs are partly dependent on its duration.[64] However, an experimental study demonstrated that large tidal volumes had only minor if any deleterious effects on lungs, despite prolonged mechanical ventilation.[25] Possibly, this is explained by the lack of a previous inflammatory insult, as for example, surgery. In fact, systemic inflammation may prime the lungs to injury by mechanical ventilation.[65]

Mechanical Ventilation Strategies to Protect Lungs during Surgery

Atelectasis and Intraoperative Mechanical Ventilation

Atelectasis develops in as much as 90% of patients undergoing general anesthesia[66] and can persist to different degrees after surgery, also surrounding pleura effusion, as illustrated in figure 2. The area of nonaerated lung tissue near to the diaphragm varies depending on the surgical procedure and patient characteristics but has been estimated in the range of 3 to 6%[67–69] to 20 to 25%[66] and even higher if calculated as amount of tissue.

Different mechanisms have been postulated to favor atelectasis formation during anesthesia, including (1) collapse of small airways,[70–72] (2) compression of lung structures,[55–58] (3) absorption of intraalveolar gas content,[53,54] and (4) impairment of lung surfactant function.[73] Mechanical ventilation strategies for general anesthesia have been importantly influenced by the progressive decrease in oxygenation

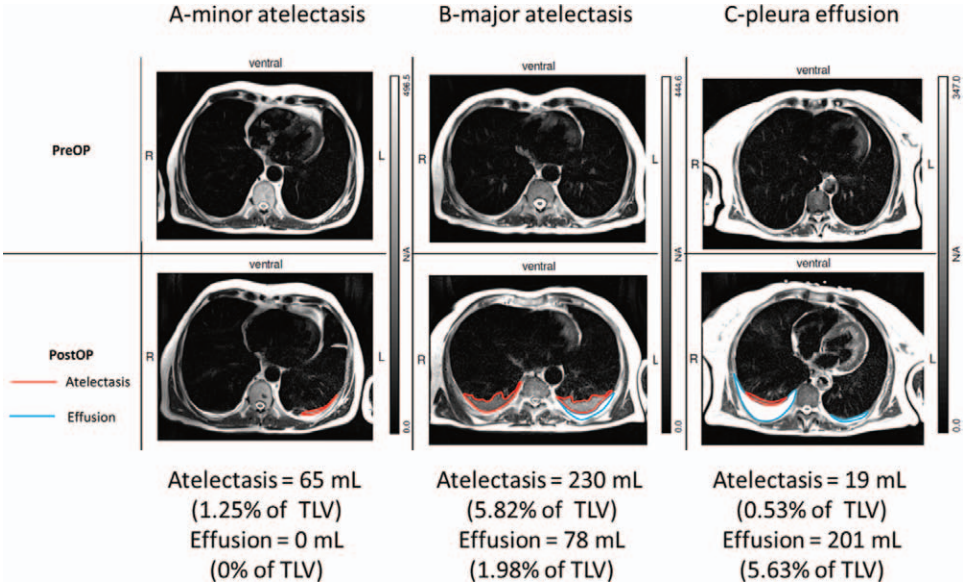

Fig. 2. Magnetic resonance imaging scans of lungs of three patients before and on the first day after open abdominal surgery. Images were obtained throughout spontaneous breathing and represent an average of total lung volume (TLV) during the breath cycles. (*A*) Minor atelectasis, (*B*) major atelectasis, (*C*) pleural effusion. Segmentation of lungs, atelectasis (*red lines*) and pleura effusion (*blue lines*), in magnetic resonance imaging scans was performed manually. Values were calculated for whole lungs. Note that the amounts of atelectasis and pleura effusion, two common postoperative pulmonary complications, are relatively low after surgery. L = left side of chest; N/A = arbitrary gray scale; PostOP = postoperative; PreOP = preoperative; R = right side of chest.

and compliance.[74] Tidal volumes up to 15 ml/kg of predicted body weight were advocated to increase the end-expiratory lung volume (EELV) and counteract atelectasis in the intraoperative period.[74] Provided there is no contraindication, PEEP and lung recruitment maneuvers may also contribute to revert or prevent the loss of EELV and closure of small airways during anesthesia.

Tidal Volumes for Intraoperative Protective Ventilation

Driven by clinical and experimental studies, tidal volumes during mechanical ventilation have been importantly reduced in patients suffering from the acute respiratory distress syndrome (ARDS) to limit lung overdistension.[75] Influenced by this practice in intensive care unit patients, a similar trend was observed in the operation room. As reported by different investigators,[76,77] average tidal volumes in the range of 6 to 9 ml/kg of predicted body weight have gained broad acceptance for noninjured lungs, in spite of experimental[25,78] and clinical[79–81] data suggesting that higher values are not associated with increased lung damage or inflammation. Furthermore, anesthesiologists have consistently reduced tidal volumes also during one-lung ventilation. Whereas values as high as 10 ml/kg have been used in the past, experimental,[82,83] and clinical[84–87] studies have suggested that tidal volumes of approximately 4 to 5 ml/kg may be more appropriate for lung protection, while still allowing adequate gas exchange. Furthermore, a small RCT showed that atelectasis did not increase significantly with low tidal volume without PEEP from induction of anesthesia until the end of surgery.[67] This is also supported by the fact that mechanical ventilation with low tidal volume and PEEP did not result in a progressive deterioration of the respiratory system compliance and gas exchange during open abdominal surgery in a larger RCT.[88] It must be kept in mind that "set" and "actual" (*i.e.*, delivered) tidal volumes can differ substantially[89] and that settings should be adjusted judiciously.

PEEP for Intraoperative Protective Ventilation

Clinical studies have shown that a PEEP of 10 cm H_2O is required to reduce or eliminate atelectasis,[69,90,91] improve compliance without increasing dead space,[92,93] and maintain EELV during general anesthesia in both nonobese and obese patients.[94] Another study in normal subjects showed that PEEP of 10 cm H_2O increased lung volume but did not improve the respiratory function compared with PEEP of 0 cm H_2O.[56] Certainly, the level of PEEP should be chosen according to the patient's particular characteristics, the particularities of the surgical approach, and patient positioning. Several targets have been proposed for a more individual titration of PEEP during general anesthesia, including the following: (1) oxygenation,[95] also combined with dead space[92] or EELV,[93] (2) mechanical properties of the respiratory system,[96] and (3) distribution of ventilation using electric impedance tomography.[97,98] However, none of these has been shown to improve patient outcome.

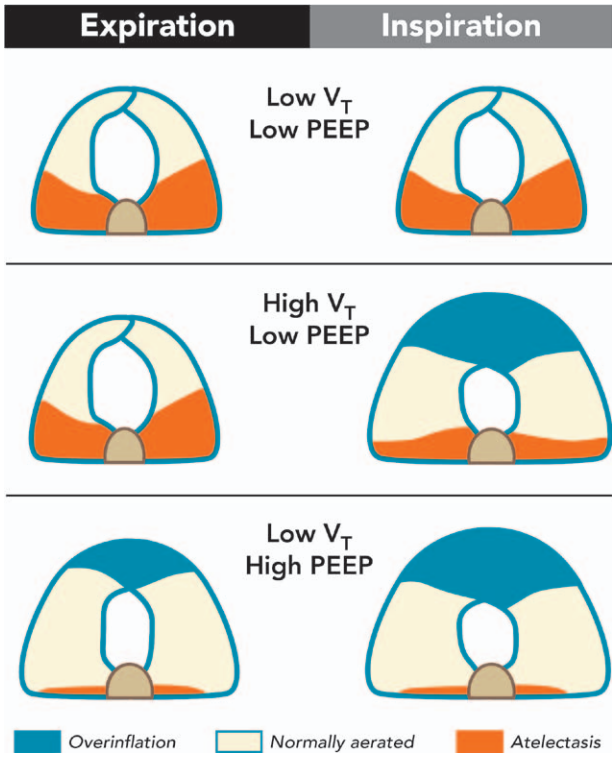

Fig. 3. Effects of high and low tidal volumes (V_T) at end-inspiration and end-expiration with low and high positive end-expiratory pressure (PEEP) during general anesthesia. Atelectatic lung regions (*red*), overinflated lung regions (*blue*), normally aerated lung regions (*white*). During ventilation with low V_T and low PEEP, higher amounts of atelectasis are present at end-expiration and end-inspiration with minimal areas of overinflation; during ventilation with high V_T and low PEEP, less atelectasis is present at end-expiration and end-inspiration, with increased areas of overinflation at end-inspiration. Furthermore, a higher amount of tissue collapsing and decollapsing during breathing is present. During ventilation with low V_T and higher PEEP, less atelectasis is present. However, higher overinflation occurs at end-inspiration and end-expiration, with minimal collapse and reopening during breathing cycling.

Although controversial, an alternative approach for PEEP during general anesthesia is the so-called "intraoperative permissive atelectasis," when PEEP is kept relatively low and recruitment maneuvers are waived. This concept aims at reducing the static stress in lungs, which is closely related to the mean airway pressure, assuming that collapsed lung tissue is protected against injury from mechanical ventilation (fig. 3). Intraoperative permissive atelectasis may be limited by deterioration in oxygenation, which could require higher inspiratory oxygen fractions. Also, shear stress may occur at the interface between collapsed and open tissue,[20] likely resulting in lung damage and inflammation, even in presence of low global stress.[99] Theoretically, intraoperative low PEEP could increase the incidence and the amount of atelectasis even in the postoperative period, resulting in further PPCs. A recent large retrospective study investigating

the association between intraoperative mechanical ventilator settings and outcomes suggested that the use of "minimal" PEEP (2.2 to 5 cm H_2O) combined with low tidal volumes (6 to 8 ml/kg) is associated with increased risk of 30-day mortality.[79] However, a large international multicenter RCT challenged the concept that "minimal" PEEP combined with low tidal volumes in the intraoperative period is harmful.[88] Also in elderly patients undergoing major open abdominal surgery, a strategy consisting of low tidal volume, PEEP 12 cm H_2O, and recruitment maneuvers increased the Pao_2 intraoperatively compared with a strategy with high tidal volume without PEEP, but this effect was not maintained in the postoperative period.[100] Even without recruitment maneuvers, PEEP improved oxygenation during upper abdominal surgery compared with zero end-expiratory pressure, but again such effects were limited to the intraoperative period and did not prevent postoperative complications.[101]

Lung Recruitment Maneuvers for Intraoperative Protective Ventilation

Positive end-expiratory pressure is most effective for preserving respiratory function if preceded by a recruitment maneuver, which must overcome the opening pressures of up to 40 cm H_2O in nonobese[102] and 40 to 50 cm H_2O in obese patients,[103] in the absence of lung injury. Recruitment maneuvers can be performed in different ways using the anesthesia ventilator, as illustrated in figure 4. Most commonly, such maneuvers are performed by "bag squeezing" using the airway pressure-limiting valve of the anesthesia machine (fig. 4A). However, recruitment maneuvers are better controlled if performed during tidal ventilation, for example, using a stepwise increase of PEEP, tidal volumes, or a combination of these (fig. 4B). Provided there are no contraindications, the inspiratory plateau pressure as high as 40 cm H_2O is more likely to result in full recruitment.[104]

In anesthesia devices that allow pressure-controlled ventilation, recruitment maneuvers can be conducted with a constant driving pressure of 15 to 20 cm H_2O and by increasing PEEP up to 20 cm H_2O in steps of 5 cm H_2O (30 to 60 s per step). After three to five breaths at a PEEP level that allows achieving the target inspiratory pressure, PEEP and tidal volume are adjusted to the respective desired levels (fig. 4C).

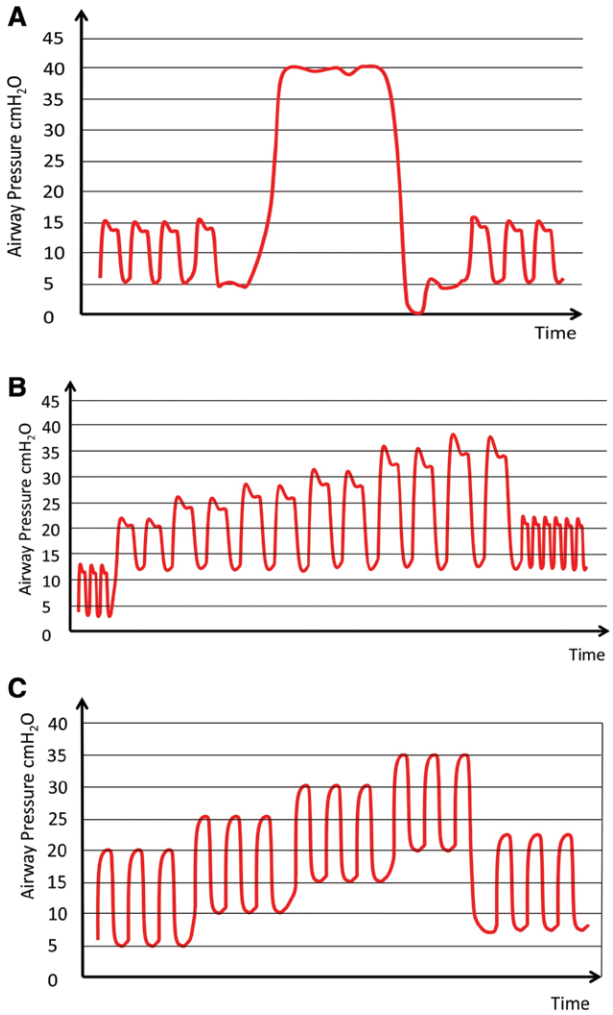

Fig. 4. Illustrative fluctuation of airway pressure during three types of lung recruitment maneuvers for intraoperative mechanical ventilation (*red lines*). (*A*) "Bag squeezing" using the airway pressure-limiting valve of the anesthesia machine. The airway pressure is difficult to control, possibly resulting in overpressure, with the risk of barotrauma, or values lower than the closing pressure of small airways when controlled mechanical ventilation is resumed, with consequent lung derecruitment. (*B*) "Stepwise increase of tidal volume" during volume-controlled ventilation. Positive end-expiratory pressure (PEEP) is set at 12 cm H_2O, the respiratory frequency at 6 to 8 breaths/min, and tidal volume increased from 8 ml/kg in steps of 4 ml/kg until the target opening pressure (*e.g.*, 30 to 40 cm H_2O) is achieved. After three to five breaths at that pressure, the PEEP is kept at 12 cm H_2O, tidal volume reduced to 6 to 8 ml/kg, and the respiratory frequency adjusted to normocapnia. (*C*) Stepwise increase of PEEP at a constant driving pressure of 15 to 20 cm H_2O in pressure-controlled ventilation. The PEEP is increased in steps of 5 cm H_2O (30 to 60 s per step) up to 20 cm H_2O. After three to five breaths at a PEEP level that allows achieving the target inspiratory pressure, PEEP and tidal volume are adjusted to the respective desired levels.

Recent Evidence for Intraoperative Protective Ventilation

Randomized Controlled Trials Using Nonclinical Primary Outcomes

The literature search identified 11 RCTs that compared a protective ventilation strategy with a nonprotective ventilation strategy during general anesthesia for surgery with regard to nonclinical primary outcome in patients undergoing thoracic surgery,[80,84,85,105,106] cardiac surgery,[95,107,108] abdominal surgery,[80,100,109] or spinal surgery,[110] as depicted in table 3. In eight RCTs, the protective ventilation strategy consisted of both lower tidal volumes and higher levels of

Table 3. Randomized Controlled Trials Using Nonclinical Primary Outcomes

Reference Published	Study Design	Patient Population/ Number	Intervention Group(s)	Control Group	Nonclinical Primary Outcomes	Secondary Outcomes
Thoracic surgery						
Wrigge *et al.*[80]	Prospective, single-center, randomized controlled trial	Adult patients undergoing major thoracic surgery, n = 34 (2 excluded)	PV: V_T: 6 ml/kg; PEEP: 10 cm H_2O; P_{aw} limit: 35 cm H_2O during TLV and OLV (n = 15)	CV: V_T: 12–15 ml/kg; ZEEP: P_{aw} limit: 35 cm H_2O during TLV and OLV (n = 17)	Inflammatory mediators in plasma: no differences between groups for TNFα, IL-1, IL-6, IL-8, IL-10, IL-12	Gas exchange: no differences between groups
Schilling *et al.*[84]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective open thoracic surgery (n = 32)	PV: V_T: 5 ml/kg during TLV and OLV; PEEP: 3 cm H_2O, TLV; PEEP: 0–2 cm H_2O, OLV; P_{aw} limit: 30 cm H_2O (n = 16)	CV: V_T: 10 ml/kg during TLV and OLV; PEEP: 3 cm H_2O, TLV; PEEP: 0–2 cm H_2O, OLV; P_{aw} limit: 30 cm H_2O (n = 16)	Inflammatory mediators in BAL: TNFα and sICAM lower during PV; no differences between groups for cell count, PMN elastase, total protein, albumin, IL-8, and IL-10	Pao_2/FIo_2: no differences between groups; $Paco_2$: higher during PV
Michelet *et al.*[85]	Prospective, single-center, randomized controlled trial	Adult patients undergoing planned esophagectomy (n = 52)	PV: V_T: 9 ml/kg, TLV; V_T: 5 ml/kg OLV; PEEP: 5 cm H_2O, TLV and OLV (n = 26)	CV: V_T: 9 ml/kg, TLV and OLV; ZEEP: TLV and OLV (n = 26)	Inflammatory mediators in plasma: IL-1β, IL-6, IL-8 lower during PV; no differences between groups for TNFα	Pao_2/FIo_2 and $Paco_2$: higher during PV; EVLWI: lower during PV; time to extubation: shorter during PV
Lin *et al.*[105]	Prospective, single-center, randomized controlled trial	Adult patients undergoing esophagectomy (n = 40)	PV: V_T: 10 ml/kg, TLV; V_T: 5–6 ml/kg OLV; PEEP: 3–5 cm H_2O, OLV (n = 20)	CV: V_T: 10 ml/kg, TLV and OLV; ZEEP: TLV and OLV (n = 20)	Inflammatory mediators in plasma: IL-6, IL-8, lower during PV	P_{peak}, P_{plat}, and R_{aw}: lower during PV
Unzueta *et al.*[106]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective open thoracotomy (n = 40)	PV: V_T: 8 ml/kg, TLV; V_T: 6 ml/kg OLV; PEEP: 8 cm H_2O, TLV and OLV; RM with stepwise PEEP/P_{aw} increase until 20/40 cm H_2O before start of OLV (n = 20)	CV: V_T: 8 ml/kg, TLV; V_T: 6 ml/kg OLV; PEEP: 8 cm H_2O, TLV and OLV; no RM before start of OLV (n = 20)	Dead space: lower during PV	Pao_2/FIo_2: higher during PV; $Paco_2$: lower during PV
Cardiac surgery						
Koner *et al.*[107]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective on-pump coronary artery bypass grafting surgery (n = 44)	(1) PV: V_T: 6 ml/kg; PEEP: 5 cm H_2O (n = 15) (2) CV + PEEP: V_T: 10 ml/kg; PEEP: 5 cm H_2O (n = 14)	(3) CV + ZEEP: V_T: 10 ml/kg; PEEP: 0 cm H_2O (n = 15)	Inflammatory mediators in plasma: no differences between groups for TNFα and IL-6	P_{plat}: lower during PV compared with both CV groups; shunt fraction: lower during PV compared with both CV + ZEEP; Pao_2/FIo_2: higher during ventilation with PEEP, (1) + (2)
Zupancich *et al.*[108]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective on-pump coronary artery bypass grafting surgery (n = 40)	PV: V_T: 8 ml/kg; PEEP: 10 cm H_2O (n = 20)	CV: V_T: 10–12 ml/kg; PEEP: 2–3 cm H_2O (n = 20)	Inflammatory mediators in plasma and BAL: IL-6, IL-8, lower during PV in both	$Paco_2$: higher during PV

(*Continued*)

Table 3. Continued

Reference Published	Study Design	Patient Population/ Number	Intervention Group(s)	Control Group	Nonclinical Primary Outcomes	Secondary Outcomes
Reis Miranda *et al.*[95]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective on-pump coronary artery bypass grafting or valve surgery (n = 62)	(1) Late open lung: V_T: 4–6 ml/kg; PEEP: 10 cm H_2O starting at postoperative ICU arrival (n = 18) (2) (1) Early open lung: V_T: 4–6 ml/kg; PEEP: 10 cm H_2O starting after intubation (n = 22)	(3) V_T: 6–8 ml/kg; PEEP: 5 cm H_2O (n = 22)	Inflammatory mediators in plasma: IL-8 decreased after CPB in both open lung groups; IL-10 decreased faster after CPB in early open lung group	Evidence of perioperative myocardial infarction (CK-MB and ECG): no differences between groups
Abdominal surgery						
Wrigge *et al.*[80]	Prospective, single-center, randomized controlled trial	Adult patients undergoing major abdominal surgery (n = 30)	PV: V_T: 6 ml/kg; PEEP: 10 cm H_2O; P_{aw} limit 35 cm H_2O (n = 15)	CV: V_T: 12–15 ml/kg; ZEEP: P_{aw} limit: 35 cm H_2O (n = 15)	Inflammatory mediators in plasma: no differences between groups for TNFα, IL-1, IL-6, IL-8, IL-10, and IL-12	Pa_{O_2}/Fi_{O_2}: no differences between groups; Pa_{CO_2}: higher during PV
Wolthuis *et al.*[109]	Prospective, single-center, randomized controlled trial	Adult patients undergoing a surgical procedure in general anesthesia ≥5 h (n = 46)	PV: V_T: 6 ml/kg; PEEP: 10 cm H_2O (n = 24)	CV: V_T: 10–12 ml/kg ZEEP: n = 22	Inflammatory mediators in plasma and BAL: lower myeloperoxidase and nucleosome level in BAL during PV	Pa_{CO_2}: higher during PV; PPCs: no differences between groups
Weingarten *et al.*[100]	Prospective, single-center, randomized controlled trial	Adult patients aged > 65 yr undergoing major open abdominal surgery under general anesthesia (n = 40)	PV: V_T: 6 ml/kg; PEEP: 12 cm H_2O RM with stepwise PEEP increase until 15 cm H_2O (n = 20)	CV: V_T: 10 ml/kg; ZEEP: no RM (n = 20)	Inflammatory mediators in plasma: no differences between groups	Pa_{O_2}/Fi_{O_2} + Pa_{CO_2}: higher during PV; compliance higher and resistance lower during PV
Spinal surgery						
Memtsoudis *et al.*[110]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective lumbar decompression and fusion in prone position under general anesthesia (n = 26)	PV: V_T: 6 ml/kg; PEEP: 8 cm H_2O (n = 13)	CV: V_T: 12 ml/kg; ZEEP: n = 13	Inflammatory mediators in plasma: no differences between groups	Pa_{CO_2}: higher during PV

BAL = bronchoalveolar lavage; CK-MB = muscle-brain type creatine kinase; CPB = cardiopulmonary bypass; CV = conventional ventilation; ECG = electrocardiogram; EVLWI =extravascular lung water index; Fi_{O_2} = inspired fraction of oxygen; ICAM = intercellular adhesion molecule; ICU = intensive care unit; IL = interleukin; OLV = one-lung ventilation; Pa_{CO_2} = partial pressure of arterial carbon dioxide; Pa_{O_2} = partial pressure of arterial oxygen; Pa_{O_2}/Fi_{O_2} = ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; P_{aw} = airway pressure; PEEP = positive end-expiratory pressure; PMN = polymorphonuclear leukocyte; PPCs = postoperative pulmonary complications; P_{peak} = peak pressure; P_{plat} = plateau pressure; PV = protective ventilation; R_{aw} = airway resistance; RM = recruitment maneuver; sICAM = soluble intercellular adhesion molecule; TLV = two-lung ventilation; TNFα = tumor necrosis factor-α; V_T = tidal volume; ZEEP = zero end-expiratory pressure.

PEEP[80,85,100,105,107–110]; in two RCTs, it consisted of either lower tidal volume,[84] a higher level of PEEP.[95] In one RCT, lung recruitment maneuvers were used during the protective ventilation strategy.[106]

The effects on inflammatory responses are slightly contradictory. Although four RCTs showed no difference in local levels of inflammatory mediators between patients on protective and those on nonprotective ventilation,[80,100,107,110] six RCTs[84,85,95,105,108,109] showed that protective strategies were associated with lower levels of inflammatory mediators.

Randomized Controlled Trials Using Clinical Primary Outcomes

In total, eight RCTs were identified that compared a protective ventilation strategy with a nonprotective ventilation strategy during surgery with regard to a clinical primary outcomes in patients planned for abdominal surgery,[88,111–113] thoracic surgery,[87,114] cardiac surgery,[115] or spinal surgery,[116] as shown in table 4. In four RCTs, the protective strategy consisted of both lower tidal volumes and higher levels of PEEP,[112–114,116] and in the four remaining RCTs, it consisted of either lower tidal volumes[87,111,115] or higher levels of PEEP.[88]

Four trials reported on PPCs in the first postoperative days, including bronchitis, hypoxemia, and atelectasis,[116] pneumonia, need for invasive or noninvasive ventilation for acute respiratory failure,[112] a modified "Clinical Pulmonary Infection Score," and chest radiograph abnormalities,[113] and hypoxemia, bronchospasm, suspected pulmonary infection, pulmonary infiltrate, aspiration pneumonitis, development of ARDS, atelectasis, pleural effusion, pulmonary edema, and pneumothorax.[88]

In a Chinese single-center RCT,[116] investigators compared protective ventilation (tidal volume 6 ml/kg and 10 cm H_2O PEEP) *versus* nonprotective (tidal volume 10 to 12 ml/kg and 0 cm H_2O PEEP) in 60 elderly patients with American Society of Anesthesiologists class II and III scheduled for spinal surgery. Patients receiving protective ventilation had less PPCs.

In a French multicenter trial (Intraoperative PROtective VEntilation),[112] protective ventilation (tidal volume 6 to 8 ml/kg and PEEP 6 to 8 cm H_2O) was compared with nonprotective ventilation (tidal volume 10 to 12 ml/kg and 0 cm H_2O PEEP) in 400 nonobese patients at intermediate to high risk of pulmonary complications after planned major abdominal surgery. The primary outcome (postoperative pulmonary and extrapulmonary complications) occurred less often in patients receiving "protective" ventilation. Such complications have been ascribed to the release of inflammatory mediators by the lungs into the systemic circulation, affecting the lungs,[117] as well as peripheral organs.[52] These patients also had a shorter length of hospital stay, but mortality was unaffected.

An Italian single-center trial[113] investigated the effectiveness of protective ventilation (tidal volume 7 ml/kg and 10 cm H_2O PEEP with recruitment maneuvers) *versus* nonprotective ventilation (tidal volume 9 ml/kg and zero end-expiratory pressure) in 56 patients scheduled for open abdominal surgery lasting more than 2 h. The modified "Clinical Pulmonary Infection Score" was lower in patients receiving protective ventilation. These patients also had fewer chest radiograph abnormalities and higher arterial oxygenation compared with patients receiving nonprotective ventilation.

Finally, in an international multicenter trial conducted in Europe and the United States (PROtective Ventilation using HIgh *vs.* LOw PEEP [PROVHILO]),[88] the PROtective VEntilation Network investigators compared PEEP of 12 cm H_2O combined with recruitment maneuvers *versus* PEEP of 2 cm H_2O without recruitment maneuvers in 900 nonobese patients at high risk for PPCs planned for open abdominal surgery under ventilation at tidal volumes of 8 ml/kg. The incidence of PPCs was not different between patients receiving protective ventilation and patients receiving nonprotective ventilation.

Challenges of Studies Using Bundles

As shown in preceding subsections Randomized Controlled Trials Using Nonclinical Primary Outcomes and Randomized Controlled Trials Using Clinical Primary Outcomes, most RCTs addressing intraoperative mechanical ventilation compared bundles of interventions consisting of tidal volumes and levels of PEEP, usually accompanied by a lung recruitment maneuver.[112–114,116] Notably, recruitment maneuvers differed between the trials. In the Italian single-center RCT,[113] investigators used incremental titration of tidal volumes until a plateau pressure of 30 cm H_2O, directly after induction of anesthesia, after any disconnection from the ventilator and immediately before extubation, similar as in PROVHILO.[88] In Intraoperative PROtective Ventilation trial,[112] recruitment was performed with a continuous positive airway pressure of 30 cm H_2O for 30 s every 30 min, also known as sustained inflation, after tracheal intubation. Finally, in the Chinese single-center RCT,[116] the recruitment maneuvers followed a similar approach, but to plateau pressures of up to 35 cm H_2O, and they were performed every 15 min. It is difficult, if not impossible, to conclude from these trials what caused the benefit, tidal volume reduction or increase of PEEP or both, and to determine the role of recruitment maneuvers. Moreover, to what extent the recruitment maneuver has succeeded in reopening lung has not been analyzed in the different studies.

The results of the PROVHILO trial, however, suggest that low tidal volumes rather than PEEP combined with lung recruitment maneuvers are responsible for lung protection in the intraoperative period. This interpretation is also supported by an analysis of different studies on the odds ratios of lower tidal volumes,[87,111,115] higher levels of PEEP,[88] their combination,[112–114,116] regarding the development of PPCs (fig. 5), as well as a recent individual patient data meta-analysis.[131]

Table 4. Randomized Controlled Trials Using Clinical Primary Outcomes

Reference Published	Study Design	Patient Population/Number	Intervention	Control Group	Clinical Primary Outcomes	Secondary Outcomes
Thoracic surgery						
Maslow *et al.*[114]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective pulmonary resection (n = 34)	PV: V_T: 5 ml/kg, TLV and OLV; PEEP: 5 cm H_2O, TLV and OLV (n = 17)	CV: V_T: 10 ml/kg, TLV and OLV; ZEEP: TLV and OLV (n = 17)	Rate of atelectasis: lower with CV; length of hospital stay: no differences between groups	$Paco_2$ and alveolar dead space: higher during PV; C_{dyn}: higher during CV
Shen *et al.*[87]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective thoracoscopic esophagectomy (n = 101)	PV: V_T: 8 ml/kg TLV; V_T: 5 ml/kg OLV; PEEP: 5 cm H_2O, TLV and OLV (n = 53)	CV: V_T: 8 ml/kg, TLV; V_T: 8 ml/kg OLV; ZEEP: TLV and OLV (n = 48)	PPCs: lower rate with PV; mortality: no difference between groups	Pao_2/Fio_2 and $Paco_2$: higher during PV; inflammatory mediators in BAL: lower IL-1β, IL-6, and IL-8
Cardiac surgery						
Sundar *et al.*[115]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective cardiac surgery (n = 149)	PV: V_T: 6 ml/kg; PEEP/Fio_2: according to ARDS Network table (n = 75)	CV: V_T: 10 ml/kg; PEEP/Fio_2: according to ARDS Network table (n = 74)	Rate of reintubation: lower with PV; number of patients requiring ventilation 6 h postoperatively: lower with PV	Gas exchange: no difference between groups
Abdominal surgery						
Treschan *et al.*[111]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective upper abdominal surgery lasting ≥3 h under combined general and epidural anesthesia (n = 101)	PV: V_T: 6 ml/kg; PEEP: 5 cm H_2O (n = 50)	CV: V_T: 12 ml/kg; PEEP: 5 cm H_2O (n = 51)	Rate of atelectasis: lower with CV	Pao_2/Fio_2: higher during CV; C_{dyn} and R_{aw}: higher during CV; Pao_2 at postoperative day 5: higher with CV
Futier *et al.*[112]	Prospective randomized controlled multicenter study	Adults patients at intermediate to high risk of pulmonary complications undergoing major abdominal surgery (n = 400)	PV: V_T: 6–8 ml/kg; PEEP: 6–8 cm H_2O (n = 200)	CV: V_T: 10–12 ml/kg; ZEEP (n = 200)	Composite primary outcome of major pulmonary or extrapulmonary complications: lower with PV	Reduced rate of atelectasis, pneumonia, need for ventilation within 7 days and sepsis with PV. Reduced length of hospital stay with PV
Severgnini *et al.*[113]	Prospective, single-center, randomized controlled trial	Adult patients undergoing elective open abdominal surgery ≥2 h n = 56 (1 excluded)	PV: V_T: 7 ml/kg; PEEP: 10 cm H_2O (n = 28)	CV: V_T: 9 ml/kg; ZEEP (n = 27)	Pulmonary function tests: improved with PV	Modified Clinical Pulmonary Infection Score: lower with PV; Pao_2 at postoperative days 1, 3, and 5: higher with PV. Rate of chest radiograph abnormalities: lower with PV. Length of hospital stay: no difference between groups

(*Continued*)

Table 4. Continued

Reference Published	Study Design	Patient Population/Number	Intervention	Control Group	Clinical Primary Outcomes	Secondary Outcomes
PROVE Network Investigators 2014[88]	Prospective, international, multicenter, randomized controlled trial	Adults patients at intermediate to high risk of pulmonary complications undergoing major abdominal surgery (n = 900)	PV: V_T: 8 ml/kg; PEEP: 12 cm H_2O; RM with stepwise increase of V_T after induction and before extubation (n = 445)	CV: V_T: 8 ml/kg; PEEP: 0–2 cm H_2O (n = 449)	Rate of PPCs: no difference between groups	Rate of intraoperative hypotension and amount of vasoactive drugs given: higher during PV. Rate of desaturation: lower during PV. Mortality and length of hospital stay: no difference between groups
Spinal surgery Ge *et al.*[116]	Prospective, single-center, randomized controlled trial	Adult patients undergoing spine fusion (n = 60)	PV: V_T: 6 ml/kg; PEEP: 10 cm H_2O; RM every 15 min (n = 30)	CV: V_T: 10–12 ml/kg; ZEEP (n = 30)	Rate of PPCs, lower with PV	Pa_{O_2}/FI_{O_2}, higher during PV

ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; C_{dyn} = dynamic compliance of the respiratory system; CV = conventional ventilation; FI_{O_2} = inspired fraction of oxygen; IL = interleukin; OLV = one-lung ventilation; $PaCO_2$ = partial pressure of arterial carbon dioxide; Pa_{O_2} = partial pressure of arterial oxygen; Pa_{O_2}/FI_{O_2} = ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; PEEP = positive end-expiratory pressure; PPCs = postoperative pulmonary complications; PROVE = PROtective VEntilation; PV = protective ventilation; R_{aw} = airway resistance; RM = recruitment maneuver; TLV = two-lung ventilation; V_T = tidal volume; ZEEP = zero end-expiratory pressure.

Certainly, these conclusions are only valid for the studied population, that is, nonobese patients at risk of PPCs undergoing elective abdominal surgery. Other patient populations could still benefit from higher levels of PEEP and recruitment maneuvers.

Challenges of Composite Outcome Measures

Composite outcome measures offer the benefit of an increased event rate, which is helpful to ensure adequate statistical power of a trial.[8] It is reasonable to combine related outcomes that represent different aspects of a single underlying pathophysiologic process, such as PPCs for VILI. There are, though, two major limitations regarding the use of composite outcomes. First, the component variables can differ importantly in terms of severity and frequency. Second, differences in the frequency of component variables in a composite outcome may be masked.

Drawbacks of Protective Ventilation

The term "protective" in the context of mechanical ventilation implies a decrease in the major components of VILI, namely atelectrauma, volutrauma, and biotrauma. However, a strategy that is protective to lungs may also cause harm to other organ systems. The potential for harm caused by protective ventilation was reported in PROVHILO trial,[88] in which patients receiving higher PEEP and lung recruitment maneuvers developed intraoperative hypotension more frequently and needed more vasoactive drugs. These findings are at least in part in line with the finding that protective ventilation was associated with a higher incidence of intraoperative hypotension in the French trial.[112]

Standard of Care versus *Unusual Settings: Were the Control Groups of Recent Trials Representative of Clinical Practice?*

In RCTs addressing intraoperative protective mechanical ventilation, the strategy used to treat control groups can play an important role when drawing conclusions for daily practice of general anesthesia. Meta-analyses suggest that lower tidal volumes are protective not only during long-term ventilation in critically ill patients[118,119] but also short-term ventilation during general anesthesia for surgery.[119] Accordingly, anesthesiologists have been using tidal volumes of approximately 8 to 9 ml/kg on average, and seldom higher than 10 ml/kg,[76] as also illustrated in figure 6A. In contrast to this practice, the tidal volumes used in the control groups of recent RCTs were as high as 9[113] to 12 ml/kg,[112] except to PROVHILO[88] (fig. 6B), which used a tidal volume of 7 ml/kg both in the intervention and in the control group. Similarly, levels of PEEP in the control arms of three of four recent RCTs[112,113,116] on protective mechanical ventilation were much lower than the standard of care at the moment the respective studies were designed (fig. 6, C and D). Taken together, these facts suggest that, among the most important recent RCTs on intraoperative protective mechanical ventilation, only the PROVHILO trial used a control

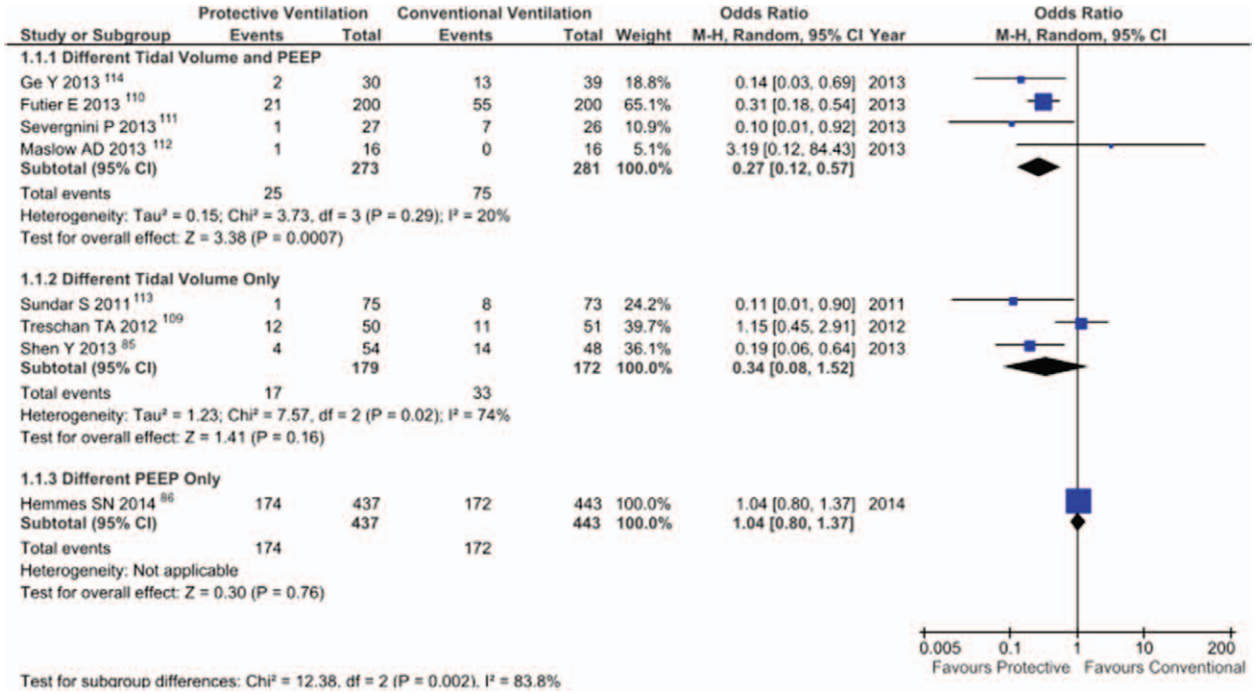

Fig. 5. Odds ratios for postoperative pulmonary complications of "protective" *versus* "nonprotective" ventilation in trials comparing different tidal volumes,[87,111,115] different tidal volumes and positive end-expiratory pressure (PEEP),[112–114,116] and different levels of PEEP.[88] *df* = degrees of freedom; M-H = Mantel-Haenszel.

group that reproduced the standard of anesthesia care at the time it was conducted. Accordingly, the PROVHILO trial addressed a major question regarding mechanical ventilation during anesthesia, namely whether the combination of high PEEP with recruitment maneuvers confers protection against PPCs. In this study, high PEEP was not individualized, but based on previous findings from computed tomography[69,90,91] and physiological studies.[92,94]

Intraoperative Mechanical Ventilation According to the Utmost Recent Evidence

A number of reviews and commentaries have suggested that intraoperative mechanical ventilation for surgery should consist of low tidal volumes (6 to 8 ml/kg), moderate levels of PEEP (6 to 8 cm H_2O), and periodic lung recruitment maneuvers (*e.g.*, every 30 min).[5,123–125] However, previous reviews and recommendations have been based on bundles, which do not permit to infer on the contribution of individual measures. Furthermore, the results of the largest RCT in this field (PROVHILO) could not be taken into account. Also, a recommendation regarding the use of positive pressure ventilation during induction and emergence of anesthesia, as proposed recently,[124] is not supported by outcome data. Currently, the only recommendations that can be given for clinical practice are summarized in figure 7. In nonobese patients without ARDS[126] undergoing open abdominal surgery, mechanical ventilation should be performed with low tidal volumes (approximately 6 to 8 ml/kg) combined with low PEEP (≤2 cm H_2O) because higher PEEP combined with recruitment maneuvers does not confer further protection against PPCs and can deteriorate the hemodynamics. If hypoxemia develops and provided that other causes have been excluded (*e.g.*, hypotension, hypoventilation, and pulmonary embolism), the F_{IO_2} should be increased first, followed by increase of PEEP, and recruitment maneuvers based on stepwise increase of tidal volume during regular mechanical ventilation, according to the rescue algorithm described in the PROVHILO trial,[88] provided no contraindication is present. In patients with ARDS[126] undergoing open abdominal surgery, intraoperative mechanical ventilation should be guided by the ARDS network protocol,[127] whereby higher PEEP values[128] may be useful in more severe ARDS.[129] If the target Pa_{O_2} (55 to 80 mmHg) or Sp_{O_2} (88 to 95%) cannot be achieved, a maximal lung recruitment maneuver with a decremental PEEP trial can be considered.[130]

Future Perspectives

Despite the increasing number of highly qualitative RCTs on intraoperative mechanical ventilation, a number of issues remain unaddressed. Although meta-analyses strongly suggest that low tidal volumes during intraoperative mechanical ventilation protect against postoperative pulmonary events, no single RCT has been able to prove this claim. Because meta-analyses in this field frequently include the studies that tested intervention bundles, for example, low tidal volume and high PEEP with recruitment maneuvers

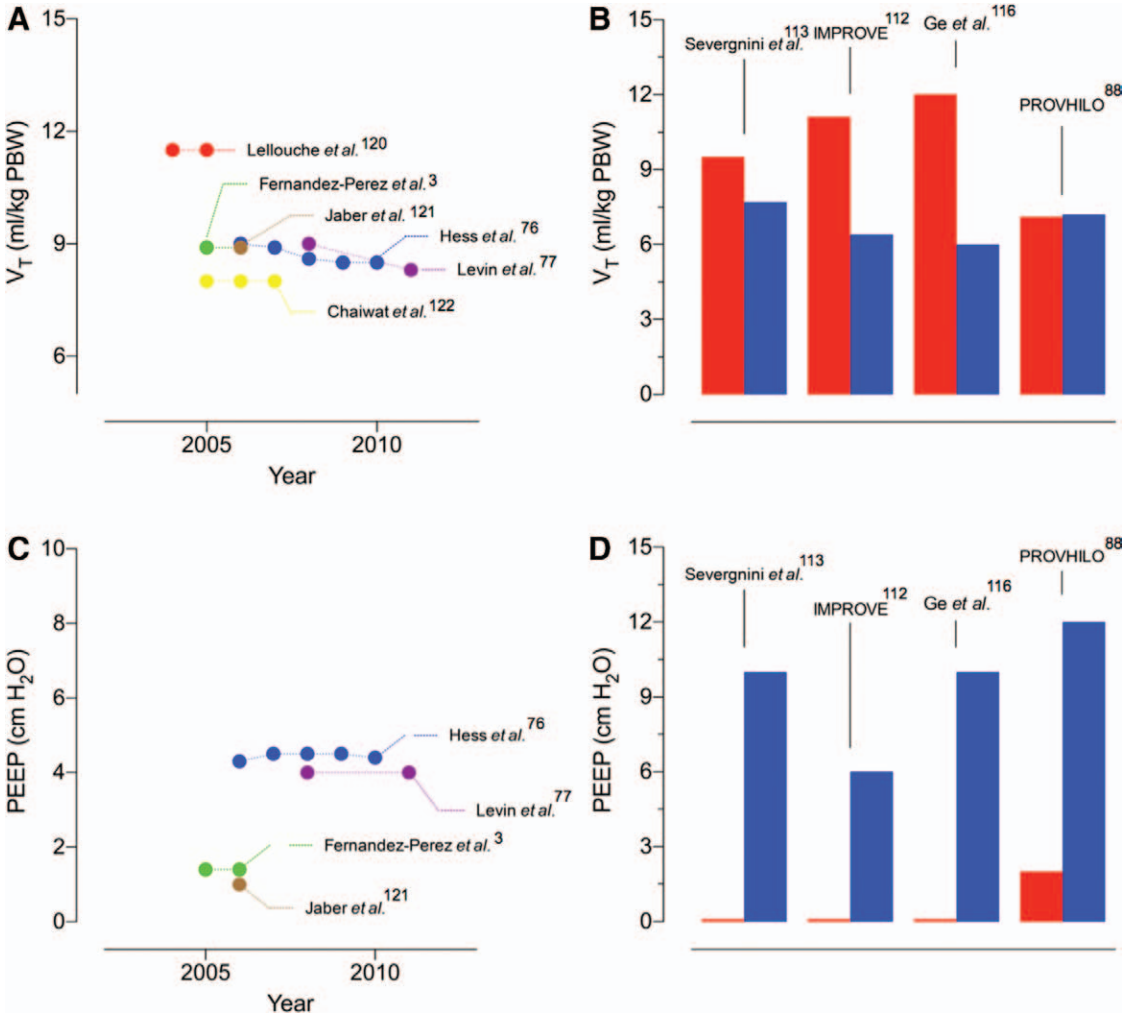

Fig. 6. Settings of tidal volume (V_T) (*A*) and positive end-expiratory pressure (PEEP) (*C*) according to observational studies of mechanical ventilation in the operation room (in Canada,[120] France,[121] and the United States[3,76,77,122]); settings of V_T (*B*) and PEEP (*D*) in "nonprotective" ventilation (*red*) and "protective" ventilation (*blue*) groups in four recent randomized controlled trials (Severgnini *et al.*,[113] Intraoperative PROtective VEntilation trial [IMPROVE],[112] Ge *et al.*,[116] and PROtective Ventilation using HIgh *vs.* LOw PEEP [PROVHILO][88]). PBW = predicted body weight.

versus high tidal volumes without PEEP, the estimation of the effects of single measures, for example, low tidal volume or PEEP, is prone to criticism. Therefore, RCTs are most relevant for clinical practice if they test single interventions, and if control groups reproduce current standards. Whereas direct testing of the hypothesis that intraoperative low tidal volumes protect against PPCs is still lacking, ethical issues preclude such a trial.

Despite convincing evidence that PEEP and recruitment maneuvers do not confer further protection and may even impair hemodynamics during a ventilatory strategy based on low tidal volumes in open abdominal surgery, we do not know whether patients with obesity or undergoing one-lung anesthesia procedures may benefit from those interventions. Also, we cannot rule out the possibility that an individual PEEP titration targeted on lung function could yield different results. Furthermore, it remains unclear how postoperative atelectasis, the most frequent of the different PPCs, influences the development of pulmonary infections and severe respiratory failure and affects other relevant outcome measures, including hospital length of stay and mortality. In addition, further studies should shed light on the potential contributions of ventilatory strategies during induction and emergence of anesthesia, as well as in the postoperative period (*e.g.*, noninvasive ventilation). Accordingly, the potential of perioperative nonventilatory measures (*e.g.*, muscle paralysis, use of short-acting neuromuscular-blocking agents, and monitoring and reversal of muscle paralysis, early mobilization, and respiratory therapy) for reducing PPCs should be investigated. Such studies are necessary to support future guidelines on the practice of perioperative mechanical ventilation and adjunctive measures in a broad spectrum of patients as well as surgical interventions, both open and laparoscopic.

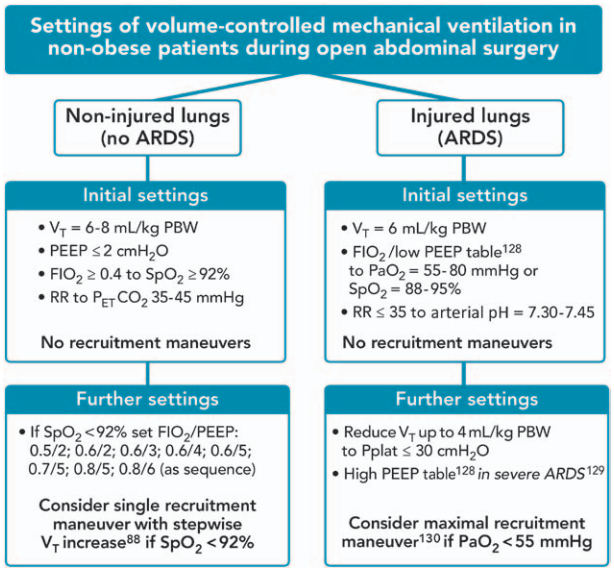

Fig. 7. Proposed settings of protective mechanical ventilation in nonobese patients during open abdominal surgery according to the concept of intraoperative permissive atelectasis. ARDS = acute respiratory distress syndrome; FIO_2 = inspiratory oxygen fraction of oxygen; PaO_2 = partial pressure of arterial oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; $PETCO_2$ = end-tidal pressure of carbon dioxide; Pplat = inspiratory airway plateau pressure; RR = respiratory rate; SpO_2 = peripheral oxygen saturation; V_T = tidal volume.

Conclusions

The potential of intraoperative lung-protective mechanical ventilation to reduce the incidence of PPCs is well established. RCTs have suggested that low tidal volumes, high PEEP, and recruitment maneuvers may be protective intraoperatively, but the precise role of each single intervention has been less clearly defined. A meta-analysis taking the utmost recent clinical data shows that the use of low tidal volumes, rather than PEEP, recruitment maneuvers, or a combination of these two, is the most important determinant of protection in intraoperative mechanical ventilation. In nonobese patients without ARDS undergoing open abdominal surgery, mechanical ventilation should be performed with low tidal volumes (approximately 6 to 8 ml/kg) combined with low PEEP because the use of higher PEEP combined with recruitment maneuvers does not confer further protection against PPCs and can deteriorate the hemodynamics. If hypoxemia develops, and provided that other causes have been excluded, for example, hypotension, hypoventilation, and pulmonary embolism, the FIO_2 should be increased first, followed by increase of PEEP, and recruitment maneuvers based on stepwise increase of tidal volume during regular mechanical ventilation. Further studies are warranted to guide intraoperative mechanical ventilation in a broader spectrum of patients and surgical interventions.

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Competing Interests

The authors declare no competing interests.

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