MORE than 200 million major surgical procedures are performed annually worldwide. Although successful surgery is a necessary condition for satisfactory postoperative outcomes, the benefits of any surgical procedure may be mitigated by the development of postoperative complications. It has been reported that 5 to 10% of all surgical patients and up to 30 to 40% of those undergoing thoracic or abdominal surgery develop postoperative pulmonary complications (PPCs). PPCs account for a substantial proportion of risks related to the surgical procedure and general anesthesia, are a major cause of postoperative morbidity and mortality, and are associated with considerable costs in hospital care. Recent findings from the Massachusetts General Hospital offered us particularly striking evidence of the harmful effect of PPCs. By analyzing the data from a cohort of 33,769 surgical cases, the authors found that unplanned reintubation within the first 3 days after surgery was associated with a 72-fold increased risk of in-hospital mortality. The ability to anticipate and prevent PPCs is therefore becoming an imperative for any perioperative care provider and is a measure of the quality and safety of care.

Mechanical ventilation is an essential supportive therapy to maintain gas exchange during general anesthesia and may provide for maintenance of anesthesia with delivery of inhaled anesthetics. However, there is accumulating evidence from both experimental and clinical studies that nonoptimal mechanical ventilation can initiate lung damage in patients with healthy lungs at the onset of ventilation. Lung-protective ventilation, as opposed to nonprotective ventilator settings using either or both high tidal volume (VT) and very low levels (<5 cm H2O) of positive end-expiratory pressure (PEEP) or even no PEEP, is becoming a routine strategy of treatment in patients with acute respiratory distress syndrome (ARDS). Although it has been suggested that this approach might be beneficial in a broader population, prophylactic lung-protective ventilation is not widely accepted in patients with healthy lungs, especially in the operating room environment. Along with other critical aspects of perioperative care, mechanical ventilation is entirely under the control of anesthesiologists, who must be aware of the potential unintended consequences of inappropriate settings and that use of physiology-oriented mechanical ventilation can reduce the risk of PPCs.

In this “Clinical Concepts and Commentary,” the current status of mechanical ventilation in the operating room and the physiology of ventilator-associated lung injury will be discussed. We will also appraise recent evidence supporting the implementation of a multifaceted bundle of prophylactic Peri-Operative Positive pressure ventilation (the “P.O.P.-ventilation” bundle) to prevent lung collapse during the perioperative period and limit subsequent PPCs. This concept is based on a simple strategy that "prevention is better than cure."
Current Status of Mechanical Ventilation in the Operating Room

The use of high VT (usually defined as a VT between 10 and 15 ml/kg) during mechanical ventilation has been historically encouraged to prevent hypoxemia and gradual loss of lung volume (i.e., atelectasis formation) associated to ventilate with low VT ventilation.8 The concept of lung-protective ventilation, which refers to the use of lower VT (calculated on the predicted body weight [PBW] rather than on the actual body weight) and PEEP, was popularized by the publication of the landmark ARDS Network low VT study in 2000,9 demonstrating reduced mortality in patients with ARDS. Although this concept has had particular resonance in the intensive care unit setting, there is a growing body of evidence to suggest that practice of high VT ventilation may still be inappropriately high in the operating room context. In recent anesthesia observational studies, both our group10 and Hess et al.,9 reported that a significant number of surgical patients (25 and 30% of patients in the two studies, respectively) continue to receive nonprotective mechanical ventilation with VT more than 10 ml/kg of PBW or more. Likewise, in a retrospective analysis of prospectively collected data,11 Blum et al. recently found no difference in intraoperative VT between patients with and without acute lung injury, suggesting that low VT ventilation may not be widely applied in operating room, even in patients who could benefit the most.

Similarly, although there is strong preclinical database supporting the use of PEEP during general anesthesia,12 PEEP is surprisingly not commonly applied in the operating room. In an observational study including 2,960 patients from 49 university and nonuniversity hospitals, we recently reported that more than 80% of patients received mechanical ventilation without PEEP, whereas 90% of patients received only very low levels of PEEP (<4 cm H2O).7 Interestingly, we also found that a lung-protective approach (which can be defined as the combination of a VT of <8 ml/kg PBW and a PEEP level >5 cm H2O) was used only sporadically. These data were later confirmed in another observational study from the Massachusetts General Hospital involving 45,550 patients between 2006 and 2011, in which the authors found that approximately 30% of patients still received nonprotective ventilation.10 It must be emphasized that these results may be somewhat optimistic because both of these two studies reported the proportion of actual body weight rather than PBW, which can lead to overtreatment and therefore should not be used to calculate VT. The same findings hold for hypoxic surgical patients receiving mechanical ventilation. In a retrospective analysis of 11,445 operative cases, Blum et al.13 found only slight differences in the intraoperative VT of patients with intraoperative hypoxemia (defined as a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen lower than 300) compared with those who had normal oxygenation, and that increasing the inspired fraction of oxygen and tolerance of high peak airway pressures represent common therapeutic options in case of hypoxemia. Although the development of ARDS is a rare condition in the postoperative period (overall incidence of 0.2%), the same study group found that high intraoperative driving pressure (defined as the difference between peak inspiratory pressure and PEEP) was independently associated with the development of postoperative ARDS (odds ratio, 1.17; 95% CI, 1.09 to 1.31).14 The authors found no statistically significant difference in the intraoperative VT and PEEP (median PEEP of 4 cm H2O in both groups) between patients who developed postoperative ARDS and those who did not. Finally, recent data have shown that intraoperative adherence to lung-protective ventilation modalities is low in patients with previously established diagnosis of ARDS and requiring general anesthesia for surgical procedures.15

The Rationale to Use Preventive Lung-protective Ventilation Strategies in Perioperative Care

It has become evident that inappropriate use of mechanical ventilation can exacerbate lung injury. Whether injurious ventilation per se may be sufficient to initiate lung damage in patients with healthy lungs exposed to a short-term period of mechanical ventilation during surgery is less clear and is subjected to controversy. There is, however, unequivocal evidence that general anesthesia promotes reduction in lung volume, which is a key determinant of atelectasis formation. Atelectasis occurs in the most dependent parts of the lungs of 90% or more of anesthetized patients from the first minutes of anesthesia induction, whether intravenous or inhalational agents are used. The exact mechanism of atelectasis formation is not fully understood, but is related to (1) a mismatch between the modified shape of the chest wall produced by anesthesia and the shape of the lung, and (2) to a gas resorption phenomenon favored by the utilization of high fraction of inspired oxygen. It must be emphasized that a causal link between the formation of intraoperative atelectasis and PPCs is not clearly defined. Nevertheless, atelectasis that develops during general anesthesia remains in the postoperative period, and alteration in both oxygenation and lung compliance is correlated with the amount of atelectasis.16

In addition, it has been shown that lung injury associated with atelectasis involves trauma of the distal airways that is generalized throughout the lungs and also leads to alveolar damage in remote nonatelectatic alveoli.17 Finally, although the initial injury is simple collapse of alveoli, the pathophysiological changes associated with atelectasis formation can result from repeated reopening of collapsed alveoli during mechanical ventilation leading to stretch-induced ultrastructural damage with both epithelial and vascular endothelium disruption and from local production and systemic release of inflammatory mediators.18

Ventilator-induced lung injury can result from cyclic overstretching of aerated alveolar areas with high VT
ventilation (volutrauma), from repeated closing (at end expiration) and opening (at the next inspiration) of lung units with the use of low VT and/or zero PEEP, resulting in ultrastructural damage at the junction of closed and open alveoli (atelectrauma), and from the application of excessive airway pressures (barotrauma). Each mechanism may trigger an inflammatory reaction in the lungs, but it has also been suggested that the physical forces generated during mechanical ventilation may also initiate and propagate a systemic release of inflammatory mediators and thus contribute to systemic organ dysfunction (fig. 1). The mechanisms underlying the biotrauma hypothesis of ventilator-induced lung injury include mechanical ventilation–induced cell necrosis and decompartmentalization (i.e., stress failure of epithelial and endothelial barriers), mechanotransduction pathways (i.e., the conversion of a mechanical stimulus into biochemical information), and direct effects on the vasculature. In an experimental model of ARDS, Imai el al. have shown that 8 h of an injurious mechanical ventilation, consisting of a combination of high VT and low PEEP, can lead to epithelial cell apoptosis in the kidney and the small intestine, accompanied by biochemical evidence of organ dysfunction. Short-term nonprotective mechanical ventilation was also shown to promote bronchoalveolar procoagulant and inflammatory changes in patients without preexisting lung injury, suggesting that mechanical ventilation per se could exert a proinflammatory stimulus and could trigger apoptotic cell death in noninjured lungs in the context of major surgery.

A possible interpretation of these results, and a way to reconcile discrepant findings, is the commonly accepted theory of a multiple-hit whereby nonprotective mechanical ventilation of previously healthy lungs can result in lung injury when combined with another aggression. An experimental study provided compelling arguments that different insults may interact to bring about greater production and release of inflammatory mediators than either alone and in a way that depends on their sequence. Although previous injury can sensitize lungs to inadequate ventilator settings, the authors found that the inflammatory mediators release was greater when injurious ventilation preceded additional insults, suggesting that mechanical ventilation can be the

Fig. 1. The biotrauma hypothesis of ventilator-induced lung injury. IL = interleukin; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; TNF = tumor necrosis factor; VT = tidal volume.
priming for subsequent pulmonary complications. Many risk factors are encountered during the perioperative period (table 1), for instance, excessive fluid administration, massive transfusion, and sepsis, which may all be responsible for additional lung aggression.

**Recent Findings in Intraoperative Lung-protective Ventilation**

A recent prospective, randomized, controlled trial explored the pulmonary effects of a prophylactic lung-protective ventilation modality in 101 patients with low-to-intermediate preoperative risk during upper abdominal surgery. The study failed to demonstrate any significant benefit in the postoperative lung function testing during the first 5 postoperative days in patients receiving low VT ventilation compared with those receiving high VT, whereas gas exchange was better with high VT. A central striking point in this study was the use of low PEEP levels in both groups, but a much more frustrating aspect was the absence of alveolar recruitment maneuver (RM) in the low VT group. Since the publication of the seminal article by Bendixen et al., it still holds true that low VT ventilation promotes atelectasis formation. Lung-protective ventilation is not straightforward and should therefore not be confined only to lowering VT. RMs are needed to fully reopen atelectasis after induction of anesthesia and PEEP should be applied with the use of lower VT to prevent progressive lung collapse and loss of aeration. The optimal level of PEEP in prophylactic lung-protective ventilation remains to be determined, but most physiological studies have suggested PEEP levels greater than 5 cm H₂O, especially in obese patients. It was therefore not surprising to assume more atelectasis in the low VT group.

Another study investigated the effects of intraoperative mechanical ventilation in patients undergoing major abdominal procedures. Of particular relevance was the use of a protective ventilation strategy combining intraoperative low VT, higher PEEP levels, and RMs. This study provides strong arguments that lung-protective ventilation improves several aspects of postoperative pulmonary function, chest radiograph, and a modified clinical pulmonary infection score during the first 5 days after surgery. The study was however not powered enough to explore more robust and meaningful postoperative outcomes. We recently conducted a multicenter study to address these shortcomings. The Intraoperative PROtective VEntilation (IMPROVE) trial was a prospective, randomized, controlled study in which a multifaceted strategy composed of low VT ventilation, moderate levels of PEEP, and repeated RMs aimed at keeping the lung open was compared with nonprotective ventilation in 400 intermediate- to high-risk patients undergoing major abdominal surgery. Consistent with previous findings in similar abdominal procedures, we found an overall postoperative respiratory failure rate of 12%. Compared with nonprotective ventilation, prophylactic lung-protective ventilation was associated with improved postoperative clinical outcomes, as suggested by a 69% reduction in the patients requiring intubation or noninvasive ventilation for postoperative respiratory failure (relative risk, 0.29; 95% CI, 0.14 to 0.61; P = 0.001). Of note, the clinical beneficial effects of the lung-protective ventilation strategy persisted for 7 days after surgery, the critical period encompassing the highest incidence of PPs. Whether intraoperative lung-protective ventilation may be beneficial in other major surgical procedures (i.e., vascular, orthopedic, or thoracic surgery) remains to be determined. Nevertheless, available data from a multicenter, randomized, controlled trial in 346 patients scheduled for intrathoracic surgery have shown that, in contrast to nonprotective ventilation, the use of a
VT of 5 ml/kg PBW and 5 to 8 cm H₂O of PEEP was associated with a lower rate of major postoperative complications (22.1 vs. 12.8%, respectively; odds ratio, 1.93; 95% CI, 1.09 to 3.43; \(P = 0.02\)).

The P.O.P. Ventilation Multifaceted Concept

Intraoperative lung-protective mechanical ventilation should ideally be the core of a multifaceted perioperative bundle of pulmonary care. The ensuing principles of prophylactic perioperative positive pressure ventilation (P.O.P.-ventilation) approach are aimed at minimizing the lung volume reduction throughout the perioperative period (fig. 2). An essential aspect is that initiation of mechanical ventilation on a collapsed lung can create the conditions of subsequent lung injury and, most importantly, that lung dysfunction induced by surgery and anesthesia can persist postoperatively. In this connection, previous findings from our group and others suggested that lung volume reduction and atelectasis formation can be effectively attenuated by preventive application of noninvasive positive pressure ventilation (NPPV) using pressure support ventilation and PEEP, or PEEP alone (continuous positive pressure ventilation), an alternative that should be considered during induction of anesthesia in patients at increased risk of respiratory complications. Most recent anesthesia ventilators were found to accurately deliver pressure support ventilation and PEEP and thus allowing easy access to NPPV in the operating room. NPPV not only improves oxygenation and the margin of safety during induction of anesthesia but also increases end-expiratory

Fig. 2. The multifaceted longitudinal (A) bundle of prophylactic Peri-Operative Positive pressure ventilation (the “P.O.P.-ventilation”) to minimize lung collapse (B) using positive pressure during the perioperative period. Intraoperative lung-protective mechanical ventilation is the core of a multifaceted perioperative bundle of pulmonary care, which should ideally include pre- and postoperative application of noninvasive respiratory support aimed at minimizing lung volume reduction during the perioperative period. Individual ranges for tidal volume and positive end-expiratory pressure (PEEP) are indicative. CPAP = continuous positive airway pressure; NIV = noninvasive ventilation; PBW = predicted body weight; PSV = pressure support ventilation; VT = tidal volume.
lung volume by recruiting partially aerated alveoli and limits atelectasis formation in both nonobese and obese patients. The effectiveness of NPPV to prevent lung collapse during preoxygenation can be further improved by applying RM immediately after tracheal intubation.30

The same applies in the early postoperative period, during which preventive application of noninvasive respiratory support can partly compensate for the multifactorial reduction in lung volume induced by surgery and anesthesia.31 With the exception of conditions that carry increased risks of extubation failure, tracheal reintubation after planned extubation is a rare event after elective surgery, with reported rates in the operating room or postanesthesia care unit between 0.1 and 0.45%.32 Early tracheal reintubation (i.e., within the minutes and first hours after planned extubation) is usually attributable to airway obstruction or collapse, residual neuromuscular blockade, or opioid-induced depressive effects,33 whereas late reintubation is mainly related to PPCs. In the absence of large randomized controlled trials, recommendations for safe practice of airway management at extubation are still based on limited scientific evidence and of unproven effectiveness in improving outcome. It is the authors’ expert opinion that every effort should be made to improve patient safety (for instance, identification of patients with an increased risk of extubation failure and reversal of residual neuromuscular blockade) but also to prevent lung collapse during extubation. In this connection, planned tracheal extubation should ideally be performed with the patient positioned in head-up rather than in supine position. In addition, routine application of 100% inspired oxygen concentration before extubation in nonhypoxemic patients and airway suctioning at extubation, which may be responsible for a dramatic loss in lung volume and atelectasis formation, should no longer be used. There is no physiological rationale to support PEEP removal before extubation because existing data did not evidenced harmful effects with the use of moderate levels of PEEP. The use of positive pressure at extubation may also help prevent loss of aeration and pulmonary aspiration. Finally, physiological studies reported that applying postoperative continuous positive airway pressure or pressure support ventilation and PEEP in selected patients can improve postoperative gas exchange and respiratory function after extubation after abdominal and thoracic procedures and could help prevent postoperative acute respiratory failure in patients at increased risk of PPCs. However, the application of postoperative NPPV requires a trained and experienced team and is usually conditioned by admission within care structures capable of providing high levels of monitoring. Use of adjunctive strategies that could help oppose loss in lung volume after tracheal extubation, such as early application of high-flow oxygen therapy that can produce moderate levels of positive airway pressure, is currently being studied.

**Risks Associated with the Use of Prophylactic Positive Pressure Lung-protective Ventilation**

There is general acceptance that increased intrathoracic pressure resulting from PEEP and/or RM may compromise hemodynamic function by impeding venous return with an increase in right atrial pressure, likely promoting a decrease in cardiac output and arterial pressure with an increase in the need of fluid and vasopressor. There is, however, no physiological data to support applying zero PEEP during general anesthesia. The hemodynamic effects of RM are widely influenced by the method of recruitment (e.g., sustained insufflation or progressive increment in PEEP level), the applied level of alveolar pressure, the properties of the underlying cardiovascular system, and the lung and chest wall mechanics. One experimental study in mechanically ventilated pigs with injured lungs indicated that RM depressed cardiac output only transiently and that the post-RM PEEP level, not the RM itself, determined the lasting effect of the RM intervention on cardiac output.34 A study in patients with ARDS found a decrease in cardiac output and arterial pressure only in nonresponders to recruitment (defined as patients with no improvement in oxygenation), whereas no hemodynamic changes occurred in responders.35 Recent studies in patients with healthy lungs during general anesthesia reported either no or only transient and reversible cardiovascular effects requiring interruption of the procedure or significant changes in blood loss and in the need for vasopressors or additional fluid requirements. We also found no significant differences in the intraoperative volume of fluids perfused and in the need of vasoactive drugs with the use of low VT, moderate PEEP levels, and repeated RMs (the multifaceted lung-protective approach) compared with nonprotective ventilation.38 One should kept in mind, however, that hypovolemia and the inhibition of the autonomic nervous system during general anesthesia can potentiate the hemodynamic effects of RM, and that optimization of preload using individualized goal-directed fluid administration may improve tolerance of the procedure. RMs should, however, be used with caution in patients with hemodynamic instability during surgery.

Little detailed information is available regarding tolerance of RM and/or high PEEP levels in patients with severe ultrastructural changes in lung architecture, such as patients with emphysema. Although these patients are at increased risk of PPCs and may benefit the most from a lung-protective ventilation strategy, RM can therefore not be recommended in routine practice until further research provides clarification.

Finally, although we and other researchers reported no major drawbacks with the use of PEEP and RMs during both open and laparoscopic procedures, whether the use of repeated RMs can be associated with surgical-related technical problems in more specific conditions deserves further research.
Future Directions in Perioperative Lung-protective Care

It would be rational to generalize the implementation of prophylactic lung-protective mechanical ventilation to all patients at increased risk of PPCs (fig. 3). Significant emphasis has been given in the last decade to the identification of patients at increased risks of PPCs (table 1). Although these patients are those who could benefit the most from the P.O.P. ventilation approach, there remains, however, a lack of research in specific areas of interest. Previous physiological studies highlighted a marked reduction in lung volume and impaired oxygenation in obese patients immediately after preoxygenation and tracheal intubation are performed, and that increased intraabdominal pressure during pneumoperitoneum further aggravates loss of lung volume. Use of PEEP and alveolar recruitment procedures was consistently shown to improve respiratory mechanics, oxygenation, and lung volume in obese patients, but whether lung-protective ventilation may be beneficial to reduce postoperative morbidity remains to be determined. Besides, in addition to confirming or refuting the benefit of lung-protective ventilation and patient populations that could benefit the most, additional trials should address the relevance of perioperative preventive positive pressure ventilation in patients scheduled for nonabdominal surgical procedures. Given the number of patients for whom the question applies, such trials would be highly feasible with great relevance for daily practice.

Conclusion

Postoperative pulmonary complications are associated with increased resource utilization, costs of care, and high mortality associated with respiratory failure that can follow surgical procedures. Anesthesiologists are becoming more aware of the value of improving perioperative care in enhancing recovery after surgery. The existing data suggest that prophylactic lung-protective mechanical ventilation, using lower VT, moderate PEEP, and RMs, is associated with better functional/physiological and clinical postoperative outcome in intermediate- to high-risk surgical patients compared with the use of nonprotective ventilation. The independent role of lower VT, PEEP, and RM to improve outcome deserves further investigations. The implementation of a bundle of perioperative care by

Fig. 3. The concept of prophylactic lung-protective mechanical ventilation in patients with healthy lungs (A) and in patients with injured lungs (B) at the onset of mechanical ventilation. Individual ranges for tidal volume (VT) and positive end-expiratory pressure (PEEP) are indicative. ABG = arterial blood gases; ETCO$_2$ = end-tidal concentration of carbon dioxide; FiO$_2$ = fraction of inspired oxygen; PacO$_2$ = partial pressure of carbon dioxide; PBW = predicted body weight; RR = respiratory rate; SpO$_2$ = peripheral oxygen saturation.
integrating prophylactic application of positive pressure (the P.O.P.-ventilation) with other key components of perioperative care, such as individualized hemodynamic optimization and early rehabilitation after surgery, may help at further reducing postoperative morbidity. Although it may take many years to implement research findings into everyday clinical practice, given that it remains easier to prevent than to cure postoperative complications, we believe it is only a question of time before this approach will become a standard of care.

Acknowledgments
Support was provided solely from institutional and/or departmental sources.

Competing Interests
Dr. Futier reports receiving consulting fees from GE Medical Systems (Buc, France) and lectures fees from Fresenius Kabi (Velizy, France) and Dr. Jaber reports receiving consulting fees from Dräger (Antony, France), Hamilton Medical (Bonaduz, Switzerland), Maquet (Orléans, France), and Fisher & Paykel (Courtaboeuf, France). No other potential conflict of interest relevant to this article was reported.

Correspondence
Address correspondence to Dr. Jaber: Département Anesthésie et Rénimation B (DAR B), Hôpital Saint-Eloi, CHU de Montpellier, 80 Avenue Augustin Fliche, 34295 Montpellier, France. s-jaber@chu-montpellier.fr. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References


