Apply Protective Mechanical Ventilation in the Operating Room in an Individualized Approach to Perioperative Respiratory Care

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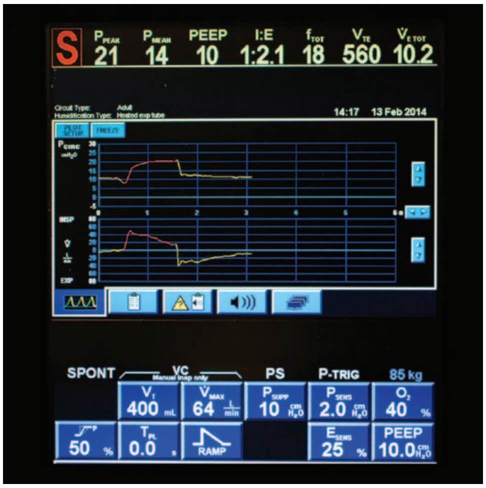
EVERY year, millions of patients worldwide receive mechanical ventilation as part of their medical management under general anesthesia. Despite its frequency, however, there are no standardized guidelines to instruct providers on optimal intraoperative ventilation strategies to reduce the risk of postoperative respiratory complications. Although "protective" mechanical ventilation with low tidal volume and low plateau pressure has gained widespread acceptance in patients with acute lung injury, optimal ventilator settings have yet to be defined for patients with normal lungs undergoing surgery. In this issue of Anesthesiology, Serpa Neto *et al.*[1] report the results of a meta-analysis on protective ventilation *versus* conventional ventilation for surgery. Their work provides important new information that may influence the way we will set our ventilator settings in the operating room in the future. Furthermore, their conclusions compel us to continue questioning how we define protective ventilation for the individual patient in the perioperative period.



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Like It *and* Lump It: What Do We Need to Know about a "Systematic Review and Individual Patient Data Meta-analysis"?

Serpa Neto *et al.*[1] conducted a "systematic review and individual patient data meta-analysis." A systematic review is an exploration, critical evaluation, and synthesis of published evidence. A meta-analysis attempts to synthesize the results from various distinct studies. In individual patient data meta-analyses, patients' individual data points are available and included in the analysis, rather than just incorporating published effect estimates. Serpa Neto *et al.*[1] combined a systematic review to identify pertinent studies, which were then included into an individual patient data meta-analysis. This approach opens the opportunity to identify all available evidence and to adjust for the same/similar confounder set to reduce heterogeneity across studies.[2] However, to ensure unbiased selection and sufficient power, an individual patient data meta-analysis is reliable only when a substantial proportion of existing studies provide individual data on study of rare outcomes, such as postoperative respiratory complications. An exaggeration of the calculated effect may occur when an outcome criterion is subjectively assessed,[3] such as the incidence of postoperative respiratory complications. In addition, inappropriate conclusions may be drawn when studies that provide individual patient data are a biased subset of all existing studies. For example, individual data may be less obtainable from studies with insignificant findings—for instance, studies that do not demonstrate an effect of higher intraoperative tidal volumes on postoperative respiratory complications may not be published. In addition, less recognized authors who report findings that may deviate from mainstream conclusions may be less likely to be invited into an individual data meta-analysis collaboration. Accordingly, the quality of the data included

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in the individual patient data meta-analysis and the sample size are important validity measures.

Ventilator-induced Lung Injury and Postoperative Respiratory Complications

Pulmonary complications, including postoperative respiratory failure, represent the second most frequent postoperative complications after surgical site infections, with an estimated incidence of 0.5% to 7.9% depending on the definition of postoperative complications. Postoperative reintubation is a severe complication, which leads to a longer hospital stay, higher cost, and increased in-hospital death rate.[4] Typically, a combination of the factors can create a "multiple-hit" scenario leading to pulmonary injury. Intraoperative pathogenetic factors include respiratory muscle dysfunction because of trauma and drug effects, excessive fluid resuscitation, inflammation (biotrauma), and ventilator-induced lung injury.[4] The magnitude of ventilator-induced lung injury depends on the interaction among patient's lung compliance and tidal volume (volutrauma), driving and plateau pressure (barotrauma), and PEEP that may help prevent repeated opening and closing of alveoli (atelectrauma). Another potential mechanism of injury is ventilator-induced diaphragmatic dysfunction, which has been identified even after a short period (hours) of immobilizing, controlled mechanical ventilation.[5]

What Is the Study of Serpa Neto *et al*. about?

The authors used the search terms "protective ventilation," "low(er) tidal volume," and "PEEP" and then included randomized controlled trials comparing "protective" with "conventional" ventilation in patients aged greater than 18 yr undergoing general anesthesia for surgery. The exposure variable, protective *versus* conventional ventilation, was then defined based on tidal volume only: protective ventilation was defined as a tidal volume 8 ml/kg or less predicted body weight (PBW) regardless of the PEEP level, and higher tidal volumes were considered as "conventional" ventilation. This definition of protective ventilation is based on the adult respiratory distress syndrome (ARDS) literature—some authors have instead suggested the use of 10 ml/kg PBW as an injurious tidal volume threshold for intraoperative mechanical ventilation,[6] which may be sufficient to keep end-inspiratory stretch reasonably low in patients with normal lungs.[7] The endpoint postoperative respiratory complications were then created subjectively based on a heterogeneous definition of respiratory complications obtained from the individual studies during follow-up. The authors controlled the effects of protective ventilation on postoperative respiratory complications for preoperative and procedural confounders. Analyzing the effects of tidal volume, the authors found 97 cases of postoperative pulmonary complications among 1,118 patients (8.7%) assigned to protective ventilation and 148 cases among 1,009 patients (14.7%) assigned to conventional ventilation (adjusted relative risk, 0.64; 95% CI, 0.46–0.88; $P < 0.01$).[1] Of note, for the analysis of PEEP effects, only data from patients who received a tidal volume lower than 8 ml/kg PBW were included in the analysis, thereby excluding from the analysis 148 of 245 patients with respiratory complications in the dataset.

What Do We Learn from the Study of Serpa Neto *et al*.?

The findings of this meta-analysis suggest that invasive mechanical ventilation during surgery translates to postoperative respiratory complications, supporting the view that physiology-oriented mechanical ventilation should be applied not only to patients with lung injury but also to patients with normal lungs. In accordance, a large meta-analysis including a significant number of high-risk patients without acute respiratory distress syndrome and with ventilation using lower tidal volumes in the intensive care unit showed a decrease in lung injury development and mortality in patients.[8] Accordingly, it is time to apply preventive mechanical ventilation with low tidal volumes and low plateau pressure whenever possible, not only in the intensive care unit but also in the operating room.

Curiosity has its own reason for existing, and an important task for physicians interested in perioperative medicine is to not stop questioning. The current study does not allow us to define an upper tidal volume threshold and a best PEEP level that is generalizable to all patients across surgical procedures and pulmonary compliance levels. There were minimal data included to compare the respiratory side effects of tidal volumes between 8 and 10 ml/kg PBW—an important range of tidal volumes frequently given in the operating room.[9] It is possible that tidal volumes in the 8 to 10 ml/kg range do not increase the risk of postoperative respiratory complications in patients with normal lungs,[10] as long as the plateau and driving pressures are kept within the normal range.[11] There are obvious differences between patients with lung injury and those with normal lung in the consequences of mechanical ventilation on strain (change in lung volume divided by initial lung volume). The lower strain applied to lung tissue during mechanical ventilation is the mechanistic explanation for the beneficial effects of lower tidal volumes. The fact that surgical patients likely have larger lung volumes at end-expiration than ARDS patients with a "baby lung," suggests that they have lower strain for similar tidal volumes. As a consequence, a larger range of tidal volumes may still result in safe lung strain. Therefore, the individual definition of a safe tidal volume depends on the surgical procedure, pulmonary compliance, and the anesthesia plan—taking also into account consequences on aeration and lung stress if a patient is allowed to breathe spontaneously or receives controlled ventilation.

The interpretation of the observation of Serpa Neto *et al.* related to effects of PEEP is even more complex. Optimal PEEP improves the compliance of the lung, and it is likely that the protective effect of PEEP is more relevant in patients who receive higher tidal volumes. Analyzing the association between PEEP and respiratory complications in the low-risk subgroup of patients ventilated with low tidal volume, Serpa

Neto *et al.*[1] reported an inverse U-shaped dose–response curve that is difficult to interpret. Compared with no PEEP, PEEP levels up to 8 cm H_2O were associated with increasing odds of postoperative respiratory complications, whereas the odds ratio for PEEP larger than 9 cm H_2O was lower than 1, suggesting a harmful effect of low PEEP and a preventive effect of high PEEP. This pattern does not follow an obvious biologically plausible pattern and is at this point inconclusive.

How Can We Apply Protective Mechanical Ventilation in the Operating Room as an Individualized Approach to Perioperative Respiratory Care?

An individualized definition of optimal mechanical ventilator settings needs to consider the underlying pulmonary morbidity, surgical procedure, and anesthesia plan. Serpa Neto *et al.*'s data suggest an increased vulnerability to respiratory complications when the tidal volume is greater than 8 to 10 ml/kg PBW—and their exploratory data point toward potential benefits of higher PEEP particularly when combined with lower tidal volume. In the operating room, religiously enforcing a tidal volume less than 8 ml/kg PBW until extubation in all patients is obviously impossible. The increasing effects on tidal volume of pain, discomfort (awake, intubated patient), and anxiety after skin closure can hardly be (and do not necessarily need to be) addressed at the end of the case. In turn, even a tidal volume of 7 ml/kg PBW applied during long surgical procedure may be injurious to patients with severe ARDS, in particular in combination with excessive respiratory muscle activation leading to high transpulmonary pressure.

Protective effects of PEEP were shown in some trials, but not in others.[11,12] It is intuitive to assume that a patient undergoing laparoscopic surgery in the Trendelenburg position should be given a higher initial PEEP level than a patient undergoing brain surgery with the upper body elevated, to optimize compliance of the respiratory system. In individualized patient care, to reduce atelectrauma, we should titrate the "best PEEP" based on dynamic compliance measurements individually to optimize aeration and avoid intermittent alveolar collapse. Future studies should also test the feasibility of brief intraoperative "best PEEP trials" to analyze the effects of PEEP on compliance to select a preventive PEEP level during surgery for the individual patient. To minimize mechanical strain, a combination of lower tidal volume and individualized PEEP seems to be more beneficial compared with the effects of lower tidal volume at zero PEEP or high PEEP with high tidal volume. Additional research is required to define for subgroups of patients based on disease entity, surgical procedure, and anesthesia plan, the best starting point PEEP to be selected following induction of anesthesia.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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