EDITORIAL

Open-lung Ventilation Strategy during General Anesthesia

What Happens Intraoperatively Stays Intraoperatively

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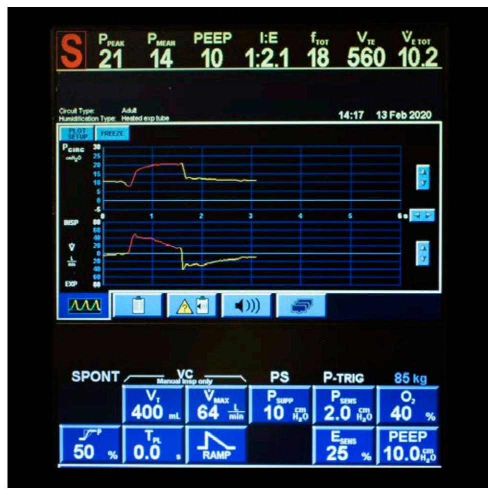
AFTER many years and much research in the field of intraoperative mechanical ventilation, optimal ventilation strategies to prevent postoperative pulmonary complications remain poorly defined. During general anesthesia for surgery, use of higher inspiratory oxygen fraction, neuromuscular blocking agents, and increased intra-abdominal pressure, due to patient positioning, laparoscopic procedure, or patient characteristics, most commonly obesity, favor the formation of atelectasis.[1] Lung recruitment maneuvers combined with positive end-expiratory pressure (PEEP) may revert atelectasis and stabilize lung units, a strategy that is usually combined with protective low tidal volumes and known as an "open-lung ventilation strategy,"[2] that is, a strategy aimed at recruiting as much lung tissue as possible for tidal ventilation. This strategy is claimed to truly treat the cause of hypoxemia that may result from atelectasis, while preventing cyclic closing and opening of lung units, or atelectrauma. Besides preventing atelectrauma, the open-lung ventilation strategy should promote more even distribution of mechanical stress across the lungs, also reducing tidal overdistension, or volutrauma. Both atelectrauma and volutrauma have been implicated in ventilator-induced lung injury, which in surgical patients can contribute to the development of postoperative pulmonary complications, especially after major surgery, when an increased global proinflammatory state is likely. Despite this appealing rationale, an open-lung ventilation strategy was not able to reduce the incidence of postoperative pulmonary complications in patients submitted to elective, on-pump cardiac surgery in the Protective Ventilation in Cardiac Surgery (PROVECS) study,[3] which is in line with findings in noncardiac surgery studies in nonobese[4,5] and obese[6] patients. With 488 included patients, the PROVECS study was unique in that it was powered to determine the effect of intraoperative ventilation strategies on clinical outcome variables. However, the PROVECS study did not investigate the possible reasons for the negative findings on clinical outcome variables.



"…'best PEEP' will always represent a compromise between atelectasis and overdistension…"

In this issue of ANESTHESIOLOGY, Lagier *et al.*[7] report on the effects of the open-lung ventilation strategy on the distribution of ventilation and lung injury in a subpopulation of the PROVECS study. In total, 86 patients were investigated, whereby 56 patients were included in the analysis of distribution of ventilation by electrical impedance tomography, and 30 patients were investigated for biomarkers of lung injury. The open-lung ventilation strategy consisted of lung recruitment with sustained pressure (30 cm H_2O for 30 s at predefined stages in the surgical intervention), PEEP of 8 cm H_2O, and tidal volume of 8 ml/kg of predicted body weight before and after cardiopulmonary bypass, and tidal volume of 3 ml/kg of predicted body weight during cardiopulmonary bypass. Of note, mechanical ventilation during cardiopulmonary bypass has

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been investigated, but is frequently not used due to surgical concerns. In the control group, patients were ventilated with PEEP of 2 cm H_2O (without recruitment maneuvers), and tidal volume of 8 ml/kg predicted body weight, except during cardiopulmonary bypass, when no mechanical ventilation was conducted. Of note, this subanalysis was preplanned, and powered for detecting differences both in the dorsal fraction of ventilation and the plasma concentration of the soluble form of the receptor for advanced glycation end-products (sRAGE), a marker of lung overdistension. The authors found that, compared to controls, the open-lung ventilation strategy effectively shifted ventilation, as measured by electrical impedance tomography, toward dependent lung regions during surgery. However, that effect was not maintained at the end of surgery and postoperative day 2. Also, the plasma concentrations of sRAGE in pulmonary venous blood at aortic declamping were higher in patients submitted to the open-lung ventilation strategy compared with controls, suggesting lung overdistension.

Lagier *et al.*[7] provide a number of possible explanations for the lack of consistent beneficial effects, and even potentially harmful effects, of the open-lung strategy in this surgical population: (1) most patients included in this subanalysis had no specific respiratory risk; (2) a semirecumbent position was used, which might have reduced lung collapse; (3) de-airing maneuvers before cardiopulmonary bypass, which were part of the surgical protocol, may have recruited lungs of controls, and cardiopulmonary bypass possibly increased the risk of lung collapse; (4) increased respiratory system compliance after sternotomy may have increased transpulmonary pressures; and (5) lack of individualization of PEEP and level of airway pressure during recruitment maneuvers could jeopardize the benefits of the open-lung ventilation strategy. Although they sound plausible, they can also be challenged.

First, given the characteristics of the surgical procedure and anesthesia, it is unlikely that patients were not at increased risk for postoperative pulmonary complications. In fact, thoracic surgery and duration of surgical intervention increase the risk of postoperative pulmonary complications.[8] Second, while electrical impedance tomography measurements were conducted in semirecumbent position, mechanical ventilation was performed by necessity in the supine position, and substantial recruitment of lungs by temporary elevation of the trunk is improbable. Third, since de-airing maneuvers before weaning from cardiopulmonary bypass were integrated in the surgical procedure, interventions whose effects are mitigated by this measure do not deserve a place in clinical routine. Fourth, a PEEP of 2 cm H_2O in an open chest during cardiopulmonary bypass is not expected to generate transpulmonary pressures that are high enough to promote consistent lung recruitment in the control group. Yet in the open-lung ventilation strategy group, the transpulmonary pressures at the end of inspiration could have been high enough to trigger and release sRAGE. Fifth, trials that used individualization of PEEP during abdominal surgery in nonobese patients submitted to abdominal surgery,[5] and morbidly obese patients undergoing bariatric surgery,[9] also failed to show beneficial effects of open-lung ventilation on clinical outcome and lung function, respectively. In addition, it must be kept in mind that the "best PEEP" may vary according to the physiologic target, and that even a "best PEEP" will always represent a compromise between atelectasis and overdistension,[10] that is, atelectrauma and volutrauma.

But there are also alternative explanations for these findings, which in our opinion were not entirely unexpected. The open-lung ventilation strategy required higher fluid administration, which has been associated with increased risk for postoperative pulmonary complications. Also, the mechanical power of ventilation, estimating that the average driving pressure and the airway pressure in the open-lung ventilation strategy and control group were 7 and 10 cm H_2O and 16 and 12 cm H_2O, respectively, and using a simplified equation,[11] was higher with the open-lung ventilation (7.4 *vs.* 4.7 J/min, respectively, average values). In fact, mechanical power has been implicated in the development of ventilator-induced lung injury. The results of some of the largest trials on intraoperative mechanical ventilation conducted so far,[4–6] together with the current physiologic knowledge, suggest that with regard to PEEP and lung recruitment maneuvers, "what happens intraoperatively stays intraoperatively," Also not unexpected, and not at all surprising, is the finding that biomarkers of lung injury can increase during the open-lung ventilation strategy. Similar results were reported in patients submitted to open abdominal surgery.[12] Yet we do not expect that this biologic effect will translate into a substantial adverse clinical outcome. But why should one take the risk and pay the price?

With their investigation, Lagier *et al.* added importantly to the knowledge in the field of intraoperative mechanical ventilation. In terms of study design, authors elegantly showed how to plan and conduct a sub-nalysis, issues that, unfortunately, are frequently overlooked. From a scientific viewpoint, the study offers perspectives for further investigation, highlighting the concept of permissive atelectasis, that is, the potential of lung rest to protect from ventilator-induced lung injury.[13] Even more relevant are the clinical implications of this study. When interpreted together with other trials,[4–6] this subanalysis emphasizes the concept of "first, do no harm." The study by Lagier *et al.* shows not only that the physiologic benefits of an open-lung ventilation strategy are restricted to the intraoperative phase of cardiac surgery, and devoid of any clinical impact, but also that this strategy promotes lung overdistension. Thus, it reinforces the recent recommendation that intraoperative recruitment maneuvers and PEEP higher than 5 cm H_2O are indicated only as part of a strategy to rescue for hypoxemia.[14]

Competing Interests

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References

1. Warner DO: Preventing postoperative pulmonary complications: The role of the anesthesiologist. Anesthesiology 2000; 92:1467–72
2. Lachmann B: Open up the lung and keep the lung open. Intensive Care Med 1992; 18:319–21
3. Lagier D, Fischer F, Fornier W, Huynh TM, Cholley B, Guinard B, Heger B, Quintana G, Villacorta J, Gaillat F, Gomert R, Degirmenci S, Colson P, Lalande M, Benkouiten S, Minh TH, Pozzi M, Collart F, Latremouille C, Vidal Melo MF, Velly LJ, Jaber S, Fellahi JL, Baumstarck K, Guidon C; PROVECS Study Group: Effect of open-lung vs conventional perioperative ventilation strategies on postoperative pulmonary complications after on-pump cardiac surgery: The PROVECS randomized clinical trial. Intensive Care Med 2019; 45:1401–12
4. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. Lancet 2014; 384: 495–503
5. Ferrando C, Soro M, Unzueta C, Suarez-Sipmann F, Canet J, Librero J, Pozo N, Peiró S, Llombart A, León I, India I, Aldecoa C, Díaz-Cambronero O, Pestaña D, Redondo FJ, Garutti I, Balust J, García JI, Ibáñez M, Granell M, Rodríguez A, Gallego L, de la Matta M, Gonzalez R, Brunelli A, García J, Rovira L, Barrios F, Torres V, Hernández S, Gracia E, Giné M, García M, García N, Miguel L, Sánchez S, Piñeiro P, Pujol R, García-Del-Valle S, Valdivia J, Hernández MJ, Padrón O, Colás A, Puig J, Azparren G, Tusman G, Villar J, Belda J; Individualized PeRioperative Open-lung VEntilation (iPROVE) Network: Individualised perioperative open-lung approach *versus* standard protective ventilation in abdominal surgery (iPROVE): A randomised controlled trial. Lancet Respir Med 2018; 6:193–203
6. Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology, Bluth T, Serpa Neto A, Schultz MJ, Pelosi P, Gama de Abreu M. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: A randomized clinical trial. JAMA 2019; 321:2292–305
7. Lagier D, Velly LJ, Guinard B, Bruder N, Guidon C, Vidal Melo MF, Alessi M-C: Perioperative open-lung approach, regional ventilation, and lung injury in cardiac surgery: A PROVECS trial substudy. Anesthesiology 2020; 133:1029–45
8. Canet J, Gallart L: Predicting postoperative pulmonary complications in the general population. Curr Opin Anaesthesiol 2013; 26:107–15
9. Nestler C, Simon P, Petroff D, Hammermüller S, Kamrath D, Wolf S, Dietrich A, Camilo LM, Beda A, Carvalho AR, Giannella-Neto A, Reske AW, Wrigge H: Individualized positive end-expiratory pressure in obese patients during general anaesthesia: A randomized controlled clinical trial using electrical impedance tomography. Br J Anaesth 2017; 119:1194–205
10. Carvalho AR, Spieth PM, Pelosi P, Vidal Melo MF, Koch T, Jandre FC, Giannella-Neto A, de Abreu MG: Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. Intensive Care Med 2008; 34:2291–9
11. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, Cazati DC, Cordioli RL, Correa TD, Pollard TJ, Schettino GPP, Timenetsky KT, Celi LA, Pelosi P, Gama de Abreu M, Schultz MJ; PROVE Network Investigators: Mechanical power of ventilation is associated with mortality in critically ill patients: An analysis of patients in two observational cohorts. Intensive Care Med 2018; 44:1914–22
12. Serpa Neto A, Campos PP, Hemmes SN, Bos LD, Bluth T, Ferner M, Güldner A, Hollmann MW, India I, Kiss T, Laufenberg-Feldmann R, Sprung J, Sulemanji D, Unzueta C, Melo MF, Weingarten TN, Boer AM, Pelosi P, Gama de Abreu M, Schultz MJ; PROVE Network Investigators: Kinetics of plasma biomarkers of inflammation and lung injury in surgical patients with or without postoperative pulmonary complications. Eur J Anaesthesiol 2017; 34:229–38
13. Pelosi P, Rocco PRM, Gama de Abreu M: Close down the lungs and keep them resting to minimize ventilator-induced lung injury. Crit Care 2018; 22:72
14. Young CC, Harris EM, Vacchiano C, Bodnar S, Bukowy B, Elliott RRD, Migliarese J, Ragains C, Trethewey B, Woodward A, Gama de Abreu M, Girard M, Futier E, Mulier JP, Pelosi P, Sprung J: Lung-protective ventilation for the surgical patient: International expert panel-based consensus recommendations. Br J Anaesth 2019; 123:898–913