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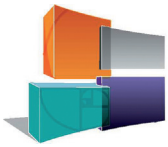

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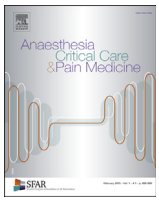

Editorial

Positive end expiratory pressure (PEEP) in the operative theatre: What's next?

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1. What is the optimal level of positive end expiratory pressure (PEEP) for ventilated patients in the operative theatre?

Despite decades of research, this question continues to be the subject of intense discussions between researchers and clinicians, without clear and definitive answer, leaving daily management uncertain. The concept of lung protection during invasive mechanical ventilation is considered a fundamental approach for patients with acute respiratory distress syndrome (ARDS) [1], and is now of growing interest for patients without pre-existing lung injury, both in intensive care units (ICU) and operating theatres (OT) [2–4].

There is a consensus that all patients on mechanical ventilation should benefit from a low tidal volume ventilation, to limit the occurrence of alveolar overdistension. However, ventilation with too low tidal volumes can also cause damage through multiple mechanisms. A recent study investigating protective ventilation in patients without ARDS showed that there is no additional benefit to use extremely low tidal volumes (i.e. < 6 mL/kg of predicted body weight, PBW) [5]. There is also tangible evidence regarding the benefits of using PEEP to prevent injuries caused by atelectrauma. However, there is no recommendation based on results from large randomised clinical trials (RCTs) for the ideal level of PEEP, most of the evidence coming from trials that compared ventilation with either a low or a high level of PEEP [4–6]. Therefore, determining the optimal level of PEEP in a given patient remains an important clinical issue on a daily basis.

Optimising mechanical ventilation is one of the greatest challenges in the care of obese patients. The pathophysiological changes induced by obesity, particularly in terms of respiratory mechanics, make these subjects at risk of difficult intubation, pulmonary complications and prolonged periods of invasive mechanical ventilation. Although there is some evidence to suggest that alveolar recruitment manoeuvres (ARMs) and a higher level of PEEP (namely, open lung strategy) improve oxygenation and pulmonary mechanics in obese patients, most of the data guiding this strategy were based on small monocentric RCTs [7], and data on patient outcomes are lacking.

In a recent JAMA article, investigators of the PROBESE (Protective Intraoperative Ventilation with Higher versus Lower Levels of Positive End-Expiratory Pressure in Obese Patients) study [8] reported the results of a large RCT conducted in 77 centres, distributed in 23 different countries and involving 2013 obese adult patients (body mass index [weight in kg divided by height in squared meters] ≥ 35 kg/m^2), with a moderate to high risk of developing postoperative pulmonary complications, and who were scheduled for laparoscopic or non-laparoscopic surgery, lasting at least 2 hours. Patients were randomised to receive a low tidal volume ventilation (7 mL/kg PBW) and a high or low level of PEEP. Patients in the high PEEP group received a fixed level of 12 cmH_2O PEEP and ARMs (performed by gradually increasing the tidal volume and possibly PEEP to reach a plateau pressure between 40 and 50 cmH_2O). ARMs were performed after intubation and repeated every hour, and after any disconnection from the ventilator (if necessary), as well as before the end of the surgery. Patients in the "low PEEP level" group received a fixed PEEP of 4 cmH_2O without ARM, a strategy chosen to reflect current best practice recommendations [9]. In both groups, the lowest FiO_2 was targeted (with a lower limit of 0.4), while maintaining oxygen saturation above 92%, measured by pulse oximetry. Further settings were conducted following practitioners habits, based on their local expertise and usual practices.

Primary outcome was a composite score including the occurrence of postoperative pulmonary complications within the first 5 days following surgery, characterised by mild, moderate or severe respiratory failure, ARDS, bronchospasm, new pulmonary infiltrates, lung infection, aspiration pneumonia, pleural effusion, atelectasis, cardiogenic oedema or pneumothorax. In the intention-to-treat analysis, patients randomised to the "high PEEP and repeated ARMs" group ($n = 989$) did not show a significant decrease in primary outcome compared to patients in the "low PEEP" group ($n = 987$), with rates of 21.3% and 23.6% respectively (absolute difference, −2.3% [95% CI, −5.9% to 1.4%]). The results

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were similar in the *per-protocol* and sensitivity analyses. There was also no significant difference when considering primary outcome's individual items or secondary endpoints, with the exception of hypoxemia, which was more frequent in the "low PEEP" group, while hypotension and bradycardia were more frequent in the "high PEEP and ARM" group. As acknowledged by the authors, since no adjustment has been made for multiple comparisons, these results should be considered exploratory.

This well-conducted study is important because it provides the first large-scale RCT containing data on patients usually not included in previous studies on protective ventilation in the operating theatre. However, these results may become disappointing for clinicians and somewhat unexpected compared to what might have been expected, based on the results of previous small RCTs. Clinicians who prefer to see the glass half full can interpret the results of the PROBESE study as suggesting that an empirical strategy with a high level of PEEP is just as ineffective as a lower level of PEEP in preventing postoperative lung complications. Other clinicians may suggest that the risk of haemodynamic complications, as demonstrated by a higher incidence of hypotension and bradycardia in the "high PEEP and ARM" group, should encourage the adoption of a strategy with a lower level of PEEP. Since the study protocol did not include a standardised haemodynamic optimisation algorithm for titration of fluid intake and administration of vasoactive drugs, caution should be exercised in its interpretation.

The results of the PROBESE trial are similar to those of a previous RCT of similar design conducted by the same group in "standard" and overweight patients [4].

Do these essentially neutral results mean that high levels of PEEP and ARMs should not be applied in patients under invasive mechanical ventilation? Maybe.

However, it is possible that the optimal level of PEEP may fall between the proposed extreme values. There is a high variability between patients in response to PEEP and ARM [10], and a single level of PEEP, applied interchangeably, cannot reflect these differences. Some may intuitively suggest that an individualised strategy for titration of PEEP, adapted to the physiology of each patient, would have been more informative [11]. However, results of the PROBESE trial were consistent with predefined subgroups. Nevertheless, it is still possible that the effects of PEEP were different in patients within the two groups. As indicated by the authors, higher level of PEEP and ARM use were associated with lower driving pressures than in the lower PEEP group, as expected from a strategy intended to achieve higher aerated lung volumes. Although the effect of the intervention may appear homogeneous at the randomisation group level, it does not exclude the possibility of significant heterogeneity at the patient level in each group. For example, a higher level of PEEP may result in low driving pressure for one patient, but with opposite effects for others. Such heterogeneity can lead to significant differences that bias the interpretation of the results [12]. In other words, a higher level of PEEP may have been beneficial but unnecessary in some patients, while a higher level may have been harmful in others.

Several other possible explanations should be considered when interpreting the results of the PROBESE trial. One of those is the study population. Among patients included in the intention to treat analysis, only 15.9% had a high risk of postoperative pulmonary complications, patients who, theoretically (and intuitively), should benefit most from protective ventilation, but who were exposed only to relatively short durations of mechanical ventilation (average duration of 3 hours in both groups). It is therefore reassuring to note that pulmonary complication rates were low in both randomisation groups, the most common complication being mild respiratory failure (defined as hypoxemia responding to an oxygen supplement of less than 2 L/min).

2. What are the implications of the PROBESE trial results and what should clinicians do?

First, it is reasonable to assume that a higher level of PEEP should not be used routinely in all patients under mechanical ventilation, obese or not. Meanwhile, should clinicians adopt the concept of permissive atelectasis and consider applying lower levels of PEEP to all patients? Nothing in this study enables to support this hypothesis. Second, from a pathophysiological point of view, it is justified to consider customised adjustments of PEEP levels rather than fixed "low" or "high" levels applied uniformly to all patients. However, it is clear that efforts to reduce postoperative pulmonary complications are not limited to providing peroperative protective ventilation and that a multimodal approach, including during the early postoperative period, is certainly necessary [13]. We hope that other treatment strategies will continue to be evaluated prospectively in order to promote more personalised approaches to patient care, either in mechanical ventilation, haemodynamics or other areas in line with future European recommendations on perioperative ventilation upcoming in the British Journal of Anaesthesia, which support personalised management of mechanical ventilation settings.

Disclosure of interest

Dr Godet reported receiving lecture fees from GE Healthcare, Fresenius Kabi, Edwards Lifesciences, Baxter, and Merck Sharp & Dohme. Dr Futier reported receiving consulting fees from Drager Medical, GE Healthcare, Edwards Lifesciences, and Orion Pharma; and lecture fees from Fresenius Kabi, Baxter, and Fisher and Paykel Healthcare. Dr Cungi declared having no competing interest.

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