Intraoperative mechanical ventilation in patients with non-injured lungs: time to talk about tailored protective ventilation?

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It is a well-established concept that general anaesthesia can impair lung function postoperatively, even in subjects with healthy lungs (1), and mechanical ventilation itself is considered to play a major role in contributing to such dysfunction. Mortality after surgery was found to be higher than expected (2), with postoperative pulmonary complications (PPCs) having a relevant impact on outcome (3,4). Following these epidemiological findings, several research groups aimed at identifying modifiable risk factors associated with PPCs, in order to plan mitigation strategies to reduce the incidence of such complications and improve patients' outcome. Among the others, several specific ventilation strategies have been found to be associated with a lower risk of developing PPCs. However, due to the low number of observed events, it is difficult to achieve a definitive answer on optimal intraoperative ventilation strategy to minimize the postoperative incidence of adverse events (5). In fact, general anaesthesia is nowadays considered as a safe procedure with a relatively low incidence of complications (6). The general tendency of the last decade was to translate the concept of "protective mechanical ventilation" borrowed by the critical care setting to non-injured lungs in operating room or intensive care and found to influence clinical outcome (7-9).

Several randomized controlled trials (RCTs) have investigated the role of tidal volume, PEEP and recruitment manoeuvres, both separately (10) or as bundles of multiple interventions (11). Even though RCTs are the gold standard to build high quality evidence, results are still not univocal. Moreover, the number of subjects that have to be included in RCTs to achieve an acceptable statistical power is high, also when predictive scores are used to screen patients and include those at higher risk for PPCs (5,12). Therefore, it is rather difficult to perform secondary analyses to identify subgroups of patients that can benefit from specific ventilation strategies, and researchers have few methodological options: designing dedicated trials for specific groups (i.e., in obese patients), pooling individual data from several RCTs (13), or analysing large retrospective databases. The latter strategy is the weakest in terms of scientific robustness, but has the advantage of being able to collect very large datasets, especially in centres using centralized automated collection of clinical data for research or administrative purposes. Definitive evidence is seldom obtained by retrospective data analysis, but several findings can be inferred and interpreted to improve the knowledge or to plan further prospective trials.

In a paper recently published on the *British Medical Journal*, Ladha and collaborators (14) analysed retrospectively a large hospital based registry study in three hospitals in Massachusetts, United States, including a total of 69,265 consecutive patients that underwent non-cardiothoracic surgery between January 2007 and August 2014. The principal outcome measure was the incidence of PPCs, defined as a composite endpoint combining several severe respiratory complications. The analysis was carried out at two stages: a first retrospective cohort comparison between patients that did or did not receive a protective ventilation strategy, followed by a secondary analysis on the effect of PEEP, tidal volume, plateau pressure and driving pressure as risk modifiers for the development of PPCs. In the retrospective threshold-based analysis, the authors essentially confirmed what was found by the majority of the prospective trials, namely that the lowest incidence of

PPCs was observed with a protective ventilation combining PEEP ≥5 cmH_2O and tidal volume ≤10 mL/kg predicted body weight to achieve a plateau pressure lower than 30 cmH_2O. The results were confirmed when using propensity score matching, and the observed reduction in observed events was around 10%. In the secondary analysis, the authors found a positively skewed distribution of the tidal volume and plateau pressure, and a bimodal distribution of PEEP, with 0 and 5 cmH_2O representing the most common settings. The latter finding suggests that most clinicians tend to apply PEEP on a standard basis, with no tailored titration. It should also be remembered that many operative room ventilators are unable to deliver an actual PEEP of 0 cmH_2O, but rather a 2-3 cmH_2O achieved PEEP due to technical characteristics of the ventilator (6,8), and that this technical limit has been overcome only in few very recent machines. The multivariable logistic regression analysis showed that lower plateau pressure and moderate PEEP levels were associated with the better outcome. Driving pressure had a role comparable to that of plateau pressure, but in the study population the low variability in PEEP makes driving and plateau pressure highly interconnected. Surprisingly, no independent effect of tidal volume was observed. This finding suggests that the harmful effect of tidal volume dynamic strain is mediated by an increase in plateau pressure linked to lung compliance, possibly reflecting lung stress. This is a relatively innovative concept in intraoperative mechanical ventilation, that might reflect what has been recently observed in the ventilation of the injured lung (15). Moreover, the risk of developing PPCs increased when plateau pressure was higher than 16 cmH_2O, suggesting that the threshold of induction of lung injury in healthy lungs could be lower than expected.

The main limit that hampers the interpretation of the results, as mentioned by the authors themselves, is that the whole analysis relies on data initially collected for administrative rather than research purposes. Many of the potential confounding factors were thoroughly tested, including the role of patient clustering due to different caregivers, other factors, like the reliability of outcome data reporting, were impossible to check. The authors used multiple imputations to deal with missing data points, including a quality check to test whether the results changed excluding imputed values. Once seen very rarely in biomedical research, multiple imputation methods are gaining acceptance among researchers when used cautiously in large datasets (16). Despite the intrinsic limits of the retrospective study design and the recourse to sophisticated statistical models, the authors were careful in interpreting the results and tried to compensate most of the potential sources of bias, at least when technically feasible. These findings are substantially in line with the findings of most recent meta analyses, concluding that a protective strategy based on low tidal volume and moderate PEEP improves outcome (7,13). However, a recent article published by the *British Journal of Anaesthesiology*, showed that low tidal volumes and low PEEP were associated with an increased mortality (17). Thus it is difficult, in such retrospective studies, to discriminate whether a specific ventilation setting was a deliberate choice a priori or rather a strategy to overcome an intraoperative gas exchange impairment. Surprises sometimes arise from randomized trials: this is the case, for instance, of the PROVHILO study (10), that found no role of high PEEP alone in preventing PPCs, suggesting that the advantages of protective ventilation found by Futier *et al*. (11) were probably due to the tidal volume. In conclusion, actual evidence coming from RCTs, observational prospective and retrospective data analysis, as well as individual data meta-analysis suggest that protective mechanical ventilation surgery should include: (I) low tidal volume targeted to 6–8 mL/kg predicted or ideal body weight; (II) plateau pressure of the respiratory system maintained below 16 cmH_2O, as much as possible; (III) low levels of PEEP equal or lower than 5 cmH_2O, without recruitment manoeuvres; (IV) PEEP between 5 and 10 cmH_2O should be considered in patients with body mass index higher than 35 kg/m^2, laparoscopy surgery in Trendelenburg position and with a duration of surgery longer than 4 h. In case of oxygen desaturation, after excluding possible common causes like endotracheal tube misplacement or secretions in the airways, it is suggested to increase inspiratory oxygen fraction up to 70% and then perform a recruitment manoeuvre with non-invasive or invasive hemodynamic continuous monitoring. However, we agree with Ladha *et al*. (14) that a universal threshold of protectiveness, applicable to every patient, cannot be identified. All the efforts should be made to achieve an acceptable gas exchange avoiding excessive delivery of tidal volume leading to increased plateau and driving pressures. Further studies are necessary to identify the optimal ventilator settings for specific subgroup of patients. In particular, the role of patient-tailored PEEP setting, ventilation in obese patients as well as those undergoing laparoscopic surgery seem to be of particular interest. The more the knowledge advances, the benefits that can be achieved by further modifying intraoperative ventilation seems to be smaller: it is now the time to study broader interventions and bundles covering both the preoperative and the postoperative care of surgical patients.

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Footnote

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