Fourth, mean age of study subjects was more than 65 yr, but their study design did not include the perioperative assessment of patients' cardiac function. Actually, in this study some of the observed endpoints for postoperative pulmonary complications, such as dyspnea, increased tracheal secretions, cough, chest pain, and lung density change in chest x-ray tests, are similar to the clinical features of cardiac insufficiency. Good-quality evidence identifies preoperative cardiac insufficiency as a significant risk factor for postoperative pulmonary complications.[2] In the noncardiac surgery patients aged 60 yr or more, moreover, incidence of postoperative myocardial injury defined by an increased troponin level is as high as 19% and there is a strong association between postoperative myocardial injury and perioperative morbidity and mortality.[9] In a cohort study of major abdominal surgery patients,[10] 33% of patients who developed postoperative pulmonary complications also had cardiovascular complications. These results suggest that a significant proportion of patients with postoperative pulmonary complications in the study by Severgnini *et al.*[1] may have cardiovascular complications that are not evaluated.

Thus, we cannot exclude possibility that existence of any imbalance in the above-mentioned factors would have confounded interpretation of their results. Furthermore, small sample size of study population may also have prevented them from excluding a type 2 error when comparing statistical differences between two groups in some endpoints, such as incidences of pulmonary complications on postoperative days 2 and 3, dyspnea, secretions and cough scores on postoperative days 1, 3, and 5, and percentage of patients in hospital on postoperative day 28. We believe that large-sample, randomized, controlled trials are still needed to define association of intraoperative ventilation strategies with postoperative pulmonary outcomes.

Competing Interests

The authors declare no competing interests.

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Lung-protective Ventilation during General Anesthesia: What about the Oxygen?

To the Editor:

We read with great interest the article by Severgnini *et al.*[1] in which the authors evaluated a protective ventilation strategy with low tidal volume (7.7 ± 0.8 ml/kg of predicted body weight), positive end-expiratory pressure (10 cm H_2O), and recruitment maneuvers (RMs) as compared with ventilation with higher tidal volumes (9.5 ± 1.1 ml/kg of predicted body weight), no positive end-expiratory pressure (zero end-expiratory pressure), and no RMs in patients undergoing open abdominal surgery and mechanically ventilated for at least 2 h. Their results showed better pulmonary functional tests, fewer alterations on chest radiograph, and higher arterial oxygenation on different postoperative days. One month later, Futier *et al.*,[2] one of Severgnini's coauthors, published a similar study on the efficacy of the protective ventilation strategy in intermediate- to high-risk patients undergoing

major abdominal surgery. The authors similarly found that a protocol based on low tidal volume (6.4 ± 0.8 ml/kg of predicted body weight), positive end-expiratory pressure 6 cm H_2O (interquartile range, 6–8), and RMs was beneficial for major pulmonary and extrapulmonary complications evaluated within the first 7 days after surgery when compared with a more "standard" treatment based on a higher tidal volume (11.1 ± 1.1 ml/kg of predicted body weight), zero end-expiratory pressure, and no RMs. Futier, Severgnini, and their coauthors contributed important findings to the controversy regarding the best tidal volume and the usefulness of positive end-expiratory pressure and RMs during general anesthesia, thus improving our knowledge on this issue. Nonetheless, in both studies, no clear indications are given about the optimal oxygen inspiratory fraction (F_{IO_2}) to be delivered during mechanical ventilation to limit the toxic effects of oxygen. In the study by Severginini *et al.*, the authors state that "*All patients were preoxygenated with F_{IO_2} 0.8 before tracheal intubation, and maintained at 0.4 during the entire anesthesia procedure, irrespective of study group*," whereas in the study by Futier *et al.*, the F_{IO_2} was 47.2 ± 7.6% and 46.4 ± 7.3% in the traditional *versus* lung-protective groups, respectively (P = 0.27). Not targeting the F_{IO_2} for arterial partial oxygen pressure and saturation (Pa_{O_2}/F_{IO_2}) could lead to an oversupply of oxygen and excessive reactive oxygen species production, which has been clearly identified as causing alveolar and organ inflammatory damage.[3–8] Moreover, cardiovascular negative effects (such as an increase in vascular resistance, reduction in cardiac output, carotid and downstream cerebral arteries vasoconstriction, or a decrease in coronary blood flow) have been demonstrated in healthy people and during medical emergencies during routine use of supplemental oxygen.[7,8] Depending on the concentration and duration of oxygen exposure, excessive production of reactive oxygen species may lead to the development of "oxidative stress" and consequently damage the lungs and other tissues.[3–8] Effectively, to quote Winslow[7]: "Oxygen: the poison is the dose." Indeed, it has been demonstrated that even oxygen administration delivered at medium concentration (6 l/min) may have negative effects on outcome even in patients with cardiac ischemia.[9] In this regard, we agree with Marino[10] who wrote: "*… why an organism that requires oxygen for survival is designed to carry on metabolism in an oxygen-limited environment? The answer may be related to the toxic potential of oxygen. Oxygen is well known for its ability to produce lethal cell injury via the production of toxic metabolites … so, limiting the oxygen concentration in the vicinity of cells may be the mechanism for protecting cells from oxygen-induced cell injury.*" That is like saying that there is surely a reason why Mother Nature provided 21% oxygen in the air we breathe. In conclusion, we believe that protective ventilation strategies should definitely be administered to patients undergoing surgery, but because oxygen clearly has a double-edged nature, we hope that forthcoming trials will include an F_{IO_2} titration for optimal oxygenation (with the use of point-of-care blood gas analyzer and lactate concentration), keeping it as low as possible to deliver appropriate oxygen for any given patient, yet avoiding hyperoxia.

Competing Interests

The authors declare no competing interests.

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In Reply:

We would like to thank Dr. Zheng *et al.*, Dr. Xue *et al.*, and Dr. Romagnoli *et al.* for their interest in our investigation[1] and their comments. In their letters, they voiced concerns about the selection of the patients included into the study and the clinical management during the perioperative period.

Dr. Zheng *et al.* emphasize the body mass index and epidural anesthesia technique as possible confounding factors. In our study, the mean body mass index was 25.9 ± 4.2 kg/m^2 and 25.0 ± 4.9 kg/m^2 in the standard and protective ventilation groups, respectively (P = 0.47). Thus, we believe that obesity did not affect our results. Epidural anesthesia