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

at the level T8 to T12 might cause a decrease in muscle tone affecting spirometer measurements in postoperative period. In our study, both groups were treated with the same type and regimen of epidural anesthesia, and the infusion rate in epidural space was 4 to 6 ml/h, at low concentration of ropivacaine. The reduced velocity of infusion plays an important role to minimize the dose administered with the less motor blockade. The level of epidural anesthesia was not always checked before the induction of general anesthesia, due to longer onset time of the drug administered. However, all patients were evaluated in the postoperative period, every day, to exclude a too high level of anesthesia and the risk of a motor block of respiratory muscles.

Dr. Xue *et al.* raise several points of criticism: first perioperative hemoglobin levels, which might be associated with increased perioperative mortality, increased postoperative pneumonia, and increased hospital length of stay; second, serum albumin level which has been shown to be an important predictor of pulmonary complications after major noncardiac surgery; third, the use of nasogastric tube after surgery associated with reduced postoperative pulmonary complications; and fourth the perioperative assessment of patients' cardiac function in older patients.

The Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score,[2] which predicts the risk of postoperative pulmonary complications, was comparable between the standard and protective ventilation groups, being 38.1 ± 8.6 and 34.8 ± 11.6 (P = 0.22), respectively (table 1). It has been shown that preoperative hemoglobin concentration lower than 10 g/dl was associated with an increased risk of postoperative pulmonary complications. In our study, the preoperative hemoglobin concentration was 13.2 ± 1.4 g/dl in the standard ventilation group and 12.3 ± 1.6 g/dl in the protective ventilation group (P = 0.04), showing no clinical relevant differences between the two groups. We did not collect the serum albumin level. However, laboratory indices of hepatic function were comparable within the two groups in the preoperative and postoperative periods. According to the clinical guidelines in our hospital, all patients undergoing open abdominal surgery, as those included in the current study, have a nasogastric tube for at least 24 h. The mean ages of our patients were 67.0 ± 9.0 and 65.5 ± 11.4 yr in the standard and protective ventilation groups, respectively. We agree with Dr. Xue that in the noncardiac surgery patients aged more than 60 yr, the risk of myocardial injury is increased. In our study, we did not measure serum troponin levels, but we did not observe severe arrhythmias or electrocardiographic alterations and for all patients similar perioperative fluid volume was administered. Overall, we did not report any clinical evidence of increased cardiac-related complications between the two groups. Finally, we agree with Dr. Xue that large-sample, randomized, controlled trials are useful to confirm the role of intraoperative ventilation strategies determining or preventing postoperative pulmonary outcomes. In August 2013, Futier *et al.*[3] published a trial reporting that an intraoperative protective

Table 1. ARISCAT Score

	Standard Ventilation (n = 27)	Protective Ventilation (n = 28)	*P* Value
Age, yr, n (%)			
≤50	2 (7.4)	3 (10.7)	1.0
51–80	24 (88.9)	24 (85.7)	1.0
>80	1 (3.7)	1 (3.6)	1.0
Preoperative SpO_2, % (mean ± SD)	96.3 ± 1.6	96.7 ± 2.3	0.28
Preoperative SpO_2, %, n (%)			
≥96	18 (66.7)	21 (75.0)	0.56
91–95	9 (33.3)	7 (25)	0.56
≤90	0	0	—
Respiratory infection in the last month, n (%)	0	0	—
Preoperative anemia (Hb <10 g/dl), n (%)	0	1 (3.6)	1.0
Hemoglobin concentration, g/dl (mean ± SD)	13.2 ± 1.4	12.3 ± 1.6	0.04
Surgical incision			
Peripheral	6	7	1.0
Upper abdomen	21	21	1.0
Intrathoracic	0	0	—
Duration of surgery, min, n (%)			
≤120	2 (7.4)	4 (14.3)	0.67
120–180	8 (29.6)	9 (32.1)	1.0
≥180	17 (63)	15 (53.6)	0.59
Emergency procedure	0	0	—

Hb = hemoglobin; SpO_2 = oxygen peripheral saturation.

ventilation strategy, with a tidal volume of 6 to 8 ml/kg of predicted body weight, a positive end-expiratory pressure of 6 to 8 cm of water, and recruitment maneuvers repeated every 30 min after tracheal intubation compared to non-protective ventilation with a tidal volume of 10 to 12 ml/kg of predicted body weight, with no positive end-expiratory pressure and no recruitment maneuvers, improved clinical outcomes and reduced healthcare utilization in the postoperative period in 400 patients at intermediate to high risk of pulmonary complications after major abdominal surgery.

Dr. Romagnoli *et al.* point out the role of oxygen titration as a component of the lung-protective strategy. We did not target the inspiratory oxygen fraction during surgery. However, all patients were preoxygenated with inspiratory oxygen fraction of 0.8 before tracheal intubation and maintained at 0.4 during the entire anesthesia procedure in both groups.

In conclusion, recent evidence from randomized, controlled trials[1,3] and meta-analysis[4] suggests that in patients at higher risk of postoperative pulmonary complications undergoing surgery, intraoperative protective mechanical ventilation with lower tidal volume (6–7 ml/kg predicted body weight) and positive end-expiratory pressure (6–10 cm H_2O) with recruitment manoeuvres improves outcome and reduces healthcare utilization compared with conventional tidal volume (9–11 ml/kg predicted body weight) without positive end-expiratory pressure and recruitment.

Competing Interests

The authors declare no competing interests.

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Vitamins in Nitrous Oxide Randomized Trial: A Few Concerns

To the Editor:

Whether intraoperative use of nitrous oxide increases the risk of adverse perioperative cardiac event has been the topic of discussion in recent time.[1] I congratulate Nagele *et al.*[2] for addressing this very pertinent and controversial topic. However, I believe that apart from the limitations described in the discussion, there are two aspects of this study that should be addressed.

First, is this an intention-to-treat analysis in its strictest form? According to figure 1 in their article, among 557 patients randomized, only 500 patients were included in the intention-to-treat analysis, thus excluding 10.23% patients from final analysis.[2] The intention-to-treat principle requires all the randomized participants to be included and analyzed according to their allocated group even though they may not have received the intended intervention.[3] Moreover, in contrary to the calculation by the authors and their doubt whether a lager sample size would have influenced their study outcome, Myles[1], in his editorial, has expressed uncertainty regarding their sample size.[2] As the result of this study has wide impact on perioperative care, a response by the authors regarding the reasons for this exclusion and its influence on the final statistical outcome will be of much help to analyze the conclusion.

Second, although the authors concluded that high-sensitivity cardiac troponin T assay is the most sensitive method to detect perioperative myocardial injury and infarction, is it justifiable to use it to detect perioperative myocardial infarction?[2] Nagele *et al.*[2] has reported that 80% patients (with similar distribution in both the randomized groups) had measurable increase in high-sensitivity cardiac troponin T level in the postoperative period with overall incidence of myocardial infarction 4.4%. Because many nonthrombotic factors frequently encountered in perioperative period are associated with increased cardiac troponin level, considering this high percentage of patients with increased high-sensitivity cardiac troponin T, its use in perioperative period runs the risk of inflated rate of diagnosis of myocardial infarction unless analytical issues with it is given due consideration.[4] Instead, its value may be more in ruling out myocardial ischemia.

Competing Interests

The author declares no competing interests.

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