

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<sup>1,3</sup> and meta-analysis<sup>4</sup> 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<sub>2</sub>O) 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.<sup>1</sup> I congratulate Nagele *et al.*<sup>2</sup> 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.<sup>2</sup> 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.<sup>3</sup> Moreover, in contrary to the calculation by the authors and their doubt whether a larger sample size would have influenced their study outcome, Myles<sup>1</sup>, in his editorial, has expressed uncertainty regarding their sample size.<sup>2</sup> 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?<sup>2</sup> Nagele *et al.*<sup>2</sup> 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.<sup>4</sup> Instead, its value may be more in ruling out myocardial ischemia.

### Competing Interests

The author declares no competing interests.

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### In Reply:

We welcome the opportunity to respond to Dr. Saika's letter and clarify two aspects of the article, adherence to the intention-to-treat principle and the role of novel high-sensitivity cardiac troponin in the diagnosis of perioperative myocardial injury and infarction.

### Intention-to-treat Analysis

As Dr. Saika correctly points out, the intention-to-treat principle is the accepted standard in the statistical analysis of randomized, controlled trials. The intention-to-treat principle was invented to circumvent two main problems during drug trials where the treatment continued over longer periods of time, namely patients stopping the treatment early (attrition) and patients switching from one trial arm to the other (crossover) in a nonrandom manner. Intention-to-treat principle allowed clinicians to determine *effectiveness* of a novel treatment under more realistic conditions rather than judging the merits of a novel drug by its maximum *efficacy* under ideal conditions. The Vitamins in Nitrous Oxide trial analysis fully adhered to the intention-to-treat principle.<sup>1</sup> The intervention in the Vitamins in Nitrous Oxide trial was an infusion of B-vitamins or placebo. The 57 patients who were excluded from the analysis were withdrawn from the study *before* receiving any treatment and therefore had to be excluded. What typically happened with these patients was that they were informed about the study, agreed to participate, signed the consent form, and then—before any intervention occurred—the surgery was cancelled, or the anesthesia team refused to use nitrous oxide, or the patient changed his mind. Thus, the intention-to-treat principle was not applicable to these withdrawn patients. Of the true intention-to-treat population (n = 500), 5 of 250 patients (2%) in the B-vitamin arm and 3 of 250 patients in the placebo arm (1.2%) did not receive nitrous oxide. Given these small numbers, we do not expect a strong influence on the study results.

### High-sensitivity Cardiac Troponins in the Diagnosis of Perioperative Myocardial Injury and Infarction

This is without a doubt a topic of high interest to the perioperative community and an area of active investigation. In a recently published ancillary study of the Vitamins in Nitrous Oxide trial, we were able to expand on these findings.<sup>2</sup> On the

basis of the three points of evidence, we have to disagree with the statement that perioperative increase in high-sensitivity cardiac troponin level reflects an inflated diagnosis of myocardial infarction. First, among higher-risk patients, that is, patients with pre-existing coronary artery disease, the risk for major perioperative cardiac events is high: the POISE trial found a 6.9% 30-day event rate for myocardial infarction, cardiac death, or nonfatal cardiac arrest.<sup>3</sup> Second, by using continuous perioperative 12-lead Holter monitoring, Landesberg *et al.*<sup>4</sup> showed nicely that more than 20% of their patient population developed myocardial ischemia. Therefore, perioperative myocardial infarction is likely under- not over-reported. Third, according to the Third Universal Diagnosis of Myocardial Infarction, the diagnosis of myocardial infarction requires both an increase/decrease pattern of a cardiac biomarker with at least one value above the 99th percentile and evidence for new ischemic electrocardiograph changes, such as ST-segment increase or depression, in continuous leads in a setting consistent with myocardial ischemia.<sup>5</sup> Most clinical 12-lead electrocardiographs are performed as spot measurements easily missing temporary ischemic events. However, cardiac troponin represents a cumulative measure of myocardial damage, and its kinetics allows the detection of myocardial injury and infarction that occurred several hours before the measurement. Thus, we believe that novel high-sensitivity cardiac troponin assays will allow us to detect more cases of perioperative myocardial infarction. This notwithstanding, there are definitely instances where perioperative cardiac troponin increase may be caused by nonischemic factors such as acute renal failure.<sup>6</sup> Thank you for giving us the opportunity to clarify these points.

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### Competing Interests

The authors declare no competing interests.

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