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## In Reply

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Second, the mild beneficial effect of perioperative inspiratory hyperoxia on postoperative late nausea was the only one of six secondary outcomes that was statistically significant, suggesting that this finding may be due to chance rather than the intervention.

Third, although no significant differences were found as to the rates of pulmonary side effects, that outcome was not accurately defined and the adverse effects may be greatly underdiagnosed, because routine pulmonary examinations have not been performed in any of the large trials. Other harms were not assessed, but recently published data suggest increased long-term mortality with 80% oxygen.<sup>8</sup> A positive risk–benefit ratio along with the administration of a high perioperative inspiratory oxygen fraction is therefore not evident.

The meta-analysis included trials at low as well as high risk of bias, and finally, the authors did not consider the risk of finding the nearly significant result by chance because of too few randomized patients, which might have tempered their conclusion. The meta-analysis presented by the authors—following the previously published meta-analyses—may only be regarded as an interim-analysis toward a conclusive answer. In a trial sequential analysis,<sup>9</sup> it can be calculated that the diversity-adjusted required information size is 9,019 randomized patients for showing a 23% relative risk reduction (fig. 1), and there are thus no conclusive answer so far, as only 5,103 patients have actually been randomized.

### Competing Interests

All authors of this letter were members of the PROXI trial steering committee investigating 80% oxygen to prevent surgical site infection (JAMA 2009; 302:1543–50) and are also authors of an upcoming Cochrane review about the effects of high perioperative inspiratory oxygen fraction for adult surgical patients (Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008884. DOI:10.1002/14651858.CD008884).

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### In Reply:

We would like to thank Drs. Hedenstierna, Belda, Meyhoff and colleagues for their interest in our meta-analysis.<sup>1</sup> We attempted to provide a comprehensive quantitative summary on the effects of perioperative high inspired oxygen fraction—definitely an on-going and passionate issue.

The main concern of Drs. Hedenstierna and Edmark is that we considered studies in which nitrous oxide was used as carrier gas, and that the variation in nitrous oxide concentrations among study groups may not have been properly controlled in all trials. Whether studies using nitrous oxide should be considered is, indeed, a relevant question in situations where nitrous oxide has been recognized as a confounding factor. For that reason, we did not consider data on postoperative nausea and vomiting from studies that were using nitrous oxide (because nitrous oxide has emetogenic properties). However, there is no evidence suggesting that nitrous oxide plays any role in the incidence of surgical site infection.<sup>2</sup> Nitrous oxide was administered in one trial only that reported data on pulmonary outcome.<sup>3</sup> In that trial, the incidence of atelectasis was significantly higher ( $P < 0.001$ ) in the group receiving 70% of nitrous oxide (*i.e.*, 30%  $F_{IO_2}$  [fraction of inspired oxygen]), suggesting either a detrimental effect of nitrous oxide or a protective effect of high  $F_{IO_2}$ , or both. In any case, the result tends to support our conclusions. We cannot exclude that, in trials that were using nitrous oxide, some variability in the concentration

of nitrous oxide may have led to different oxygen regimens in some patients. This, however, would most probably not have affected our conclusions. If some patients in “high  $F_{IO_2}$ ” groups had actually received a “not so high  $F_{IO_2}$ ,” and some patients in “normal  $F_{IO_2}$ ” groups had received a “higher than normal  $F_{IO_2}$ ,” this would have weakened the beneficial effects of high oxygen fraction. Thus, our conclusions could have indeed been too conservative and the true beneficial effects of high  $F_{IO_2}$  would actually be even more pronounced. Drs. Hedenstierna and Edmark are also skeptical about our conclusions on postoperative atelectasis. We fully agree with their view that the occurrence of perioperative atelectasis is of multifactorial etiology. Yet, the question is not so much whether intraoperative atelectases occur in surgical patients, as there is general agreement that this happens, but whether or not intraoperative high oxygen regimens increase the risk of clinically relevant postoperative atelectasis. To date, there is no evidence from randomized controlled trials to suggest that this is the case.

Dr. Belda and colleagues suggest an interesting method to better allow for potential sources of heterogeneity in meta-analyses. Although they agree that high  $F_{IO_2}$  should be considered to reduce the risk of surgical site infection, and that this intervention may provide protection throughout a large range of surgeries, they argue that additional trials, with standardized outcome measures and including high-risk patients, will be needed to ensure adequate power and to guarantee wide applicability of these results. We agree that further large trials including patients at high risk of surgical site infection may be warranted. However, it should be highlighted that trials in patients who are not receiving prophylactic antibiotics are probably not ethically acceptable anymore. Thus, the challenge will be to confirm the anti-infective efficacy of high oxygen regimens in surgical patients who are receiving prophylactic antibiotics concomitantly and in whom the baseline risk of infection will be, accordingly, low.

Finally, Dr. Meyhoff and colleagues nicely highlight strengths and weaknesses of meta-analyses. We would like to reassure Dr. Meyhoff that we did not have, as they seem to suggest, any bias in favor, or against high inspired oxygen. One may, or may not, agree with our methodological choices, yet our process was overt; every step of the critical appraisal of included and excluded studies, as well as the rationale behind all quantitative analyses, were transparent, clearly described, and reproducible. Also, we have pointed out for the first time that almost all patients in these trials had received prophylactic antibiotics. This is a serious methodological issue that needs to be addressed when analyzing the anti-infective efficacy of high oxygen regimens and it is surprising that this problem has not been pointed out in previous similar analyses. We are looking forward to the conclusions of the preannounced Cochrane review on the same subject, and we do hope that Dr. Meyhoff and colleagues will take advantage of the methodological considerations depicted

in our publication to further our understanding on the clinical relevance of high inspired oxygen fraction during surgery.

### Competing Interests

The authors declare no competing interests.

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## Permanent Diaphragm Paralysis after Shoulder Rotator Cuff Repair: Interscalene Block Is Not the Only Factor

*To the Editor:*

We read with interest the case series “Surgical Treatment of Permanent Diaphragm Paralysis after Interscalene Nerve Block for Shoulder Surgery.”<sup>1</sup> We agree with the conclusion made by authors that the current practice of regional anesthetic blocks should continue to focus on technical accuracy, including use of ultrasound guidance. We would like to point out that in 3 of the 14 patients listed in the authors’ report, no guidance was used (either ultrasound or nerve stimulation) for performing the interscalene brachial plexus block (ISB). This is not a currently accepted standard of practice.<sup>2</sup> Apart from the factors mentioned in the report, there are several other etiological factors that one needs to consider with regard to phrenic nerve injury in this subset of patients. These may include use of superficial cervical plexus block along with ISB, presence of local or systemic sepsis, intraoperative stretch during arthroscopic surgery, effect of excessive irrigating fluid near the nerves, and occult preexisting neurapraxia. The information on these factors is not available from the case series. We also