In recent time, the perioperative administration of high fraction of inspired oxygen (FIO₂) has been of great interest to surgeons and anesthesiologists alike. Surgical wounds tend to have lower oxygen tension than normal tissue, and impaired oxygenation is associated with adverse clinical outcomes. Conversely, it has been hypothesized that increasing tissue oxygen tension might exert beneficial effects. This, in turn, can be achieved relatively easy by administering higher FIO₂.¹

After extensive experimental work, the first large randomized controlled trial was published in 2000.² Investigators from Austria, Germany, and the United States collaboratively randomized 500 participants across several trial sites to receive 80% or 30% FIO₂ and evaluated wounds for signs of infection. In the 80% group, surgical site infections fell to nearly half of that of the 30% group. However, subsequent trials could not consistently reproduce these results.³,⁴ Meanwhile, concerns on potential adverse effects such as atelectasis, respiratory failure, cardiovascular complications, and even mortality due to the use of high FIO₂ were raised.⁵ In 2016, when both the World Health Organization and the Centers for Disease Control and Prevention independently strongly recommended the use of high perioperative FIO₂ for the prevention of surgical site infections, it sparked an academic debate.⁶,⁷ The validity of the evidence for the benefits was challenged, and concerns of potential harms were raised.⁸ Not much later, the critical care world was shaken up by a systematic review that indicated liberal oxygen therapy increased mortality in critically ill patients.⁹ Although these data were not representative of the perioperative use of high FIO₂, it did fuel the discussion. Since the initial recommendations, new evidence had emerged,¹⁰ and some published trials had come under scrutiny.¹¹,¹² The World Health Organization decided to update its analysis and issued an independent systematic review, specifically on the adverse effect of the use of high FIO₂. The updated analysis did not show a definite beneficial effect of the use of high perioperative FIO₂ overall, but there was evidence of a reduction of surgical site infection risk in surgical patients under general anesthesia with tracheal intubation.¹³ However, the evidence for this beneficial effect became weaker.¹³ The other review, specifically on adverse events, demonstrated no definite signal of harm with 80% FIO₂ in adult surgical patients undergoing general anesthesia, and concluded that there is little evidence on safety-related issues to discourage its use in patients undergoing surgery.¹⁴ The guidelines got revised to reflect the new evidence, now suggesting—instead of recommending—the use of high FIO₂ perioperatively in patients under general anesthesia with endotracheal intubation, and concluding that additional high-quality trials are needed.¹⁵ The discussion will likely continue.

In this issue of Anesthesia & Analgesia, Cohen et al.⁶ tested an interesting new hypothesis: does the use of high perioperative FIO₂ reduce postoperative pain and opioid use? Postoperative pain is common and promotes opioid use. Surgical wounds have high lactate concentration, and the corresponding acidic environment has been associated with pain. Increasing tissue oxygen tension could reduce lactate concentration and possibly the related pain. Use of hyperbaric medicine has shown promising results in the past. The authors conducted a post hoc analysis on a large, single-center, alternating cohort study that assigned 30% (or the lowest FIO₂ to maintain hemoglobin saturation at ≥95%) or 80% O₂ to adults undergoing colorectal surgery. Further anesthetic management, such as the use of proactive recruitment manoeuvres or optimization of positive end-expiratory pressure (PEEP), was not controlled. The primary outcome was pain and opioid consumption. After exclusion of patients with regional anesthesia or missing records of pain or opioid administration, a stunning 4702 patients were eligible for analysis who were well balanced across the 2 treatment assignments. No meaningful difference was found in pain scores or opioid use. The authors concluded that supplemental oxygen does not reduce postoperative pain or opioid consumption. Notably, the underlying study with a composite outcome of deep and organ space surgical site infection, healing-related wound complications, and

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mortality as primary end point also found no benefit of the use of high FiO₂.

First and foremost, these authors should be complimented for this enormous effort. With an innovative design, they have managed to allocate an incredible number of patients to 2 different strategies under clinical equipoise, with remarkable balance between the 2 groups. This is an impressive accomplishment.

When we take a closer look at the results, we find that there is no objective measure of tissue or PaO₂, making it impossible to assess whether the protocol used in this setting actually established a difference in cellular oxygen tension. It stands out that the actual administered FiO₂ had a median of 44% (interquartile range, 39–55) in the control group and 81% (interquartile range, 77–82) in the intervention group. This shows that there likely was some overlap between the 2 groups. Although this probably reflects the real-life scenario where caregivers attempt to use the lowest FiO₂ feasible while maintaining hemoglobin saturation at ≥ 95%, it does risk bias toward the null hypothesis of no effect. But probably more interesting was that it shows that the caregivers involved almost never felt that it was feasible to maintain hemoglobin saturation at ≥ 95% using 30% FiO₂. When we compare this with data from the 2007 Enigma trial, in which anesthesiologists were given similar instructions in the control group, nearly all the caregivers managed to use 30% FiO₂ (median, 30; interquartile range, 30–32). It is remarkable that the caregivers in the present cohort needed much more inspired oxygen to maintain adequate hemoglobin saturation. It suggests that significant ventilation–perfusion mismatch occurred in some patients, and we can only speculate what interventions clinicians instituted in response. Could administration of high FiO₂ in the intervention group have masked the conditions that led caregivers to increase FiO₂ to maintain adequate hemoglobin saturation? It stands out that the actual administered FiO₂ had a remarkable balance between the 2 groups. This is an example of likely overlapping results that might have led to more consistent and reliable results.

The present study indicates that 80% FiO₂ compared to the lowest feasible FiO₂ under the perioperative conditions at this trial site does not meaningfully change clinical outcomes. But it also indicates that perioperative care has changed substantially since the early encouraging results. If the premise of improved outcomes through improved oxygenation is pursued further, a broadened understanding of tissue oxygen tension during anesthesia is needed. Future studies should include measurement of tissue and PaO₂, standardized ventilation management with proactive recruitment maneuvers and a driving pressure–guided institution of PEEP, as well as pain, fluid, and temperature management protocols.

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REFERENCES