Modification of the World Health Organization Global Guidelines for Prevention of Surgical Site Infection Is Needed

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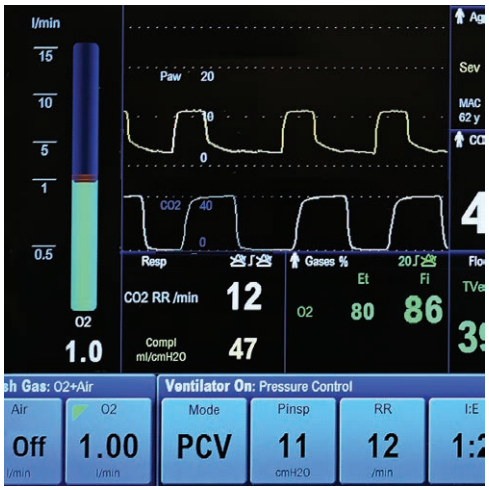
In 2016, the World Health Organization (WHO) published recommendations to reduce surgical site infection.[1] The guidelines, based on a meta-analysis of the literature, concluded that any patient being anesthetized, intubated, and mechanically ventilated for surgery should receive 80% O_2 during the anesthesia and, if feasible, for 2 to 6 h after surgery. The recommendations did not include pediatric patients and anesthesia administered without tracheal intubation, and noted that uncertainties still remained and further research was needed. However, the statistical analysis was immediately met by criticism by us,[2] and the conclusions that were drawn were considered insufficiently supported.[3] A letter to the authors of the WHO guidelines demonstrated further weaknesses in the analysis.[4] Similar criticism has been presented by others.[5–7]



"[T]he absence of harm, but without any benefit, should not be enough to encourage general use of hyperoxia."

The criticism has in part been addressed in two new systematic reviews by the WHO group.[8,9] Three new randomized clinical trials have been added, including one already published before the initial guidelines,[10] and two trials have been excluded because of suspected fraud.[11] Meta-analysis of all trials with an inspired oxygen concentration of 80% *versus* 30 to 40% to detect or reject a 20% relative risk reduction would need more than 14,000 participants in a random effects model. This number is based on: (1) an expected frequency of 12.7% surgical site infection in the control group in the new WHO guidelines[8,9]; (2) maximal type 1 error of $\alpha = 5\%$; (3) maximal type 2 error of $\beta = 10\%$; and (4) heterogeneity adjustment by a diversity of 54% in the meta-analysis.[12] The sample size for a single trial addressing a 20% relative risk reduction with the parameters listed in points 1 to 3 is 6,594; therefore, the required information size in a random effects meta-analysis addressing the same question, but with heterogeneity adjustment, is 6,594 multiplied by 2.17, which is 14,367. However, thus far, only 7,993 participants have been randomized in the new WHO guidelines.[8,9]

By performing a trial sequential analysis of trials listed in the new WHO guidelines, we estimate a relative risk of 0.91 and confidence interval adjusted for sparse data and multiple testing of (0.72 to 1.15).[13] A confidence interval not excluding 1 indicates risk for harm and the possibility of absence of effect and is thus inconclusive. A subgroup analysis of endotracheally intubated and mechanically ventilated patients, as done in the WHO guidelines, would still need 14,000 patients, but only 6,235 had been randomized. Therefore, a meta-analysis of all randomized trials addressing an inspired oxygen concentration of 80% *versus* 30 to 40% is inconclusive and a meta-analysis of a subgroup of these trials (*e.g.*, those who were endotracheally intubated and mechanically ventilated) is even more inconclusive. Furthermore, these meta-analyses include several trials with overall high risk of bias which is associated with underestimation of harm and overestimation of benefit.[14] Increased mortality after exposure to hyperoxia cannot be excluded.[15] Given these weaknesses, it is also surprising that the Centers for Disease Control and Prevention (CDC) recommended that surgical patients receive an increased oxygen concentration during and after surgery.[16]

After publication of the 2016 WHO guidelines, additional studies on perioperative hyperoxia appeared. Two studies have

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Accepted for publication May 6, 2019. From the Department of Medical Sciences, Clinical Physiology (G.H.), and the Department of Surgical Sciences, the Hedenstierna Laboratory (G.P., A.L.), Uppsala University, Sweden; the Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen (C.S.M.); the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital (J.W.); and the Department of Anesthesia, Rigshospitalet University of Copenhagen (L.S.R.), Denmark.

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been based on a much larger number of patients than in previous studies. One was a retrospective analysis of administrative data from almost 74,000 patients undergoing noncardiothoracic surgery,[17] and the other, a prospective intervention study of surgical site infections in more than 5,700 patients undergoing intestinal surgery, much larger than any previous prospective study on perioperative hyperoxia.[18] None of these detected any benefit of hyperoxia, and the retrospective study found an increased frequency of pulmonary complications.[17] The intervention study by Kurz *et al.*[18] was designed with an alternating protocol, *i.e.* the inspired oxygen concentration was alternated between 30 to 40% and 80% at 2-week intervals for more than 3 yr. It can be considered a quasi-randomized trial, that is traditionally ineligible for a Cochrane systematic review of interventions, and WHO only included randomized controlled trials. The 2019 WHO update recognizes these two large studies, but takes no further downgrading of the conclusions when considering these important data from almost 80,000 patients. The Kurz *et al.* trial[18] does not add evidence of a beneficial effect of 80% inspired oxygen concentration *versus* 30 to 40% on surgical site infections in the subgroup of endotracheally intubated and mechanically ventilated patients,[18] as it found no significant difference between the two groups (relative risk = 0.99; 95% confidence interval, 0.85, 1.14; P = 0.85).

Another subgroup analysis claimed benefit of hyperoxia in patients undergoing colorectal surgery.[19,20] However, when limiting the analysis to studies of low risk of bias, there was no effect.[19] Other studies have found the risk of harm in abdominal surgery patients to involve significantly increased 30-day and long-term mortality,[21,22] shorter time to cancer recurrence or death,[23] and long-term risk of myocardial infarction.[24] In a study of similar surgical patients, however, no difference in mortality was seen.[25]

Interestingly, a new analysis of the large study by Kurz *et al.*[18] concluded that "clinicians should not refrain from using hyperoxia for fear for provoking respiratory complications."[26] This is another aspect of potential effects of hyperoxia and quite different from the initial focus on surgical site infection.[1,8,16] One variable that was used to support the conclusion was the postoperative arterial hemoglobin saturation, as measured noninvasively in the postanesthesia care unit. However, this is a poor indicator of oxygenation impairment,[27] and if the patients are given supplemental oxygen, as 77% of the patients were, the value is even more limited. Thus, an unconvincing observation can easily be extrapolated to suggest no harm in other aspects. The analysis of the Kurz study also assessed postoperative lung complications, showing no difference between the 30 to 40% and 80% oxygen groups. Most patients in that study were classified as American Society of Anesthesiologists physical status II and III, with only a limited number having metastatic cancer (10%) or cardiovascular disease (between 5% and 15%), as indicated in the description of the patient material. This is at variance with the poorer outcome that has been reported in patients with cardiovascular disease and cancer, as mentioned previously.[23,24] It thus appears that in some patient categories hyperoxia is harmful, though not necessarily in others. Even the absence of harm, but without any benefit, should not be enough to encourage general use of hyperoxia.

Increased mortality has also been found with increasing arterial oxygen tension in intensive care patients.[28–31] In a subsequent clinical practice guideline, it was recommended to stop supplemental oxygen therapy for acutely ill medical patients if transcutaneous oxygen saturation reaches 96%.[32] These patients are most likely exposed to hyperoxia for longer time, but the observations do agree with the findings during anesthesia,

We thus conclude that recommending hyperoxia has very little scientific support and it may instead be erroneous and possibly harmful.[17] We urgently suggest that the use of perioperative hyperoxia according to the WHO recommendations, as well as the CDC recommendations, be discontinued. Alternatively, the WHO guidelines and the CDC recommendations should be modified.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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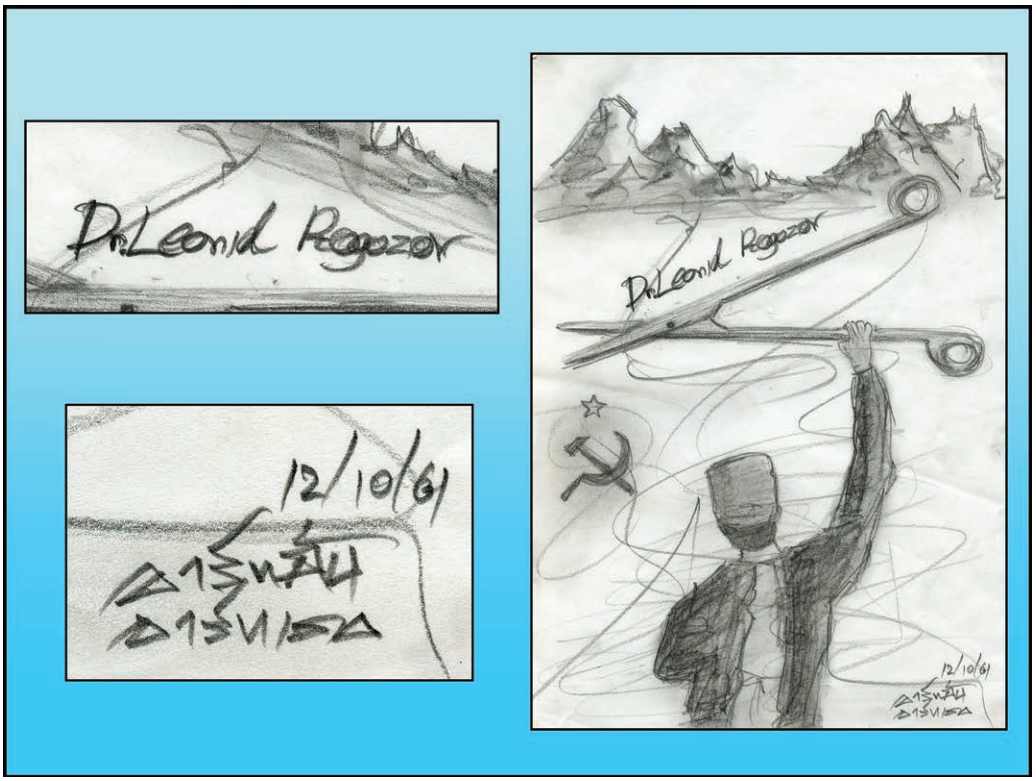
May Day of 1961 and Self-appendectomy with Novocaine in Antarctica: Leonid Rogozov's 0.5% Solution?



The sole physician to a 13-man Soviet team of researchers at isolated Novolazarevskaya Station in Antarctica, Dr. Leonid Ivanovich Rogozov (1934 to 2000) diagnosed his own appendicitis in late April of 1961. Using a mirror and syringefuls of 0.5% Novocaine (procaine), Rogozov performed self-surgery under a supplemented field block on May Day, successfully removing his appendix. His surgical feat made headlines worldwide and was even memorialized "12/10/61" by Thai artist Artchan Artthex (*lower left*). Titled "Dr. Leonid Rogozov" (*upper left*), this graphite-on-paper features a rear view of the surgically gowned Rogozov with the peaks of Antarctica in the background (*right*). (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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