Increased Long-Term Mortality After a High Perioperative Inspiratory Oxygen Fraction During Abdominal Surgery: Follow-Up of a Randomized Clinical Trial

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The impact of anesthetic management on long-term complications is increasingly recognized. One variable that can be optimized is the wound oxygen tension, which commonly is low in the perioperative phase. Wound oxygenation may be increased in adequately perfused tissue by a high inspiratory oxygen fraction (FiO₂), and this is associated with increased bacterial eradication through oxidative killing by neutrophils, however, high oxygen tissue tension also increase neovascularization, collagen formation, and epithelialization. After 3 positive randomized trials, a high perioperative FiO₂ (80%) was recommended to prevent postoperative wound infections. However, one of the largest and most recent trials, the PROXI trial, reported no reduction in surgical site infection and 30-day mortality in patients given 80% oxygen. In this follow-up study of the PROXI trial we assessed the association between long-term mortality and perioperative oxygen fraction in patients undergoing abdominal surgery.

**METHODS:** From October 8, 2006, to October 6, 2008, 1386 patients underwent elective or emergency laparotomy and were randomized to receive either 80% or 30% oxygen during and for 2 hours after surgery. The follow-up date was February 24, 2010. Survival was analyzed using Kaplan-Meier statistics and the Cox proportional hazards model.

**RESULTS:** Vital status was obtained in 1382 of 1386 patients after a median follow-up of 2.3 years (range 1.3 to 3.4 years). One hundred fifty-nine of 685 patients (23.2%) died in the 80% oxygen group compared to 128 of 701 patients (18.3%) assigned to 30% oxygen (HR, 1.30 [95% confidence interval, 1.03 to 1.64]; P = 0.03). In patients undergoing cancer surgery, the HR was 1.45; 95% confidence interval, 1.10 to 1.90; P = 0.009; and after noncancer surgery, the HR was 1.06; 95% confidence interval, 0.69 to 1.65; P = 0.79.

**CONCLUSIONS:** Administration of 80% oxygen in the perioperative period was associated with significantly increased long-term mortality and this appeared to be statistically significant in patients undergoing cancer surgery but not in noncancer patients. (Anesth Analg 2012;115:849–54)
informed consent was obtained from all patients included in 14 Danish hospitals between October 8, 2006, and October 6, 2008. Patients were aged 18 years or older and scheduled for elective or emergency laparotomy. Exclusion criteria were surgery performed under general anesthesia within the preceding 30 days, chemotherapy for malignancy within 3 months of study inclusion, inability to give informed consent, and preoperative arterial oxygen saturation below 90% without supplemental oxygen. The participants were randomized centrally by the Copenhagen Trial Unit, an external department assuring allocation concealment and adequate generation of the allocation sequence.

The patients were randomized to either the 80% or the 30% oxygen group with stratification for: trial site, diabetes mellitus, elective or emergency surgery, and body mass index (<30 kg/m² or ≥30 kg/m²). The trial protocol standardized several important aspects of perioperative care, including prophylactic antibiotics administration, epidural analgesia, temperature and glucose control, absence of preoperative oral bowel preparation, and standardized general anesthesia without nitrous oxide. Perioperative fluids were only administered to replace deficits or measured loss, aiming at a postoperative body weight increase of <1 kg. Blood loss was replaced 1:1 with IV colloids, and blood transfusion was initiated if blood loss exceeded 20 mL/kg. An FIO₂ of 1.0 was used at induction of anesthesia until tracheal intubation and again immediately before tracheal extubation. After tracheal intubation, patients were given an FIO₂ of 0.80 or 0.30 according to the randomization. The first 2 hours after tracheal extubation, the intervention (FIO₂ of 0.80 or 0.30) was delivered through a nonrebreathing facemask with a reservoir (High Concentration Oxygen Mask, Intersurgical Ltd, Wokingham, UK) with a flow of 14 L of O₂ and 2 L of air per minute in the 80% oxygen group and 2 L of O₂ and 14 L of air per minute in the 30% oxygen group. The patients’ lungs were ventilated to assure normocapnia. FIO₂ was increased to ensure arterial oxygen saturation above 94% and arterial oxygen tension above 9 kPa (67.5 mm Hg). Two hours after surgery, supplemental oxygen was administrated only at the physician’s discretion and according to usual clinical practice. The intervention was blinded to patients, surgeons, the staff on the wards, outcome assessors, statisticians, and, in addition, author blinding was used.

The follow-up date was February 24, 2010. Vital status was obtained from the Danish Civil Registration System (www.cpr.dk), in which all Danish citizens are registered with a unique 10-digit number. We calculated time from anesthesia to death or follow-up date. If a patient emigrated in the follow-up period, the date of emigration was used for censoring. In the original protocol, the primary outcome measure was surgical site infection within 30 postoperative days and a secondary outcome was mortality within 30 days of surgery and anesthesia. However, the primary outcome for this follow-up study was all-cause mortality within the extended follow-up period. Cancer and noncancer surgery were defined according to the postoperative histological examination of the specimen obtained during surgery.

Statistical Analysis
All primary survival analyses were performed using Kaplan-Meier statistics and unadjusted Cox proportional hazards model. A secondary adjusted analysis was performed for survival until end of follow-up using the following design variables as adjusting covariates: age, body mass index, daily smoking, emergency surgery, ASA physical status score, diabetes mellitus, cardiovascular disease other than hypertension, cancer surgery, perioperative blood transfusion, and trial site. A sensitivity analysis was performed where we excluded patients who did not receive the oxygen treatment per protocol, i.e., an FIO₂ ≥0.60 for >1 hour (in the 30% oxygen group), an FIO₂ <0.60 for >1 hour (in the 80% oxygen group), use of the oxygen mask <1 hour, or when no FIO₂ data were available. Sample size was calculated for our original study to detect or reject a 33% relative risk reduction in the primary outcome of surgical site infection given an event rate of 16% in the 30% oxygen group, 5% type 1 error risk, 80% power, and 10% patient dropout rate. All intervention effect estimates were reported with 95% confidence limits and a 2-sided P < 0.05 was considered statistically significant. Analyses were performed using SAS for Windows, version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS
One thousand three hundred eighty-six patients were included in the modified intention-to-treat analysis of the PROXI trial. At follow-up, four patients were no longer Danish citizens, and vital status was obtained in the remaining 1382 patients (99.7%) after a median follow-up of 2.3 years (range 1.3 to 3.4 years). Patient characteristics were similar in the 2 groups (Table 1). At follow-up, 159 of 685 patients (23.2%) had died in the 80% oxygen group compared to 128 of 701 patients (18.3%) patients assigned to 30% oxygen (unadjusted hazards ratio [HR], 1.30 [95% confidence interval [CI], 1.03 to 1.64], P = 0.03) (Fig. 1). The analysis adjusted for design variables showed a similar HR, 1.31 (95% CI, 1.03 to 1.66), P = 0.03 (Table 2). Increasing age, blood transfusion, cancer surgery, emergency surgery, and ASA physical status category III and IV were significantly associated with higher long-term mortality, whereas a high body mass index was associated with a significantly lower long-term mortality (Table 2), e.g., 148 of 667 patients (22.2%) with body mass index 18.5 to 24.9 kg/m² were deceased at follow-up compared to 30 of 213 patients (14.1%) with body mass index ≥30 kg/m². There were no significant differences in long-term mortality between the trial sites. One hundred fifty patients (10.8%) did not receive the oxygen treatment per protocol, but the HR for long-term mortality was virtually identical when these patients were excluded, 1.31 (95% CI, 1.02 to 1.67), P = 0.03 when comparing 80% with 30% oxygen.

We performed supplemental analyses for treatment effect heterogeneity, i.e., different effects of 80% oxygen in subgroups. Among patients undergoing cancer surgery, 118 of 352 patients (33.5%) died in the 80% oxygen group compared to 89 of 362 patients (24.6%) in the 30% oxygen group (unadjusted HR, 1.45 [95% CI, 1.10 to 1.90], P = 0.009) (Fig. 2). After noncancer surgery, long-term mortality was 41 of 333 patients (12.3%) in 80% oxygen group versus
Table 1. Characteristics of 1,386 Patients Scheduled for Laparotomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>80% oxygen group (n = 685)</th>
<th>30% oxygen group (n = 701)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64 (27–85)</td>
<td>64 (34–84)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>286:399</td>
<td>293:408</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 (18–35)</td>
<td>25 (19–35)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>188 (27%)</td>
<td>195 (28%)</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>205 (30%)</td>
<td>211 (30%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>35 (5.1%)</td>
<td>34 (4.9%)</td>
</tr>
<tr>
<td>Alcohol consumption &gt;48 g/day</td>
<td>28 (4.1%)</td>
<td>35 (5.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>51 (7.5%)</td>
<td>53 (7.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>207 (30%)</td>
<td>186 (27%)</td>
</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>124 (18%)</td>
<td>96 (14%)</td>
</tr>
<tr>
<td>Epidural analgesia</td>
<td>473 (69%)</td>
<td>498 (71%)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal procedures</td>
<td>303 (44%)</td>
<td>330 (47%)</td>
</tr>
<tr>
<td>Other surgery</td>
<td>382 (56%)</td>
<td>371 (53%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>352 (51%)</td>
<td>362 (52%)</td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>63 (9.2%)</td>
<td>45 (6.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>270 (39%)</td>
<td>294 (42%)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>128 (38–310)</td>
<td>132 (35–295)</td>
</tr>
<tr>
<td>Peroperative blood transfusion</td>
<td>121 (17.7%)</td>
<td>121 (17.3%)</td>
</tr>
</tbody>
</table>

Values are median (5%–95% range). All characteristics have less than 0.5% missing data.

Table 2. Variables Associated with Long-Term Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazards ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% oxygen</td>
<td>1.31</td>
<td>(1.03–1.66)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age per yr</td>
<td>1.03</td>
<td>(1.02–1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index per kg/m²</td>
<td>0.97</td>
<td>(0.95–1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>1.49</td>
<td>(1.02–2.16)</td>
<td>0.04</td>
</tr>
<tr>
<td>ASA physical status class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.44</td>
<td>(0.96–2.16)</td>
<td>0.08</td>
</tr>
<tr>
<td>III</td>
<td>3.54</td>
<td>(2.24–5.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV</td>
<td>12.53</td>
<td>(5.30–29.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.30</td>
<td>(0.98–1.72)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.43</td>
<td>(0.98–2.09)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.86</td>
<td>(0.63–1.17)</td>
<td>0.33</td>
</tr>
<tr>
<td>Cancer surgery</td>
<td>2.52</td>
<td>(1.83–3.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peroperative blood transfusion</td>
<td>1.64</td>
<td>(1.26–2.14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are as calculated by adjusted Cox proportional hazards model. Cardiovascular disease is defined as any cardiovascular disease other than hypertension.
39 of 339 patients (11.5%) in the 30% oxygen group (unadjusted HR, 1.06 [95% CI, 0.69 to 1.65], P = 0.79) (Fig. 3). There was no significant interaction (P = 0.24) between the intervention effect of 80% oxygen and whether cancer surgery or noncancer surgery was performed. Patients with a surgical site infection did not have significantly higher long-term mortality compared to patients without surgical site infection (61 of 272 patients, 22.4% versus 226 of 1114 patients, 20.3%, respectively, unadjusted HR, 1.12 [95% CI, 0.85 to 1.49], P = 0.43).

**DISCUSSION**

In this follow-up study of a randomized clinical trial comparing 80% oxygen with 30% oxygen during abdominal surgery, we found that a high \( F_{O_2} \) of 80% was associated with increased long-term mortality. The difference appeared to be statistically significant in patients undergoing cancer surgery but not in noncancer patients.

The primary strength of our study is the almost complete follow-up (99.7%) and the high validity of data concerning vital status in Denmark.\(^{16}\) No other trials have evaluated the direct association between supplemental oxygen and mortality beyond 30 days after surgery, that is, without the interference of other potentially influential gases especially nitrous oxide.\(^{8}\)

Some study limitations must be mentioned. First, it must be emphasized that long-term mortality was not the primary outcome of our trial, and this follow-up study was performed to explore the safety of high perioperative \( F_{O_2} \) during abdominal surgery because an apparent substantially higher point-estimate of the 30-day mortality (e.g., a 50% mortality increase) was found in the 80% oxygen group. Our results can therefore generate new hypotheses, but they do not prove causality. Second, some patients in the 2 groups were given an oxygen fraction that was different from the allocated fraction. Seven percent of the patients in the 30% oxygen group needed an \( F_{O_2} \) ≥0.60 for >1 hour to keep arterial oxygen saturation above 94% in accordance with safety measures in clinical practice. In the 80% oxygen group, 2% of the patients received an \( F_{O_2} <0.60 \); however, the observed mortality HR was not altered when we excluded those patients who did not receive the oxygen treatment per protocol. Third, laparoscopic abdominal procedures were not included, and the results of this trial are thus only generalizable to a general surgical population undergoing laparotomy.

The observed difference in long-term mortality is difficult to explain and the following three aspects must be considered in the interpretation:

First, because a larger sample size is required to detect or reject a HR of 1.30, given the median survival times and follow-up, our finding may be considered a result of an “early” or “preliminary” analysis, which may be comparable to an interim-analysis in a larger trial. As such, it is well recognized that a more restrictive, and lower, significance level is needed to avoid spurious statistical significance (e.g., \( P < 0.001 \) for an interim-analysis halfway to the required sample size).\(^{19,20}\) Our result, exhibiting a \( P \) value of 0.03, may therefore be a type 1 error, because the \( P \) value is considerably higher than what would be required to stop a randomized trial for benefit at an interim-analysis.\(^{21,22}\)

The ability to replicate study findings should always be considered, and it may be calculated that in this study there is only approximately 50% probability of finding a \( P \) value of 0.03 or less for increased long-term mortality with 80% oxygen, if another 1400 patients were studied with the same intervention effect.\(^{23}\) Furthermore, we recognize that this follow-up was not preplanned, but performed for safety reasons because a higher point-estimate of 30-day mortality was found in the 80% oxygen group. Further studies are required before an association between perioperative hyperoxia and long-term mortality is established beyond reasonable doubt.

The second aspect is imbalances between the groups, which should always be carefully evaluated in a randomized trial, however the numerous recorded baseline characteristics were very similar in the 2 groups, and the risk of an unknown imbalance is less with our stratified randomization and the relatively large number of patients.

The third reason for the observed difference may be a true adverse effect of a high oxygen fraction. Until now, 4544 patients have been included in the 10 trials investigating 80% versus 30% perioperative oxygen,\(^{6–8,10,24–29}\) and the reported 30-day mortality is overall 34 of 2772 patients (1.2%) versus 38 of 2799 patients (1.4%), respectively. A 3.5-year follow-up of the ENIGMA trial\(^{8}\) found no significant difference in long-term mortality (HR, 0.98; 95% CI, 0.80 to 1.20) in 1660 patients randomized to receive either 70% nitrous oxide in 30% oxygen or 80% oxygen in 20% nitrogen.\(^{30}\) The combination of the 2 interventions, 80% oxygen and nitrous oxide, however, only allows a conclusion that long-term mortality is not significantly different in patients receiving 80% oxygen compared to patients receiving 70% nitrous oxide. The pathophysiological rationale behind the ENIGMA trial suggested that nitrous oxide alone may be associated with increased long-term cardiovascular morbidity and mortality.\(^{31}\)

It is nevertheless surprising to find a significantly increased mortality in our 80% oxygen group after 2.3 years. If there were a true difference, such a negative effect of 80% oxygen does not appear to be related to the immediate postoperative harm that may be related to very high \( F_{O_2} \) such as pulmonary atelectasis and respiratory failure. A possible intervention effect is more likely to occur through different mechanisms, specifically in cancer patients, because the majority of the observed differences occurred in this subgroup, although we recognize that there was a higher power to detect a difference with the higher overall mortality among cancer patients.

Anesthesia may have long-term effects on cancer recurrence,\(^{1}\) because numerous perioperative factors affect the clearing of tumor cells that remain in the body after otherwise curative surgery.\(^{32}\) Those factors include neovascularization, growth factors, and immunosuppression.\(^{32}\) Supplemental perioperative oxygen has a strong positive effect on neovascularization,\(^{3}\) whereas growth factor stimulation and the effect on local immunological factors are not fully understood.\(^{14,33}\) High levels of oxygen increase erythropoietin production, which is a potent cellular growth factor.\(^{33}\) In addition, supplemental oxygen promotes formation of reactive oxygen species,\(^{3,34}\) which may promote
DNA damage.\textsuperscript{34} Neovascularization, erythropoietin, and oxidative stress may thus lead to growth of remaining tumor cells after otherwise curative surgery.

It must be noted though that most of the articles published in the experimental setting support a tumor-suppressive effect of oxygen,\textsuperscript{13,14,33,35} which further renders the finding of a higher mortality at the end of follow-up in the 80% oxygen group in our study controversial. A test of interaction between the intervention effect of 80% oxygen and whether cancer surgery or noncancer surgery was performed was not statistically significant. The lack of a statistically significant test of interaction may, however, have been due to lack of power of the test of interaction.

Other potentially adverse biological mechanisms of a high oxygen concentration could include lung damage caused by perioperative oxidative stress and airway inflammation, especially in patients with chronic obstructive lung disease.\textsuperscript{12,36} The cardiovascular system may be affected by perioperative arterial vasoconstriction,\textsuperscript{37} reduced coronary bloodflow,\textsuperscript{11} or oxidative stress and DNA damage\textsuperscript{4,38} leading to accelerated atherosclerosis or plaque rupture.\textsuperscript{12,36,38}

At this stage, the main finding of the present study is not explained by a convincing mechanism, but it definitely does not support the contention that a high perioperative FiO\textsubscript{2} is beneficial on long-term all-cause mortality. Further studies are required to evaluate the cause of death, when cancer recurrence and emergence of new or latent cancer will be of great relevance.

The PROXI trial was probably underpowered to detect well-known risk factors for death such as diabetes mellitus and current smoking. It is also noteworthy that increasing body mass index was associated with lower long-term mortality. An almost identical association between body mass index and 1-year mortality was found in a cohort study of 1064 patients undergoing major noncardiac surgery,\textsuperscript{39} and it is documented that obesity itself is not a risk factor for major postoperative complications during hospitalization.\textsuperscript{40} These apparently better outcomes for obese patients may be attributed to selection bias and confounding by indication with differences in the management of obese patients, and the amount of preoperative weight loss was not measured. In our trial, surgical site infection was not associated with a significantly higher long-term mortality, suggesting that most surgical site infections were not severe.\textsuperscript{41}

Common indications for supplemental oxygen have been prevention of surgical wound infection and postoperative nausea and vomiting. Before the results of the PROXI trial, a statistically significant reduction of surgical site infection could be documented,\textsuperscript{9} but when the results of the PROXI trial are added, the potential benefit of supplemental oxygen to prevent surgical site infection is outweighed and a clinically relevant effect is yet to be demonstrated. The initially reported positive effect of supplemental oxygen on the incidence of postoperative nausea and vomiting was not confirmed in a meta-analysis.\textsuperscript{42}

We conclude that administration of 80% oxygen during, and for 2 hours after abdominal surgery, compared to 30% oxygen, is associated with a significantly increased long-term all-cause mortality that appears to be statistically significant in patients undergoing cancer surgery but not in noncancer patients. Until a clinical benefit of 80% perioperative oxygen is well-documented, we recommend abstaining from administering FiO\textsubscript{2} above what is needed to maintain sufficient arterial oxygen saturation.

DISCLOSURES

Name: Christian S. Meyhoff, MD, PhD.

Contribution: The author helped design the study, conduct the study, analyze the data, and prepare the manuscript.

Attestation: Christian S. Meyhoff attests to the integrity of the original data and the analysis.

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Contribution: The author helped design the study, analyze the data, and prepare the manuscript.

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Contribution: The author helped design the study, analyze the data, and prepare the manuscript.

Name: Karl B. Christensen, PhD.

Contribution: The author helped analyze the data and prepare the manuscript.

Name: Lars S. Rasmussen, MD, PhD, DMSc.

Contribution: The author helped design the study, conduct the study, analyze the data, and prepare the manuscript.

Attestation: Lars S. Rasmussen attests to the integrity of the original data and the analysis.

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REFERENCES


Eighty Percent Oxygen and Long-Term Mortality