Effect of Intraoperative High Inspired Oxygen Fraction on Surgical Site Infection, Postoperative Nausea and Vomiting, and Pulmonary Function

Systematic Review and Meta-analysis of Randomized Controlled Trials

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This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Intraoperative high inspired oxygen fraction (FIO2) is thought to reduce the incidence of surgical site infection (SSI) and postoperative nausea and vomiting, and to promote postoperative atelectasis.

Methods: The authors searched for randomized trials (till September 2012) comparing intraoperative high with normal FIO2 in adults undergoing surgery with general anesthesia and reporting on SSI, nausea or vomiting, or pulmonary outcomes.

Results: The authors included 22 trials (7,001 patients) published in 26 reports. High FIO2 ranged from 80 to 100% (median, 80%); normal FIO2 ranged from 30 to 40% (median, 30%). In nine trials (5,103 patients, most received prophylactic antibiotics), the incidence of SSI decreased from 14.1% with normal FIO2 to 11.4% with high FIO2; risk ratio, 0.77 (95% CI, 0.59–1.00). After colorectal surgery, the incidence of SSI decreased from 19.3 to 15.2%; risk ratio, 0.78 (95% CI, 0.60–1.02). In 11 trials (2,293 patients), the incidence of nausea decreased from 24.8% with normal FIO2 to 19.5% with high FIO2; risk ratio, 0.79 (95% CI, 0.66–0.93). In patients receiving inhalational anesthetics without prophylactic antiemetics, high FIO2 provided a significant protective effect against both nausea and vomiting. Nine trials (3,698 patients) reported on pulmonary outcomes. The risk of atelectasis was not increased with high FIO2.

Conclusions: Intraoperative high FIO2 further decreases the risk of SSI in surgical patients receiving prophylactic antibiotics, has a weak beneficial effect on nausea, and does not increase the risk of postoperative atelectasis.

Both authors were more cautious.8,9 Skepticism has been partly related to the fact that high FIO2 may have deleterious
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Benefit and Harm of Intraoperative High FiO\(_2\)

**Table 1.** Characteristics of Included Randomized Controlled Trials Reporting on Surgical Site Infection

<table>
<thead>
<tr>
<th>First Author</th>
<th>Comparison (N° Analyzed)</th>
<th>Surgery</th>
<th>Carrier Gas</th>
<th>Epidural Analgesia</th>
<th>Fluid Regimen</th>
</tr>
</thead>
</table>
| Greif\(^5\)  | 1. Fio\(_2\) 30% (250)  
2. Fio\(_2\) 80% (250) | Colorectal | Air\(^*\) | No data | Aggressive |
| Pryor\(^66\) | 1. Fio\(_2\) 35% (80)  
2. Fio\(_2\) 80% (80) | Major abdominal | N\(_2\)O | No data | Aggressive |
| Belda\(^4\)  | 1. Fio\(_2\) 30% (143)  
2. Fio\(_2\) 80% (148) | Colorectal | Air | No data | Aggressive |
| Mayzler\(^62\) | 1. Fio\(_2\) 30% (19)  
2. Fio\(_2\) 80% (19) | Colorectal | Air/N\(_2\)O | No data | Aggressive |
| Myles\(^64\) | 1. Fio\(_2\) 30% (1,015)  
2. Fio\(_2\) 80% (997) | Any ≥2 h; excluding cardiac or one-lung ventilation | Air/N\(_2\)O | 100% | Not standardized |
| Meyhoff\(^63\) | 1. Fio\(_2\) 30% (701)  
2. Fio\(_2\) 80% (685) | Abdominal | Air | 70% | Restrictive |
| Bickel\(^58\) | 1. Fio\(_2\) 30% (103)  
2. Fio\(_2\) 80% (107) | Appendectomy | Air/N\(_2\)O | No data | Aggressive |
| Schietroma\(^28\) | 1. Fio\(_2\) 30% (37)  
2. Fio\(_2\) 80% (35) | Colorectal | Air | No data | Aggressive |
| Thibon\(^30\)  | 1. Fio\(_2\) 30% (208)  
2. Fio\(_2\) 80% (226) | Abdominal, gynecologic, breast | Air | No data | No data |

Quality assessment: R (randomization): 0 = none or pseudo-randomization, 1 = yes but not specified, 2 = yes and adequate; C (concealment of treatment allocation): 0 = none, 1 = yes; B (blinding): 0 = none, 1 = yes but not specified, 2 = yes and adequate; F (follow-up): 0 = none, 1 = reported but intention-to-treat analysis not possible, 2 = reported and intention-to-treat analysis possible. Trials are listed in alphabetical order.

\(^*\) Nitrogen. \(\dagger\) Standardized 3-point scoring method. \(\ddagger\) Standardized 4-point scoring method.

ASEPSIS = scoring system for wound infection; CDC = Centers for Disease Control and Prevention Scoring System for wound infection; Fio\(_2\) = inspired oxygen fraction; N\(_2\)O = nitrous oxide.
Both SSI and PONV remain a crucial topic for anesthetists and surgeons, as they represent a significant clinical and economical burden; SSI may lead to prolonged length of stay and increased hospital costs, whereas PONV symptoms are among the most frequent adverse effects of anesthesia and surgery, and they are also associated with incremental costs. Meta-analyses of clinical trials addressing the potential benefit of high FIO2 in surgical patients have reported conflicting results. A number of further relevant clinical trials studying these issues have been published recently. The aim of our study was to update previously published meta-analyses, and to provide a comprehensive quantitative summary of the most important, potentially beneficial (decrease in the risk of SSI or PONV) and harmful (increase in the risk of pulmonary complications) effects of intraoperative high inspired FIO2 on surgical patients.

**Materials and Methods**

We followed the PRISMA guidelines for reporting the meta-analyses of randomized controlled trials.

**Eligibility Criteria**

We searched for fully published reports of randomized comparisons of intraoperative high FIO2 (experimental intervention) versus normal (i.e., “low”) FIO2 (control intervention). A high FIO2 was defined as an FIO2 of 50% or more, and a normal FIO2 as an FIO2 of less than 50%.

In trials with a limited high-to-normal FIO2 ratio, the difference in oxygen regimens may be too small and consequently the high FIO2 regimen may not have the scope to show efficacy. In addition, such trials may produce positive results by random chance. Consequently, there was an arbitrary pre hoc decision to include only studies where the normal FIO2 value was less than, or equal to, half of the high FIO2 value.

We considered studies that were performed in adult patients (≥18 yr) undergoing any surgical procedure with general anesthesia and that reported on at least one of the three outcomes: (1) SSI; (2) PONV; (3) intra- or postoperative pulmonary outcomes.

Data from animal studies or abstracts were not considered. Reports of patients undergoing surgery with regional anesthesia, patients undergoing one-lung surgery, or patients receiving high FIO2 in other settings than general anesthesia for surgery as, for instance, patients ventilated in the intensive care or in the prehospital setting, were excluded. Studies where supplemental oxygen was administered only postoperatively, or for a restricted time during anesthesia (for instance, at induction or during a short period before extubation), were not considered.

**Table 1. (Continued)**

<table>
<thead>
<tr>
<th>Temperature Goal</th>
<th>Prophylactic Antibiotics, %</th>
<th>Blood Transfusion, %</th>
<th>Perioperative Tissue O2 Measure</th>
<th>Pain Control</th>
<th>Definition of Infection</th>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>100</td>
<td>30</td>
<td>Yes</td>
<td>Not standardized</td>
<td>ASEPSIS</td>
<td>2 1 2 2</td>
</tr>
<tr>
<td>No</td>
<td>99</td>
<td>4</td>
<td>No</td>
<td>Not standardized†</td>
<td>Standardized</td>
<td>2 1 2 2</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>15</td>
<td>No</td>
<td>Standardized</td>
<td>ASEPSIS</td>
<td>2 1 2 2</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>0</td>
<td>No</td>
<td>Standardized†</td>
<td>Not standardized</td>
<td>2 0 1 1</td>
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<tr>
<td>Yes</td>
<td>90</td>
<td>No data</td>
<td>No</td>
<td>Not standardized</td>
<td>Not standardized</td>
<td>2 0 2 2</td>
</tr>
<tr>
<td>Yes</td>
<td>94</td>
<td>18</td>
<td>No</td>
<td>Standardized</td>
<td>CDC</td>
<td>2 1 2 2</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>0</td>
<td>No</td>
<td>Not standardized†</td>
<td>Standardized†</td>
<td>1 0 1 0</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>No data</td>
<td>No</td>
<td>Standardized†</td>
<td>CDC</td>
<td>2 0 2 2</td>
</tr>
<tr>
<td>Yes</td>
<td>52</td>
<td>2</td>
<td>No</td>
<td>No data</td>
<td>CDC</td>
<td>2 0 2 2</td>
</tr>
</tbody>
</table>
Information Sources
We performed a variety of high-sensitivity and low-specificity searches for relevant reports in the MEDLINE, Embase, and Central Databases. Key words ("oxygen," "supplemental," and "anesthesia") were combined using the Boolean meanings of "and" and "or." The last electronic search was done in September 2012. Bibliographies of retrieved articles were searched for additional references. We applied no restriction on language.

Study Selection
Retrieved articles were reviewed for inclusion by one author (Dr. Hovaguimian), and criteria for inclusion were independently checked by another author (Dr. Lysakowski). Queries were resolved through discussion with a third author (Dr. Tramèr).

Risk of Biases in Individual Studies
Quality of data reporting was assessed by one author (Dr. Hovaguimian) and was independently checked by another (Dr. Lysakowski), using a modified 4-items, 7-points Oxford scale taking into account method of randomization, concealment of treatment allocation, degree of blinding, and reporting of drop-outs, as previously described.32 Consensus was reached by discussion with a third author (Dr. Tramèr).

Because potential confounding factors (for instance, carrier gas or fluid regimen) may directly affect the occurrence of SSI, regardless of the FiO2,1,33,34 we retrieved such information from each study. For the analysis of SSI data, nitrous oxide was not regarded as a potential confounding factor.35 However, for the analyses of PONV data, we excluded data from studies that used nitrous oxide as a carrier gas, because nitrous oxide has emetogenic properties.36

Data Extraction Process
One author (Dr. Hovaguimian) extracted all relevant information from original reports. Another author (Dr. Lysakowski) independently checked all extracted data. Discrepancies were resolved by discussion with a third author (Dr. Tramèr).

Data Items
Definitions of SSI were taken as reported in the original reports. Three distinct PONV outcomes were analyzed:57 nausea, vomiting (including retching), and a composite endpoint (i.e., nausea and/or vomiting/retching). Cumulative incidences of these outcomes were extracted for two time periods, an early period (0–6 h), and a late period (0–24 h).

Pulmonary complications were defined as any adverse event occurring intra- or postoperatively and affecting the lower respiratory tract and/or interfering with normal test values related to lung integrity (blood gases, spirometry, chest imagery, arterial oxygen saturation measure by pulse oximetry, and postoperative oxygen requirements).

Synthesis of Results
For dichotomous data, we calculated risk ratios (RR) with 95% CI. When the 95% CI around the RR point estimate did not include 1, the difference between experimental and control group was considered statistically significant.

For continuous data, weighted mean differences with 95% CI were calculated. We performed formal heterogeneity testing. When the data were homogeneous (P ≥ 0.1), we used a fixed effect model to combine data from independent trials. When the data were heterogeneous, we searched for sources of heterogeneity. For example, if one study showed results that were completely out of range of the others, we searched for likely reasons explaining the difference and performed a sensitivity analysis excluding that study, when deemed appropriate. When no source could be identified that explained the heterogeneity, we combined the data using a random effects model. Sources of heterogeneity to be sought were not prespecified.

Analyses were performed using STATA 11 (Version 11; StataCorp, College Station, TX), RevMan (Computer Program, version 5.1.6; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and Microsoft Excel 12.2.3. for Mac (Microsoft Corporation, Redmond, WA).

Results

Study Selection
We retrieved 204 articles (fig. 1). Of 45 potentially relevant randomized trials, 19 were excluded after more thorough examination. In four, the FiO2 in control patients was more than 50%.38–41 Data from six studies could not be extracted for meta-analysis: four reported measures of associations42–45 and two provided results in graphical format only.46,47 Three included data from children.48–50 In three trials, the oxygen fraction administrated in the control group was more than half of that administrated in the experimental group; two of those compared 50 with 30%,51,52 and one compared 60 with 45%.53 One trial was using nitrous oxide as a carrier gas and reported on PONV outcomes only.54 Finally, two studies were recently retracted due to ethical concerns.55

We eventually included data from 22 randomized trials (7,001 patients) that were reported in 26 articles.5–7,27–30,55–72 Seven reports with additional data from 900 patients have not been considered for any previously published meta-analyses.27–30,61,69,70 Two articles reporting on pulmonary outcomes56 and PONV,77 respectively, were subgroup analyses of a multicenter study that reported on SSI.5 Results of...
Table 2. Characteristics of Included Randomized Controlled Trials Reporting on Postoperative Nausea and Vomiting

<table>
<thead>
<tr>
<th>First Author</th>
<th>Comparison (N° Analyzed) (Data Not Considered)</th>
<th>Carrier Gas</th>
<th>Surgery</th>
<th>Prophylactic Antiemetics</th>
<th>Anesthesia Technique</th>
<th>Intraoperative Analgesia</th>
<th>Postoperative Analgesia</th>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatnagar57</td>
<td>1. FIO2 30% (20)  2. FIO2 50% (20)  3. FIO2 80% (20)</td>
<td>Air</td>
<td>Breast</td>
<td>No</td>
<td>Inhalational (isoflurane)</td>
<td>Meperidine</td>
<td>Not standardized</td>
<td>R 0 C 0 0 F 0</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Goll6</td>
<td>1. FIO2 30% (80)  2. FIO2 80% (79)</td>
<td>Air*</td>
<td>Gynecological laparoscopy</td>
<td>No</td>
<td>Inhalational (isoflurane)</td>
<td>Fentanyl</td>
<td>Not standardized (pirntamid)</td>
<td>2 1 2 0 F 0</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greif7</td>
<td>1. FIO2 30% (119)  2. FIO2 80% (112)</td>
<td>Air*</td>
<td>Colorectal</td>
<td>No</td>
<td>Inhalational (isoflurane)</td>
<td>Sufentanil</td>
<td>Paracetamol Tamadol Piritramid Paracetamol Codeine Morphine</td>
<td>2 1 2 0 F 0</td>
</tr>
<tr>
<td>Joris59</td>
<td>1. FIO2 30% (50)  2. FIO2 80% (50)</td>
<td>Not specified</td>
<td>Thyroid</td>
<td>No</td>
<td>Inhalational (sevo-flurane)</td>
<td>Fentanyl Ketorolac</td>
<td></td>
<td>1 0 2 0 F 0</td>
</tr>
<tr>
<td>McKeen27</td>
<td>1. FIO2 30% (145)  2. FIO2 80% (147)</td>
<td>Air*</td>
<td>Gynecological laparoscopy</td>
<td>No</td>
<td>Inhalational (desflurane)</td>
<td>Fentanyl Piritramid Diclofenac Oxycodone</td>
<td>2 1 2 2 F 0</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Piper65</td>
<td>1. FIO2 40% (125)  2. FIO2 80% (125)  3. FIO2 40% (131)</td>
<td>Air</td>
<td>Laparoscopic cholecystectomy</td>
<td>Dolasetron</td>
<td>Inhalational (desflurane)</td>
<td>Fentanyl</td>
<td></td>
<td>1 1 1 2 F 0</td>
</tr>
<tr>
<td>Purhonen68</td>
<td>1. FIO2 30% (50)  2. FIO2 80% (49)</td>
<td>Air*</td>
<td>Gynecological laparoscopy</td>
<td>No</td>
<td>Inhalational (sevo-flurane)</td>
<td>Fentanyl Ketorolac</td>
<td>Paracetamol Ibuprofen Fentanyl Diclofenac Meperidine</td>
<td>2 0 2 1 F 0</td>
</tr>
<tr>
<td>Purhonen67</td>
<td>1. FIO2 30% (28)  2. FIO2 80% (29)</td>
<td>Air*</td>
<td>Breast</td>
<td>No</td>
<td>Inhalational (sevo-flurane)</td>
<td>Fentanyl Ketorolac</td>
<td>Paracetamol Diclofenac Meperidine</td>
<td>2 0 2 2 F 0</td>
</tr>
<tr>
<td>Šimurina29</td>
<td>1. FIO2 30% (36)  2. FIO2 80% (36)</td>
<td>Air</td>
<td>Gynecological laparoscopy</td>
<td>No</td>
<td>Inhalational (sevo-flurane)</td>
<td>Not standardized</td>
<td>Not standardized</td>
<td>2 0 2 2 F 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thibon30</td>
<td>1. FIO2 30% (208)  2. FIO2 80% (226)</td>
<td>Not specified</td>
<td>Abdominal, gynecologic, and breast</td>
<td>No</td>
<td>Mixed (inhalational, intravenous, or both)</td>
<td>Fentanyl Remifentanil NSAIDs Morphine Meperidine</td>
<td>Not standardized</td>
<td>2 0 2 2 F 0</td>
</tr>
<tr>
<td>Turan71</td>
<td>1. FIO2 30% (279)  2. FIO2 80% (280)</td>
<td>Air*</td>
<td>Any</td>
<td>Ondansetron Dexamethason Droperidol</td>
<td>Mixed (inhalational or intravenous)</td>
<td></td>
<td></td>
<td>2 2 1 1 F 0</td>
</tr>
</tbody>
</table>

Quality assessment: R (randomization): 0 = none or pseudo-randomization, 1 = yes but not specified, 2 = yes and adequate; C (concealment of treatment allocation): 0 = none, 1 = yes; B (blinding): 0 = none, 1 = yes but not specified, 2 = yes and adequate; F (follow-up): 0 = none, 1 = reported but intention-to-treat analysis not possible, 2 = reported and intention-to-treat analysis possible. Trials are listed in alphabetical order.

* Nitrogen.

FIO2 = inspired oxygen fraction; NSAIDs = nonsteroidal antiinflammatory drugs.
### Table 3. Characteristics of Included Randomized Controlled Trials Reporting on Pulmonary Outcomes

<table>
<thead>
<tr>
<th>First Author</th>
<th>Comparison (N° Analyzed) (Data Not Considered)</th>
<th>Surgery</th>
<th>Additional Characteristics</th>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal</td>
<td>1. FIO2 40% (9) 2. FIO2 100% (9) [3. FIO2 40% + N2O (9)]</td>
<td>Laparoscopic cholecystectomy</td>
<td>No data</td>
<td>No</td>
</tr>
<tr>
<td>Akça</td>
<td>1. FIO2 30% (14) 2. FIO2 80% (16)</td>
<td>Colorectal</td>
<td>No data</td>
<td>No</td>
</tr>
<tr>
<td>Kotani</td>
<td>1. FIO2 30% (30) 2. FIO2 100% (30)</td>
<td>Orthopedic</td>
<td>No data</td>
<td>No</td>
</tr>
<tr>
<td>Mackintosh</td>
<td>1. FIO2 30% (25) 2. FIO2 &gt;90% (25) [3. FIO2 30% no PEEP (25)] [4. FIO2 &gt;90% no PEEP (25)]</td>
<td>Any elective surgery (open abdominal, airways, neuro excluded)</td>
<td>No data</td>
<td>No</td>
</tr>
<tr>
<td>Meyhoff</td>
<td>1. FIO2 30% (701) 2. FIO2 80% (685)</td>
<td>Abdominal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Myles</td>
<td>1. FIO2 30% (1,015) 2. FIO2 80% (997)</td>
<td>Any &gt;2 h; excluding cardiac or one-lung ventilation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Staehr</td>
<td>1. FIO2 30% (111) 2. FIO2 80% (102)</td>
<td>Laparotomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Staehr</td>
<td>1. FIO2 30% (15) 2. FIO2 80% (20)</td>
<td>Gynecologic laparotomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Zoremba</td>
<td>1. FIO2 40% (71) 2. FIO2 80% (71)</td>
<td>Minor peripheral</td>
<td>No data</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Quality assessment: R (randomization): 0 = none or pseudo-randomization, 1 = yes but not specified, 2 = yes and adequate; C (concealment of treatment allocation): 0 = none, 1 = yes; B (blinding): 0 = none, 1 = yes but not specified, 2 = yes and adequate; F (follow-up): 0 = none, 1 = reported but intention-to-treat analysis not possible, 2 = reported and intention-to-treat analysis possible. Trials are listed in alphabetical order. Staehr 2011 and 2012 are subgroup analyses of Meyhoff 2009.

BMI = body mass index; ETCO2 = end-tidal carbon dioxide; FIO2 = inspired oxygen fraction; N2O = nitrous oxide; PEEP = positive end-expiratory pressure; TV = tidal volume; VC = volume-controlled ventilation.

### Study Characteristics

Included reports were published between 2000 and 2012 (tables 1–3). The median quality score was 5.5 (range, 2–7). In experimental groups, intraoperative FIO2 ranged from 80 to 100% (median, 80%), in controls ranged from 30 to 40% (median, 30%).

### Synthesis of Results

#### Surgical Site Infection

Nine studies (5,103 patients) reported on the incidence of SSI (table 1).4,5,28,30,58,62–64,66 Six studies considered SSI as an infection occurring within 14 days postoperatively, and two within 30 days;30,62 one trial did not mention the duration of follow-up.28 Seven studies used a standardized method for SSI assessment: three considered the ASEPSIS scoring system,4,5,58 two used the definition of the Centers for Disease Control and Prevention,10,63 and two considered a prospectively determined scoring system.28,66 In all trials except one,30 90–100% of patients received prophylactic antibiotics.

Surgical Site Infection. Nine studies (5,103 patients) reported on the incidence of SSI (table 1).4,5,28,30,58,62–64,66 Six studies considered SSI as an infection occurring within 14 days postoperatively, and two within 30 days;30,62 one trial did not mention the duration of follow-up.28 Seven studies used a standardized method for SSI assessment: three considered the ASEPSIS scoring system,4,5,58 two used the definition of the Centers for Disease Control and Prevention,10,63 and two considered a prospectively determined scoring system.28,66 In all trials except one,30 90–100% of patients received prophylactic antibiotics.
Because data were heterogeneous ($P_{\text{hetero}} = 0.03$), we used a random effects model. Because it has been argued that patients undergoing colorectal surgery may particularly benefit from a high $F_{\text{Io}_2}$ regimen,24,26 we performed a subgroup analysis including all patients undergoing colorectal surgery. Four trials were performed exclusively in patients undergoing colorectal surgery,4,5,28,62 and from four, data from patients undergoing colorectal surgery could be extracted.30,63,64,66 When all colorectal surgery data were combined ($n = 1,977$), there was an average incidence of SSI of 19.3% with normal $F_{\text{Io}_2}$ and of 15.2% with high $F_{\text{Io}_2}$; RR, 0.78 (95% CI, 0.60–1.02; fig. 2B). The data were homogenous ($P_{\text{hetero}} = 0.19$). We additionally performed a meta-analysis using a fixed effect model; the RR was 0.80 (95% CI, 0.66–0.97).

**PONV.** Eleven trials (2,293 patients) reported dichotomous data on presence or absence of nausea or vomiting (table 2).6,7,27,29,30,57,59,65,67,68,71 When combining all data, only prevention of late nausea showed statistical significance in favor of high $F_{\text{Io}_2}$ (fig. 3A). With normal $F_{\text{Io}_2}$, the average incidence of late nausea was 24.8%, with high $F_{\text{Io}_2}$ was 19.5%; RR, 0.79 (95% CI, 0.66–0.93).

Because propofol and prophylactic antiemetics reduce the underlying risk of PONV, we performed a sensitivity analysis including exclusively data from patients who received an inhalational anesthetic without prophylactic antiemetics.6,7,27,29,57,59,67,68,71 As expected, incidences of PONV outcomes in patients receiving normal $F_{\text{Io}_2}$ were increased (fig. 3B). With normal $F_{\text{Io}_2}$, the average incidence of late nausea was 33.7%, with high $F_{\text{Io}_2}$ was 29.3%; RR, 0.75 (95% CI, 0.62–0.90). With normal $F_{\text{Io}_2}$, the average incidence of late vomiting was 26.2%, with high $F_{\text{Io}_2}$ was 19.2%; RR, 0.72 (95% CI, 0.56–0.92). When analyzing the composite endpoint, PONV, no statistical significance was reached.

**Pulmonary Outcomes.** Nine trials (3,698 patients) reported on pulmonary outcomes (table 3).55,56,60,61,63,64,69,70,72 Six articles reported on atelectasis using chest radiographs and/or thoracic computed tomography scans for diagnosis (table 4); however, two of those49,50 were subgroup analyses reporting...
Benefit and Harm of Intraoperative High F\textsubscript{IO\textsubscript{2}}

### A

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N(^o) trials</th>
<th>N(^o) of patients with endpoint/Total N(^o) of patients (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early nausea</td>
<td>9</td>
<td>182/907 (20.0%) / 196/912 (21.5%)</td>
<td>0.93 (0.78 to 1.10)</td>
</tr>
<tr>
<td>Early vomiting</td>
<td>9</td>
<td>74/907 (8.2%) / 87/912 (9.5%)</td>
<td>0.68 (0.37 to 1.25)*</td>
</tr>
<tr>
<td>Early PONV</td>
<td>10</td>
<td>201/1103 (18.2%) / 214/1090 (19.6%)</td>
<td>0.93 (0.80 to 1.09)</td>
</tr>
<tr>
<td>Late nausea</td>
<td>9</td>
<td>152/780 (19.5%) / 195/787 (24.8%)</td>
<td>0.79 (0.66 to 0.93)</td>
</tr>
<tr>
<td>Late vomiting</td>
<td>8</td>
<td>158/769 (20.8%) / 165/767 (21.5%)</td>
<td>0.86 (0.63 to 1.18)*</td>
</tr>
<tr>
<td>Late PONV</td>
<td>9</td>
<td>309/827 (37.4%) / 321/882 (36.4%)</td>
<td>1.04 (0.92 to 1.16)</td>
</tr>
</tbody>
</table>

Fig. 3. (A) Impact of high oxygen fraction on postoperative nausea and vomiting. Showing summary of meta-analyses. Inhalational anesthesia without antiemetic prophylaxis. Early = cumulative incidence to 6 h postoperatively; F\textsubscript{IO\textsubscript{2}} = inspired oxygen fraction; Late = cumulative incidence to 24 h postoperatively; PONV = postoperative nausea and vomiting (composite endpoint of any nausea and/or vomiting events). *Random effects model; all others, fixed effect model.

### B

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N(^o) trials</th>
<th>N(^o) of patients with endpoint/Total N(^o) of patients (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early nausea</td>
<td>7</td>
<td>137/502 (27.3%) / 161/508 (31.7%)</td>
<td>0.85 (0.71-1.02)</td>
</tr>
<tr>
<td>Early vomiting</td>
<td>7</td>
<td>68/502 (13.5%) / 76/508 (15.0%)</td>
<td>0.71 (0.33-1.54)*</td>
</tr>
<tr>
<td>Early PONV</td>
<td>7</td>
<td>138/472 (29.2%) / 165/478 (34.5%)</td>
<td>0.80 (0.58-1.09)*</td>
</tr>
<tr>
<td>Late nausea</td>
<td>7</td>
<td>110/375 (29.3%) / 149/383 (33.7%)</td>
<td>0.75 (0.62-0.90)</td>
</tr>
<tr>
<td>Late vomiting</td>
<td>6</td>
<td>68/355 (19.2%) / 95/363 (26.2%)</td>
<td>0.72 (0.56-0.92)</td>
</tr>
<tr>
<td>Late PONV</td>
<td>7</td>
<td>206/422 (48.8%) / 238/478 (49.8%)</td>
<td>0.96 (0.85-1.08)</td>
</tr>
</tbody>
</table>

Fig. 3. (B) Impact of high oxygen fraction on postoperative nausea and vomiting. Inhalational anesthesia without antiemetic prophylaxis. Early = cumulative incidence to 6 h postoperatively; F\textsubscript{IO\textsubscript{2}} = inspired oxygen fraction; Late = cumulative incidence to 24 h postoperatively; PONV = postoperative nausea and vomiting (composite endpoint of any nausea and/or vomiting events). *Random effects model; all others, fixed effect model.

on the same outcomes as the original larger study.\(^{63}\) Thus, data from four trials, two small\(^{56,60}\) and two large\(^{63,64}\) could be combined (fig. 4). The average incidence of atelectasis with high F\textsubscript{IO\textsubscript{2}} was 8.3%, with normal F\textsubscript{IO\textsubscript{2}} was 10.6%; RR, 0.93 (95% CI, 0.59–1.46).

Three small trials reported on perioperative blood gas analyses (table 4).\(^{55,60,69}\) In one,\(^{55}\) there was an evidence of statistically significant worsening of the intraoperative PaO\textsubscript{2}/F\textsubscript{IO\textsubscript{2}} ratio in patients receiving 100% F\textsubscript{IO\textsubscript{2}} (use of positive end-expiratory pressure and postoperative PaO\textsubscript{2}/F\textsubscript{IO\textsubscript{2}} ratio was not reported). The two other studies failed to show any detrimental effect on the postoperative PaO\textsubscript{2}/F\textsubscript{IO\textsubscript{2}} ratio with supplemental oxygen,\(^{60,69}\) despite the use of 100% oxygen and no positive end-expiratory pressure in one trial.\(^{60}\)

Three small studies reported on lung function (table 4).\(^{56,69,72}\) In two studies, spirometry values were not different in patients receiving high or normal F\textsubscript{IO\textsubscript{2}}.\(^{56,69}\) The third, including 142 moderately obese patients, reported on a variety of postoperative spirometric values that were significantly worsened with high oxygen fraction.\(^{72}\) Specifically, there was a linear decrease in postoperative lung function with increasing body mass index in the high-oxygen group.

Two studies reported on postoperative Sp\textsubscript{O\textsubscript{2}} values.\(^{69,72}\) Both failed to show a significant decrease in the 24-h postoperative Sp\textsubscript{O\textsubscript{2}} in patients exposed to high F\textsubscript{IO\textsubscript{2}}.

Finally, one trial showed no difference in postoperative oxygen requirements among patients ventilated with a high or normal F\textsubscript{IO\textsubscript{2}}.\(^{61}\)

### Discussion

We performed a systematic review and meta-analysis of clinical trials testing the role of high F\textsubscript{IO\textsubscript{2}} in patients undergoing surgery with general anesthesia. We studied outcomes that are relevant in this context, i.e., SSI, PONV, and pulmonary complications. We analyzed data from 22 randomized trials (including 7,001 patients) that were reported in 26 articles.
When combining data of all eligible patients, regardless of the type of surgery, the risk of SSI decreased by 23% with high FiO₂ (RR, 0.77), and the difference was borderline statistically significant. When selecting patients undergoing colorectal surgery, the RR point estimate was similar, and depending on the statistical model that was used, the 95% CI included (random effects model) or excluded (fixed effect model) equality. Previous meta-analyses have yielded conflicting results on the potential benefit of high FiO₂ on SSI. Three reported on a significant reduction in the incidence of SSI.²⁰,²²,²⁴ A fourth analysis, similar to ours, reported on a statistically significant result in favor of high FiO₂ when a fixed effect model was used but failed to show any benefit with a random effects model.²¹ Finally, a fifth analysis reported on a protective effect with high FiO₂ in patients undergoing colorectal surgery only, but not in patients undergoing other abdominal surgeries.³⁶ Many authors have considered that subgroup as the most likely to profit from a high FiO₂.²⁴,²⁶ The question then is, whether this benefit is of clinical relevance. Although the degree of antiinfective efficacy of high FiO₂ seems weak and perhaps disappointing, it seems to be similar to conventional antibiotic prophylaxis in many surgical settings.⁷³ In addition, as most patients in these trials had received prophylactic antibiotics, we may conclude on the efficacy of high FiO₂ as a supplemental antiinfection strategy only; the efficacy of high FiO₂ alone remains unclear and would be difficult to test from an ethical perspective because the administration of prophylactic antibiotics is widely considered as standard of care. In some trials, the incidence of SSI in controls was very low and in others it was more than 20%, despite prophylactic antibiotics. High FiO₂ appeared to be effective independent of the baseline risk of infection (fig. 2A).

The potentially beneficial effect of high FiO₂ on the incidence of PONV has been contentious, too. In 2007, an international consensus panel did not recommend supplemental oxygen for the prevention of PONV.³⁴ In 2008, two meta-analyses were addressing the potential benefit of high FiO₂ on PONV; one concluded that supplemental oxygen reduced the incidence of postoperative vomiting only²⁵ and the other was unable to identify any beneficial effect of high FiO₂.²³ In our analysis, there was some evidence that high FiO₂ decreased the incidence of both nausea and vomiting in patients receiving an inhalational anesthetic and no prophylactic antiemetics. The baseline risk (i.e., the incidence of PONV in controls) was increased in this context, and this may explain why high FiO₂ had more scope to show antiemetic efficacy. However, absolute risk reductions suggested that approximately 15 patients needed to receive high FiO₂ for one not to be nauseous or to vomit who would have done so had they received normal FiO₂. This degree of prophylactic antiemetic efficacy is weak, as numbers-needed-to-treat of 3–5 (absolute risk reduction, 20–30%) may be expected from an effective pharmacological antiemetic intervention in the surgical setting.³⁴ In addition, when analyzing the composite endpoint, PONV, no benefit was evident.

Nine trials reported on a large variety of pulmonary outcomes, including atelectasis, blood gases, lung spirometry, or postoperative SpO₂. Results were difficult to compare as outcome measures differed among studies. Dichotomous data on presence or absence of atelectasis could be combined from two small and two large trials. The result was clearly negative. Two studies reported on postoperative PaO₂/FiO₂ ratio. Both failed to show any detrimental effect of high FiO₂ on postoperative gas exchange, despite using ventilation settings known to acutely worsen pulmonary atelectasis (i.e., administration of 100% FiO₂ without positive end-expiratory pressure) in one trial. Additionally, in three studies reporting on surrogate outcomes, there was no evidence of pulmonary harm when using a high FiO₂ regimen. Only one trial, conducted in moderately obese patients, reported on a detrimental effect of high FiO₂ on spirometric values postoperatively.

Our aim was to combine data from well-controlled trials that had the scope to show beneficial or harmful effects of high FiO₂, if there were any. Our study differs twofold from previously published similar meta-analyses.²⁰–²⁶ First, none of the previously published meta-analyses attempted to provide a complete picture of the potentially beneficial (SSI and PONV) and harmful (pulmonary complications) effects of high FiO₂. Second, our selection criteria were stricter. For instance, we excluded studies where oxygen was delivered via a facemask in awake patients with regional anesthesia,⁷⁵–⁷⁹ or where supplemental oxygen was provided to patients in the postoperative period only.⁸⁰–⁸² Finally, to ensure that the trials had the scope of showing an effect with high FiO₂, we arbitrarily defined that, for eligibility, the value of the normal FiO₂ had to be less than, or equal to, half of the high FiO₂ value.

Included trials were performed in patients undergoing different surgical procedure, with a variety of anesthetic regimens. Ideally, we would adjust these analyses for potential confounding factors; in practice, this was not feasible as the number of analyzed trials was limited. Critical analysis of all included trials suggested that they did not differ that much regarding potential confounders (tables 1–3). In addition, a certain degree of clinical heterogeneity ensures wide applicability, or external validity, of the results of these analyses. Because all trials were performed in adults only, the results may not be applicable to children. We did not include data from children,⁸⁸–⁹⁰ as there is an argument, at least when testing the efficacy of an antiemetic intervention in the surgical setting, to distinguish between children and adults.⁹³ Also, because trials reporting on SSI included mainly patients undergoing abdominal surgery, extrapolation of our results to other types of surgery remains speculative. Concerning antibiotic prophylaxis, it has been argued that its efficacy in reducing the risk of wound infection may
Table 4. Impact of High Oxygen Fraction on Pulmonary Outcomes

<table>
<thead>
<tr>
<th>First Author</th>
<th>Comparison</th>
<th>High Fio₂</th>
<th>Normal Fio₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fio₂, %</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>Postoperative atelectasis Akça³⁶</td>
<td></td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>Kotani⁶⁰</td>
<td></td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Meyhoff⁶³</td>
<td></td>
<td>80</td>
<td>685</td>
</tr>
<tr>
<td>Myles⁶⁴</td>
<td></td>
<td>80</td>
<td>997</td>
</tr>
<tr>
<td>Staehr⁷⁰*</td>
<td></td>
<td>80</td>
<td>102</td>
</tr>
<tr>
<td>Staehr⁶⁹*</td>
<td></td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Perioperative blood gases</td>
<td></td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td>Agarwal⁵⁵</td>
<td></td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Kotani⁶⁰</td>
<td></td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Staehr⁶⁹*</td>
<td></td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Postoperative lung function Akça⁵⁶</td>
<td></td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>Staehr⁶⁹*</td>
<td></td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Zoremba⁷²</td>
<td></td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>Postoperative Spo₂</td>
<td></td>
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<td>20</td>
</tr>
<tr>
<td>Staehr⁶⁹*</td>
<td></td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Zoremba⁷²</td>
<td></td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>Postoperative O₂ requirement</td>
<td>Mackintosh⁶¹</td>
<td></td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

* Staehr 2011 and Staehr 2012 are subgroup analyses of Meyhoff 2009.

CT = computed tomography; FEV₁ = forced expiratory volume in 1 s; Fio₂ = inspired oxygen fraction; FVC = forced vital capacity; IQR = interquartile range; O₂ = oxygen; PaO₂ = arterial partial oxygen pressure; Spo₂ = arterial oxygen saturation by pulse oximetry.
### Table 4. Impact of High Oxygen Fraction on Pulmonary Outcomes (Continued)

<table>
<thead>
<tr>
<th>First Author</th>
<th>Comparison</th>
<th>Definition of Endpoint</th>
<th>Results</th>
<th>Statistical Significance, <em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akça</td>
<td>Postoperative atelectasis</td>
<td>Comparison of pre- and postoperative chest radiograph by a physician unaware of patient’s group assignment</td>
<td>High FIO₂: 44% Normal FIO₂: 36%</td>
<td>0.94</td>
</tr>
<tr>
<td>Kotani</td>
<td>Postoperative atelectasis</td>
<td>Present if described in the radiologist’s evaluation of chest radiograph or CT scan (not routinely prescribed for all patients)</td>
<td>High FIO₂: 7.9% Normal FIO₂: 7.1%</td>
<td>0.60</td>
</tr>
<tr>
<td>Meyhoff</td>
<td>Postoperative atelectasis</td>
<td>Present if described in chest radiograph or CT scan (not routinely prescribed for all patients)</td>
<td>High FIO₂: 23% Normal FIO₂: 17%</td>
<td>“Not significant” (no value reported)</td>
</tr>
<tr>
<td>Myles</td>
<td>Postoperative atelectasis</td>
<td>All chest radiographs and CT were evaluated for infiltrate and atelectasis by the attending radiologist, who was blinded to allocation (not routinely prescribed for all patients)</td>
<td>High FIO₂: 7.5% Normal FIO₂: 13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Staehr</td>
<td>Postoperative atelectasis</td>
<td>All chest radiographs and CT were evaluated for infiltrate and atelectasis by the attending radiologist, who was blinded to allocation (not routinely prescribed for all patients)</td>
<td>High FIO₂: 8.8% Normal FIO₂: 6.3%</td>
<td>0.76</td>
</tr>
<tr>
<td>Agarwal</td>
<td>Intraoperative PaO₂/FIO₂ ratio</td>
<td>Intraoperative PaO₂/FIO₂ ratio</td>
<td>High FIO₂: 351.5 (SD, 22.9) Normal FIO₂: 558 (SD, 46.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Kotani</td>
<td>Intraoperative PaO₂/FIO₂ ratio</td>
<td>PaO₂/FIO₂ ratio 24 h postoperatively</td>
<td>High FIO₂: 389 (SD, 56) Normal FIO₂: 393 (SD, 49)</td>
<td>“Not significant” (no value reported)</td>
</tr>
<tr>
<td>Staehr</td>
<td>Intraoperative PaO₂/FIO₂ ratio</td>
<td>PaO₂/FIO₂ ratio 90 min postoperatively (kPa)</td>
<td>High FIO₂: 50 (IQR, 42–57) Normal FIO₂: 56 (IQR, 37–60)</td>
<td>0.66</td>
</tr>
<tr>
<td>Zoremba</td>
<td>Spirometry (FEV₁, FVC, FEV₁/FVC ratio)</td>
<td>Spirometry (FEV₁, FVC, FEV₁/FVC ratio)</td>
<td>A variety of lung function parameters with no significant difference between groups, 24 h postoperatively</td>
<td>0.70</td>
</tr>
<tr>
<td>Staehr</td>
<td>Spirometry (functional residual capacity), 2 h postoperatively (ml)</td>
<td>Spirometry (functional residual capacity), 2 h postoperatively (ml)</td>
<td>High FIO₂: 1,633 (IQR, 1,343–1,948) Normal FIO₂: 1,615 (IQR, 1,375–2,318)</td>
<td>0.70</td>
</tr>
<tr>
<td>Zoremba</td>
<td>Spirometry (mid-expiratory flow, FEV, forced inspiratory vital capacity)</td>
<td>Spirometry (mid-expiratory flow, FEV, forced inspiratory vital capacity)</td>
<td>A variety of lung function parameters “significantly” worse with high FIO₂ compared with normal FIO₂ at 0.5, 2, and 24 h</td>
<td>0.70</td>
</tr>
<tr>
<td>Mackintosh</td>
<td>O₂ requirement to maintain SpO₂ &gt;90%, 24 h postoperatively</td>
<td>O₂ requirement to maintain SpO₂ &gt;90%, 24 h postoperatively</td>
<td>High FIO₂: 0 l/min (IQR, 0–0) Normal FIO₂: 0 l/min (IQR, 0–0)</td>
<td>No statistically significant difference between groups</td>
</tr>
</tbody>
</table>

CT = computed tomography; FEV₁ = forced expiratory volume in 1 s; FIO₂ = inspired oxygen fraction; FVC = forced vital capacity; IQR = interquartile range; O₂ = oxygen; PaO₂ = arterial partial oxygen pressure; SpO₂ = arterial oxygen saturation by pulse oximetry.

* Staehr 2011 and Staehr 2012 are subgroup analyses of Meyhoff 2009.
be assumed for all types of surgery, even ones where no clinical trial data exist.\textsuperscript{73}

In conclusion, intraoperative high F\textsubscript{IO2} may be regarded as a supplemental strategy to further decrease the risk of SSI in patients receiving prophylactic antibiotics. Indirect comparison suggests that the degree of efficacy is similar to antibiotic prophylaxis in many surgical settings. However, the efficacy of high F\textsubscript{IO2} \textit{per se}, and in the absence of antibiotic prophylaxis, remains unknown. High F\textsubscript{IO2} reduces the risk of PONV to some extent, although mainly in patients with inhalation anesthetics and without prophylactic antiemetics. Finally, intraoperative high F\textsubscript{IO2} does not increase the risk of postoperative atelectasis.

The authors thank Pascal Thibon, M.D., M.Sc., Staff Infection Control Physician and Epidemiologist, Antenne, Régionale de Lutte contre les Infections Nosocomiales de Basse-Normandie, Centre Hospitalier Universitaire de Caen, Caen, France, who kindly responded to our inquiries.

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Fig. 4. Impact of high oxygen fraction on postoperative atelectasis. On the Forrest plot, trials are listed in alphabetical order. On the event rate scatter, sizes of bubbles are proportional to sizes of trials. F\textsubscript{IO2} = inspired oxygen fraction.
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mental oxygen concentration on recovery from general
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ing anaesthesia for abdominal hysterectomy on postope-
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tension on hemodynamics and pulmonary gas exchange in
patients undergoing coronary artery surgery. J Cardiothorac Vasc
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patients undergoing coronary artery surgery. J Cardiothorac Vasc
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an evidence-based bundle for preventing surgical site in-
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