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How to cite

HOVAGUIMIAN, Frederique et al. 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. In: Anesthesiology, 2013, vol. 119, n° 2, p. 303–316. doi: 10.1097/ALN.0b013e31829aaff4

This publication URL: https://archive-ouverte.unige.ch/unige:32864
Publication DOI: 10.1097/ALN.0b013e31829aaff4

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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CME

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 (F_{IO_2}) 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 F_{IO_2} 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 F_{IO_2} ranged from 80 to 100% (median, 80%); normal F_{IO_2} 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 F_{IO_2} to 11.4% with high F_{IO_2}; 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 F_{IO_2} to 19.5% with high F_{IO_2}; risk ratio, 0.79 (95% CI, 0.66–0.93). In patients receiving inhalational anesthetics without prophylactic antiemetics, high F_{IO_2} 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 F_{IO_2}.

Conclusions: Intraoperative high F_{IO_2} 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.

What We Already Know about This Topic

- There have been conflicting findings regarding the role of high inspired oxygen fraction and perioperative outcomes

What This Article Tells Us That Is New

- Intraoperative high inspired oxygen fraction decreases the risk of surgical site infection in surgical patients receiving prophylactic antibiotics, has a weak beneficial effect on nausea, and does not increase the risk of postoperative atelectasis

IT has been claimed that patients undergoing surgery with general anesthesia were benefiting from a higher than normal inspired oxygen fraction (F_{IO_2}).[1,2] Some authors have suggested that a high F_{IO_2} was a simple, inexpensive, and low-risk intervention, and that the broader use of this technique should be encouraged in patients undergoing major abdominal procedures.[3] Randomized trials have reported on a reduced risk of surgical site infection (SSI) in patients who were ventilated with 80% F_{IO_2} during surgery.[4,5] It was also shown that patients who were ventilated with high F_{IO_2} intraoperatively had a reduced incidence of postoperative nausea and vomiting (PONV).[6,7]

Other authors were more cautious.[8,9] Skepticism has been partly related to the fact that high F_{IO_2} may have deleterious

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Received from the Division of Anesthesiology, Department of Anesthesiology, Clinical Pharmacology, and Critical Care, Geneva University Hospitals, Geneva, Switzerland. Submitted for publication July 9, 2012. Accepted for publication March 14, 2013. Support was provided solely from institutional and/or departmental sources. Presented at the Euroanaesthesia Meeting, June 9–12, 2012, Paris, France. Supplementary material is freely accessible on the author's Web site at http://www.hcuge.ch/anesthesie/data.htm.

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 Anesthesiology 2013; 119:303-16

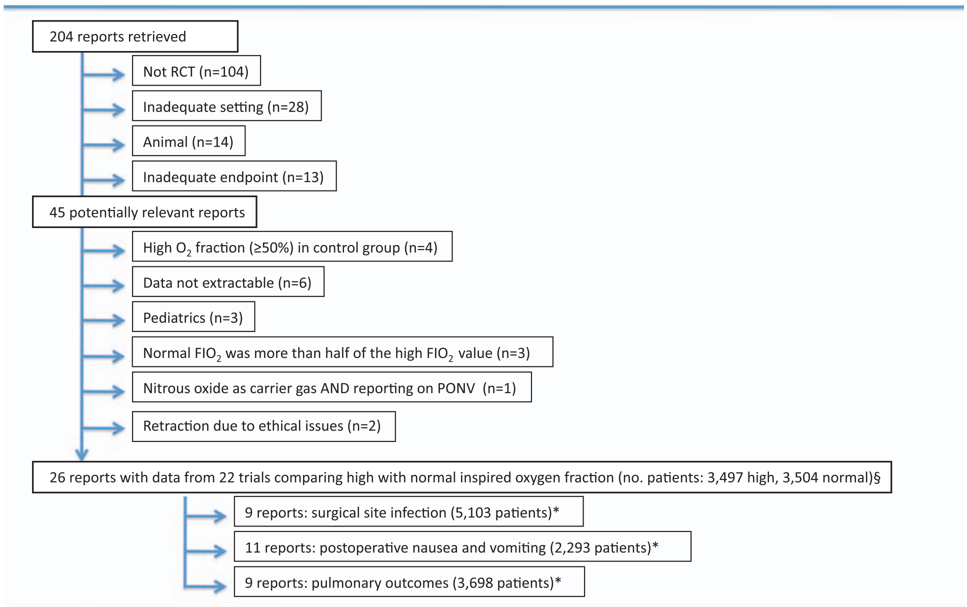

Fig. 1. Study selection. §Four reports were subgroup analyses. *Numbers do not add up because some reports reported on two endpoints. FIO_2 = inspired oxygen fraction; High = FIO_2 ≥50%; normal = FIO_2 <50%; O_2 = oxygen; PONV = postoperative nausea and vomiting; RCT = randomized controlled trial.

effects on the airways. One hundred percent oxygen at induction or at the end of general anesthesia has been suggested to promote atelectasis over a few minutes,[10–12] and to cause alteration in gas exchange.[13]

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

First Author	Comparison (N° Analyzed)	Surgery	Carrier Gas	Epidural Analgesia	Fluid Regimen
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_2O	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_2O	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_2O	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_2O	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. † Standardized 3-point scoring method. ‡ 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_2O = 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,[14–16] whereas PONV symptoms are among the most frequent adverse effects of anesthesia and surgery, and they are also associated with incremental costs.[17–19] Meta-analyses of clinical trials addressing the potential benefit of high F_{IO_2} in surgical patients have reported conflicting results.[20–26] A number of further relevant clinical trials studying these issues have been published recently.[27–30] 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 F_{IO_2} on surgical patients.

Materials and Methods

We followed the PRISMA guidelines for reporting the meta-analyses of randomized controlled trials.[31]

Eligibility Criteria

We searched for fully published reports of randomized comparisons of intraoperative high F_{IO_2} (experimental intervention) *versus* normal (*i.e.*, "low") F_{IO_2} (control intervention). A high F_{IO_2} was defined as an F_{IO_2} of 50% or more, and a normal F_{IO_2} as an F_{IO_2} of less than 50%.

In trials with a limited high-to-normal F_{IO_2} ratio, the difference in oxygen regimens may be too small and consequently the high F_{IO_2} 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 F_{IO_2} value was less than, or equal to, half of the high F_{IO_2} 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 F_{IO_2} 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*)

Additional Characteristics						Quality Assessment			
Temperature Goal	Prophylactic Antibiotics, %	Blood Transfusion, %	Perioperative Tissue O_2 Measure	Pain Control	Definition of Infection	R	C	B	F
Yes	100	30	Yes	Not standardized	ASEPSIS	2	1	2	2
No	99	4	No	Not standardized	Standardized†	2	1	2	2
Yes	100	15	No	Standardized	ASEPSIS	2	1	2	2
Yes	100	0	No	Standardized	Not standardized	2	0	1	1
Yes	90	No data	No	Not standardized	Not standardized	2	0	2	2
Yes	94	18	No	No data	CDC	2	1	2	2
Yes	100	0	No	Not standardized	ASEPSIS	1	1	2	0
Yes	100	No data	No	Standardized	Standardized‡	1	0	1	0
Yes	52	2	No	No data	CDC	2	0	2	2

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 F_{IO_2},[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:[37] 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 homogenous ($P \geq 0.1$), 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 F_{IO_2} in control patients was more than 50%.[38–41] Data from six studies could not be extracted for meta-analysis: four reported measures of associations[42–45] 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.‖#

We eventually included data from 22 randomized trials (7,001 patients) that were reported in 26 articles.[4–7,27–30,55–72] 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 outcomes[56] and PONV,[7] respectively, were subgroup analyses of a multicenter study that reported on SSI.[5] Results of

‖ Ochmann C, Tuschy B, Beschmann R, Hamm F, Rohm KD, Piper SN: Supplemental oxygen reduces serotonin levels in plasma and platelets during colorectal surgery and reduces postoperative nausea and vomiting. Eur J Anaesthesiol 2010; 27:1036–43.

Fujii Y, Itakura M: Supplemental intraoperative oxygen prevents postoperative nausea and vomiting in patients undergoing gynecological laparoscopic surgery. Anesth Resusc 2008; 44:47–50.

Table 2. Characteristics of Included Randomized Controlled Trials Reporting on Postoperative Nausea and Vomiting

First Author	Comparison (N° Analyzed) (Data Not Considered)	Carrier Gas	Surgery	Additional Characteristics: Prophylactic Antiemetics	Anesthesia Technique	Intraoperative Analgesia	Postoperative Analgesia	Quality Assessment: R	C	B	F
Bhatnagar[57]	1. FIO_2 30% (20) 2. FIO_2 50% (20) 3. FIO_2 80% (20)	Air	Breast	No	Inhalational (isoflurane)	Meperidine	Not standardized	2	0	0	0
Goll[6]	1. FIO_2 30% (80) 2. FIO_2 80% (79) [3. FIO_2 30% + ondansetron (81)]	Air*	Gynecological laparoscopy	No	Inhalational (isoflurane)	Fentanyl	Not standardized (piritramid)	2	1	2	0
Greif[7]	1. FIO_2 30% (119) 2. FIO_2 80% (112)	Air*	Colorectal	No	Inhalational (isoflurane)	Sufentanil	Paracetamol Tramadol Piritramid	2	1	2	0
Joris[59]	1. FIO_2 30% (50) 2. FIO_2 80% (50) [3. FIO_2 30% + droperidol (50)]	Not specified	Thyroid	No	Inhalational (sevoflurane)	Fentanyl Ketorolac	Paracetamol Codeine Morphine	1	0	2	0
McKeen[27]	1. FIO_2 30% (145) 2. FIO_2 80% (147)	Air*	Gynecological laparoscopy	No	Inhalational (desflurane)	Fentanyl	Piritramid Diclofenac	2	1	2	2
Piper[65]	1. FIO_2 40% (125) 2. FIO_2 80% (125) 3. FIO_2 40% (131)	Air	Laparoscopic cholecystectomy	Dolasetron	Inhalational (desflurane)	Fentanyl	Paracetamol Oxycodone	1	1	1	2
Purhonen[68]	1. FIO_2 30% (50) 2. FIO_2 80% (49)	Air*	Gynecological laparoscopy	No	Inhalational (sevoflurane)	Fentanyl Ketorolac Paracetamol	Paracetamol Ibuprofen Fentanyl	2	0	2	1
Purhonen[67]	1. FIO_2 30% (28) 2. FIO_2 80% (29) [3. FIO_2 30% + ondansetron (28)]	Air*	Breast	No	Inhalational (sevoflurane)	Fentanyl	Diclofenac Meperidine	2	0	2	2
Šimurina[29]	1. FIO_2 30% (36) 2. FIO_2 80% (36) [3. FIO_2 50% (36)]	Air	Gynecological laparoscopy	No	Inhalational (sevoflurane)	Not standardized	Not standardized	2	0	2	2
Thibon[30]	1. FIO_2 30% (208) 2. FIO_2 80% (226)	Not specified	Abdominal, gynecologic, and breast	No	Mixed (inhalational, intravenous, or both)	Fentanyl Remifentanil NSAIDs Morphine	Not standardized	2	0	2	2
Turan[71]	1. FIO_2 30% (279) 2. FIO_2 80% (280)	Air*	Any	Ondansetron Dexamethason Droperidol	Mixed (inhalational or intravenous)	Meperidine	Not standardized	2	2	1	1

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.

FIO_2 = inspired oxygen fraction; NSAIDs = nonsteroidal antiinflammatory drugs.

Table 3. Characteristics of Included Randomized Controlled Trials Reporting on Pulmonary Outcomes

First Author	Comparison (N° Analyzed) (Data Not Considered)	Surgery	Additional Characteristics: Epidural Analgesia	Mean BMI >30 kg/m²	Standardized Ventilation	PEEP, mmHg	Quality Assessment: R	C	B	F
Agarwal[55]	1. F_{IO_2} 40% (9) 2. F_{IO_2} 100% (9) [3. F_{IO_2} 40% + N_2O (9)]	Laparoscopic cholecystectomy	No data	No	VC, TV 8 ml/kg ET_{CO_2} 35–40 mmHg	No data	2	0	0	1
Akça[56]	1. F_{IO_2} 30% (14) 2. F_{IO_2} 80% (16)	Colorectal	No data	No	VC, TV 10 ml/kg ET_{CO_2} 35 mmHg	0	2	1	2	0
Kotani[60]	1. F_{IO_2} 30% (30) 2. F_{IO_2} 100% (30)	Orthopedic	No data	No	VC, TV 10 ml/kg ET_{CO_2} 35–45 mmHg	0	2	1	2	0
Mackintosh[61]	1. F_{IO_2} 30% (25) 2. F_{IO_2} >90% (25) [3. F_{IO_2} 30% no PEEP (25)] [4. F_{IO_2} >90% no PEEP (25)]	Any elective surgery (open abdominal, airways, neuro excluded)	No data	No	TV 6–10 ml/kg ET_{CO_2} 35–45 mmHg	0 or 3–5	2	2	1	2
Meyhoff[63]	1. F_{IO_2} 30% (701) 2. F_{IO_2} 80% (685)	Abdominal	Yes	No	Not standardized	No data	2	1	2	2
Myles[64]	1. F_{IO_2} 30% (1,015) 2. F_{IO_2} 80% (997)	Any >2 h; excluding cardiac or one-lung ventilation	Yes	No	Not standardized	No data	2	0	2	2
Staehr[70]	1. F_{IO_2} 30% (111) 2. F_{IO_2} 80% (102)	Laparotomy	Yes	Yes	Not standardized	No data	2	2	1	2
Staehr[69]	1. F_{IO_2} 30% (15) 2. F_{IO_2} 80% (20)	Gynecologic laparotomy	Yes	No	TV 8–10 ml/kg ET_{CO_2} 4.5–6 kPa	5	2	2	1	2
Zoremba[72]	1. F_{IO_2} 40% (71) 2. F_{IO_2} 80% (71)	Minor peripheral	No data	Yes	TV 8 ml/kg ET_{CO_2} 4–4.7 kPa	10	1	0	2	2

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; ET_{CO_2} = end-tidal carbon dioxide; F_{IO_2} = inspired oxygen fraction; N_2O = nitrous oxide; PEEP = positive end-expiratory pressure; TV = tidal volume; VC = volume-controlled ventilation.

another multicenter study reporting on SSI and pulmonary outcomes[63] were reported in two further articles; one concentrated on pulmonary outcomes in obese patients[70] and the other on pulmonary outcomes in patients scheduled for laparotomy for ovarian cancer.[69]

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 F_{IO_2} 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,[30,63] and two considered a prospectively determined scoring system.[28,66] In all trials except one,[30] 90–100% of patients received prophylactic antibiotics.

Surgeries were colorectal, appendectomy, abdominal, and gynecologic. Two trials reported on abdominal and nonabdominal procedures.[30,64] The baseline risk of SSI, *i.e.*, the incidence of SSI in patients receiving normal F_{IO_2}, ranged from 7[30] to 27%.[28] When data were combined, there was an average incidence of 14.1% with normal F_{IO_2} and of 11.4% with high F_{IO_2}; RR, 0.77 (95% CI, 0.59–1.00; fig. 2A).

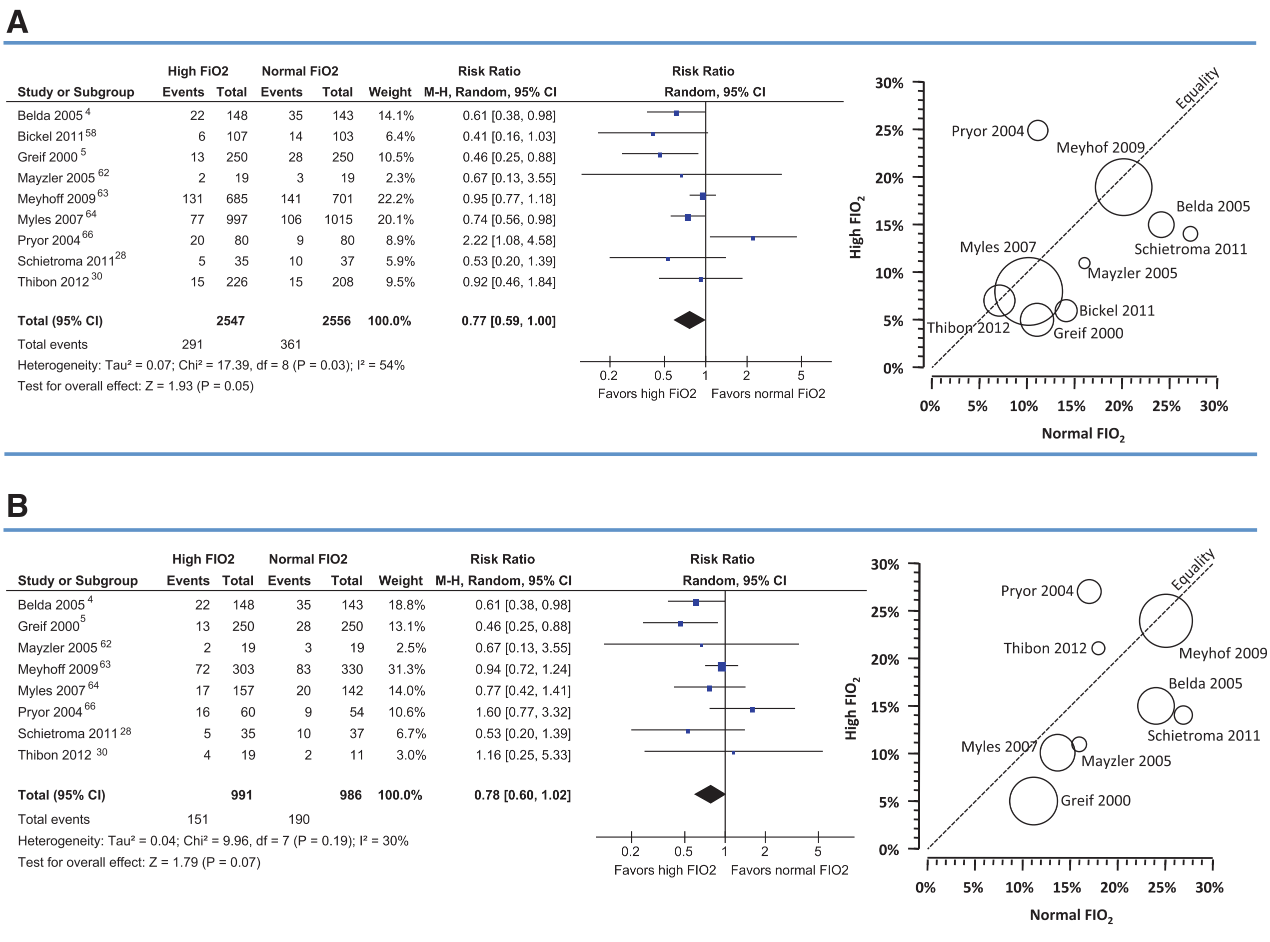

Fig. 2. (*A*) Impact of high oxygen fraction on surgical site infection. Included all surgeries. Surgeries were colorectal, appendectomy, abdominal, any except cardiac or one-lung, major abdominal, and gynecologic inclusive breast. (*B*) Impact of high oxygen fraction on surgical site infection. Included colorectal surgery only. On the Forrest plots, trials are listed in alphabetical order. On the event rate scatters, sizes of *bubbles* are proportional to sizes of trials. F_{IO_2} = inspired oxygen fraction.

Because data were heterogeneous (P_{hetero} = 0.03), we used a random effects model.

Because it has been argued that patients undergoing colorectal surgery may particularly profit from a high F_{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_{IO_2} and of 15.2% with high F_{IO_2}; RR, 0.78 (95% CI, 0.60–1.02; fig. 2B). The data were homogenous (P_{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_{IO_2} (fig. 3A). With normal F_{IO_2}, the average incidence of late nausea was 24.8%, with high F_{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] As expected, incidences of PONV outcomes in patients receiving normal F_{IO_2} were increased (fig. 3B). With normal F_{IO_2}, the average incidence of late nausea was 33.7%, with high F_{IO_2} was 29.3%; RR, 0.75 (95% CI, 0.62–0.90). With normal F_{IO_2}, the average incidence of late vomiting was 26.2%, with high F_{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 those[69,70] were subgroup analyses reporting

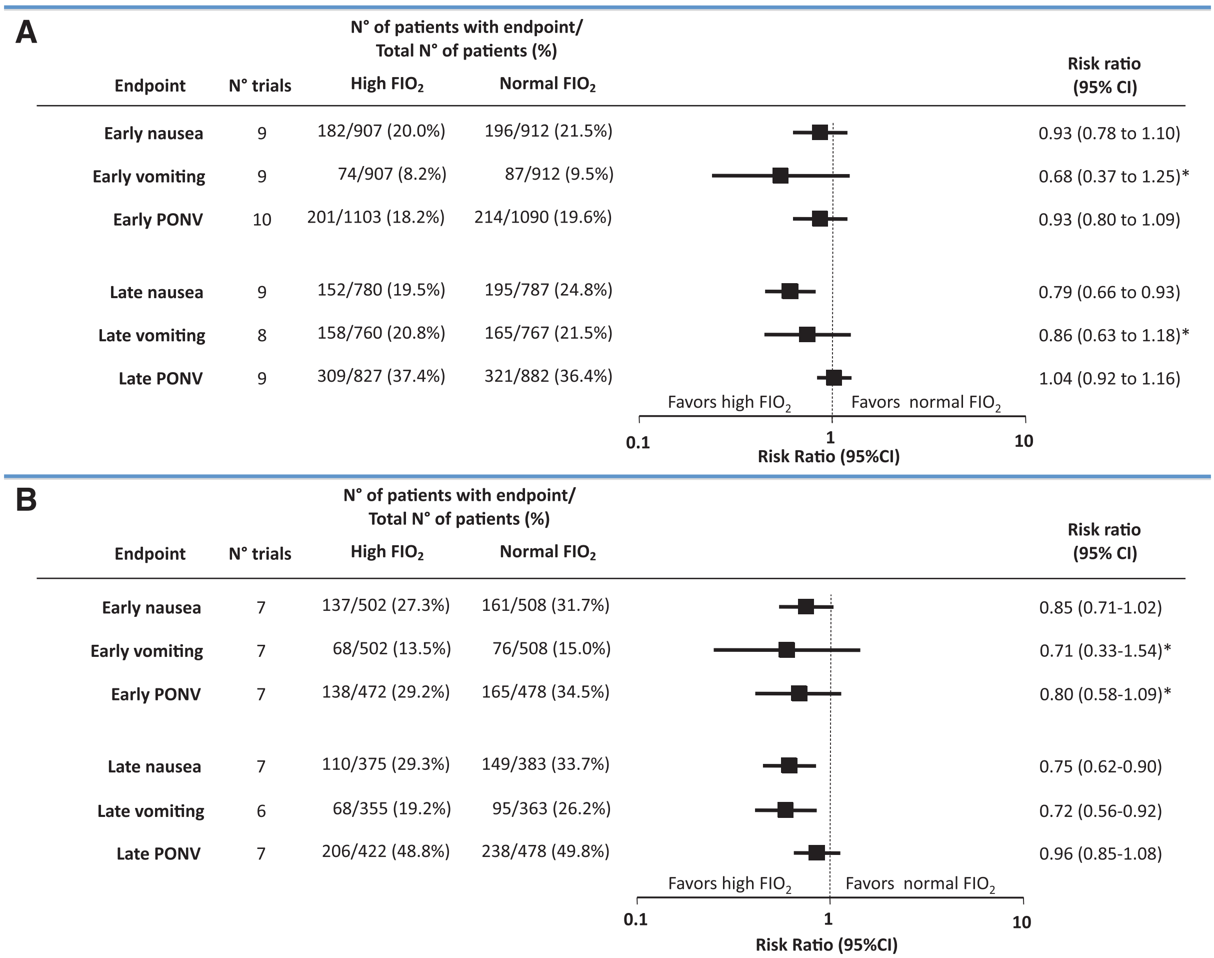

Fig. 3. (*A*) Impact of high oxygen fraction on postoperative nausea and vomiting. Showing summary of meta-analyses. (*B*) Impact of high oxygen fraction on postoperative nausea and vomiting. Inhalational anesthesia without antiemetic prophylaxis. Early = cumulative incidence to 6 h postoperatively; F_{IO_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_{IO_2} was 8.3%, with normal F_{IO_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 Pa_{O_2}/F_{IO_2} ratio in patients receiving 100% F_{IO_2} (use of positive end-expiratory pressure and postoperative Pa_{O_2}/F_{IO_2} ratio was not reported). The two other studies failed to show any detrimental effect on the postoperative Pa_{O_2}/F_{IO_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_{IO_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_{O_2} values.[69,72] Both failed to show a significant decrease in the 24-h postoperative Sp_{O_2} in patients exposed to high F_{IO_2}.

Finally, one trial showed no difference in postoperative oxygen requirements among patients ventilated with a high or normal F_{IO_2}.[61]

Discussion

We performed a systematic review and meta-analysis of clinical trials testing the role of high F_{IO_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 F_{IO_2} (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 F_{IO_2} 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 F_{IO_2} 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 F_{IO_2} in patients undergoing colorectal surgery only, but not in patients undergoing other abdominal surgeries.[26] Many authors have considered that subgroup as the most likely to profit from a high F_{IO_2}.[24,26] The question then is, whether this benefit is of clinical relevance. Although the degree of antiinfective efficacy of high F_{IO_2} 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 F_{IO_2} as a supplemental antiinfection strategy only; the efficacy of high F_{IO_2} 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 F_{IO_2} appeared to be effective independent of the baseline risk of infection (fig. 2A).

The potentially beneficial effect of high F_{IO_2} 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.[74] In 2008, two meta-analyses were addressing the potential benefit of high F_{IO_2} on PONV; one concluded that supplemental oxygen reduced the incidence of postoperative vomiting only[25] and the other was unable to identify any beneficial effect of high F_{IO_2}.[23] In our analysis, there was some evidence that high F_{IO_2} 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 F_{IO_2} had more scope to show antiemetic efficacy. However, absolute risk reductions suggested that approximately 15 patients needed to receive high F_{IO_2} for one not to be nauseous or to vomit who would have done so had they received normal F_{IO_2}. 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.[74] 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 Sp_{O_2}. 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 Pa_{O_2}/F_{IO_2} ratio. Both failed to show any detrimental effect of high F_{IO_2} on postoperative gas exchange, despite using ventilation settings known to acutely worsen pulmonary atelectasis[11] (*i.e.*, administration of 100% F_{IO_2} 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 F_{IO_2} regimen. Only one trial, conducted in moderately obese patients, reported on a detrimental effect of high F_{IO_2} 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 F_{IO_2}, 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 F_{IO_2}. 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 F_{IO_2}, we arbitrarily defined that, for eligibility, the value of the normal F_{IO_2} had to be less than, or equal to, half of the high F_{IO_2} 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,[48–50] 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.[83] 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

	Comparison			
	High FIO_2		Normal FIO_2	
First Author	FIO_2, %	Number of Patients	FIO_2, %	Number of Patients
Postoperative atelectasis				
Akça[56]	80	16	30	14
Kotani[60]	100	30	30	30
Meyhoff[63]	80	685	30	701
Myles[64]	80	997	30	1,015
Staehr[70]*	80	102	30	111
Staehr[69]*	80	20	30	15
Perioperative blood gases				
Agarwal[55]	100	9	40	9
Kotani[60]	100	30	30	30
Staehr[69]*	80	20	30	15
Postoperative lung function				
Akça[56]	80	16	30	14
Staehr[69]*	80	20	30	15
Zoremba[72]	80	71	40	71
Postoperative SpO_2				
Staehr[69]*	80	20	30	15
Zoremba[72]	80	71	40	71
Postoperative O_2 requirement				
Mackintosh[61]	>90	50	30	50

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

CT = computed tomography; FEV_1 = forced expiratory volume in 1 s; FIO_2 = inspired oxygen fraction; FVC = forced vital capacity; IQR = interquartile range; O_2 = oxygen; PaO_2 = arterial partial oxygen pressure; SpO_2 = arterial oxygen saturation by pulse oximetry.

Table 4. (*Continued*)

Definition of Endpoint	Results	Statistical Significance, *P* Value
Comparison of pre- and postoperative chest radiograph by a physician unaware of patient's group assignment	High F_{IO_2}: 44% Normal F_{IO_2}: 36%	0.94
Postoperative CT scan obtained in all patients and evaluated by a physician unaware of patient's group assignment	High F_{IO_2}: 94% Normal F_{IO_2}: 64%	0.12
Comparison of pre- and postoperative chest radiograph by a physician unaware of patient's group assignment	High F_{IO_2}: 23% Normal F_{IO_2}: 17%	"Not significant" (no value reported)
Present if described in the radiologist's evaluation of chest radiograph or CT scan (not routinely prescribed in all patients)	High F_{IO_2}: 7.9% Normal F_{IO_2}: 7.1%	0.60
Present if described in chest radiograph or CT scan (not routinely prescribed for all patients)	High F_{IO_2}: 7.5% Normal F_{IO_2}: 13%	<0.001
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)	High F_{IO_2}:8.8% Normal F_{IO_2}:6.3%	0.76
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)	High F_{IO_2}: 25% Normal F_{IO_2}: 13%	0.51
Intraoperative Pa_{O_2}/F_{IO_2} ratio	High F_{IO_2}: 351.5 (SD, 22.9) Normal F_{IO_2}: 558 (SD, 46.6)	<0.0001
Pa_{O_2}/F_{IO_2} ratio 24 h postoperatively	High F_{IO_2}: 389 (SD, 56) Normal F_{IO_2}: 393 (SD, 49)	"Not significant" (no value reported)
Pa_{O_2}/F_{IO_2} ratio 90 min postoperatively (kPa)	High F_{IO_2}: 50 (IQR, 42–57) Normal F_{IO_2}: 56 (IQR, 37–60)	0.66
Spirometry (FEV_1, FVC, FEV_1/FVC ratio)	A variety of lung function parameters with no significant difference between groups, 24 h postoperatively	
Spirometry (functional residual capacity), 2 h postoperatively (ml)	High F_{IO_2}: 1,633 (IQR, 1,343–1,948) Normal F_{IO_2}: 1,615 (IQR, 1,375–2,318)	0.70
Spirometry (mid-expiratory flow, FEV, forced inspiratory vital capacity)	A variety of lung function parameters "significantly" worse with high F_{IO_2} compared with normal F_{IO_2} at 0.5, 2, and 24 h	
Sp_{O_2} <95%, 72 h postoperatively	High F_{IO_2}: 35% Normal F_{IO_2}: 13%	0.15
Sp_{O_2}, 24 h postoperatively	High F_{IO_2}: 97.5% (SD, 1.70) Normal F_{IO_2}: 98% (SD, 2.0)	0.105
O_2 requirement to maintain Sp_{O_2} >90%, 24 h postoperatively	High F_{IO_2}: 0 l/min (IQR, 0–0) Normal F_{IO_2}: 0 l/min (IQR, 0–0)	No statistically significant difference between groups

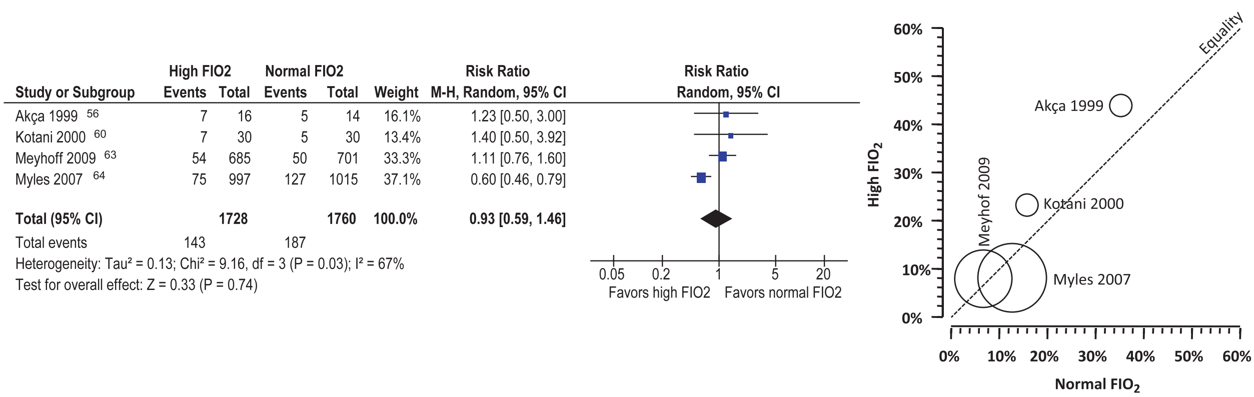

Fig. 4. Impact of high oxygen fraction on postoperative atelectasis. On the Forrest plot, trials are listed in alphabetical order. On the event rate scatter, sizes of *bubbles* are proportional to sizes of trials. F_{IO_2} = inspired oxygen fraction.

be assumed for all types of surgery, even ones where no clinical trial data exist.[73]

In conclusion, intraoperative high F_{IO_2} 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_{IO_2} *per se*, and in the absence of antibiotic prophylaxis, remains unknown. High F_{IO_2} reduces the risk of PONV to some extent, although mainly in patients with inhalation anesthetics and without prophylactic antiemetics. Finally, intraoperative high F_{IO_2} 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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