High Intraoperative Inspired Oxygen Does Not Increase Postoperative Supplemental Oxygen Requirements

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ABSTRACT

Background: Although a high fraction of inspired oxygen (FIO_2) could reduce surgical site infection, there is concern it could increase postoperative pulmonary complications, including hypoxemia. Intraoperative positive end-expiratory pressure can improve postoperative pulmonary function. A practical measure of postoperative pulmonary function and the degree of hypoxemia is supplemental oxygen requirement. We performed a double-blind randomized 2 × 2 factorial study on the effects of intraoperative FIO_2 0.3 *versus* more than 0.9 with and without positive end-expiratory pressure on the primary outcome of postoperative supplemental oxygen requirements in patients undergoing lower risk surgery.

Methods: After Institutional Review Board approval and consent, 100 subjects were randomized using computer-generated lists into four treatment groups (intraoperative FIO_2 0.3 *vs.* more than 0.9, with and without 3–5 cm H_2O positive end-expiratory pressure). Thirty minutes and 24 h after extubation, supplemental oxygen was discontinued. Arterial oxygen saturation by pulse oximetry was recorded 15 min later. If oxygen saturation decreased to less than 90%, supplemental oxygen was added incrementally to maintain saturation more than 90%.

Results: Nearly all subjects required supplemental oxygen in the postanesthesia care unit. Nonparametric Wilcoxon rank sum test demonstrated no statistically significant difference between groups in supplemental oxygen requirements at 45 min and 24 h after tracheal extubation ($P = 0.56$ and 0.98, respectively).

Conclusions: Use of intraoperative FIO_2 more than 0.9 was not associated with increased oxygen requirement, suggesting it does not induce postoperative hypoxemia beyond anesthetic induction and surgery. Therefore, it may be reasonable to use high inspired oxygen in surgical patients with relatively normal pulmonary function.

What We Already Know about This Topic

- High inspired oxygen concentrations during operations may reduce surgical site infections but could also increase postoperative atelectasis

What This Article Tells Us That Is New

- The use of high inspired oxygen concentrations during low risk operations did not induce postoperative hypoxemia compared with use of lower oxygen concentrations

DESPITE advances in management of patients undergoing surgery, including aseptic technique, prophylactic antibiotics, and laparoscopic surgery, wound infection and failure remain common complications of surgery. Wound complications are associated with prolonged hospitalization, increased resource consumption, and even increased mortality. More than 300,000 surgical site infections (SSI) occur each year in the United States and cost more than $1 billion.[1] Patient factors are a major determinant of wound outcome following surgery.[2] Comorbidities such as diabetes and cardiac disease contribute, but environmental stressors and the individual's response to stress may be equally important. Wounds are exquisitely sensitive to hypoxia, which is both common and preventable.[3,4] Perioperative management can promote postoperative wound healing and resistance to infection. Along with aseptic technique and prophylactic antibiotics, maintaining perfusion and oxygenation of

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the wound is paramount. Interventions to maintain normal wound perfusion such as maintaining normothermia,[5] providing adequate intravascular volume,[6,7] and minimizing pain[8] reduce SSI. In patients undergoing major surgery in whom normal wound perfusion is maintained, provision of high inspired oxygen (80%) intraoperatively and for a few hours after surgery significantly reduces the risk of SSI by 25–50%,[4,9–12] although a more recent study found no difference.[13]

A single study demonstrating reduced SSI with maintenance of intraoperative normothermia[5] rapidly changed practice. Guidelines for preventing SSI incorporated normothermia within 3 yr,[14] and pay-for-performance measures[15] did soon after. When the first study of high inspired oxygen,[4] performed by the same group and with nearly identical design, was published 4 yr later, adoption was neither universal nor rapid. Why the difference? There are a number of reasons for the rapid adoption of intraoperative warming, including demonstration of other benefits to normothermia[16,17] and the appeal of returning physiology perturbed by anesthesia to normal. High inspired oxygen (F_{IO_2} more than 0.8), on the other hand, has known toxicities, including pulmonary fibrosis with long-term use,[18] reversibly reduced vital capacity with 12–24 h continuous use,[19] and absorption atelectasis (approximately 5–9%) even with brief use, such as preoxygenation for induction of anesthesia.[20–22]

If the impact of high inspired oxygen on arterial P_{O_2} is minor and reversible, then benefits of high inspired oxygen may outweigh the risks. If high inspired oxygen is associated with postoperative hypoxemia, however, the risks may outweigh the benefits. We performed a pragmatic trial looking at the impact of high inspired oxygen, through any mechanism, on postoperative oxygen requirement, a surrogate for hypoxemia when nearly all patients require postoperative supplemental oxygen.

The object of our study was to investigate the effect of high (more than 90%) *versus* standard (30%) inspired oxygen on postoperative supplemental oxygen requirements to determine if high F_{IO_2} was safe in patients who were at low risk for SSI. Rusca *et al.*[23] demonstrated that positive end-expiratory pressure (PEEP)/continuous positive airway pressure at 6 cm H_2O during induction and maintenance prevented formation of atelectasis regardless of F_{IO_2}. We therefore simultaneously investigated whether addition of PEEP would reduce the effect of high inspired oxygen, if any. We hypothesized that a brief exposure to nearly 100% oxygen would not cause an increased postoperative oxygen requirement.

Materials and Methods

Subjects

This study was approved by the University of Utah Institutional Review Board for Human Subjects (Salt Lake City, Utah), was conducted in accordance with their guidelines, and was registered with clinicaltrials.gov (NCT00715741). All subjects gave written informed consent before participation. Potential subjects who were adults aged 18–70 yr scheduled for general endotracheal anesthesia at the University of Utah Hospital operating room or the Huntsman Cancer Hospital operating room with expected hospital stay more than 24 h postoperatively were screened for enrollment. Exclusion criteria included: major (open) abdominal, spine, or craniotomy surgeries; prone position; preoperative room air arterial oxygen saturation by pulse oximetry (S_{PO_2}) less than 90%; diagnosed obstructive sleep apnea with home continuous positive airway pressure device use; surgical plan for use of electrocautery or laser devices near the airway; planned postoperative intubation or intensive care unit admission; recent (within 3 weeks) chemotherapy; history of bleomycin use or home oxygen use; spontaneous pneumothorax; emergency surgery; pregnancy; and/or patient refusal.

Protocol

A randomized clinical trial using a 2 (F_{IO_2}: 2 levels) × 2 (PEEP: 2 levels) factorial design was employed to study the effect of inspired oxygen and PEEP on postoperative supplemental oxygen requirement. Subjects were blinded to group assignment. Anesthesia providers caring for the subjects were aware of group assignment but were unaware of the purpose of the study and were instructed not to inform anyone else of group assignment. Investigators were blinded to the group assignment until data collection had been completed. Monitors and flow meters were not covered for patient safety considerations. Investigators, however, remained blinded to study group assignment because they were not present in the operating room until the patient was receiving 100% oxygen in preparation for extubation. Statistical analysis was performed by an investigator (NLP) blinded to group assignment. Subjects were block randomized in a 1:1 ratio using Research Randomizer,‡‡ a web-based generator of customized sets of random numbers, to the following four groups: F_{IO_2} more than 0.9 + 3–5 cm H_2O PEEP; F_{IO_2} more than 0.9 + PEEP; F_{IO_2} 0.3 + 3–5 cm H_2O PEEP; F_{IO_2} 0.3 + PEEP. PEEP of 3–5 cm H_2O was chosen because it was the institutional standard. Randomization cards were placed in security (opaque) envelopes and numbered sequentially. Potential subjects were identified from the operating room schedule and contacted by investigators the day before surgery to explain the study and explore the possibility of enrollment. All subjects who expressed interest *via* telephone were approached on the day of surgery and informed consent was obtained. Once informed consent was completed, the subject was assigned a study number and the appropriate envelope was given to the clinical anesthesia provider. The anesthesia provider (attending anesthesiologist, anesthesia resident, or certified registered nurse anesthetist) was instructed to open the envelope on arrival in the operating

‡‡ http://www.randomizer.org/. Accessed July 27, 2011.

room to learn the assigned F_{IO_2} and level of PEEP. Providers were instructed not to report group assignment to investigators, operating room personnel, or subjects. Questions were referred to the senior investigator (HWH), who was not involved in data collection or statistical analysis. Upon completion of the surgery, the instructions and group assignment were placed back into the opaque envelope by the anesthesia provider and sealed. The anesthesia record was also not available to the investigator until all data had been collected on the respective patient.

The induction and maintenance of inhalation anesthesia were at the discretion of the anesthesia team. Providers were instructed to administer F_{IO_2} 1.0 for at least 3 min before induction of anesthesia in all subjects. After successful tracheal intubation, the assigned F_{IO_2} and PEEP were administered and maintained until the end of the procedure. For subjects assigned to F_{IO_2} more than 0.9, providers were instructed to administer only oxygen and vapor (no air or nitrous oxide) at a flow rate of 2 l/min. For subjects assigned to F_{IO_2} 0.3, providers were instructed to mix oxygen and air (no nitrous oxide) at a total flow rate of 2 l/min to achieve the target F_{IO_2}. Anesthesia providers were instructed to maintain the assigned F_{IO_2} throughout the case unless adjustment was clinically indicated. Providers were instructed to maintain end-tidal carbon dioxide at 35–45 mmHg, and tidal volume at 6–10 ml/kg lean body weight (LBW). LBW was calculated using the Devine equation[24]: LBW_{men} (in kilograms) = 50 + 2.3 kg per inch more than 5 feet. LBW_{women} = 45.5 + 2.3 kg per inch more than 5 feet. LBW was calculated by investigators and provided to the clinical anesthesia provider on the front of the randomization envelope.

At the end of surgery, 100% oxygen was administered for about 5 min before extubation of the trachea. Investigators were present in the operating room at emergence to record the precise time of tracheal extubation, but were not in the operating room until 100% oxygen was being administered and randomization paperwork was sealed in the opaque envelope provided to the anesthesia provider at the beginning of the case. On arrival in the postanesthesia care unit (PACU), the anesthesia provider sealed the anesthesia record in an envelope provided by the researcher and the envelope was not opened until the completion of all data collection.

Investigators remained with subjects in the PACU for the first hour after tracheal extubation. Supplemental oxygen was discontinued 30 min after extubation of the trachea. Subjects were then allowed to rest quietly with minimal stimulation. Sp_{O_2} (measured using pulse oximetry) and hemodynamic variables were observed continuously and recorded 15 min after initial removal of supplemental oxygen. Because of patient safety, if at any time the subject's Sp_{O_2} decreased to less than 90%, supplemental oxygen was added incrementally (beginning with 0.5 l/min) *via* nasal cannula to prevent hypoxemia. The amount of supplemental oxygen required to keep a subject's Sp_{O_2} at 90% or more was also recorded. The same procedure was followed 22–26 h later in the subject's hospital room. Supplemental oxygen (if still in use) was discontinued when the patient was resting quietly in bed with no interruption planned for 15 min. Sp_{O_2} and hemodynamic variables were then recorded using the same protocol as in the PACU. Oxygen administration during the first 24 h was standardized. Our institution has a strict protocol for postoperative administration and weaning of supplemental oxygen based on keeping Sp_{O_2} more than 90%. Continuous pulse oximetry is commonly employed, either based on physician order or at the discretion of floor nurses and respiratory therapy.

Preoperative subject characteristics including age, gender, smoking status, Sp_{O_2}, hemoglobin, temperature, weight, height, and body mass index were recorded at the time of enrollment in the study to ensure compliance with inclusion and exclusion criteria (table 1). Operative and postoperative events including type of surgery, duration of surgery, ventilation variables, fluid input and output, temperature, and opioid administration were extracted from the written and electronic medical record after completion of data collection at 24 h. All opioids administered were converted to micrograms of fentanyl equivalence using an online opioid conversion calculator.§§

Sample Size Estimate

Sample size planning was performed in nQuery Advisor version 7.0 (Statistical Solutions, Saugus, MA). A change in Sp_{O_2} of 2% or greater was considered clinically significant for the purpose of our study. Using the value of 2%, a SD of 2%, and a two-tailed analysis, an initial sample size of 21 subjects per group (four groups) was calculated to yield 80% power ($\beta = 0.2$) to detect a statistically significant difference ($\alpha = 0.05$). We increased the planned sample size to 100 to allow for stratification for smoking status as well. After the first 20 subjects were enrolled in the study, we recognized that almost no patients in the PACU would maintain Sp_{O_2} at 90% or more without addition of supplemental oxygen. When it became clear that the outcome of interest would be supplemental oxygen requirement, we performed a second sample size calculation using data from the first 20 subjects. Given that a difference in supplemental oxygen use of 0.5 l/min would not be clinically significant, a sample size of 12 per each group would have 80% power to detect a twofold change in means using a two-group Student *t* test with 0.05 two-sided difference. Thus, we completed study enrollment of 100 subjects as planned.

Statistical Analysis

Data with normal distribution are reported as mean (SD). Those with skewed distribution are reported as median (interquartile range). The distribution of supplemental oxygen requirement was compared between groups using the Wilcoxon rank sum test. Because of the factorial design with

§§ http://www.globalrph.com/narcotic.cgi. Accessed July 27, 2011.

Table 1. Preoperative Subject Characteristics

	F_{IO_2} 0.3 + PEEP (n = 25)	F_{IO_2} >0.9 + PEEP (n = 25)	F_{IO_2} 0.3, No PEEP (n = 25)	F_{IO_2} >0.9, No PEEP (n = 25)
Age (years)	47 (13)	46 (15)	45 (12)	46 (13)
Gender				
Male (n = 45)	12	13	10	10
Female (n = 55)	13	12	15	15
Smoking status				
Yes (n = 9)	1	4	2	2
No (n = 79)	22	18	19	20
Quit (n = 12)	2	3	4	3
Spo_2 (%)	95 (2)	95 (3)	95 (2)	96 (2)
Hemoglobin (g/dL)	14 (2)	13 (2)	13 (2)	13 (2)
Temperature (°C)	36.7 (0.5)	36.5 (0.5)	36.7 (0.5)	36.5 (0.5)
Weight (kg)	82 (19)	83 (14)	83 (17)	76 (16)
Height (cm)	173 (12)	171 (12)	172 (10)	172 (12)
Body mass index	27 (6)	28 (6)	28 (7)	26 (4)

Results reported as mean (SD).

F_{IO_2} = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; Spo_2 = arterial oxygen saturation by pulse oximetry.

complete balance of sample sizes, the two F_{IO_2} groups and the two PEEP groups were combined for analysis and analyzed separately. Administration of opioids, length of surgery, and preoperative Spo_2 were compared using a two-way ANOVA test using two-tailed hypothesis testing. $P < 0.05$ was considered statistically significant. Statistical software was R version 2.12.0 (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria), in particular the nonparametric statistics R package coin 1.0–17.

An exploratory data analysis by multivariable median regression was performed to identify putative covariates that were related to PACU oxygen administration. The covariates entered into regression were surgery category, sex, smoking history, assigned PEEP, assigned F_{IO_2}, preoperative Spo_2, duration of surgery (intubation time), body mass index, normalized intraoperative fluid administration, blood loss, operative and PACU fentanyl equivalents administration, and age. The standard errors were estimated by bootstrapping. This analysis was performed in R using the quantile regression package quantreg 4.53.

Patient Safety

The Institutional Review Board did not require a formal data safety monitoring board for this minimal risk study. In order to maximize the safety of our study, the principal investigator (HWH) did not participate in subject recruitment or data collection in order to be able to make decisions when questions arose. Data were reviewed weekly for evidence of adverse effects by two authors not involved in data collection (HWH, JW).

Results

Data were collected between June 2008 and July 2009. During the course of the study, 1,300 patients were assessed for eligibility (fig. 1), of whom 1,183 were excluded based on entry criteria, six refused to participate, and 111 were enrolled. Of these, 11 subjects were excluded intraoperatively before investigators were aware of study assignment because of a change in the surgical plan (seven were changed to same-day discharge and four were converted from laparoscopic to open abdominal procedures). Only nine smokers were enrolled in the study because of the low rate of smoking in Utah (less than 12%). We screened only 50 smokers in the 1,300 patients, but most of them were excluded based on pulmonary disease (room air Spo_2 less than 90% or home oxygen use). Therefore, no separate analysis of smokers was performed.

Mean F_{IO_2} was 0.93 (median 0.9, interquartile range 0.9–0.9) in the more than 0.9 group and 0.35 (median 0.3, interquartile range 0.3–0.3) in the 0.3 group. There were few deviations from study protocol (fig. 1). Nine subjects assigned to the F_{IO_2} 0.3 group required a higher F_{IO_2} to maintain adequate oxygenation. The median F_{IO_2} in these subjects was 0.53 (interquartile range 0.44–0.6). No subjects were lost to follow-up and all were included in the analysis on an intention to treat basis. No adverse events related directly to study enrollment were identified.

There was no statistically significant difference between the four groups with respect to the amount of supplemental oxygen required to maintain Spo_2 at 90% or more, or between the two F_{IO_2} groups (0.3 and 0.9 or more) at 45 min (95% CI, −0.5–0.5; $P = 0.56$; fig. 2A) or 24 h after tracheal extubation (95% CI, −0.5–0.5; $P = 0.09$, fig. 2B) with respect to the amount of supplemental oxygen required to maintain Spo_2 at 90% or more. There was no statistically significant difference between the two PEEP groups (0 cm H_2O and 3–5 cm H_2O) at 45 min (95% CI, −1.0–0.5; $P = 0.13$, fig. 2C) or 24 h after tracheal extubation (95% CI, −0.5–0.5; $P = 0.98$, fig. 2D) with respect to the amount of

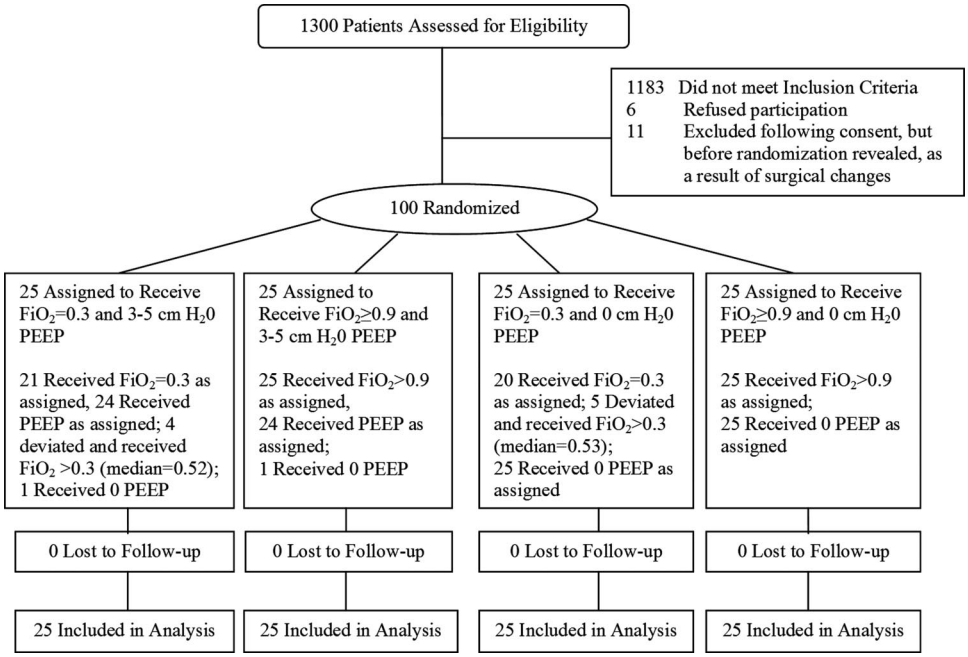

Fig. 1. Study profile, including total patients assessed, excluded, enrolled, randomized, and completed data collection. F_{IO_2} = fraction of inspired oxygen; PEEP = positive end-expiratory pressure.

supplemental oxygen required to maintain Sp_{O_2} at 90% or more. Most subjects required 0.5–1 l/min *via* nasal cannula in the PACU, whereas most subjects required no supplemental oxygen 24 h postoperatively, regardless of the F_{IO_2} or PEEP group assigned (table 2). Given the almost universal requirement for supplemental oxygen and the correction of low Sp_{O_2} with supplemental oxygen, there were no statistically significant differences in absolute Sp_{O_2} data (table 3).

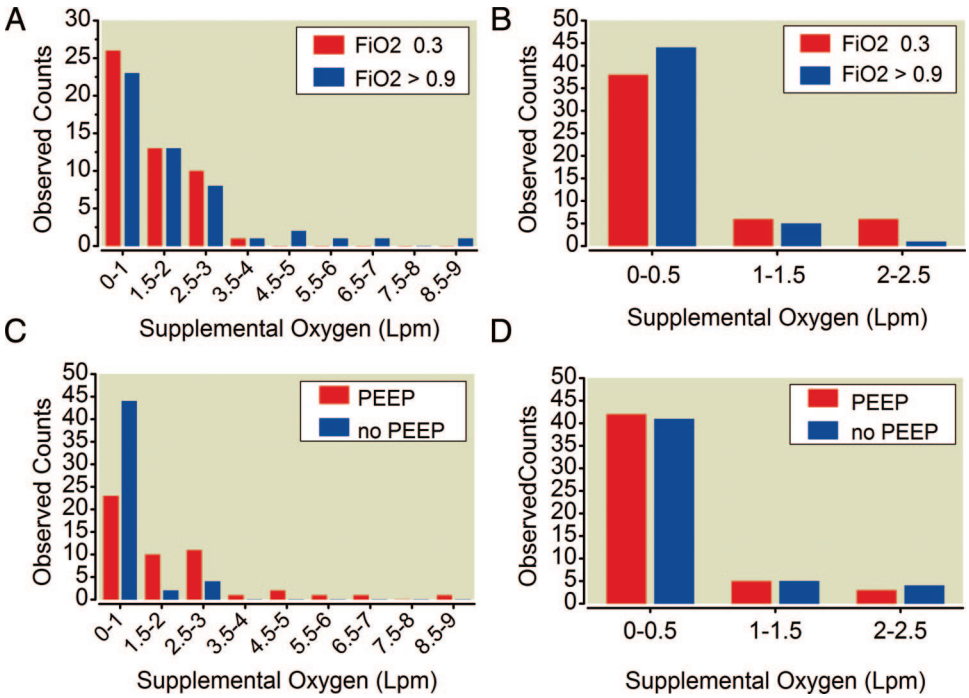

Fig. 2. Histograms showing supplemental oxygen required to keep SpO_2 at more than 90% in the postanesthesia care unit (PACU) and on postoperative day 1 (POD1). (*A*) In the PACU 45 min after tracheal extubation for F_{IO_2} 0.3 *versus* F_{IO_2} more than 0.9 groups. (*B*) On POD1 for F_{IO_2} 0.3 *versus* F_{IO_2} more than 0.9 groups. (*C*) In the PACU 45 min after tracheal extubation for 0 cm H_2O PEEP *versus* 3–5 cm H_2O PEEP groups. (*D*) On POD1 for 0 cm H_2O PEEP *versus* 3–5 cm H_2O PEEP groups. F_{IO_2} = fraction of inspired oxygen; IQR = interquartile range; Lpm = l/min; PACU = postanesthesia care unit; PEEP = positive end-expiratory pressure; POD1 = postoperative day 1.

Table 2. Postanesthesia Care Unit and Postoperative Day 1 Supplemental Oxygen Requirement

	F_{IO_2} 0.3 (n = 50)	F_{IO_2} >0.9 (n = 50)	+PEEP (n = 50)	No PEEP (n = 50)
PACU				
Supplemental oxygen Requirement (l/min)	0.5 (0–1.4)	1 (0–2)	0.5 (0–1)	1 (0–2)
POD1				
Supplemental oxygen Requirement (l/min)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

Results reported as median (interquartile range). No statistically significant differences between groups.

F_{IO_2} = fraction of inspired oxygen; PACU = postanesthesia care unit; PEEP = positive end-expiratory pressure; POD1 = postoperative day 1.

Five subjects had a high supplemental oxygen requirement at 45 min after extubation, all of them in the 0.9 F_{IO_2} group (fig. 2A). One subject required 8 l/min of oxygen. There were seven outliers (oxygen requirement more than 2 l/min) at 24 h, one in the F_{IO_2} more than 0.9 group and six in the F_{IO_2} 0.3 group.

There was no statistically significant difference between the four groups with respect to the amount of opioids given intraoperatively, immediately postoperatively in the PACU, and within 24 h postoperatively (table 4). In addition, there was no statistically significant difference between the groups with respect to length of surgery, type of surgery, preoperative saturation, and American Society of Anesthesiologists class.

The exploratory analysis showed that only the preoperative Spo_2 was significantly and inversely associated with PACU oxygen administration ($P = 0.035$).

Discussion

Use of high (more than 90%) inspired oxygen was not associated with increased oxygen requirement 45 min or 24 h after tracheal extubation. This suggests that whatever the pulmonary effects of high inspired oxygen, the balance does not require a change in postoperative management. Factors that could cause postoperative hypoxemia include absorption, compression, and loss of surfactant atelectasis; increased ventilation/perfusion mismatch, hypoventilation caused by opioids, other drugs, or pain; pulmonary edema; and other patient comorbidities. Although we didn't measure any of these directly, absorption atelectasis is most likely to be different given the only difference between the groups was F_{IO_2}. Therefore, it seems reasonable to conclude that the extent of absorption atelectasis induced by high inspired oxygen is not sufficient to induce postoperative hypoxemia beyond that caused by other factors. Hypoventilation induced by opioids and/or pain and increased oxygen requirements in subjects with mild preoperative pulmonary impairment (Spo_2 90–94%) appear to make a larger contribution to postoperative Spo_2 and oxygen requirement. Therefore, it may be reasonable to employ high F_{IO_2} even in lower risk surgery to improve wound oxygenation and possibly reduce SSI.

Edmark *et al.*[22] measured atelectasis by computerized tomographic scan immediately after 5 min of preoxygenation with 60, 80, or 100% oxygen, a variable period of apnea, and 1.5 min ventilation in 36 healthy volunteers. They found 0.3 +/− 0.3 cm^2 (less than 1%) in the 60% group, 1.3 +/− 1.2 cm^2 (1–5%) in the 80% group, and 9.8 +/− 5.2 cm^2 (1–20%) in the 100% group. The study measured time to reach 90% SpO_2. Volunteers in the 100% group were apneic for about twice as long (7 min *vs.* 3.5 min) as those in the 60% group, which may have affected results. Agarwal *et al.*[21] found that ventilation with F_{IO_2} 0.4 *versus* 1.0 intraoperatively improved Pa_{O_2}/F_{IO_2} ratio after preoxygenation with 100% oxygen reduced it. PEEP was not applied. Benoit *et al.*[25] evaluated the effect of high F_{IO_2} (1.0 *vs.* 0.4) during 10 min before extubation after subjects were extubated and breathing room air. Percent atelectasis was greater in the F_{IO_2} 1.0 groups (8.3 +/− 6.2% in the F_{IO_2} 1.0 group and 6.8 +/− 3.4% in the F_{IO_2} 1.0 plus vital capacity maneuver group *vs.* 2.6 ± 1.1% in the F_{IO_2} 0.4 plus vital capacity maneuver group), although it was fairly small in all groups. All patients in our study were exposed to F_{IO_2} more than 0.9 (100% administered oxygen, with end-tidal oxygen reduced by nitrogen washout and anesthetic vapor) during induction and emergence. Thus, the lack of difference we found may be

Table 3. Preoperative and Postoperative Spo_2

F_{IO_2}/PEEP Spo_2%	>90%/0 (n = 25)	>90%/3–5 (n = 25)	30%/0 (n = 25)	30%/3–5 (n = 25)
Preop Spo_2%, median (IQR)	96 (96–97)	96 (94–97)	95 (94–97)	95 (94–96)
PACU Spo_2%, median (IQR)	95 (93–96)	94 (92–96)	96 (93–97)	93 (92–95)
POD1 Spo_2%, median (IQR)	95 (93–97)	94 (93–96)	94 (91–96)	95 (94–96)

Preoperatively, Spo_2 values were recorded on room air. Postoperatively, they were recorded after 15 min on room air, if tolerated, or on the minimum flow of oxygen (in 0.5 l/min increments) required to maintain Spo_2 90% or more. Results presented as median (interquartile range); there were no statistically significant differences between groups.

F_{IO_2} = fraction of inspired oxygen; IQR = interquartile range; PACU = postanesthesia care unit; PEEP = positive end-expiratory pressure; POD1 = postoperative day 1; Spo_2 = arterial oxygen saturation by pulse oximetry.

Table 4. Operative and Postoperative Subject Characteristics

	F_{IO_2} 0.3 + PEEP (n = 25)	F_{IO_2} >0.9 + PEEP (n = 25)	F_{IO_2} 0.3, No PEEP (n = 25)	F_{IO_2} >0.9, No PEEP (n = 25)
Surgical category				
Breast (n = 17)	6	1	5	5
Robotic prostatectomy (n = 21)	5	6	5	5
Orthopedic (n = 20)	6	7	4	3
Gynecological (n = 22)	4	7	5	6
Laparoscopic abdominal (n = 18)	3	4	5	6
Amputation (n = 2)	1	0	1	0
Surgical variables				
Duration of anesthesia (min)	195 (121–241)	187 (136–214)	237 (177–269)	179 (158–239)
Intraoperative opioids*	470 (320–530)	430 (250–600)	600 (450–780)	450 (350–570)
Ventilation variables				
Tidal volume (mL)	602 ± 113	575 ± 104	589 ± 135	587 ± 107
Tidal volume (mL/kg LBW)	9.2 ± 1.9	8.9 ± 1.5	9.3 ± 2.1	9.1 ± 1.1
Frequency	9 ± 1	10 ± 2	10 ± 2	9 ± 2
Actual PEEP (cm H_2O)	5 (4, 5)	5 (4, 5)	0 (0, 0)	0 (0, 0)
Actual F_{IO_2}	0.34 ± 0.08	0.93 ± 0.03	0.36 ± 0.13	0.93 ± 0.04
Peak inspiratory pressure	25 (15, 28)	24 (18, 28)	23 (20, 29)	20 (16, 23)
End-tidal carbon dioxide	37 ± 2	38 ± 2	37 ± 2	38 ± 4
Inputs/Outputs				
Estimated blood loss (ml)	100 (50–200)	150 (100–200)	150 (75–400)	100 (50–200)
Urine output (ml)	50 (0–250)	100 (0–200)	120 (40–200)	110 (0–200)
Crystalloids (ml)	1,500 (1,100–2,500)	1,800 (1,100–2,700)	2,500 (2,000–3,000)	1,800 (1,500–2,400)
Crystalloids (ml/kg per hr)	8 (6–10)	8 (6–10)	8 (6–10)	8 (7–11)
Temperature				
PACU	36.7 ± 0.4	36.7 ± 0.4	36.8 ± 0.5	36.5 ± 0.5
POD1	36.8 ± 0.5	37.0 ± 0.7	36.9 ± 0.5	36.8 ± 0.6
Postoperative opioids*				
PACU	50 (25–170)	30 (0–120)	60 (30–150)	80 (30–130)
POD1	60 (50–150)	100 (0–240)	130 (30–200)	120 (40–220)

Results reported as median (interquartile range) or mean (SD).

* Opioids reported in mcg fentanyl equivalents. Postoperative opioids were defined as any opioid given in the PACU until data collection on POD 1 (22–26 h after extubation).

F_{IO_2} = fraction of inspired oxygen; LBW = low birth weight; PACU = postanesthesia care unit; PEEP = positive end-expiratory pressure; POD1 = postoperative day 1.

related to similar amounts of absorption atelectasis developed during induction and emergence.

In contrast to previous studies,[26,27] which demonstrated reduced atelectasis (and therefore an inferred decrease in hypoxemia) with PEEP, subjects in the PEEP group exhibited no reduction in postoperative supplemental oxygen requirement. This may have been because of the low PEEP administered (3–5 cm H_2O), a difference in model, or a difference in sensitivity of measurements. PEEP 3–5 cm H_2O was chosen because it is the institutional norm. In retrospect, 5–10 cm H_2O might have been better. It is difficult to draw any conclusion about PEEP except 5 cm H_2O (the median value administered) was not effective in reducing postoperative supplemental oxygen requirements in our subjects. Anesthesia providers did not generally use recruitment maneuvers, but this was not controlled. Recruitment maneuvers (outside of PEEP) are rarely used at our institution in the types of cases included in our study.

Hypoxemia and supplemental oxygen requirement are common after surgery, because of a variety of factors. We were interested in whether absorption atelectasis induced by high inspired oxygen caused detrimental effects postoperatively. We did not measure atelectasis directly, so we cannot draw direct conclusions about the degree of atelectasis or the contribution of absorption atelectasis to supplemental oxygen requirement. The standard measure of atelectasis is computerized tomography.[28] Computerized tomographic scans are expensive; require transport of a patient when careful monitoring is critical; do not measure the contribution of absorption atelectasis; are not validated because there is no true gold standard measure of atelectasis; usually rely on a single cut; and may be confounded by fluid in the lung, variations in blood supply, and dense tissue adjacent to the lung.[28] Therefore, we chose a pragmatic outcome: supplemental oxygen requirement. The inclusion and exclusion criteria were designed to help eliminate confounding sources

of hypoxemia and atelectasis, so that our findings are likely related to changes in absorption atelectasis. Subjects in the prone position and those with preoperative room air Spo_2 at less than 90% or a diagnosis of obstructive sleep apnea with home continuous positive airway pressure use were excluded. Carpagnano *et al.*[29] showed that hyperoxia may increase oxidative stress markers in patients with pulmonary disease, a secondary consideration in excluding potential subjects with pulmonary disease. Because higher intraoperative inspired oxygen provides benefit to those undergoing major (open) abdominal, spine, or craniotomy surgery,[4,9–12] it would not have been ethical to assign them to a lower Fio_2 group.

Five subjects had high supplemental oxygen requirement 45 min after extubation, all of them in the more than 0.9 Fio_2 group (fig. 2A). One subject required 8 l/min of oxygen. His PACU respiratory rate was 8 breaths/min and the anesthesia team considered naloxone administration. He developed inspiratory and expiratory wheezing and was later treated with albuterol. He required no supplemental oxygen 24 h later. Factors that may have contributed to high oxygen requirement by the other four outliers included opioids administered immediately before or during testing and relatively low preoperative Spo_2 values (92–94%). One subject was a smoker and one received a larger than average dose of opioid intraoperatively. There were seven outliers (oxygen requirement more than 2 l/min) at 24 h, one in the Fio_2 more than 0.9 group and six in the Fio_2 0.3 group. Of these, six had Spo_2 90–94% preoperatively (fig. 2B).

Interestingly, all of the outliers in the PACU were assigned PEEP intraoperatively (fig. 2A, C). Tusman *et al.*[30] evaluated alveolar recruitment in healthy lungs in children during general anesthesia and found that PEEP of 5 cm H_2O or more was required to prevent newly recruited alveoli from collapsing. Rusca *et al.*[23] found that 6 cm H_2O PEEP prevented atelectasis formation during induction of anesthesia, but they did not study lower levels of PEEP. Neumann *et al.*[26] showed that 10 cm H_2O PEEP and a vital capacity recruitment maneuver reduced atelectasis in subjects ventilated with 100% oxygen. In our study, of the subjects who were assigned PEEP, no subjects received more than 5 cm H_2O, whereas 42% received less than 5 cm H_2O. Therefore, PEEP may have been insufficient to have a postoperative benefit on oxygen requirement, or our outcome measures may not have been sensitive enough to detect a benefit.

All subjects in the more than 90% group received the assigned treatment, as did all subjects in both PEEP groups. In the Fio_2 0.3 group, 9/50 subjects received Fio_2 more than 0.3. In all cases this was a clinical decision by the anesthesia team in response to decreased Spo_2. The Fio_2 used in these nine subjects was: 0.4, 0.43, 0.44, 0.44, 0.53, 0.6, 0.6, 0.7, and 0.79. These subjects were analyzed in their originally assigned group, following an intention to treat analysis. None of the subjects who required more than 2 l/min H_2O postoperatively from the Fio_2 0.3 group required increased Fio_2 intraoperatively.

We had a higher rate of increased intraoperative oxygen requirement (9/50) than previous similar studies.[10] This is likely related to the high altitude of Salt Lake City. The University of Utah Hospitals are at about 4,700 feet above sea level and ambient barometric pressure averages 635–640 mmHg (blood gas machine barometer). Previous studies demonstrated the rate of absorption atelectasis is inversely related to barometric pressure.[31] Despite this increased predilection for absorption atelectasis at altitude, we did not observe a difference between the more than 90% and 30% inspired oxygen groups.

The need for supplemental oxygen is less sensitive than absolute Spo_2, but subject safety required that we put a "floor" on the lowest Spo_2 values (90%) while on room air only. We considered obtaining arterial blood gas measurements. This would have been a more sensitive and precise measure. It would also have increased subject risk and study cost and decreased subject recruitment. Moreover, the issue of the need for supplemental oxygen would have remained.

Because we excluded subjects with severe pulmonary disease, the results cannot be generalized to that population, who may have an increased susceptibility to oxidative damage from high inspired oxygen.[19] This group should be investigated, as there are also some data that suggest potential benefit of short-term increased inspired oxygen in such patients.[22]

Summary

Use of high (more than 90%) inspired oxygen was not associated with an increased oxygen requirement 45 min or 24 h after tracheal extubation. This suggests that absorption atelectasis induced by high inspired oxygen is not sufficient to induce postoperative hypoxemia beyond that associated with anesthesia/surgery induced atelectasis, at least in patients with relatively normal pulmonary function. Our results add meaningful information to the debate on appropriate intraoperative inspired oxygen levels, and suggest that it is reasonable to use high inspired oxygen in surgical patients.

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