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Respiration and the Airway

RESPIRATION AND THE AIRWAY

High intraoperative inspiratory oxygen fraction and risk of major respiratory complications

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Abstract

Background. High inspiratory oxygen fraction (FI_{O_2}) may improve tissue oxygenation but also impair pulmonary function. We aimed to assess whether the use of high intraoperative FI_{O_2} increases the risk of major respiratory complications.
Methods. We studied patients undergoing non-cardiothoracic surgery involving mechanical ventilation in this hospital-based registry study. The cases were divided into five groups based on the median FI_{O_2} between intubation and extubation. The primary outcome was a composite of major respiratory complications (re-intubation, respiratory failure, pulmonary oedema, and pneumonia) developed within 7 days after surgery. Secondary outcomes included 30-day mortality. Several predefined covariates were included in a multivariate logistic regression model.
Results. The primary analysis included 73 922 cases, of whom 3035 (4.1%) developed a major respiratory complication within 7 days of surgery. For patients in the high- and low-oxygen groups, the median FI_{O_2} was 0.79 [range 0.64–1.00] and 0.31 [0.16–0.34], respectively. Multivariate logistic regression analysis revealed that the median FI_{O_2} was associated in a dose-dependent manner with increased risk of respiratory complications (adjusted odds ratio for high *vs* low FI_{O_2} 1.99, 95% confidence interval [1.72–2.31], *P*-value for trend <0.001). This finding was robust in a series of sensitivity analyses including adjustment for intraoperative oxygenation. High median FI_{O_2} was also associated with 30-day mortality (odds ratio for high *vs* low FI_{O_2} 1.97, 95% confidence interval [1.30–2.99], *P*-value for trend <0.001).
Conclusions. In this analysis of administrative data on file, high intraoperative FI_{O_2} was associated in a dose-dependent manner with major respiratory complications and with 30-day mortality. The effect remained stable in a sensitivity analysis controlled for oxygenation.
Clinical trial registration. NCT02399878.

Key words: oxygen; postoperative complications; respiratory insufficiency; respiratory therapy

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Editor's key points

This retrospective registry study explored the relationship between inspiratory oxygen fraction (FI_{O_2}) during surgery and postoperative pulmonary complications (PPCs)

- Intraoperative FI_{O_2} data were available for 5837 patients, which represents 8% of the whole cohort.
- In this subset, the incidence of dichotomized composite PPCs at 7 days was higher in those with a higher median FI_{O_2} during surgery, and this association remained after adjusting for potentially confounding variables.
- These associations should be interpreted with caution, and more robust data are needed to inform clinical practice.

Postoperative respiratory complications are relatively common, with incidences estimated to range from ~3 to 40% studied,[1–3] and lead to a longer hospital stay, higher costs, and increased mortality.[4]

A high intraoperative inspiratory oxygen fraction (FI_{O_2}) may reduce the incidence of surgical site infection,[5–7] but the adverse effects remain to be investigated fully. Preoxygenation with 100% oxygen results in atelectasis within a few minutes of induction of anaesthesia.[8 9] Few studies have investigated the effect of intraoperative FI_{O_2} on clinically significant respiratory complications.[10] A recent Cochrane review concluded that evidence is insufficient to support the routine use of a high FI_{O_2} during anaesthesia and surgery, as a significant effect on respiratory insufficiency could not be detected.[11] The number of patients included in the analysis was, however, too small to allow a firm conclusion.

Knowledge about potential pulmonary oxygen toxicity also has important implications in critically ill patients, because hundreds of millions of patients receive oxygen therapy every year during mechanical ventilation in the emergency room, intensive care unit (ICU), and operating theatre.[4] In order to increase the arterial oxygen content, clinicians may decide either to increase the FI_{O_2} or to apply a high level of PEEP. An optimal risk–benefit analysis requires knowledge about the consequences of a high inspiratory oxygen concentration for the pulmonary outcome.

In this study, we aimed to investigate the association between intraoperative FI_{O_2} and major respiratory complications, wound dehiscence, ICU admission, and mortality in patients undergoing non-cardiothoracic surgery. Our primary hypothesis was that high intraoperative FI_{O_2} increases the risk of major postoperative respiratory complications independently of predefined markers of co-morbidity and surgical complexity.

Methods

Study design and setting

This was an analysis of data on file on consecutively enrolled adult patients undergoing non-cardiothoracic surgery with tracheal intubation at Massachusetts General Hospital and two affiliated community hospitals between January 2007 and August 2014. Exclusion criteria were as follows: age <18 yr; surgery within 4 weeks before the procedure; or missing information in any of the variables used in the primary regression model (FI_{O_2} or predefined covariates). Approval was obtained from the Partners Institutional Review Board at Massachusetts General Hospital (Boston, MA, USA; protocol no. 2015P000074), and the study was registered at ClinicalTrials.gov (NCT02399878) before any data retrieval.

Data source

Data from two databases, the Anaesthesia Information Management System (AIMS) and the Research Patient Data Registry, were retrieved and combined to provide peri- and postoperative information. All outcomes were identified by incidence of diagnostic codes within the indicated time frame after surgery derived from the World Health Organization International Statistical Classification of Diseases and Related Health Problems, 9th revision (ICD-9) or Current Procedural Terminology (CPT) procedure codes (for a full list, see Supplementary material Table S1). Respiratory outcomes have been validated previously based on chart review.[4 12]

Outcome measures

The primary outcome was a composite of major respiratory complications (re-intubation, respiratory failure, pulmonary oedema, and pneumonia) developed within 7 days of surgery. Secondary outcomes were wound dehiscence within 21 days, admission to the ICU within 7 days, and mortality within 7 and 30 days of surgery. Exploratory outcomes were stroke within 30 days and myocardial infarction or positive troponin test within 30 days after surgery.

Exposure and covariate data

The exposure variable was the median intraoperative FI_{O_2} between intubation and extubation. The FI_{O_2} is prospectively recorded every minute in AIMS. Information on the following potential confounders was collected and included in the logistic regression analysis: sex, age, BMI, ASA physical status classification, Score for Prediction Of Postoperative Respiratory Complications (SPORC),[12] chronic obstructive pulmonary disease (COPD), Charlson comorbidity index (CCI),[13] duration of anaesthesia, opioid,[14 15] volatile anaesthetics,[15 16] fluid administration, blood transfusion, median intraoperative PEEP and tidal volume per body weight,[8] dosage of intermediate-acting non-depolarizing neuromuscular blocking agents (NMBA-ED95),[15–17] emergent/non-emergent surgery, inpatient/ambulatory surgery, Procedural Severity Score (PSS) for morbidity/mortality,[18] and surgical service.

For exploratory and sensitivity analyses, information about FI_{O_2} measured in different time frames during the surgical procedure, such as FI_{O_2} during the first minute after tracheal intubation and during the last minute before extubation, and the peripheral oxygen saturation (Sp_{O_2})/FI_{O_2} assessed 5 min after intubation and median intraoperative Sp_{O_2}, were analysed. In addition, we included the last train-of-four (TOF) count obtained before extubation and the Score for Preoperative Prediction of Obstructive Sleep Apnoea (SPOSA) [Shin et al, BMC Anesthesiology 2017, under revision].

Statistical analysis

Continuous and ordinal variables are described as the median (interquartile range [IQR]/(range)) and categorical variables as number (percentage), if not otherwise specified. Based on their ranking and in order to adjust for non-linear relationship, continuous variables, including median FI_{O_2}, were divided into

quintiles and ordinal variables were divided into clinically relevant categories.[8 15] The associations between FI_{O_2} and outcomes were examined across all five groups of FI_{O_2} using the significance of the Pearson partial correlation coefficient as the *P*-value for trend in an *a priori*-defined logistic regression model including the following predefined covariates: sex, age, BMI, ASA, COPD, CCI, SPORC, duration of anaesthesia, opioids, volatile anaesthetics, fluid administration, blood transfusion, PEEP, tidal volume per predicted body weight, NMBA-ED95, emergency surgery, admission type, PSS morbidity score, and surgical service. When analysing the risk of mortality, PSS morbidity score was replaced by PSS score for mortality.

Sensitivity analyses

Several sensitivity analyses were conducted to evaluate the association between FI_{O_2} and respiratory complications further; these analyses included evaluation of the association between the median FI_{O_2} and the risk of major respiratory complications within subgroups of patients stratified for estimated propensity score for assignment to the highest FI_{O_2} quintile. The propensity score was calculated using a logistic regression model, with treatment status (receiving a high median FI_{O_2}) as the dependent variable.

In order to address the effects of the duration of exposure to high inspiratory concentration of oxygen, we assessed the association between cumulative minutes of receiving a high median FI_{O_2} and the primary outcome (see the Supplementary material).

Exploratory analyses

Additional exploratory analyses were performed.

One could argue that the association between FI_{O_2} and major postoperative respiratory complications might be an epiphenomenon of a pre-existing impairment of oxygenation despite extensive confounder control. In an exploratory analysis, we included the Sp_{O_2}/FI_{O_2} measured 5 min after intubation in the regression model. We also repeated the primary analysis in the subgroup of patients with pre-existing COPD. Furthermore, we added FI_{O_2} variables representing distinct parts of the surgical procedure to our multivariate adjusted analysis. We also controlled for the last TOF count obtained before extubation in an additional exploratory analysis.

In order to evaluate further whether the association between median FI_{O_2} and risk of respiratory complications might be an epiphenomenon of impaired intraoperative oxygenation, we reran the primary analysis including median intraoperative partial pressure of oxygen (Pa_{O_2})/median intraoperative FI_{O_2} in the list of covariates in patients who received an intraoperative arterial blood gas analysis.

Moreover, to investigate the impact of variation by individual providers on respiratory complication rate, we used a mixed-effects logistic regression, with individual provider as a random effect variable.

To evaluate the effect of FI_{O_2} on non-pulmonary organs, the associations between FI_{O_2} and risk of myocardial infarct as well as stroke were evaluated using the same confounder control as for the primary analysis.

In order to control for a possible bias related to missing data, we also conducted multiple imputation by chained equations.[8] Missing variables were imputed using all variables included in the primary analysis except inclusion and exclusion criteria.

The analyses were performed using SPSS version 20 (IBM) and SAS version 9.3. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs), and a two-tailed *P*-value of <0.05 is considered to be statistically significant.

Full details of methods are available in the Supplementary material.

Results

A total of 138 996 surgical cases between 2007 and 2014 were assessed for eligibility (Fig. 1). After exclusion, based on the predefined criteria, the cohort for the primary analysis consisted of 73 922 cases, and was divided into quintiles according to median intraoperative FI_{O_2} (Table 1). The median FI_{O_2} in the group receiving the lowest oxygen concentrations (low FI_{O_2}) was 0.31 [range 0.16–0.34] and in the group receiving the highest oxygen concentrations (high FI_{O_2}) 0.79 [range 0.64–1.00]. All groups were similar in terms of patient characteristics and other ventilatory settings. The composite outcome of major respiratory complications within 7 days of surgery occurred in 3035 (4.1%) cases, of whom 780 (1.1%) had pneumonia, 1979 (2.7%) had pulmonary oedema, 949 (1.3%) had respiratory failure, and 243 (0.3%) were re-intubated (Table 2). Wound dehiscence within 21 days was diagnosed in 311 (0.4%) cases, and 2293 (3.1%) cases were admitted to the ICU within the first 7 postoperative days. Fifty-six (0.1%) and 394 (0.5%) patients died within 7 and 30 days after surgery, respectively.

Primary analysis

Logistic regression revealed a higher risk of major respiratory complications with increasing intraoperative median FI_{O_2} in a dose-dependent fashion (adjusted OR for high FI_{O_2} *vs* low FI_{O_2} 1.99, 95% CI [1.72–2.31], *P* for trend <0.001; Table 3).

Secondary analyses

We found a higher risk of mortality within 7 and 30 days after surgery with higher median FI_{O_2} in a dose-dependent fashion (7-day mortality, adjusted OR for high FI_{O_2} *vs* low FI_{O_2} 2.09, 95% CI [0.81–5.43], *P* for trend=0.03; and 30-day mortality, adjusted OR for high FI_{O_2} *vs* low FI_{O_2} 1.97, 95% CI [1.30–2.99], *P* for trend <0.001; Table 3). There was no significant dose-dependent association between median FI_{O_2} and risk of wound dehiscence or admission to the ICU within 7 days after surgery (Table 3).

Sensitivity analyses

The mean value of the median FI_{O_2} in patients with major respiratory complications was significantly higher than in patients without complications [mean (SD) 0.56 (0.20) and 0.51 (0.17), respectively, $P<0.001$].

The association between median FI_{O_2} and risk of major respiratory complications was also statistically significant when adjusting only for sex, age, ASA status, and duration of anaesthesia (Supplementary material Fig. S1).

The results of the primary analysis remained robust when repeated within subgroups of cases stratified based on their estimated propensity score for receiving high FI_{O_2} (Fig. 2).

The result of the primary analysis was unchanged when repeated in only the 42 875 cases with anaesthesia of longer duration (>120 min), with an adjusted OR = 2.03 (95% CI [1.70–2.43], *P* for trend <0.001) for the composite respiratory outcome, high FI_{O_2} *vs* low FI_{O_2}.

The risk of major respiratory complications did increase with increased exposure to high FI_{O_2} (adjusted OR for median

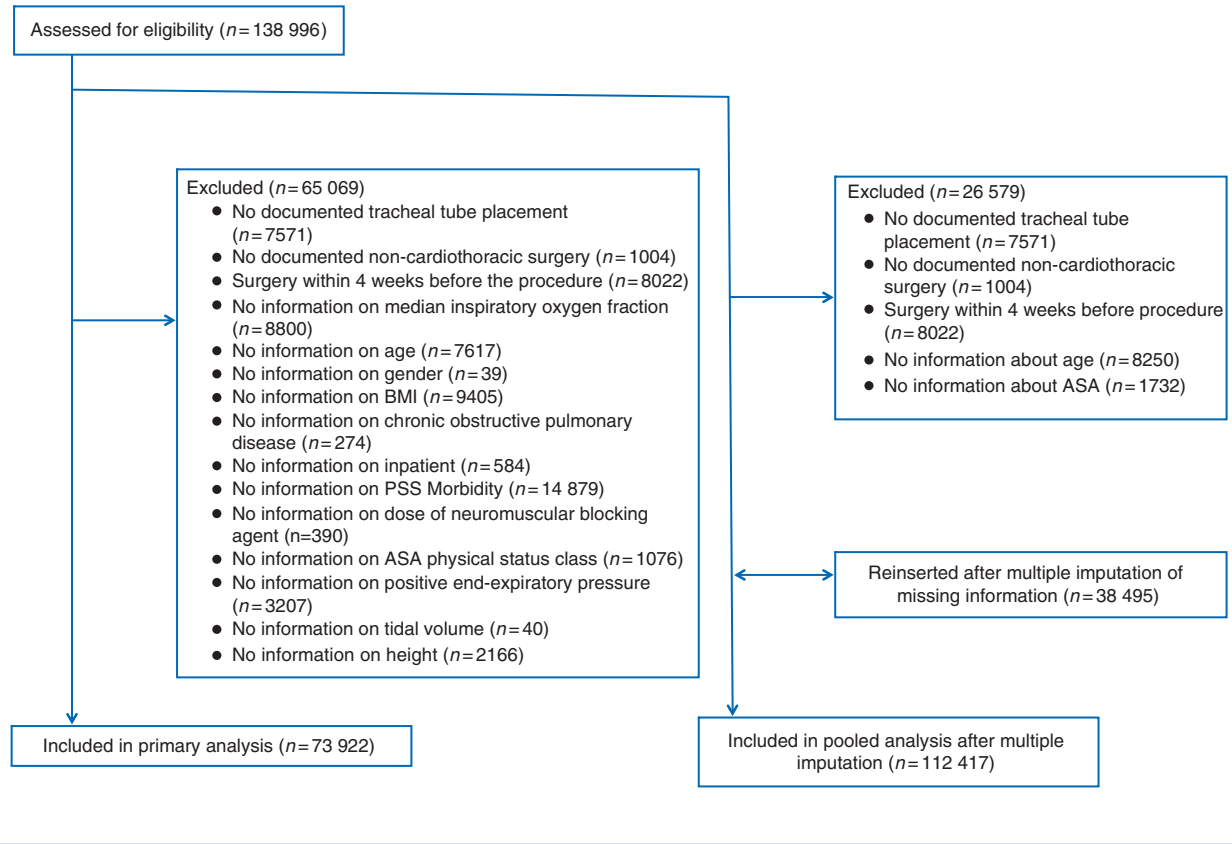

Fig 1 Flow of patients through study.

96 min [IQR 72–147] *vs* 9 min [IQR 7–11] with FI_{O_2} >0.60 2.22, 95% CI [1.93–2.56], *P* for trend <0.001; Supplementary material Fig. S2), suggesting dose dependence.

After excluding patients who died within 7 days of surgery, the median FI_{O_2} was still associated with the risk of a major respiratory complications (adjusted OR high FI_{O_2} *vs* low FI_{O_2} 1.98, 95% CI [1.70–2.30], *P* for trend <0.001). Also, assuming that patients who died within 7 days of surgery had a major respiratory complication did not change the association.

Exploratory analyses

The primary analysis was repeated after adding the Sp_{O_2}/FI_{O_2} ratio obtained 5 min after intubation as a covariate to the model. The results were similar to those found in the primary analysis (adjusted OR of respiratory complications high FI_{O_2} *vs* low FI_{O_2} 2.10, 95% CI [1.79–2.46], *P* for trend <0.001; Supplementary material Fig. S3). The results also remained stable when controlling for high risk of obstructive sleep apnoea (SPOSA >7; adjusted OR of respiratory complications high FI_{O_2} *vs* low FI_{O_2} 1.99, 95% CI [1.72–2.31], *P* for trend <0.001). The incidence of major respiratory complications in patients with COPD was 6.6%, and the effect of intraoperative FI_{O_2} on the risk of a major respiratory complication was similar to that of the total cohort (Supplementary material Fig. S4).

Data on intraoperative Pa_{O_2} were available in 5837 of the included patients. Approximately 61% (*n*=3533) of the patients had a median Pa_{O_2} >20 kPa, and 33% in the group receiving the highest oxygen concentrations had a median Pa_{O_2} >40 kPa. The median Pa_{O_2} values in each FI_{O_2} quintile are shown in Supplementary material Fig. S5. The *P*-value for trend between intraoperative FI_{O_2} and risk of respiratory complications remained significant when adding median Pa_{O_2}/median FI_{O_2} as covariate to the model (adjusted OR for high FI_{O_2} *vs* low FI_{O_2} 1.62, 95% CI [1.20–2.19], *P* for trend <0.001; Supplementary material Fig. S6). Likewise, the results were not affected by adding median Sp_{O_2} as covariate to the model (Supplementary material Fig. S7).

The association of median FI_{O_2} retained its effect size even after accounting for additional FI_{O_2} variables measured during different time intervals of the procedure (Supplementary material Table S2).

The results of the primary analysis also remained robust when repeated across decile groups based on the median FI_{O_2}, and no clear threshold for a safe FI_{O_2} with regard to risk of respiratory complications could be identified (Supplementary material Fig. S8).

The increase in risk of respiratory complications associated with high FI_{O_2} remained significant when including individual anaesthesia provider as a random effect variable to the model in addition to all the other fixed effect variables from the primary analysis (adjusted OR for high *vs* low FI_{O_2} 1.46, 95% CI [1.30–1.64], *P* for trend <0.001).

The association between median FI_{O_2} and postoperative respiratory complications remained stable after including the last

Table 1 Baseline and intraoperative characteristics of patients undergoing general anaesthesia. Data are reported as the median [interquartile range] and (range) or, where indicated, number (percentage). *Morphine was calculated as the total intraoperative morphine equivalent dose. †Other surgery is endoscopy, oral or maxillofacial, plastic, radiology, transplant, vascular, wound, burn, bronchoscopy, or anaesthetic service. CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FI_{O_2}, median intraoperative inspiratory oxygen fraction; MAC, minimal alveolar concentration; PSS morbidity, Procedure Severity Score for morbidity; RBCs, red blood cells; Sp_{O_2}, peripheral oxygen saturation; SPORC, Score for Prediction of Postoperative Respiratory Complications

Parameter	Group 1 (*n*=15 150)	Group 2 (*n*=14 586)	Group 3 (*n*=18 213)	Group 4 (*n*=14 282)	Group 5 (*n*=11 691)
Median FI_{O_2}	0.31 [0.28–0.32] (0.16–0.34)	0.41 [0.37–0.44] (0.35–0.46)	0.52 [0.49–0.54] (0.47–0.55)	0.58 [0.57–0.60] (0.56–0.63)	0.79 [0.70–0.95] (0.64–1.00)
Age (yr)	55 [42–66]	56 [45–67]	55 [43–66]	55 [43–66]	57 [44–67]
Sex (male) [*n* (%)]	7107 (47)	6826 (47)	7762 (43)	4968 (35)	5160 (44)
BMI (kg m^{-2})	27 [24–31]	28 [24–32]	28 [24–33]	27 [23–31]	27 [24–33]
ASA class ≥III [*n* (%)]	3756 (25)	3866 (27)	4973 (27)	4000 (28)	5456 (39)
CCI	1 [0–2]	1 [0–2]	1 [0–2]	1 [0–3]	1 [0–3]
COPD [*n* (%)]	2713 (18)	2906 (20)	3752 (21)	2948 (21)	2919 (25)
SPORC	0 [0–3]	0 [0–3]	0 [0–3]	0 [0–3]	1 [0–3]
Emergency [*n* (%)]	562 (4)	519 (4)	739 (4)	666 (5)	694 (5)
Inpatients [*n* (%)]	12 595 (83)	11 732 (80)	14 698 (81)	10 388 (73)	9098 (63)
Duration of anaesthesia (min)	155 [105–225]	148 [95–220]	153 [98–232]	125 [80–205]	89 [51–163]
Median tidal volume per kilogram predicted bodyweight(ml kg^{-1})	8.2 [7.3–9.2]	8.3 [7.4–9.4]	8.4 [7.5–9.5]	8.6 [7.6–9.7]	8.4 [7.2–9.6]
Median PEEP (cm H_2O)	5 [3–5]	5 [4–5]	5 [4–5]	5 [3–5]	5 [2–5]
Non-depolarizing neuromuscular blockers [*n* (%)]	12 768 (84)	11 949 (81)	15 490 (85)	11 559 (81)	7834 (67)
Age-adjusted MAC	1.0 [0.9–1.1]	0.9 [0.8–1.1]	0.9 [0.7–1.0]	0.8 [0.6–1.0]	0.7 [0.5–0.9]
Total i.v. fluid (ml)	1400 [1000–2250]	1500 [1000–2300]	1500 [1000–2500]	1300 [950–2000]	1000 [700–2000]
Morphine* (mg)	5 [0–10]	5 [1–10]	5 [1–10]	4 [0–8]	3 [0–7]
Units of RBCs	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]
Median Sp_{O_2} (%)	99 [98–99]	99 [98–100]	100 [99–100]	100 [99–100]	100 [99–100]
PSS morbidity	34 [25–49]	33 [25–46]	34 [27–49]	34 [27–54]	43 [28–54]
Surgical procedure [*n* (%)]					
General surgery	2396 (16)	3171 (22)	6236 (34)	5866 (41)	4617 (40)
Orthopaedics	4409 (29)	3870 (27)	3216 (18)	1795 (13)	1039 (9)
Gynaecology	718 (5)	1108 (8)	2027 (11)	1786 (13)	1015 (9)
Neurosurgery	2638 (17)	1536 (11)	1352 (7)	793 (6)	355 (3)
Urology	1054 (7)	1696 (12)	2028 (11)	1063 (7)	745 (6)
Other surgery†	3935 (26)	3205 (22)	3354 (18)	2979 (21)	3920 (34)

Table 2 Incidences of major postoperative complications and other outcomes in patients undergoing general anaesthesia. Data are reported as number (percentage) or, where indicated, median [range]. FI_{O_2}, median intraoperative inspiratory oxygen fraction; ICU, intensive care unit

Parameter	Group 1 (*n*=15 150)	Group 2 (*n*=14 586)	Group 3 (*n*=18 213)	Group 4 (*n*=14 282)	Group 5 (*n*=11 691)	Total cohort (*n*=73 922)
FI_{O_2} (median [range])	0.31 [0.16–0.34]	0.41 [0.35–0.46]	0.52 [0.47–0.55]	0.58 [0.56–0.63]	0.79 [0.64–1.00]	
Major respiratory complications	459 (3.0)	489 (3.4)	716 (3.9)	566 (4.0)	805 (6.9)	3035 (4.1)
Respiratory failure	140 (0.9)	141 (1.0)	243 (1.3)	184 (1.3)	241 (2.1)	949 (1.3)
Re-intubation	38 (0.3)	36 (0.2)	57 (0.3)	50 (0.4)	62 (0.5)	243 (0.3)
Pneumonia	104 (0.7)	131 (0.9)	181 (1.0)	137 (1.0)	227 (1.9)	780 (1.1)
Pulmonary oedema	300 (2.0)	322 (2.2)	444 (2.4)	379 (2.7)	534 (4.6)	1979 (2.7)
Wound dehiscence	71 (0.5)	79 (0.5)	68 (0.4)	46 (0.3)	47 (0.4)	311 (0.4)
ICU admission	514 (3.4)	448 (3.1)	532 (2.9)	425 (3.0)	374 (3.2)	2293 (3.1)
Mortality within 7 days	9 (0.1)	6 (0.1)	7 (0.1)	7 (0.1)	27 (0.2)	56 (0.1)
Mortality within 30 days	41 (0.3)	50 (0.3)	77 (0.4)	76 (0.5)	150 (1.3)	394 (0.5)
Stroke	118 (0.8)	62 (0.4)	70 (0.4)	46 (0.3)	45 (0.4)	341 (0.5)
Myocardial infarction	36 (0.2)	35 (0.2)	34 (0.2)	32 (0.2)	35 (0.3)	172 (0.2)
Positive troponin test	46 (0.3)	50 (0.3)	58 (0.3)	51 (0.4)	79 (0.6)	279 (0.4)

Table 3 Relationship between median intraoperative inspiratory oxygen fraction and major postoperative complications in patients undergoing general anaesthesia. Data are reported as the median (range) or as adjusted odds ratio [95% confidence interval] with Group 1 as the reference group. *P-value of the partial correlation coefficient. FI_{O_2}, median intraoperative inspiratory oxygen fraction; ICU, intensive care unit; PCC, partial correlation coefficient

Parameter	Group 1 (*n*=15 150)	Group 2 (*n*=14 586)	Group 3 (*n*=18 213)	Group 4 (*n*=14 282)	Group 5 (*n*=11 691)	PCC [95% CI]/ P-value*
Median FI_{O_2}	0.31 (0.16–0.34)	0.41 (0.35–0.46)	0.52 (0.47–0.55)	0.58 (0.56–0.63)	0.79 (0.64–1.00)	
Major respiratory complications	Reference	1.14 [0.99–1.31]	1.29 [1.13–1.48]	1.38 [1.19–1.60]	1.99 [1.72–2.31]	0.05 [0.04–0.05]/ P<0.001
Pulmonary oedema	Reference	1.13 [0.96–1.34]	1.18 [1.00–1.39]	1.37 [1.15–1.64]	1.94 [1.62–2.32]	0.04 [0.03–0.05]/ P<0.001
Pneumonia	Reference	1.32 [1.02–1.73]	1.36 [1.05–1.77]	1.26 [0.95–1.67]	1.72 [1.30–2.28]	0.02 [0.01–0.03]/ P<0.001
Respiratory failure	Reference	1.07 [0.84–1.37]	1.39 [1.10–1.76]	1.53 [1.10–1.96]	2.03 [1.58–2.62]	0.03 [0.02–0.03]/ P<0.001
Re-intubation	Reference	1.10 [0.69–1.75]	1.40 [0.90–2.19]	1.73 [1.08–2.78]	2.41 [1.49–3.90]	0.01 [0.00–0.02]/ P=0.002
Wound dehiscence	Reference	1.21 [0.87–1.68]	0.91 [0.64–1.30]	0.93 [0.62–1.38]	1.12 [0.74–1.71]	−0.002 [−0.01 to 0.01]/ P=0.57
ICU admission	Reference	1.22 [1.06–1.41]	1.29 [1.12–1.49]	1.58 [1.35–1.85]	1.64 [1.38–1.95]	−0.003 [−0.01 to 0.00]/ P=0.48
Mortality within 7 days	Reference	0.68 [0.24–1.97]	0.61 [0.21–1.74]	0.63 [0.21–1.86]	2.09 [0.81–5.43]	0.008 [0.00–0.02]/ P=0.03
Mortality within 30 days	Reference	1.31 [0.86–2.00]	1.42 [0.95–2.13]	1.38 [0.90–2.10]	1.97 [1.30–2.99]	0.018 [0.01–0.03]/ P<0.001
Stroke	Reference	0.76 [0.55–1.04]	0.84 [0.60–1.16]	0.83 [0.56–1.22]	0.90 [0.59–1.37]	−0.015 [−0.02 to − 0.01]/ P<0.001
Myocardial infarction	Reference	1.01 [0.68–1.77]	0.94 [0.57–1.57]	1.22 [0.71–2.08]	1.24 [0.69–2.20]	0.002 [−0.01 to 0.01]/ P=0.55
Positive troponin test	Reference	1.17 [0.77–1.77]	1.02 [0.67–1.55]	1.14 [0.73–1.78]	1.44 [0.92–2.26]	0.007 [0.00–0.01]/ P=0.05

documented TOF count as an additional covariate to the model (adjusted OR for respiratory complications high *vs* low FI_{O_2} 1.88 CI [1.56–2.26], *P* for trend <0.001).

A pooled analysis after multiple imputation revealed that the effect of FI_{O_2} on respiratory complication rate was similar to the primary analysis (adjusted OR high FI_{O_2} *vs* low FI_{O_2} 1.70, 95% CI [1.51–1.92]; see Fig. 1 and Supplementary material Fig. S9).

Acute myocardial infarction was diagnosed in 172 (0.2%) patients, and 279 (0.4%) patients had a positive troponin test (Table 2). The risk of cardiac injury was not significantly associated with high oxygen in a dose-dependent fashion (Table 3). Finally, 341 (0.5%) patients had a stroke after surgery, but the risk was not associated with FI_{O_2} (Tables 2 and 3).

Discussion

In an analysis of administrative data on file from a large cohort of surgical patients undergoing intraoperative mechanical ventilation for non-cardiothoracic surgery, we found that high median intraoperative FI_{O_2} was significantly associated with a composite outcome of major postoperative respiratory complications. High FI_{O_2} was also associated with increased risk of 30-day mortality. Our analyses controlled for a predefined set of confounding variables and were robust across a series of sensitivity analyses including markers of surgical complexity, co-morbidities, pulmonary function, intraoperative oxygenation, and duration of exposure.

The analyses in this study were made on basis of a large data set that reflects routine clinical practice. Data were retrieved from accurate and prospective recording of intraoperative management and postoperative complications. Before initiating data analysis, we finalized the protocol, including definitions of risk factors and outcomes, and registered the study at ClinicalTrials.gov. The observational design allowed us to collect a large number of events, which provided the analysis with sufficient power to detect differences in relatively infrequent complications. A specific strength relates to the availability of arterial blood gas analyses, which allowed us to discriminate between supranormal arterial oxygen tension (hyperoxygenation) and adequate treatment of hypoxic respiratory failure. However, some important limitations must be mentioned. First, we adjusted for a large number of different risk factors and performed several sensitivity analyses, including propensity scoring, in order to reduce the risk of confounding. Optimally, our results should be confirmed in a future randomized controlled trial. However, because of the low event rate of clinically meaningful respiratory complications in patients undergoing surgery, and multiple risk factors (co-morbidities and procedure-related factors), a randomized controlled trial would need to be conducted in several thousand patients.

Residual and unmeasurable confounding cannot be eliminated. For example, we are not able to know why the anaesthesia provider decided to use the oxygen fraction recorded. Our oxygenation data clearly exclude the possibility that the

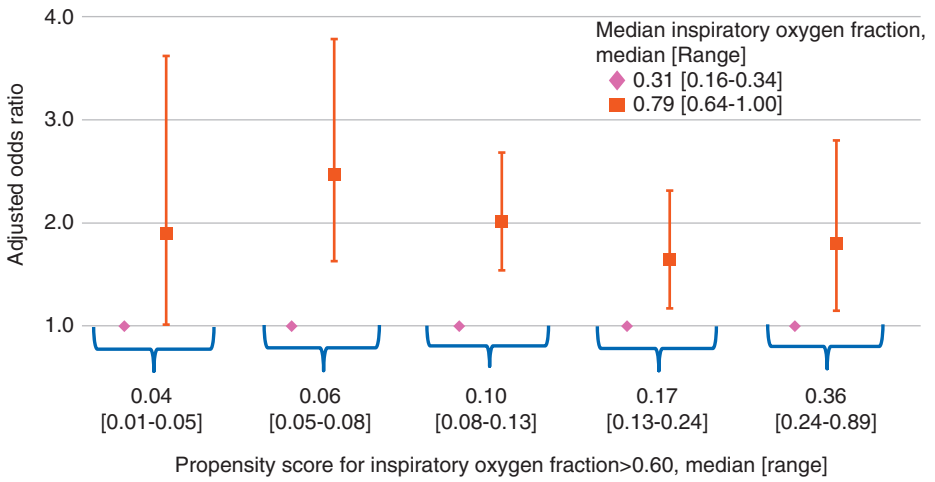

Fig 2 Multivariable logistic regression analysis examining the association between median intraoperative inspiratory oxygen fraction FI_{O_2} and risk of major postoperative respiratory complications in each subgroup of patients based on their estimated propensity score for receiving high FI_{O_2}. Patients are divided into five groups based on their propensity score for being in the quintile with the highest median FI_{O_2} values (FI_{O_2}>0.63). In each subgroup, the odds of developing a respiratory complication in the highest quintile of FI_{O_2} is compared with the odds in the lowest quintile of FI_{O_2} presented as odds ratio [95% confidence interval]. The logistic regression analysis is adjusted for sex, age, BMI, ASA classification, score for prediction of respiratory complications, Charlson comorbidity index, pre-existing chronic obstructive pulmonary disease, duration of anaesthesia, opioids, volatile anaesthetics, fluid administration, units of packed red blood cells, PEEP, tidal volume per predicted body weight, non-depolarizing neuromuscular blocking agents, emergency surgery, ambulatory surgery, Procedure Severity Score for morbidity, and surgical type.

association between FI_{O_2} and respiratory complications is attributable to baseline hypoxia. Rather, many anaesthetists apparently hyperoxygenate their patients, and a likely explanation for our finding is that the value of FI_{O_2} was selected based on personal preference of the anaesthesia provider. Our institution has no standard operating procedure for intraoperative FI_{O_2} value. One could argue that the anaesthesia provider is a confounding variable of the association between FI_{O_2} and respiratory complications. Therefore, we accounted for clustering of patients by provider. We found that the association between the FI_{O_2} and the risk of respiratory complications remained unchanged from the primary analysis. Data on postoperative management that could have influenced the occurrence of respiratory outcomes were not available. However, it is unlikely that those are directly related to intraoperative FI_{O_2} values and their association with respiratory complication rates.

The median FI_{O_2} throughout the procedure might not adequately represent the burden of a high oxygen concentration. Therefore, in additional exploratory analyses we included the FI_{O_2} measured during distinct parts of the surgical procedure to evaluate whether the observed effect of median FI_{O_2} in occurrence of respiratory complications was affected. We observed that the FI_{O_2} measured immediately after intubation and before extubation, or the range of FI_{O_2} used during the procedure, did not explain any variance of postoperative respiratory complications. In addition, adding these variables to the primary regression model did not change the association between median FI_{O_2} and respiratory complications (see Supplementary material Table S2). We did not include information on FI_{O_2} values before intubation because the accuracy of this variable will depend on multiple factors.

Residual neuromuscular block is associated with respiratory complications. In our study, we controlled for neuromuscular blocking agent dose and neostigmine dose and for the last TOF count documented before extubation as a potential indicator of postoperative residual neuromuscular block. Furthermore, we extended the analysis and included additional confounders (epidural analgesia, driving pressure, duration of hypotension, and ventilation mode) in an exploratory analysis. This did not change the primary results (Supplementary material, Results section). The partial correlation coefficients between FI_{O_2} and respiratory complications were small, but we did not expect to see a close correlation between FI_{O_2} and respiratory complication rate because only a fraction of the occurrence of postoperative respiratory complications can be explained by oxygen toxicity.

There is substantial controversy among clinicians on the appropriate FI_{O_2} settings to be used during intraoperative mechanical ventilation. This is because proposed advantageous effects of hyperoxia, such as reduction of surgical wound infection[5–7] and increased time for desaturation, could be offset by deleterious effects, such as the increase in atelectasis,[19] oxidative stress to the lungs,[20] and exacerbation of cancer effects.[21] Our results show that anaesthetists provide values of FI_{O_2} that result in intraoperative oxygen saturations above the average observed in normal humans at rest. Yet, despite this evidence and those potentially major effects, only few studies have investigated the association between perioperative oxygen concentration and postoperative respiratory complications.[22–24] We found a significant association between intraoperative FI_{O_2} and major postoperative complications, which is in contrast to previously conducted, smaller studies,[22–23] one larger controlled trial in 1386 patients,[24] and two systematic reviews,[7 11] which failed to show an effect of FI_{O_2} despite the observation of specific physiological effects in both high and low FI_{O_2} groups.

Several mechanisms might contribute to an oxygen-related lung injury. High alveolar oxygen concentration leads to faster collapse of small lung units as a result of absorption of oxygen-rich gas into the blood from closed off alveoli or alveoli with very low ventilation/perfusion ratios.[25] The resulting atelectasis leads to intrapulmonary shunt and impaired oxygenation.[25] The amount of atelectasis depends on the oxygen concentration and the duration of high oxygen administration.[25 26] Atelectasis is likely to be a focus of infection and may contribute to additional pulmonary complications.[26] Severe atelectasis may even be a contributing early mechanism of ventilator-associated lung injury, as animal studies have shown that non-lobar atelectasis also leads to inflammation and alveolar injury in the non-atelectatic areas.[27 28]

Another plausible mechanism behind the oxygen-related lung injury is hyperoxia-induced oxidative stress.[20] Hyperoxia and inflammation accelerate the formation of reactive oxygen species and cellular damage.[20] The innate antioxidant system normally protects against excessive radicals but becomes overwhelmed in the event of prolonged hyperoxia.[20] The oxygen-related injury may be of particular relevance to patients with underlying lung pathology.[29]

The oxygen-related injury also applies to non-pulmonary organs. High-flow oxygen to patients with myocardial infarction and normoxia leads to elevated creatinine kinase and larger infarct size,[30] probably by increased coronary vascular resistance, reduced coronary blood flow and cardiac index, and generation of reactive oxygen species.[31 32] Hyperoxia may thus be hypothesized to increase the risk of myocardial infarction after surgery.[33] Finally, in a study of patients admitted to the ICU after resuscitation from cardiac arrest, arterial hyperoxia was independently associated with increased in-hospital mortality.[34] However, we found no significant association between high FI_{O_2} and cardiac or cerebral morbidity. This may be a result of lack of power to detect these outcomes in our study.

We did find a significant dose–response association between administrated oxygen and 30-day mortality. Increased long-term mortality has also been reported in patients randomized to a high FI_{O_2} during abdominal surgery.[21] It is possible that the increased risk of mortality associated with increased FI_{O_2} in our study is related to an impairment of cardiac function. Moreover, it is possible that our finding of increased occurrence of pulmonary oedema with hyperoxia may be explained in part by cardiogenic pulmonary oedema secondary to myocardial injury.[35] A significant association between hyperoxia and increased morbidity was also found in a recently published trial, where patients admitted to the ICU were randomly allocated to standard or conservative oxygen therapy.[36] We did not find any significant association between wound dehiscence and FI_{O_2}. However, the incidence was significantly lower than reported in prospective trials.[24]

Hyperoxia increases the tolerance to apnoea and hypopnea and is frequently used by anaesthetists to prevent intraoperative hypoxia in critical situations, such as before induction and during emergence from anaesthesia.[19] In a similar way, in critically ill patients in the operating room or the ICU, Pa_{O_2} may be kept well above the normal range in order to prevent hypoxia and because this is considered as to be without associated risks. In our subgroup of patients who had an arterial blood gas analysis done, >60% of the patients had a median Pa_{O_2} >20 kPa. The patients in this subgroup received a high FI_{O_2} with a median of 0.53 [range 0.22–0.99], had a median Pa_{O_2}/FI_{O_2} of 57 kPa [range 20–340 kPa], and the association between FI_{O_2} and respiratory complications was unchanged (see Supplementary material). This observation, together with that of a dose–response relationship between median FI_{O_2} and respiratory complications, supports the hypothesis that increases in FI_{O_2} in our studied patients were not merely targeting the maintenance of a specific value of normal blood oxygenation. Instead, they produced supraphysiological conditions, which could have resulted in the observed complications through the mechanisms discussed above. The contribution of supraphysiological oxygenation could have been either as an independent factor or as a factor synergistic with that of lung injury from other causes (the 'two-hit' hypothesis) in producing further deterioration.

Clinical and scientific implications

Our data suggest that oxygen therapy should be titrated to normal values unless there is clear evidence of benefits, because supraphysiological oxygen values are found in many patients. In this analysis of administrative data on file, our results showed a rather consistent pattern of a two-fold increase in the risk of respiratory complications for an absolute increase in FI_{O_2} from the lowest quintile of 0.31 to the highest quintile of 0.80. The same pattern was observed for 30-day mortality. We hope that our data will inform the design of prospective studies on the effects of FI_{O_2} in the perioperative period. Of note, direct clinical conclusions that change the clinical treatment of our patients may only be drawn with caution. In fact, oxygenation data obtained during surgery were available in only a fraction of our patients. Based on our data, the role of perioperative oxygenation should be investigated further in large observational studies and optimally in a well-designed and conducted randomized controlled trial. However, because of relatively low incidences of these outcomes among the general surgical population, we recommend that the focus should be on a population of increased susceptibility to postoperative complications or patients admitted to the ICU, who are intubated and mechanically ventilated in the absence of hypoxic respiratory failure.

In this analysis of administrative data on file, a high intraoperative FI_{O_2} was associated in a dose-dependent manner with the postoperative occurrence of major respiratory complication within 7 days, and with 30-day mortality independently of predefined risk factors. This finding was robust in a series of sensitivity analyses including intraoperative oxygenation.

Authors' contributions

Study design: A.K.S.-R., C.S.M., M.R.G., J.L.W., T.K., L.S.R., M.E.
Acquisition of data: A.K.S.-R., F.T.S., K.S.L., S.D.G., M.I.N., M.E.
Data analysis: A.K.S.-R., F.T.S., M.F.V.M., T.K., L.S.R., M.E.
Data interpretation: A.K.S.-R., C.S.M., M.F.V.M., M.R.G., J.L.W., K.S.L., T.K., L.S.R., M.E.
Drafting the manuscript: A.K.S.-R., L.S.R., M.E.
Revision of the work critically for important intellectual content: all authors
Study guarantor, who takes responsibility for the integrity of the work as a whole: M.E.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

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