

## 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 pre-defined 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

Editorial decision: March 31, 2017; Accepted: April 18, 2017

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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,<sup>1-3</sup> and lead to a longer hospital stay, higher costs, and increased mortality.<sup>4</sup>

A high intraoperative inspiratory oxygen fraction ( $FI_{O_2}$ ) may reduce the incidence of surgical site infection,<sup>5-7</sup> but the adverse effects remain to be investigated fully. Preoxygenation with 100% oxygen results in atelectasis within a few minutes of induction of anaesthesia.<sup>8-9</sup> Few studies have investigated the effect of intraoperative  $FI_{O_2}$  on clinically significant respiratory complications.<sup>10</sup> 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.<sup>11</sup> 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.<sup>4</sup> 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 post-operative 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.<sup>4,12</sup>

**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),<sup>12</sup> chronic obstructive pulmonary disease (COPD), Charlson comorbidity index (CCI),<sup>13</sup> duration of anaesthesia, opioid,<sup>14-15</sup> volatile anaesthetics,<sup>15-16</sup> fluid administration, blood transfusion, median intraoperative PEEP and tidal volume per body weight,<sup>8</sup> dosage of intermediate-acting non-depolarizing neuromuscular blocking agents (NMBA-ED95),<sup>15-17</sup> emergent/non-emergent surgery, inpatient/ambulatory surgery, Procedural Severity Score (PSS) for morbidity/mortality,<sup>18</sup> 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

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