Oxygen administration during surgery and postoperative organ injury: observational cohort study

David R McIlroy,[1] Matthew S Shotwell,[2] Marcos G Lopez,[1] Michelle T Vaughn,[3] Joanna S Olsen,[4] Cassandra Hennessy,[2] Jonathan P Wanderer,[1,5] Matthew S Semler,[6] Todd W Rice,[6] Sachin Kheterpal,[3] Frederic T Billings IV,[1,6] on behalf of the Multicenter Perioperative Outcomes Group

[1]Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA
[2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA
[3]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA
[4]Department of Anesthesiology, Oregon Health and Science University, Portland, OR, USA
[5]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA
[6]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Correspondence to: F T Billings IV
frederic.t.billings@vumc.org
(ORCID 0000-0001-7135-7785)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;379:e070941
http://dx.doi.org/10.1136/bmj-2022-070941

Accepted: 12 October 2022

ABSTRACT

OBJECTIVE

To examine whether supraphysiological oxygen administration during surgery is associated with lower or higher postoperative kidney, heart, and lung injury.

DESIGN

Observational cohort study.

SETTING

42 medical centers across the United States participating in the Multicenter Perioperative Outcomes Group data registry.

PARTICIPANTS

Adult patients undergoing surgical procedures ≥120 minutes' duration with general anesthesia and endotracheal intubation who were admitted to hospital after surgery between January 2016 and November 2018.

INTERVENTION

Supraphysiological oxygen administration, defined as the area under the curve of the fraction of inspired oxygen above air (21%) during minutes when the hemoglobin oxygen saturation was greater than 92%.

MAIN OUTCOMES

Primary endpoints were acute kidney injury defined using Kidney Disease Improving Global Outcomes criteria, myocardial injury defined as serum troponin >0.04 ng/mL within 72 hours of surgery, and lung injury defined using international classification of diseases hospital discharge diagnosis codes.

RESULTS

The cohort comprised 350 647 patients with median age 59 years (interquartile range 46-69 years), 180 546 women (51.5%), and median duration of surgery 205 minutes (interquartile range 158-279 minutes). Acute kidney injury was diagnosed in 19 207 of 297 554 patients (6.5%), myocardial injury in 8972 of 320 527 (2.8%), and lung injury in 13 789 of 312 161 (4.4%). The median fraction of inspired oxygen was 54.0% (interquartile range 47.5%-60.0%), and the area under the curve of supraphysiological inspired oxygen was 7951% min (5870-11 107% min), equivalent to an 80% fraction of inspired oxygen throughout a 135 minute procedure, for example. After accounting for baseline covariates and other potential confounding variables, increased oxygen exposure was associated with a higher risk of acute kidney injury, myocardial injury, and lung injury. Patients at the 75th centile for the area under the curve of the fraction of inspired oxygen had 26% greater odds of acute kidney injury (95% confidence interval 22% to 30%), 12% greater odds of myocardial injury (7% to 17%), and 14% greater odds of lung injury (12% to 16%) compared with patients at the 25th centile. Sensitivity analyses evaluating alternative definitions of the exposure, restricting the cohort, and conducting an instrumental variable analysis confirmed these observations.

CONCLUSIONS

Increased supraphysiological oxygen administration during surgery was associated with a higher incidence of kidney, myocardial, and lung injury. Residual confounding of these associations cannot be excluded.

TRIAL REGISTRATION

Open Science Framework osf.io/cfd2m

WHAT IS ALREADY KNOWN ON THIS TOPIC:

Most patients receiving general anesthesia are administered oxygen in excess of that required to maintain adequate arterial oxygen saturation

Harmful effects of supraphysiological oxygen administration have been established at a molecular level, but the clinical relevance of these effects during surgery remain uncertain

Existing perioperative trials have been insufficiently powered to detect small but potentially important effects of supraphysiological oxygen administration on organ injury

WHAT THIS STUDY ADDS

Increased supraphysiological oxygen administration was associated with a small but clinically significant greater risk of acute kidney, myocardial, and lung injury in a large, diverse cohort of adults undergoing a surgical procedure of at least 120 minutes' duration

An adequately powered randomized trial is required to guide best practice for intraoperative oxygen administration

Introduction

The consequences of hypoxemia during surgery and the presumed safety of hyperoxemia have made the administration of supplemental oxygen a foundational component of anesthesia. In addition to an improved safety margin in the event of airway compromise, a high fraction of inspired oxygen (FIO_2) has been thought to offer several other advantages to patients during surgery. These advantages include a reduction in ischemic tissue injury by increasing perioperative arterial and tissue oxygen tension, lower risk of surgical site infection, and improved healing of anastomotic sites.[1-3] Potentially harmful effects of supplemental oxygen administration, however, are also well described and include generation of reactive

oxygen species that modify cellular lipids, DNA, and proteins, vasoconstriction in myocardial and cerebral tissue beds, and suppression of intracellular signaling pathways that confer cellular protection during ischemia and reperfusion.[4-11]

It has been estimated that >80% of patients undergoing general anesthesia are exposed to oxygen administration in excess of that required to maintain normal blood oxygen levels.[12] Supraphysiological oxygenation has been suggested as contributing to pulmonary, myocardial, and renal injury,[13 14] but clinical evidence is limited, and a best practice strategy for selection of intraoperative FIO_2 remains unknown. This multicenter cohort study tested the hypothesis that administration of oxygen that is estimated to be in excess of that required to maintain hemoglobin saturation during surgery is associated with increased kidney injury, myocardial injury, and lung injury.

Methods

We conducted a retrospective observational cohort study to evaluate the association between oxygen administration during surgery and postoperative organ injury in adult patients undergoing general anesthesia. We used data from the Multicenter Perioperative Outcomes Group (MPOG) to sample a large, diverse, multicenter cohort with granular data on intraoperative oxygenation and postoperative outcomes. MPOG developed the multicenter electronic health record registry in 2009 to enable outcomes research and quality improvement.[15] University affiliated and privately owned community hospitals transmit data monthly to a central database. Standardized data validation efforts at each center before data submission include automated data quality checks and manual clinician case audits. These locally extracted perioperative data are then mapped to MPOG developed standardized, interoperable concepts and submitted to the central repository where they undergo additional validation procedures before integration into the Coordinating Centre database.

The protocol for the study was reviewed and approved by the MPOG perioperative clinical research committee before accessing the data. The methods and statistical analysis plan were then published and registered on Open Science Framework on 23 August 2020 (osf.io/cfd2m, see online supplement) before performing the analysis. The Vanderbilt University Medical Center Institutional Review Board approved this study with waiver of informed consent (IRB No 181872).

Study cohort

We included non-pregnant patients aged ≥18 years undergoing inpatient surgical procedures of ≥120 minutes' duration with general anesthesia and endotracheal intubation from 1 January 2016 to 22 November 2018. Patients who were intubated before surgery or underwent airway surgery including bronchoscopy, jet ventilation, or one lung ventilation were excluded. Patients were also excluded when the intraoperative period was greater than five minutes without an FIO_2 or a hemoglobin oxygen saturation (SpO_2) recorded, or <60 FIO_2 or SpO_2 measurements for the entire procedure. Patients in whom the SpO_2 decreased to <90% for more than three consecutive minutes were excluded to limit confounding by indication. Repeat surgical procedures for a given patient within 90 days of a previously included procedure were also excluded.

Intraoperative oxygenation

For each patient we examined minute-to-minute FIO_2 and SpO_2 data. To estimate the amount of oxygen that might be in excess of that required to maintain hemoglobin saturation, supraphysiological oxygen administration was defined as the area under the curve of FIO_2 above 21% during minutes when the corresponding SpO_2 was >92% (AUC_{FIO2}). We excluded minutes when the SpO_2 was ≤92% because current guidelines recommend targeting an SpO_2 >92% and increased FIO_2 during these minutes might be required to achieve appropriate blood oxygen levels and therefore not considered in excess.[16 17] For minutes when the FIO_2 or SpO_2 was missing for up to five minutes, we imputed a value as the mean of the preceding value and the subsequent documented value. We chose AUC_{FIO2} to quantify oxygen exposure because the intensity and the duration of supraphysiological oxygen administration impact oxygen dose.

Outcomes

Primary outcomes were acute kidney injury (AKI), myocardial injury, and lung injury. AKI was defined according to creatinine based Kidney Disease Improving Global Outcomes criteria, specifically a 0.3 mg/dL or greater increase within 48 hours or a 50% or greater increase from baseline within seven days of surgery.[18] Patients with preoperative renal failure (estimated glomerular filtration rate <15 mL/min/1.73 m^2) or no measured creatinine within 60 days preoperatively were excluded from analysis of AKI. Myocardial injury was defined as troponin I >0.04 ng/mL within 72 hours of surgery.[19] Patients with biochemical evidence of preoperative myocardial injury (plasma troponin greater than upper limit of normal within 42 days before surgery) or those undergoing cardiac surgery or surgery for pacemaker or defibrillator placement, cardiac ablation, or other cardiac catheterization procedures that could increase plasma troponin independent of myocardial injury were excluded from analysis of myocardial injury. Serum creatinine and troponin were measured in high risk patient populations routinely based on medical center and provider practices, or according to clinical indication. In the primary analysis, patients without postoperative measurement of serum creatinine or troponin were assumed not to have suffered the outcome of interest (AKI or myocardial injury) based on the assumption that the laboratory data necessary for diagnosis were not obtained because there was no clinical indication for measurement. Lung injury

was defined using international classification of diseases, ninth revision or tenth revision (ICD-9 or ICD-10) hospital discharge diagnosis codes, as endorsed by international consensus guidelines, Agency for Healthcare Research and Quality Patient Safety Indicator reports for postoperative respiratory failure, and previously published clinical registry postoperative lung injury studies (supplementary table 1).[20-24]

Secondary outcomes were 30 day mortality, hospital length of stay, and stroke (added post hoc and defined using ICD codes at hospital discharge). Appendicitis or pancreatitis, defined using ICD codes at hospital discharge (supplementary table 2), were analyzed as a negative control in a post hoc analysis because higher oxygen exposure is unlikely to be related to their development. Centers that did not report the data source (eg, ICD codes or laboratory testing) for a specific outcome were excluded from analysis of that outcome.

Patient and procedure characteristics

We collected patient demographics, medical history ICD diagnostic codes,[25] and preoperative laboratory values for serum creatinine, hemoglobin, lactate, and troponin. Operative data included procedural categorization using anesthesia and surgery Current Procedural Terminology procedure codes (supplementary table 3), duration of surgery, volume of crystalloid administration, red blood cell transfusion, intraoperative hypotension (defined as mean arterial pressure <60 mm Hg), median positive end expiratory pressure applied, and exposure to inhaled nitrous oxide.

Statistical analysis

The associations between oxygen administration (AUC_{FIO2}) and the primary endpoints were evaluated using multivariable logistic regression. Mortality and length of stay were analyzed using logistic and linear regression, respectively. Each model was adjusted for a prespecified set of baseline covariates and potential confounders including age, sex, race, body mass index, American Society of Anesthesiologists (ASA) physical status, Agency for Healthcare Research and Quality (AHRQ) Elixhauser comorbidity index,[26] chronic pulmonary disease, emergency surgery, nitrous oxide exposure (defined as the area under the curve of the fraction of inspired nitrous oxide throughout surgery), median tidal volume, median intraoperative positive end expiratory pressure, volumes of intraoperative intravenous crystalloid and packed red blood cells, and intraoperative hypotension. We also adjusted for the presence of preoperative serum creatinine, hemoglobin, troponin, and lactate data, and their values when present because the decision to order each of these laboratory tests, independent of the result, might be associated with intraoperative oxygen administration and outcomes. Missing data for covariates were addressed with multiple imputation and the chained equations method with predictive mean matching to generate five datasets with complete covariate information.[27] Statistical analyses were implemented separately for each completed dataset with results pooled using Rubin's rules.[28] The effects of quantitative variables were modeled using a flexible splines method with quantitative and graphical regression diagnostics examined to evaluate the suitability of constructed models and any nonlinear effects. Odds ratios comparing the 75th with the 25th centile of AUC_{FIO2}, with 95% confidence intervals, are presented together with P values representing the overall statistical significance across the entire range of AUC_{FIO2} for each outcome of interest. Bonferroni correction was used for the three primary endpoints (P value threshold of 0.0167 was considered for statistical significance) to preserve the overall type 1 error rate of 5% across the family of primary endpoints.

To further explore the association between oxygen administration and organ injury and to test the robustness of the primary analyses, we conducted several prespecified sensitivity analyses redefining the exposure variable (AUC_{FIO2}), restricting the cohort, and conducting an instrumental variable analysis. We redefined the oxygen exposure variable excluding minutes for which the SpO_2 was <90% and <96%, two alternate SpO_2 thresholds that providers might use as a trigger to increase the level of supplemental oxygen administration and limit hypoxia. We also redefined the AUC_{FIO2} exposure variable using an FIO_2 threshold >40% (instead of >21%) to focus on the effects of increased oxygen administration occurring with higher FIO_2 values, a more conservative definition of excess oxygen administration. In additional analyses we restricted the cohort in several ways. We included only patients who maintained $SpO_2 \geq 96\%$ throughout all of anesthesia maintenance to further explore for evidence of residual confounding by indication and to exclude patients who might have alveolar hyperoxia but not arterial hyperoxemia. Anesthesia maintenance was defined to exclude the first and last 15 minutes of the procedure, reflecting anesthesia induction and emergence when transient desaturation below 96% is common but unlikely to affect maintenance oxygenation. Separately, we excluded patients who died within the diagnostic window for each organ injury, providing they had not developed that organ injury before death (519 patients for AKI, 261 for myocardial injury, and none for lung injury); we excluded patients for whom the outcome data of interest were missing to explore for a potential effect of detection bias; and we excluded cardiac surgery in a post hoc analysis.

Next, an instrumental variable sensitivity analysis was undertaken using the two stage predictor substitution method.[29] We set the typical FIO_2 administered by each anesthesiologist as an instrumental variable because some anesthesiologists might typically provide more or less oxygen to patients than other anesthesiologists, independent of patient or procedure factors. Additional post hoc analyses adjusted for duration of surgery, excluded

intraoperative covariates because AUC_{FIO2} could impact intraoperative factors (see causal pathway diagram, supplementary fig 1), and repeated the primary analysis using a stabilized inverse probability of treatment weighting approach to estimate the average treatment effect. Propensity scores were calculated using a linear regression method adjusting for each of the baseline covariates and potential confounders listed above.[30] The stabilized weights were then used to assess the unadjusted association between supraphysiological oxygen exposure and each of the primary outcomes, using weighted logistic regression. All statistical analyses were implemented using R version 4.2.1, with add on packages mice for multiple imputation, rms for regression methods, and WeightIt for stabilized inverse probability of treatment weighting methods.[31]

Subgroup analyses explored the consistency of effect across age, sex, race, diabetes, preoperative hemoglobin concentration, type of procedure, and duration of surgery categories. A multiple degree of freedom test was used to assess interaction.

Patient and public involvement

The rationale and design of the study were discussed with surgical patients participating in a concurrent trial of oxygen administration being led by a subgroup of the investigators. This input informed the design of the current study, including the selection of outcome measures. Given the deidentified and retrospective nature of the dataset and the design, no patients were involved in implementing the study, interpreting the results, or reporting the results.

Results

In total, 535 085 patients met eligibility criteria. After application of exclusion criteria, the study cohort comprised 350 647 patients from 42 centers and 3839 anesthesiologists (fig 1). Median age of the cohort was 59 years (interquartile range 46-69 years), 180 546 (51.5%) were women, 245 096 (69.9%) were white, 37 533 (10.7%) were black, 139 727 (40.1%) had ASA physical status I or II, and 177 796 (51.0%) had ASA physical status III. Diabetes was present in 45 614 of 350 647 patients (13.0%), hypertension in 148 370 of 350 647 (42.3%), chronic kidney disease in 29 645 of 350 647 (8.5%), and end stage renal disease in 6091 of 350 647 patients (1.7%). Surgery was categorized as emergent in 24 602 of 350 647 patients (7.1%). The median preoperative serum hemoglobin and creatinine concentrations in the cohort were 13.2 g/dL (interquartile range 11.8-14.3 g/dL) and 0.86 mg/dL (0.71-1.03 mg/dL), respectively. The median duration of surgery was 205 minutes (interquartile range 158-279 minutes), and at least one episode of hypotension was noted in 148 388 of 350 647 patients (47.4%; table 1).

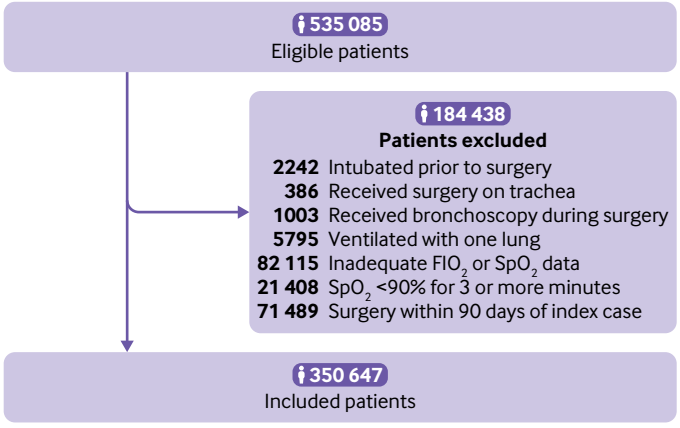

Fig 1 | Numbers of eligible, excluded, and included patients. FIO_2=fraction of inspired oxygen; SpO_2=arterial hemoglobin oxygen saturation

Postoperative serum creatinine was measured in 203 686 of 350 647 patients (58.1%) and troponin in 34 851 of 350 647 (9.9%). AKI was identified in 19 207 of 297 554 patients (6.5%), myocardial injury in 8972 of 320 527 (2.8%), lung injury in 13 789 of 312 161 (4.4%), stroke in 3298 of 312 161 (1.1%), and appendicitis or pancreatitis in 3211 of 312 161 (1.0%). The median hospital length of stay was 3.0 days (interquartile range 1.0-5.0 days). There were 30 day mortality follow-up data for 309 929 of 350 647 patients (88.4%), and 2468 of 309 929 patients (0.8%) died within 30 days of surgery. AKI, myocardial injury, and lung injury were each associated with increased hospital length of stay and increased 30 day mortality (supplementary table 4).

Intraoperative oxygen administration and organ injury

The median number of FIO_2 measurements for each procedure was 220 (interquartile range 164-313), and the median FIO_2 was 54.0% (47.5%-60.0%). The median SpO_2 was 100% (98%-100%), and in 47 268 of 350 647 patients (13.5% of the cohort) in whom an arterial blood gas was measured, PaO_2 was 208 mm Hg (160-260 mm Hg). The median AUC_{FIO2} was 7951% min (5870-11 107% min). This value is equivalent, for example, to an 80% FIO_2 throughout a 135 minute procedure or a 60% FIO_2 throughout a 204 minute procedure, without hemoglobin desaturation. There was one or more SpO_2 values <96% in 119 549 procedures (34.1%).

Supraphysiological oxygen administration was associated with the development of postoperative AKI, independent of all factors included as covariates. Patients at the 75th centile of AUC_{FIO2} had 26% greater odds of AKI than patients at the 25th centile of AUC_{FIO2} (odds ratio 1.26, 95% confidence interval 1.22 to 1.30; fig 2, upper panel; P<0.001). Increased supraphysiological oxygen administration was associated with AKI in all prespecified and post hoc sensitivity analyses (table 2), including when the anesthesiologist's practice pattern for oxygen administration was used as an instrumental variable (1.08, 1.01 to 1.15).

Supraphysiological oxygen administration was also associated with myocardial injury. Patients at the 75th centile of AUC_{FIO2} had 12% greater odds of myocardial injury than patients at the 25th centile (odds ratio 1.12,

Table 1 | Cohort characteristics, separated into thirds of increased oxygen administration (AUC_{FIO2})

Characteristic	Unmeasured or missing (%)	AUC_{FIO2}* 2672-6520% min (n=116 883)	AUC_{FIO2} 6520-9830% min (n=116 882)	AUC_{FIO2} 9830-27 100% min (n=116 882)
Age (years)	0.0	57 (44-69)	59 (47-69)	60 (49-69)
Female sex	0.1	61 654 (52.8)	61 288 (52.5)	57 604 (49.3)
Race	15.4			
Black	—	12 178 (12.4)	12 806 (12.8)	12 549 (12.7)
White	—	81 016 (82.8)	82 188 (82.3)	81 892 (82.8)
Other†	—	4631 (4.7)	4842 (4.8)	4513 (4.6)
Hispanic ethnicity	0.0	935 (0.8)	1285 (1.1)	1402 (1.2)
Body mass index	6.3	28.0 (23.2-32.7)	28.3 (24.5-33.3)	28.6 (24.8-33.5)
ASA physical status classification	0.6			
ASA class ≤2	—	53 190 (45.8)	47 288 (40.7)	39 249 (33.8)
ASA class 3	—	55 754 (48.0)	60 394 (51.9)	61 648 (53.1)
ASA class ≥4	—	7131 (6.1)	8614 (7.4)	15 199 (13.1)
Medical history	0.0			
AHRQ Elixhauser comorbidity index score	—	0 (0-7)	0 (0-9)	0 (0-11)
Congestive heart failure	—	5299 (4.5)	6209 (5.3)	8852 (7.6)
Arrhythmia	—	14 149 (12.1)	16 617 (14.2)	23 671 (20.3)
Valvular disease	—	4595 (3.9)	5194 (4.4)	9101 (7.8)
Pulmonary circulation disorder	—	2145 (1.8)	2534 (2.2)	3911 (3.3)
Peripheral vascular disease	—	6546 (5.6)	7644 (6.5)	10 724 (9.2)
Paralysis	—	1934 (1.7)	2144 (1.8)	2394 (2.0)
Other neurologic disorders	—	5955 (5.1)	6170 (5.3)	6991 (6.0)
Chronic pulmonary disease	—	13 941 (11.9)	15 252 (13.0)	16 666 (14.3)
Hypertension	—	44 940 (38.4)	49 241 (42.1)	54 189 (46.4)
Diabetes	—	13 490 (11.5)	15 243 (13.0)	16 881 (14.4)
Hypothyroidism	—	10 976 (9.4)	11 592 (9.9)	12 263 (10.5)
Chronic kidney disease	—	8459 (7.2)	9800 (8.4)	11 386 (9.7)
End stage renal disease‡	—	1690 (1.4)	2228 (1.9)	2173 (1.9)
Liver disease	—	4377 (3.7)	5027 (4.3)	6077 (5.2)
Peptic ulcer disease	—	632 (0.5)	685 (0.6)	789 (0.7)
AIDS/HIV	—	203 (0.2)	198 (0.2)	216 (0.2)
Lymphoma	—	904 (0.8)	907 (0.8)	859 (0.7)
Metastatic cancer	—	7036 (6.0)	10 657 (9.1)	14 374 (12.3)
Solid tumor without metastases	—	17 540 (15.0)	25 869 (22.1)	31 317 (26.8)
Rheumatoid arthritis or collagen vascular disease	—	3124 (2.7)	3112 (2.7)	3509 (2.6)
Coagulopathy	—	4095 (3.5)	4582 (3.9)	8000 (6.8)
Obesity	—	20 015 (17.1)	21 521 (18.4)	22 995 (19.7)
Weight loss	—	4429 (3.8)	4950 (4.2)	7314 (6.3)
Fluid and electrolyte disorder	—	12 322 (10.5)	14 414 (12.3)	21 759 (18.6)
Blood loss anemia	—	1130 (1.0)	1152 (1.0)	1385 (1.2)
Deficiency anemia	—	2599 (2.2)	2744 (2.3)	2794 (2.4)
Alcohol abuse	—	481 (0.4)	524 (0.4)	853 (0.7)
Drug abuse	—	2930 (2.5)	2508 (2.1)	2734 (2.3)
Psychoses	—	637 (0.5)	556 (0.5)	621 (0.5)
Depression	—	12 394 (10.6)	12 850 (11.0)	13 964 (11.9)
Surgery characteristics	—			
Surgery duration (min)	0.0	153 (135-181)	204 (171-243)	304 (243-390)
Emergency surgery	0.6	10 226 (8.8)	7778 (6.7)	6598 (5.7)
Surgery procedure category	17.1			
Head	—	9456 (10.0)	9270 (10.0)	11 396 (11.7)
Neck	—	6445 (6.8)	5429 (5.6)	5000 (5.1)
Spine and spinal cord	—	12 721 (13.4)	14 191 (14.6)	14 436 (14.8)
Open heart	—	969 (1.0)	1375 (1.4)	6455 (6.6)
Intrathoracic	—	992 (1.0)	1706 (1.7)	3115 (3.2)
Extrathoracic	—	2437 (2.6)	2733 (2.8)	3773 (3.9)
Upper abdomen	—	114 997 (15.8)	16 128 (16.5)	16 758 (17.1)
Lower abdomen	—	11 069 (11.7)	11 279 (11.6)	9692 (9.9)
Gynecological or pelvic	—	2599 (2.7)	2790 (2.9)	2680 (2.7)
Male reproductive or urological	—	8174 (8.6)	12 987 (13.3)	11 964 (12.2)
Extremity	—	20-749 (21.8)	15 506 (15.9)	9762 (10.0)
Other (includes burn, obstetric, radiologic)	—	4392 (4.6)	3643 (3.7)	2731 (2.8)
Crystalloid volume administered (mL)	0.0	1500 (1000-2000)	1800 (1200-2500)	2500 (1700-3750)
Received pRBC transfusion	0.0	2663 (2.3)	4340 (3.7)	12 465 (10.7)
Mean arterial pressure <60 mm Hg	10.7	52 087 (45.8)	48 920 (47.8)	47 381 (48.9)
Baseline (preoperative) laboratory data	—			

(*Continued*)

Table 1 | Continued

Characteristic	Unmeasured or missing (%)	AUC_{FIO2}* 2672-6520% min (n=116 883)	AUC_{FIO2} 6520-9830% min (n=116 882)	AUC_{FIO2} 9830-27 100% min (n=116 882)
Hemoglobin (g/dL)	33.2	13.1 (11.6- 14.3)	13.2 (11.8-14.3)	13.2 (11.8-14.4)
Creatinine (mg/dL)	37.1	0.85 (0.71-1.01)	0.86 (0.71-1.03)	0.87 (0.72-1.05)
Lactate (mmol/L)	91.4	1.3 (0.9-1.9)	1.3 (0.9-1.8)	1.8 (0.9-1.8)
Troponin (ng/mL)	97.7	0.03 (0.01-0.10)	0.03 (0.01-0.09)	0.05 (0.02-0.19)
Intraoperative mechanical ventilation	—			
Tidal volume (mL)	4.0	481 (431-540)	488 (436-546)	495 (441-555)
PEEP (cm H_2O)	0.0	5 (4-5)	5 (4-5)	5 (4-5)
Received nitrous oxide	0.0	35 659 (30.5)	28 893 (24.7)	26 243 (22.5)
$FINO_2$, area under the curve§ (% min)	0.0	0 (0-6)	0 (0-0)	0 (0-0)
Intraoperative oxygenation	—			
FIO_2 median (%)	0.0	48 (43-54)	55 (50-60)	58 (54-78)
FIO_2 mean (%)	0.0	54 (48-59)	60 (55-67)	64 (58-78)
FIO_2, area under the curve* (% min)	0.0	5217 (4412-5870)	7951 (7200-8814)	12 978 (11 107-16 335)
SpO_2 mean (%)	0.0	99 (98-100)	99 (98-100)	99 (98-100)
PaO_2, mean (mm Hg)	87.1	173 (128-218)	194 (149-239)	222 (175-277)

Categorical variables are reported as N (%) and continuous variables as median (interquartile range).
ASA=American Society of Anesthesiologists; $FINO_2$=fraction of inspired nitrous oxide; FIO_2=fraction of inspired oxygen; PaO_2=arterial partial pressure of oxygen; pRBC=packed red blood cells; PEEP=positive end expiratory pressure; SpO_2=peripheral hemoglobin oxygen saturation.
*Area under the curve of the fraction of inspired oxygen above 21% (air) during minutes when SpO_2 was >92%.
†American Indian, Asian, Middle Eastern, multiracial.
‡Stage 5 chronic kidney disease (current renal replacement therapy or estimated glomerular filtration rate <15 mL/min/1.73 m^2).
§Area under curve of fraction of inspired nitrous oxide during surgery.

95% confidence interval 1.07 to 1.17; fig 2, middle panel; P<0.001). Increased supraphysiological oxygen administration was associated with myocardial injury in all prespecified and post hoc sensitivity analyses (table 2), although excluding procedures that did not measure troponin postoperatively attenuated the magnitude of the association between the 75th and 25th AUC_{FIO2} centiles (1.05, 1.00 to 1.11), but not the overall statistical significance (P<0.001). The association remained robust when the anesthesiologist's practice pattern for supraphysiological oxygen administration was used as an instrumental variable (1.29, 1.19 to 1.39).

Supraphysiological oxygen administration was associated with lung injury. Patients at the 75th centile of AUC_{FIO2} had 14% greater odds of lung injury than patients at the 25th centile (odds ratio 1.14, 1.12 to 1.16; fig 2, lower panel; P<0.001). Increased supraphysiological oxygen administration was associated with lung injury in all prespecified and post hoc sensitivity analyses (table 2), with the exception of an inverse association between increased supraphysiological oxygen administration and lung injury when using the anesthesiologist for each procedure as an instrumental variable (0.93, 0.88 to 0.98).

Secondary outcomes

Increased supraphysiological oxygen administration was associated with stroke (P<0.001) and 30 day mortality (P=0.03), independent of all factors included as covariates. Patients at the 75th centile of AUC_{FIO2} had 9% greater odds of stroke than patients at the 25th centile (odds ratio 1.09, 95% confidence interval 1.05 to 1.13) and 6% greater odds of 30 day mortality (1.06, 0.98 to 1.15). Increased supraphysiological oxygen administration was associated with decreased hospital length of stay (P<0.001). Patients at the 75th centile of AUC_{FIO2} had a 0.20 day shorter length of stay compared with patients at the 25th centile (−0.28 to −0.11), an effect unchanged after excluding patients who died before discharge. Supplementary table 5 reports results from sensitivity analyses for secondary outcomes.

Subgroup and other exploratory analyses

No consistent evidence was found that the association between increased supraphysiological oxygen administration and organ injuries differed according to age, sex, race, diabetes, baseline hemoglobin, or surgical procedure. Associations between increased oxygen administration and organ injury were greatest in procedures of shorter duration (fig 3). Despite additionally adjusting for duration of surgery, the association between supraphysiological oxygen administration and organ injury persisted (supplementary fig 2). In an analysis of a negative control, increased oxygen exposure was not associated with an increased composite endpoint of appendicitis or pancreatitis. Patients at the 75th centile of AUC_{FIO2} had 22% lesser odds of appendicitis or pancreatitis than patients at the 25th centile (odds ratio 0.78, 95% confidence interval 0.74 to 0.82).

Discussion

Principal findings

In a large, heterogeneous, and contemporary cohort of patients undergoing a wide range of surgical procedures requiring general anesthesia, the incidence of postoperative AKI, myocardial injury, and lung injury was each higher in patients exposed to increased supraphysiological oxygen administration during surgery.

Comparison with other studies

Although supplemental oxygen is routinely administered to almost all patients during surgery, the

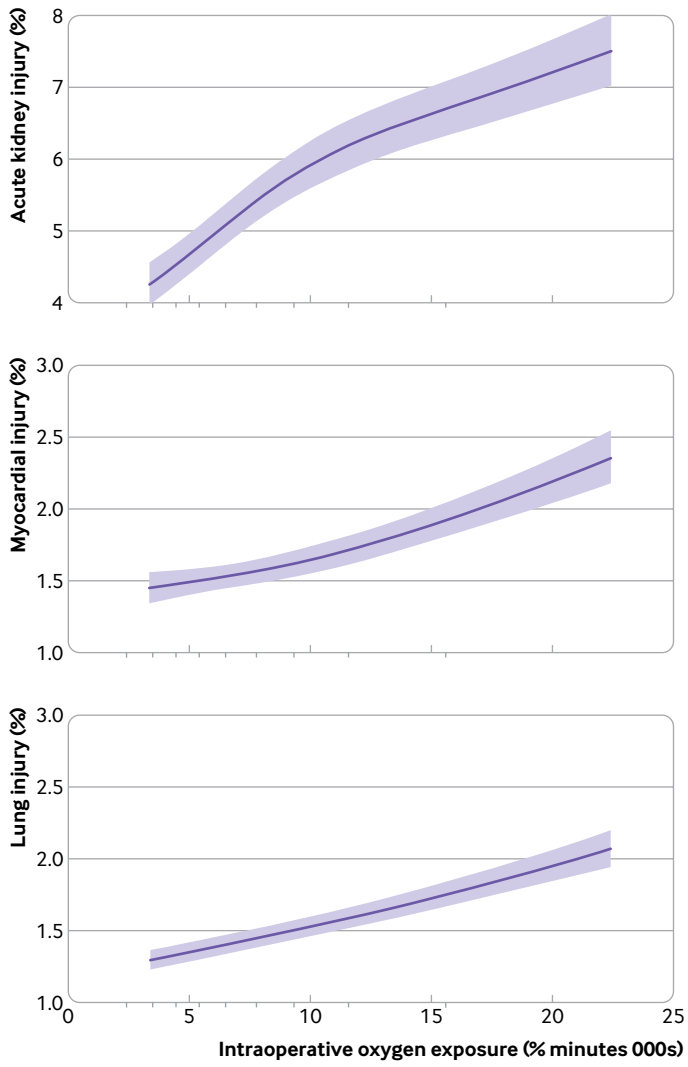

Fig 2 | Association between intraoperative oxygen exposure and acute kidney injury, myocardial injury, and lung injury, adjusted for factors included as covariates (age, sex, race, body mass index, American Society of Anesthesiologists status, Agency for Healthcare Research and Quality Elixhauser comorbidity index, chronic pulmonary disease, emergency surgery, preoperative serum creatinine, hemoglobin, troponin and lactate concentrations, nitrous oxide exposure, median tidal volume, median intraoperative positive end expiratory pressure, volumes of intraoperative intravenous crystalloid and packed red blood cells administrations, and intraoperative hypotension). Tick marks on x axes identify each decile of patients

best practice for intraoperative oxygen administration remains unknown. Few definitive and generalizable clinical trials powered to detect reasonable effect sizes have tested the effect of avoiding excess oxygen intraoperatively. In the cardiac surgery population, McGuinness and colleagues randomized 298 patients and found no effect on AKI from targeting intraoperative oxygen administration to achieve a PaO_2 of 75-90 mm Hg compared with usual oxygenation strategies; however, oxygen administration was not controlled before and after cardiopulmonary bypass, and hyperoxemia occurred in both treatment groups.[32] Shaefi and colleagues randomly assigned 100 patients undergoing cardiac surgery to an FIO_2 of 35% before and after cardiopulmonary bypass and a PaO_2 of 100-150 mm Hg during cardiopulmonary bypass or to an FIO_2 of 100% throughout the entire intraoperative period. They found no effect of intraoperative oxygen exposure on postoperative cognitive function or on renal failure, stroke, pneumonia, atrial fibrillation, or death, although the study was underpowered for most of these events.[33] More recently, Holse and colleagues randomly assigned 600 patients undergoing major non-cardiac surgery to an FIO_2 of 30% or 80% during surgery and for the first two hours after surgery. They reported no difference in myocardial injury defined as area under the curve for high sensitivity troponin T within three days of surgery.[34] In a post hoc analysis of an alternating intervention trial that tested the effect of 80% versus 30% FIO_2 on surgical site infection in patients undergoing colorectal surgery, Ruetzler and colleagues found no effect of oxygen treatment on AKI or a composite cardiovascular outcome.[35] The trial was not designed with the primary goal of normoxia in the 30% FIO_2 study arm,[36] and a median FIO_2 of almost 40% was observed in this group. In other moderate sized perioperative trials in patients undergoing abdominal surgery, FIO_2 did not affect surgical site infection, but a signal for increased late mortality was noted in patients assigned to hyperoxia.[37 38]

In a large registry based study of 73 922 non-cardiothoracic surgery patients, a dose dependent association was observed between median intraoperative FIO_2 and postoperative respiratory complications.[39] Additionally, in an observational cohort of 2926 patients undergoing cardiac surgery, the AUC of PaO_2 above 300 mm Hg was independently associated with AKI.[40] In a post hoc analysis of the VISION observational cohort study, each 0.10 increase in median FIO_2 was independently associated with a 17% increase in the incidence of myocardial injury.[41] Measures to estimate excess oxygen exposure, however, and strategies to address potential confounding by indication were limited in these observational studies. In aggregate, there remains equipoise on the impact of hyperoxia on postoperative organ injury, and the optimal approach to perioperative oxygen administration remains uncertain.

Strengths and limitations of study

The current study used continuous minute-to-minute FIO_2 and SpO_2 data to precisely measure oxygen administration and arterial oxygen saturation throughout each procedure. Specifically excluding periods of hemoglobin oxygen desaturation from the quantification of supraphysiological oxygen administration was one of several strategies that aimed to isolate excess oxygen exposure and limit confounding by indication. However, a portion of the calculated supraphysiological FIO_2 might have been necessary to achieve a corresponding SpO_2 >92% and therefore not be in excess. Precise quantification of excess oxygenation is impossible without continuous PaO_2 monitoring. The sensitivity analyses that substituted an FIO_2 threshold of 40% rather than 21% for the estimation of excess oxygen exposure provided a more stringent measure of excess oxygen

Table 2 | Associations between intraoperative supraphysiological oxygen administration and patient outcomes

Analysis	Acute kidney injury	Estimate (95% CI)	P value	Myocardial injury	Estimate (95% CI)	P value	Lung injury	Estimate (95% CI)	P value
Primary analysis	19 207/297 554 (6.5)	1.26 (1.22 to 1.30)	<0.001	8972/320 527 (2.8)	1.12 (1.07 to 1.17)	<0.001	13 789/312 161 (4.4)	1.14 (1.12 to 1.16)	<0.001
Sensitivity analyses—redefined exposure									
Excluding minutes when SpO_2<96%	19 207/297 554(6.5)	1.21 (1.18 to 1.25)	<0.001	8.972/320 527 (2.8)	1.09 (1.04 to 1.13)	<0.001	13 789/312 161 (4.4)	1.11 (1.09 to 1.13)	<0.001
Excluding minutes when SpO_2<90%	19 207/297 554 (6.5)	1.26 (1.22 to 1.30)	<0.001	8972/320 527 (2.8)	1.12 (1.07 to 1.17)	<0.001	13 789/312 161 (4.4)	1.14 (1.12 to 1.16)	<0.001
Redefining excess FIO_2 as AUC>0.4	19 207/297 554 (6.5)	1.13 (1.10 to 1.17)	<0.001	8972/320 527 (2.8)	1.08 (1.04 to 1.13)	<0.001	13 789/312 161 (4.4)	1.12 (1.11 to 1.14)	<0.001
Sensitivity analyses—cohort restriction									
Excluding patients with any SpO_2<96%	11 535/197 213 (5.8)	1.24 (1.19 to 1.30)	<0.001	5612/214642 (2.6)	1.15 (1.09 to 1.21)	<0.001	7274/204 626 (3.6)	1.10 (1.08 to 1.13)	<0.001
Excluding patients with early mortality	19 207/297 046 (6.5)	1.26 (1.22 to 1.30)	<0.001	8972/320 266 (2.8)	1.12 (1.08 to 1.17)	<0.001	13 789/307 540 (4.5)	1.14 (1.12 to 1.16)	<0.001
Excluding patients with missing outcome data	19 207/186 178 (10.3)	1.21 (1.17 to 1.25)	<0.001	8972/28 987 (31.0)	1.05 (1.00 to 1.11)	<0.001	13 789/312 161 (4.4)	1.14 (1.12 to 1.16)	<0.001
Excluding patients undergoing cardiac surgery	18 173/289 398 (6.3)	1.25 (1.21 to 1.30)	<0.001	8972/320 527 (2.8)	1.12 (1.07 to 1.17)	<0.001	12 423/302 347 (4.1)	1.14 (1.12 to 1.16)	<0.001
Sensitivity analysis—instrumental variable	19 207/297 554 (6.5)	1.08 (1.01 to 1.15)	<0.001	8972/320 527 (2.8)	1.29 (1.19 to 1.39)	<0.001	13 789/312 161 (4.4)	0.93 (0.88 to 0.98)	0.004
Sensitivity analysis—adjusted for surgery duration	19 207/297 531 (6.5)	1.14 (1.10 to 1.18)	<0.001	8972/320 501 (2.8)	1.17 (1.11 to 1.22)	<0.001	13 785/312 138 (4.4)	1.14 (1.11 to 1.17)	<0.001
Sensitivity analysis—no intraoperative covariates	19 207/297 554 (6.5)	1.39 (1.35 to 1.43)	<0.001	8972/320 527 (2.8)	1.08 (1.04 to 1.13)	<0.001	13 789/312 161 (4.4)	1.20 (1.18 to 1.22)	<0.001
Sensitivity analysis—sIPTW	19 207/297 554 (6.5)	1.42 (1.38 to 1.46)	<0.001	8972/320 527 (2.8)	1.19 (1.15 to 1.24)	<0.001	13 789/312 161 (4.4)	1.20 (1.18 to 1.21)	<0.001

Estimates (95% confidence intervals) represent odds of acute kidney injury, myocardial injury, and lung injury between 75th and 25th centiles of intraoperative AUC_{FIO2}; and P values represent statistical significance across entire range of AUC_{FIO2}. All analyses were adjusted for age, sex, race, body mass index, ASA status, AHRQ Elixhauser comorbidity index, chronic pulmonary disease, emergency surgery, preoperative serum creatinine, hemoglobin, troponin and lactate concentrations, nitrous oxide exposure, median tidal volume, median intraoperative positive end expiratory pressure, volumes of intraoperative intravenous crystalloid and packed red blood cells administrations, and intraoperative hypotension.
Stabilized weights in sIPTW analysis ranged from 0 to 6.5, with median 1.0 (interquartile range 0.87-1.14).
AHRQ=Agency for Healthcare Research and Quality; ASA=American Society of Anesthesiologists; AUC=area under curve; AUC_{FIO2}=area under the curve of FIO_2 above 21% during minutes when corresponding oxygen saturation was >92%; FIO_2=fraction of inspired oxygen; sIPTW=stabilized inverse probability treatment weighting; SpO_2=arterial hemoglobin oxygen saturation.

exposure and yielded similar results to the primary analyses.

There are several limitations to the current analyses. The use of diagnosis codes to identify lung injury, while endorsed by international consensus guidelines for standardized endpoints in perioperative medicine,[20 21] might have reduced precision for identification of this endpoint. The decision to categorize patients who did not receive postoperative creatinine or troponin measurement as not having developed AKI or myocardial injury, respectively, while conservative, introduced some degree of detection bias. A prespecified sensitivity analysis excluding patients who did not receive postoperative creatinine or troponin measurement from the AKI and myocardial injury analyses yielded similar results to the primary analysis.

The observational nature of the study and titratable nature of the intervention mean that an effect of unmeasured residual confounding or of simultaneity cannot be excluded.[42] Imbalance between unmeasured and unknown variables, including drug use, diet, and center specific factors not accounted for by model covariates, might have impacted the association between supraphysiological oxygen administration and organ injury.

The metric of supraphysiological oxygen exposure (AUC_{FIO2}) was influenced by duration of surgery. This reflected our hypothesis that the intensity and duration of exposure impact any oxygen toxicity, but assumed that intensity and duration were biologically interchangeable. In sensitivity analyses conducted to account for the effect of duration on oxygen exposure, the associations between supraphysiological oxygen administration and organ specific injury persisted.

Adding the anesthesiologist as an instrumental variable, another technique to limit confounding from patient or procedure level factors, produced a mixed effect on the association between oxygen exposure and each of the organ injuries evaluated, including an inverse association with lung injury. The instrumental variable analysis is a potentially useful strategy but assumes that the instrumental variable correlates with the exposure of interest (in this case oxygen administration) and has no effect on the outcome, except for that mediated through the exposure.[43] This latter assumption might not be true given many anesthesiologists specialize in the care of specific patient populations undergoing particular types of surgery that inherently have more or less risk of organ injury independent of oxygen exposure.

The large sample size, drawn from geographically diverse populations, ensured precision and generalizability of the results. The effect size for the association between excess oxygen exposure and adverse outcomes was small, highlighting the possibility that such an effect might be missed in small trials. For example, a trial of 12 000 patients would be required to achieve 80% power to detect a 15% relative risk reduction in a perioperative event with baseline incidence of 10%, such as AKI. With more than 200

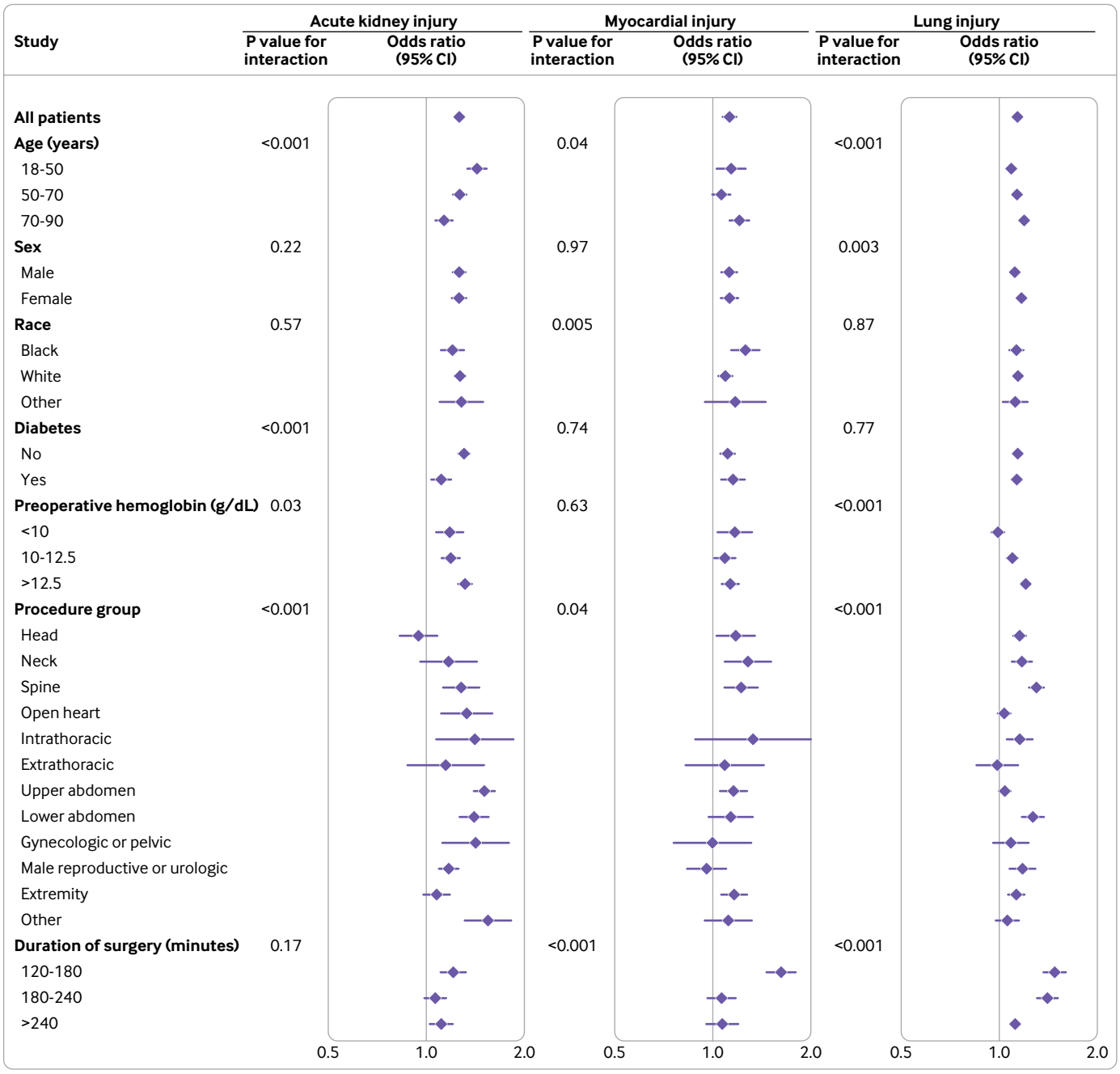

Fig 3 | Associations between increased intraoperative oxygen exposure and acute kidney injury, myocardial injury, and lung injury in all patients and in subgroups, adjusted for impact of factors included as covariates (age, sex, race, body mass index, American Society of Anesthesiologists status, Agency for Healthcare Research and Quality Elixhauser comorbidity index, chronic pulmonary disease, emergency surgery, preoperative serum creatinine, hemoglobin, troponin and lactate concentrations, nitrous oxide exposure, median tidal volume, median intraoperative positive end expiratory pressure, volumes of intraoperative intravenous crystalloid and packed red blood cells administrations, and intraoperative hypotension). Point estimates and bars represent odds ratios and 95% confidence intervals for organ injury associated with 75th centile compared with 25th centile of AUC_{FIO2}. P values represent statistical significance for each factor to modify association between oxygen exposure and organ injury, assessed with multiple degree of freedom test. AUC_{FIO2}=area under the curve of FIO_2 (fraction of inspired oxygen) above 21% during minutes when the corresponding oxygen saturation was >92%

million major surgical procedures performed globally each year,[44] even a small effect of excess oxygen would impact a large number of patients.

Conclusions and policy implications

In conclusion, increased intraoperative oxygen exposure was associated with adverse renal, cardiac, and pulmonary outcomes in a large, diverse cohort of surgical patients. A large clinical trial to detect small but clinically significant effects on organ injury and patient centered outcomes is needed to guide oxygen administration during surgery.

We acknowledge all patients whose data contributed to this work, all participating Multicenter Perioperative Outcomes Group (MPOG)

centers for reporting data to MPOG central, Michelle Romanowski from Department of Anesthesiology, University of Michigan (Ann Arbor, MI, USA) for data query development, and the MPOG perioperative clinical research committee for reviewing, vetting, and approving the study design and statistical analysis plan. The authors acknowledge MPOG collaborators, including Germaine Cuff, Robert E Freundlich, Andrea Kurz, Bhiken I Naik, Michael R Mathis, and Robert B Schonberger for contributions to protocol development and final manuscript review.

Contributors: DRM, MSSh, MTV, JSO, JPW, MSSe, TWR, SK, and FTB conceived of and designed the study. MTV, JPW, SK, and FTB collected the data. MSSh, MTV, CH, and FTB analyzed the data. DRM, MSSh, MGL, MTV, CH, MSSe, SK, and FTB drafted the manuscript. DRM, MSSh, MGL, MTV, JSO, CH, JPW, MSSe, TWR, SK, and FTB revised the manuscript. FTB guarantees the manuscript and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: MGL received funding from United States National Institutes of Health (NIH) grant K23GM129662. MWSe received funding from NIH grant K23HL143053. FTB received funding from NIH grants R01GM112871 and R35GM145375 and an Association of University Anesthesiologists' IMPACT award specific to this study. Funding was also provided by departmental and institutional resources at each contributing medical center. Funding to support underlying electronic health record data collection into the Multicenter Perioperative Outcomes Group registry was provided by Blue Cross Blue Shield of Michigan/Blue Care Network as part of the Blue Cross Blue Shield of Michigan/Blue Care Network Value Partnerships program. Although Blue Cross Blue Shield of Michigan/Blue Care Network and Multicenter Perioperative Outcomes Group work collaboratively, the opinions, beliefs and viewpoints expressed by the authors do not necessarily reflect the opinions, beliefs, and viewpoints of Blue Cross Blue Shield of Michigan/Blue Care Network or any of its employees. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from United States NIH, Association of University Anesthesiologists, departmental and institutional resources at each contributing medical center, Blue Cross Blue Shield of Michigan/Blue Care Network for the submitted work; DRM is chair of the data safety and monitoring board for the HOT-ROX trial (ACTRN12619000115134), an investigator initiated, multicenter international, randomized controlled trial of restrictive FIO_2, liberal FIO_2, and usual FIO_2 in surgical patients; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Vanderbilt University Medical Center Institutional Review Board approved this study (IRB No 181872).

Data sharing: Cohort data may be obtained upon reasonable request. Analytical code used for the present analysis can be made available with approval from the senior author of the manuscript. Individual patient data will not be made publicly available.

The lead author (FTB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: Results of the study will be disseminated through a patient panel convened by a subgroup of the investigators leading a clinical trial of anesthesia technique in a similar surgical patient population and also through social media, to enhance clinician and public awareness.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Greif R, Akça O, Horn EP, Kurz A, Sessler DI, Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000;342:161-7. doi:10.1056/NEJM200001203420303
2 García-Botello SA, García-Granero E, Lillo R, López-Mozos F, Millán M, Lledó S. Randomized clinical trial to evaluate the effects of perioperative supplemental oxygen administration on the colorectal anastomosis. *Br J Surg* 2006;93:698-706. doi:10.1002/bjs.5370
3 Allegranzi B, Zayed B, Bischoff P, et al, WHO Guidelines Development Group. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;16:e288-303. doi:10.1016/S1473-3099(16)30402-9
4 Wenk M, Van Aken H, Zarbock A. The new World Health Organization recommendations on perioperative administration of oxygen to prevent surgical site infections: a dangerous reductionist approach?*Anesth Analg* 2017;125:682-7. doi:10.1213/ANE.0000000000002256
5 Helmerhorst HJF, Schultz MJ, van der Voort PHJ, de Jonge E, van Westerloo DJ. Bench-to-bedside review: the effects of hyperoxia during critical illness. *Crit Care* 2015;19:284. doi:10.1186/s13054-015-0996-4
6 Zhilyaev SY, Moskvin AN, Platonova TF, Gutsaeva DR, Churilina IV, Demchenko IT. Hyperoxic vasoconstriction in the brain is mediated by inactivation of nitric oxide by superoxide anions. *Neurosci Behav Physiol* 2003;33:783-7. doi:10.1023/A:1025145331149
7 Mouren S, Souktani R, Beaussier M, et al. Mechanisms of coronary vasoconstriction induced by high arterial oxygen tension. *Am J Physiol* 1997;272:H67-75.
8 Eltzschig HK, Bratton DL, Colgan SP. Targeting hypoxia signalling for the treatment of ischaemic and inflammatory diseases. *Nat Rev Drug Discov* 2014;13:852-69. doi:10.1038/nrd4422
9 Billings FT4th, Pretorius M, Schildcrout JS, et al. Obesity and oxidative stress predict AKI after cardiac surgery. *J Am Soc Nephrol* 2012;23:1221-8. doi:10.1681/ASN.2011090940
10 Lopez MG, Pandharipande P, Morse J, et al. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. *Free Radic Biol Med* 2017;103:192-8. doi:10.1016/j.freeradbiomed.2016.12.039
11 Lopez MG, Hughes CG, DeMatteo A, et al. Intraoperative oxidative damage and delirium after cardiac surgery. *Anesthesiology* 2020;132:551-61. doi:10.1097/ALN.0000000000003016
12 Suzuki S, Mihara Y, Hikasa Y, et al, Okayama Research Investigation Organizing Network (ORION) investigators. Current ventilator and oxygen management during general anesthesia: a multicenter, cross-sectional observational study. *Anesthesiology* 2018;129:67-76. doi:10.1097/ALN.0000000000002181
13 Schwarte LA, Schober P, Loer SA. Benefits and harms of increased inspiratory oxygen concentrations. *Curr Opin Anaesthesiol* 2019;32:783-91. doi:10.1097/ACO.0000000000000791
14 Torbati D, Tan GH, Smith S, et al. Multiple-organ effect of normobaric hyperoxia in neonatal rats. *J Crit Care* 2006;21:85-93, discussion 93-4. doi:10.1016/j.jcrc.2005.09.057
15 Colquhoun DA, Shanks AM, Kapeles SR, et al. Considerations for integration of perioperative electronic health records across institutions for research and quality improvement: the approach taken by the Multicenter Perioperative Outcomes Group. *Anesth Analg* 2020;130:1133-46. doi:10.1213/ANE.0000000000004489
16 Beasley R, Chien J, Douglas J, et al. Thoracic Society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'Swimming between the flags'. *Respirology* 2015;20:1182-91. doi:10.1111/resp.12620
17 O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group, BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017;72(Suppl 1):ii1-90. doi:10.1136/thoraxjnl-2016-209729
18 Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179-84. doi:10.1159/000339789
19 Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361:868-77. doi:10.1056/NEJMoa0903515
20 Abbott TEF, Fowler AJ, Pelosi P, et al, StEP-COMPAC Group. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *Br J Anaesth* 2018;120:1066-79. doi:10.1016/j.bja.2018.02.007
21 Jammer I, Wickboldt N, Sander M, et al, European Society of Anaesthesiology (ESA) and the European Society of Intensive Care Medicine (ESICM), European Society of Anaesthesiology, European Society of Intensive Care Medicine. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88-105. doi:10.1097/EJA.0000000000000118

22 Ladha K, Vidal Melo MF, McLean DJ, et al. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *BMJ* 2015;351:h3646. doi:10.1136/bmj.h3646
23 Saager L, Hesler BD, You J, et al. Intraoperative transitions of anesthesia care and postoperative adverse outcomes. *Anesthesiology* 2014;121:695-706. doi:10.1097/ALN.0000000000000401
24 Kheterpal S, Vaughn MT, Dubovoy TZ, et al. Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER): a multicenter matched cohort analysis. *Anesthesiology* 2020;132:1371-81. doi:10.1097/ALN.0000000000003256
25 Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9. doi:10.1097/01.mlr.0000182534.19832.83
26 Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ Elixhauser Comorbidity Index. *Med Care* 2017;55:698-705. doi:10.1097/MLR.0000000000000735
27 van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in *R. J Stat Softw* 2011;45:1-67. https://www.jstatsoft.org/v45/i03/ doi:10.18637/jss.v045.i03.
28 Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991;10:585-98. doi:10.1002/sim.4780100410
29 Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. *J Am Stat Assoc* 1996;91:444-55. doi:10.1080/01621459.1996.10476902.
30 Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-60. doi:10.1097/00001648-200009000-00011
31 Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies. R package version 0.13.1. 2022. Available from: https://CRAN.R-project.org/package=WeightIt
32 McGuinness SP, Parke RL, Drummond K, et al, SO-COOL investigators. A multicenter, randomized, controlled phase IIb trial of avoidance of hyperoxemia during cardiopulmonary bypass. *Anesthesiology* 2016;125:465-73. doi:10.1097/ALN.0000000000001226
33 Shaefi S, Shankar P, Mueller AL, et al. Intraoperative oxygen concentration and neurocognition after cardiac surgery. *Anesthesiology* 2021;134:189-201. doi:10.1097/ALN.0000000000003650
34 Holse C, Aasvang EK, Vester-Andersen M, et al, VIXIE Trial Group. Hyperoxia and antioxidants for myocardial injury in noncardiac surgery: a 2 × 2 factorial, blinded, randomized clinical trial. *Anesthesiology* 2022;136:408-19. doi:10.1097/ALN.0000000000004117
35 Ruetzler K, Cohen B, Leung S, et al. Supplemental intraoperative oxygen does not promote acute kidney injury or cardiovascular complications after noncardiac surgery: subanalysis of an alternating intervention trial. *Anesth Analg* 2020;130:933-40. doi:10.1213/ANE.0000000000004359
36 Kurz A, Kopyeva T, Suliman I, et al. Supplemental oxygen and surgical-site infections: an alternating intervention controlled trial. *Br J Anaesth* 2018;120:117-26. doi:10.1016/j.bja.2017.11.003
37 Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS, PROXI Trial Group. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. *Anesth Analg* 2012;115:849-54. doi:10.1213/ANE.0b013e3182652a51
38 Ferrando C, Aldecoa C, Unzueta C, et al, iPROVE-O2 Network. Effects of oxygen on post-surgical infections during an individualised perioperative open-lung ventilatory strategy: a randomised controlled trial. *Br J Anaesth* 2020;124:110-20. doi:10.1016/j.bja.2019.10.009
39 Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, et al. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. *Br J Anaesth* 2017;119:140-9. doi:10.1093/bja/aex128
40 Bae J, Kim J, Lee S, et al. Association between intraoperative hyperoxia and acute kidney injury after cardiac surgery: a retrospective observational study. *J Cardiothorac Vasc Anesth* 2021;35:2405-14. doi:10.1053/j.jvca.2020.11.054
41 Pedersen SS, Holse C, Mathar CE, et al. Intraoperative inspiratory oxygen fraction and myocardial injury after noncardiac surgery: results from an international observational study in relation to recent controlled trials. *Anesth Analg* 2022;135:1021-30. doi:10.1213/ANE.0000000000006042
42 Leisman DE. The Goldilocks effect in the ICU-when the data speak, but not the truth. *Crit Care Med* 2020;48:1887-9. doi:10.1097/CCM.0000000000004669
43 Labrecque J, Swanson SA. Understanding the assumptions underlying instrumental variable analyses: a brief review of falsification strategies and related tools. *Curr Epidemiol Rep* 2018;5:214-20. doi:10.1007/s40471-018-0152-1
44 Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;372:139-44. doi:10.1016/S0140-6736(08)60878-8

Web appendix: supplement