Supplement

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

Contents

1. Power analysis

In a cohort of patients submitted to MPOG from Vanderbilt University Medica Center the incidence of AKI, myocardial injury, and lung injury was 11.4%, 1.7% and 3.2% respectively. Assuming an incidence of organ injurie ranging between 1.5-11%, a sample of 300,000 patients would provide approximately 90% power to detect a 2-5% difference in odds of each of these outcomes, with type-1 error rate of 5%, when comparing patients stratified by the median AUC_{FIO2}. This is based on unadjusted logistic regression with dichotomous exposure, a simplified but conservative version of the planned analysis.

2. Alternative measurements of excess oxygen exposure

The median (interquartile range) AUC_{FIO2} was 7,690 (5,631-10,814) %•minutes when minutes during which the SpO_2 was less than 96% were excluded from the calculation and 7,963 (5,880-11,124) %•minutes when minutes during which the SpO_2 was less than 90% were excluded from the calculation. When excess oxygen was redefined as the AUC of FIO_2 greater than 40%, the AUC_{FIO2} was 3,971 (2,595-6,131) %•minutes.

3. **Supplementary Table 1.** Diagnostic codes for perioperative lung injury

ICD-9	ICD-10	Diagnosis
518.51		Acute resp failure following trauma and surgery
518.52		Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery
518.81		Acute resp failure
518.84		Acute and chronic resp failure
	J80	Acute respiratory distress syndrome
	J95.1	Acute pulmonary insufficiency following thoracic surgery
	J95.2	Acute pulmonary insufficiency following non-thoracic surgery
	J95.821	Acute postprocedural respiratory failure
	J95.822	Acute and chronic postprocedural respiratory failure
	J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
	J96.01	Acute respiratory failure with hypoxia
	J96.02	Acute respiratory failure with hypercapnia
	J96.20	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
	J96.21	Acute and chronic respiratory failure with hypoxia
	J96.22	Acute and chronic respiratory failure with hypercapnia
	J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
	J96.91	Respiratory failure, unspecified with hypoxia
	J96.92	Respiratory failure, unspecified with hypercapnia

The lung injury endpoint was defined in the study cohort according to the presence of any one or more of these International Classification of Diseases, Ninth Revision/Tenth Revision (ICD-9 or ICD-10) codes, derived from hospital discharge diagnoses and complications data, and as endorsed by international consensus guidelines .[1,2] Selection of codes was based on the Agency for Healthcare Research and Quality (AHRQ) Patient Safety Indicator reports for postoperative respiratory failure and previously published large clinical studies that used registry data to study lung injury.[3–7]

References

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4. **Supplementary Table 2.** Diagnostic codes for stroke, appendicitis, and pancreatitis

ICD-9	ICD-10	Diagnosis
43301		Occlusion and stenosis of basilar artery with cerebral infarction
43311		Occlusion and stenosis of carotid artery with cerebral infarction
43321		Occlusion and stenosis of vertebral artery with cerebral infarction
43331		Occlusion and stenosis of multiple precerebral arteries with cerebral infarction
43381		Occlusion and stenosis of other specified precerebral artery with cerebral infarction
43391		Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
43401		Cerebral thrombosis with infarction
43411		Cerebral embolism with infarction
43491		Cerebral artery occlusion, unspecified with cerebral infarction
99702		Iatrogenic cerebrovascular infarction or hemorrhage
	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
	I63.1	Cerebral infarction due to embolism of precerebral arteries
	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
	I63.4	Cerebral infarction due to embolism of cerebral arteries
	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
	I63.6	Cerebral infarction due to cerebral venous thrombosis
	I63.8	Other cerebral infarction
	I63.9	Cerebral infarction, unspecified
540.0		Acute appendicitis with generalized peritonitis
540.1		Acute appendicitis with peritoneal abscess
540.9		Acute appendicitis without peritonitis
541		Appendicitis unqualified
542		Other appendicitis
	K35	Acute appendicitis with generalized peritonitis
	K35.2	Acute appendicitis with peritoneal abscess
	K35.20	Acute appendicitis without peritonitis
	K35.21	Appendicitis unqualified
	K35.3	Other appendicitis
	K35.30	Acute appendicitis
	K35.31	Acute appendicitis with generalized peritonitis
	K35.32	Acute appendicitis with generalized peritonitis without abscess
	K35.33	Acute appendicitis with generalized peritonitis with abscess
	K35.8	Acute appendicitis with localized peritonitis
	K35.80	Acute appendicitis with localized peritonitis without perforation or gangrene
	K35.89	Acute appendicitis with localized peritonitis and gangrene, without perforation
	K35.890	Acute appendicitis with perforation and localized peritonitis, without abscess
	K35.891	Acute appendicitis with perforation and localized peritonitis, with abscess
577.0		Acute pancreatitis
	K85	Acute pancreatitis
	K85.0	Idiopathic acute pancreatitis
	K85.00	Idiopathic acute pancreatitis without necrosis or infection
	K85.01	Idiopathic acute pancreatitis with uninfected necrosis
	K85.02	Idiopathic acute pancreatitis with infected necrosis
	K85.1	Biliary acute pancreatitis
	K85.10	Biliary acute pancreatitis without necrosis or infection
	K85.11	Biliary acute pancreatitis with uninfected necrosis
	K85.12	Biliary acute pancreatitis with infected necrosis
	K85.3	Drug induced acute pancreatitis
	K85.30	Drug induced acute pancreatitis without necrosis or infection
	K85.31	Drug induced acute pancreatitis with uninfected necrosis
	K85.32	Drug induced acute pancreatitis with infected necrosis

K85.8	Other acute pancreatitis
K85.80	Other acute pancreatitis without necrosis or infection
K85.81	Other acute pancreatitis with uninfected necrosis
K85.82	Other acute pancreatitis with infected necrosis
K85.9	Acute pancreatitis, unspecified
K85.90	Acute pancreatitis without necrosis or infection, unspecified
K85.91	Acute pancreatitis with uninfected necrosis, unspecified
K85.92	Acute pancreatitis with infected necrosis, unspecified

5. **Supplementary Table 3**. Procedural categorization coding using primary anesthesia current procedural terminology (CPT) codes

CPT code	Procedure body region/surgery type
00160, 00162, 00164, 00100, 00102, 00170, 00172, 00174, 00176, 00120, 00124, 00126, 00103, 00140, 00142, 00144, 00145, 00147, 00148, 00190, 00192, 00210, 00211, 00212, 00214, 00215, 00216, 00218, 00220, 00222, 00104	Head
00300, 00320, 00322, 00326, 00350, 00352	Neck
00640, 00600, 00604, 00620, 00622, 00625, 00626, 00630, 00632, 00634, 00635, 00670	Spine and spinal cord
00550, 00560, 00561, 00562, 00563, 00566, 00567, 00580	Open heart
00500, 00520, 00522, 00524, 00528, 00529, 00539, 00540, 00541, 00546, 00548, 00542, 00530, 00532, 00534, 00537	Intrathoracic
00400, 00410, 00402, 00404, 00406, 00450, 00452, 00454, 00470, 00472, 00474	Extrathoracic
00700, 00702, 00730, 00731, 00732, 00740, 00750, 07520, 00754, 00756, 00790, 00792, 00794, 00796, 00797, 00770	Upper abdomen
00800, 00802, 00820, 00810, 00811, 00812, 00813, 00830, 00832, 00834, 00836, 00840, 00844, 00848, 00866, 00902, 00904, 00880, 00882	Lower abdomen
00842, 00948, 00950, 00952, 00846, 00851, 00942, 00944, 00906, 00940	Gynecologic
01112, 01130, 01160, 01120, 01140, 01150, 01170, 01173, 01180, 01190	Pelvic
00862, 00868, 00864, 00870, 00872, 00873, 00865, 00908, 00910, 00912, 00914, 00916, 00918, 00860	Urologic
00921, 00922, 00924, 00926, 00928, 00930, 00932, 00934, 00936, 00938, 00920	Male reproductive system
01200, 01220, 01340, 01380, 01390, 01420, 01462, 01490, 01202, 01210, 01212, 01214, 01215, 01230, 01232, 01234, 01250, 01320, 01360, 01382, 01392, 01400, 01402, 01404, 01464, 01470, 01472, 01474, 01480, 01482, 01484, 01486, 01260, 01270, 01272, 01274, 01430, 01432, 01440, 01442, 01444, 01500, 01502, 01520, 01522	Lower extremity
01620, 01680, 01682, 01730, 01820, 01860, 01610, 01622, 01630, 01634, 01636, 01638, 01710, 01712, 01714, 01716, 01732, 01740, 01742, 01744, 01756, 01758, 01760, 01810, 01829, 01830, 01832, 01650, 01652, 01654, 01656, 01670, 01770, 01772, 01780, 01782, 01840, 01842, 01844, 01850, 01852	Upper extremity
01916, 01920, 01922, 01924, 01925, 01926, 01930, 01931, 01932, 01933, 01935, 01936	Radiologic
01951, 01952, 01953	Burn
01958, 01960, 01961, 01968, 01967, 01962, 01963, 01969, 01964, 01965, 01966	Obstetric
01990, 01991, 01992, 01995, 01996, 01999	Other

6. **Supplementary Table 4**. Association between acute kidney injury (AKI), myocardial injury, and lung injury with 30-day mortality and hospital length of stay (hLOS)

	AKI n/N (%)	No AKI n/N (%)	p-value
30-day mortality	615 / 18,349 (3.4%)	1725 / 274,533 (0.6%)	<0.001
h-LOS, median (IQR)	5.0 (3.0, 9.0)	3.0 (1.0, 5.0)	<0.001

	Myocardial injury n/N (%)	No myocardial injury n/N (%)	p-value
30-day mortality	354 / 9,905 (3.6%)	1,705 / 285,277 (0.6%)	<0.001
h-LOS, median (IQR)	6.0 (3.0, 11.0)	3.0 (1.0, 5.0)	<0.001

	Lung injury n/N (%)	No lung injury n/N (%)	p-value
30-day mortality	1,352 / 12,860 (10.5%)	1,121 / 299,116 (0.4%)	<0.001
h-LOS, median (IQR)	9.0 (5.0, 19.0)	3.0 (1.0, 5.0)	<0.001

7. **Supplementary Table 5**. Associations between intraoperative oxygen exposure and secondary outcomes. Event rates (%) are reported for categorical outcomes and 50th (25^{th}, 75^{th}) percentiles and number of eligible cases for length of stay (LOS). Estimates (95% confidence intervals) represent the odds ratio of stroke or mortality at 30 days or the difference in average hospital LOS between the 75th and the 25th percentiles of the intraoperative AUC_{FIO2}. P-values represent the statistical significance across the entire range of AUC_{FIO2}.

Analysis	Stroke	Estimate (95% CI)	P-value	LOS (days)	Estimate (95% CI)	P-value	Mortality	Estimate (95% CI)	P-value
Primary analysis	3,298 / 312,161 (1.1%)	1.09 (1.05 to 1.13)	<0.001	3.0 (1.0-5.0)	-0.20 (-0.28 to -0.11)	<0.001	2,468 / 309,929 (0.8%)	1.06 (0.98 to 1.15)	0.04
Sensitivity analyses - redefined exposure									
Excluding minutes where SpO_2 <96%	3,298 / 312,161 (1.1%)	1.09 (1.05 to 1.13)	<0.001	3.0 (1.0-5.0)	-0.15 (-0.23 to -0.07)	<0.001	2,468 / 309,929 (0.8%)	1.02 (0.95 to 1.10)	0.09
Excluding minutes where SpO_2 <90%	3,298 / 312,161 (1.1%)	1.10 (1.05 to 1.13)	<0.001	3.0 (1.0-5.0)	-0.18 (-0.27 to -0.10)	<0.001	2,468 / 309,929 (0.8%)	1.06 (0.98 to 1.15)	0.04
Redefining excess FIO_2 as AUC >0.4	3,298 / 312,161 (1.1%)	1.07 (1.04 to 1.11)	<0.001	3.0 (1.0-5.0)	0.05 (-0.02 to 0.13)	<0.001	2,468 / 309,929 (0.8%)	1.11 (1.03 to 1.20)	0.02
Sensitivity analyses - cohort restriction									
Excluding cases with any SpO_2 <96%	2,153 / 204,626 (1.1%)	1.11 (1.06 to 1.17)	<0.001	3.0 (1.0-5.0)	-0.21 (-0.31 to -0.10)	<0.001	1,499 / 205,004 (0.7%)	1.10 (1.00 to 1.22)	0.05
Excluding cases with early mortality	3,298 / 305,848 (1.1%)	1.09 (1.05 to 1.13)	<0.001	3.0 (1.0-5.0)	-0.21 (-0.29 to -0.12)	<0.001	NA	NA	NA
Excluding cardiac surgery cases	3,081 / 302,347 (1.0%)	1.11 (1.06 to 1.15)	<0.001	3.0 (1.0-5.0)	-0.20 (-0.28 to -0.11)	<0.001	2,341 / 300,671 (0.8%)	1.08 (1.00 to 1.17)	0.17

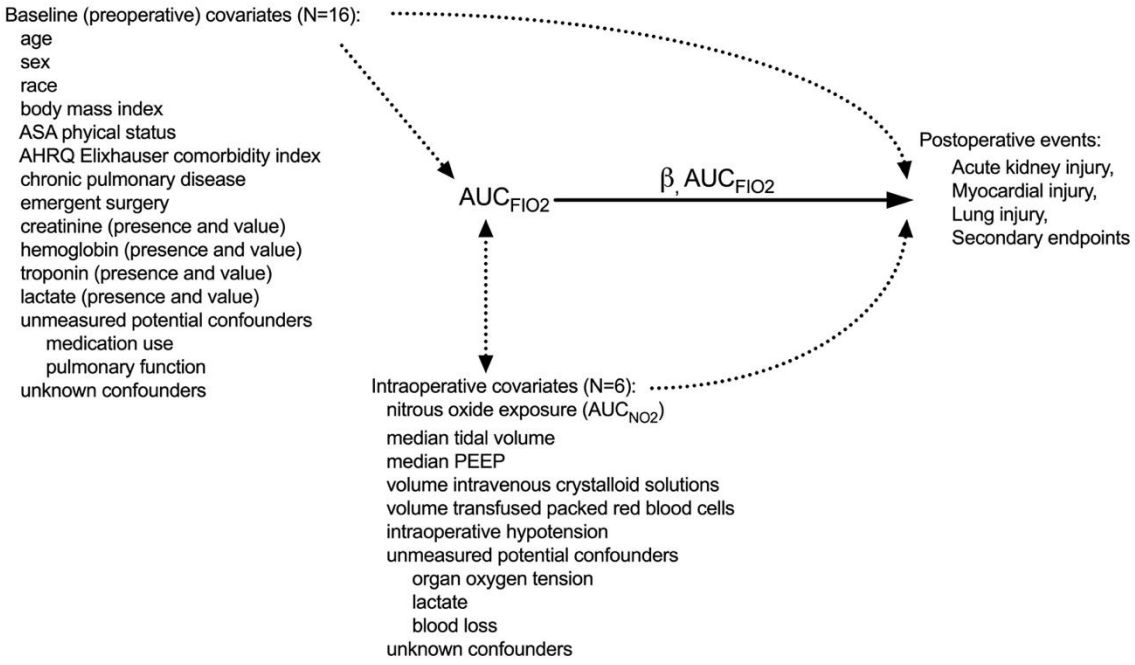
All analyses were adjusted for age, sex, BMI, ASA status, AHRQ Elixhauser comorbidity index, chronic pulmonary disease, emergency surgery, preoperative serum creatinine, hemoglobin, troponin and lactate concentrations, nitrous oxide exposure, median intraoperative PEEP, volumes of intraoperative intravenous crystalloid and packed red blood cells administrations, and intraoperative hypotension. SpO_2, arterial hemoglobin oxygen saturation; FIO_2, fraction of inspired oxygen; NA, not applicable.

8. **Supplementary Table 6**. Estimates of the rates of acute kidney injury, myocardial injury, and lung injury for patients receiving 30% and 80% FIO_2. Only 1% of cases received a median FIO_2 of 30% or less in this cohort, limiting accuracy of these estimates. Estimates were adjusted for all the covariates included in the primary analyses and duration of surgery.

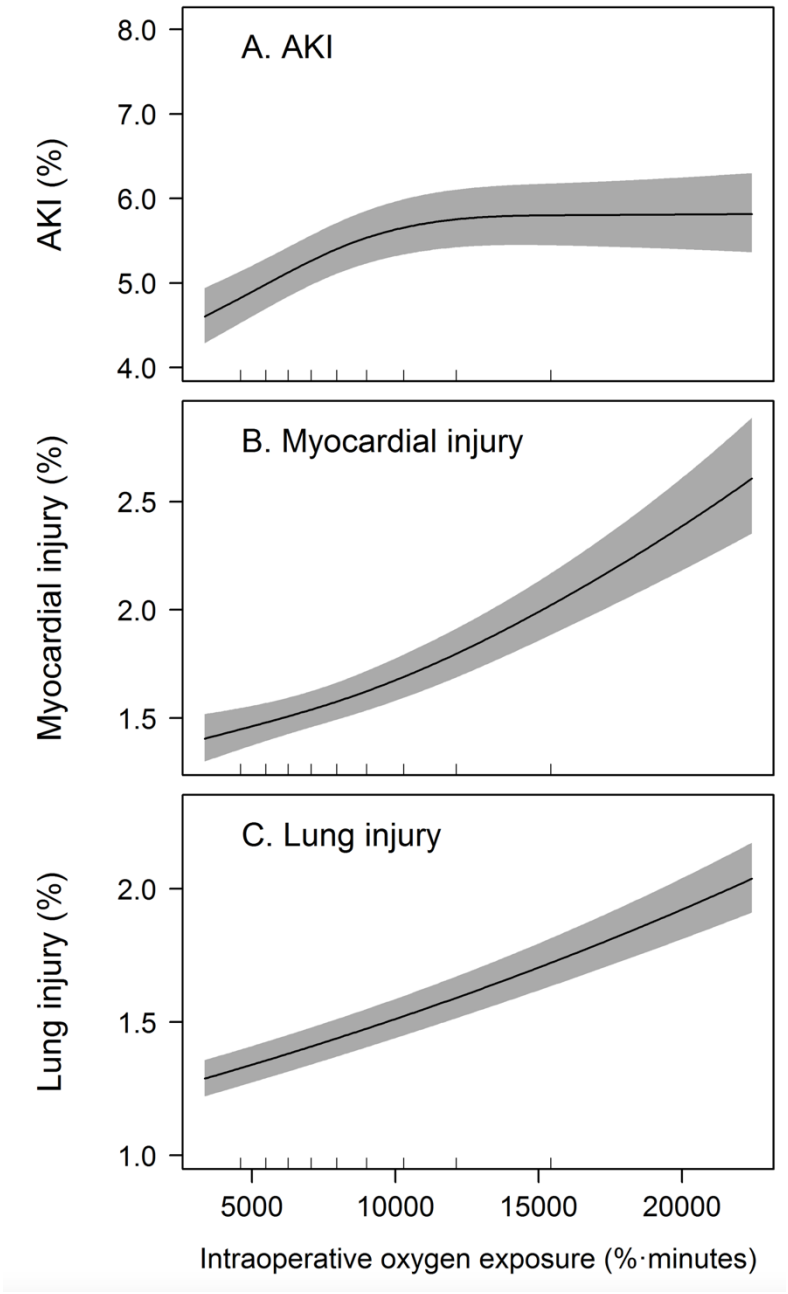
	Median FIO_2 30%	Median FIO_2 80%
Acute kidney injury	5.21% (4.80 to 5.67)	5.62% (5.29 to 5.97)
Myocardial injury	1.83% (1.67 to 2.02)	2.02% (1.90 to 2.15)
Lung injury	1.10% (1.00 to 1.17)	1.82% (1.72 to 1.92)

9. **Supplementary Figure 1.** Causal pathway diagram depicting potential framework of associations

Causal pathway diagram. Arrows depict potential relationships between factors, and directionality shows the temporal relations between factors. Baseline (preopeartive) and intraoperative covariates were chosen for their potential to confound the measurement of the association between the primary exposure (AUC_{FIO2}) and postoperative organ injury outcomes (acute kidney injury, myocardial injury, lung injury, and other secondary endpoints). β captures the estimate of the association between the 75th and 25th percentile of AUC_{FIO2} and organ injury, adjusted for baseline and intraoperative covariates. A sensitivity analysis was conducted that excluded intraoperative covariates (potential colliders) since the primary exposure could affect these factors. The impact of unmeasured potential confounders and unknown confounders is not accounted for in β, AUC_{FIO2}.



10. **Supplementary Figure 2.** Independent associations between intraoperative oxygen exposure and organ injury in models that were adjusted for covariates included in primary models and duration of surgery. **A**. acute kidney injury (AKI), **B**. myocardial injury, and **C**. lung injury. Tick marks on the x-axis identify each decile of cases. P<0.001 for each organ injury.



11. **Protocol** (as posted on Open-Source Framework 8/23/2020, osf.io/cfd2m)

Title:	Intraoperative oxygen exposure and postoperative outcomes
Principal Investigator:	Frederic (Josh) Billings, Vanderbilt University
Co-Investigators:	David McIlroy, Vanderbilt University Matthew Shotwell, Vanderbilt. University Marcos Lopez, Vanderbilt University Joanna Olsen, Oregon Health Science University Shelley Vaughn, University of Michigan Jennifer Morse, Vanderbilt University Jonathan Wanderer, Vanderbilt University Matthew Semler, Vanderbilt University Sachin Kheterpal, University of Michigan
Type of Study:	Multicenter observational cohort
IRB Status:	IRB Approved
Aims:	The aims of this study are to: 1. Estimate patient intraoperative oxygen exposure across a large heterogenous cohort of medical centers, surgeries, and anesthesiologists. 2. Test the hypothesis that excess intraoperative oxygen exposure is associated with an increased risk of postoperative kidney injury, myocardial injury, lung injury, and other secondary endpoints.
Patients/Participants:	Adult patients receiving surgery at Multicenter Perioperative Outcomes Group (MPOG) participating medical centers with general anesthesia, tracheal intubation, and mechanical ventilation during surgery who are at increased risk of poor outcomes, defined as patients admitted to the hospital following surgery of at least two hours duration.
Proposed statistical analysis:	We will estimate the odds of postoperative AKI, myocardial injury, and lung injury (three primary endpoints) associated with exposure to intraoperative hyperoxygenation. The exposure will be quantified as a primary definition of the area-under-the-curve (AUC) of the fraction of inspired oxygen (FIO_2) above 0.21 for minutes when the SpO_2 is >92%, using logistic regression and adjusted for potential confounders (variables assumed to be associated with intraoperative FIO_2 administration *and* postoperative organ injury).

INTRODUCTION

Oxygen is one of the most widely used therapies during anesthesia, but the optimal FIO_2 during surgery remains unknown. High FIO_2 has been thought to offer many advantages, including an improved safety margin for airway manipulation, increasing perioperative arterial and wound tissue oxygen tension to enhance oxidative killing by neutrophils (1,2), improved healing of anastomotic sites (3,4), and decreased postoperative nausea and vomiting (5,6). Hyperoxia, however, has also been found to have a host of adverse effects, including promotion of absorption atelectasis (7), direct lung toxicity (8), increased airway inflammation (9), impaired regulation of blood glucose (10), and changes in cardiac index and peripheral vascular resistance (11-13). Clinical data on the effect of intraoperative FIO_2 has been equally conflicting. Initial data suggested that hyperoxia may play a role in decreasing surgical site infections (3,4), although recent clinical trials have failed to confirm this effect (14-17), and the existing studies have a high level of heterogeneity and risk for bias (18,19). Data from the ICU and cardiology literature suggest that hyperoxia may have a harmful effect on patient outcomes. The Oxygen-ICU trial demonstrated a significant increase in mortality when ICU patients were randomized to hyperoxic PaO_2 values up to 150 mm Hg, a level considered conservative by intraoperative standards (20). The AVOID study randomized ST elevation myocardial infarction patients to a supplemental oxygen group vs. air and found increased infarction size, recurrent MI, and arrhythmias in the oxygenation group (21). The PROXI trial, in a post-hoc analysis, reported an increase in perioperative myocardial infarction and long-term mortality in patients exposed to high FIO_2 while undergoing cancer surgery (22,23). A recent large registry study examined over 70,000 patients undergoing non-cardiothoracic surgery and found a dose-dependent association between intraoperative FIO_2 and major respiratory complications, as well as 30-day mortality (24). The DETO2X-AMI trial, however, failed to demonstrate any differences in clinical outcomes between patients with acute myocardial infarctions provided 2 liters/minute nasal cannula oxygen vs. ambient air, despite significantly more hypoxemia events in the ambient air group (25). A best-practice strategy for administration of intraoperative FIO_2 remains unknown.

We will test the hypothesis that excess intraoperative oxygen administration is associated with postoperative kidney injury, myocardial injury, lung injury and secondary endpoints.

METHODS

Study design:

Multicenter observational cohort study

Study sites:

Multicenter Perioperative Outcomes Group (MPOG) participating medical centers

Study population:

The inclusion/exclusion criteria for the study are broad to capture a wide set of intraoperative oxygenation practices, a diverse patient population, and a patient population receiving a diverse set of surgical procedures. At the same time, we will exclude patients with known confounders (to limit indication bias).

Inclusion criteria:

- 18 years of age or older
- Duration of surgery of at least 120 minutes

- General anesthesia with tracheal intubation and mechanical ventilation
- Surgery from January 1, 2016 through November 22nd, 2018

Exclusion criteria:

- Pregnancy
- Outpatient surgery, defined according to surgical scheduling (i.e., patients who are scheduled outpatient but then are admitted to the hospital remain excluded)
- Airway surgery or bronchoscopy, documented using procedural codes
- One-lung or jet ventilation, documented by anesthesiologist
- Preoperative tracheal intubation
- Infrequent documentation of oxygenation during a case defined as any intraoperative periods of 5 minutes or more in which there are no FIO_2 or SpO_2 measurements or less than 60 intraoperative FIO_2 or SpO_2 measurements during the case.
- Intraoperative arterial hemoglobin desaturation (SpO_2 <90% for more than three consecutive minutes), since these patients likely require a higher FIO_2 to maintain SpO_2 (i.e., high FIO_2 is needed to oxygenate Hb rather than excessive of that required to oxygenate Hb), and these patients likely have factors that will confound the association between higher FIO_2 and organ injury, factors that are independently associated with both need for increased FIO_2 and increased organ injury.
- Previous participation in the study within 90 days (i.e., repeat surgery)
- Renal replacement therapy (for the AKI outcome)
- No preoperative creatinine measurement (for the AKI outcome)
- Cardiac, pacemaker, defibrillator, cardiac ablation, or cardiac catheterization surgery (for the myocardial injury outcome)
- Preoperative myocardial injury, indicated by elevated preoperative troponin within 42 days prior to surgery (for the myocardial injury outcome)

Primary definition of oxygen exposure (independent variable):

We will measure intraoperative oxygen exposure using minute-to-minute FIO_2 and SpO_2 data. These data are part of current intraoperative vital sign data feeds into MPOG. FIO_2 data will be collected from intubation to extubation, or from intubation until out of room time for patients who are not extubated in the operating room. **Oxygen exposure will be quantified as the AUC of FIO_2 above 0.21 (air) during surgery for minutes when the corresponding SpO_2 is greater than 92%.** We will exclude the FIO_2 for minutes when the oxygen saturation is less than or equal to 92% in the area under the AUC calculation because we seek to quantify **excess oxygen delivery** as opposed to necessary oxygen delivery. We will also conduct a sensitivity analysis to further address potential confounding by indication, during which we will exclude cases in which patients have had any SpO_2 less than 96%, since anesthesiologists may increase FIO_2 following a decrease in SpO_2 and not subsequently decrease FIO_2 after SpO_2 increases.

For minutes when the FIO_2 is not available, we will assign the FIO_2 as the mean between the previous value and the subsequent value if the missing period is $\leq$ five minutes. If there is no FIO_2 measurement for more than five minutes, the case will be excluded. Likewise, for minutes when the SpO_2 is not available, we will assign the SpO_2 as the mean between the previous value and the subsequent value if the missing period is $\leq$ five minutes. If there is no SpO_2 measurement for more than five minutes, the case will be excluded.

Outcomes:

Primary endpoints of the study are three metrics of specific organ injury that may reflect oxygen toxicity or oxygen debt and include:

- Acute kidney injury (**AKI**), defined using the creatinine criteria of KDIGO consensus criteria (26). Stage I AKI is a 0.3 mg/dl creatinine increase within 48 hours of surgery or 50% increase within 7 days of surgery, stage II is a 100% increase within 7 days, and stage III is a 200% increase, increase to greater than 4.0 mg/dl, or initiation of dialysis within 7 days of surgery. The AKI endpoint will be defined as AKI as any of stage.
- Myocardial injury in patients undergoing non-cardiac surgery (**MINS**), defined as plasma concentrations of troponin I > 0.04 ng//ml within 72 hours of surgery(27).
- **Lung injury**, defined by the presence of International Classification of Diseases, Ninth Revision/Tenth Revision (ICD-9 or ICD-10) lung injury codes, derived from hospital discharge diagnoses and complications data, and as endorsed by international consensus guidelines (**Table 1**)(28,29). Selection of codes was based on previously published agency for healthcare research and quality (AHRQ) Patient Safety Indicator reports for postoperative respiratory failure and previously published clinical studies that used registry data to study postoperative lung injury (30-33).

Secondary endpoints include:

- 30-day mortality
- Length of stay, defined as the number of days from day of surgery to day of discharge including the day of surgery and the day of discharge

For those patients discharged from hospital prior to completion of the prespecified temporal window for definition of each individual organ injury (i.e. <7 days for AKI; <72 hours for MINS), we will assume they did not develop this organ injury following hospital discharge. We will collect additional patient characteristics to describe the cohort and covariates for adjusted analyses as described below.

Pre-operative variables collected will be age, sex, BMI, ASA physical status classification, past medical history including diagnosis of heart failure, diabetes, chronic pulmonary disease, and other medical conditions using the Elixhauser comorbidity list and baseline labs including hematocrit, creatinine, lactate, and troponin measured prior to surgery.

We will record the specific surgery for each patient, the surgery type, and whether the surgery was emergent.

Intraoperative data collected will include minute-to-minute FIO_2, minute-to-minute SpO_2, minute-to-minute fraction of inspired nitrous oxide, duration of anesthesia, total fluid administration, total packed red blood cell transfusion, intraoperative hypotension, median intraoperative PEEP and TV per kg IBW. Definitions for these variables are outlined in **Table 2**. Postoperative data used to calculate organ injury include creatinine, troponin I, discharge and mortality data, and diagnosis codes.

Preliminary data to estimate Power and Sample Size:

To estimate power and sample size to complete this study and accomplish the Aims above, we queried the MPOG database and calculated numbers of existing eligible patients, assessed current intraoperative oxygenation practices, and estimated organ injury in a subset of MPOG centers. In these centers, we examined all cases from adult patients who received surgery from 1/1/2016 to 12/31/2017 with general anesthesia for at least one hour, were admitted to the hospital postoperatively, and had serum basic metabolic panel measured preoperatively and postoperatively. We excluded cases from patients who were pregnant or who underwent procedures on the trachea or bronchus. A total of 137,497 cases from 103,398

patients met these inclusion/exclusion criteria. These patients received the full spectrum of surgical procedures including neurologic, ENT, cardiac, trauma, orthopedic, burn, intra-abdominal, urologic, gynecologic, and transplant surgery performed at these medical centers.

AKI affected 15,690 of these cases (11.4%). Specifically, KDIGO stage 1 AKI was diagnosed in 12,380 cases (9.0%), stage 2 AKI in 2386 (1.7%), and stage 3 in 924 cases (0.7%).

Clinicians ordered a cardiac troponin I within 72 hours of surgery in 19,370 cases (14.1%) either to evaluate suspected myocardial injury/infarction or for surveillance purposes. In the subset of patients submitted from Vanderbilt University Medical Center in 2017 (N=19,169) the median (25th, 75th percentile) age was 56 years (42, 67), and 45.1% were female. The 10th, 25th 50th, 75th, and 90th administered FIO_2 was 0.50, 0.54, 0.58, 0.82, and 0.96, and the 10th, 25th 50th, 75th, and 90th SpO2 was 96%, 98%, 99%, 100%, and 100%. Myocardial injury (troponin I > 0.04 ng//ml within 72 hours of surgery) was diagnosed in 319 of the 19,169 patients (1.7%) in which it was measured. In addition, 140 (0.7%) died during hospitalization following surgery.

Lung injury was diagnosed in 3.2% of cases using AHRQ criteria.

If AKI, MINS, and lung injury affect between 11% and 1.5% of patients in the current study, with a two-sided test and type I error rate of 1%, 300,000 patients will provide approximately 90% power to detect a 5% to 12.5% difference in the odds of each of these organ injuries (AKI, MI, or lung injury), when comparing patients stratified by the median AUC of FIO_2 above 0.21 during surgery. This approximate power analysis is based on unadjusted logistic regression with dichotomous exposure, which is a simplified but conservative version of the planned analysis. The data in the planned study provide an excellent opportunity to measure the effect of intervention overall, but also affords the opportunity for robust analyses of heterogeneity of treatment effect in important subgroups (outlined in statistical analyses plan below).

Data Checking:

Quantile and tabular summaries will be computed for all analysis variables and reviewed by a clinical expert to assess for inconsistent or nonsensical values, and to evaluate the plausibility of extreme values. For each variable, we set validity criteria prior to statistical analysis (**Table 3)**. Values that do not meet the validity criteria will be considered missing.

Missing Data:

In computing the primary exposure variable (AUC of FIO_2 above 0.21 during surgery), missing FIO_2 data will be imputed or cases excluded as described in the "Definition of oxygen exposure" section above.

For each of the outcomes of interest, only centers who reported the outcome will be included in the analysis for that outcome. Within centers providing data for each outcome, we will assign patients without outcome data as not having the event as follows: patients without creatinine or myocardial enzyme data will be considered not to have suffered AKI or myocardial injury, respectively, based on the assumption that these labs were not measured because there was no indication for monitoring or clinical suspicion of AKI or myocardial injury. Similarly, when preoperative hemoglobin, creatinine, lactate, and troponin are treated as potential confounders, we will additionally condition on the indicator variable that takes value one when the lab is measured, and zero otherwise. Patients with missing length of stay will be excluded from analysis of that outcome.

As a sensitivity analysis (see Statistical Analyses section) we will exclude patients who lack outcome data from analysis of that outcome. This will reduce the number of patients in the cohort and bias the results to only those who have outcomes measured, but it

will also restrict the analysis to a better phenotyped subgroup and reduce the effects of outcome misclassification. We will not assign any patient as having experienced an event unless there is documentation of that event.

Notwithstanding the methods described above, missingness in potential confounding variables, including perioperative laboratory measurements, will be addressed using multiple imputation. The chained equations method with predictive mean matching (PMM) will be used to generate five complete datasets. Statistical analyses will be implemented separately for each completed dataset and the results pooled using Rubin's rules.

Provider Practice Variation in FIO_2 Administration:

We anticipate that the observed variation in delivered FIO_2 may be explained in part by patient-level factors and also in part by physician-level factors. Some anesthesiologists may typically administer a higher or lower FIO_2 than other anesthesiologists, independent of patient factors. Unlike variation in FIO_2 delivery that is driven by patient characteristics, variation in FIO_2 delivery by providers that is unrelated to patient characteristics may strengthen analysis of a causal pathway between excess FIO_2 and outcomes by providing opportunity to conduct an *instrumental variable analysis.* An instrumental variable analysis will mitigate the effect of indication bias and help assess the robustness of the findings of the primary analysis.

The instrumental variable analysis will leverage variation in provider practice while testing the hypothesis that intraoperative FIO_2 is associated with postoperative organ injury. The instrumental variable will be the provider's FIO_2 prescribing practice. We will calculate this variable by measuring the median FIO_2 for each case then calculate the median of these values across all the cases for each provider. Additional details of the instrumental variable analysis are provided in the following section.

Statistical Analyses:

We will use multivariable logistic regression for analysis of the primary endpoint where the independent variable of interest will be intraoperative hyperoxygenation, quantified as the area-under-the-curve (AUC) of FIO_2 above 0.21 for intraoperative minutes when the SpO_2 was >92%. The model will also adjust for *a priori* determined potential confounders of the association between intraoperative FIO_2 administration and postoperative organ injury. These potential confounders include age, sex, BMI, ASA status, AHRQ Elixhauser Comorbidity Index (34), chronic pulmonary disease, emergency surgery, preoperative hemoglobin concentration and its "ordered" indicator (as described in the Missing Data section), preoperative creatinine concentration and its "ordered" indicator, preoperative troponin concentration and its "ordered" indicator, preoperative lactate concentration and its "ordered" indicator, nitrous oxide exposure (quantified as the AUC for intraoperative fraction of inhaled nitrous oxide, measured in a similar manner as FIO_2), median intraoperative PEEP, intraoperative fluid and blood administration, and intraoperative hypotension (see Table 2). We will use indicator variables for the preoperative labs used as covariates including hemoglobin, creatinine, troponin, and lactate because many cases will not have one or more of these labs associated with it, and the decision to order one or more of the labs (indication for ordering) may be associated with intraoperative oxygen administration and outcomes. Even though there may be a significant degree of missingness for some of these labs, we do not want to exclude them as covariates because they could confound the relationship between oxygen exposure and organ injury.

The effects of quantitative covariates will be modeled using a flexible splines method. Quantitative and graphical regression diagnostics will be examined. In the event that the fully adjusted regression model is not estimable, or when there is other evidence of overfitting, the

model complexity will be reduced by omitting terms (beginning with nonlinear terms), by categorizing or grouping variables, or by using a regularization technique (e.g., LASSO). Results for the primary endpoints will be presented as odds ratios comparing the 75^{th} versus 25^{th} percentile of the primary exposure variable, with 95% confidence intervals.

Pre-specified sensitivity analyses will include **1)** varying the metric of oxygen exposure, **2)** restricting the cohort for analysis based on data density and specific subgroups, and **3)** an instrumental variable (attending anesthesiologist) analysis:

1. Varying the metric of oxygen exposure. It is recognized that oxygen exposure may have been varied according to degrees of observed hypoxemia and other unidentified factors that may impact our outcomes of interest (confounding by indication). Moreover, it remains unknown if any toxicity associated with excess oxygen exposure is dependent on the partial pressure of oxygen within the alveolus (PAO_2) or within the arterial circulation (PaO_2) Therefore, in addition to our primary calculation of oxygen exposure as the AUC of FIO_2 above 0.21 (air) during surgery – excluding those minutes where SpO_2 <92% , we will re-calculate oxygen exposure as:
    - AUC of FIO_2 above 0.21 (air) during surgery – excluding those minutes where SpO_2 <96%. The rationale for this is that an SpO_2 <96% likely reflects a PaO_2 that is also <100 mmHg, and clinicians may increase FIO_2 if SpO_2 <96% even though the patient is not hypoxic. While variations in FiO_2 during these periods may reflect hyperoxia within the alveoli (PAO_2) it is unlikely that hyperoxemia of the blood reaching other organs was simultaneously present. In contrast, a hyperoxic inspired gas in the presence of an observed SpO_2 96% is consistent with true hyperoxemia of blood being delivered to other organs.
    - AUC of FIO_2 above 0.21 (air) during surgery – excluding those minutes where SpO_2 <90%. The rationale for this is that an SpO_2 <90% likely reflects the oxygen content of arterial blood reaching the steep part of classical Hb-O_2 dissociation curve where further hemoglobin desaturation may significantly compromise tissue O_2 delivery, and because clinicians will most likely increase FIO_2 if the SpO_2 decreases below 90%. Increased FIO_2 in this context is not oxygenation in excess of that needed to maintain hemoglobin saturation, rather it is FIO_2 required to oxygenate hemoglobin. Increasing FIO_2 and oxygen delivery in this context may be considered non-modifiable due to the risk of end-organ hypoxia.
    - We will also explore the association between hyperoxia and organ injury under an alternative FIO_2 threshold of 0.4, measuring the AUC of FIO_2 above 0.4.
2. Restricting the cohort for analysis
    - We will exclude patients for each organ injury who died within the diagnostic window for that organ injury AND did not first develop the organ injury prior to death, to account for the potential competing risk of "early" death. Specifically, some patients may die prior to completion of the prespecified temporal window for the definition of each specific individual organ injury (i.e. <7 days for AKI; <72 hours for MINS; duration of hospitalization for ALI). By excluding these patients, the competing risk between "early" death and each organ-specific injury is eliminated, while retaining the full spectrum of severity of organ injury including organ injury that culminates in mortality. This analysis may produce a purer effect estimate of the association between hyperoxygenation and each organ-specific injury than what could be achieved with a composite of organ injury or death (another technique that addresses competing risk of early death).

- We will repeat the analysis for each outcome after excluding all patients in which that outcome is not measured to address the potential effect of ascertainment bias (as referenced in the Missing Data section).
- We will exclude all patients who had any oxygen desaturation during maintenance anesthesia, defined as any SpO_2<96% that occurred exclusive of induction (defined as the first 15 minutes of the case) and emergence (defined as the last 15 minutes of the case) of anesthesia. Although we have already excluded FIO_2 data when SpO_2<93% from the calculation of "excess oxygen exposure" (reflecting that the higher FIO_2 may be clinically indicated during these periods), it is plausible that clinicians who increased FIO_2 in response to a desaturation may continue to administer an increased FIO_2 even after SpO_2 subsequently increases, potentially creating residual and unrecognized confounding by indication in patients who experienced even a brief intraoperative oxygen desaturation.
- We will conduct additional pre-specified subgroup analyses for the primary outcomes (AKI, MINS, and lung injury) according to age (patients separated into those <50 years old, those 50-70, and those >70), sex, diabetes, preoperative hemoglobin concentration (patients separated into those <10 g/dl, 10-12.5, and >12.5), procedure type (patients separated by surgery body region/type (see **Table 4**), and duration of surgery (patients separated into those whose surgery is 120-180 minutes duration, 180-240, and greater than 240 minutes). The subgroup analysis according to duration of surgery will facilitate an exploration of the temporal component of any observed risk between cumulative hyperoxic exposure and adverse outcomes to better understand whether short-duration high-intensity hyperoxia should be considered an equivalent exposure to long-duration low-intensity hyperoxia. Subgroup analysis according to duration of surgery will also allow us to explore the potential confounding effect of surgery duration on the association between FIO_2 AUC and outcomes. We will examine if these factors modify any association between oxygen exposure and outcomes.

3. Anesthesiologist instrumental variable analysis
    - We will additionally implement the primary analysis using an instrumental variable method. The instrument will be the typical FIO_2 for each anesthesiologist (see FIO_2 Administration Practice Patterns and Provider Clustering section above). We will use the two-stage predictor substitution (2SPS) method. In the first stage we will regress the measured FIO_2 AUC values onto the typical median FIO_2 values for each provider (i.e., the median FIO_2 across all cases for the provider of the median FIO_2 within each case, as described above). In the second stage, the predicted FIO_2 AUC from the first stage will be substituted for the measured FIO_2 AUC in the primary analysis.

Secondary endpoints will be evaluated using linear, logistic, proportional hazards, and cumulative logit regression methods as appropriate, but otherwise similar to the analysis of the primary endpoint.

Finally, to partially examine the clinical relevance of kidney injury, myocardial injury, and lung injury, we will evaluate the associations between these outcomes with 30-day mortality and hospital length of stay.

Limitations:

The major limitation of this study is the indication bias for intraoperative FIO_2. We will attempt to control this limitation by eliminating FIO_2 data from the AUC calculation of oxygen exposure when the SpO_2 is < 92% (and by eliminating FIO_2 data from the AUC

calculation of oxygen exposure when the SpO_2 is < 90% or < 96% in sensitivity analyses), eliminating cases in which the SpO_2 is < 90% for three or more minutes, adjusting for confounders associated with FIO_2 and outcomes in our analyses, performing a sensitivity analysis in patients who never had any SpO_2 < 96%, and conducting an instrumental variable sensitivity analysis.

Table 1. ICD-9/10 codes used to identify patients with lung injury

ICD-9	ICD-10	Diagnosis
518.51		Acute respiratory failure following trauma and surgery
518.52		Pulmonary insufficiency following trauma and surgery
518.81		Acute respiratory failure
518.84		Acute and chronic respiratory failure
	J80	Acute respiratory distress syndrome
	J95.1	Acute pulmonary insufficiency following thoracic surgery
	J95.2	Acute pulmonary insufficiency following non-thoracic surgery
	J95.821	Acute postprocedural respiratory failure
	J95.822	Acute and chronic postprocedural respiratory failure
	J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
	J96.01	Acute respiratory failure with hypoxia
	J96.02	Acute respiratory failure with hypercapnia
	J96.20	Acute and chronic respiratory failure, unspecified whether with hypoxia or
	J96.21	Acute and chronic respiratory failure, with hypoxia
	J96.22	Acute and chronic respiratory failure, with hypercapnia
	J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
	J96.91	Respiratory failure, unspecified with hypoxia
	J96.92	Respiratory failure, unspecified with hypercapnia

Table 2. Intraoperative characteristic definitions

Variable	Definition	Description
Duration of procedure	Total procedure time	Total minutes from in room to out of room
Fluid administration	ml of crystalloid	Total ml of crystalloid fluids
Blood transfusion	ml of packed red blood cells transfused	Total ml of packed red blood cells transfused
Intraoperative hypotension	AUC of MAP <60 mmHg	AUC of MAP<60 mm Hg
Measured Tidal Volume	TV in mL/kg/IBW	Median intraoperative TV in mL/kg/IBW
PEEP- measured	Median intraoperative PEEP	Median intraoperative PEEP in cm of H_2O
FIO_2	Intraoperative fraction of inspired oxygen	Minute to minute FIO_2 from intubation to extubation, or out of operative room for patients who remain intubated
Oxygen Saturation (SpO_2)	Intraoperative oxygen saturation	Minute to minute arterial hemoglobin oxygen saturation from intubation to extubation, or out of operative room for patients who remain intubated
Nitrous Oxide administration	Amount of nitrous oxide used for duration of case	AUC of intraoperative nitrous use (% minutes)

Table 3. Lower and upper thresholds for continuous variables used in regression modeling. Values outside of these thresholds set to missing.

Variable	Lower Threshold	Upper Threshold
Age (years)	18	125
BMI (kg/m^2)	14	80
Creatinine, baseline (mg/dl)	0.20	15.00
Hemoglobin, baseline (g/dl)	4.0	20.0
Hematocrit, baseline (%)	12.0	60.0
Total crystalloid equivalents (ml)	1	25000
pRBC, intraop (ml)	0	30000
Length of stay (days)	1.00	500
Peep (cm H_2O)	0.00	30.00
Troponin, preop (ng/ml)	0.00	500
Lactate, preop (mmol/l)	0.00	30
Case duration (minutes)	120	1440
AHRQ Elixhauser Comorbidity Index	-32.00	99.00

Table 4. Categories of procedures

Category	Grouping
Head	Peripheral/Other
Neck	Peripheral/Other
Thoracic - Extrathoracic	Thoracic/Abdominal
Thoracic - Intrathoracic	Thoracic/Abdominal
Abdominal – Upper abdomen	Thoracic/Abdominal
Abdominal – Lower abdomen	Thoracic/Abdominal
Perineum	Peripheral/Other
Pelvis	Peripheral/Other
Upper and lower extremity	Peripheral/Other
Spine/Cord	Peripheral/Other
Other	Peripheral/Other

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