Intraoperative Fraction of Inspired Oxygen and Postoperative Outcomes (MPOG PCRC 60)

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- Disclosures

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Outline

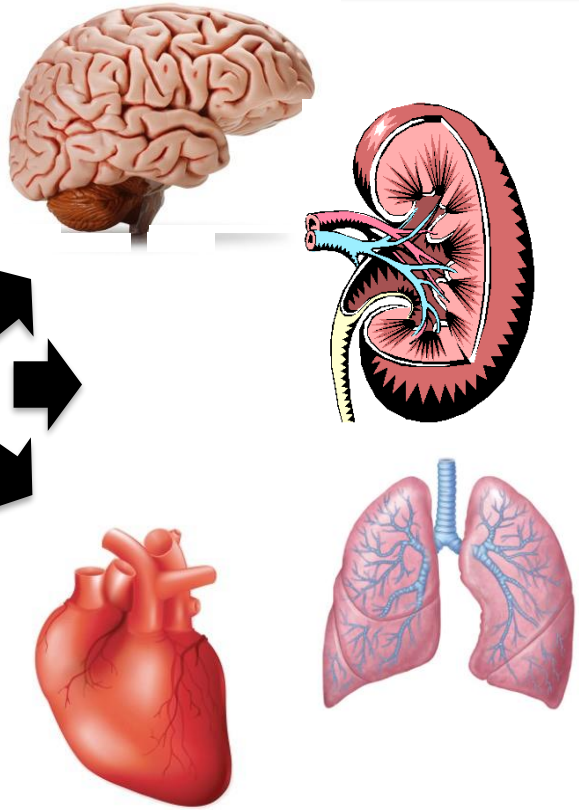
- Background and rationale for study
- Study design
- Execution (and challenges)
- Preliminary results
- Future plans

Background and rationale: Oxygen

Protection from Hypoxia during Surgery?

Increased tissue pO_2

Bactericidal killing



Oxygen Toxicity during Surgery?

$O_2^{-}\bullet$

H_2O_2

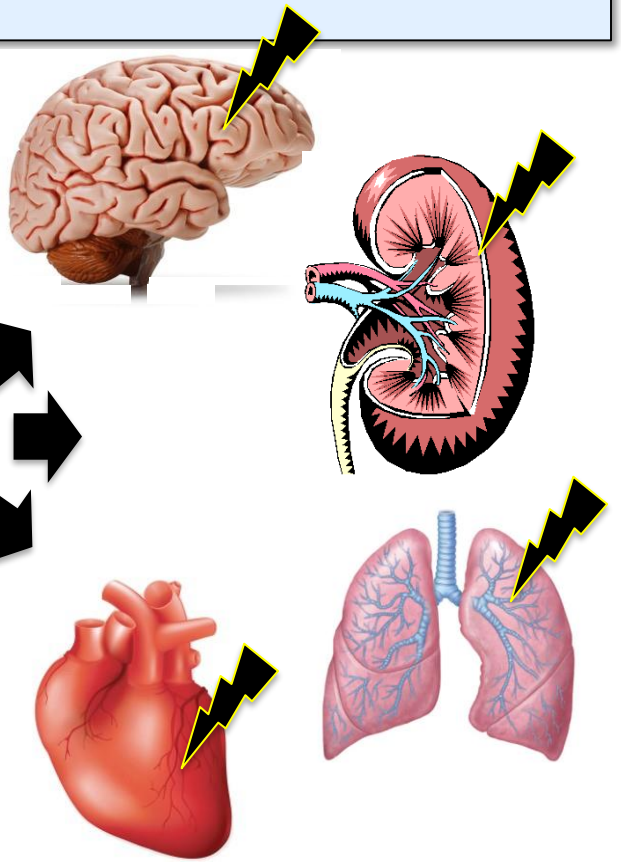
$OH\bullet$

$ONOO^-$

HIF1a

Oxidative Damage

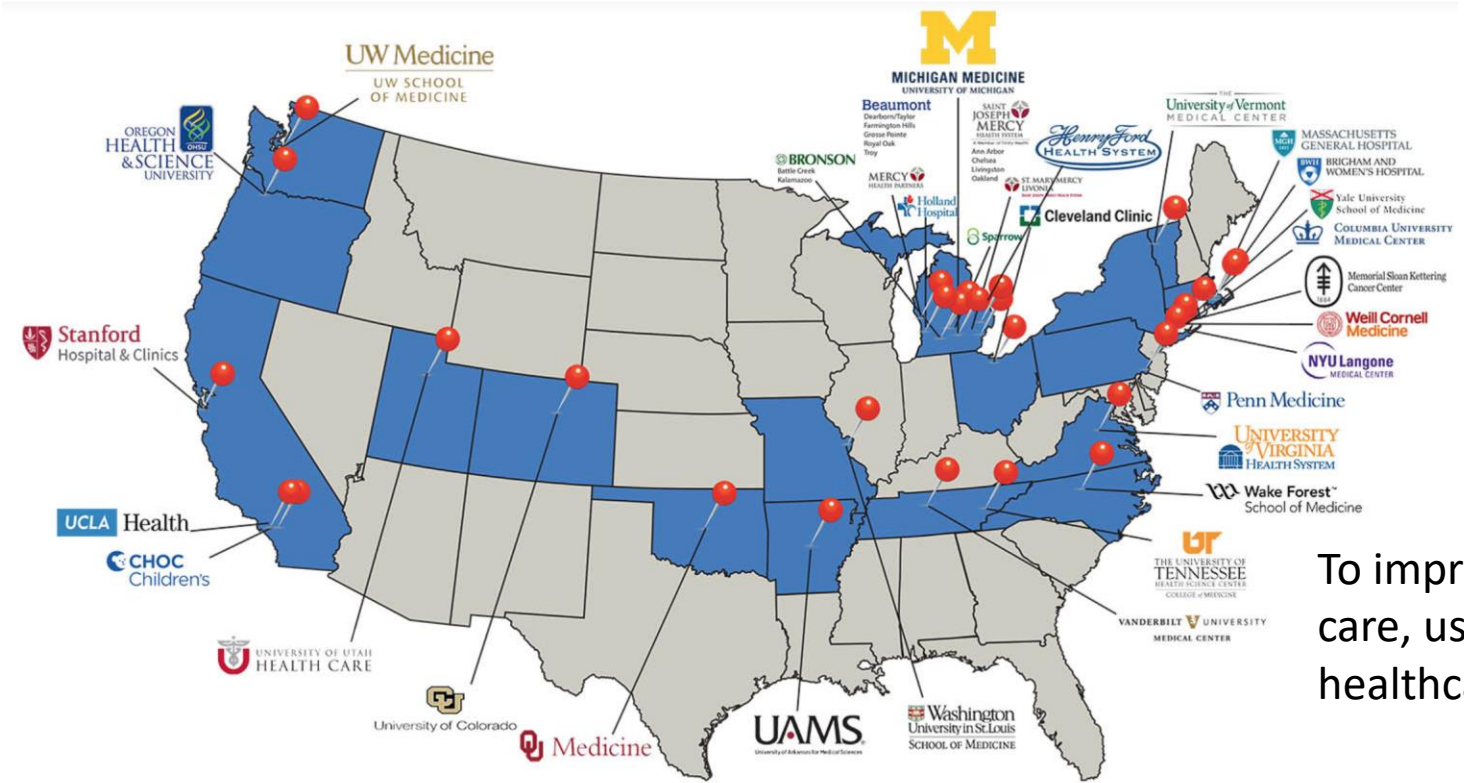
Altered gene expression



Broad objective

To generate evidence that informs the debate on best practice for intraoperative oxygen administration

Multicenter Perioperative Outcomes Group (MPOG)



To improve patient care, using electronic healthcare data.

Specific Aims

1. Explore the association between intraoperative O_2 delivery and adverse perioperative outcomes

2. Generate preliminary data to support funding for a clinical trial testing the impact of strategies for varied intraoperative F_iO_2

3. Vet MPOG centers for quality/completeness of current data delivery

Primary hypothesis

Excess (modifiable) intraoperative oxygenation is associated with postoperative organ injury

Methods

- Multicenter observational cohort study of patients at participating MPOG centers
- Inclusion criteria
  - Adults, duration of surgery >120 minutes, GA with ETT
- Exclusion criteria
  - Outpatient surgery or repeat surg within 90d
  - Pregnant, jet ventilation, airway surgery, one-lung ventilation
  - Intraop desaturation (SpO_2 <90% for ≥3 min)
  - Infrequent documentation of FiO2 or SpO2 (≥ 5min of missing data)

Exposure variable (Oxygen)

Oxygen exposure quantified as the AUC of FiO_2 above 0.21 (air) calculated for minutes during surgery when the SpO_2 is >92%.

The FiO_2 for minutes when the oxygen saturation ≤92% is NOT included in the AUC calculation as this may be considered necessary oxygen delivery rather than excess (and therefore modifiable) oxygen delivery

Outcomes variables

- **Co-primary outcomes**

  1. AKI defined by creatinine-based KDIGO criteria

  2. Myocardial injury in patients undergoing non-cardiac surgery (MINS) defined using concentrations of troponin I or troponin T above ULN within 72 hours of surgery

Outcomes variables

- **Secondary outcomes**

  30-d mortality

  Acute lung injury (AHRQ criteria)

  Surgical site infection (NSQIP defined)

  Peak postoperative lactate within 24 hours of surgery

  In-hospital MI (ICD codes)

  In-hospital cardiac arrest, stroke

Missing data

Oxygen exposure: Imputed when FiO_2 gap <5 mins

Case excluded if longer gap in FiO_2

Outcomes:

Only centers providing a NON-ZERO event count for any given outcome will be included in the analysis of that outcome.

Once a center was included, patients without measurement data (eg troponin or creatinine) considered NON-EVENTS

Statistical Analysis Plan

For co-primary endpoints:

Multivariable mixed-effects logistic regression

Including modeling of heterogeneity among centers

Adjusted for pre-specified covariates (potential confounders)

age, BMI, ASA status, Elixhauser comorbidity index, emergency surgery, preop Hb, S_{Cr}, N_2O exposure, PEEP, intraoperative fluid/blood administration and intraoperative hypotension

Statistical Analysis Plan – sensitivity analyses

Recalculate O_2 exposure as:

AUC of FIO_2 above 0.21 (air) during surgery – excluding those minutes where SpO2 <96%

While variations in FiO2 during these periods may reflect hyperoxia within the alveoli (PAO2) it is unlikely that hyperoxemia of the blood reaching other organs was simultaneously present.

?Excess P_AO_2 vs P_aO_2

Statistical Analysis Plan – sensitivity analyses

Restricting the cohort for analysis:

Complete case analysis (excl patients with no outcome)

Excluding centers reporting low frequency of outcome measurement (eg troponin data)

Subgroup Analyses:

Age, high-risk, sex, preoperative Hb, duration of surgery

Limitations

- Unmeasured/unrecognized confounding by indication
  - The same factors that placed patients at increased risk for adverse outcomes may have led clinicians to administer a higher FiO2

- Ascertainment bias
  - The same factors that led to a higher F_iO_2 administration may also lead to greater surveillance for outcomes

Challenges

- Identifying study cohort within existing MPOG variable structure
- Inconsistent methods by centers of providing data to MPOG (eg OI vs F_iO_2)
- Understanding and handling missing data
- Identifying and handling data that is in inconsistent with dictionary definition (eg in-hosp mortality)
- Using outcomes such as troponin (varied ULN, changing assays)

Challenges

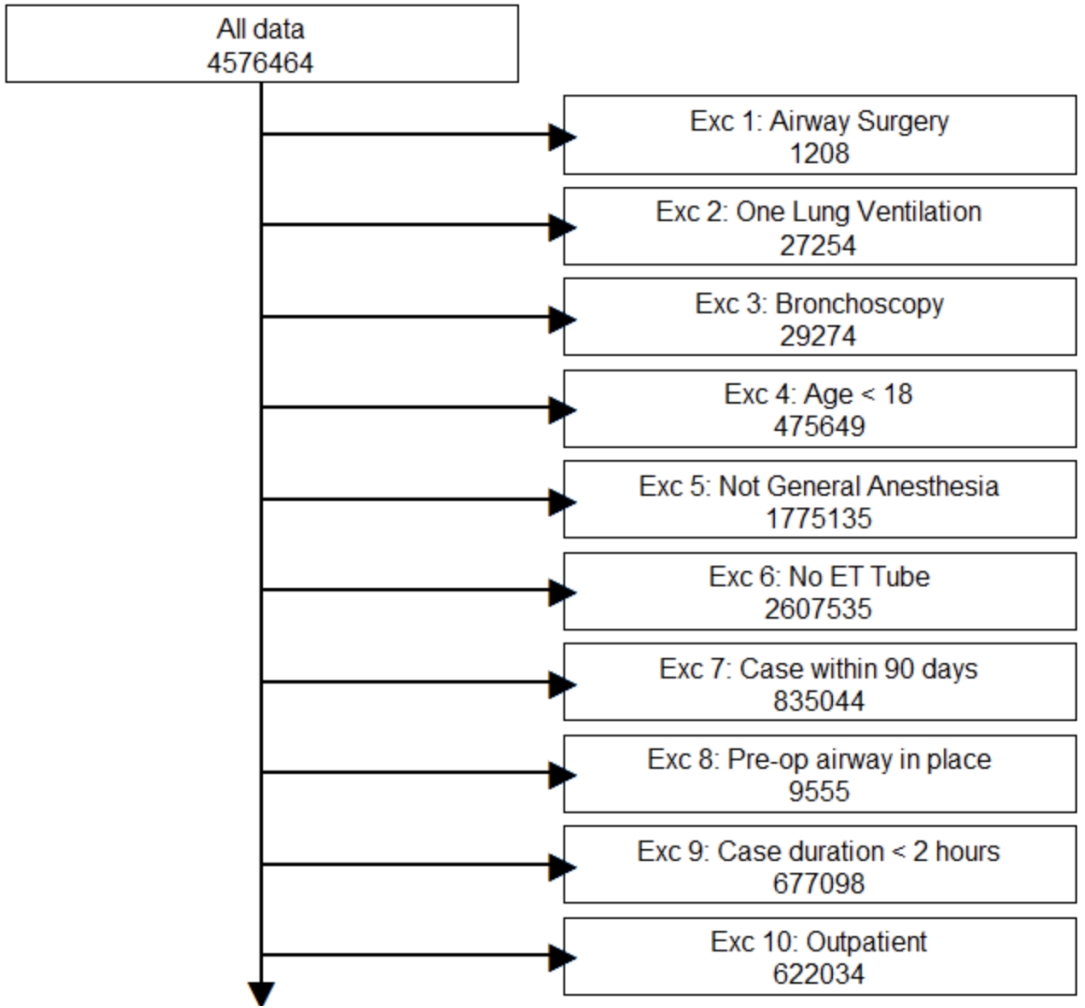
16 months … and ongoing

1000’s of emails

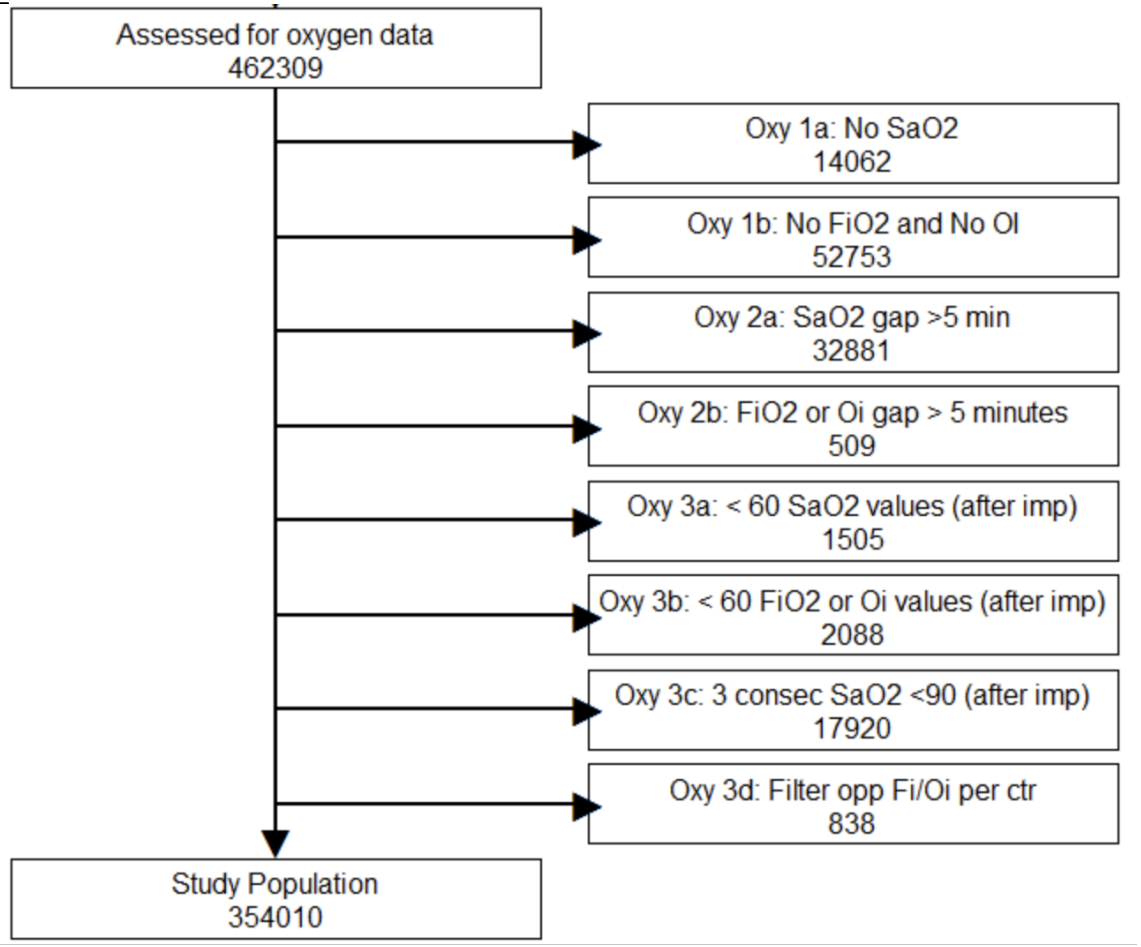
countless hours

Results

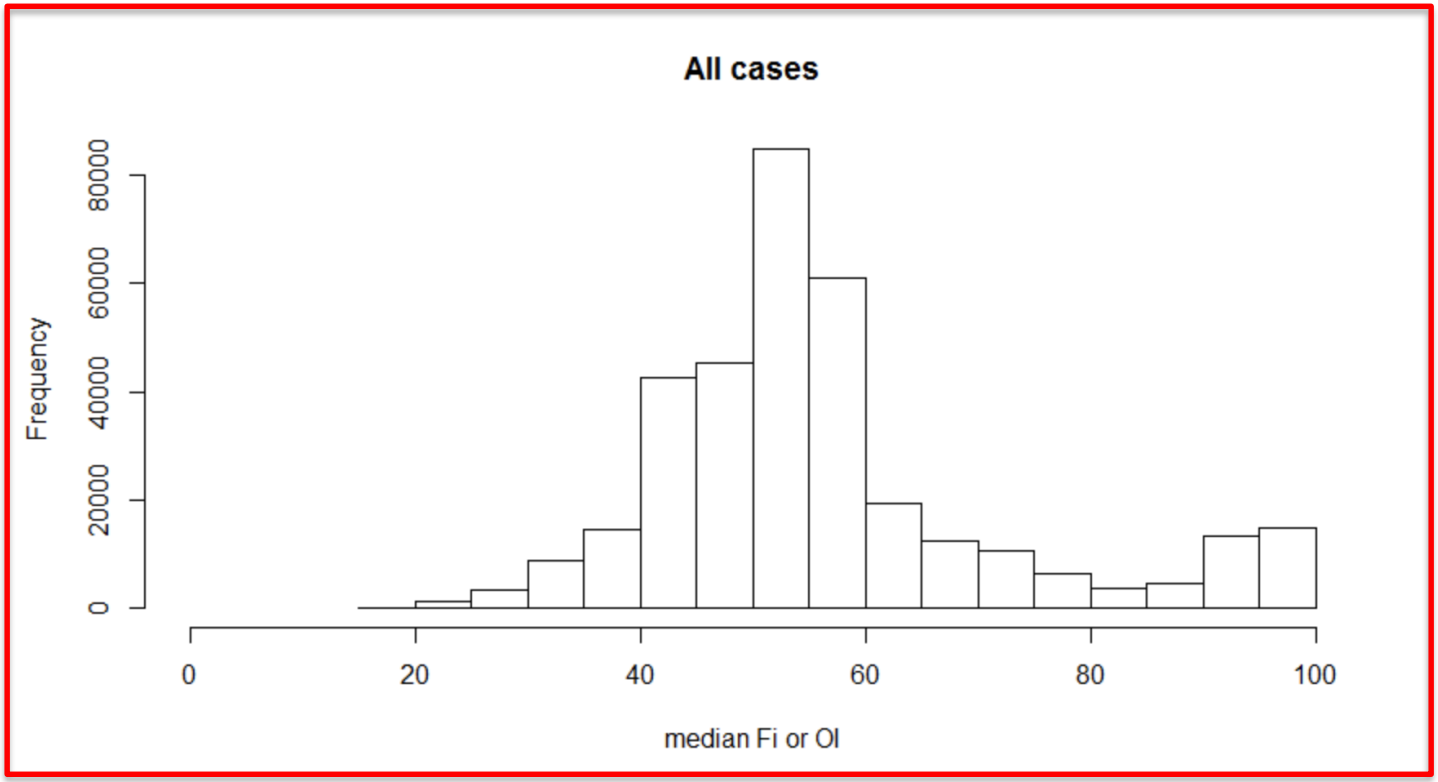
Study Flow Chart



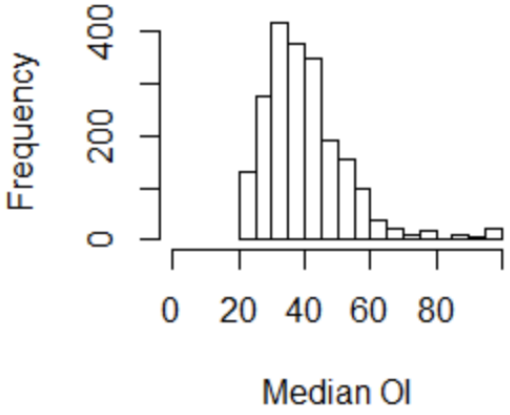
Study Flow Chart

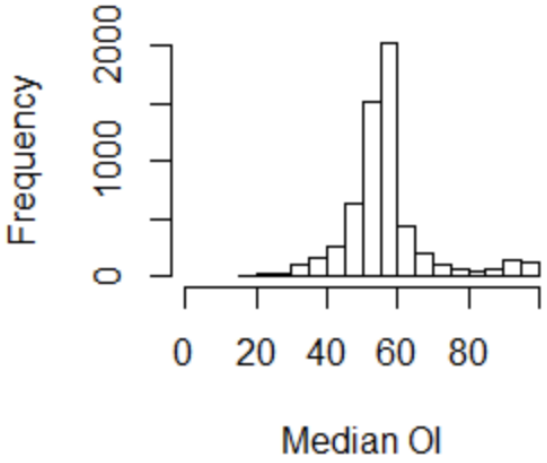


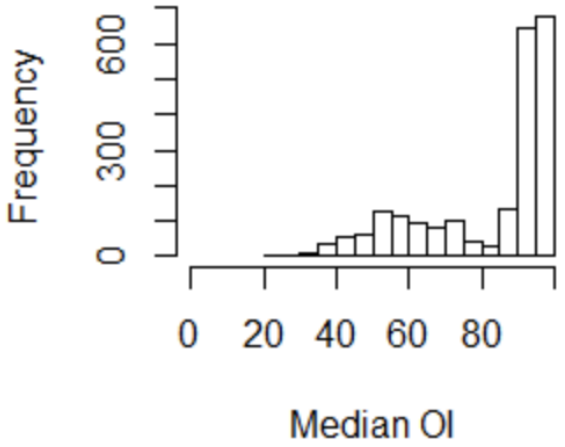
O_2 administration – Median F_iO_2 per case



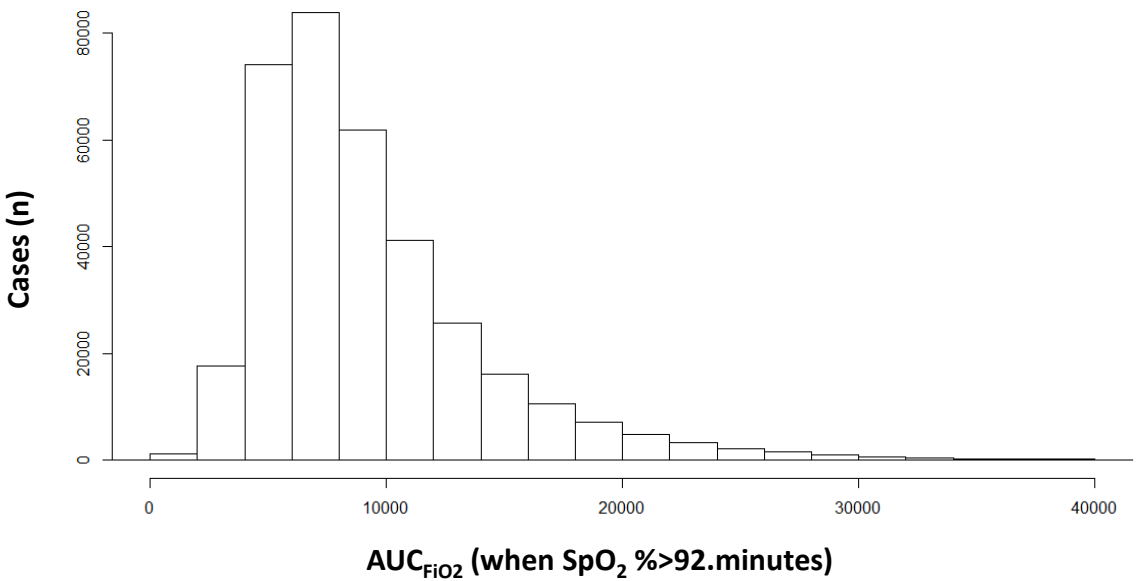
O_2 administration – Median F_iO_2 per case – by center







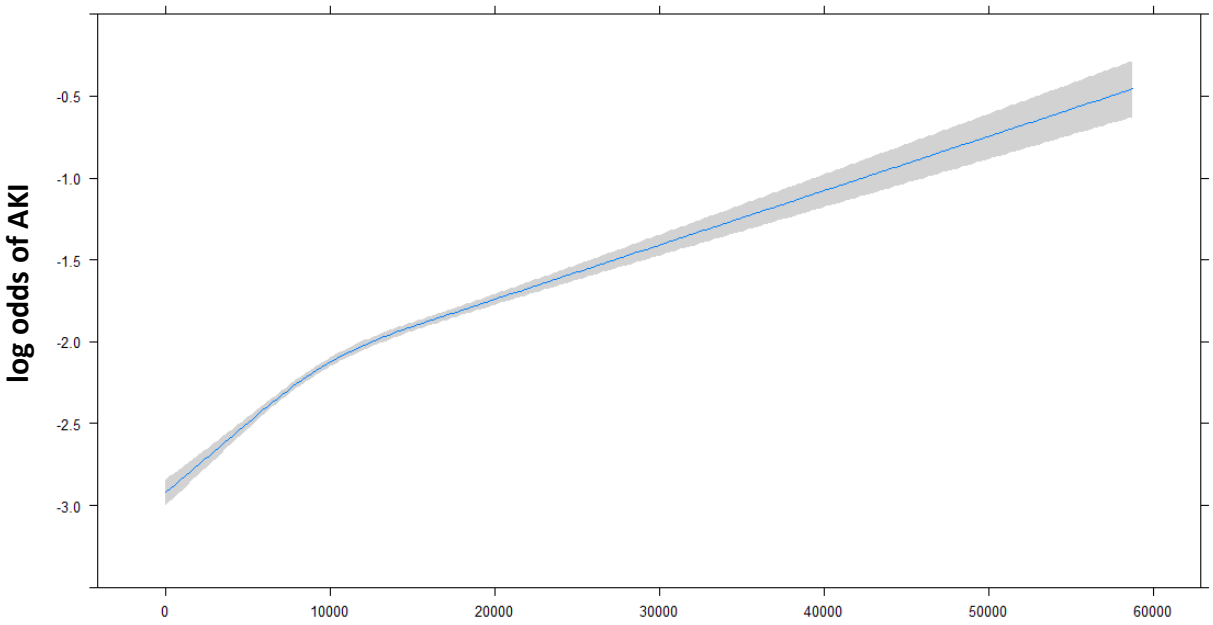
Oxygen exposure – calculated AUC



Outcomes - AKI

AKI status	N (%)
No AKI	172,393 (48.7%)
Stage 1 AKI	16,345 (4.6%)
Stage 2 AKI	2344 (0.7%)
Stage 3 AKI	806 (0.2%)
Insufficient data	156,003 (44.1%)
Preoperative renal failure	6119 (1.7%)

Outcomes – AKI



Outcomes – AKI: subgroup analysis by duration of surgery

Future plans

- Complete data cleaning and analysis
- Manuscript preparation (Anesthesiology)
- Pragmatic clinical trial informed by current data
  - Characterize current variation usual practice
  - Primary endpoint and plausible effect size
  - Logistics and feasibility

Supplemental Oxygen Therapy during Surgery

- Reduce tissue hypoxia?
- Increase reperfusion injury?
- Increase the production of ROS?
- Increase the production of ATP?
- Increase atelectasis?
- Suppress HIF signaling
- Decrease surgical site infection?

WHO global guidelines for the prevention of surgical site infection

World Health Organization

Strong guideline recommendations

- Patients with known nasal carriage of *S. aureus* should receive **intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexadine gluconate body wash.**
- **Mechanical bowel preparation alone (without the administration of oral antibiotics) should NOT be used** in adult patients undergoing elective colorectal surgery.
- In patients undergoing any surgical procedure, **hair should either NOT be removed or, if absolutely necessary, should only be removed with a clipper**. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room.
- **Surgical antibiotic prophylaxis (SAP) should be administered before surgical incision**, when indicated.
- **SAP should be administered within 120 min before incision**, while considering the half-life of the antibiotic.
- **Surgical hand preparation should be performed** either by scrubbing with a suitable antimicrobial soap and water or using a suitable alcohol-based handrub before donning sterile gloves.
- **Alcohol-based antiseptic solutions based on CHG for surgical site skin preparation should be used** in patients undergoing surgical procedures.
- Adult patients undergoing general anaesthesia with endotracheal intubation for surgical procedures should receive **80% fraction of inspired oxygen intraoperatively** and, if feasible, in the immediate postoperative period for 2–6 h.
- **Surgical antibiotic prophylaxis administration should not be prolonged** after completion of the operation.

2016

Protection from Hypoxia during Surgery?

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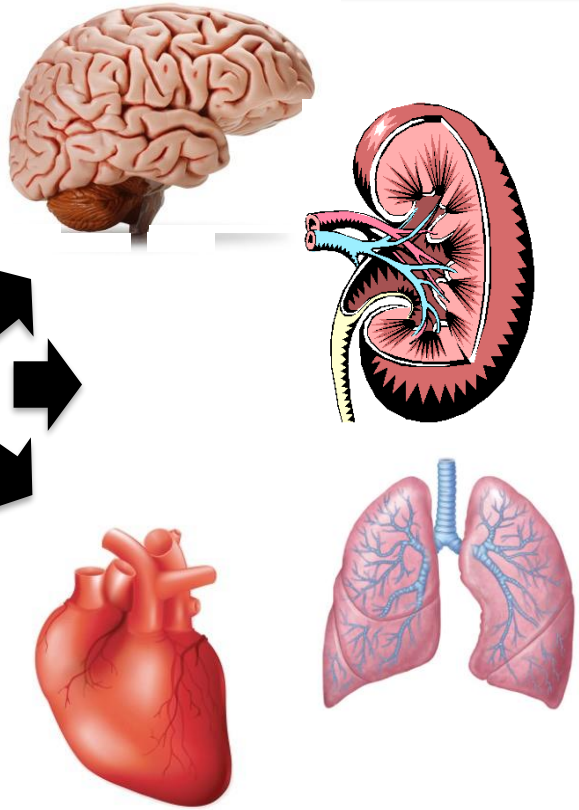
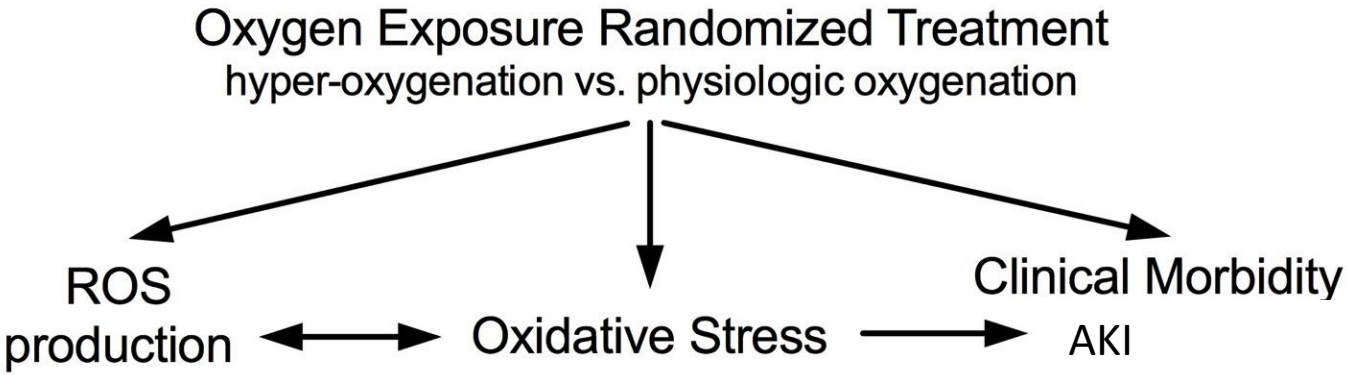
Bactericidal killing



Risk of Oxygen during Cardiac Surgery (ROCS) Trial



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Lopez *et al, Trials,* 2017.