

AWARD NUMBER: W81XWH-17-C-0241

TITLE: Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

PRINCIPAL INVESTIGATOR: Adit Ginde, MD, MPH

CONTRACTING ORGANIZATION: Funded by the Department of Defense/SOCOM

REPORT DATE: February 28th, 2020

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Final Technical Report

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1. **INTRODUCTION:** Oxygen therapy has undisputed importance in the care of critically ill medical and trauma patients to treat and prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. The overall objective is to determine the feasibility, safety, and potential effectiveness of targeted normoxia as a strategy to conserve oxygen and improve clinical outcomes in critically ill trauma patients.
2. **KEYWORDS:** oxygenation, oxygen delivery, mechanical ventilation, normoxia, hyperoxia, hypoxia, critically ill, trauma, prolonged field care, limited resources, traumatic brain injury, hemorrhage

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

- Aim 1. Define standard care for oxygen titration in critically ill trauma patients.

- 1) Obtain official 'not- human subjects research' determination from the Colorado Multiple Institutional Review Board—**Month 2:** 100% complete
 - 2) Perform literature review—**Month 2:** 100% complete
 - 3) Complete Delphi Stage 1—**Month 4:** 100% complete
 - 4) Complete Delphi Stage 2—**Month 6:** 100% complete
 - 5) Complete Delphi Stage 3—**Month 8:** 100% complete
 - 6) Complete Delphi Stage 4—**Month 11:** Not required
 - 7) Submit main manuscript for publication—**Month 14:** 100% complete

- Aim 2. Compare the effectiveness of targeted normoxia and relative hyperoxia in critically ill trauma patients.

- 1) Obtain IRB approval—**Month 2:** 100% complete
 - 2) Obtain USAMRMC ORP approval—**Month 5:** 100% complete
 - 3) Complete data collection—**Month 8:** 100% complete
 - 4) Complete primary data analysis—**Month 12:** 100% complete
 - 5) Submit main manuscript for publication—**Month 15:** 95% complete

- Aim 3. Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.

- 1) Finalize intervention and case report forms—**Month 9:** 100% complete
 - 2) Obtain IRB approval—**Month 11:** 100% complete
 - 3) Obtain USAMRMC ORP approval—**Month 14:** 100% complete
 - 4) Integrate clinical decision report in electronic medical record—**Month 14:** 100% complete
 - 5) Train clinical staff on intervention—**Month 15:** 100% complete
 - 6) Launch intervention period—**Month 16:** 100% complete
 - 7) Complete intervention period—**Month 21:** 100% complete

- 8) Complete primary data analysis—**Month 22:** 100% complete
- 9) Submit manuscript for publication—**Month 24:** 90% complete

▪ **What was accomplished under these goals?**

AIM 1:

- Published systematic review manuscript Journal of Trauma (2019) PMID: 31162333
- Delphi consensus presented at SOMSA 2019
- Delphi consensus presented at MHSRS 2019
- Delphi consensus manuscript drafted and under final review

AIM 2:

- Primary and Secondary Analysis complete
- Oral presentation at MHSRS 2019
- SOMSA 2020 (selected for poster presentation)
- Manuscript drafted and under final review

AIM 3:

- Local IRB approval
- HRPO approval
- Implementation completed
- Data collection completed
- Primary data analysis complete
- SOMSA 2020 (selected for oral presentation)
- Early draft of manuscript in process

Follow-on Work: Two multicenter trials

Strategy to Avoid Excessive Oxygenation (SAVE-O2) in Major Burn Patients

- Grant # MTEC-19-08-MULTI-0043

Strategy to Avoid Excessive Oxygenation (SAVE-O2) in Critically Ill Trauma Patients

- Selected for funding; funding # W81XWH-20-2-0001

▪ **How were the results disseminated to communities of interest?**

- CoERCCC presentation (Nov 2018)
- SOMSA Delphi presentation (April 2019)
- Capability Development Integration Directorate (CDID) presentation (April 2019)
- Oxygen Standardization Coordinating Group (OSCG) presentation (July 2019)
- Presented Delphi consensus in poster form MHSRS (August 2019)
- Presented AIM2 data analysis in oral form MHSRS (August 2019)

- Terry Adirim, MD, MPH, MBA (Acting Principal Deputy Assistant Secretary of Defense for Health Affairs) site visit (September 2019)
- Col Michael Davis, MD (Director of Combat Casualty Care Research Program) site visit (October 2019)
- CoERCCC presentation (Nov 2019)

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

- **What was the impact on the development of the principal discipline(s) of the project?**
 - Helped to define current standard care/best practices for oxygenation in critically ill trauma patients and collected important preliminary data leading to definitive multicenter trial funding
- **What was the impact on other disciplines?**
Nothing to Report
- **What was the impact on technology transfer?**
Nothing to report
- **What was the impact on society beyond science and technology?**
Nothing to Report

5. **CHANGES/PROBLEMS:**

Nothing to Report

- **Changes in approach and reasons for change**
Nothing to report
- **Actual or anticipated problems or delays and actions or plans to resolve them**
Delay in manuscript(s) publications: There were delays in the final analysis phase of AIM3. Further delays have occurred in manuscript completion and submission due in part to the large number of co-authors that have participated in the project.

ACTION PLAN:

We will work diligently over the next few months to finalize manuscripts and prepare for submission to relevant medical civilian and/or military journals.

- **Changes that had a significant impact on expenditures**

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- **Significant changes in use or care of human subjects:**

Nothing to report

- **Significant changes in use or care of vertebrate animals:**

N/A

- **Significant changes in use of biohazards and/or select agents:**

N/A

6. PRODUCTS:

- **Publications, conference papers, and presentations**

- *CoERCCC presentation 2018

- *Delphi Consensus presented at SOMSA 2019

- *CDID presentation 2019

- * Systematic review published Journal of Trauma and Acute Care Surgery 2019

- * OSGC presentation 2019

- *Delphi Consensus poster presentation MHSRS 2019

- * AIM2 Data oral presentation at MHSRS 2019

- * Col Davis, MS USAF site visit to the University of Colorado

- * CoERCCC presentation 2019

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Dr. Adit Ginde, MD, MPH
Project Role:	Principle Investigator
Researcher Identifier:	Not Available
Nearest person month worked:	0.93
Name:	Erin Anderson, RN
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	12

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Change to PI other support:

See Below
PREVIOUS SUPPORT

Title: *Vitamin D Supplementation and Immunosenesence in Older Long-Term Care Residents*

Funding Agency: NIH/NIA Paul B. Beeson Career Development Award in Aging Research (K23)

Role: Principal Investigator

Description/Aims: The research goals of this K23 Award are to evaluate the role of vitamin D supplementation in 1) prevention of acute respiratory infection and 2) immune responses to influenza and varicella zoster virus (shingles) vaccine in older long-term care residents.

Funding Period: 9/2011-8/2015

Amount: \$736,213

Time Commitment: 75%

Agency Contact: Judy Hannah, 301-496-676, hannahj@nia.nih.gov

Title: *Proton Pump Inhibitors for Prevention of Septic Acute Kidney Injury*

Funding Agency: NIH/Colorado Clinical and Translational Sciences Institute (CCTSI)
Independent Investigator Award

Role: Principal Investigator

Description/Aims: The goals of this study are to better understand the dose and timing of proton pump inhibitor therapy to define the therapeutic window for kidney protection during experimental sepsis and to evaluate the association between early proton pump

inhibitor therapy and acute kidney injury severity in human patients hospitalized for septic shock.

Funding Period: 4/2014-6/2015

Amount: \$60,000

Time Commitment: 5%

Agency Contact: Tim Lockie, 720-848-6660, tim.lockie@cuanschutz.edu

Title: *Reevaluation of Systemic Early neuromuscular blockade (ROSE)*

Funding Agency: NHLBI/Massachusetts General Hospital Prevention and Early Treatment of Acute Lung Injury Network

Role: Co-Site PI/Co-Investigator

Description/Aims: The goal of this phase III trial is to determine the efficacy and safety of neuromuscular blockade in reducing mortality of emergency department and intensive care unit patients with moderate-severe acute respiratory distress syndrome.

Funding Period: 11/2015-6/2018

Amount: \$291,050

Time Commitment: 1%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)*

Funding Agency: NHLBI/Massachusetts General Hospital Prevention and Early Treatment of Acute Lung Injury Network

Role: Principal Investigator

Description/Aims: The goal of this phase III trial is to determine if early administration of vitamin D reduces 90-day mortality in critically ill, vitamin D deficient patients at high-risk for developing acute respiratory distress syndrome (ARDS). I will lead the conduct of a 3,000 patient, 48-institution randomized controlled trial.

Funding Period: 5/2016-1/2019

Amount: \$13,218,470

Time Commitment: 10%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Targeting Steroid Resistance During Acute Exacerbations of COPD with Respiratory Failure – The AECOPD Resistance Study*

Funding Agency: NIH/Colorado Clinical and Translational Sciences Institute (CCTSI) Team Science Award (PI: Vandivier)

Role: Co-Investigator

Description/Aims: The goals of this study is to determine the mechanisms and clinical implications of steroid resistance in emergency department patients during acute exacerbation of chronic obstructive pulmonary disease with respiratory failure who require mechanical ventilation and ICU admission.

Funding Period: 7/2016-6/2018

Amount: \$100,000

Time Commitment: 1%

Agency Contact: Tim Lockie, 720-848-6660, tim.lockie@cuanschutz.edu

Title: *Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat-Injured Special Operations Forces*

Funding Agency: Department of Defense/U.S. Special Operations Command

Role: PD/PI

Description/Aims: The goal of this application is to determine the feasibility, safety, and potential effectiveness of targeted normoxia as a strategy to conserve oxygen and improve clinical outcomes in critically ill trauma patients.

Award Number: W81XWH-17-C-0241

Funding Period: 09/29/17-01/28/20

Amount: \$274,272

Time Commitment: 10%

Agency Contact: Douglas Simpson, douglas.simpson@socom.mil

Title: *Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS)*

Funding Agency: Johns Hopkins University -The Marcus Foundation, Inc

Role: SubAward PI

Description/Aims: The goal of this study is to test the efficacy of vitamin C, thiamine, and steroids in reducing in-hospital mortality in critically ill patients with sepsis.

Award Number: #2393 (Rothman)

Funding Period: 10/01/18-12/31/19

Amount: \$219,394

Time Commitment: 2%

Agency Contact: Amanda Bistran-Hall, 410-361-7999, abistral@jhmi.edu

CURRENT SUPPORT

Title: *Colorado PETAL Clinical Center*

Funding Agency: National Heart, Lung, and Blood Institute (NHLBI) (Moss / Ginde)

Role: PD/PI

Description/Aims: The goal of this application is to participate in the selection and conduct of clinical trials for the prevention and early treatment of acute lung injury across a network of 12 clinical centers. Our clinical center includes two academic and four community hospitals in the greater Denver area and a robust infrastructure for recruitment of critically ill emergency department and intensive care unit patients into clinical trials.

Award Number: 1U01HL123010

Funding Period: 06/17/14-04/30/21

Amount: \$373,520

Time Commitment: 12.5%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Prevention and Early Treatment of Acute Lung Injury (PETAL) Network: "Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)*

Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)

Role: Co-Investigator

Description/Aims: The goal of this phase III trial is to determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) or a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

Award Number: U01HL123009 (Shapiro/Douglas)

Funding Period: 06/17/2014-04/30/21

Amount: \$293,207

Time Commitment: 2.5%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Brain Oxygen Optimization in Severe Traumatic Brain Injury – Phase 3 (BOOST-3)*

Funding Agency: National Institute of Neurological Diseases and Stroke (NINDS)

Role: Co-Investigator

Description/Aims: The goal of this study to determine if there is evidence of clinical efficacy of a treatment protocol based on brain tissue oxygenation (PbtO₂) monitoring compared to treatment based on intracranial pressure (ICP) monitoring alone.

Award Number: U01NS099046 (Barsan)

Funding Period: 07/01/18-06/30/23

Amount: \$8,525,394

Time Commitment: 1%

Agency Contact: Maria Mendoza-Puccini, 301-496-9135, maria.mendoza.puccini@nih.gov

Title: *EMS-TruShoC’ – A Prospective Trial of Low-Dose, High-Frequency, On-Site Training to Improve Trauma Field Care in Austere Settings*

Funding Agency: Defense Health Agency (J9, Research and Development Directorate); US Department of the Air Force (59th Medical Wing)

Role: Co-Investigator

Description/Aims: The goal of this project is to implement EMS-TruShoC in an austere setting and assess the resultant educational and clinical outcomes. These prehospital trauma resuscitation concepts will inform future efforts to translate into USSOF and conventional military prehospital training and sustaining knowledge.

Award Number: FA8650-18-2-6934 (Mould-Millman/Schauer)

Funding Period: 07/30/18-07/29/20

Amount: \$155,000

Time Commitment: 1.75%

Agency Contact: Clifford Johnson, 937-713-9922, Clifford.johnson.4@us.af.mil

Title: *Vitamin D to Improve Outcomes by Leveraging Early Treatment: Long-term Brain Outcomes in Vitamin D Deficient Patients (VIOLET BUD)*

Funding Agency: Vanderbilt - National Heart, Lung, and Blood Institute (NHLBI)

Role: SubAward PI/Co-Investigator

Description/Aims: The goal of this project is to determine the effect of vitamin D repletion on long-term cognitive outcomes in critically ill patients.

Award Number: R56HL141567 (Han)

Funding Period: 09/05/18-08/31/20

Amount: \$92,352

Time Commitment: 10%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Precision Medicine Approach to Vitamin D3 Administration in Critical Illness*

Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)

Role: SubAward PI/Co-Investigator

Description/Aims: The goal of this study is using a precision medicine approach to investigate the clinical, genetic, and biochemical factors that determine response to vitamin D3 administration in critical illness.

Award Number: R01HL544166 (Leaf)

Funding Period: 07/01/19-06/30/23

Amount: \$18,610

Time Commitment: 5%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Influenza Vaccine Effectiveness for Preventing Laboratory-Confirmed Severe Influenza-Associated Illness in US Adults*

Funding Agency: Centers for Disease Control and Prevention (CDC)

Role: SubAward PI/Co-Investigator

Description/Aims: The goal of this study is to understand the role of influenza infection in critical illness and the effectiveness of influenza vaccines for mitigating influenza-associated morbidity and mortality.

Award Number: 75D30119C05670 (Self)

Funding Period: 07/10/19-07/09/20

Amount: \$82,371

Time Commitment: 1%

Agency Contact: Vallerie Redd, 770-488-2845

Title: *The Impact of Fluid Resuscitation on Glycocalyx Degradation in Septic Shock*

Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)

Role: Co-Investigator (PI: Shapiro/Schmidt)

Description/Aims: The goal of this project is to determine the mechanism of intravenous fluid resuscitation in glycocalyx degradation and adverse clinical outcomes in septic shock.

Award Number: R01HL149422 (Shapiro/Schmidt)

Funding Period: 09/01/19-05/31/23

Amount: \$11,000

Time Commitment: 1%

Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Establishing the Epidemiology and Outcomes of Combat-Relevant Prolonged Trauma Care: A Prospective Multicenter Prehospital Pilot Study in South Africa*

Funding Agency: Department of Defense (USAMCMR)

Role: Co-Investigator

Award Number: BA190054 (Mould Millman)

Description/Aims: The goal of this project is to assess the effect of prolonged durations of prehospital care, and key prehospital interventions, on morbidity and mortality of patients with combat-like injuries.

Funding Period: 09/30/19-09/29/21

Amount: \$1,725,977

Time Commitment: 5%

Agency Contact: Jennifer Shankle, 301-619-2193, Jennifer.e.shankle.civ@mail.mil

Title: *Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Major Burn Patients: An Approach to Reduce Warfighter Morbidity, Deployed Logistical Burden of Oxygen, and Readiness Costs*

Funding Agency: Department of Defense/ Medical Technology Enterprise Consortium (MTEC)

Role: Principal Investigator

Description/Aims: The goal of this study is to determine the feasibility, safety, and effectiveness of the targeted normoxia approach to conserve oxygen and improve clinical outcomes in major burn patients.

Funding Period: 01/30/2020-01/31/2023

Amount: \$913,737

Time Commitment: 10%

Agency Contact: Kathy Zolman, 843-760-4349, kathy.zolman@ati.org

Title: *Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care*

Funding Agency: Department of Defense (Joint Warfighter Medical Research Program)

Role: Principal Investigator

Description/Aims: The goal of this study is to determine the feasibility, safety, and effectiveness of the targeted normoxia approach to conserve oxygen and improve clinical outcomes in critically injured patients

Funding Period: 03/01/2020- 02/28/2023

Amount: \$982,969

Time Commitment: 25%

Agency Contact: Sandy Snyder, 301-619-7047, sandy.j.snyder.civ@mail.mil

OVERLAP

None.

- **What other organizations were involved as partners?**
- Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**

Nothing to Report

- **QUAD CHARTS:**

Attached

9. APPENDICES:

- CoERCCC presentation 2018
- SOMSA Delphi Consensus presentation 2019
- CDID presentation 2019
- Systematic review manuscript
- Delphi consensus abstract
- AIM 2 Observational abstract
- Oxygen standardization coordinating group
- Delphi consensus poster MHSRS 2019
- Observational AIM 2 data presentation MHSRS 2019
- Col Davis, MD site visit presentation
- AIM 3 pilot trial abstract
- CoERCCC presentation 2019

Targeted Normoxia to Conserve Oxygen and Improve Outcomes in Combat Injured Special Forces



W81XWH-17-C-0241

PIs: Adit A. Ginde, MD, MPH; MAJ Steven Schauer, DO, MS



University of Colorado
Anschutz Medical Campus
School of Medicine

My Background

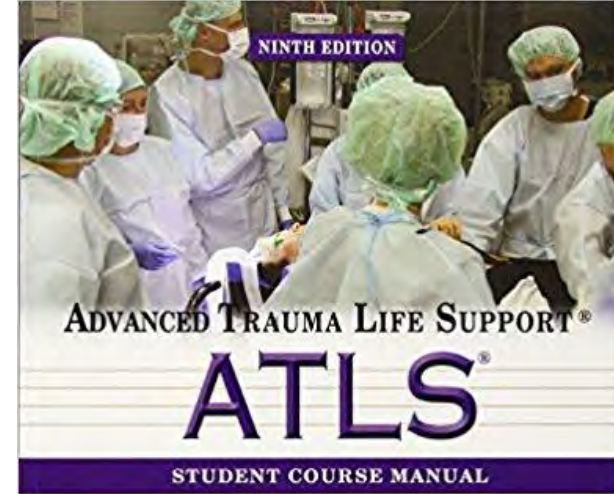
- ▶ Professor, University of Colorado
 - ▶ Vice Chair for Research,
Emergency Medicine & Anesthesiology
 - ▶ Practicing emergency medicine physician
 - ▶ Multicenter clinical trials in critical care
 - ▶ NIH PETAL Network
- 

Significance



- ▶ Supplemental oxygen key to avoid morbidity from hypoxia
- ▶ Excessive oxygen in EnRoute Care
 - Common practice
 - Unlikely to benefit; may cause harm
 - Expands mission size, weight, and logistics
- ▶ Gap: Limited data on optimal oxygen titration targets in critically injured patients

Current State



- ▶ “Oxygenated inspired air is best provided via a tight fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”
- ▶ “The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation... a pulse oximeter reading greater than 90%.”

COMBAT CASUALTY CARE

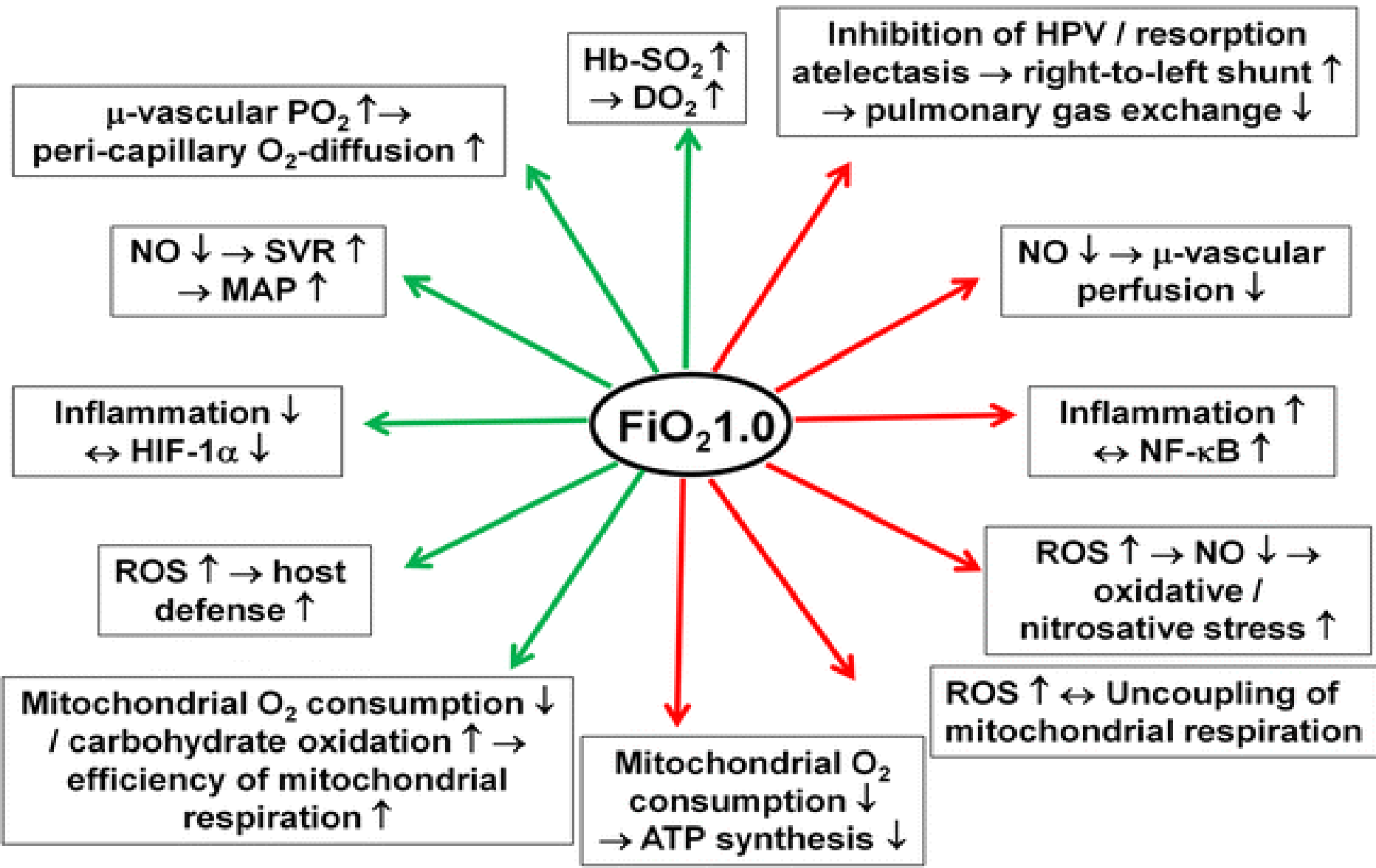
Lessons Learned from OEF and OIF

Edited by

Eric Savitsky, MD

Colonel Brian Eastridge, MD

Hyperoxia Physiology



Rationale for Normoxia

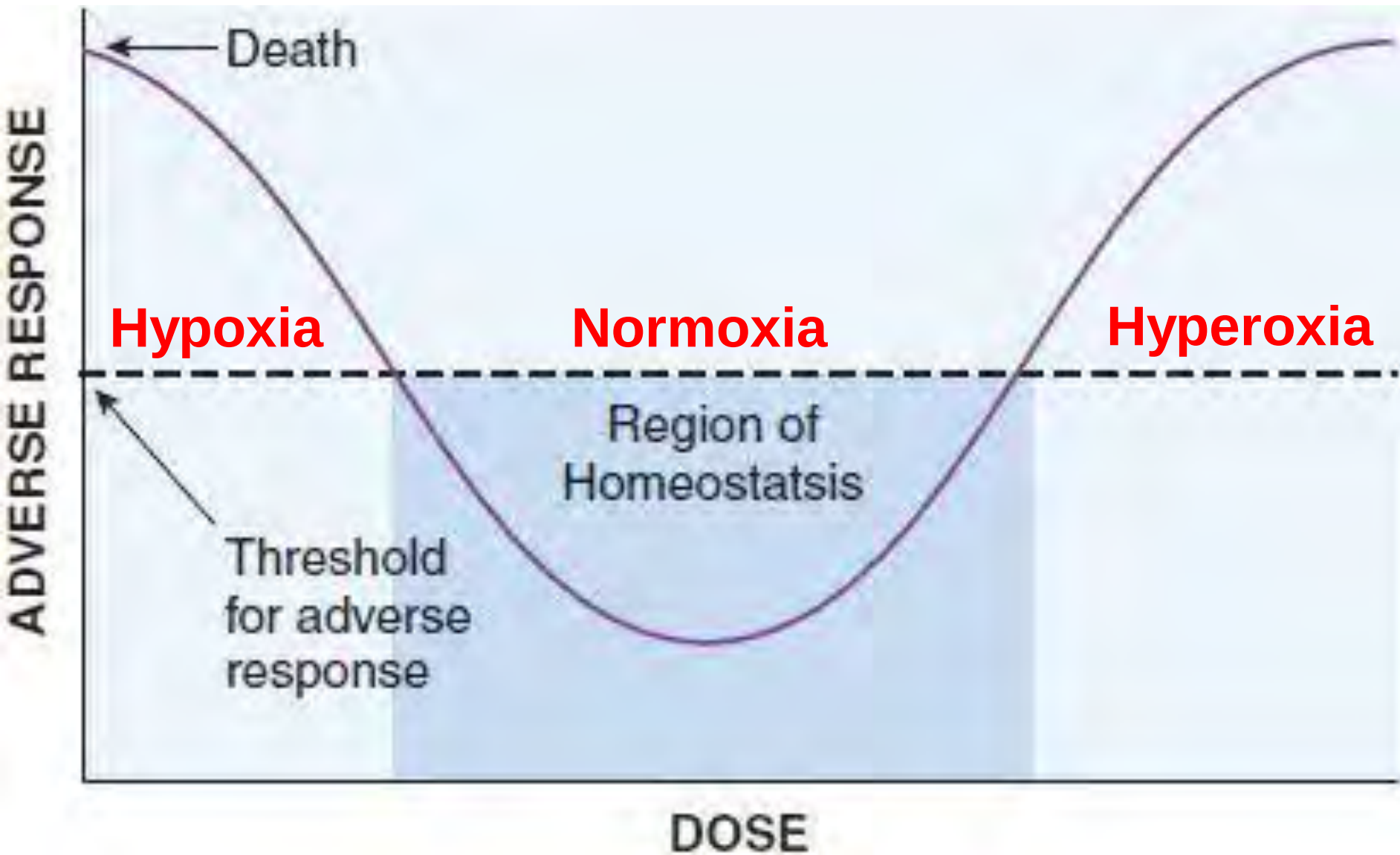
Hypoxia

- ▶ Anaerobic metabolism
- ▶ Cell death (necrosis)
- ▶ Brain = 20% O₂ consumption

Hyperoxia

- Vasoconstriction
- Oxidative stress
- Pro-inflammatory
- Decreased mucociliary clearance in lung

Oxygen as a drug



Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis



Lancet 2018; 391: 1693-705

Derek K Chu†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani*

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis



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Interpretation: In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94-96%

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

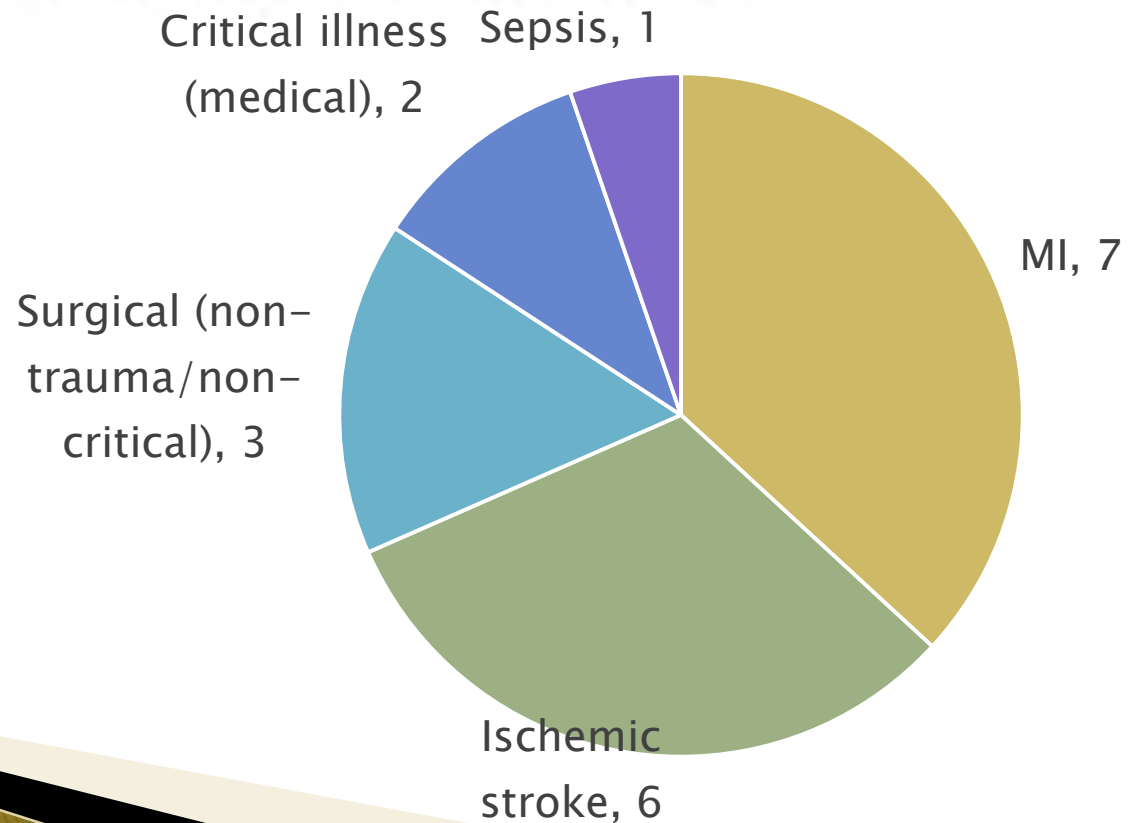


Lancet 2018; 391: 1693-705

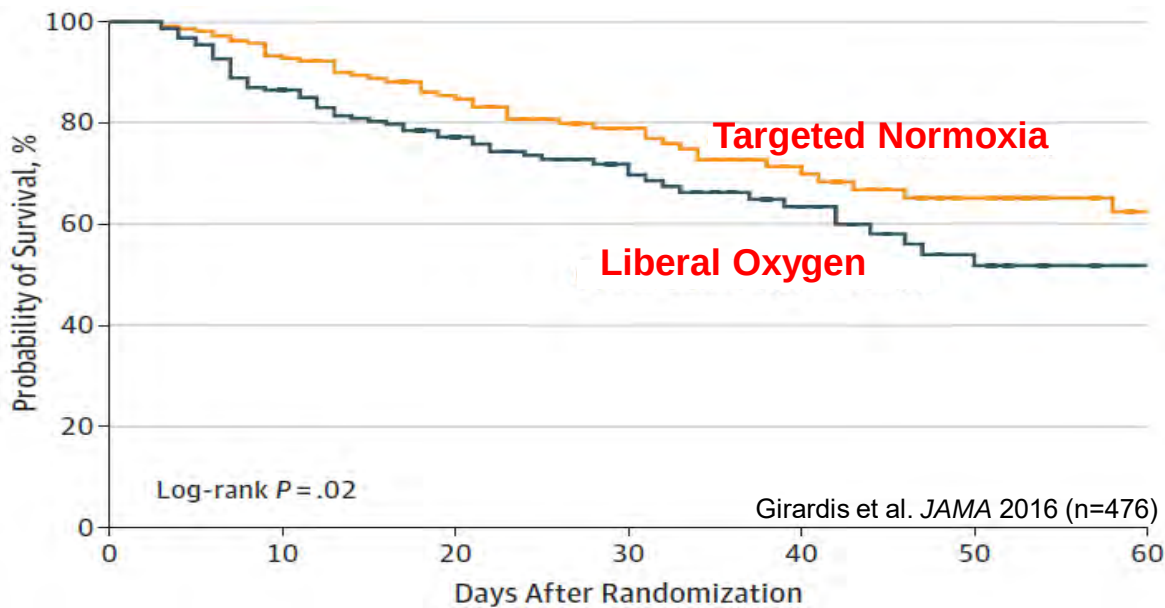
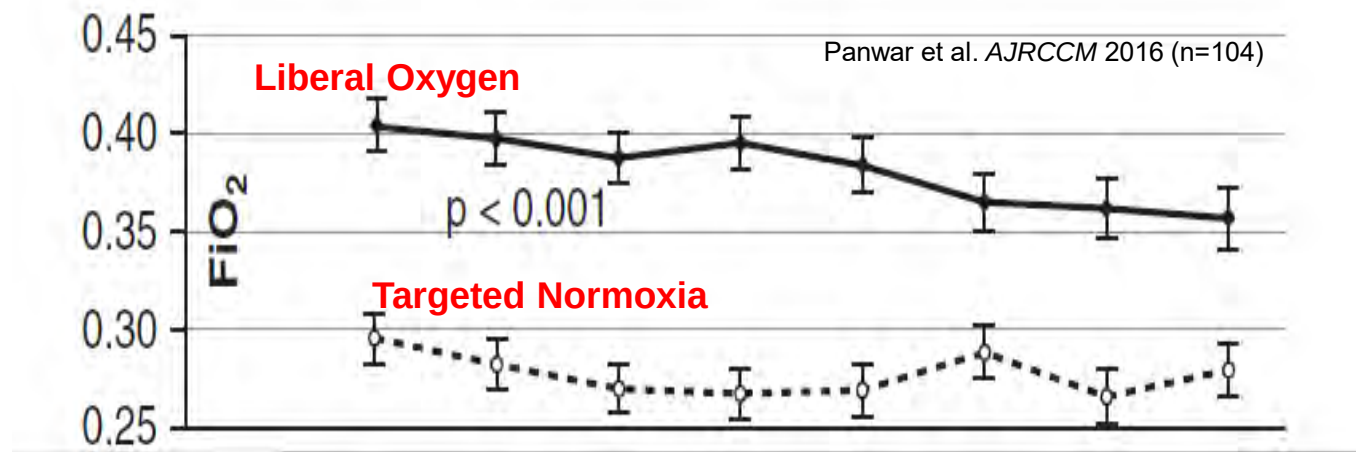
Derek K Chu*†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani

Interpretation In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94–96%. These results support the conservative administration of oxygen therapy.

But...no trauma



Critical Care Trials (non-trauma)



Question

How do we advance definitive evidence for safe and effective oxygen targets in CCC/ERC?



Specific Aims—SOCOM

1. Define current standard care for oxygen titration in critically ill trauma patients
 - Systematic review of existing relevant evidence
 - SMEs to define consensus-based definitions
2. Compare effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
 - Retrospective cohort study to define the association between oxygenation and clinical outcomes
3. Develop and pilot test a targeted normoxia intervention in critically ill trauma patients
 - Demonstrate safe and feasible implementation
 - Prepare for large, multicenter trial

Systematic Review

- ▶ **Included (n=43)**
 - 17 trauma studies
 - 26 non-trauma critical illness
- ▶ **Conclusions**
 - Overall association between lower oxygen/normoxia and improved clinical outcomes
 - Few trauma specific articles
 - 14 out of 17 related exclusively to TBI
 - No high quality/RCT data
 - Supports need for further trauma-specific studies/RCTs, particularly beyond TBI

Expert Panel (Military, n=13)

Last Name	First Name	Speciality	Institution
Becker	Tyson	Trauma Surgery	SAMMC
Chung	Kevin	Critical Care	SAMMC
Keenan	Sean	Emergency Medicine	SOCOM/SOCEUR
Mason	Philip	Critical Care	SAMMC
Miles	Ethan	Other	Ft. Benning
Oh	John	Trauma Surgery	Penn State
Redman	Theodore	Emergency Medicine	Ft. Campbell
Reisburg	Jamie	Other	Ft. Carson
Rush	Stephen	Other	USAF
Tobin	Josh	Critical Care	USC
Walrath	Benjamin	Emergency Medicine	Naval Medical Center
Wilson	Ramey	Other	SOCAFRICOM

Expert Panel (Civilian, n=18)

Last Name	First Name	Speciality	Institution
Brainard	Jason	Critical Care	Denver
Cohen	Mitchell	Trauma Surgery	Denver
Cotton	Bryan	Trauma Surgery	Houston
Doshi	Pratik	Critical Care	Houston
Guyette	Franklin	Emergency Medicine	Pittsburgh
Huang	David	Critical Care	Pittsburgh
Idrovo	Juan-Pablo	Trauma Surgery	Denver
Khan	Akram	Critical Care	Oregon
McIntyre	Robert	Trauma Surgery	Denver
Moore	Ernest	Trauma Surgery	Denver
Newgard	Craig	Emergency Medicine	Oregon
Nunez	Timothy	Trauma Surgery	Vanderbilt
Rice	Todd	Critical Care	Vanderbilt
Schreiber	Martin	Trauma Surgery	Oregon
Self	Wesley	Emergency Medicine	Vanderbilt
Sperry	Jason	Trauma Surgery	Pittsburgh
Wang	Henry	Emergency Medicine	Houston
Wright	Franklin	Trauma Surgery	Denver

Initial Rationale

1) Aim for “normoxia”

- Aim for maintaining “normal” oxygen levels
- The goal is to prevent hypoxia, not to achieve hyperoxia
- Data do not support hyperoxia as the target, may be worse
- Hypoxic episodes associated with worse outcomes, may need cushion to prevent hypoxia

Initial Rationale

1) Aim for “normoxia”

- Aim for maintaining “normal” oxygen levels
- The goal is to prevent hypoxia, not to achieve hyperoxia
- Data do not support hyperoxia as the target, may be worse
- Hypoxic episodes associated with worse outcomes, may need cushion to prevent hypoxia

2) Cultural norms need to be challenged

- Generous oxygen entrenched in clinical practice
- Oxygen titration decisions are made to avoid hypoxia but typically not to achieve hyperoxia
- Convenience is a driver of hyperoxia in current practice

Initial Rationale

1) Aim for “normoxia”

- Aim for maintaining “normal” oxygen levels
- The goal is to prevent hypoxia, not to achieve hyperoxia
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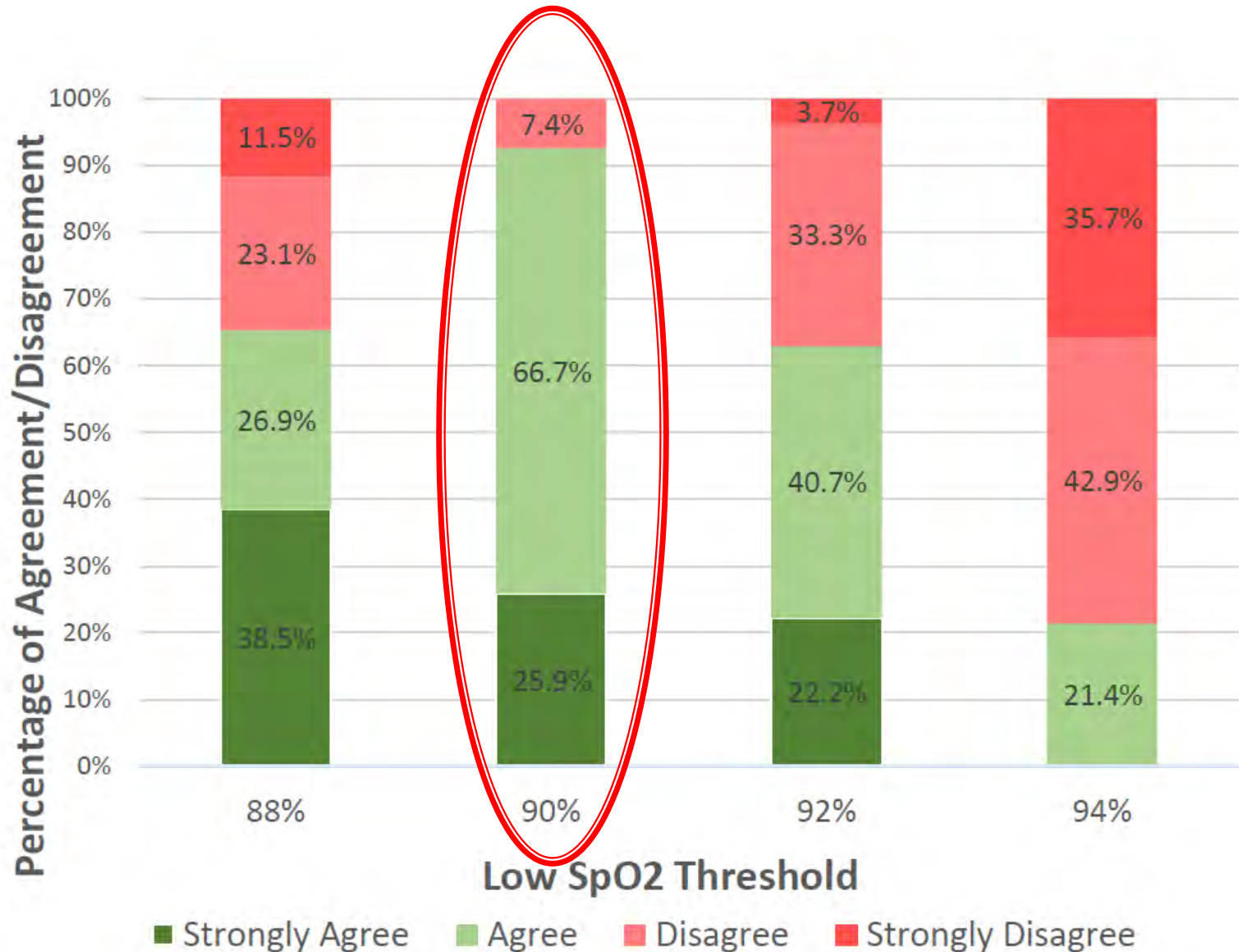
2) Cultural norms need to be challenged

- Oxygen titration decisions are made to avoid hypoxia not to achieve hyperoxia
- Convenience is a driver of hyperoxia in current practice
- Reliance on a comfort buffer to avoid hypoxia is valued over physiological evidence

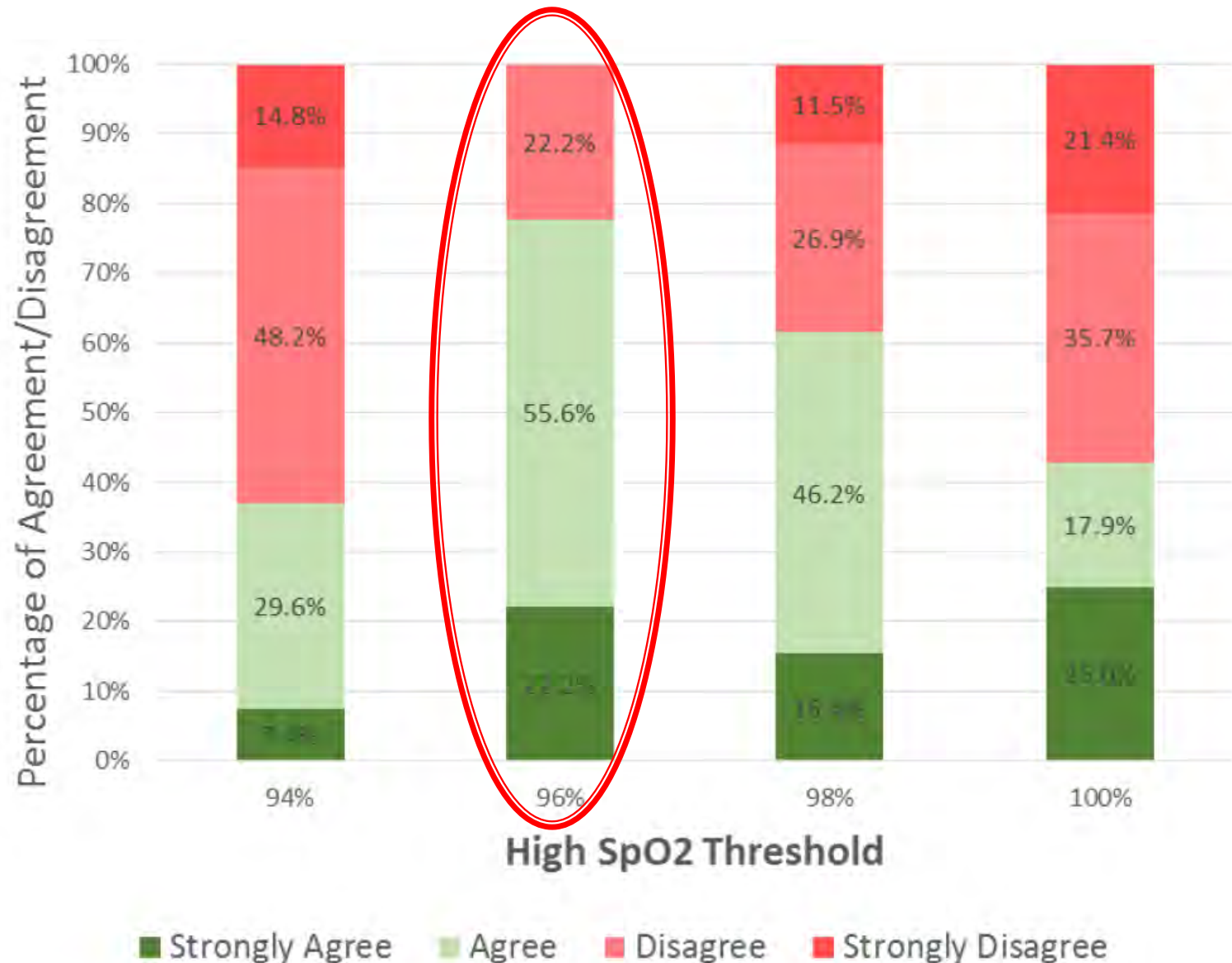
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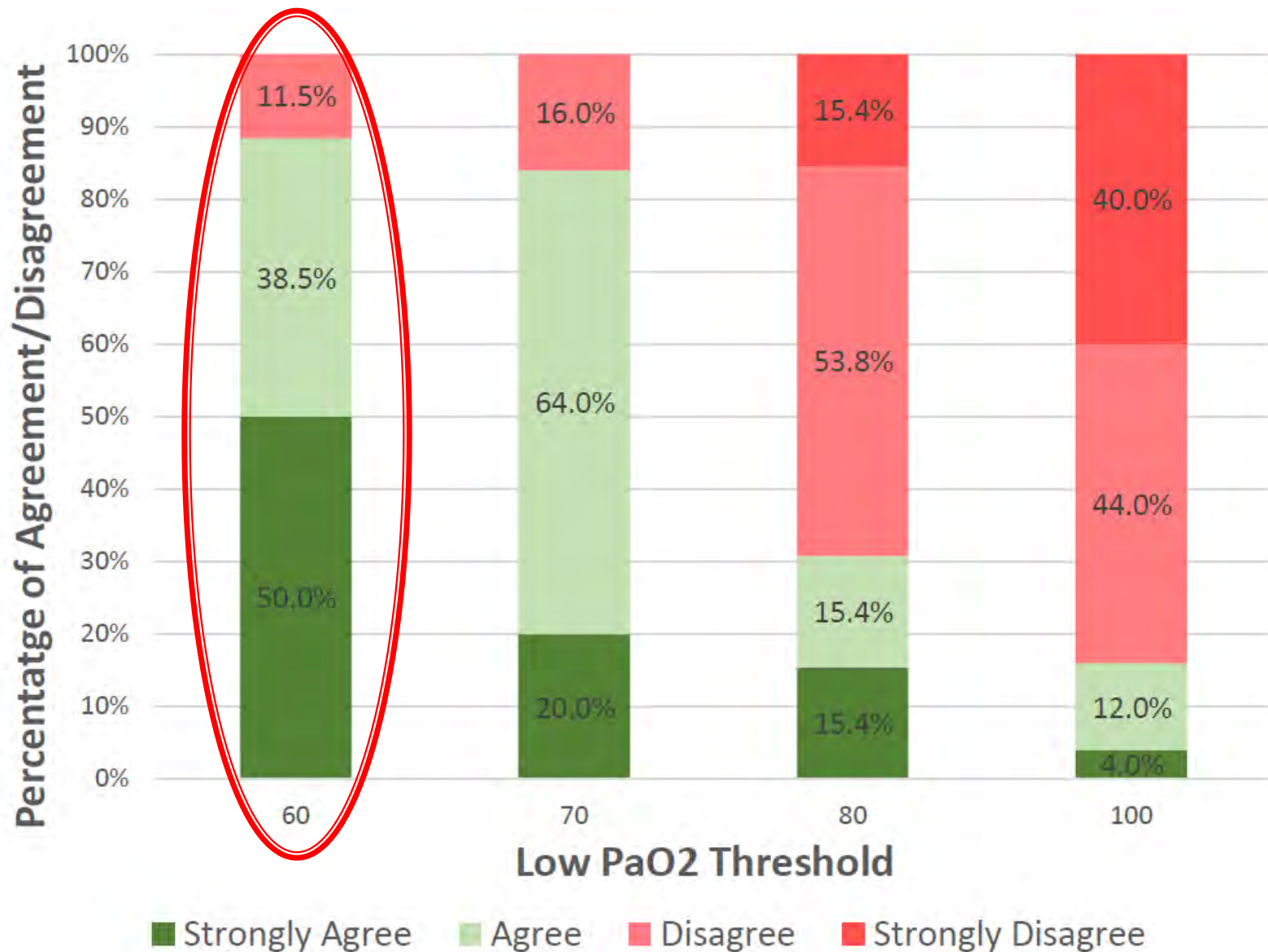
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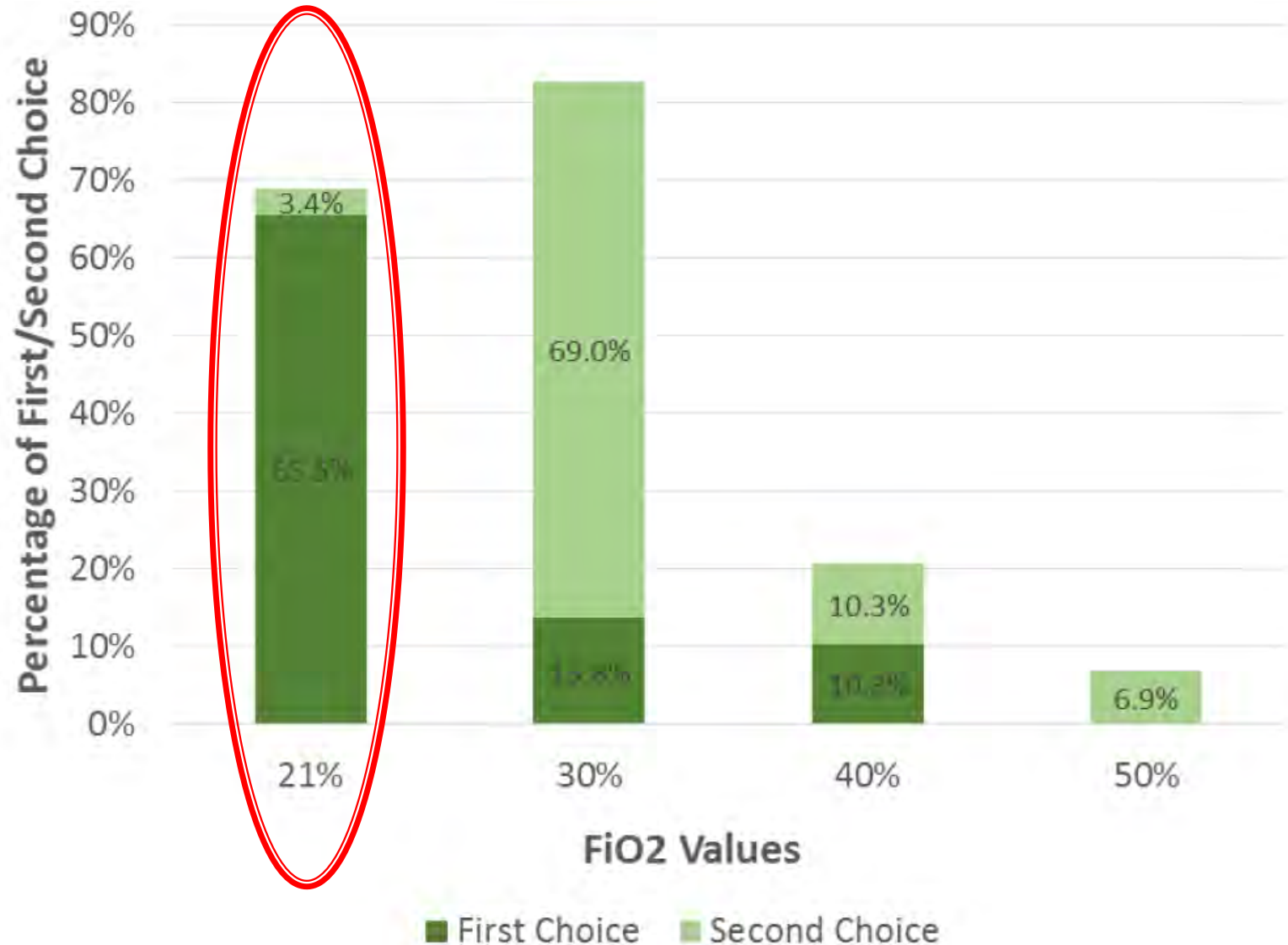
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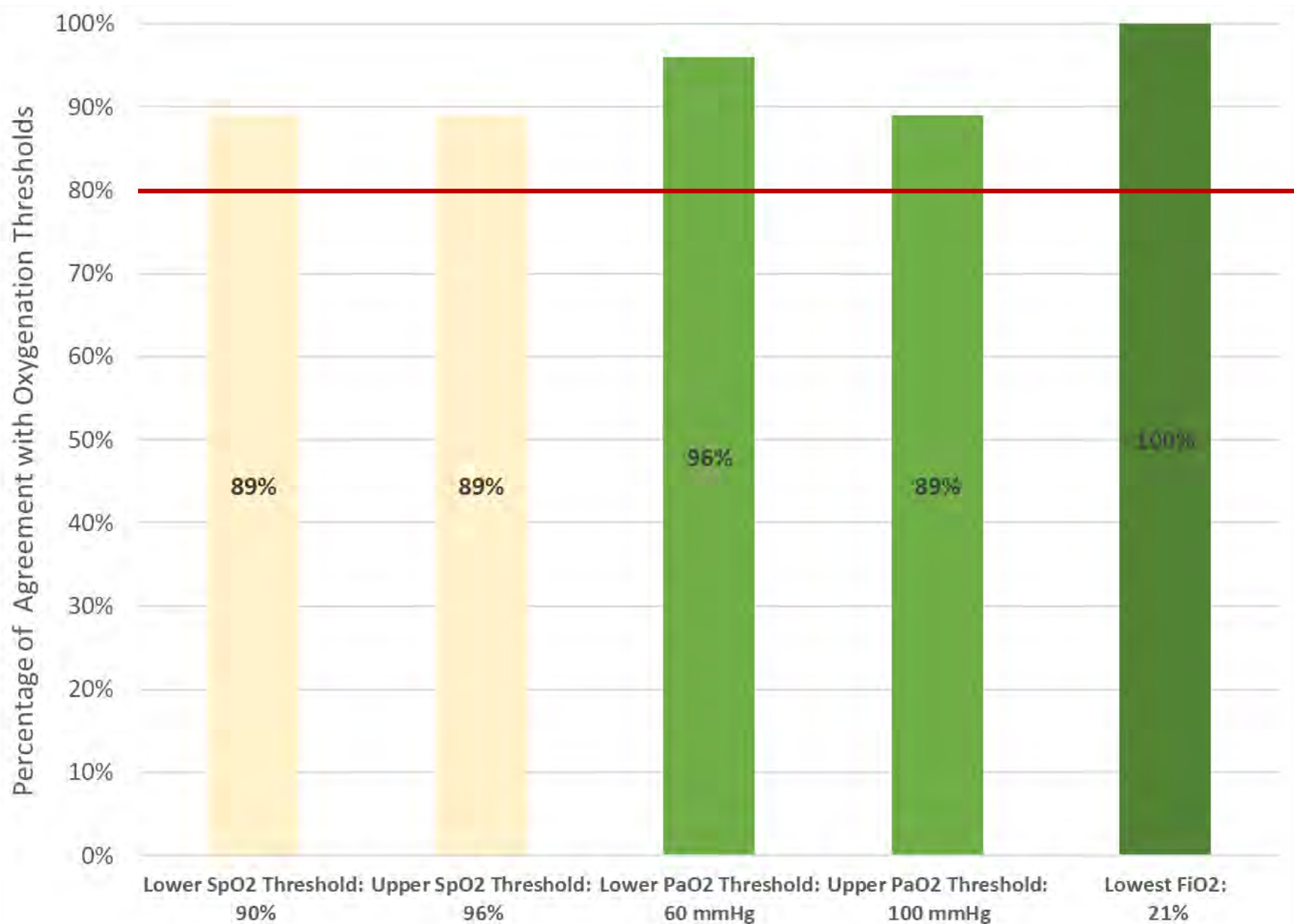
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Lowest FiO2 to Maintain Oxygenation



Final Vote



Special considerations

- Severe TBI: 33%
- Hemorrhagic shock: 11%
- Lowest SpO₂ in resource limited settings
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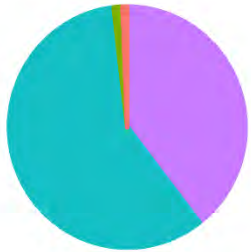
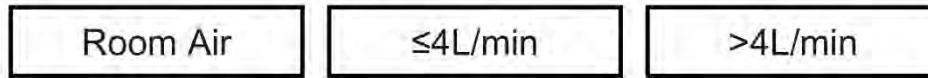


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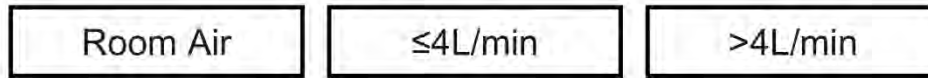
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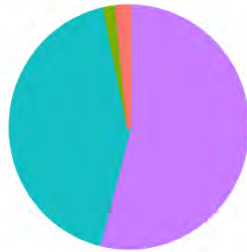
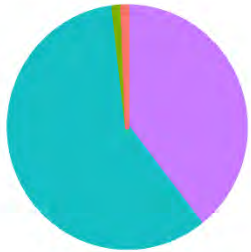


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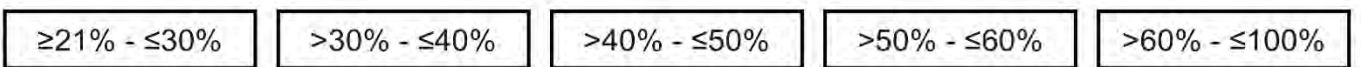
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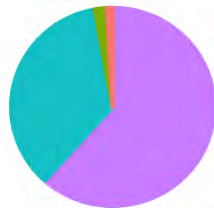
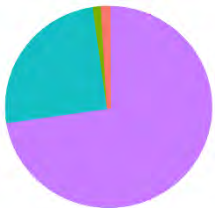
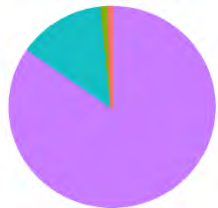
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FiO₂ (%)



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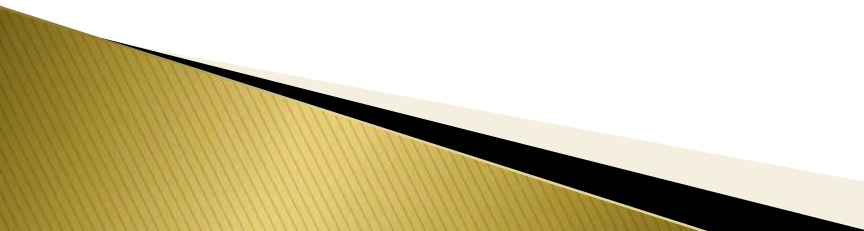
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Multicenter Normoxia Trial

- ▶ **Goal:** definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
 - Particularly important for ERC/PFC
 - ▶ **Design:** cluster randomized, stepped wedge implementation trial
 - ▶ **Human subjects issues:** minimal risk, waiver of informed consent (efficient, cost savings)
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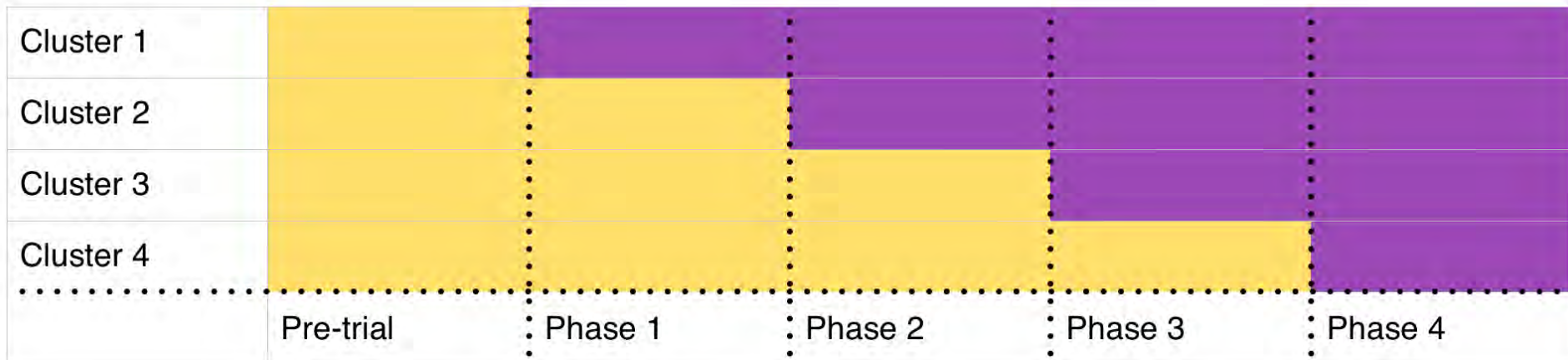
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Proposed Sites



Stepped wedge design

- ▶ Each site implements intervention in a staggered fashion with order randomized



Time →



Other activities

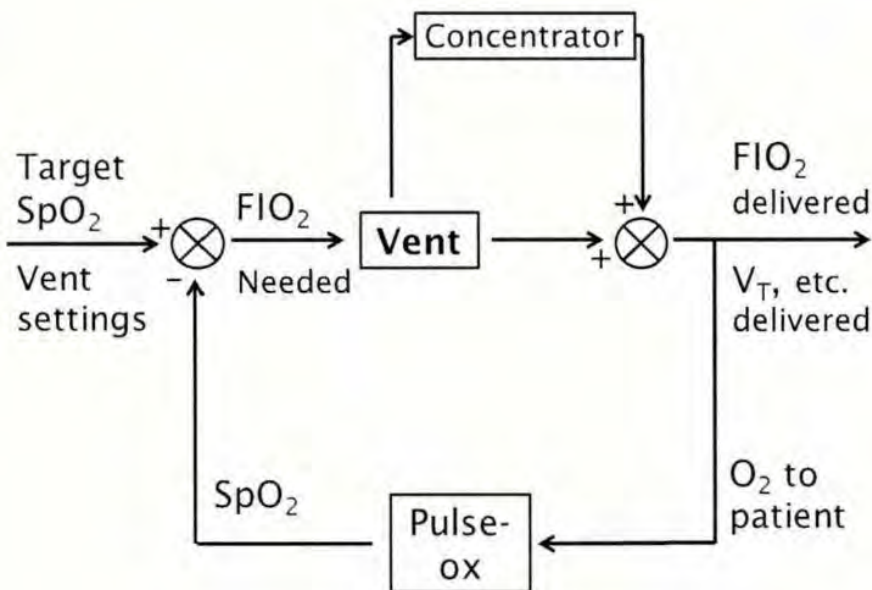
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 - Focus on ERC
 - Knowledge product is critical
 - Broad implementation requires definitive evidence

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 - Testing SpO₂ 88–92%, 92–96%, >96%
 - Medical critical illness



Technology/Solutions

- ▶ Portable oxygen concentrators
 - Benefit greatly by decreased oxygen requirement
- ▶ Pulse oxygen delivery
- ▶ Rebreathing system
- ▶ Autonomous closed loop control



Contact

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adit.ginde@ucdenver.edu
Phone: 720-848-6777



University of Colorado
Anschutz Medical Campus
School of Medicine

Targeted Normoxia to Conserve Oxygen and Improve Outcomes in Combat Injured Special Forces



W81XWH-17-C-0241

PIs: Adit A. Ginde, MD, MPH; MAJ Steven Schauer, DO, MS



University of Colorado
Anschutz Medical Campus
School of Medicine

My Background

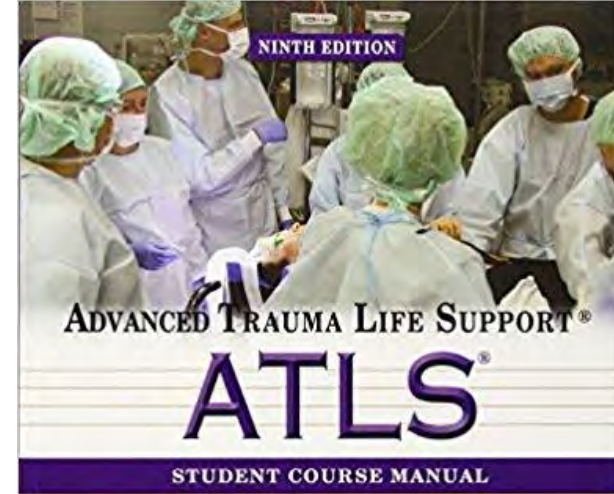
- ▶ Professor, University of Colorado
 - ▶ Vice Chair for Research,
Emergency Medicine & Anesthesiology
 - ▶ Practicing emergency medicine physician
 - ▶ Multicenter clinical trials in critical care
 - ▶ NIH PETAL Network
- 

Significance



- ▶ Supplemental oxygen key to avoid morbidity from hypoxia
- ▶ Excessive oxygen in EnRoute Care
 - Common practice
 - Unlikely to benefit; may cause harm
 - Expands mission size, weight, and logistics
- ▶ Gap: Limited data on optimal oxygen titration targets in critically injured patients

Current State



- ▶ “Oxygenated inspired air is best provided via a tight fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”
- ▶ “The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation... a pulse oximeter reading greater than 90%.”

COMBAT CASUALTY CARE

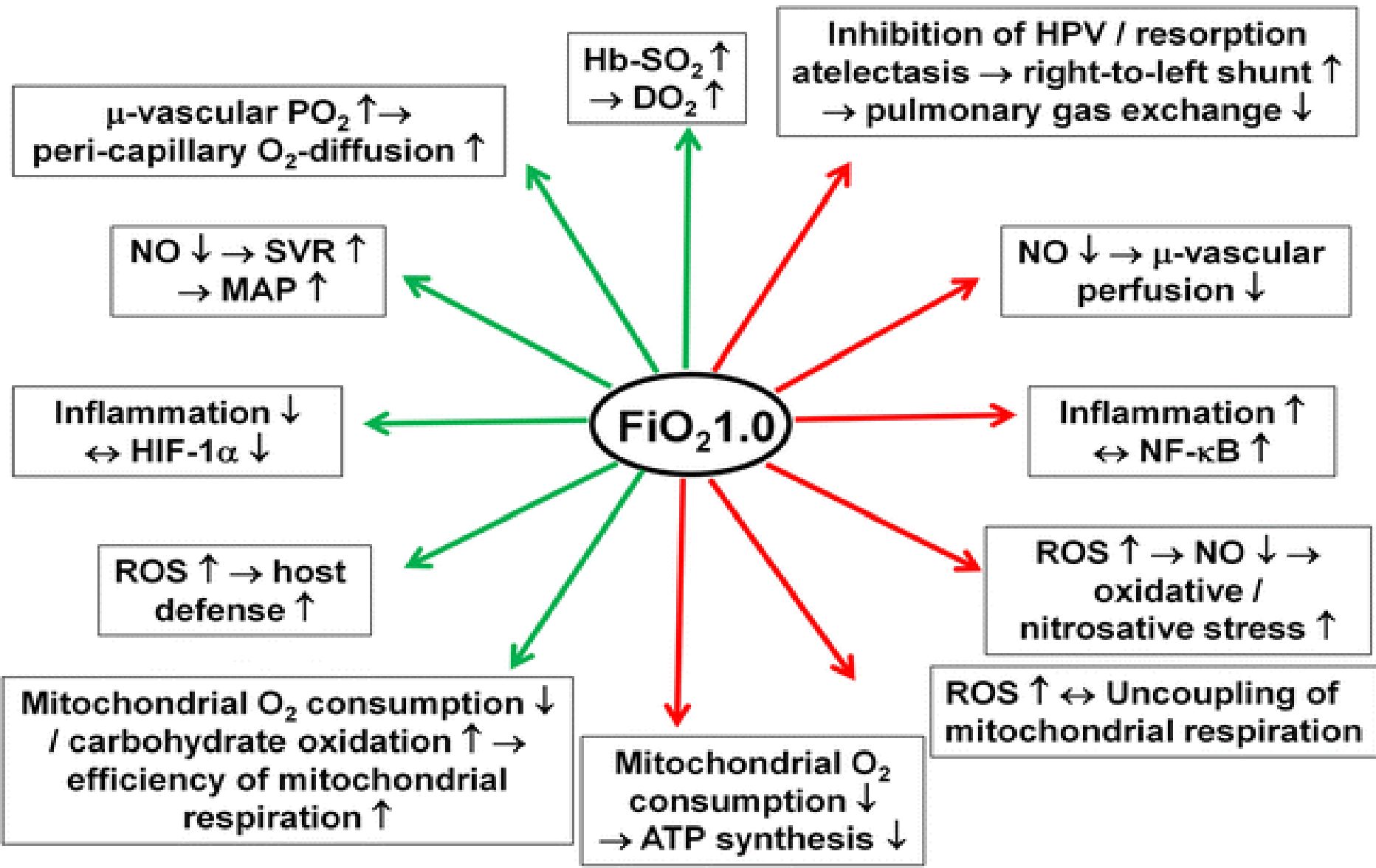
Lessons Learned from OEF and OIF

Edited by

Eric Savitsky, MD

Colonel Brian Eastridge, MD

Hyperoxia Physiology



Rationale for Normoxia

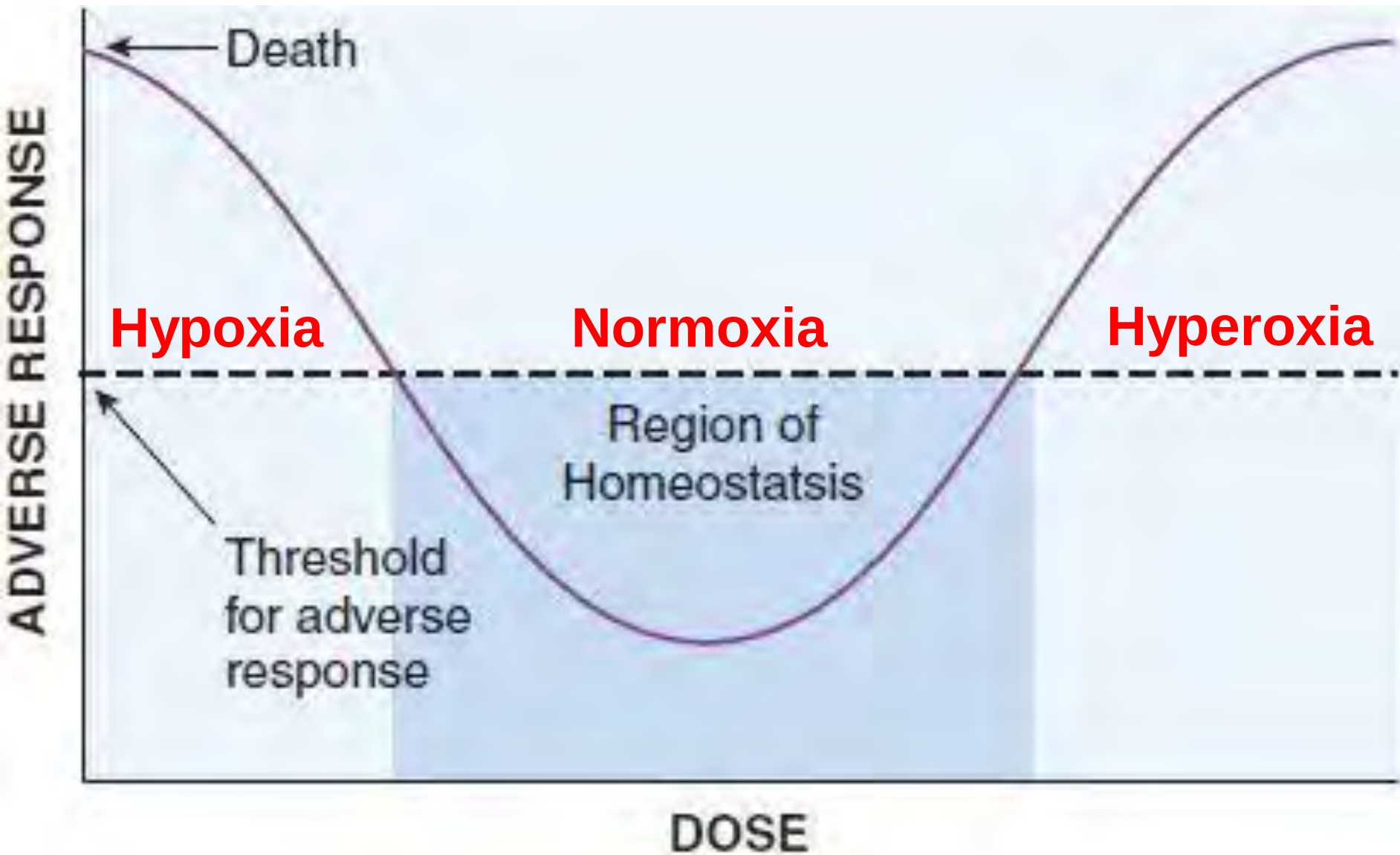
Hypoxia

- ▶ Anaerobic metabolism
- ▶ Cell death (necrosis)
- ▶ Brain = 20% O₂ consumption

Hyperoxia

- Vasoconstriction
- Oxidative stress
- Pro-inflammatory
- Decreased mucociliary clearance in lung

Oxygen as a drug



Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis



Lancet 2018; 391: 1693-705

Derek K Chu†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani*

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Interpretation: In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94-96%

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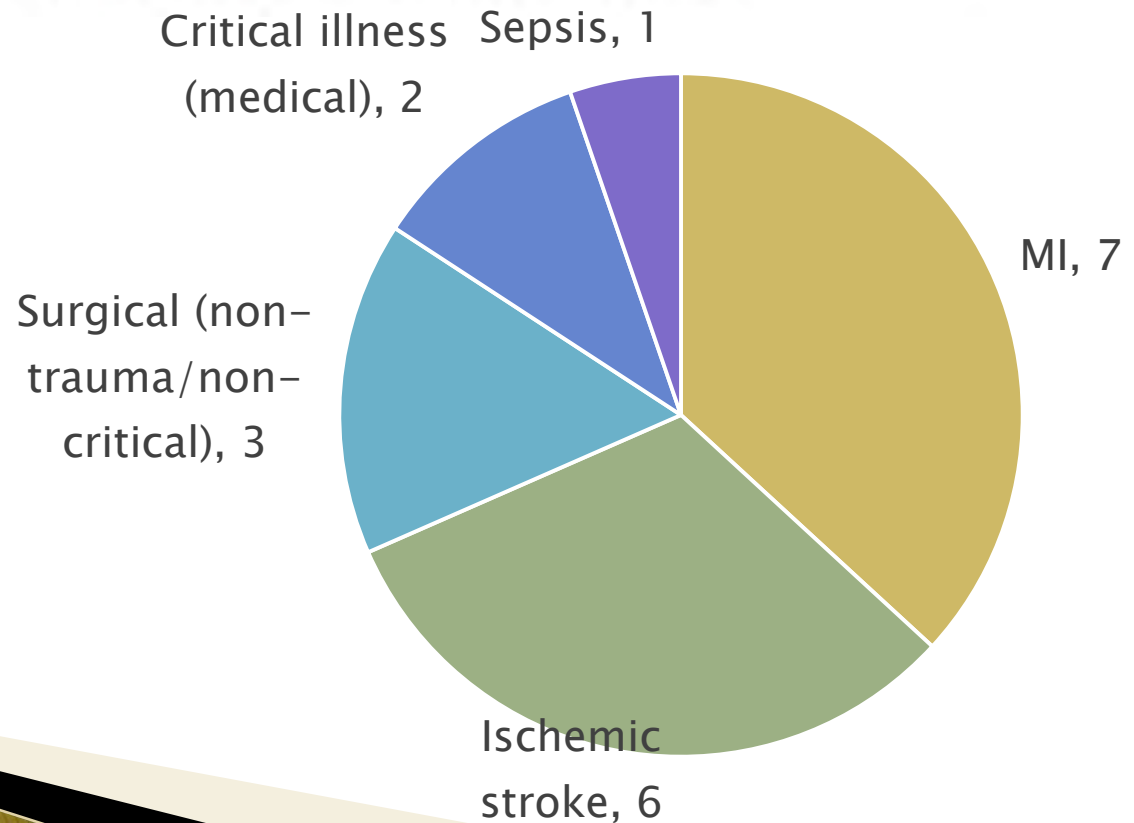


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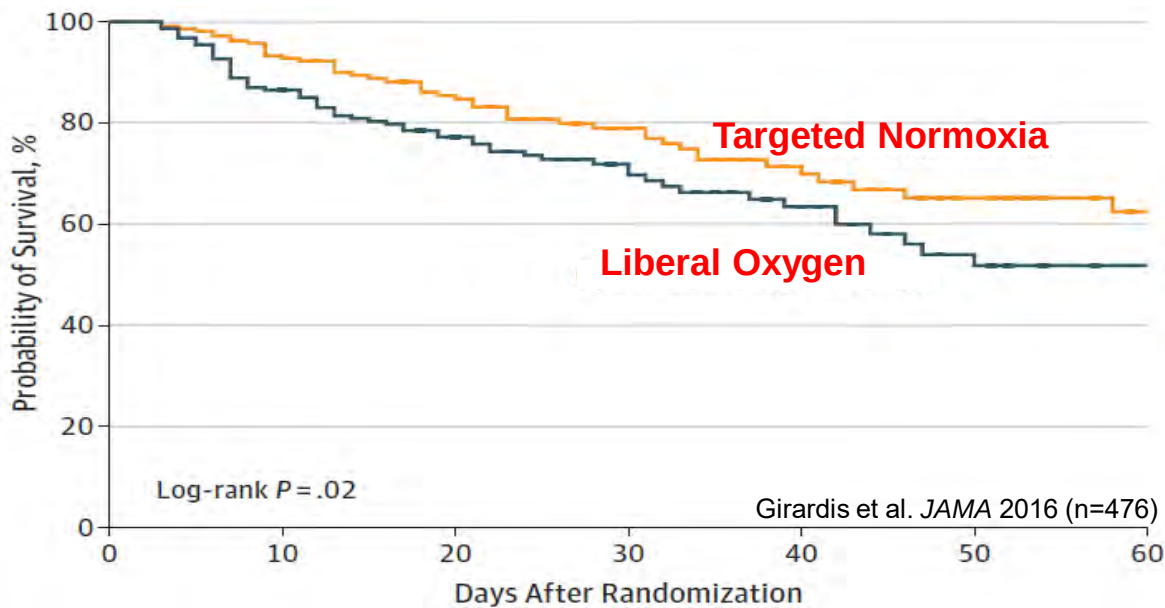
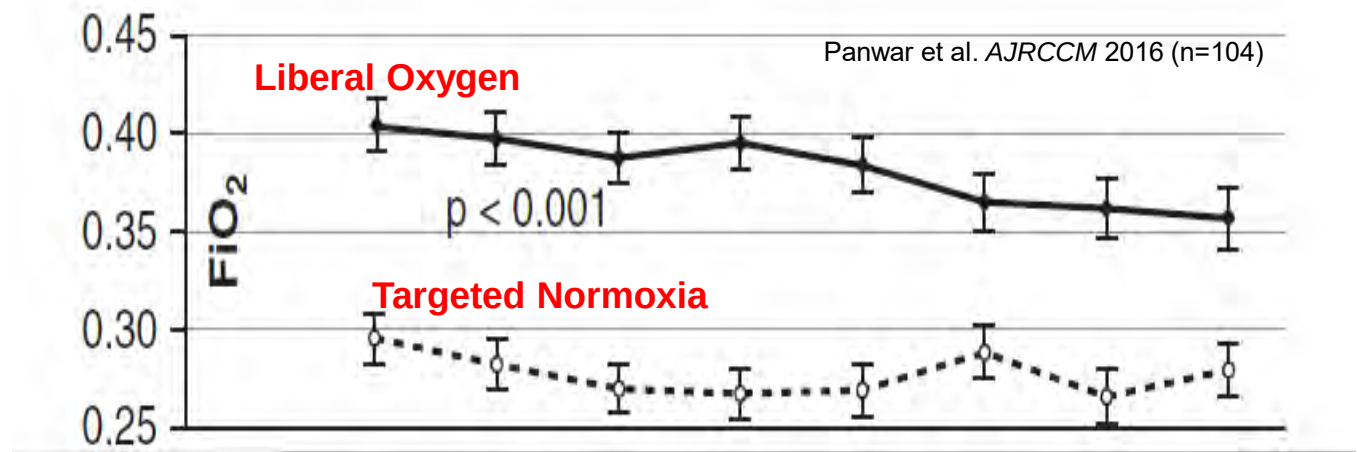
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Interpretation In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94–96%. These results support the conservative administration of oxygen therapy.

But...no trauma



Critical Care Trials (non-trauma)



Question

How do we advance definitive evidence for safe and effective oxygen targets in CCC/ERC?



Specific Aims—SOCOM

1. Define current standard care for oxygen titration in critically ill trauma patients
 - Systematic review of existing relevant evidence
 - SMEs to define consensus-based definitions
2. Compare effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
 - Retrospective cohort study to define the association between oxygenation and clinical outcomes
3. Develop and pilot test a targeted normoxia intervention in critically ill trauma patients
 - Demonstrate safe and feasible implementation
 - Prepare for large, multicenter trial

Systematic Review

- ▶ **Included (n=43)**
 - 17 trauma studies
 - 26 non-trauma critical illness
- ▶ **Conclusions**
 - Overall association between lower oxygen/normoxia and improved clinical outcomes
 - Few trauma specific articles
 - 14 out of 17 related exclusively to TBI
 - No high quality/RCT data
 - Supports need for further trauma-specific studies/RCTs, particularly beyond TBI

Expert Panel (Military, n=13)

Last Name	First Name	Speciality	Institution
Becker	Tyson	Trauma Surgery	SAMMC
Chung	Kevin	Critical Care	SAMMC
Keenan	Sean	Emergency Medicine	SOCOM/SOCEUR
Mason	Philip	Critical Care	SAMMC
Miles	Ethan	Other	Ft. Benning
Oh	John	Trauma Surgery	Penn State
Redman	Theodore	Emergency Medicine	Ft. Campbell
Reisburg	Jamie	Other	Ft. Carson
Rush	Stephen	Other	USAF
Tobin	Josh	Critical Care	USC
Walrath	Benjamin	Emergency Medicine	Naval Medical Center
Wilson	Ramey	Other	SOCAFRICOM

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Brainard	Jason	Critical Care	Denver
Cohen	Mitchell	Trauma Surgery	Denver
Cotton	Bryan	Trauma Surgery	Houston
Doshi	Pratik	Critical Care	Houston
Guyette	Franklin	Emergency Medicine	Pittsburgh
Huang	David	Critical Care	Pittsburgh
Idrovo	Juan-Pablo	Trauma Surgery	Denver
Khan	Akram	Critical Care	Oregon
McIntyre	Robert	Trauma Surgery	Denver
Moore	Ernest	Trauma Surgery	Denver
Newgard	Craig	Emergency Medicine	Oregon
Nunez	Timothy	Trauma Surgery	Vanderbilt
Rice	Todd	Critical Care	Vanderbilt
Schreiber	Martin	Trauma Surgery	Oregon
Self	Wesley	Emergency Medicine	Vanderbilt
Sperry	Jason	Trauma Surgery	Pittsburgh
Wang	Henry	Emergency Medicine	Houston
Wright	Franklin	Trauma Surgery	Denver

Initial Rationale

1) Aim for “normoxia”

- Aim for maintaining “normal” oxygen levels
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- Data do not support hyperoxia as the target, may be worse
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2) Cultural norms need to be challenged

- Generous oxygen entrenched in clinical practice
- Oxygen titration decisions are made to avoid hypoxia but typically not to achieve hyperoxia
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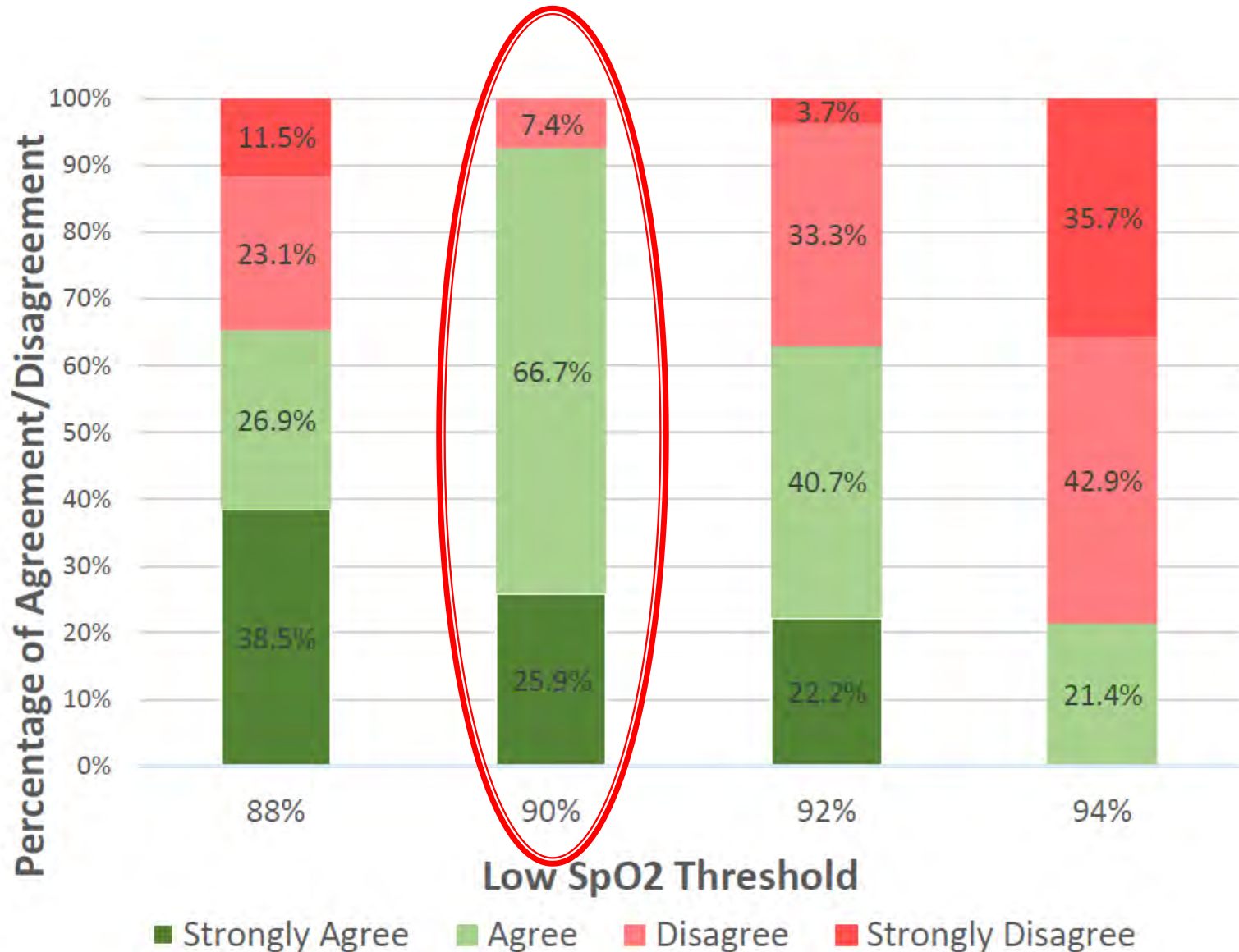
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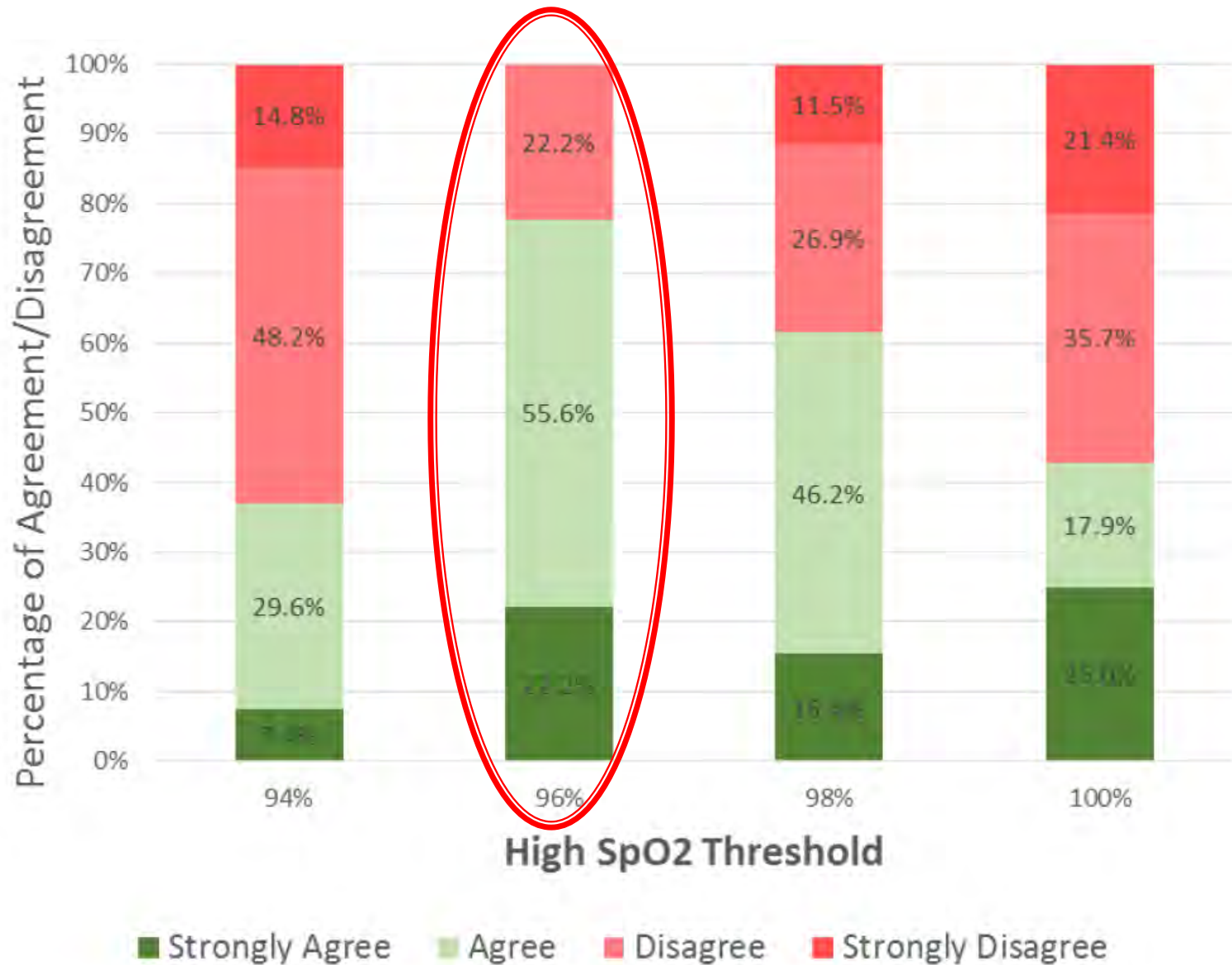
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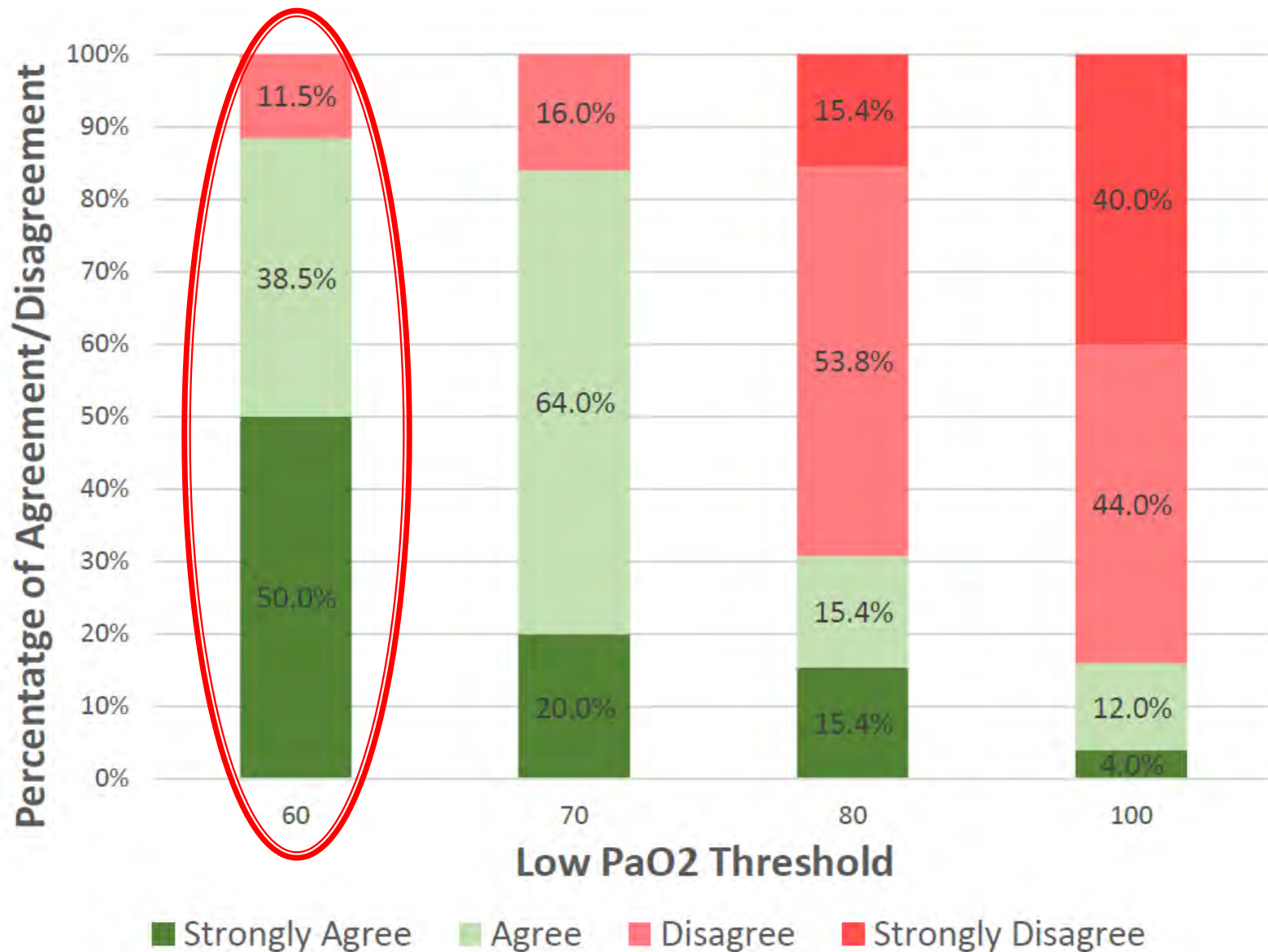
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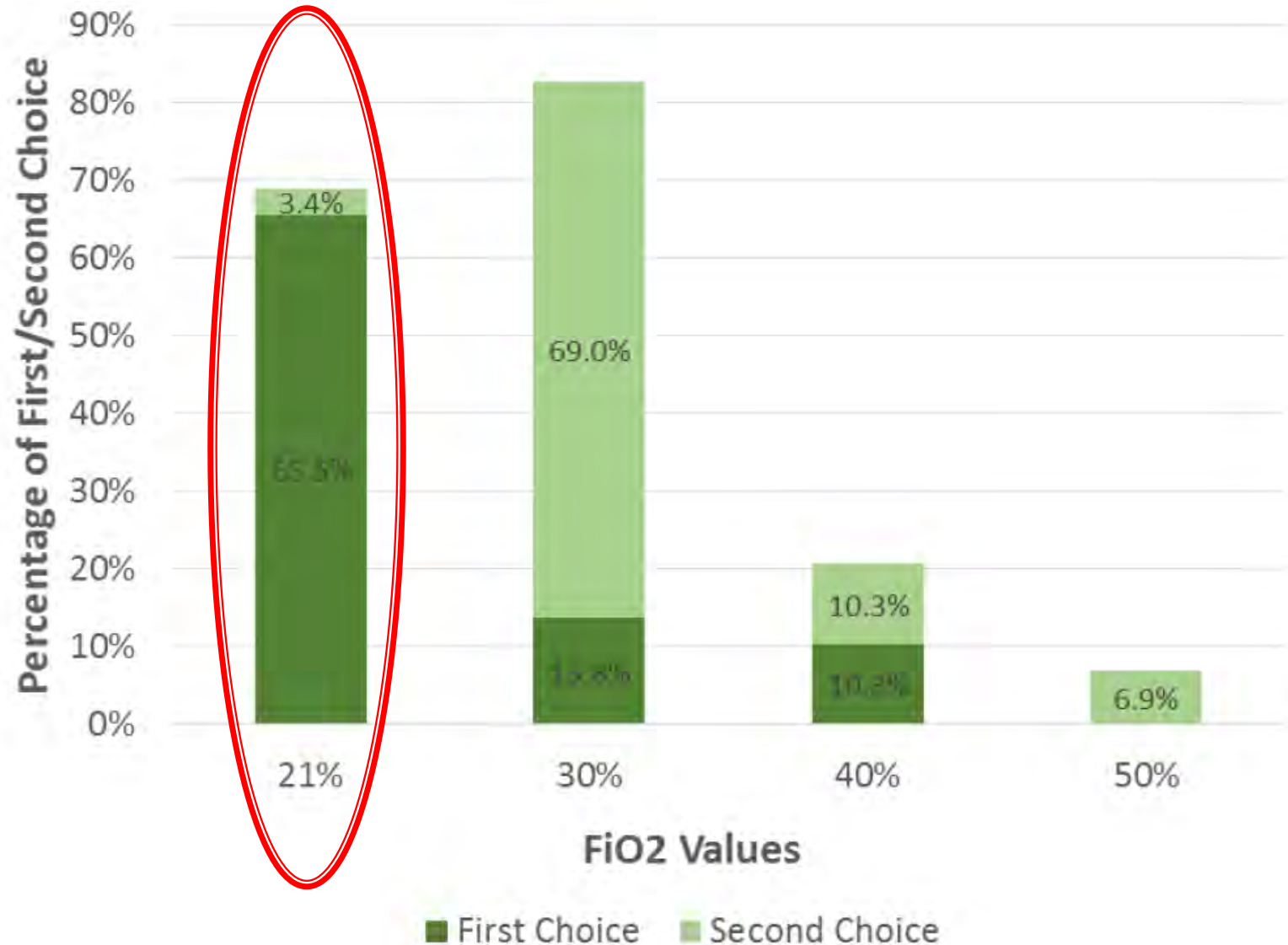
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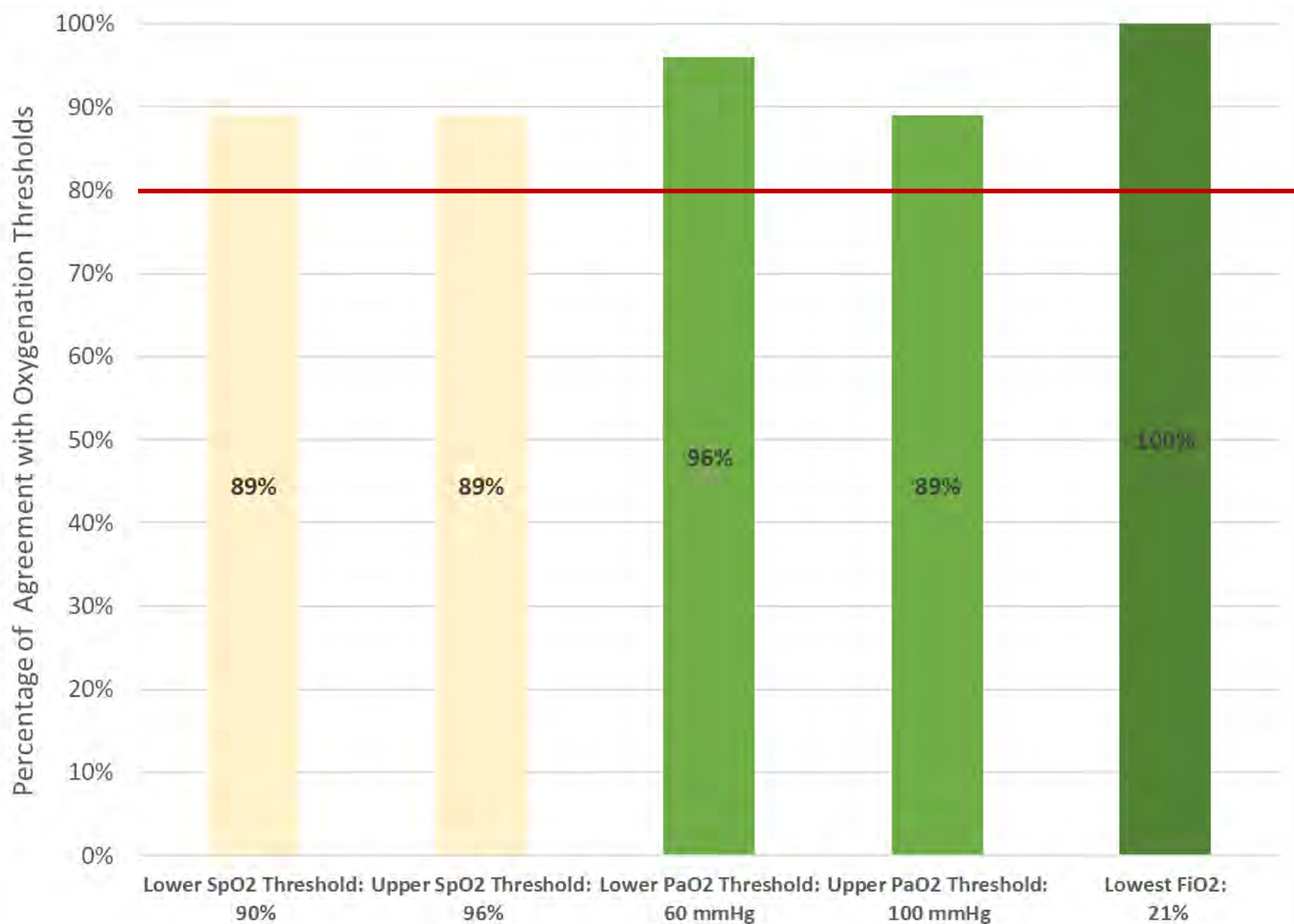
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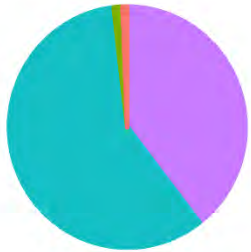
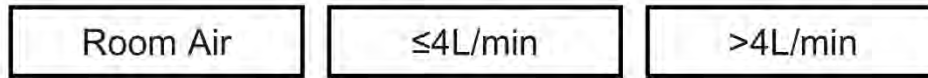


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as measured by SpO₂



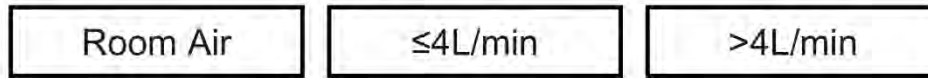
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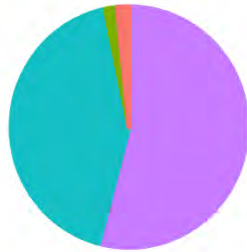
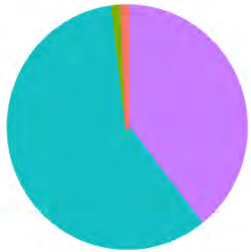


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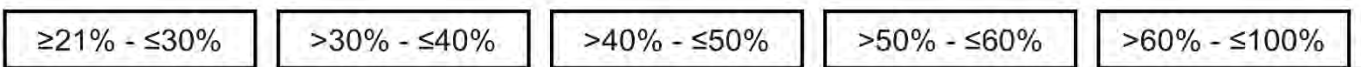
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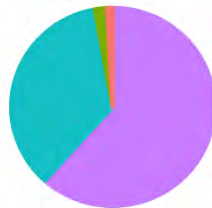
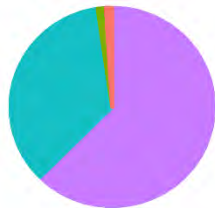
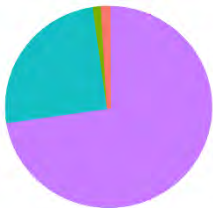
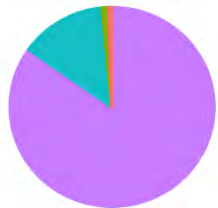
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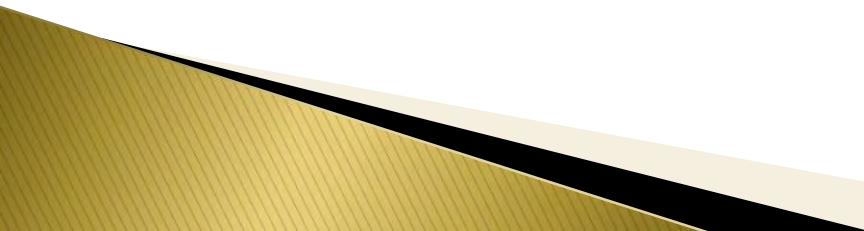
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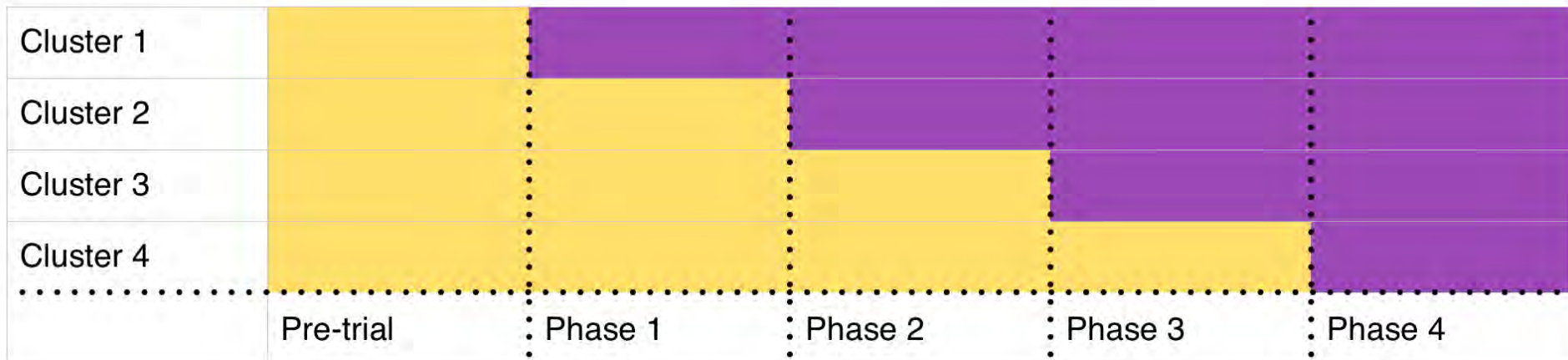
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Time →

Control Condition	
Experimental Condition	

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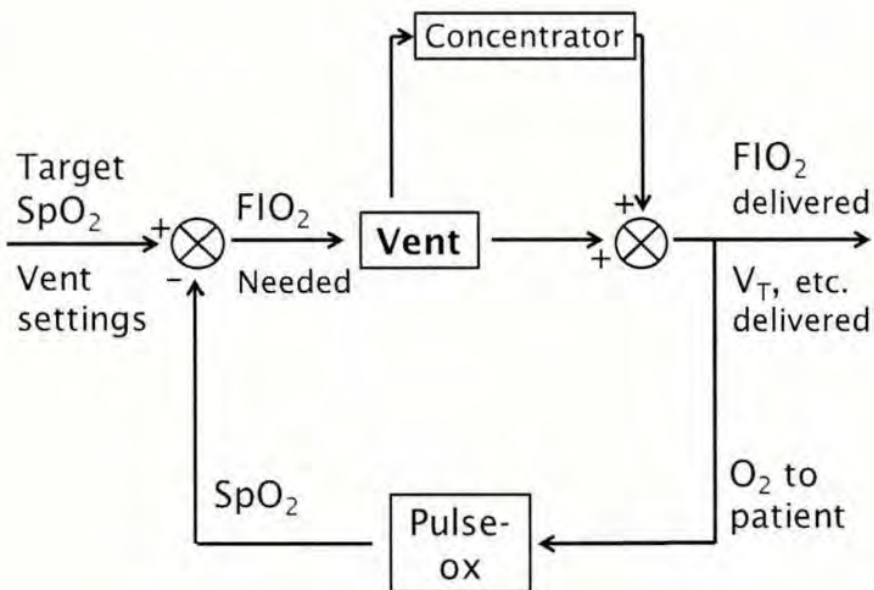
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A Consensus-Based Recommendation for Oxygenation Targets in Critically Injured Patients

Steven Schauer, DO, MS
MAJ USA MC
09 May 2019



UNCLASSIFIED



Conflicts of Interest

None.

All grant funding comes from various Department of Defense Agencies.

I do not accept any commercial funding.





Disclaimer

Opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force, the Department of the Army, or the Department of Defense.





Acknowledgements

Co-Investigators at the University of Colorado – Denver

Adit Ginde, MD, MPH

Vikhyat Bebarta, MD

Erin Anderson, RN

Jacqueline Jones, PhD

Funding – Special Operations Command (BAA - SO160106)

Thanks to all our expert participants! (some in audience now)





Methods

Ethics

- » Submitted proposal to University of Colorado IRB → exempt survey determination

Survey

- » Surveys on REDCap (Research Electronic Data Capture)
- » Multi-stage Delphi consensus process
- » Invited selected experts both military and civilian with experience in operational medicine, critical care, trauma, emergency medicine, and prehospital medicine to participate

Performed systematic review of available literature → provided to the expert participants





Expert Participants

LTC Tyson Becker	Jason Haukoos	LTC Ethan Miles
Jason Brainard	David Huang	Ernest Moore
COL Kevin Chung	Juan-Pablo Idrovo	Craig Newgard
Mitchell Cohen	COL Sean Keenan	LTC Timothy Nunez
Brian Cotton	Akram Khan	COL (ret) John Oh
Pratik Doshi	LtCol Philip Mason	LTC Ted Redmon
Franklin Guyette	Robert McIntyre	LTC Jamie Reisburg
Todd Rice	LtCol Stephen Rush	Martin Schreiber
Wesley Self	Jason Sperry	CDR Joshua Tobin
CDR Benjamin Walrath	Henry Wang	LTC Ramey Wilson
Franklin Wright		





Results

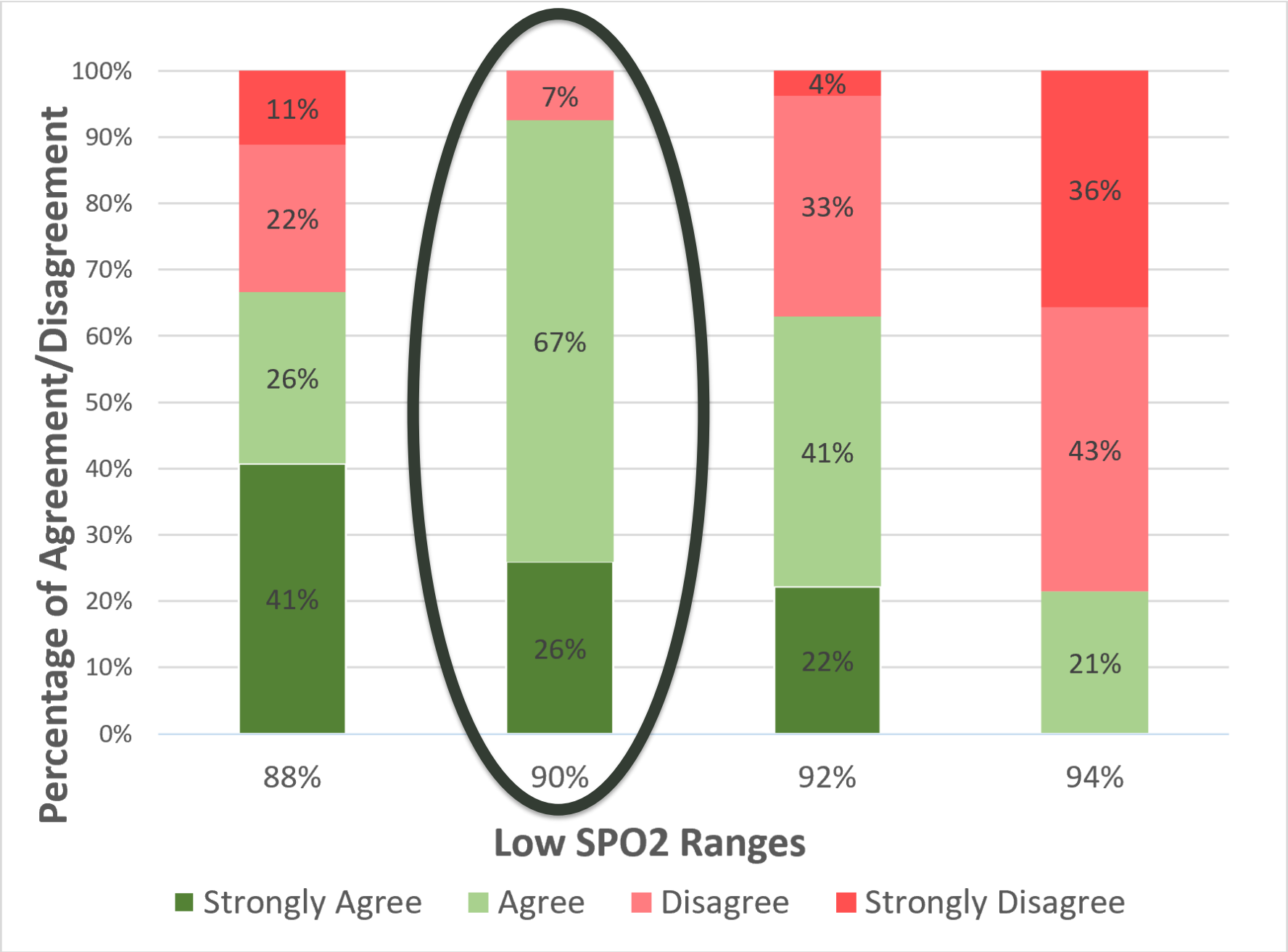
Of the 31 invited experts, 26 completed the first round, 28 completed the second round, 27 completed the final round; all participated in at least one round

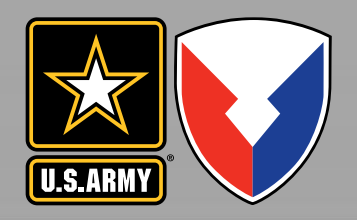
- » Round 1 → narrowed the potential SpO2 range to 88-100% and PaO2 to 60-300mmHg
 - » Only 20% noted changes based on presence of TBI or hemorrhagic shock
- » Round 2 → narrowed to 90-96% and 60-100mmHg targets
 - » Lowest acceptable FiO2 21% (ambient air)
- » Round 3 → 89% accepted the limits at 90-96% and upper limit of 100mmHg, 96% accepted lower at 60mmHg
 - » All accepted lowest FiO2 at 21%
 - » 33% recommended higher oxygenation for TBI and 11% for hemorrhagic shock
 - » Resource limited setting most recommended lower target of 88%





A. Agreement with Lower SpO2 Thresholds in Delphi Stage 2





B. Agreement with Higher SpO2 Thresholds in Delphi Stage 2



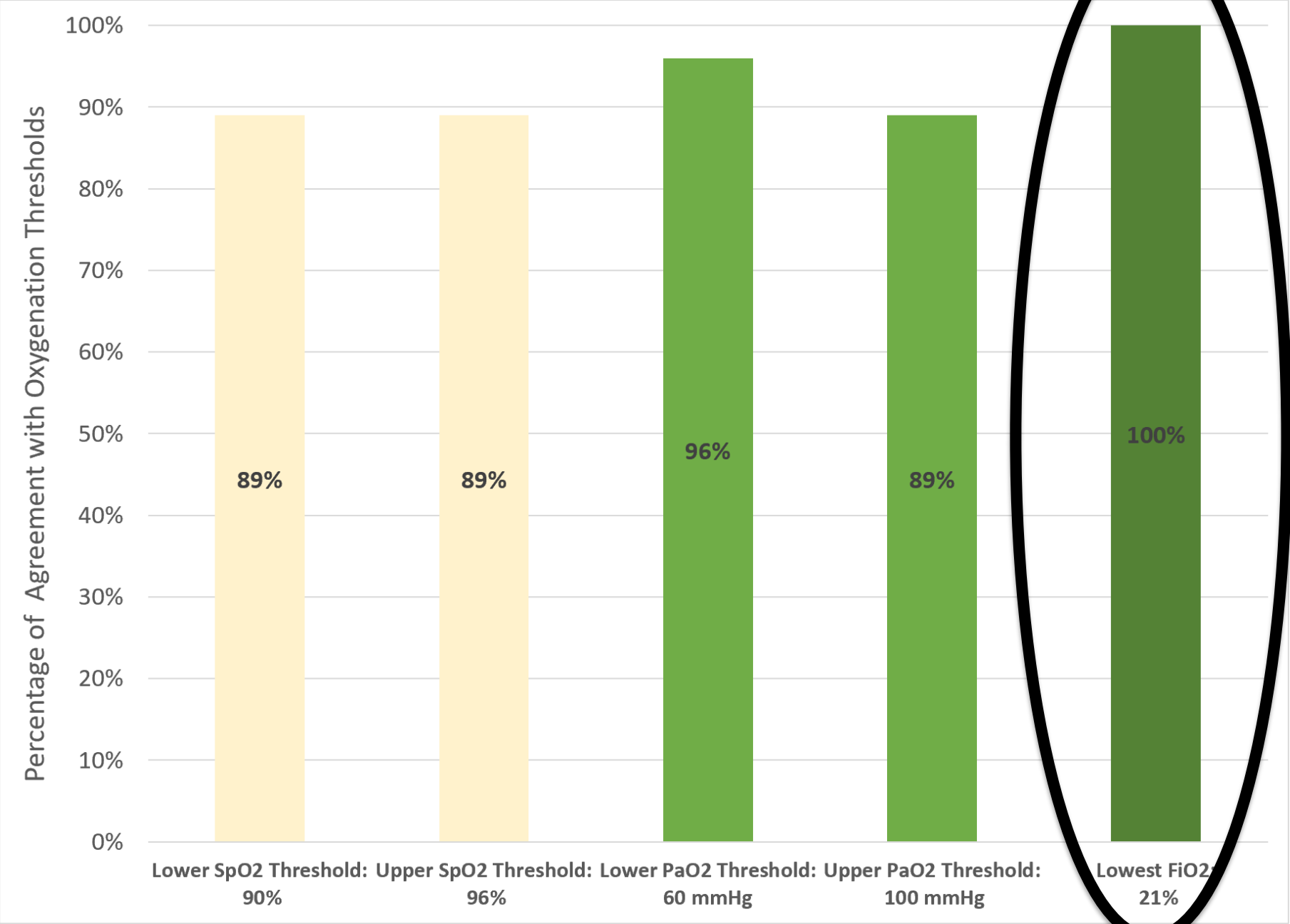


Agreement with Lowest Acceptable FiO2 in Delphi Stage 2





Figure 6: Delphi Percentage of Agreement with Oxygenation Thresholds





Conclusions

Consensus-based standard for oxygenation targets in critically injured patients

SpO₂ 90-96% (88-96% with resource-limitations)

PaO₂ 60-100 mmHg

Lowest acceptable FiO₂ 21%

Adjustments for TBI, burns, major hemorrhage, etc. likely not needed

Expert consensus → prospective, clinical validation needed





The End

Questions?
Comments?
Feedback?

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Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

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BACKGROUND:	Oxygen therapy is frequently administered to critically ill trauma patients to avoid hypoxia, but optimal oxygenation strategies are not clear.
METHODS:	We conducted a systematic review of oxygen targets and clinical outcomes in trauma and critically ill patients. We searched Ovid MEDLINE, Cochrane Library, Embase, and Web of Science Core Collection from 1946 through 2017. Our initial search yielded 14,774 articles with 209 remaining after abstract review. We reviewed full text articles of human subjects with conditions of interest, an oxygen exposure or measurement, and clinical outcomes, narrowing the review to 43 articles. We assessed article quality using Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria.
RESULTS:	Of the 43 final studies meeting inclusions criteria, 17 focused on trauma and 26 studies focused on medical and/or surgical critical illness without trauma specifically. Four trauma studies supported lower oxygenation/normoxia, two supported higher oxygenation, and 11 supported neither normoxia nor higher oxygenation (five neutral and six supported avoidance of hypoxia). Fifteen critical illness studies supported lower oxygenation/normoxia, one supported higher oxygenation, and 10 supported neither normoxia nor higher oxygenation (nine neutral and one supported avoidance of hypoxia). We identified seven randomized controlled trials (four high quality, three moderate quality). Of the high-quality randomized controlled trials (none trauma-related), one supported lower oxygenation/normoxia and three were neutral. Of the moderate-quality randomized controlled trials (one trauma-related), one supported higher oxygenation, one was neutral, and one supported avoidance of hypoxia.
CONCLUSION:	We identified few trauma-specific studies beyond traumatic brain injury; none were high quality. Extrapolating primarily from nontrauma critical illness, reduced oxygen administration targeting normoxia in critically ill trauma patients may result in better or equivalent clinical outcomes. Additional trauma-specific trials are needed to determine the optimal oxygen strategy in critically injured patients. (<i>J Trauma Acute Care Surg.</i> 2019;00: 00–00. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)
LEVEL OF EVIDENCE:	Systematic review, Level IV.
KEY WORDS:	Oxygenation; hyperoxia; trauma; critical care.

Oxygen is frequently administered to critically injured patients to prevent hypoxia and enhance oxygen delivery.^{1,2} Excessive oxygen supplementation often occurs in clinical practice leading to hyperoxia.³ While the detrimental effects of hypoxia in trauma patients are well described, hyperoxia may also have adverse effects.³

Limited evidence in critically ill patients indicates that even modest amounts of hyperoxia may be harmful. Several studies demonstrate an increase in morbidity and mortality among patients receiving supraphysiologic levels of oxygen.^{4–7} However, most studies focus exclusively on medical patients, as reflected by prior systematic reviews on this topic.^{2,8–12} Data

are sparse in critically ill trauma patients, and no systematic reviews focused on this population have been published. There is also significant heterogeneity in the definition of hyperoxia with arterial partial pressures of oxygen ranging from 100 mm Hg to 300 mm Hg. Recent studies have identified safe upper limits of oxygen saturation (SpO₂) at 96% and partial pressure of oxygen (PaO₂) at 150 mm Hg^{4,5,13} in critically ill patients without trauma. It remains unclear how to apply these findings to critically ill trauma patients.

Beyond patient morbidity, the avoidance of hyperoxia may also improve resource utilization. Both far-forward combat areas and en route care rely on a limited supply of oxygen and other supplies. The extent to which hyperoxia is not beneficial or even harmful would decrease the logistic burden of oxygen procurement in forward military operations and other austere settings.

Defining optimal oxygenation targets are highly relevant to reduce morbidity associated with both hyperoxia and hypoxia. In resource-limited settings this carries further benefit. While some evidence exists to support the avoidance of hyperoxia in other patient populations,¹² understanding of the evidence relevant to critically ill trauma patients is lacking. Therefore, we conducted a systematic review of clinical trials and epidemiological studies of oxygen targets and clinical outcomes in trauma and critically ill patients.

Submitted: January 10, 2019, Revised: March 14, 2019, Accepted: May 4, 2019, Published online: May 30, 2019.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

DOI: 10.1097/TA.0000000000002392

J Trauma Acute Care Surg
Volume 00, Number 00

METHODS

We conducted a systematic review using the Cochrane Collaboration approach. We prepared the protocol and review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines.¹⁴

Study Eligibility Criteria

Population

We conducted a systematic review of the optimal oxygen target ranges relevant to critically ill trauma patients. We included studies evaluating adult human patients from both civilian and military populations.

Search Strategy and Data Sources

A medical librarian (K.S.) conducted a comprehensive literature search from 1946 to 2017. Our search focused on trauma (i.e., acute bodily injury) and critical illness (i.e., requiring intensive care unit [ICU] level of care). We identified relevant publications by searching Ovid MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Versions, 1946 to present), Cochrane Library (via Wiley, including Cochrane Database of Systematic Reviews,

Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, and NHS Economic Evaluation Database, 1992 to present), Embase (via Elsevier, Embase.com, 1947 to present), and Web of Science Core Collection (via Thomson Reuters, including Science Citation Index Expanded 1974 to present, and Social Sciences Citation Index 1974 to present). We excluded animal studies, conference abstracts, conference papers, and conference reviews. We included randomized controlled trials, prospective interventional, and observation (prospective and retrospective) studies. Other systematic reviews, meta-analyses, or narrative reviews were not included. See Supplemental Digital Content, Appendix, <http://links.lww.com/TA/B430> for database search strategies.

The comprehensive literature search yielded 14,777 non-duplicate articles for title/abstract review (DJD, ELA; Fig. 1). We excluded articles not using human subjects and subjects younger than 18 years. We included patients who had trauma but no critical illness, trauma with critical illness or critical illness without trauma. Two authors (D.J.D., E.L.A.) independently reviewed full text for all articles to identify human research studies with trauma or critical illness and analysis of oxygen exposure/measurement and clinical outcomes (i.e., mortality, length of stay [LOS], or

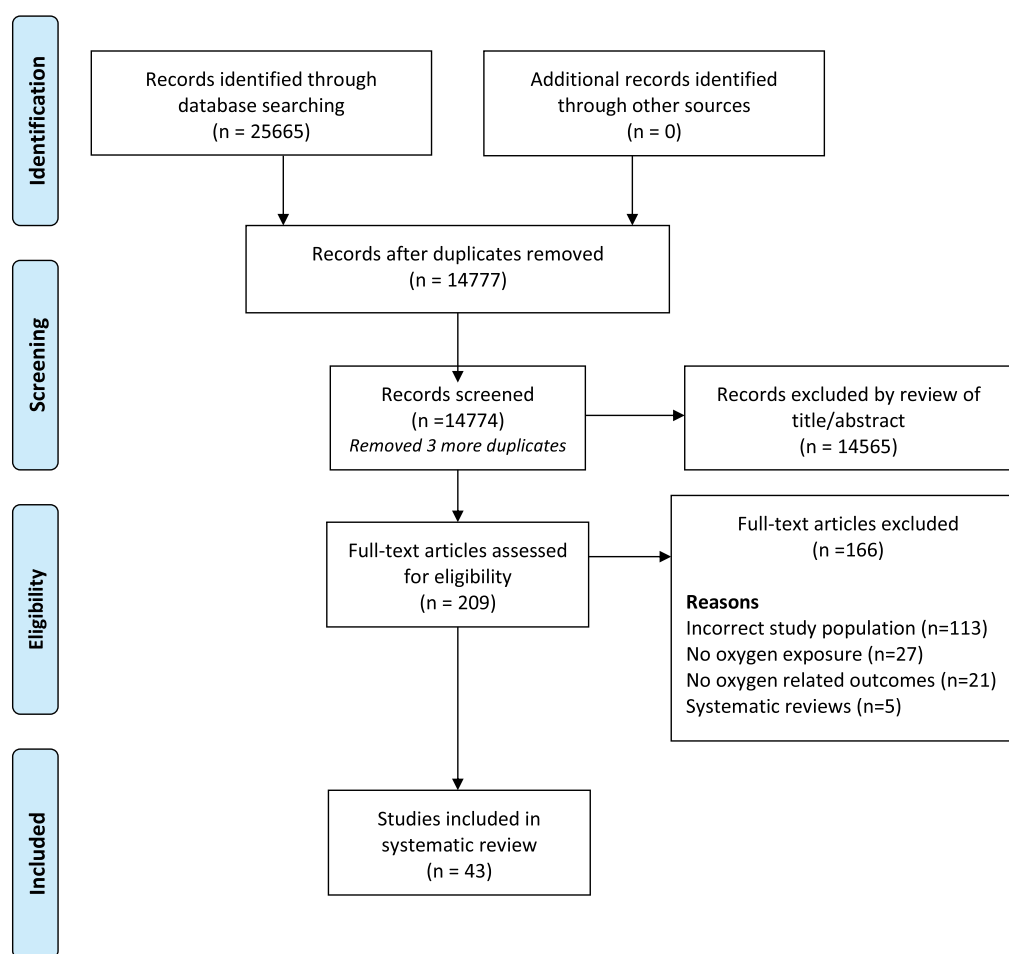


Figure 1. PRISMA flow diagram for article selection in systematic review.

acute organ injury). A third author (A.A.G.) reviewed articles when there was not consensus among the primary reviewers. Final determination was made by complete consensus of all three reviewers. The final search yielded 43 articles for inclusion in this systematic review.

Quality Assessment

Two authors (D.J.D. and E.L.A.) independently completed risk of bias assessments for each included article using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria to determine the quality of the evidence.¹⁵ Disagreements were settled with a third author (A.A.G.).

Outcomes

Our primary outcome was mortality, typically in-hospital, as reported in the primary study. Secondly, we evaluated hospital LOS, ICU LOS, and acute organ injury (including duration of mechanical ventilation and ventilator free days). Acute organ injury varied by study but included Glasgow Coma Scale (GCS) or modified Rankin Scale at discharge as well as new liver, cardiovascular, or renal failure defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or greater for the corresponding organ occurring 48 hours or more after ICU admission.⁴

Data Synthesis

Patient and study characteristics were reviewed independently by two authors (D.J.D. and E.L.A.). Disagreements were settled by a third author (A.A.G.). When we identified multiple outcomes of interest, all were included, noting when one of the outcomes was clearly indicated as the primary outcome of that study. Due to the paucity of randomized controlled trials directly comparing levels of oxygen delivery, we did not perform meta-analysis nor other quantitative synthesis of the results.

RESULTS

Study Characteristics

Of the 43 final studies included in our systematic review, 17 focused on trauma, of which 14 of 17 were exclusively TBI and 11 of 17 studies were critically ill trauma patients (most predominately TBI). The remaining 26 studies focused on medical and surgical critical illness without trauma specifically. All studies were from the civilian setting.

Trauma studies are summarized in Table 1. None were high-quality evidence, eight were moderate-quality evidence, and nine were low-quality evidence studies. The specific definitions of lower oxygenation/normoxia, and higher oxygenation/hyperoxia varied substantially between studies. Four trauma studies supported lower oxygenation/normoxia, two supported higher oxygenation, and 11 supported neither normoxia nor higher oxygenation (five neutral relative to clinical outcomes and six supported avoidance of hypoxia).

The critical illness (nontrauma) studies were comprised of four high-quality evidence, four moderate-quality evidence, and 18 low-quality evidence studies (Table 2). Fifteen critical illness studies supported lower oxygenation/normoxia, one supported higher oxygenation, and 10 supported neither normoxia nor higher oxygenation (nine neutral relative to clinical outcomes and one supported avoidance of hypoxia).

Overall there were seven randomized controlled trials (four high-quality, three moderate-quality). Of the high-quality randomized controlled trials (none trauma-focused), one study supported lower oxygenation/normoxia and three were neutral. Of the moderate-quality randomized controlled trials (one trauma-related), one study supported higher oxygenation, one was neutral, and one supported avoidance of hypoxia. These results are summarized in Figure 2.

Primary Outcome

Our primary outcome was mortality which was reported in 13 of the 17 trauma studies^{18,22–30,33,35,36,50} and 21 of the 26 critical illness studies, including two of the four critical illness studies, which were high-quality evidence.^{3–7,17,21,31,37–39,41–48,51} The majority of these studies reported in-hospital mortality; however, two studies reported 30-day mortality,^{17,18} while two studies reported 6-month mortality.^{20,22} (Tables 1 and 2). A statistically significant difference in mortality was noted for the avoidance of hypoxia in TBI patients in three studies^{23,30,34} while the study by DesPrez et al.²⁷ was the only trauma study with predominately non-TBI trauma patients, which reported a statistically significant mortality difference in favor of normoxia (Fig. 2).

Secondary Outcomes

Hospital LOS was reported in one trauma study and six critical illness studies.^{5,6,29,32,48,49,52} Three studies reported longer hospital LOS (at least 1 day) with higher oxygenation and four studies were neutral. Intensive care unit LOS was reported in two trauma studies and seven critical illness studies.^{6,13,29,32,36,40,48,49,52} Three studies reported longer ICU LOS with higher oxygenation, six studies were neutral, and one study reported shorter ICU LOS with higher oxygenation (but not necessarily hyperoxia) for mechanically intubated patients with TBI. Ventilator-free days were reported in one trauma study and six critical illness studies.^{5,6,27,32,38,40,52} Three studies reported higher ventilator free days with normoxia vs. higher oxygenation, and four studies were neutral. Other acute organ injury was reported in nine critical illness studies and three trauma studies.^{4,6,7,13,16,17,19,34,35,45,52} These secondary outcomes include neurologic outcomes such as GCS score or modified Rankin Scale at discharge as well as new liver, cardiovascular or renal failure defined as a SOFA score of 3 or greater for the corresponding organ occurring 48 hours or more after ICU admission.⁴ These findings are summarized in Tables 1 and 2.

DISCUSSION

Our systematic review demonstrates that no high-quality evidence and only one (moderate quality) randomized controlled trial has been published analyzing optimal oxygen administration in trauma patients and clinical outcomes. Even with a low-quality assessment, few trauma-specific studies were identified beyond traumatic brain injury. We extrapolated some evidence from medical and surgical (nontrauma) critical illness, where there is a growing literature base and some randomized controlled trials. Normoxia for critically ill patients was most commonly defined as SpO₂ of 88% to 96% or a PaO₂ 60 mm Hg to 150 mm Hg; however, significant heterogeneity in this definition exists. Notably if a patient was not receiving

TABLE 1. Trauma Articles Included in Systematic Review (n = 17)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
da Costa (2017) ¹⁵	Prospective observational/ single center/Brazil n = 200 Mean age: 37 y Population of interest: Trauma: 100% TBI: 65% (GCS score <9, ISS >16)	Data Collection: 4 time points from scene of trauma to 24 h postadmission -Arterial hemoglobin O ₂ saturation prior to supplemental oxygen	Primary: 30-d Mortality	No Oxygen vs. Oxygen 30-d Mortality: OR, 0.988 (0.981–0.995)	A 1% increase in arterial hemoglobin O ₂ saturation was associated with a 1.2% decrease in the odds of mortality in trauma patients	II	Supports Avoidance of Hypoxia
Taher (2016) ²⁸	RCT/single center/Iran n = 68 Mean age: 43 y Population of interest: Trauma: 100% TBI: 100% Mechanically ventilated: 100%	Data Collection: During the first 6 h of admission Intervention: -80% FIO ₂ Control: -50% FIO ₂	Primary: Glasgow Outcome Scale (GOS)	FIO ₂ 80% vs. FIO ₂ 50% GOS at Discharge: p value 0.723 GOS at 6 mo: p value 0.024	FIO ₂ of 80% was associated with improved neurological outcome when compared to an FIO ₂ of 50% in severe TBI patients	II	Supports Higher Oxygenation
Mascia (2007) ¹⁶	Prospective observational/ multicenter/Italy n = 86 Mean age: 45 y Population of interest: Trauma: 100% TBI: 100% (GCS score <9) Mechanically ventilated: 100%	Data Collection: 1st 24 h of admission - Mean PaO ₂	Primary: Acute Lung Injury	High PaO ₂ /FIO ₂ vs. Low PaO ₂ /FIO ₂ Acute Lung Injury: OR, 0.98 (0.98–0.99), p = 0.04	Low PaO ₂ /FIO ₂ ratios were associated with the development of acute lung injury when compared to higher PaO ₂ /FIO ₂ ratios in TBI patients	II	Supports Avoidance of Hypoxia
Chi (2006) ¹⁷	Prospective observational/ multicenter/USA N = 150 Mean age: 34 y Population of interest: Trauma: 100% TBI: 100% (GCS score ≤ 12, AIS score ≥ 3)	Data Collection: Prehospital Oxygen -SpO ₂ < 92% (Hypoxic) *occurred at least once -SpO ₂ ≥ 92% (Not Hypoxic)	Primary: In-Hospital Mortality	Hypoxic vs. Not Hypoxic Mortality: OR, 2.66 (p = 0.04)	Hypoxia in the prehospital setting significantly increases the odds of mortality in severe TBI patients	II	Supports Avoidance of Hypoxia
Davis (2004) ¹⁸	Prospective observational/ multicenter/USA (San Diego) n = 426 Mean age: 35 y Population of interest: Major trauma = 100% TBI: 100% (GCS score 3–8) Mechanically ventilated: 100%	Data Collection: Prehospital -Lowest Preintubation SpO ₂ -Lowest Postintubation SpO ₂ *received oxygen for 60 seconds prior to rapid sequence intubation medications	Primary: In-Hospital Mortality	Hypoxia in preintubation and postintubation In-Hospital Mortality: Preintubation: OR, 0.31 (0.06–1.56) Postintubation: OR, 1.39 (0.35–5.55)	Lowest SpO ₂ before or after paramedic intubation is not associated with an increase in mortality for major trauma patients	II	Neutral

Continued next page

TABLE 1. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Tolias (2004) ¹⁹	Prospective observational/ multicenter/USA n = 52 Mean age: 34 y Population of Interest: Trauma: 100% · TBI: 100% · Mechanically ventilated: 100%	Data Collection: Starting within 6 h of admission to ICU Intervention: - FIO ₂ = 100% for 24 h Control: Historical cohort, matching intervention group - FIO ₂ per usual care	Primary: Neurological Outcomes by GOS	FIO₂ 100% vs. Historical FIO₂ Mean GOS 3 mo: p = NS Mean GOS 6 mo: p = NS	Hyperoxia did not change clinical outcomes in severe TBI patients when compared to the historical control group	II	Neutral
Manley (2001) ²⁰	Prospective observational/ single center/ USA (San Francisco) n = 107 Mean age: 46 y Population of Interest: Trauma: 100% · TBI: 100% (GCS score ≤ 12) · ICU: 60%	Data Collection: In the emergency department - Any Hypoxia Episode (SpO ₂ < 92%)	Primary: in-hospital mortality	Hypoxia on in hospital mortality in TBI patients Mortality: OR, 1.26 (0.56–2.83); p = 0.57	Hypoxia showed no increase in in-hospital mortality in TBI patients	II	Neutral
Gentleman (1992) ²¹	Prospective observational/ single center/ United Kingdom n = 600 Mean age: 33 y Population of Interest: Trauma: 100% · TBI: 100% (used CT scan to determine)	Data Collection: Prior to ICU admission - PaO ₂ : <70 mm Hg (hypoxia)	Primary: 6 mo Mortality	PaO₂ of <70 mm Hg (hypoxia) and Hypotension No Systemic Insult: 43% (199) Hypoxia or Hypotension: 74% (75) Hypoxia and hypotension: 100% (8)	Hypoxia with or without hypotension increased the risk of mortality in TBI patients	II	Supports Avoidance of Hypoxia
Fujita (2017) ²²	Retrospective/ multicenter/Japan n = 129 Mean age: not reported Population of Interest: Trauma: 100% · TBI: 100% (GCS score 4–8)	Data Collection: First day of admission - PaO ₂ just prior to hypothermia	Survival to hospital discharge (secondary) Discharge GCS score (primary)	PaO₂ (continuous) and Clinical Outcomes Survival: OR, 1.008 (0.983–1.000); p = 0.037 GCS score: OR, 1.452 (1.027–20.53); p = 0.035	Hyperoxemia was associated with improved neurological outcomes and a decrease in mortality in TBI patients	III	Supports Higher Oxygenation

Continued next page

TABLE 1. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
DesPrez (2017) ²³	Retrospective/Multicenter/ USA (Vanderbilt) N = 329 Mean age: 51 y Population of Interest: Critically Ill: 100% · Trauma = 52% · Medical = 31% · Mechanically ventilated: 100%	Data Collection: Recorded for each ICU day - Lowest PaO ₂ /FIO ₂ - Highest SpO ₂ /FIO ₂ - Oxygen saturation index calculated: SpO ₂ × MAP × 100 FIO ₂	Primary: In-Hospital Mortality Secondary: ventilator-free days	Oxygen Saturation Index and Clinical Outcomes Mortality: OR, 1.128 (1.056–1.424); <i>p</i> < 0.008 Ventilator-free days: OR, –0.167 (–0.284 to –0.050); <i>p</i> = 0.005	Increased OSI was associated with higher in-hospital mortality and fewer ventilator-free days in critically ill patients	III	Supports Normoxia
Russell (2017) ²⁴	Retrospective/single center/USA N = 471 Mean age: 42 y Population of Interest: Trauma: 100% · Mechanically ventilated: 100% · TBI: 56%	Data Collection: - Highest PaO ₂ in the first 24 h of ICU admission with corresponding FIO ₂	Primary: in-hospital mortality	Hyperoxia vs. Normoxia Maximum PaO ₂ : OR, 1.27 (0.72–2.25); <i>p</i> = 0.41 FIO ₂ : OR, 0.94 (0.77–1.15); <i>p</i> = 0.54	Hyperoxia was not associated with higher in-hospital mortality or worse neurological outcomes in TBI patients when compared to normoxia	III	Neutral
Raj (2013) ²⁵	Retrospective/multicenter/ Finland n = 1,116 Mean age: 54 y Population of Interest: Trauma: 100% (GCS score <12)	Data Collection: Based on Highest measured alveolar-arterial O ₂ gradient or Lowest measured PaO ₂ value during first 24 h of ICU admission - PaO ₂ : <75 mm Hg (hypoxemia) - PaO ₂ : 75–100 mm Hg (normoxemia) - PaO ₂ : >100 mm Hg (hyperoxemia)	Primary: 6-mo Mortality Secondary: In-Hospital Mortality	Hyperoxemia/Hypoxemia vs. Normoxemia in TBI 6 mo mortality hypoxemia vs. Normoxemia: OR, 0.90 (0.57–1.41); <i>p</i> = 0.65 Hyperoxemia vs. normoxemia: OR, 0.88 (0.63–1.22); <i>p</i> = 0.43 Hyperoxemia vs. hypoxemia: OR, 0.97 (0.63–1.50); <i>p</i> = 0.90 In-hospital mortality hypoxemia vs. normoxemia: 1.01 (0.63–1.62); <i>p</i> = 0.97 Hyperoxemia vs. Normoxemia: 0.94 (0.65–1.36); <i>p</i> = 0.75 Hyperoxemia vs. hypoxemia: 0.93 (0.59–1.47); <i>p</i> = 0.77	Hypoxemia, Normoxemia, and Hyperoxemia had similar 6 mo and in-hospital mortality in critically ill TBI patients	III	Neutral
Brenner (2012) ²⁶	Retrospective/Single center/USA (Baltimore) n = 1,547 Mean age: 41 y Population of Interest: Trauma: 100% · TBI: 100% (AIS score ≥3)	Data Collection: 1st 24 h of hospitalization - PaO ₂ : <100 mm Hg - PaO ₂ : 100–200 mm Hg - PaO ₂ : >200 mm Hg * ABGs were taken at four different time points and averaged to be placed within the three categories stated above	Primary: In-Hospital Mortality	Pao ₂ Comparisons in TBI Pao ₂ < 100 vs. 100–200 mm Hg: OR, 2.20 (1.33–3.63) Pao ₂ > 200 vs. 100–200 mm Hg: OR, 1.50 (1.15–1.97) Pao ₂ > 0.59 > 200 vs. 100 mm Hg: OR, 0.59 (0.35–1.00)	Higher and lower PaO ₂ levels within 24 h of admission were associated with an increase in mortality and worse functional outcomes in severe TBI patients	III	Supports Normoxia

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ABG, arterial blood gas; AIS, Abbreviated Injury Scale; AKI, acute kidney injury; CPC, cerebral performance categories; GRADE, Grading of Recommendations Assessment Development and Education; GOS, Glasgow Outcome Scale; HLOS, hospital length of stay; IMV, invasive mechanical ventilation, ISS, Injury Severity Score; OI, Oxygen Index; OSI, Oxygen Saturation Index; OR, odds ratio; n, arterial blood; SSI, surgical site infection; VFD, ventilator-free days.

*Bold emphasis represents, $p < 0.05$.

TABLE 2. Nontrauma Critical Care Articles Included in Systematic Review (n = 26)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Supports Evidence
Giradis (2016) ⁴	RCT/Single center/Italy N = 434 Mean Age: 64 y Population of Interest: Critically Ill: 100% • Medical: 38% • Surgical: 62%	Conservative: During entire ICU stay - PaO ₂ : 70–100 mm Hg - SpO ₂ : 94–98% Conventional: - PaO ₂ : ≥ 150 mm Hg - SpO ₂ : 97–100%	Primary: ICU Mortality	Conservative vs. Conventional Oxygenation ICU Mortality: 0.086 (0.017–0.150); p = 0.01	Conservative oxygen therapy was associated with a decrease in mortality, organ failure and infections when compared with the conventional oxygen group	I	Supports Normoxia
Panwar (2016) ⁵	RCT/Multicenter/ Australia/NZ/France N = 104 Mean Age: 62 y Population of Interest: Critically Ill: 100% • Trauma: 4% • Surgical: 35% • Mechanically ventilated: 100%	Intervention: Every 4 h d 0–7 Conservative: - Target SpO ₂ : 88–92% - Actual Mean SpO ₂ : 93% Liberal: - Actual Target SpO ₂ : ≥ 96% - Mean SpO ₂ : 97%	90 d Mortality (secondary) Mean AUC for oxygenation values (primary)	SpO ₂ 88–92% vs. SpO ₂ ≥ 96% 90 d Mortality: Conservative: 21 Liberal: 19; p = 0.74 Mean AUC for oxygen values: Conservative: 93%; Liberal: 97% p = <0.001	Conservative oxygen therapy is feasible and appears safe to implement in mechanically ventilated patients in the ICU, compared to liberal oxygenation therapy	I	Neutral
Parke (2016) ³¹	RCT/Multicenter/ Australia/NZ N = 298 Mean Age: 65 y Population of Interest: Cardiac Surgery: 100% • Cardiopulmonary bypass: 100%	Data Collection: During cardiopulmonary bypass Intervention: - PaO ₂ : 75–90 mm Hg Control: - SpO ₂ : ≥ 99%	Primary: Acute Kidney Injury (AKI) (primary) Hospital LOS (secondary)	PaO ₂ 75–90 mm Hg vs. SpO ₂ ≥ 99% Acute Kidney Injury: OR, 5.8 (–16.1–4.7); p = 0.28 Hospital LOS: Control: 8.9 Intervention: 9.0; p = 0.65	Normoxia and hyperoxia had a similar incidence of acute kidney injury, IMV duration, ICU LOS, and hospital LOS in cardiac bypass surgery patients	I	Neutral
Smit (2016) ³²	RCT/Single center/ Netherlands N = 50 Mean Age: 67 y Population of Interest: Critically Ill: 100% • Coronary artery bypass graft (CABG) surgery	Intervention: - PaO ₂ : 130–150 mm Hg during CBP - PaO ₂ : 80–100 mm Hg in ICU Control: - PaO ₂ : 200–220 mm Hg during CBP - PaO ₂ : 130–150 mm Hg in ICU * Timing of PaO ₂ was not defined * FIO ₂ was adjusted to keep PaO ₂ values within target range for protocol	Primary: Myocardial Injury (CK-MB)	Conservative vs. Conventional Oxygenation PaO ₂ CBP: p = <0.0001 PaO ₂ ICU: p = 0.034	Hyperoxia and normoxia groups had similar clinical outcomes in critically ill CABG patients	I	Neutral

Continued next page

TABLE 2. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Stolmeijer (2014) ³³	Prospective/Single center/Netherlands N = 83 Mean Age: 61 y Population of Interest: Critically Ill: 100% · Two or more SIRS criteria · Suspicion of infection Mechanically Ventilated: 100%	Data Collection: On arrival to ED placed on: - FIO ₂ : 0.4 (Venti Mask) 5 min after supplemental oxygen: - PaO ₂ : >71 mm Hg, FIO ₂ down-titrated to a normal SpO ₂ - PaO ₂ : <71 mm Hg, flow rate increased to 15 L/min with FIO ₂ 0.6–0.8 Hyperoxia: PaO ₂ > 101 mm Hg Normoxia: PaO ₂ 70–100 mm Hg	Primary: In-Hospital Mortality	Hyperoxia vs. Normoxia on in-hospital mortality Normoxia: $p = 0.199$ Hyperoxia: $p = 0.199$	Hyperoxia and normoxia had similar in-hospital mortality in mechanically ventilated sepsis patients	II	Neutral
Suzuki (2014) ⁶	Prospective Interventional/ Single center/Australia n = 105 Mean age: 58 y Population of Interest: Critically Ill: 100% · Mechanically Ventilated: 100%	Data Collection: - SpO ₂ : 90–92% (Conservative) - Target at clinicians discretion (Conventional)	Hospital Survival at 28 d (secondary) Oxygenation in the first 10 d (primary)	Conservative vs. Conventional Oxygenation Hospital Survival at 28 d: OR, 0.35 (0.12–1.06); $p = 0.062$ Change in Oxygenation in the first 10 d: Conventional: SpO ₂ 98.4% Conservative: SpO ₂ 95.5% $p = <0.001$	Conservative oxygen therapy was feasible, safe and associated with some improvement in clinical outcomes in mechanically ventilated patients	II	Supports normoxia
Young (2014) ³⁴	RCT/Multicenter/ New Zealand N = 18 Mean Age: 67 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%	Data Collection: Prehospital oxygenation targets (median) Intervention (conservative): - SpO ₂ : 90–94% Control (standard): - SpO ₂ : ≥95%	Primary: Prehospital oxygen saturations ICU LOS Hospital LOS	Standard vs. Conservative Oxygen Prehospital Median: Standard: SpO ₂ 95.8% (92.3–96.5) Conservative: SpO ₂ 79.5 (75.8–90.3) $p = 0.046$ ICU LOS: Standard: 43 d (39.3–93) (51.5–188.6) Hospital LOS: Standard: 129.4 d (51.5–188.6) Conservative: 95.3 d (27.7–657.9)	In a small pilot trial, conservative oxygen titration in prehospital setting after cardiac arrest was not feasible due to hypoxic episodes	II	Supports avoidance of hypoxia

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TABLE 2. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Lee (2010) ⁴⁷	RCT/Single center/ South Korea N = 56 Mean Age: 55 y Population of Interest: Isolated valvular heart surgery • Surgery: 100% • ICU: 100% • Mechanical Ventilation: 100%	Data Collection: During reperfusion Intervention: - FIO ₂ : 0.7 (hyperoxia) Control: - FIO ₂ : 0.5 (normoxia)	Postoperative: Hospital LOS ICU LOS Ventilator Time	Hyperoxia vs. Normoxia Ventilator Time: Hyperoxia: 13 h Normoxia: 16 h; $p = 0.15$ ICU LOS: Hyperoxia: 3.1 d Normoxia: 2.9 d; $p = 0.409$ Hospital LOS: Hyperoxia: 11.5 d Normoxia: 11.2 d; $p = 0.780$	Oxygenation strategy was not associated with clinical outcomes	II	Neutral
Helmerhorst (2017) ³⁵	Retrospective/Multicenter/ Netherlands N = 14,441 Mean age: 65 y Population of Interest: Critically Ill: 100% • ICU: 100% • Mechanically Ventilated: 83% • Surgical: 44%	Data Collection: 1st PaO ₂ , highest PaO ₂ , worst PaO ₂ and average PaO ₂ within the first 24 h of hospital stay - PaO ₂ : >200 mm Hg (Severe Hyperoxia) - PaO ₂ : 120–200 mm Hg (Mild Hyperoxia) - PaO ₂ : 60–120 mm Hg (Normoxia)	Primary: In-Hospital Mortality	Mild Hyperoxia/Severe Hyperoxia vs. Normoxia In Hospital Mortality Mild Hyperoxia: OR, 0.91 (0.79–1.05) In Hospital Mortality Severe Hyperoxia: OR, 1.11 (0.92–1.34)	Hyperoxemia was not associated with a statistically significant change in mortality or ventilator-free days when compared to normoxia in critically ill mechanically ventilated patients	III	Neutral
Johnson (2017) ⁷	Retrospective/Multicenter/ United States N = 544 Mean Age: 61 y Population of Interest: Critically Ill: 100% • Cardiac Arrest: 100%	Data Collection: Median PaO ₂ values 1 h to 48 h in timed increments - PaO ₂ : >300 mm Hg (Hyperoxemia) - PaO ₂ : 60–300 mm Hg (Normoxia) - PaO ₂ : <60 mm Hg (Hypoxemia)	Survival at hospital discharge (secondary) Neurological outcomes at hospital discharge (primary)	Hyperoxemia/Hypoxemia vs. Normoxia Survival at hospital discharge: 1 h Hypoxemia vs. Normoxia: OR, 0.79 (0.41–1.52) 1 h Hyperoxemia vs. Normoxia: OR, 1.50 (0.93–2.44) 12 h Hypoxemia vs. Normoxia: OR, 0.71 (0.26–1.94) 12 h Hyperoxemia vs. Normoxia: OR, 0.17 (0.03–0.89) 48 h Hypoxemia vs. Normoxia: OR, 2.97 (0.23–38.84) 48 h Hyperoxemia vs. Normoxia: OR, 0.22 (0.02–2.04) * Similar results for neurological outcomes*	There was no association between PaO ₂ and neurological outcome within the first 48 h after cardiac arrest among survivors. Hyperoxemia was associated with some evidence of lower survival.	III	Supports normoxia

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TABLE 2. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Scherthaner (2017) ³⁶	Retrospective/Single center/Germany N = 475 Mean Age: 69 y Population of Interest: Critically Ill: 100% · Noninvasive ventilation: 100%	Observational Groups: - PaO ₂ : >97.5 mm Hg (Hyperoxemia) - PaO ₂ : <97.5 mm Hg (Normoxemia) (peak PaO ₂ level used for grouping)	Primary: In-Hospital Mortality Long Term Mortality	Hyperoxemia vs. Normoxemia In-Hospital Mortality: 28% vs. 13%; <i>p</i> = 0.05 Long Term Mortality > 97.5 mm Hg: OR, 1.69 (1.19–2.42); <i>p</i> = 0.004	Hyperoxemia was associated with higher in-hospital mortality and long term mortality when compared to normoxemia in patients receiving noninvasive mechanical ventilation	III	Supports normoxia
Staehr-Rye (2017) ³⁷	Retrospective/ Multicenter/USA N = 73922 Mean Age: 56 y Population of Interest: Surgery (nonthoracic): 100% · Mechanically Ventilated: 100%	Data Collection: Median FIO ₂ intraoperatively - Group 1: 0.31 (reference) - Group 2: 0.41 - Group 3: 0.52 - Group 4: 0.58 - Group 5: 0.79	7-d mortality 30-d mortality (secondary) Major respiratory complications (primary)	High FIO₂ vs. Low FIO₂ 7-d mortality: OR, 2.09 (0.81–5.43) 30-d mortality: OR, 1.97 (1.30–2.99) Respiratory complications: OR, 1.99 (1.72–2.31)	There is a dose-dependent association between high intraoperative FIO ₂ with higher major respiratory complications and 30 d mortality, when compared to low intraoperative FIO ₂	III	Supports normoxia
Wang (2017) ³⁸	Retrospective/ Multicenter/USA N = 9186 Mean Age: 65 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%	Data Collection: Based on first, last or any measurement within the first 24 h - PaO ₂ : ≥300 mm Hg (Hyperoxemia) - PaO ₂ : 60–299 mm Hg (Normoxia) - PaO ₂ : <60 mm Hg (Hypoxemia) * ROC protocol did not dictate the timing or frequency of ABG measurements	Primary: In-Hospital Mortality	Hyperoxemia/Hypoxemia vs. Normoxemia Initial PaO₂ hyperoxemia vs. normoxemia: OR, 1.10 (0.97–1.26) Initial PaO₂ Hypoxemia vs. Normoxemia: OR, 1.58 (1.30–1.92) Final PaO₂ Hyperoxemia vs. Normoxemia: OR, 1.60 (1.26–2.04) Final PaO₂ Hypoxemia vs. Normoxemia: OR, 3.06 (2.42–3.86) Any PaO₂ Hyperoxemia vs. Normoxemia: OR, 1.25 (1.11–1.41) Any PaO₂ Hypoxemia vs. Normoxemia: OR, 1.76 (1.54–2.02)	Hyperoxemia and hypoxemia were both associated with higher mortality when compared to the normoxia group in cardiac arrest patients with ROSC	III	Supports normoxia
Christ (2016) ³⁹	Retrospective/Single center/Germany N = 134 Mean Age: 69 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%	Data Collection: ABGs within 60 min after hospital admission - Hyperoxia - Normoxia * PaO ₂ thresholds not defined	Primary: Survival to hospital discharge	Hyperoxia vs. Normoxia Survival to discharge: Hyperoxia: 54.3% Normoxia 34.3%; <i>p</i> = 0.04	Hyperoxia in the short period postarrest is associated with higher survival in cardiac arrest patients	III	Supports higher oxygenation

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TABLE 2. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Six (2016) ⁴⁰	Retrospective/Single center/France N = 503 Mean Age: 60 y Population of Interest: Critically Ill: 100% · Mechanically Ventilated: 100% · Ventilator acquired pneumonia (VAP)	Data Collection: Daily PaO ₂ - PaO ₂ > 120 mm Hg (Hyperoxemia) * One PaO ₂ > 120 mm Hg was considered a day with hyperoxemia * hypoxemia and normoxemia were not defined	Primary: Hyperoxemia related to the development of VAP	Hyperoxemia related to the development of VAP VAP: OR, 1.68 (1.16–2.42); p = 0.006	Hyperoxemia is an independent risk factor in the development of ventilator acquired pneumonia in mechanically ventilated patients	III	Supports normoxia
Elmer (2015) ⁴¹	Retrospective/Single center/USA (Pittsburgh) N = 184 Mean Age: 60 y Population of interest: critically ill: 100% Postcardiac arrest: 100% Mechanically ventilated: 100%	Data Collection: PaO ₂ first 24 h, in hourly intervals - PaO ₂ > 300 mm Hg (severe hyperoxia) - PaO ₂ : 101–299 mm Hg (moderate hyperoxia) - PaO ₂ : 60–100 mm Hg (normoxia) - PaO ₂ < 60 mm Hg (hypoxia)	Primary: Survival to hospital discharge	Relationship of PaO₂ levels in first 24 h and Survival to Discharge Severe Hyperoxia: OR, 0.84 (0.72–0.98); p = 0.02 Moderate Hyperoxia: OR, 1.01 (0.96–1.05); p = 0.79 Normoxia: OR, 0.74 (0.47–1.16); p = 0.20 Hypoxia: OR, 1.01 (0.99–1.03); p = 0.25	Severe hyperoxia PaO ₂ > 300 mm Hg was associated with lower survival in cardiac arrest patients with ROSC	III	Supports normoxia
Rincon (2015) ⁴²	Retrospective/Multicenter/ USA (Philadelphia) N = 1388 Mean Age: 63 y Population of Interest: Critically Ill: 100% · Mechanically Ventilated: 100% · Intracerebral Hemorrhage	Observational Groups: Any of the first ABGs or follow up ABGs - PaO ₂ < 60 mm Hg (Hypoxia) - PaO ₂ > 300 mm Hg (Hyperoxia) * Normoxia defined as no episodes of hypoxia or hyperoxic	Primary: In-Hospital Mortality	Hyperoxia and Hypoxia vs. Normoxia Hyperoxia: OR, 2.5 (1.1–6.1); p = 0.04 Hypoxia: OR, 1.9 (1.2–3.3); p = <0.0001	Both hyperoxia and hypoxia was associated with higher in-hospital mortality when compared to normoxia in mechanically ventilated intracranial hemorrhage patients	III	Supports normoxia
Wang (2015) ⁴³	Retrospective/Single center/Taiwan N = 550 Mean Age: 68 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%	Data Collection: First value after first sustained ROSC - PaO ₂ - PaCO ₂	Survival to hospital discharge (secondary) Favorable neurological status at discharge (primary)	Oxygenation and Favorable Neurological Outcome Survival: PaO ₂ 70–240 mm Hg: OR, 1.85 (1.21–2.85); p = 0.00 Favorable Neurological Outcome: PaO ₂ 70–240 mm Hg: OR, 1.96 (1.08–3.64); p = 0.03	PaO ₂ of 70–240 mm Hg was associated with favorable neurological outcomes and a higher survival to discharge in cardiac arrest patients with ROSC.	III	Supports normoxia

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TABLE 2. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Rincon (2014) ⁴⁴	Retrospective/Multicenter/USA (Philadelphia) N = 2894 Mean Age: 61 y Population of Interest: Critically Ill: 100% · Mechanically Ventilated: 100% · Stroke, Subarachnoid Hemorrhage (SAH) · Intracranial hemorrhage	Observational Groups: First ABG within the first 24 h of admission to the ICU - PaO ₂ : <60 mm Hg (Hypoxia) - PaO ₂ : 60–300 mm Hg (Normoxia) - PaO ₂ : >300 mm Hg (Hyperoxia)	Primary: In-Hospital Mortality	Normoxia vs. Hyperoxia/ Hypoxia In-Hospital Mortality Hyperoxia: OR, 1.22 (1.04–1.48); <i>p</i> = 0.04 Hypoxia: OR, 0.88 (0.71–1.10)	Hyperoxia, but not hypoxia, was associated with higher in-hospital mortality in critically ill stroke patients, when compared to normoxia	III	Supports normoxia
Ihle (2013) ⁴⁵	Retrospective/ Multicenter/Canada N = 584 Mean Age: 64 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%	Data Collection: PaO ₂ within first 24 h in ICU - PaO ₂ : <60 mm Hg (hypoxia) - PaO ₂ : 60–299 mm Hg (normoxia) - PaO ₂ : ≥300 mm Hg (hyperoxia)	Primary: In-Hospital mortality	Hypoxia/hyperoxia vs. Normoxia Hypoxia vs. normoxia: OR, 0.93 (0.47–1.87) Hyperoxia vs. Normoxia: OR, 1.20 (0.51–2.82)	Hyperoxia and hypoxia, when compared with normoxia, had no association with in-hospital mortality in postcardiac arrest patients	III	Neutral
Janz (2012) ⁴⁰	Retrospective/Single center/USA (Nashville) N = 170 Mean Age: 61 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%	Data Collection: - Highest PaO ₂ within 1st 24 h postcardiac arrest	Primary: In-Hospital Mortality Secondary: Poor neurological outcome at discharge	High PaO₂ values in relation to in-hospital mortality and poor neurological outcomes In-Hospital mortality: OR, 1.439 (1.028–2.015); <i>p</i> = 0.03 Poor neurological outcomes: OR, 1.485 (1.032–2.136); <i>p</i> = 0.03	High PaO ₂ levels in the postarrest setting were associated with increased risk of in-hospital mortality and poor neurological outcomes at discharge	III	Supports normoxia
Young (2012) ⁴⁶	Retrospective/Multicenter/ Australia/NZ N = 2643 Mean Age: 66 y Population of Interest: Critically Ill: 100% · Mechanically ventilated: 100% · Ischemic Stroke: 100%	Observational Groups: Most abnormal PaO ₂ during the first 24 h of admission in the ICU, defined as the PaO ₂ associated with the highest alveolar-arterial (A-a) gradient	Primary: In-Hospital Mortality	Most abnormal PaO₂ and Mortality PaO ₂ 0–69: OR, 1.14 (0.76–1.72) PaO ₂ > 69–83: OR, 1.15 (0.76–1.74) PaO ₂ > 83–93: OR, 0.99 (0.65–1.51) PaO ₂ > 93–103: OR, 1.48 (0.97–2.26) PaO ₂ > 103–117: OR, 0.94 (0.62–1.53) PaO ₂ > 117–140: OR, 1.01 (0.67–1.53) PaO ₂ > 140–174: OR, 1.20 (0.80–1.81) PaO ₂ > 174–226: OR, 0.82 (0.55–1.22) PaO ₂ > 226–341: OR, 1.01 (0.69–1.47) PaO ₂ > 341–611: OR, 1.00 (reference)	The most abnormal PaO ₂ within 24 h was not associated with in-hospital mortality in mechanically ventilated stroke patients	III	Neutral

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TABLE 2. (Continued)

Author/Year	Study Design/ Participants/Inclusion Criteria	Oxygen Exposure	Outcome Measures	Results*	Conclusions	GRADE Level of Evidence	Support of Evidence
Kilgannon (2011) ⁴⁷	Retrospective/Multicenter/ USA N = 4459 Mean age: 64 y Population of interest: Critically ill: 100% • Cardiac arrest: 100%	Data collection: First PaO ₂ in ICU - PaO ₂ : >300 mm Hg (hyperoxia) - PaO ₂ : 60–300 mm Hg (Normoxia) - PaO ₂ : <60 mm Hg (Hypoxia)	Primary: In-Hospital Mortality	PaO₂ (continuous) and Mortality In-hospital mortality: OR, 1.06 (1.05–1.07) for rise of 25 mm Hg; <i>p</i> < 0.001	A 25 mm Hg increase of PaO ₂ showed a 6% increase in the odds of death in cardiac arrest patients	III	Supports normoxia
Kilgannon (2010) ⁵	Retrospective/multicenter/ USA N = 6326 Mean Age: 64 y Population of Interest: Critically Ill: 100% • Cardiac Arrest: 100%	Data Collection: First ABG in ICU - PaO ₂ : >300 mm Hg (Hyperoxia) - PaO ₂ : 60–300 mm Hg (Normoxia) - PaO ₂ : <60 mm Hg (Hypoxia)	Primary: In-Hospital Mortality	Oxygenation and mortality Hypoxia vs. normoxia: OR, 1.3 (1.1–1.5); <i>p</i> = 0.009 Hyperoxia vs. normoxia: OR, 1.8 (1.5–2.2); <i>p</i> < 0.01	Arterial hyperoxia associated with higher in-hospital mortality compared to normoxia and hypoxia	III	Supports normoxia
de Jonge (2008) ⁴⁸	Retrospective/Multicenter/ Netherlands n = 3,322 Mean age: 62 y Population of Interest: Ist 24 h/ entire ICU stay Critically Ill: 100% • Surgery: 100%	Data Collection: Mean PaO ₂ during the entire ICU stay - PaO ₂	Primary: In-Hospital Mortality	Mean PaO₂ on mortality for the entire ICU stay PaO₂, 60 mm Hg: OR, 1.63 (1.16–2.3)/ PaO₂, 60–80 mm Hg: OR, 1.51 (1.18–1.96) PaO₂, 80–95 mm Hg: OR, 1.25 (0.99–1.57) PaO₂, 95–123 mm Hg: N/A PaO₂ > 123 mm Hg: OR, 1.04 (0.64–1.68)	High PaO ₂ values within the first 24 h of hospital stay and lower PaO ₂ values during the entire ICU stay had higher odds of mortality in critically ill patients	III	Supports normoxia
Brown (2006) ⁴⁹	Retrospective/Single center/USA (Spokane) N = 36 Mean Age: Not reported Population of interest: critically ill: 100% Mechanically ventilated: 100% Cardiopulmonary bypass	Data Collection: During Cardiopulmonary bypass - PaO ₂ 300–350 mm Hg (hyperoxia) - PaO ₂ 150–250 mm Hg (normoxia)	ICU LOS Ventilator Time	Hyperoxia vs. Normoxia ICU LOS: Hyperoxic: 38.6 d Normoxic: 29.2 d; <i>p</i> = 0.42 Ventilator Time: Hyperoxic: 9.4 h Normoxic: 7.2 h; <i>p</i> = 0.10	Hyperoxia and normoxia had similar clinical outcomes in patients receiving cardiopulmonary bypass	III	Neutral

*Bold emphasis represents, *p* < 0.05.

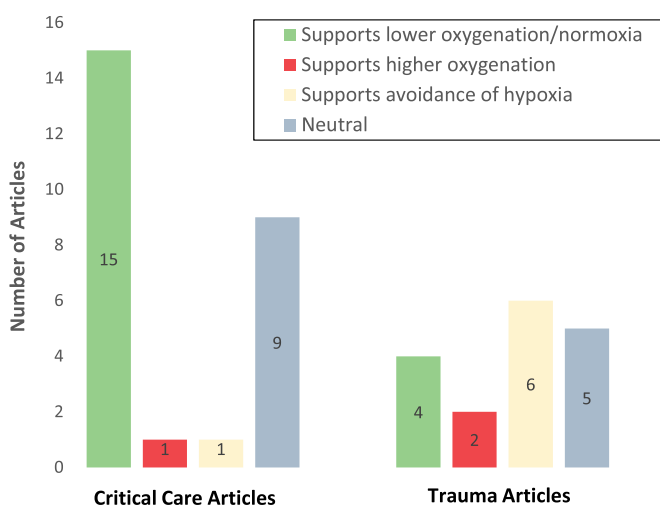


Figure 2. Summary of oxygenation-related conclusions of included trauma and nontrauma critical care articles. A majority of critical care articles supported lower oxygen targets (normoxia). Trauma articles (mostly traumatic brain injury) had heterogeneous results.

supplemental oxygen (i.e., room air), this would not qualify as modifiable hyperoxia regardless of the their SpO_2 or PaO_2 . Based on these studies, we found an association between reduced oxygen administration targeting normoxia and better or equivalent clinical outcomes. Several studies showed an association between avoidance of hypoxia and improved outcomes—this indicates a balanced assessment is indicated.

Only four high-quality randomized control trials (RCTs) were identified in our systematic review, all focusing on nontrauma critically ill patients.^{4,5,13,52} Two focused primarily on cardiac surgical patients, while the other two enrolled mixed medical and surgical populations (most were medical). None of these trials enrolled trauma patients. The two trials focusing on cardiac surgery patients demonstrated no difference between normoxia and higher oxygenation in a variety of ICU outcomes. However, the trials by Girardis et al.⁴ and Panwar et al.⁵ demonstrated safety and possibly efficacy for normoxia in critically ill patients (mostly medical). Both trials compared “conservative” oxygen therapy (SpO_2 94–98% and 88–92%, respectively) with “liberal” oxygen therapy ($SpO_2 \geq 97\%$ and $\geq 96\%$, respectively). Conservative oxygen therapy, a surrogate for normoxia, was feasible and safe in one pilot trial⁵ and was associated with lower mortality in the other.⁴ Collectively, these trials represent the highest level of evidence included in this systematic review and highlight the need for additional and larger clinical trials with a specific focus on trauma patients.

Overall limited and low-quality evidence exists for trauma patients. The balance of evidence suggests that avoidance of hypoxia is of paramount importance in critically ill trauma patients, which likely reflects current clinical practice. However, emerging evidence supporting avoidance of hyperoxia may be similarly important. Several low-quality studies suggest that trauma patients, like other critically ill patients, may experience harm from aggressive oxygen administration.^{27,29,30,50} The optimal level of oxygenation in trauma patients remains unknown. Future studies are needed to clarify oxygen targets for noninvasive pulse oximetry

and arterial oxygen measurements, which we believe will have importance to the civilian and military settings.

Oxygenation may be represented as a continuum. The competing interests of avoiding both hyperoxia and hypoxia must be addressed in each clinical situation. For example, patients with TBI are at high risk for cerebral ischemia due to insufficient cerebral blood flow and oxygen delivery. Eight of the included trauma studies, predominately TBI patients, support either the avoidance of hypoxia or higher supplemental oxygen delivery.^{18,20,23,26,33–36} The remainder of the included trauma studies, again mostly comprised of TBI patients, were neutral or supported normoxia. One possible conclusion from these data is to avoid hypoxia at all costs by allowing permissive hyperoxia in TBI patients. Another would be to titrate supplemental oxygen to normoxia in TBI patients. Further investigation is needed to better elucidate ideal oxygenation targets in this patient population.

It is possible that hyperoxia, similar to other exposures, may display dose-dependent adverse effects. Unfortunately, many of the studies in this systematic review analyzed either the initial PaO_2/SpO_2 on admission or the highest/lowest value during the ICU or hospital course. Therefore, the dose-dependent nature of oxygen toxicity is nearly impossible to elicit from the currently available data. One important area of future research includes examining the association between total time spent with hyperoxia with outcomes in critically ill trauma patients. Second, targeted research is needed to drive optimal clinical parameters for the lower and upper limits for oxygen saturations (readily measurable in almost all settings).

Of note, the World Health Organization released a guideline in 2016 recommending the usage of 80% fraction of inspired oxygen (FIO_2) intraoperatively to prevent surgical site infection.⁵³ This recommendation was based on conflicting data from some small clinical trials. Indeed, a recent Cochrane Review of 28 RCTs² demonstrated no difference in the rate of surgical site infection if a high FIO_2 ($>60\%$) was used intraoperatively. The authors could not support the routine use of high intraoperative FIO_2 due to the significant risk of adverse events, including mortality and lack of benefit for surgical site infections.

A recently published systematic review and meta-analysis¹² examined 25 RCTs related to oxygenation in acute illness and found increased mortality with liberal/excessive oxygen administration. However, most trials were in nontrauma and noncritically ill patients, limiting relevance to critically ill trauma patients. Only three studies overlapped with the current systematic review (two critical illness trials^{4,5} and one trauma,³⁶ specifically TBI). Therefore, this meta-analysis is complimentary but minimally overlapping to our systematic review, which focuses specifically on evidence relevant to critically ill trauma patients.

We identified four relevant ongoing trials addressing hyperoxia or optimal oxygen titration: ACTRN12615000957594, NCT03174002, NCT02713451, and NCT02321072. All of these trials include a broad population of critically ill patients (mostly medical) without a specific focus on trauma. Accordingly, randomized controlled trials to determine the optimal oxygen titration in critically ill trauma patients are urgently needed.

Limitations of this systematic review include a paucity of high-quality evidence that met inclusion criteria. As noted previously, only four high-quality RCTs were identified for this systematic review, and none of these were trauma-specific. A

second limitation of this review is the broad range of definitions for both hyperoxia and normoxia. Within the 43 included publications, hyperoxia or conventional treatment was defined as anything from a PaO₂ of 120 mm Hg or greater to a PaO₂ of 300 mm Hg or greater. Occasionally SpO₂ was used to make this distinction, and these values ranged from SpO₂ of 95% or greater to SpO₂ of 99% or greater. We defined the most common ranges used to define normoxia. However, without a standardized definition for hyperoxia, it is more challenging to evaluate specific oxygenation thresholds. The role of nitrogen remains unclear and is beyond the scope of this study. Another limitation is the differences between TBI patients and those with other forms of traumatic injuries such as the titration of oxygen to maintain cerebral perfusion. Most of the included trauma studies enrolled TBI as their primary patient population. In routine clinical care, there may be a correlation between severity of TBI and amount of supplemental oxygen administered, particularly early in the hospital course to avoid hypoxia and cerebral ischemia. The avoidance of hypoxia, rather than targeting hyperoxia, has become an emerging theme in TBI populations which requires specific prospective interventional study. Another limitation is the challenge of creating conclusions from predominantly observational research.

CONCLUSION

In this systematic review of oxygenation in critically ill trauma patients, there were few trauma-specific studies identified beyond TBI; none were high quality. Extrapolating primarily from lower-quality studies and from nontrauma critical illness, the preponderance of evidence supports an association between reduced oxygen administration with targeted normoxia and better or equivalent clinical outcomes. Whether this translates to trauma-specific populations remains unclear. Avoidance of hypoxia was also associated with better outcomes in several studies, including TBI/trauma. This systematic review supports the need for prospective, trauma-specific investigation to determine the optimal oxygenation strategy that is most applicable to trauma care.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORSHIP

D.J.D., E.L.A., A.A.G. participated in the study conception and design. D.J.D., E.L.A., K.D., A.A.G. participated in the acquisition of data. D.J.D., S.G.S., E.L.A., J.J., K.D., C.C., V.S.B., A.A.G. participated in the analysis and interpretation of data. D.J.D., A.A.G. participated in the drafting of the article. D.J.D., S.G.S., E.L.A., J.J., K.D., C.C., V.S.B., A.A.G. participated in the critical revision. A.A.G. takes responsibility for the article as a whole.

DISCLOSURE

This trial was supported by the Department of Defense/ US Special Operations Command (USSOCOM) (W81XWH-17-C-0241). This manuscript expresses the authors' opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government. There are no other funding disclosures or conflicts of interest to declare.

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Consensus-Based Recommendation for Oxygenation Targets in Critically Injured Patients

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Background: Prehospital oxygen supplementation frequently occurs, even in the combat setting. Consensus on optimal oxygenation targets remains unclear.

Methods: We conducted a three-round modified Delphi process to reach consensus among military and civilian experts in trauma surgery, emergency medicine, and critical care. The focus of the electronic survey process was defining oxygen titration goals, including oxygen saturation (SpO₂), arterial oxygenation (PaO₂), and fraction of inspired oxygen (FiO₂) in critically injured patients. We also evaluated differences in specific trauma subgroups.

Results: Of the 31 invited experts (13 military, 18 civilian), 26 completed the first round, 28 completed the second round, and 27 completed the final round. All experts participated in at least one round. In the first (open-ended) round, we narrowed the potential SpO₂ range to 88-100% and PaO₂ range 60-300 mmHg. TBI, hemorrhagic shock, and resource-limited settings had at least 20% of respondents who would alter targets. In the second round, the highest agreement was for a lower SpO₂ threshold 90%, upper SpO₂ threshold 96%, lower PaO₂ threshold 60 mmHg, upper PaO₂ threshold 100 mmHg, and for lowest acceptable FiO₂ of 21%. In the final round, 89% of experts accepted the lower and upper SpO₂ thresholds (90% and 96%) and upper PaO₂ threshold (100 mmHg); 96% of experts accepted the lower PaO₂ threshold (60 mmHg); and all accepted the lowest acceptable FiO₂ (21%). For subgroups, 33% of experts recommended a higher oxygenation target for TBI and 11% for hemorrhagic shock. Most (84%) recommended a lower oxygenation target for resource-limited settings (majority recommending SpO₂ 88%).

Conclusion: We defined a consensus-based standard for oxygenation targets in critically injured patients as SpO₂ 90-96% (88-96% with resource-limitations), PaO₂ 60-100 mmHg, and lowest acceptable FiO₂ 21%. These standards represent expert consensus, but higher quality prospective data is needed to validate these findings.

Disclosures: Funded by the Department of Defense/SOCOM (W81XWH-17-C-0241). This abstract expresses the authors' opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.

Association between Hyperoxia, Supplemental Oxygen, and Mortality in Critically Injured Patients

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Background: Oxygen therapy has undisputed importance in combat casualty care to treat and prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. Emerging evidence indicates that even modest hyperoxia may increase morbidity and mortality, but limited evidence exists specifically for trauma patients. In addition, oxygen is a limited resource that is challenging to obtain in austere settings—e.g., prolonged field care and en route care, requiring substantial resources, space, weight and logistics to procure. In this study, we evaluated the association between hyperoxia and supplemental oxygen delivery with in-hospital mortality in critically injured patients.

Methods: We conducted a multicenter, retrospective observational cohort study at the two Level I and one Level II trauma centers in Colorado. We defined our cohort of critically injured patients as having an ICD-10 code for injury/trauma and requiring admission to the intensive care unit within 24 hours of emergency department arrival from October 2015 to June 2018. The primary predictor was oxygenation, defined by all recorded oxygen saturation (SpO₂) values measured during the first 7 days of hospitalization. We defined the oxygen exposure as the following categories based on our prior consensus work: hyperoxia (97-100%), normoxia (90-96%), borderline hypoxia (88-89%), or hypoxia (<88%), with each individual patient's oxygen exposure defined as the proportion and cumulative duration of time spent in each category during the first 7 days of hospitalization. The primary clinical outcome was in-hospital mortality, which we analyzed using time dependent covariates with a Cox regression model. We calculated hazard ratios for the interaction of the SpO₂ and FiO₂ values. The results were adjusted for demographics (age, sex, race/ethnicity), mechanism of injury, APACHE II Score, Elixhauser comorbidities (stratified by cardiopulmonary and non-cardiopulmonary), and cigarette smoking status.

Results: We included 3,288 visits that met our case definition for critically injured patients. The median age was 54 years (IQR 34-69), and patients were 66% male, 67% non-Hispanic white, 8% non-Hispanic black, and 16% Hispanic. Blunt trauma mechanism was present in 66% of cases, 72% arrived by EMS, and the mean APACHE II score was 9.6 (SD 6.8). The primary outcome of in-hospital mortality occurred in 252 (7.7%) of patients, with 41% of cases requiring mechanical ventilation and the mean hospital length of stay among survivors was 10 days (SD 15.9). Mean ventilator free days to day 28 was 24 (SD 8.4) and mean hospital free days to day 90

was 74 days (SD 24). Of the 226,057 patient-hours recorded, 108,296 (46%) had hyperoxia, 108,296 (52%) had normoxia, 3,858 (2%) had borderline hypoxia, and 3,177 (1%) had hypoxia. During hyperoxia, the adjusted risk of mortality was higher for higher fraction of inspired oxygen (FiO₂): at SpO₂ of 100%, the adjusted hazard ratios for FiO₂ at 100%, 80%, and 60% were 11.7 (95%CI 5.2-6.2), 5.5 (95%CI 2.6-11.6), and 2.0 (95%CI 1.0-4.2), respectively and for FiO₂ at 21% and 30% were 0.14 (95%CI 0.08-0.26) and 0.29(95%CI, 0.18-0.46), respectively. Similarly, at SpO₂ of 96%, the adjusted hazard ratios for FiO₂ at 100%, 80%, and 60% were 14.5 (95%CI 6.7-31.4), 7.5 (95%CI 3.7-15.1), and 3.2 (95%CI 1.6-6.1), respectively and for FiO₂ at 21% and 30% were 0.32 (95%CI 0.19-0.53) and 0.58 (95%CI, 0.37-0.90), respectively.

Conclusion: In this large multicenter cohort of critically injured civilian patients, hyperoxia was present during nearly half of the time during the first 7 days of hospitalization. During hyperoxia, higher oxygen administration was associated with a greater risk of mortality, while lower oxygen administration was associated with a lower risk of mortality. Prospective interventional studies are required to determine the causal association between hyperoxia and clinical outcomes and optimal target oxygen concentrations in critically injured patients.

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Character count: 4,061 (with spaces)

Association between Hyperoxia, Supplemental Oxygen, and Mortality in Critically Injured Patients

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David J. Douin, MD, Caroline Ledbetter, MPH, Yang Wang, PhD,
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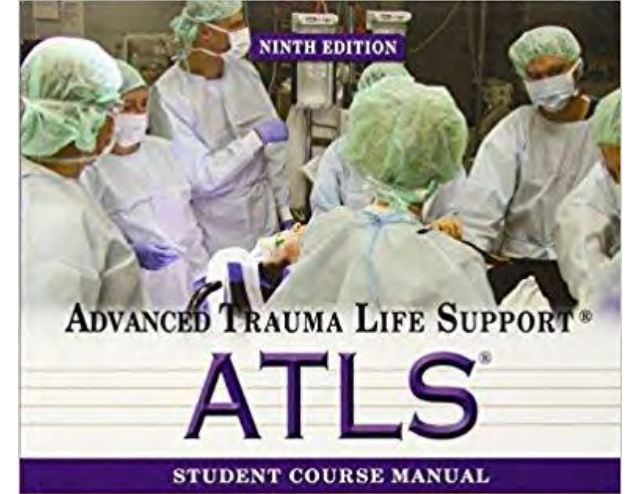


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Anschutz Medical Campus
School of Medicine

Disclosures

- ▶ Authors have no conflicts of interest to report.
 - ▶ Project Funding
 - **USSOCOM W81XWH-17-C-0241**
 - ▶ This presentation expresses authors' own opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.
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Current State



- ▶ “Oxygenated inspired air is best provided via a tight-fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”
- ▶ “The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation... a pulse oximeter reading greater than 90%.”

COMBAT CASUALTY CARE

Lessons Learned from OEF and OIF

Edited by
Eric Savitsky, MD
Colonel Brian Eastridge, MD

Paradigm Shift



- ▶ Supplemental oxygen key to avoid morbidity from hypoxia
- ▶ Excessive oxygen in En Route Care
 - Common practice
 - Unlikely to benefit; may cause harm
 - Expands mission weight, cube, and logistics/power; safety issues
- ▶ Gap: Limited data on optimal oxygen titration targets in critically injured patients

Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

**David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN,
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J Trauma Acute Care Surg 2019 May

Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

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Vikhyat S. Bebarta, MD, and Adit A. Ginde, MD, MPH, *Aurora, Colorado*

► Conclusions

- Overall association between lower oxygen/normoxia and improved clinical outcomes
- Few trauma specific articles
 - 14 out of 17 trauma related exclusively to TBI
 - No high quality/clinical trial data
- Supports need for further trauma-specific studies/clinical trials, particularly beyond TBI

Objective

To evaluate the association between hyperoxia and supplemental oxygen delivery with in-hospital mortality in critically injured patients



Methods

- ▶ **Design:** Multicenter retrospective observational cohort
 - Two Level 1 and one Level 2 civilian trauma centers in Colorado
 - ▶ **Cohort:** ICD-10 code for trauma + ICU admission (2015–18)
 - ▶ **Exposure:** SpO₂ and FiO₂ during the first 7d of hospitalization
 - Hyperoxia: SpO₂ 97–100%
 - Normoxia: SpO₂ 90–96%
 - Hypoxia: SpO₂ <88% (borderline: 88–89%)
 - FiO₂ categories: 21%, 22–30%, 31–40%, >40%
- 

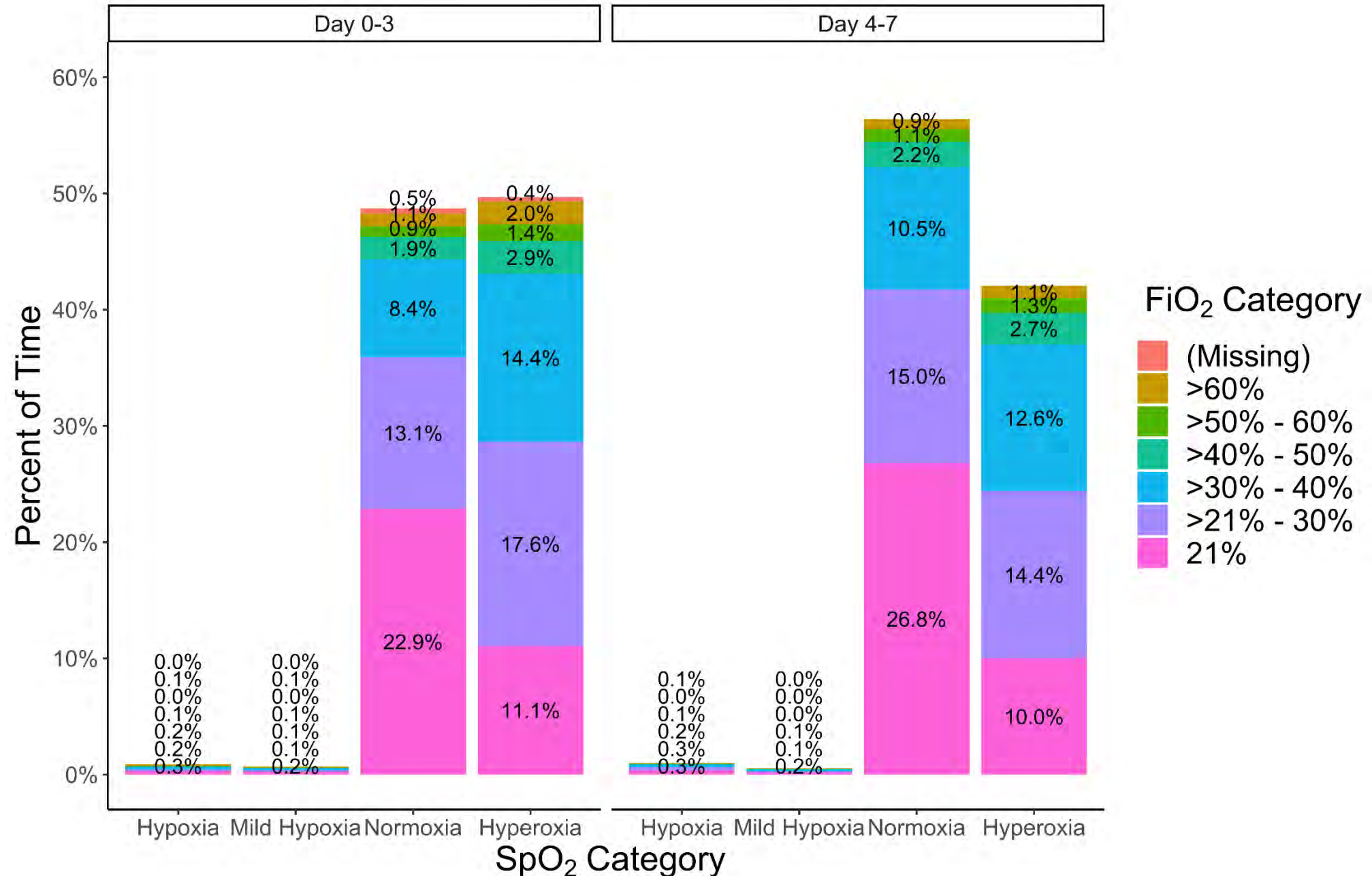
Analysis

- ▶ **Primary Outcome: In-Hospital Mortality**
 - Cox proportion hazard model with time-varying covariates
 - All available SpO2 and FiO2 data used (constant between measurements)
 - Non-linear association and interaction incorporated
- ▶ **Ventilator Free Days to Day 28**
 - Negative binomial distribution in general linear model
- ▶ **Hospital Free Days to Day 90**
 - Poisson distribution in a general linear model
- ▶ Adjusted for demographics, injury mech, APACHE II Score, comorbidities (cardiopulmonary and non-cardiopulmonary), and smoking

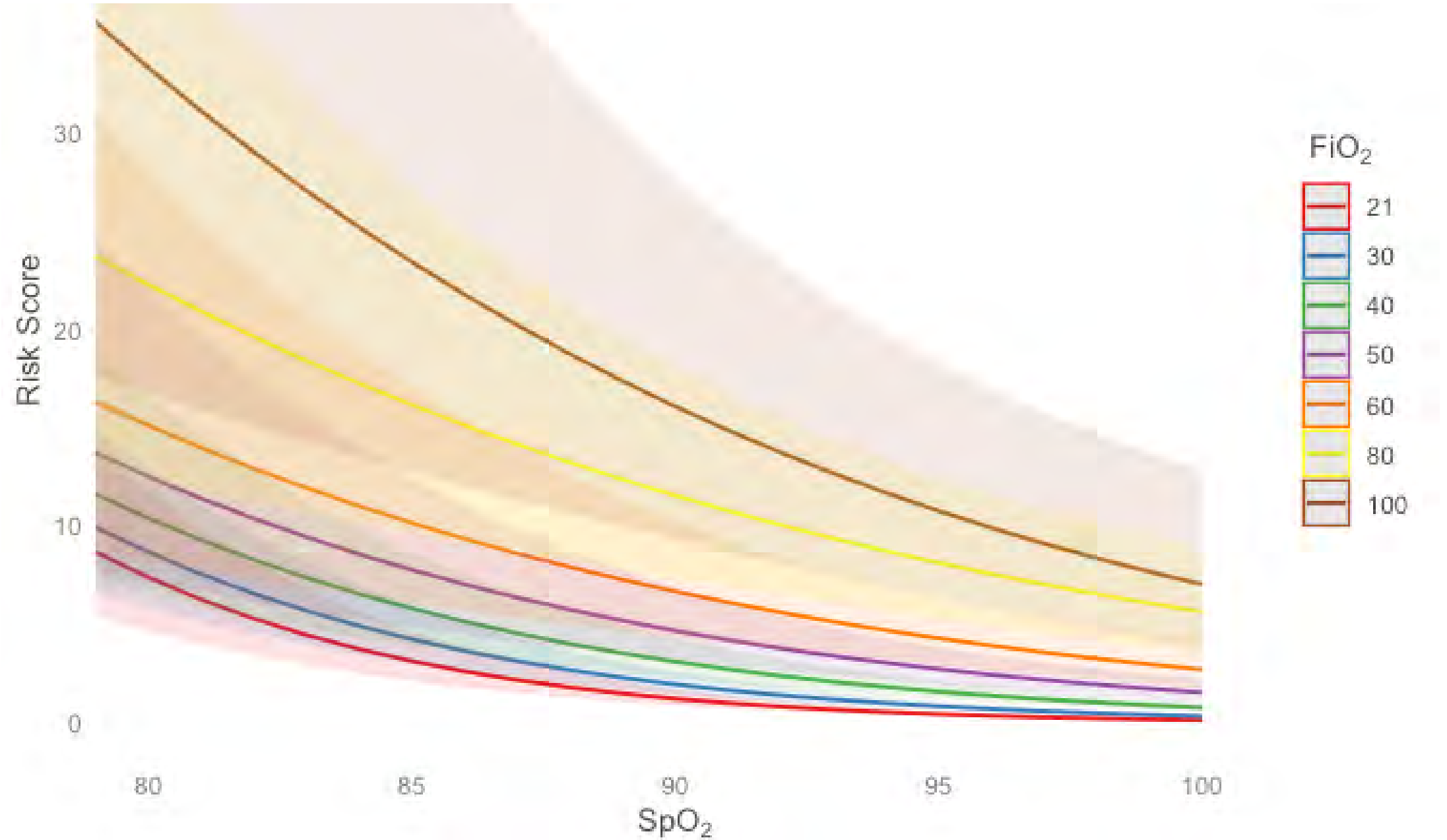
Results—Characteristics

- ▶ **Cohort Size:** n=3,464 patients
- ▶ **Demographics:** mean age 53y, male 65%, white 68%
- ▶ **Mechanism:** fall 35%, MVC 31%, burn 8%, penetrating 7%
- ▶ **Clinical:** EMS arrival 73% , mech vent 41%, mean APACHE 8
- ▶ **Outcomes**
 - In-Hospital Mortality 7.6%
 - VFD 23.7 days (of 28)
 - HFD 73.7 days (of 90)

Percentage of Time Spent in SpO2 / FiO2 categories



Adjusted Mortality Risk by SpO₂ & FiO₂



Adjusted Incident Rate Ratios for VFD and HFD

SpO2 category (FiO2)	VFD	HFD
Normoxia (21%)	1.09 (1.07–1.10)	1.07 (1.06–1.07)
Normoxia (22–30%)	1.04 (1.03–1.06)	1.03 (1.03–1.04)
Normoxia (31–40%)	1.01 (1.00–1.03)	1.01 (1.01–1.02)
Normoxia (>40%)	0.98 (0.97–1.00)	0.98 (0.98–0.99)
Hyperoxia (21%)	1.02 (1.01–1.04)	1.02 (1.01–1.02)
Hyperoxia (22–30%)	1.00 (0.98–1.01)	0.99 (0.99–1.00)
Hyperoxia (31–40%)	0.99 (0.97–1.00)	0.98 (0.98–0.99)
Hyperoxia (>40%)	Reference	Reference

Limitations

- ▶ Retrospective data
- ▶ Observational—confounding by indication
- ▶ Geographically limited, higher elevation
- ▶ Primary endpoint (mortality) is uncommon



Conclusions

- ▶ Hyperoxia common in critically ill trauma patients
- ▶ During hyperoxia, higher oxygen administration associated with higher mortality and morbidity (lower VFD, HFD)
- ▶ Lower oxygen administration and targeting normoxia may result in better clinical outcomes
 - Additional logistical/operational benefit
- ▶ **Future directions:** multicenter interventional trial



Questions?

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School of Medicine

- Oxygen supplementation is frequently used in critically injured trauma casualties in the combat setting.
- Oxygen supplies in the deployed setting are limited
- We currently lack oxygen supplementation specific guidelines for the combat setting



Objectives

We sought to develop and expert consensus panel on oxygen targets for critically injured trauma patients maximizing outcomes while minimizing oxygen use.

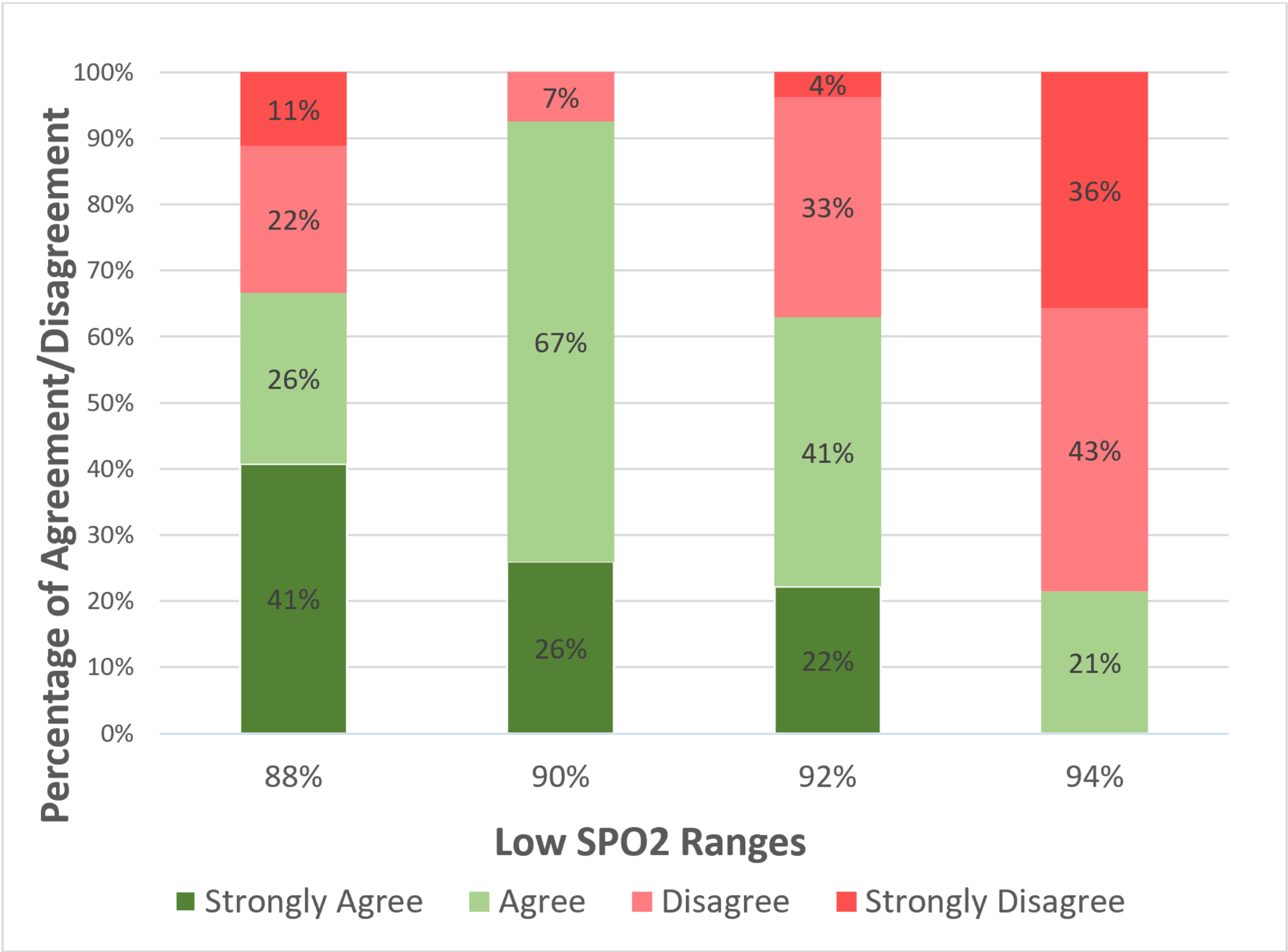
Methods

- We conducted a prospective study using the multi-stage, modified Delphi consensus process of subject matter experts across many disciplines of medicine and surgery including both military and non-military physicians
- Provided them with a systematic review of available literature in advance to help inform their opinions

Results

- 31 invited experts → 26 completed first round, 28 completed second round, 27 completed the final round, all participated in at least one round
- When caveating limited resources, the expert panel felt a target SPO2 of 88-96% was ideal

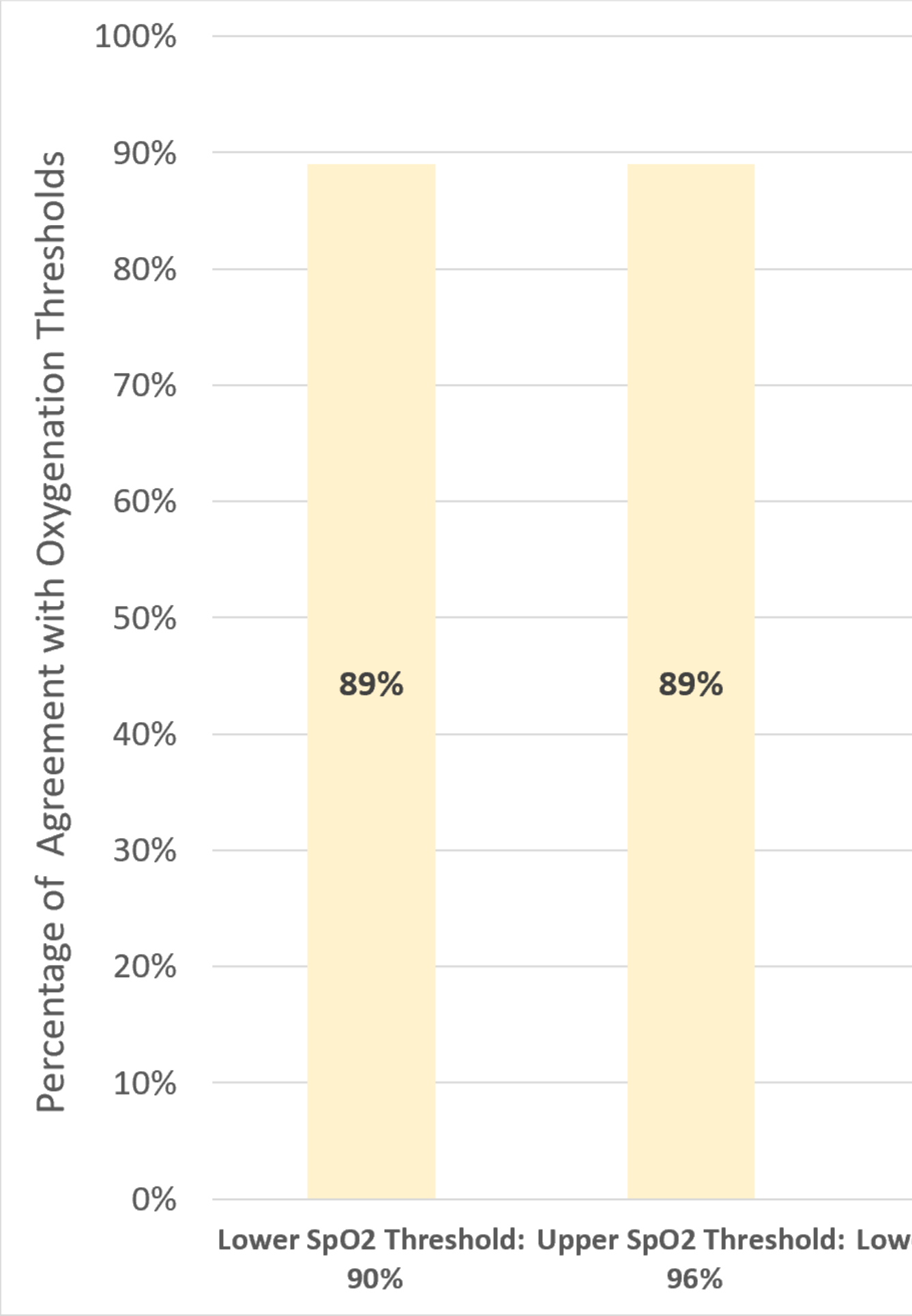
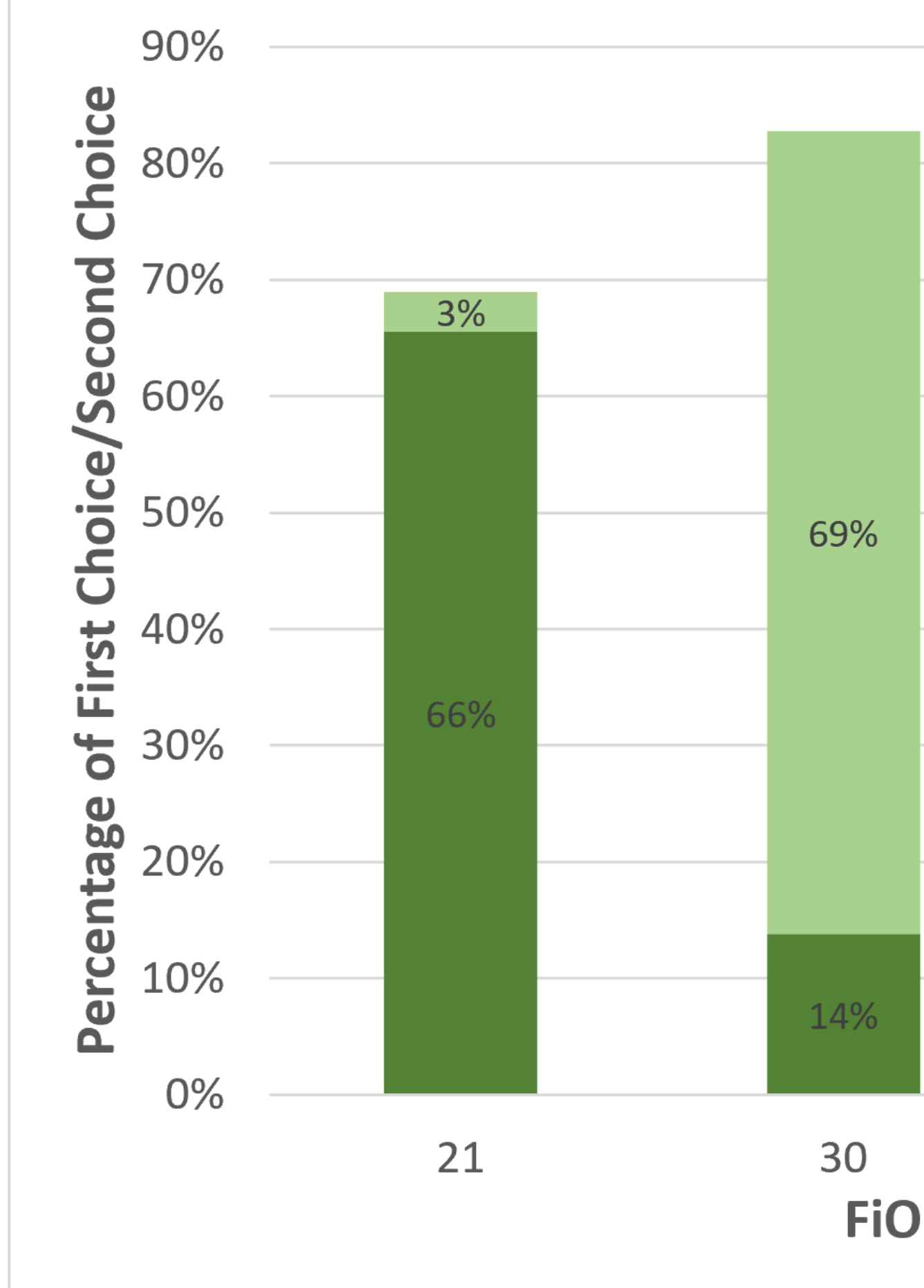
A. Agreement with Lower SpO2 Thresholds in Delphi Stage 2



B. Agreement with Higher SpO2 Thresholds in Delphi Stage 2



Agreement with Lowest Acceptable FiO2



Conclusion

- Target SPO2 range is 90-96%
- Target SPO2 range in resource limited setting is 88-96%
- PAO2 target is 60-100mmHg
- Lowest acceptable FiO2 is 21

Function

Our study was supported by the S grant W81XWH-17-C-0241.

Statement

The Colorado Multiple Institutional Review Board and I determined this study was exempt from IRB oversight.

Targeted Normoxia to Conserve Oxygen and Improve Outcomes in Combat Injured Special Forces



W81XWH-17-C-0241

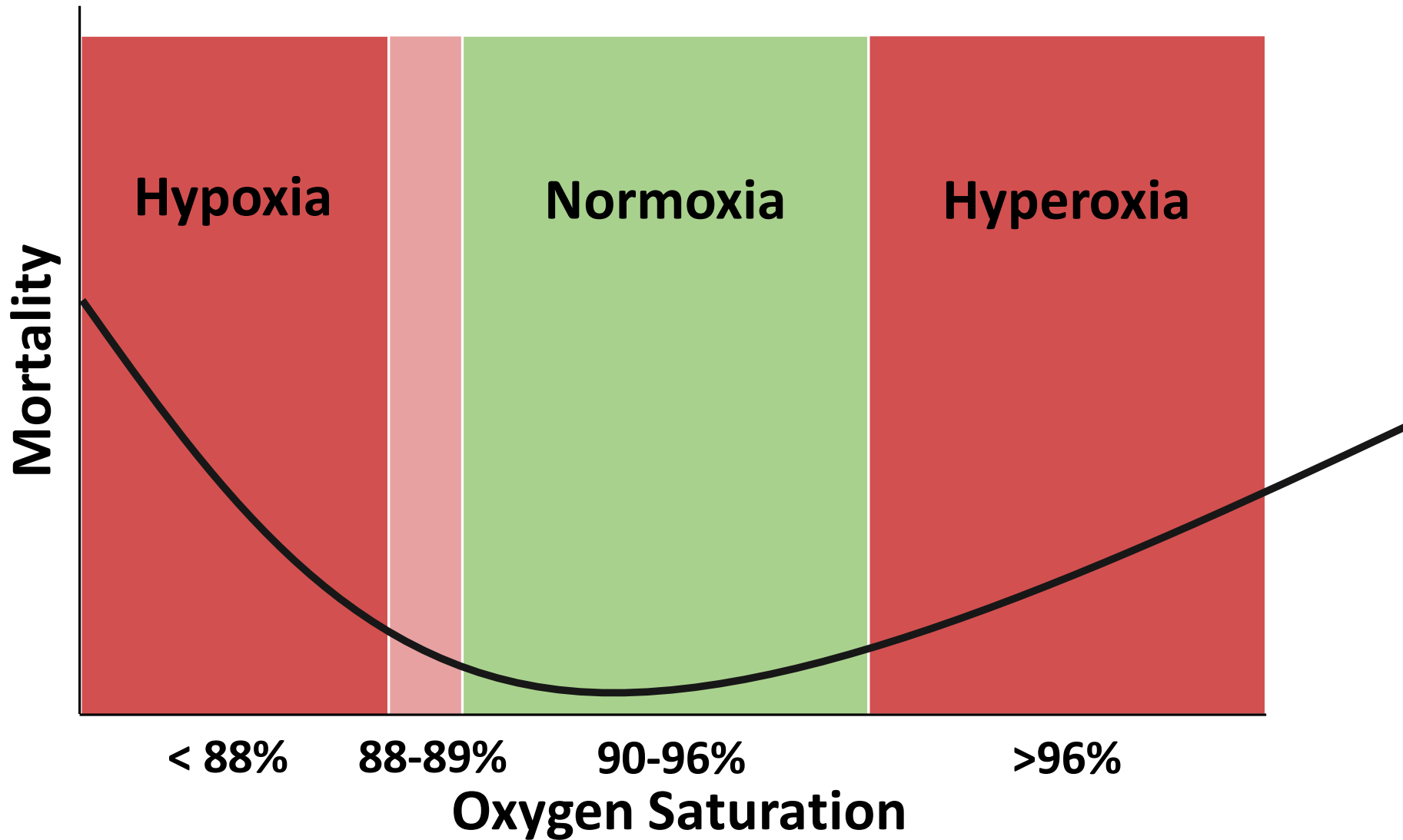
**PIs: Adit A. Ginde, MD, MPH, University of Colorado
MAJ Steven Schauer, DO, MS, USAISR/59 MDW**

Significance



- Supplemental oxygen key to avoid morbidity from hypoxia
- Excessive oxygen
 - Common practice
 - Unlikely to benefit; may cause harm
 - Expands mission weight, cube, and logistics; safety issues
- Gap: Limited data on optimal oxygen titration targets in critically injured patients

Normoxia: Avoids hypoxia AND hyperoxia





Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

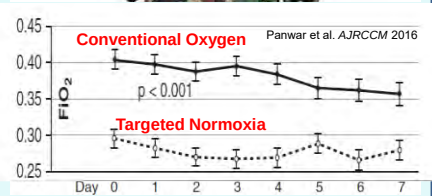
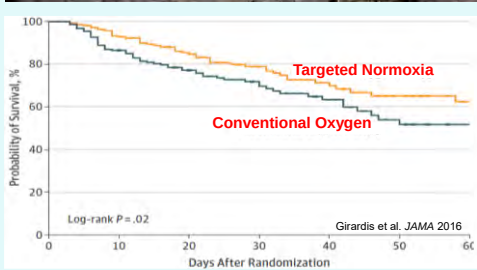
PI: Adit Ginde, MD, MPH; MAJ Steven Schauer, DO, MS **Org:** University of Colorado Denver/USAISR **Award Amount:** \$519,119

Study Aims

- Aim 1:** Define standard care for oxygen titration in critically ill trauma patients
- Aim 2:** Compare the effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
- Aim 3:** Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.

Approach

Aim 1 is a Delphi process with subject matter experts to define normoxia targets (minimizing supplemental oxygen) after major trauma and develop consensus clinical practice guidelines. **Aim 2** is a retrospective cohort study to measure severity-adjusted clinical outcomes of normoxia, compared with relative hyperoxia (conventional oxygen) in critically ill trauma patients. **Aim 3** is a pilot implementation study of the targeted normoxia study to test the feasibility of implementation in critically ill trauma patients.



Targeted normoxia improves survival and conserves oxygen in medical patients. We will study in trauma.

Timeline and Cost

Activities	CY	17	18	18	19
Define standard care					
Comparative effectiveness study					
Pilot test intervention					
Develop large scale intervention					
Estimated Budget		\$256K		\$263K	

Goals/Milestones

CY17 Goals (3 months) – Preparatory Work

- ☑ Design survey and identify experts/respondents (Aim 1)
- ☑ Develop electronic chart abstraction tool (Aim 2)
- ☑ Obtain IRB approvals (Aims 1 and 2)

CY18 Goals (12 months) – Define Normoxia Targets

- ☑ Begin Delphi process (Aim 1)
- ☑ Begin data collection (Aim 2)
- ☑ Analyze responses and develop clinical practice guideline (Aim 1)
- ☑ Complete data collection and analysis (Aim 2)
- ☑ Disseminate results (Aims 1 and 2)
- ☑ Develop intervention and case report forms (Aim 3)
- ☑ Obtain IRB approval (Aim 3)

CY19 Goals (9 months) – Implementation Results and Next Steps

- ☑ Implement intervention and begin data collection (Aim 3)
- ☐ Complete data collection and analysis (Aim 3)
- ☐ Disseminate results (Aim 3)
- ☐ Prepare for large scale implementation

Aim 1a: Systematic Review

- **Included (n=43)**
 - 17 trauma studies
 - 26 non-trauma critical illness
- **Conclusions**
 - Overall association between lower oxygen/ normoxia and improved clinical outcomes
 - Few trauma specific articles
 - 14 out of 17 related exclusively to TBI
 - No high quality/RCT data
 - Supports need for further trauma-specific studies/RCTs, particularly beyond TBI

Aim 1b: Expert Panel (Military)

Last Name	First Name	Speciality	Institution
Becker	Tyson	Trauma Surgery	SAMMC
Chung	Kevin	Critical Care	SAMMC
Keenan	Sean	Emergency Medicine	SOCOM/SOCEUR
Mason	Philip	Critical Care	SAMMC
Miles	Ethan	Other	Ft. Benning
Oh	John	Trauma Surgery	Penn State
Redman	Theodore	Emergency Medicine	Ft. Campbell
Reisburg	Jamie	Other	Ft. Carson
Rush	Stephen	Other	USAF
Tobin	Josh	Critical Care	USC
Walrath	Benjamin	Emergency Medicine	Naval Medical Center
Wilson	Ramey	Other	SOCAFRICOM

Also 18 civilian experts part of the panel

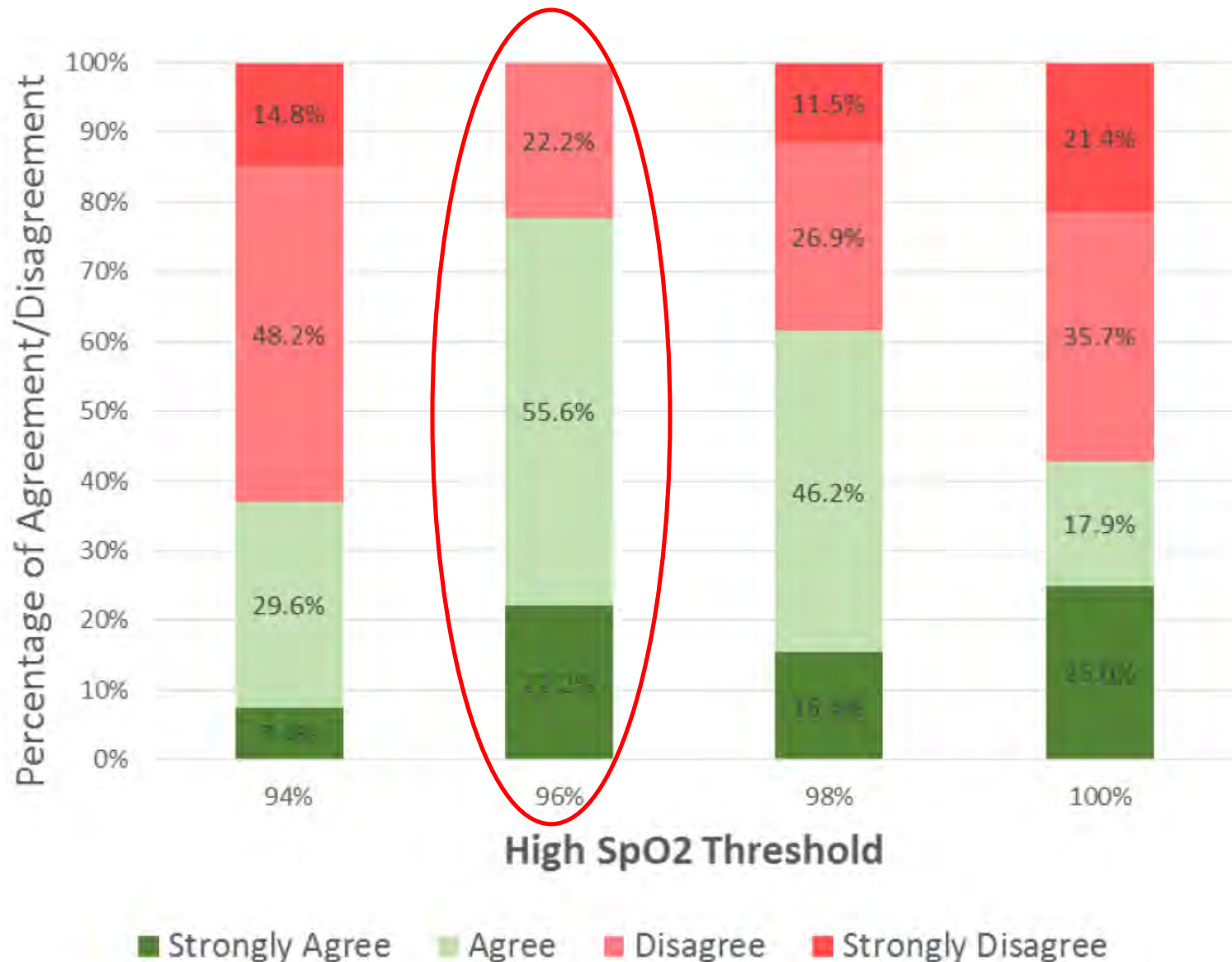
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Aim 1b: SpO2 low threshold



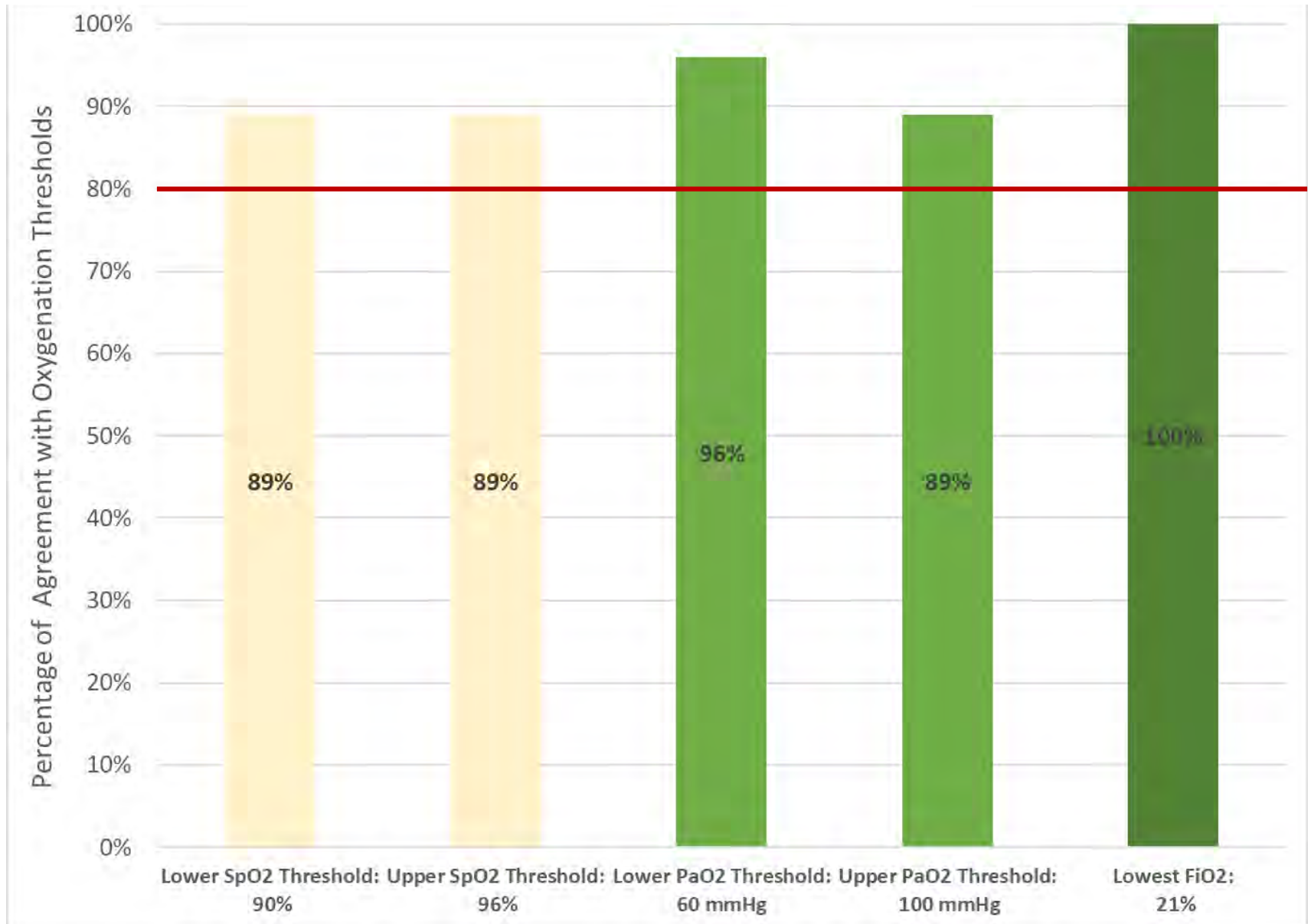
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Aim 1b: SpO2 high threshold



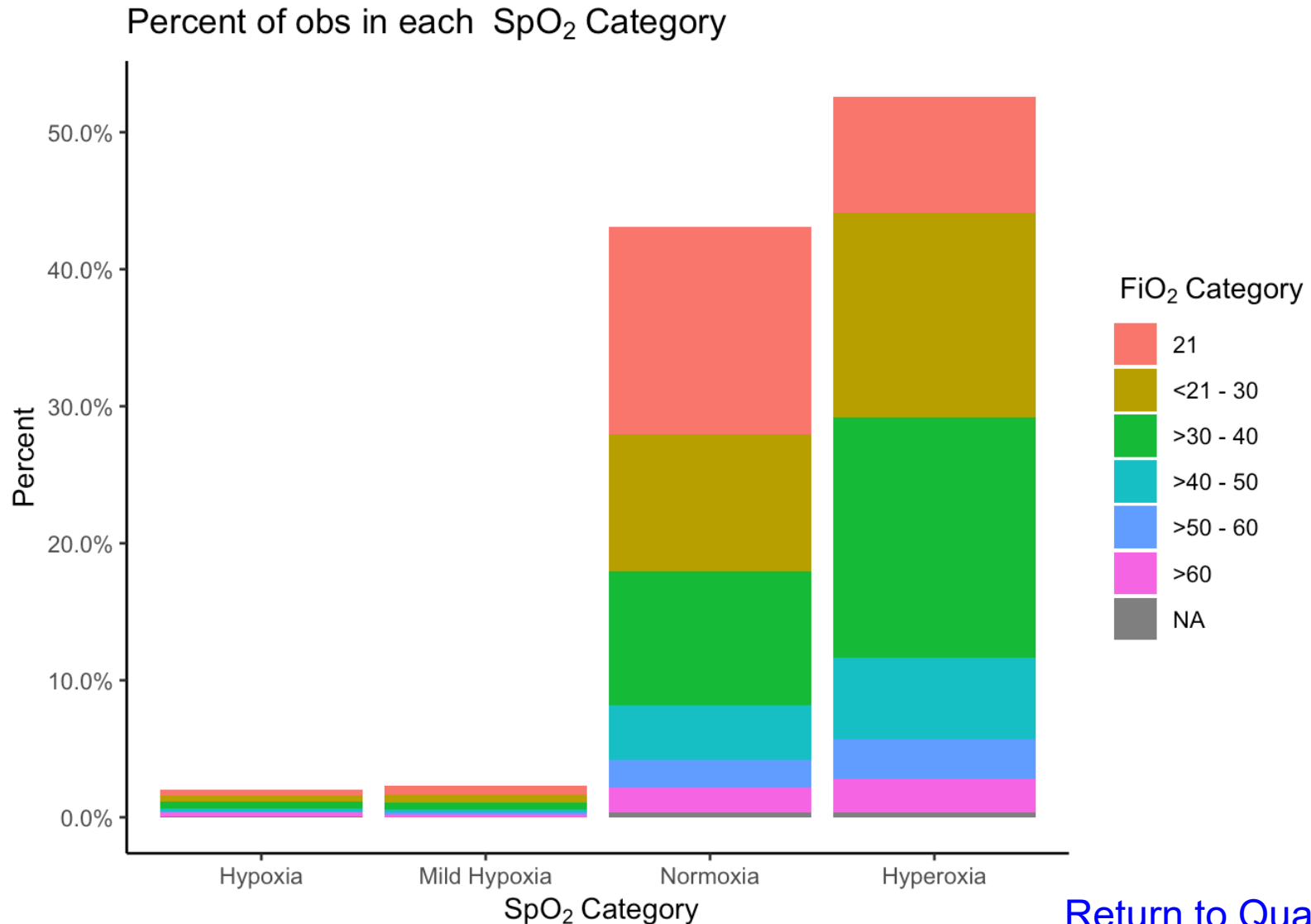
[Return to Quad Chart](#)

Aim 1b: Final Vote for SpO2, PaO2, and lowest FiO2



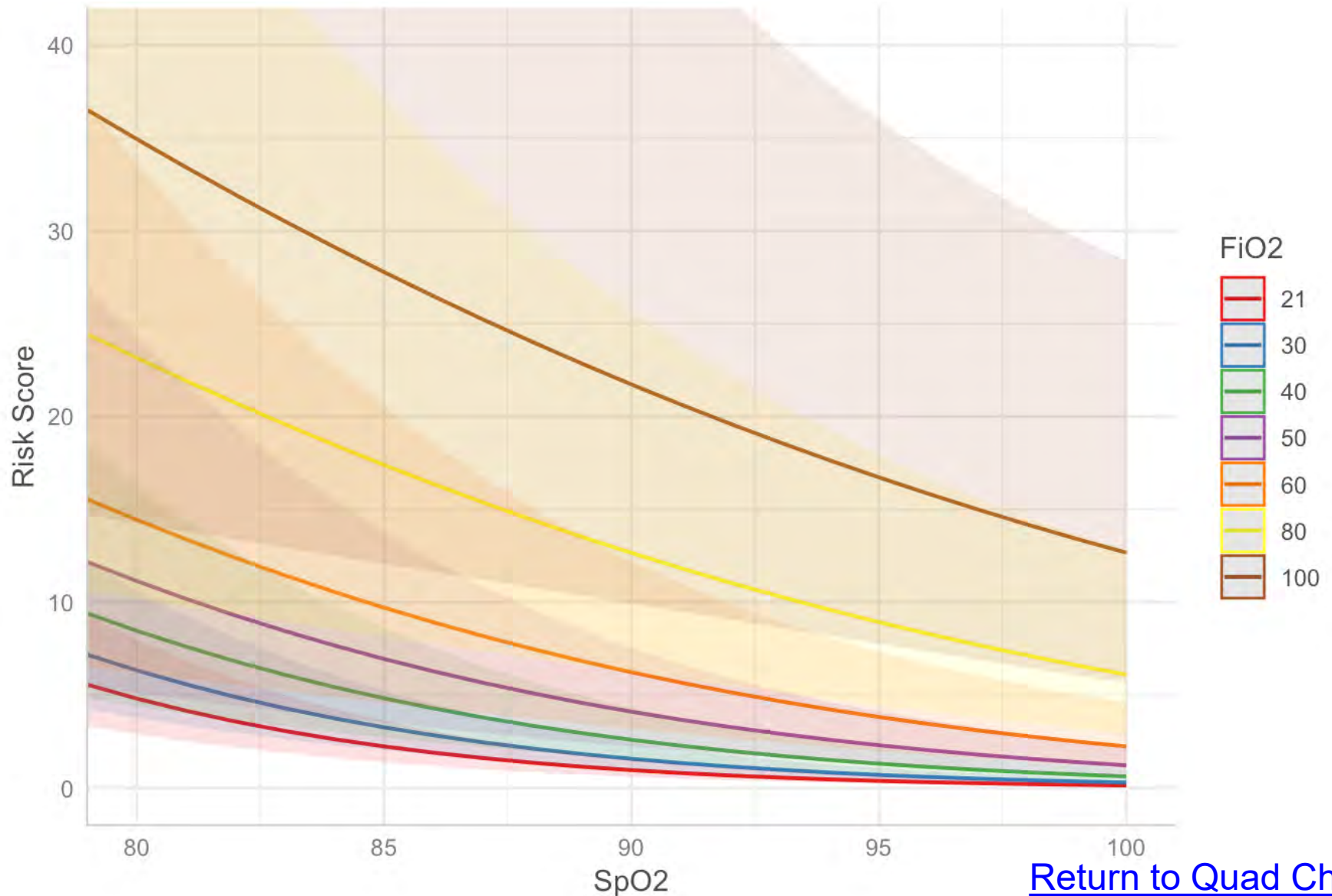
[Return to Quad Chart](#)

Aim 2: Most patients on supplemental oxygen are **hyperoxic**



[Return to Quad Chart](#)

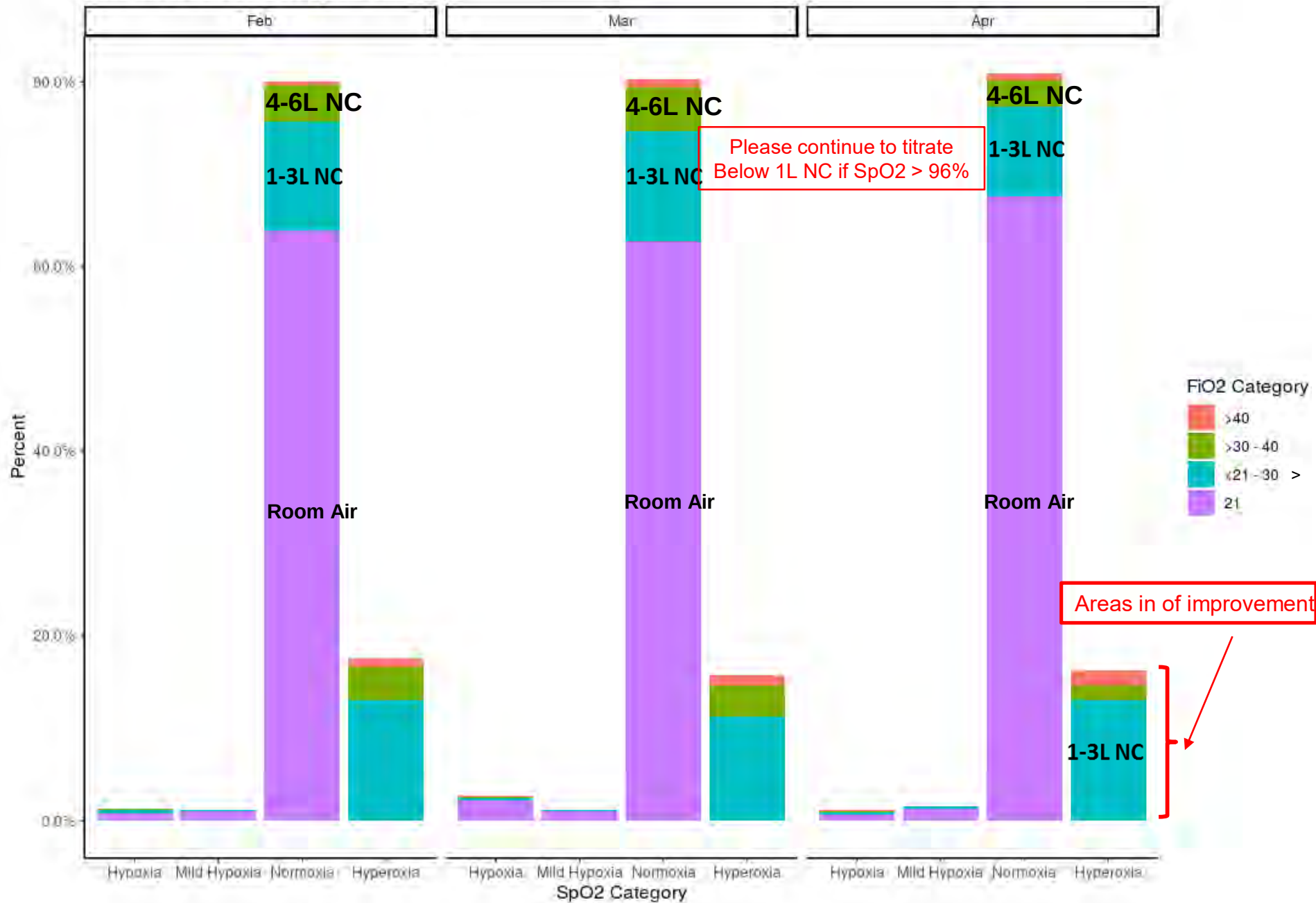
Higher oxygen supplementation associated with **increased mortality** at all SpO2 levels



Aim 3: Pilot Intervention Launched

- Finalized standard care definitions for oxygen
- Approved IRB applications
 - Colorado IRB review—approved (waiver of consent)
 - DoD/HRPO second level review—approved
- Implementation
 - Data collection strategy
 - Stakeholder engagement
 - Electronic clinical decision support
- Demonstrate feasibility and safety

Percent of obs in each SpO2 category





U.S. AIR FORCE



Multicenter Implementation Trial of Targeted Normoxia Strategy to Inform Oxygen Requirements for Combat Casualty Care

Military PI: MAJ Steven Schauer, DO, MS
Civilian PI: Adit Ginde, MD, MPH

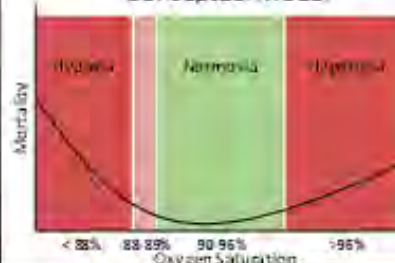
Org: USAISR/59 MDW
Org: University of Colorado Denver

Problem, Hypothesis and Military Relevance

- Oxygen is a limited resource that is challenging to obtain in combat settings
- Critical to determine oxygen requirements for combat injured to optimize care and conserve oxygen
- Hypothesis: Targeted normoxia will reduce harm from hypoxia/hyperoxia and reduce need for oxygen
- Findings will provide immediate actionable data to define oxygen requirements for critically injured warfighters and inform changes to CPGs



Conceptual Model



Stepped Wedge Cluster Randomized Trial



Proposed Solution

Aim 1. Measure the impact of targeted normoxia implementation on oxygen consumption/requirements

Aim 2. Determine the safety of targeted normoxia

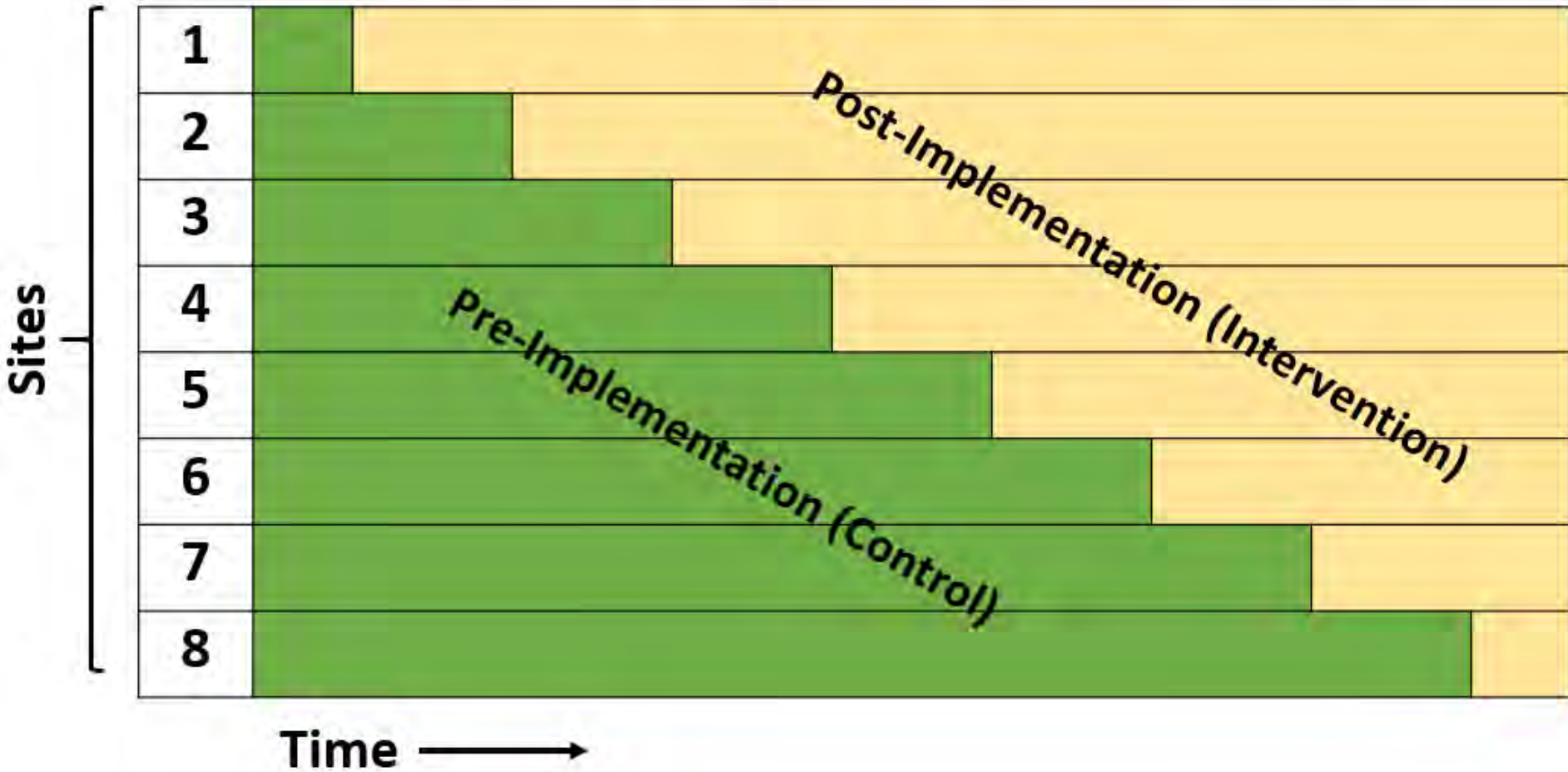
Aim 3. Determine the effectiveness of targeted normoxia on patient-centered outcomes

Approach: Multicenter cluster randomized, stepped wedge implementation trial targeted normoxia (goal SpO2 90-96%). Waiver of consent greatly enhances efficiency (EFIC not required). Enrollment of critically ill trauma patients at 8 centers (anticipated n=6240).

Timeline and Total Cost

Activities	Year 1	Year 2	Year 3
Preparatory Work			
Implementation			
Data Collection			
Analysis/Dissemination			
Estimated Budget (\$K)	\$1289	\$1389	\$1125

Stepped Wedge Cluster Randomized Trial

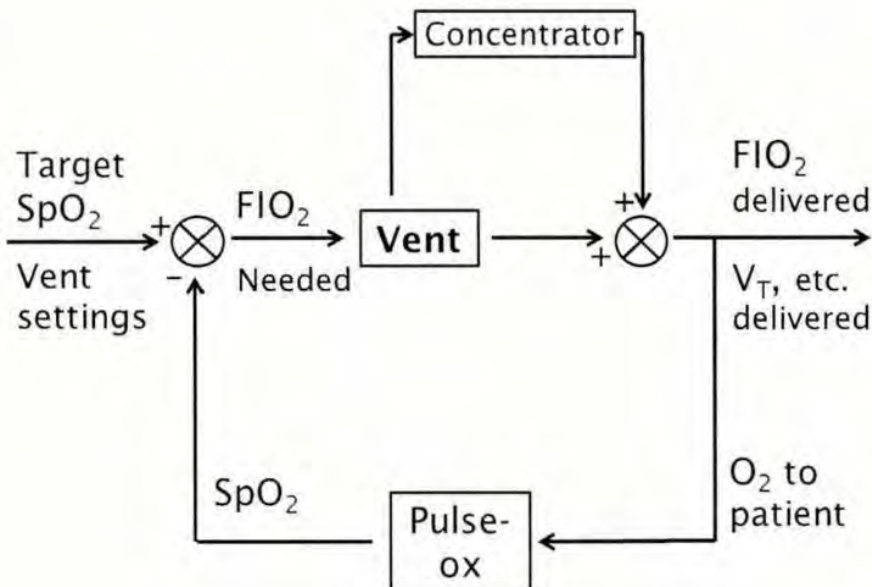


Multicenter Normoxia Trial

- **Goal:** definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
 - Particularly important for ERC/PFC
- **Design:** cluster randomized, stepped wedge implementation trial (8 sites, n~6240 patients)
- **Human subjects issues:** minimal risk, waiver of informed consent (efficient, cost savings)

Technology/Materiel Solutions

- Portable oxygen concentrators
 - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control



[Return to SOCOM Quad Chart](#)
[Return to Multicenter Quad Chart](#)

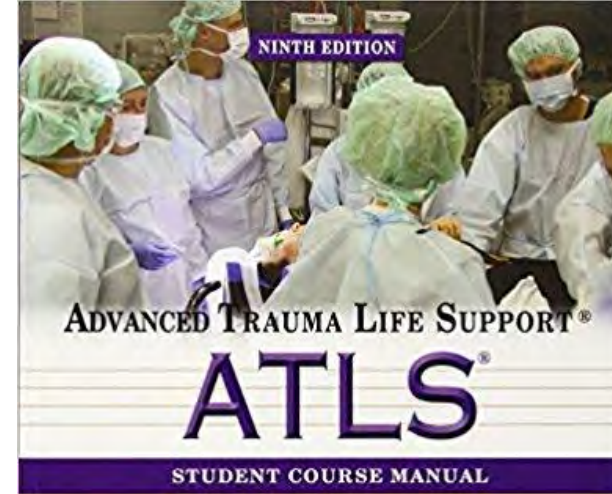


University of Colorado
Anschutz Medical Campus
School of Medicine

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Combat Casualty Care

PIs: Adit A. Ginde, MD, MPH,
University of Colorado
MAJ Steven Schauer, DO, MS,
USAISR/59 MDW

Current State



- “Oxygenated inspired air is best provided via a tight-fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”
- “The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation... a pulse oximeter reading greater than 90%.”

COMBAT CASUALTY CARE

Lessons Learned from OEF and OIF

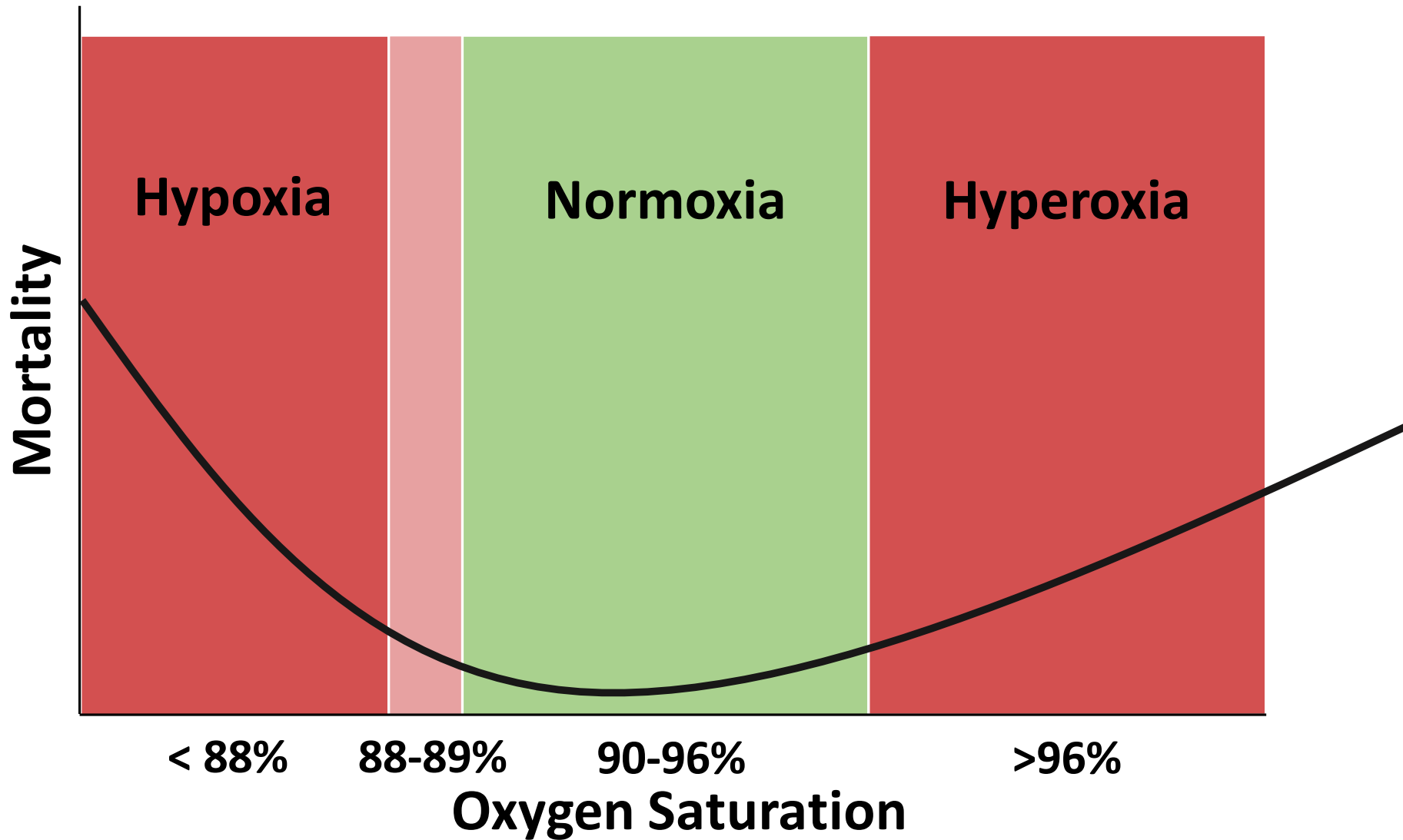
Edited by
Eric Savitsky, MD
Colonel Brian Eastridge, MD

Significance



- Supplemental oxygen key to avoid morbidity from hypoxia
- Excessive oxygen
 - Common practice
 - Unlikely to benefit; may cause harm
 - Expands mission weight, cube, and logistics; safety issues
- Gap: Limited data on optimal oxygen titration targets in critically injured patients

Normoxia: Avoid hypoxia AND hyperoxia



Incidence of Hyperoxia in Combat Wounded in Iraq and Afghanistan: A Potential Opportunity for Oxygen Conservation

MAJ Steven G. Schauer, DO, MS†‡§; MAJ Michael D. April, MD, DPhil, MSc†; LTC Jason F. Naylor, PA-C ||; Nee-Kofi Mould-Millman, MD¶; Col Vikhyat S. Bebarta, MD‡ ||; LTC Tyson E. Becker, MD†; Lt Col Joseph K. Maddry, MD*†‡§; Adit A Ginde, MD, MPH¶*

- **Conclusions:** ...more than 1 in 5 casualties overall had documented hyperoxia..., 1 in 3 intubated, and almost 1 in 2 TBI casualties. With limited oxygen supplies in theater and logistical challenges with oxygen resupply, efforts to **avoid unnecessary oxygen supplementation** may have material impact on preserving this scarce resource and **avoid potential detrimental clinical effects from supraphysiologic oxygen concentrations.**



Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

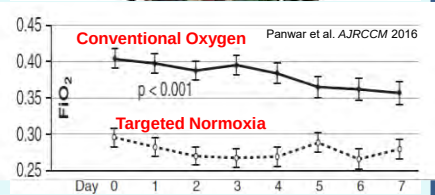
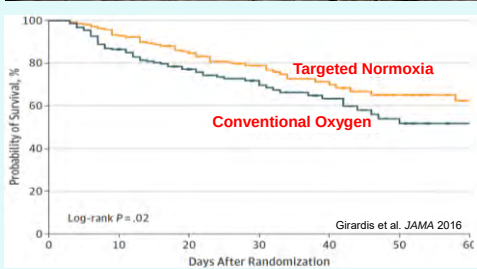
PI: Adit Ginde, MD, MPH; MAJ Steven Schauer, DO, MS Org: University of Colorado Denver/USAISR Award Amount: \$519,119

Study Aims

- **Aim 1:** Define standard care for oxygen titration in critically ill trauma patients
- **Aim 2:** Compare the effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
- **Aim 3:** Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.

Approach

Aim 1 is a Delphi process with subject matter experts to define normoxia targets (minimizing supplemental oxygen) after major trauma and develop consensus clinical practice guidelines. Aim 2 is a retrospective cohort study to measure severity-adjusted clinical outcomes of normoxia, compared with relative hyperoxia (conventional oxygen) in critically ill trauma patients. Aim 3 is a pilot implementation study of the targeted normoxia study to test the feasibility of implementation in critically ill trauma patients.



Targeted normoxia improves survival and conserves oxygen in medical patients. We will study in trauma.

Timeline and Cost

Activities	CY	17	18	18	19
Define standard care					
Comparative effectiveness study					
Pilot test intervention					
Develop large scale intervention					
Estimated Budget		\$256K		\$263K	

Goals/Milestones

CY17 Goals (3 months) – Preparatory Work

- ☑ Design survey and identify experts/respondents (Aim 1)
- ☑ Develop electronic chart abstraction tool (Aim 2)
- ☑ Obtain IRB approvals (Aims 1 and 2)

CY18 Goals (12 months) – Define Normoxia Targets

- ☑ Begin Delphi process (Aim 1)
- ☑ Begin data collection (Aim 2)
- ☑ Analyze responses and develop clinical practice guideline (Aim 1)
- ☑ Complete data collection and analysis (Aim 2)
- ☑ Disseminate results (Aims 1 and 2)
- ☑ Develop intervention and case report forms (Aim 3)
- ☑ Obtain IRB approval (Aim 3)

CY19 Goals (9 months) – Implementation Results and Next Steps

- ☑ Implement intervention and begin data collection (Aim 3)
- ☐ Complete data collection and analysis (Aim 3)
- ☐ Disseminate results (Aim 3)
- ☐ Prepare for large scale implementation

Aim 1a: Systematic Review

SYSTEMATIC REVIEW

J Trauma Acute Care Surg 2019 October

Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN,
Kristen DeSanto, MS, Cord W. Cunningham, MD, MPH,
Vikhyat S. Bebarta, MD, and Adit A. Ginde, MD, MPH, *Aurora, Colorado*

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Aim 1a: Systematic Review

- **Included (n=43)**
 - 17 trauma studies
 - 26 non-trauma critical illness
- **Conclusions**
 - Overall association between lower oxygen/ normoxia and improved clinical outcomes
 - Few trauma specific articles
 - 14 out of 17 related exclusively to TBI
 - No high quality/RCT data
 - Supports need for further trauma-specific studies/RCTs, particularly beyond TBI

Aim 1b: Expert Panel (Military)

Last Name	First Name	Speciality	Institution
Becker	Tyson	Trauma Surgery	SAMMC
Chung	Kevin	Critical Care	SAMMC
Keenan	Sean	Emergency Medicine	SOCOM/SOCEUR
Mason	Philip	Critical Care	SAMMC
Miles	Ethan	Other	Ft. Benning
Oh	John	Trauma Surgery	Penn State
Redman	Theodore	Emergency Medicine	Ft. Campbell
Reisburg	Jamie	Other	Ft. Carson
Rush	Stephen	Other	USAF
Tobin	Josh	Critical Care	USC
Walrath	Benjamin	Emergency Medicine	Naval Medical Center
Wilson	Ramey	Other	SOCAFRICOM

Also 18 civilian experts part of the panel

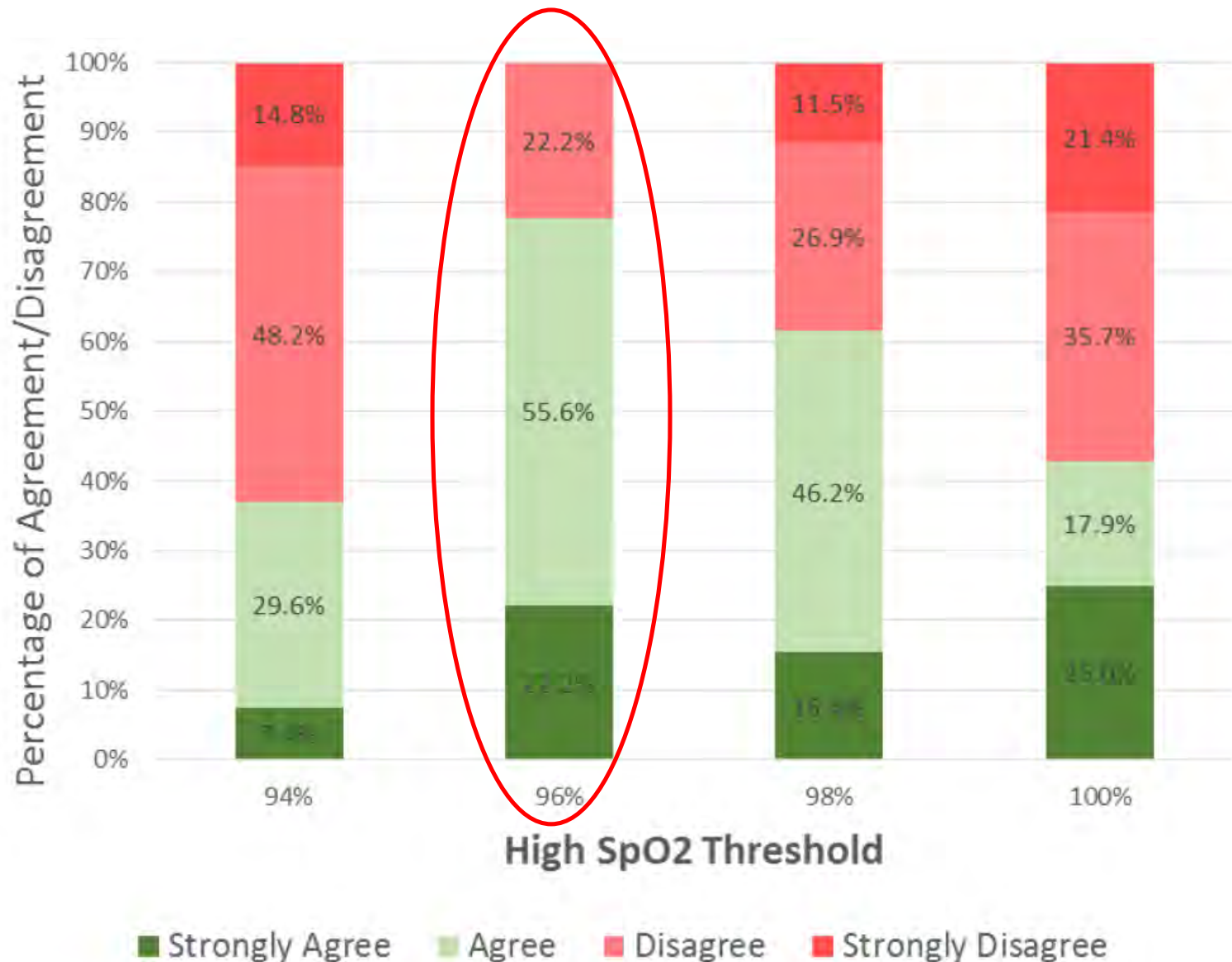
[Return to Quad Chart](#)

Aim 1b: SpO2 low threshold



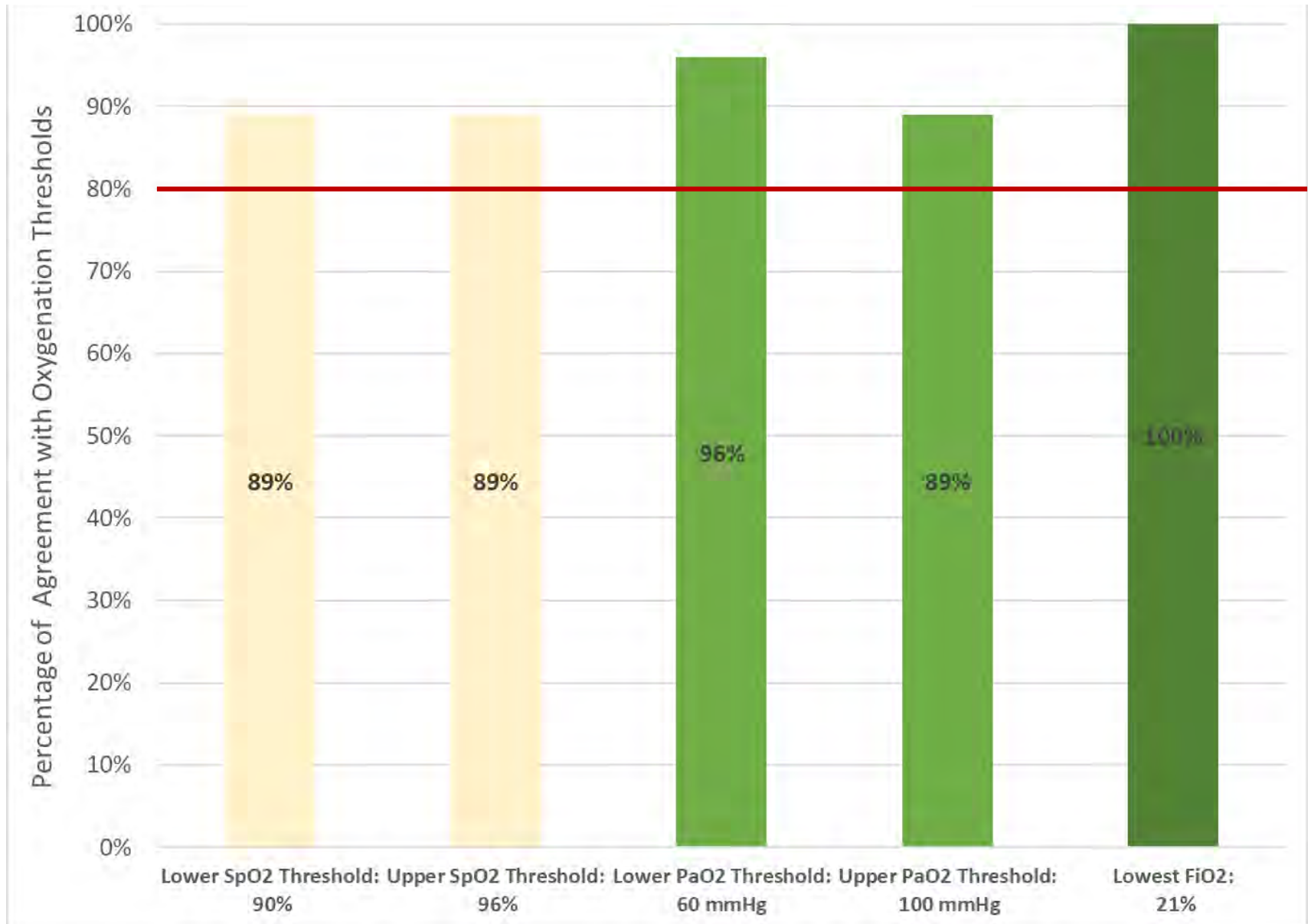
[Return to Quad Chart](#)

Aim 1b: SpO2 high threshold



[Return to Quad Chart](#)

Aim 1b: Final Vote for SpO2, PaO2, and lowest FiO2



[Return to Quad Chart](#)

Special considerations

- Severe TBI: 33% would increase SpO2 range
- Hemorrhagic shock: 11% would increase SpO2 range
- Lowest SpO2 in resource limited settings
 - 85-86%: 27% respondents
 - 87-88%: 58% respondents
 - 89-90%: 15% respondents
- No signal to change recommendation for:
 - major burn, mechanical ventilation, thoracic trauma

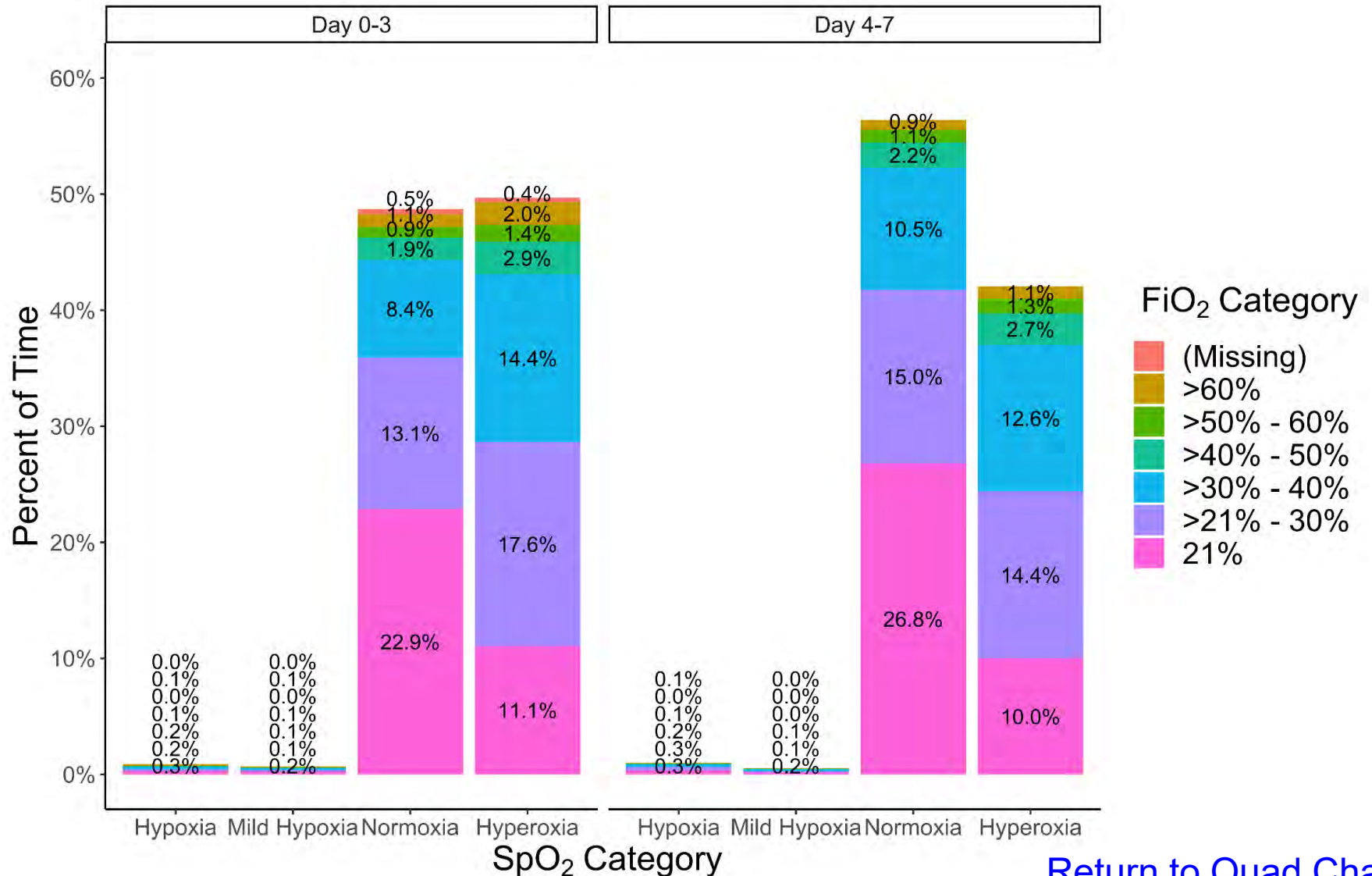


Aim 2: Observational Study

- **Cohort Size:** n=3,464 patients
- **Demographics:** mean age 53y, male 65%, white 68%
- **Mechanism:** fall 35%, MVC 31%, burn 8%, penetrating 7%
- **Clinical:** EMS arrival 73% , mech vent 41%, mean APACHE 8
- **Outcomes**
 - In-Hospital Mortality 7.6%
 - VFD 23.7 days (of 28)
 - HFD 73.7 days (of 90)

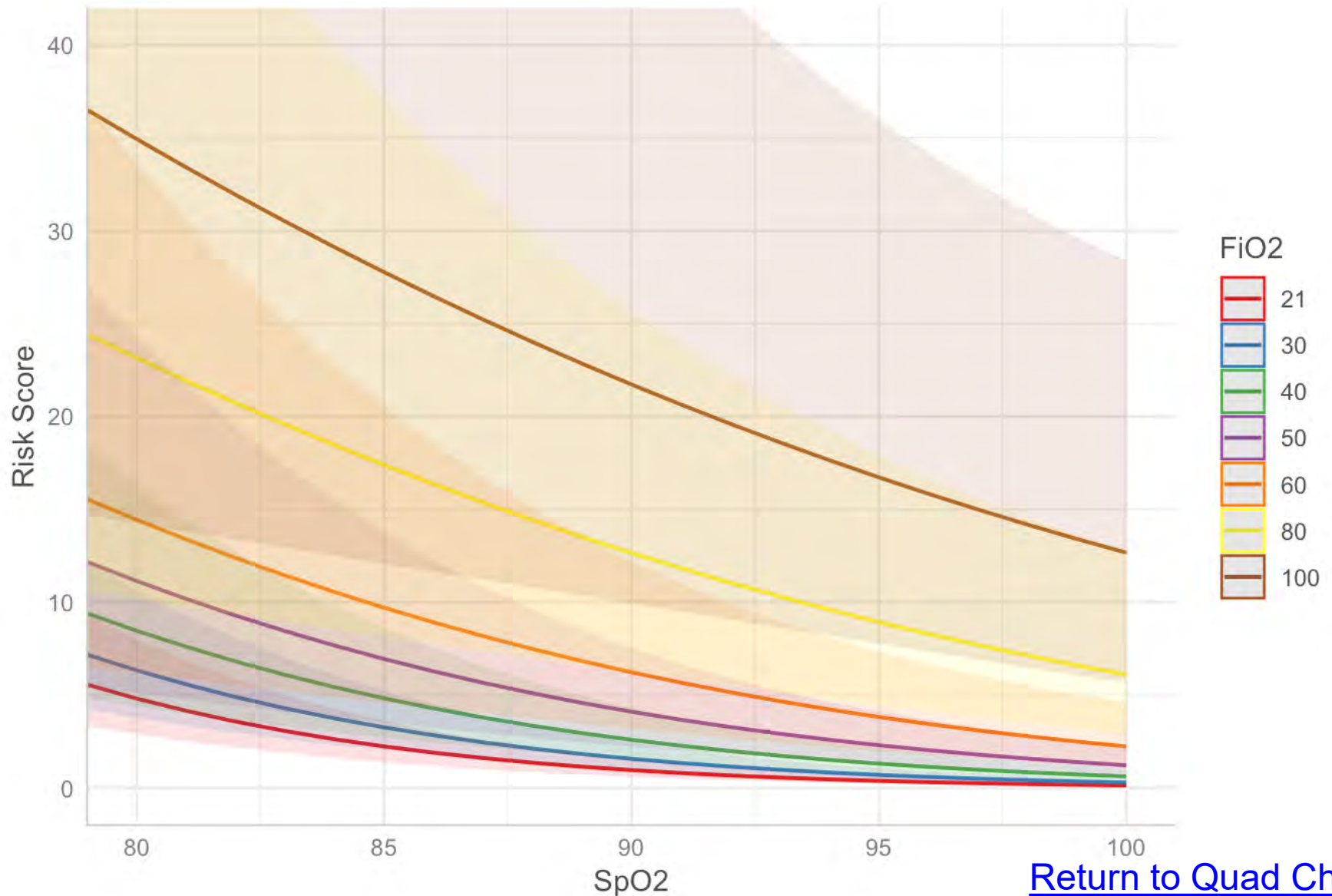
Aim 2: Observational Study

Most pts on supplemental O2 are **hyperoxic**



[Return to Quad Chart](#)

Higher oxygen supplementation associated with **increased mortality** at all SpO2 levels



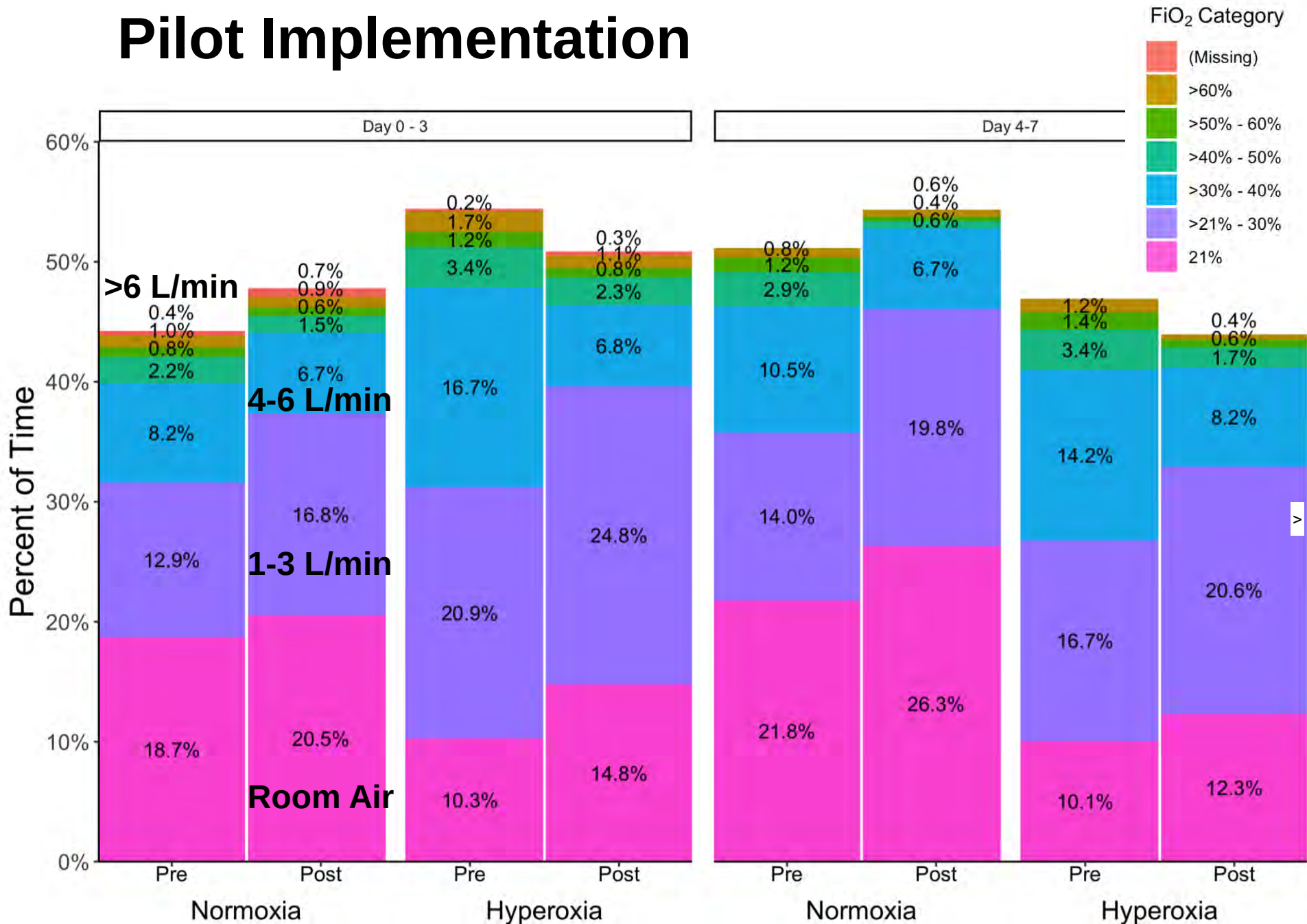
Adjusted Incident Rate Ratios for VFD and HFD

SpO2 category (FiO2)	VFD	HFD
Normoxia (21%)	1.09 (1.07-1.10)	1.07 (1.06-1.07)
Normoxia (22-30%)	1.04 (1.03-1.06)	1.03 (1.03-1.04)
Normoxia (31-40%)	1.01 (1.00-1.03)	1.01 (1.01-1.02)
Normoxia (>40%)	0.98 (0.97-1.00)	0.98 (0.98-0.99)
Hyperoxia (21%)	1.02 (1.01-1.04)	1.02 (1.01-1.02)
Hyperoxia (22-30%)	1.00 (0.98-1.01)	0.99 (0.99-1.00)
Hyperoxia (31-40%)	0.99 (0.97-1.00)	0.98 (0.98-0.99)
Hyperoxia (>40%)	Reference	Reference

Aim 3: Pilot Intervention

- Finalized standard care definitions for oxygen
- Approved IRB applications
 - Colorado IRB review—approved (waiver of consent)
 - DoD/HRPO second level review—approved
- Implementation
 - Data collection strategy
 - Stakeholder engagement
 - Electronic clinical decision support
- Demonstrated feasibility and safety
 - n=201 post-intervention (Jan-July 2019)

Pilot Implementation



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Aim 3: Pilot Intervention

- Significantly increased normoxia and reduced FiO₂/supplementation oxygen administration
- No increase in hypoxia
- Mortality, VFD, HFD were similar in pre- and post-implementation groups

Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care



PI: Adit Ginde, MD, MPH

Organization: University of Colorado Denver

Co-PI: MAJ Steven Schauer, DO, MS

Organization: Army Institute for Research

Award Amount: \$3,825,868

Objective

Our **overall objective** is to determine oxygen titration goals for combat injured to optimize care by reducing harm associated with hypoxia and hyperoxia and to conserve limited oxygen supply

Aim 1. Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients

Aim 2. Determine the safety of targeted normoxia

Aim 3. Determine the clinical effectiveness of targeted normoxia

Approach

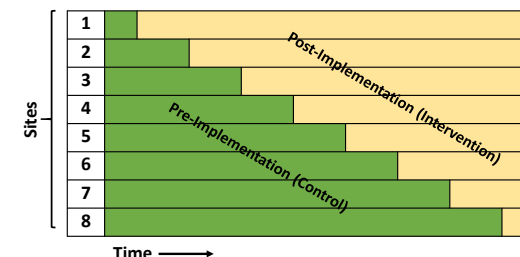
Multicenter cluster randomized, stepped wedge implementation trial of the targeted normoxia approach (SpO2 90-96%). Efficiency will be greatly enhanced by a waiver of informed consent since protocol implementation is minimal risk (EFIC not required).

Impact

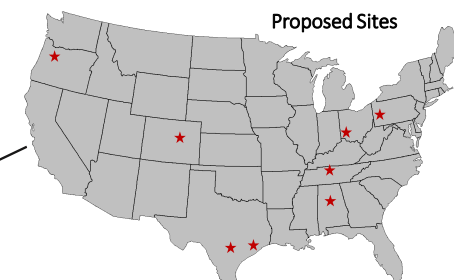
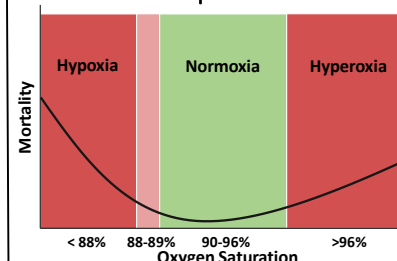
Our findings will provide immediately actionable data to define oxygenation practices in critically injured warfighters and civilians and aid in the development of clinical practice guidelines.



Stepped Wedge Cluster Randomized Trial



Conceptual Model



Timeline and Cost

Activities	Year 1	Year 2	Year 3
Preparatory Work	■		
Implementation		■	■
Data Collection		■	■
Analysis/Dissemination			■
Estimated Budget (\$K)	\$1347	\$1278	\$1201

Goals/Milestones

Year 1 Goals (12 months) – Preparatory Work

- ☐ Obtain IRB/HRPO approval
- ☐ Develop Standard Operating Procedure Documents (SOPs)
- ☐ Create Site Materials
- ☐ Site Initiation Visits/Training
- ☐ Develop Data Collection Infrastructure
- ☐ Begin Site Implementation

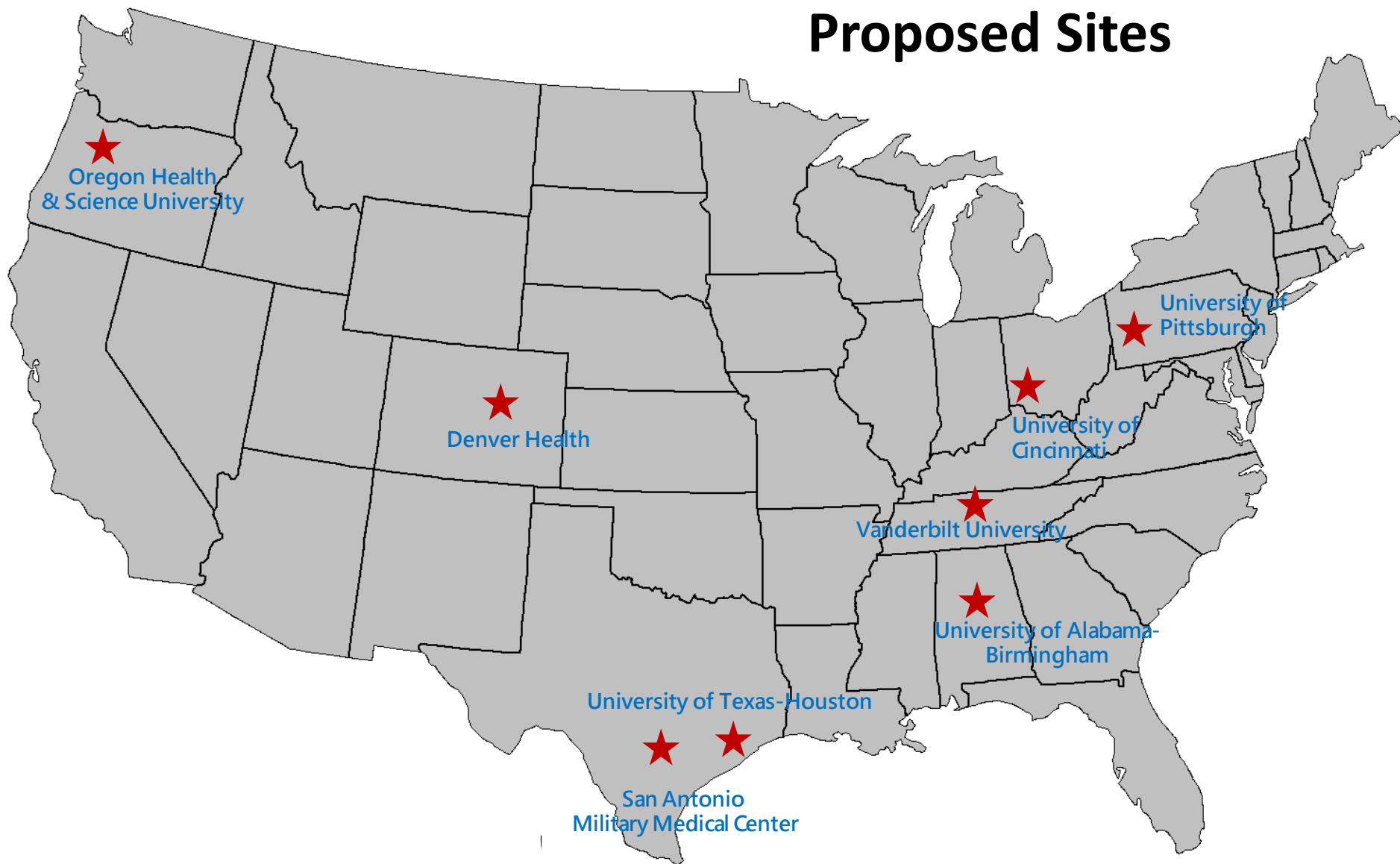
Year 2 Goals (12 months) – Implementation

- ☐ Randomized Implementation
- ☐ Site Monitoring
- ☐ Data Collection

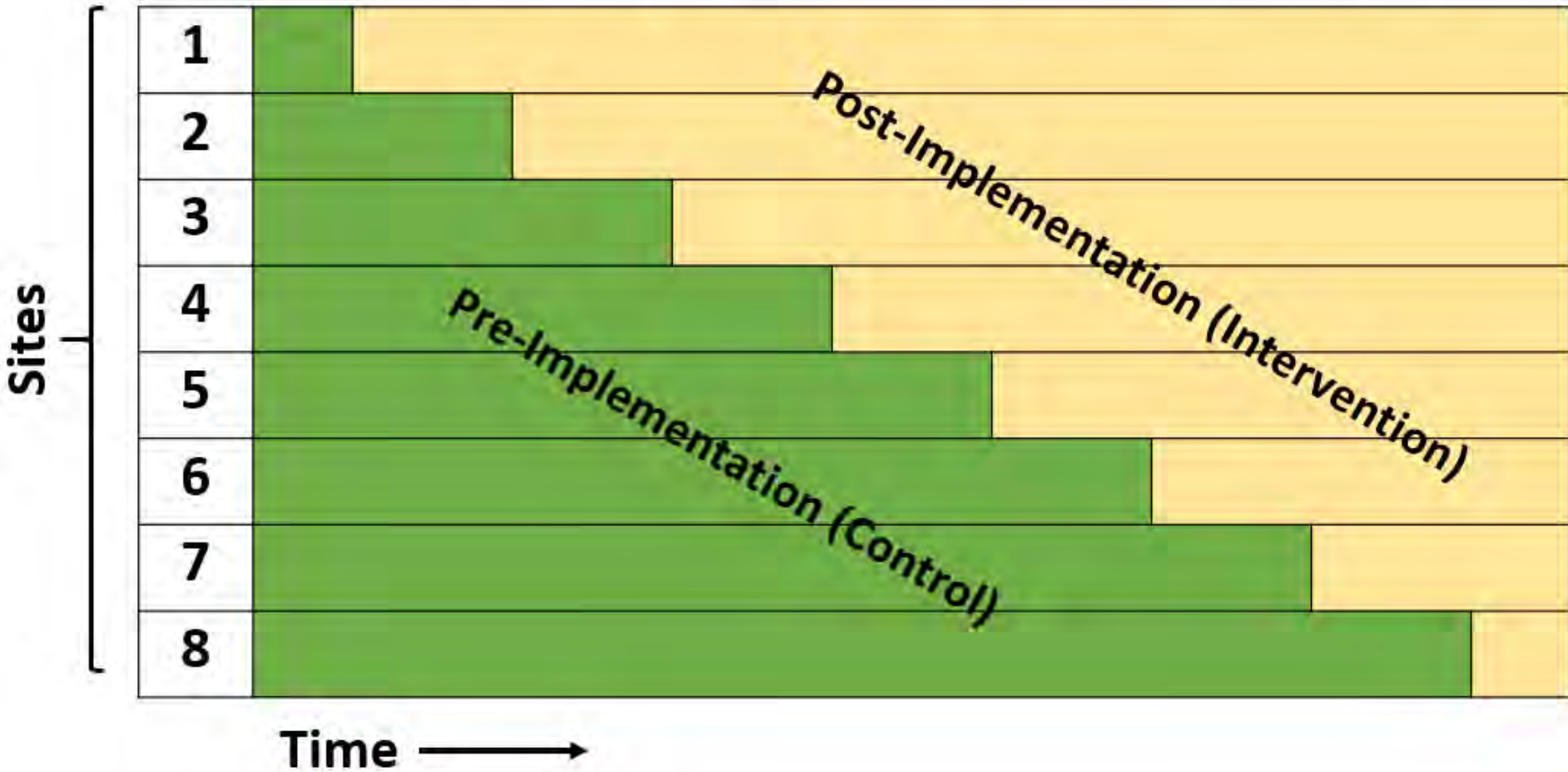
Year 3 Goals (12 Months) –Data Collection/Data Analysis

- ☐ Randomized Implementation/Site Monitoring
- ☐ Data Collection
- ☐ Data Analysis
- ☐ Dissemination

Proposed Sites



Stepped Wedge Cluster Randomized Trial



Multicenter Normoxia Trial (JWMRP)

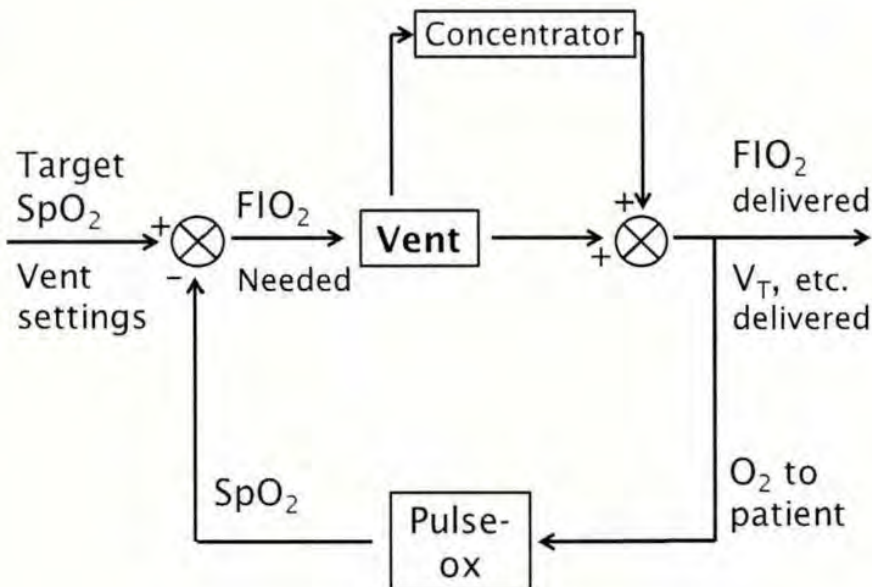
- **Goal:** definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
 - Particularly important for ERC/PFC
 - Focus on polytrauma
- **Design:** cluster randomized, stepped wedge implementation trial (8 sites, n~6240 patients)
- **Human subjects issues:** minimal risk, waiver of informed consent (efficient, cost savings)

Multicenter Normoxia Trial (MTEC)

- **Goal:** major burn-specific evidence to inform CPG and oxygen requirements
 - Particularly important to focus on burn wound healing
- **Design:** cluster randomized, stepped wedge implementation trial (6 sites, n~2340 patients)
- **Sites:** U.S. Army Institute of Surgical Research, University of Alabama-Birmingham, University of Cincinnati, University of Colorado, University of Pittsburgh, Vanderbilt University

Technology/Materiel Solutions

- Portable oxygen concentrators
 - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control



[Return to SOCOM Quad Chart](#)
[Return to Multicenter Quad Chart](#)

Transition Plan

- Inform a change to **CPGs** (e.g., JTS, CCATT) and **TCCC guidelines** related to oxygen
- Submit findings to DTIC; present at MHSRS and SOMSA
- Continue work with CDID/AMMED Joint Oxygen Working Group
- Disseminate to military leadership/training agencies including:
 1. Joint Trauma System (CPG)
 2. USAF Air Mobility Command (CPG)
 3. Special Operations Command (CPG and training)
 4. Tri-service Health Readiness Center of Excellence
 5. CCATT Pilot Unit (QI/QC process)
 6. CSTARS/CCATT/TCCET course directors (training)
 7. CoTCCC and CoERCCC (guidelines)
 8. Navy Corpsmen training program (training)

[Return to SOCOM Quad Chart](#)

[Return to Multicenter Quad Chart](#)

Discussion/Questions

Adit A. Ginde, MD, MPH

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Phone: 720-848-6777



University of Colorado
Anschutz Medical Campus

School of Medicine

Pilot Implementation Trial of Targeted Normoxia to Reduce Oxygen Requirements for Critically Injured Patients

David J. Douin, MD¹, Erin L. Anderson, RN¹, Caroline Ledbetter, MPH², MAJ Steven G. Schauer, DO, MS^{3,4}, Franklin L. Wright, MD¹, Robert T. Neumann, MD,¹ Col Vikhyat S. Bebarta, MD^{1,4}, Adit A. Ginde, MD, MPH¹

¹ University of Colorado School of Medicine, Aurora, CO

² Colorado School of Public Health, Aurora, CO

³ US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX

⁴ US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA Lackland, TX

Background: Generous oxygen supplementation and hyperoxia are common in civilian and combat trauma patients but unlikely improves outcomes. We evaluated an intervention to reduce oxygen administration by targeting normoxia in critically injured patients.

Methods: We conducted a quasi-experimental before-after study in the ED and ICUs at a Colorado Level 1 trauma center in 2018-19. Our cohort had an ICD-10 code for injury/trauma and required ICU admission within 24 hours of arrival. The clinical team implemented a multimodal intervention to target normoxia, defined as SpO₂ 90-96% during the ED and ICU course. The focus was to decrease FiO₂/supplemental oxygen for SpO₂ >96%. The intervention group was eligible patients for 6 months after the normoxia implementation and the control group was 12 months prior to the implementation. The primary outcome was SpO₂ and FiO₂ during the first 7 days of hospitalization.

Results: The 572 patients were mean age 54 years, 69% male, 54% non-Hispanic white, 79% blunt trauma mechanism, and mean APACHE II score 10.5. Hospital mortality occurred in 6.5% of patients. The use of no supplemental oxygen (FiO₂ 21% or room air) increased 30.8% of patient-hours (control) to 37.5% (intervention) and use of high volume oxygen (FiO₂ >30%) decreased from 36.5% to 21.0%, respectively. Normoxia or use of no supplemental oxygen increased from 58.3% (control) to 65.1% (intervention). The incidence of hypoxia (SpO₂ <88%) was similar in the control (1.1%) and intervention (1.0%) periods. Clinical outcomes were similar: hospital mortality (difference 2.3%; 95%CI, -2.5 to 7.1%), ventilator-free days (difference 0.0 days; 95%CI, -1.5 to 1.6), and hospital-free days (difference 2.1 days; 95%CI, -2.2 to 6.3).

Conclusion: The normoxia intervention decreased supplemental oxygen use and increased normoxia without increasing hypoxia. This pilot study was underpowered for clinical outcomes; a larger multicenter trial will determine the impact on clinical outcomes.

Disclosures: Funded by the Department of Defense/SOCOM (W81XWH-17-C-0241). This abstract expresses the authors' opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.



University of Colorado
Anschutz Medical Campus
School of Medicine

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Combat Casualty Care

**PIs: Adit A. Ginde, MD, MPH,
University of Colorado**

**MAJ Steven Schauer, DO, MS,
USAISR/59 MDW**

Vik Bebarta, MD, Col, USAF IMA, 59th
MDW/ST, Univ of Colorado,
Director, CU Center for COMBAT Research

Today

Knowledge Gap/Needs on hyperoxia

Current literature

USSOCOM Normoxia Project Summary

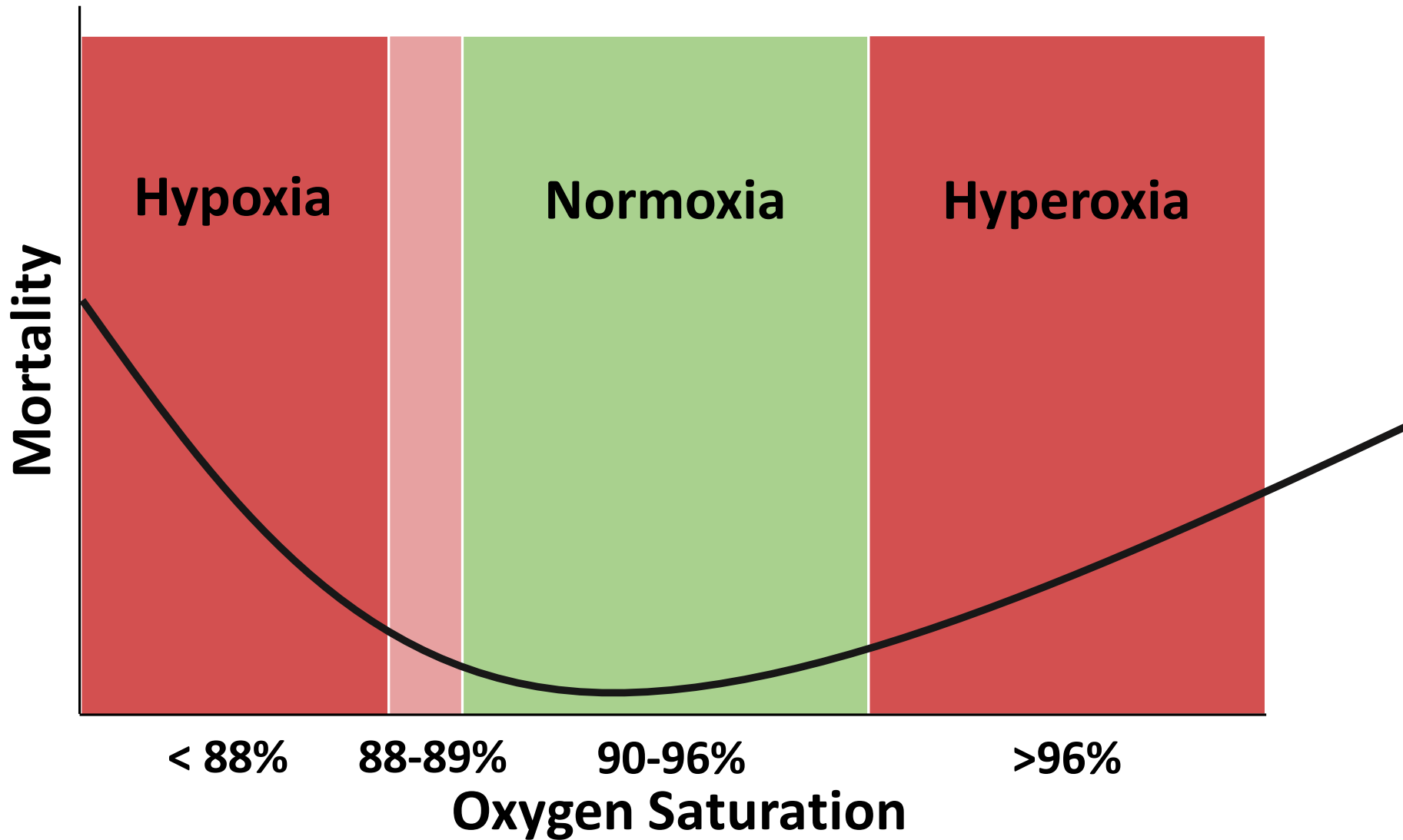
USAMRDC Normoxia multicenter trial (SAVE-O2)

Significance



- Supplemental oxygen – avoids morbidity from hypoxia
- Excessive oxygen
 - Common practice and in written into training documents
 - Unlikely to benefit; may cause harm
 - Expands mission weight, cube, and logistics; safety issues, cost
 - Excess O₂ bad for critical medical pts, no clear data in trauma
- Gap: Limited data on optimal oxygen titration targets in critically injured patients

Normoxia: Avoid hypoxia AND hyperoxia



Incidence of Hyperoxia in Combat Wounded in Iraq and Afghanistan: A Potential Opportunity for Oxygen Conservation

MAJ Steven G. Schauer, DO, MS†‡§; MAJ Michael D. April, MD, DPhil, MSc†; LTC Jason F. Naylor, PA-C ||; Nee-Kofi Mould-Millman, MD¶; Col Vikhyat S. Bebarta, MD‡ ||; LTC Tyson E. Becker, MD†; Lt Col Joseph K. Maddry, MD*†‡§; Adit A Ginde, MD, MPH¶*

May 2019

Conclusions:

...1 in 5 casualties overall, 1 in 3 intubated, and almost 1 in 2 TBI casualties had documented hyperoxia.

Avoiding unnecessary O₂ supplementation may

1. Have material impact on preserving this scarce resource (logistics and cost)
2. Avoid potential detrimental clinical effects from supraphysiologic oxygen concentrations.



Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

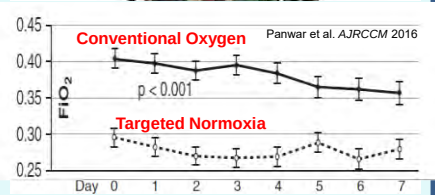
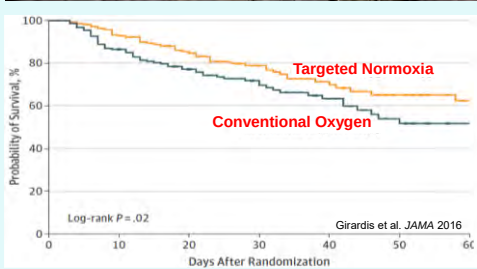
PI: Adit Ginde, MD, MPH; MAJ Steven Schauer, DO, MS Org: University of Colorado Denver/USAISR Award: W81XWH-17-0241

Study Aims

- **Aim 1:** Define standard care for oxygen titration in critically ill trauma patients
- **Aim 2:** Compare the effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
- **Aim 3:** Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.

Approach

Aim 1 is a Delphi process with subject matter experts to define normoxia targets (minimizing supplemental oxygen) after major trauma and develop consensus clinical practice guidelines. Aim 2 is a retrospective cohort study to measure severity-adjusted clinical outcomes of normoxia, compared with relative hyperoxia (conventional oxygen) in critically ill trauma patients. Aim 3 is a pilot implementation study of the targeted normoxia study to test the feasibility of implementation in critically ill trauma patients.



Targeted normoxia improves survival and conserves oxygen in medical patients. We will study in trauma.

Timeline and Cost

Activities	CY	17	18	18	19
Define standard care					
Comparative effectiveness study					
Pilot test intervention					
Develop large scale intervention					

Goals/Milestones

CY17 Goals (3 months) – Preparatory Work

- ☑ Design survey and identify experts/respondents (Aim 1)
- ☑ Develop electronic chart abstraction tool (Aim 2)
- ☑ Obtain IRB approvals (Aims 1 and 2)

CY18 Goals (12 months) – Define Normoxia Targets

- ☑ Begin Delphi process (Aim 1)
- ☑ Begin data collection (Aim 2)
- ☑ Analyze responses and develop clinical practice guideline (Aim 1)
- ☑ Complete data collection and analysis (Aim 2)
- ☑ Disseminate results (Aims 1 and 2)
- ☑ Develop intervention and case report forms (Aim 3)
- ☑ Obtain IRB approval (Aim 3)

CY19 Goals (9 months) – Implementation Results and Next Steps

- ☑ Implement intervention and begin data collection (Aim 3)
- ☐ Complete data collection and analysis (Aim 3)
- ☐ Disseminate results (Aim 3)
- ☐ Prepare for large scale implementation

Aim 1a: Systematic Review

SYSTEMATIC REVIEW

Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN,
Kristen DeSanto, MS, Cord W. Cunningham, MD, MPH,
Vikhyat S. Bebarta, MD, *and* Adit A. Ginde, MD, MPH, *Aurora, Colorado*

J Trauma Acute Care Surg 2019 October

Conclusions

Lower oxygen/ normoxia → improved outcomes

Few trauma specific articles; No high quality/RCT data

Supports need for trauma-specific studies/RCTs, particularly beyond TBI

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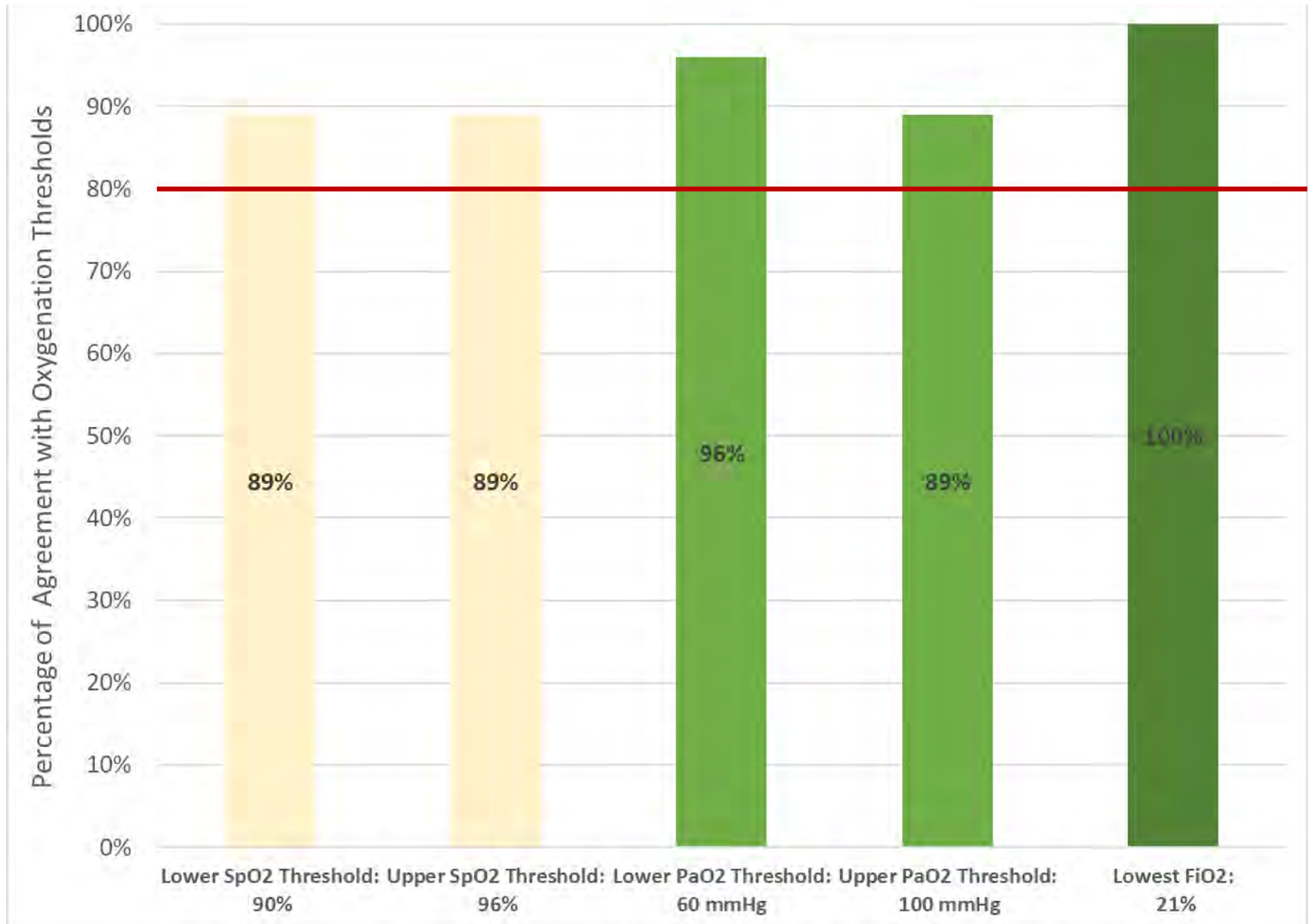
Aim 1b: Expert Panel (Military)

Last Name	First Name	Speciality	Institution
Becker	Tyson	Trauma Surgery	SAMMC
Chung	Kevin	Critical Care	SAMMC
Keenan	Sean	Emergency Medicine	SOCOM/SOCEUR
Mason	Philip	Critical Care	SAMMC
Miles	Ethan	Other	Ft. Benning
Oh	John	Trauma Surgery	Penn State
Redman	Theodore	Emergency Medicine	Ft. Campbell
Reisburg	Jamie	Other	Ft. Carson
Rush	Stephen	Other	USAF
Tobin	Josh	Critical Care	USC
Walrath	Benjamin	Emergency Medicine	Naval Medical Center
Wilson	Ramey	Other	SOCAFRICOM

Also 18 civilian experts part of the panel

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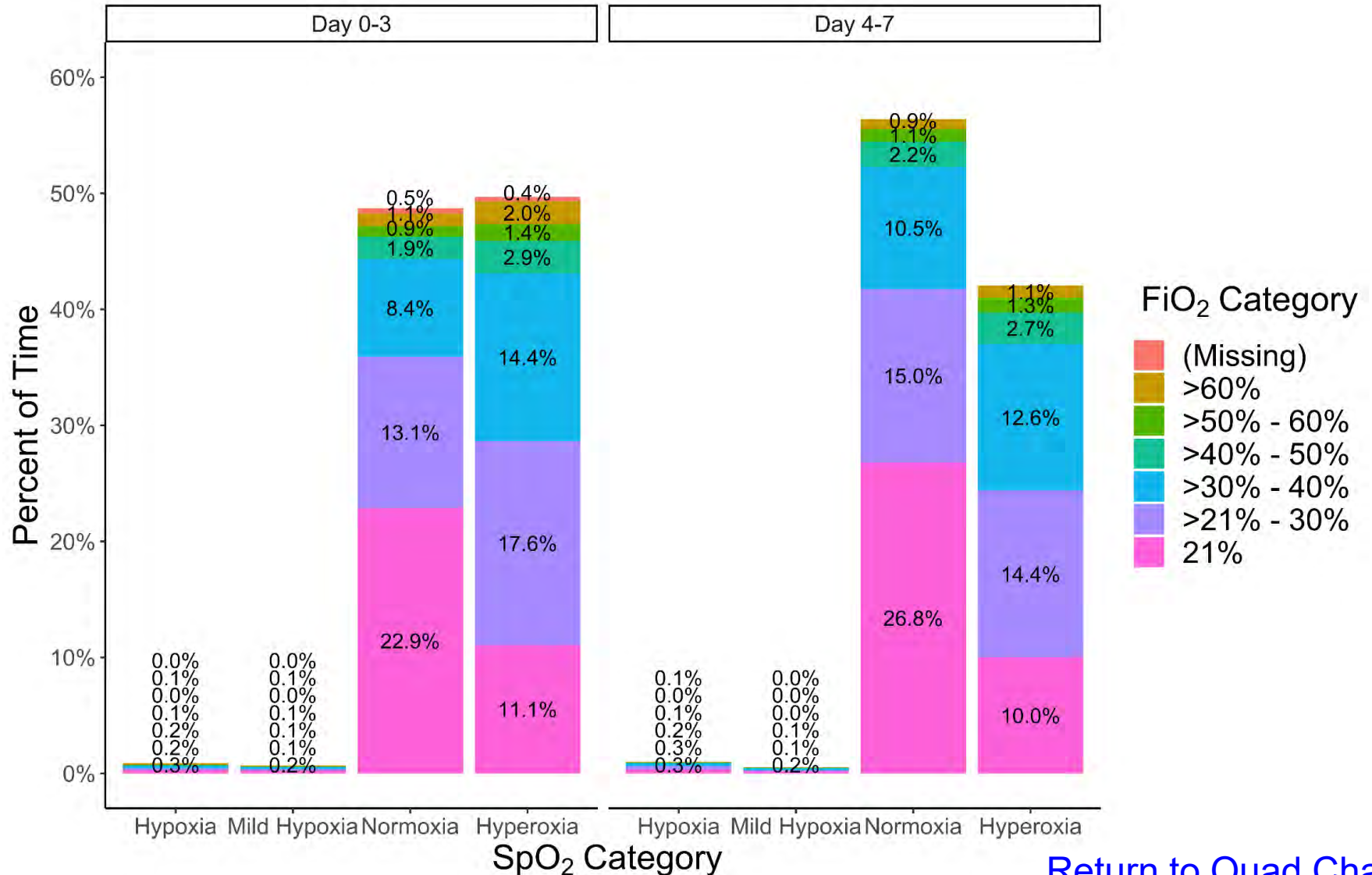
Aim 1b: Final Vote for SpO2, PaO2, and lowest FiO2



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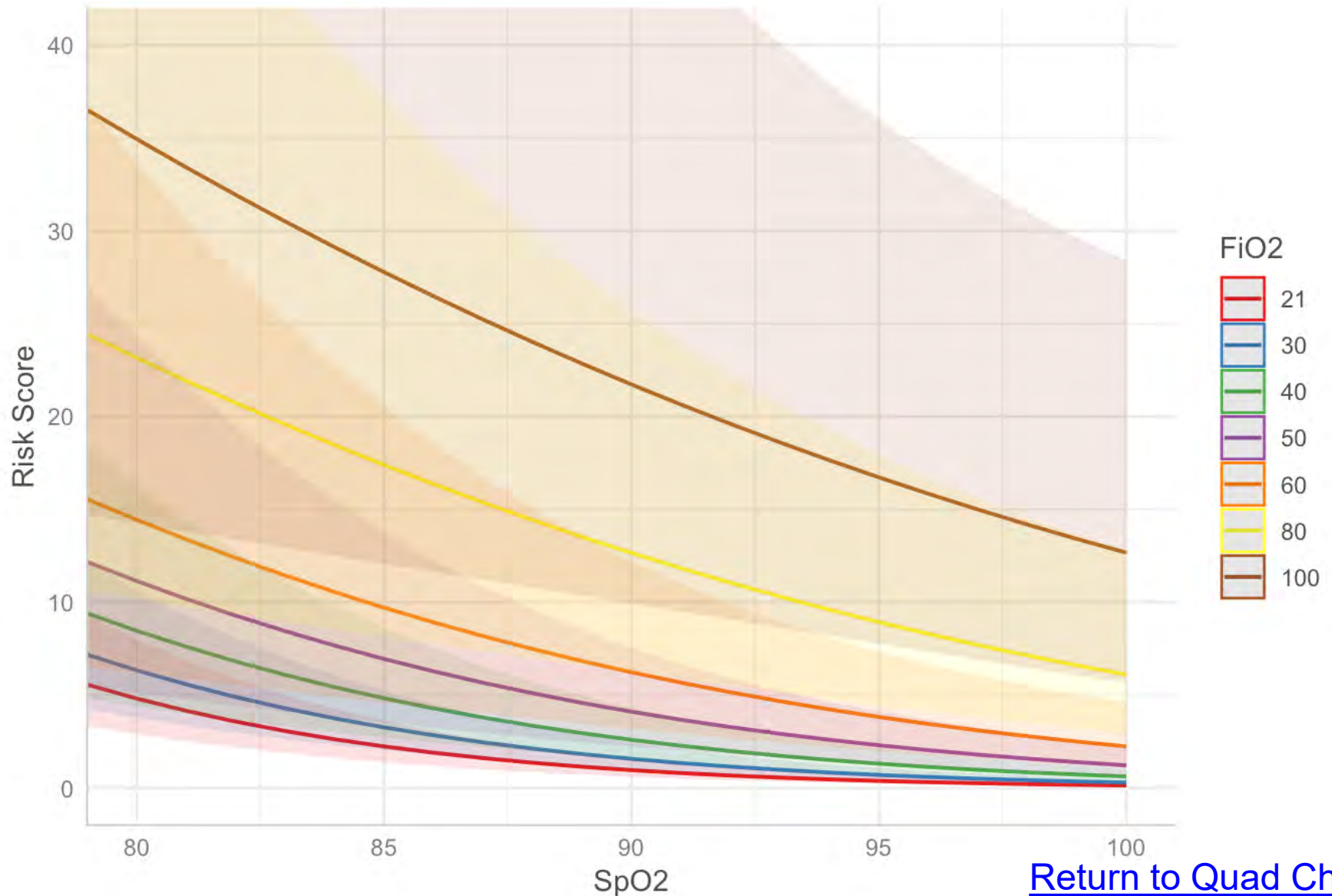
Aim 2: Observational Study

Most pts on supplemental O2 are **hyperoxic**



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Higher oxygen supplementation associated with **increased mortality** at all SpO2 levels



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Aim 3: Pilot Intervention

- Finalized standard care definitions for oxygen
- Approved IRB applications
 - Colorado IRB review—approved (waiver of consent)
 - DoD/HRPO second level review—approved
- Implementation
 - Data collection strategy
 - Stakeholder engagement
 - Electronic clinical decision support
- Demonstrated feasibility and safety
 - n=201 post-intervention (Jan-July 2019)

Aim 3: Pilot Intervention

- We significantly increased normoxia and reduced FiO₂/oxygen administration
- No increase in hypoxia
- Mortality, Vent FD, Hospital FD were similar in pre- and post-implementation groups
- Clinical outcomes to be evaluated in multicenter trial

Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care



PI: Adit Ginde, MD, MPH

Organization: University of Colorado Denver

Co-PI: MAJ Steven Schauer, DO, MS

Organization: Army Institute for Research

Awarded: JWPR

Objective

Our **overall objective** is to determine oxygen titration goals for combat injured to optimize care by reducing harm associated with hypoxia and hyperoxia and to conserve limited oxygen supply

Aim 1. Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients

Aim 2. Determine the safety of targeted normoxia

Aim 3. Determine the clinical effectiveness of targeted normoxia

Approach

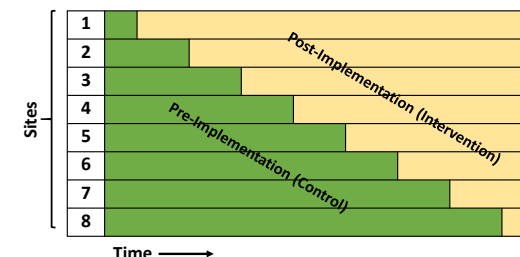
Multicenter cluster randomized, stepped wedge implementation trial of the targeted normoxia approach (SpO2 90-96%). Efficiency will be greatly enhanced by a waiver of informed consent since protocol implementation is minimal risk (EFIC not required).

Impact

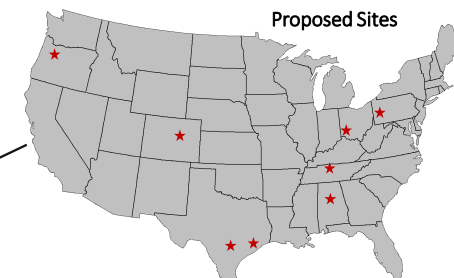
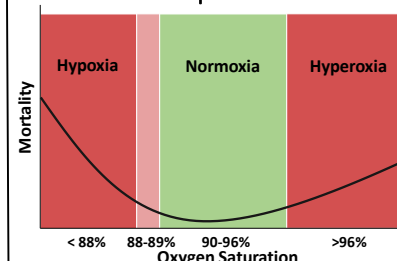
Our findings will provide immediately actionable data to define oxygenation practices in critically injured warfighters and civilians and aid in the development of clinical practice guidelines.



Stepped Wedge Cluster Randomized Trial



Conceptual Model



Timeline and Cost

Activities	Year 1	Year 2	Year 3
Preparatory Work	■		
Implementation		■	■
Data Collection		■	■
Analysis/Dissemination			■
	■	■	■

Goals/Milestones

Year 1 Goals (12 months) – Preparatory Work

- ☐ Obtain IRB/HRPO approval
- ☐ Develop Standard Operating Procedure Documents (SOPs)
- ☐ Create Site Materials
- ☐ Site Initiation Visits/Training
- ☐ Develop Data Collection Infrastructure
- ☐ Begin Site Implementation

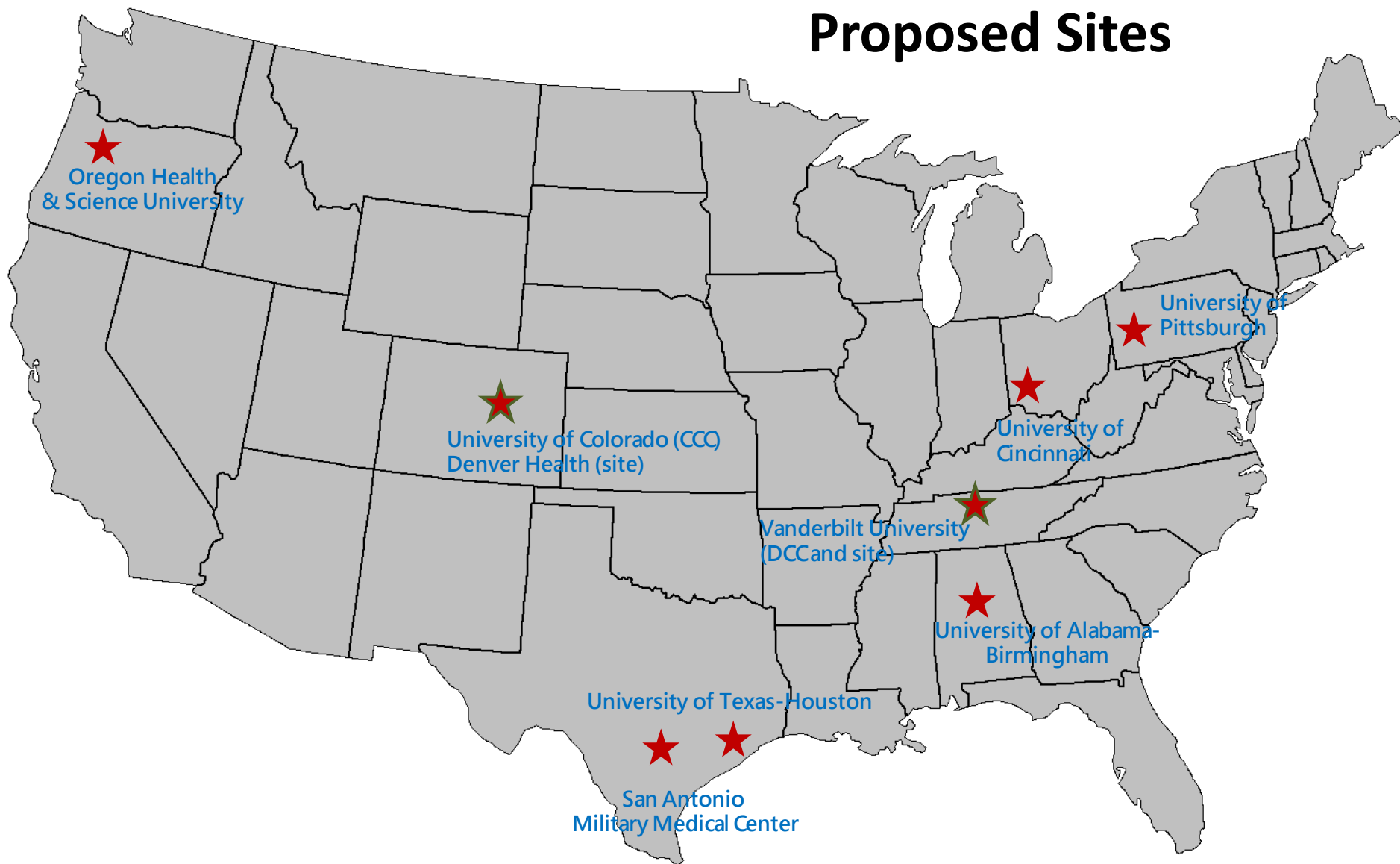
Year 2 Goals (12 months) – Implementation

- ☐ Randomized Implementation
- ☐ Site Monitoring
- ☐ Data Collection

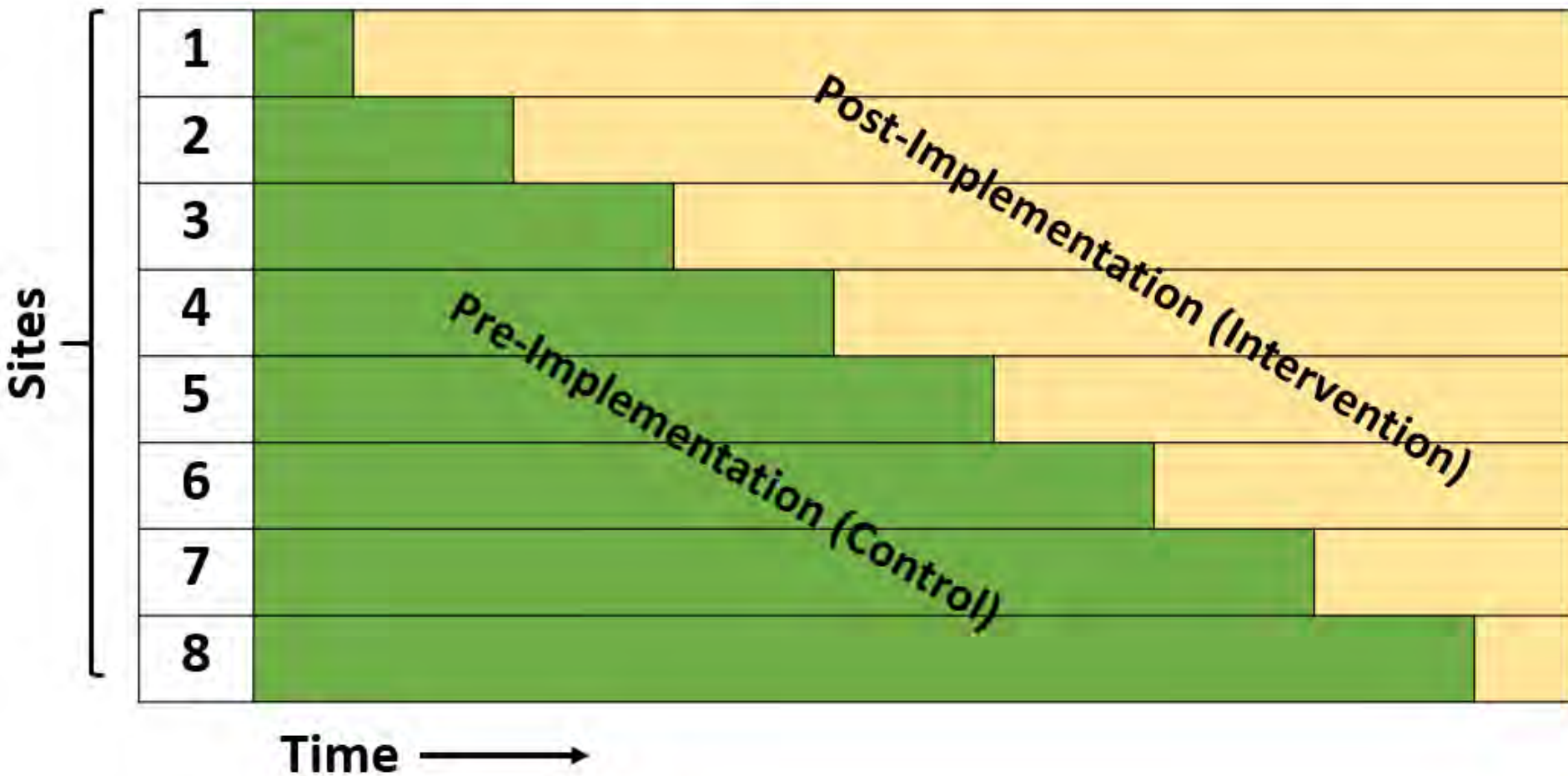
Year 3 Goals (12 Months) –Data Collection/Data Analysis

- ☐ Randomized Implementation/Site Monitoring
- ☐ Data Collection
- ☐ Data Analysis
- ☐ Dissemination

Proposed Sites



Stepped Wedge Cluster Randomized Trial



Multicenter Normoxia Trial (JWMRP)

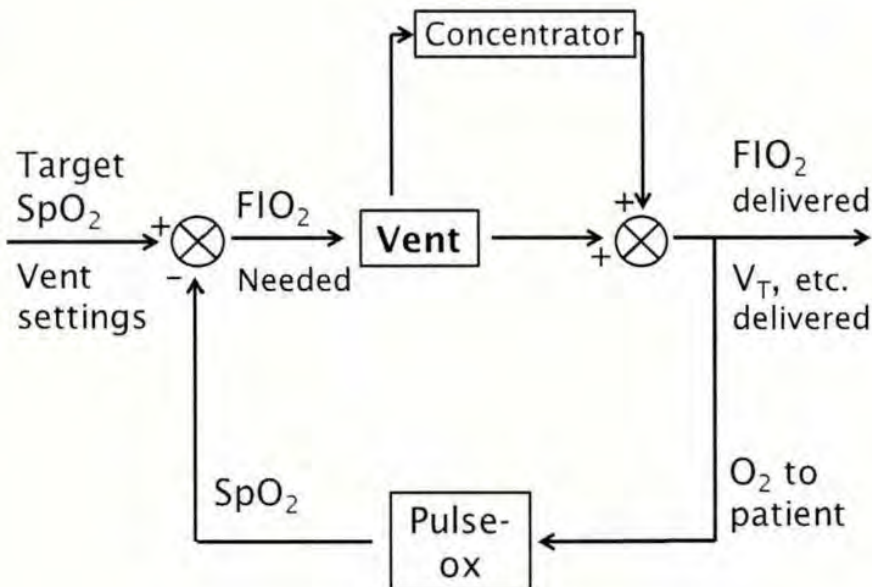
- **Goal:** definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
 - Particularly important for ERC/PFC
 - Focus on polytrauma
- **Design:** cluster randomized, stepped wedge implementation trial (8 sites, n~6240 patients); Trauma surgeons at Site Co-PIs
- **Human subjects issues:** minimal risk, waiver of informed consent (efficient, cost savings)

Multicenter Normoxia Trial (MTEC)

- **Goal:** major burn-specific evidence to inform CPG and oxygen requirements
 - Particularly important to focus on burn wound healing
- **Design:** cluster randomized, stepped wedge implementation trial (6 sites, n~2340 patients); Burn surgeons Site CO-Pis.
- **Sites:** U.S. Army Institute of Surgical Research, University of Alabama-Birmingham, University of Cincinnati, University of Colorado, University of Pittsburgh, Vanderbilt University

Technology/Materiel Solutions

- Portable oxygen concentrators
 - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control



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CU Anschutz Center for **CO**mbat **M**edicine and **BAT**tlefield (**COMBAT**) Research

Mission: To improve the care of combat related injury and illness through innovation, research, and advanced development with military and civilian collaboration



Emergency Medicine



Surgery



CU Center for COMBAT Research – Anschutz Medical Campus



Anesthesiology



Dean of the School of Medicine



CU Anschutz Center for COMBAT Research

Focused on high priority, high impact, pragmatic, forward combat casualty care solutions

Three Level 1 trauma centers, prehospital, bioengineering, etc

Getting “products” out the door



Discussion/Questions

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