AWARD NUMBER: W81XWH-20-2-0001

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

PRINCIPAL INVESTIGATOR: Adit Ginde, MD, MPH

CONTRACTING ORGANIZATION: Regents of the University of Colorado, Aurora, CO

REPORT DATE: March 2022

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
March 2022	Annual	01Mar2021-28Feb2022

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-20-2-0001

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. Adit Ginde MD, MPH

Erin Anderson, RN

E-Mail: erin.l.anderson@cuanschutz.edu and adit.ginde@cuanschutz..edu

5d. PROJECT NUMBER
001146918

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Regents of the University of Colorado,
Ilana Speigel
13001 E 17Th Place
Aurora CO, 80045-2571

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES N/A

14. ABSTRACT

Background: Oxygen therapy has undisputed importance in combat casualty care to treat/prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. Emerging evidence indicates that even modest hyperoxia can increases morbidity/mortality, however limited evidence exists specifically for trauma patients. In addition, oxygen is a limited resource that is challenging to obtain in austere settings eg, prolonged field care and enroute care, requiring
substantial resources, space, weight and logistics to procure. Therefore, it is critical 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.

Preliminary Data: From our prior USSOCOM-funded work, we recently published a trauma-specific systematic literature review of oxygen targets along with an expert consensus of military and civilian experts in trauma surgery, emergency medicine, critical care, and military operational medicine. Our findings demonstrate remarkable potential to reduce oxygen requirements by implementing a consensus- based definition ofnormoxia, based on a goal oxygen saturation of90-96°10. \Ve also pilot-tested the targeted normoxia intervention to demonstrate feasibility and safety for the proposed multicenter implementation trial.

Objective/Hypothesis: Our objecllve is to determine the feasibility, safety, and effectiveness oftbc targeted normoxia approach to conserve oxygen and improve clinical outcomes in critically injured patients. We

hypothesize that more targeted use of oxygen therapy, to limit exposure to both hyperoxia and hypoxia, will safely reduce the needs for concentrated oxygen in the deployed, combat setting.

Specific Aims: \Ve will conduct a prospective multicenter clinical trial, achieving the following aims:

Aim 1. Measure the impact of targeted normoxia on oxygen requirements in critically injured patients. We will define the oxygen requirements for critically injured patients along with determining the proportion requiring high levels of supplemental oxygen (anticipated *to* be low). Specific to the resource-limited setting, we will estimate the potential reductions in oxygen consumption using the targeted normoxia approach.

Aim 2. Determine the safety of targeted normoxia. compared to conventional oxygenation. Specifically, we will determine the rate and duration of hypoxic and hyperoxic events for the targeted normoxia approach, compared to conventional oxygenation that relies on generous oxygen administration.

Aim 3. Determine the clinical effectiveness of the targeted normoxia approach. Specifically, we will compare hospital mortality, neurological status at discharge, hospital-free and ventilator-free days, and time to room air.

Project Design: We will conduct a multicenter, stepped wedge cluster randomized trial of the targeted normoxia approach in adult emergency department trauma patients, with a focus on those admitted to the intensive care unit. Consistent with our current pilot study of targeted normoxia (approved by local IRB and HRPO), \Ve \Viii conduct this trial under a waiver of consent since the implementation of this protocol is minimal risk (exception from informed consent [EFIC] is not required).

Proposed sites: Denver Health, Oregon Health and Sciences University, San Antonio Military .Medical Center, University of Alabama-Birmingham 1 University of Cincinnati, University of Pittsburgh, University of Texas Houston, Vanderbilt University
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. Our lessons learned will optimize patient outcomes while conserving oxygen supplies, which will reduce weight, volume, and logistical burdens in deployed, combat settings. Furthermore, our findings will impact materiel solutions such as portable oxygen concentrators and closed loop oxygenation/ventilation systems.

Military Benefit: Our research proposal will fill a critical gap in knowledge of safe and effective oxygenation targets in critical combat casualties. These results will define best practices for oxygen titration that can supplant current practices of liberal/excessive oxygen administration and optimize care of combat injured.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	110	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Table of Contents

1. **INTRODUCTION:** Oxygen therapy has undisputed importance in the care of critically ill medical and trauma patients to treat and prevent morbidity associated with hypoxemia. However, generous supplemental oxygen is routine, and often results in hyperoxemia. The objective is to determine the effectiveness of a multimodal educational intervention to reduce supplemental oxygen use in critically injured patients. We will also evaluate the safety and effectiveness of the more targeted use of oxygen therapy.

2. **KEYWORDS:** oxygenation, oxygen delivery, mechanical ventilation, normoxemia, hyperoxemia, hypoxemia, critically ill, trauma, prolonged field care, limited resources, traumatic brain injury, hemorrhage

3. **ACCOMPLISHMENTS:**

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

Goals/Milestones

Major Task 1: Preparatory Work
Local IRB Reliance – *01MAY2020- **100% complete***
Finalize Protocol – *01JUNE2020- **100% Complete***
Central IRB Approval – *01JUL2020- **100% Complete***
HRPO Approval – *01SEP2020- **100% complete***
Develop Data Collection Infrastructure – *01SEP2020- **100% complete***
Develop Standard Operating Procedures (SOPs) – *01SEP2020-**100% complete***
Create Site Materials – *01SEP2020- **100% complete***
Site Initiation Visits/Training – ***75% complete***

- Site 1: Oregon Health and Sciences University – *28SEP2020*
- Site 2: San Antonio Military Medical Center – *10DEC2020*
- Site 3: Denver Health – *03MAR2021*
- Site 4: University of Cincinnati – *08JUL2021*
- Site 5: University of Texas – Houston – *24SEP2021*
- Site 6: Vanderbilt University Medical Center – *07JAN2022*

Major Task 2: Implementation
Randomized Implementation – *01OCT2020 – **75% complete***
Site Monitoring – *01OCT2020 – **75% complete***
Site Maintenance/Retraining – *01OCT2020 – **75% complete***

Major Task 3: Data Collection/Data Analysis
Data Collection – *01OCT2020 – **75% complete***
Data Management/Cleaning – *01OCT2020 – **75% complete***
Data Analysis – *01NOV2020 – **No interim analysis will be completed for this trial***
Dissemination of Results – *01APR2021*
Report Findings- *01FEB2023*

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

AIM 1:
- Received Local IRB Reliance Agreements
- Finalize Protocol Core Protocol
- Received local IRB approval
- Received HRPO Approval
- Developed and Finalized Data Collection Infrastructure
- Develop and Disseminated Standard Operating Procedures (SOPs) to Sites
- Developed and Disseminated Site Materials
- Successfully Completed Six Site Initiation Visits/Training
    - Site 1: Oregon Health and Sciences University – 28SEP2020
    - Site 2: San Antonio Military Medical Center – 10DEC2020
    - Site 3: Denver Health – 03MAR2021
    - Site 4: University of Cincinnati – 08JUL2021
    - Site 5: University of Texas – Houston – 24SEP2021
    - Site 6: Vanderbilt University Medical Center – 07JAN2022

AIM 2:
- Began Randomized Implementation at the first six sites
    - Site 1: Oregon Health and Sciences University – 15OCT2020
    - Site 2: San Antonio Military Medical Center – 15JAN2021
    - Site 3: Denver Health – 15APR2021
    - Site 4: University of Cincinnati – 15JUL2021
    - Site 5: University of Texas – Houston – 15OCT2021
    - Site 6: Vanderbilt University Medical Center – 15JAN2022
- Began and continued Site Monitoring at: Oregon Health and Sciences University; San Antonio Military Medical Center; Denver Health; University of Cincinnati; University of Texas – Houston; Vanderbilt University Medical Center
- Began and continued Site Maintenance/Retraining at: Oregon Health and Sciences University; San Antonio Military Medical Center; Denver Health; University of Cincinnati; University of Texas – Houston; Vanderbilt University Medical Center

AIM 3:
-Continued data collection at Oregon Health and Sciences University and San Antonio Military Medical Center, and began data collection at: Denver Health; University of Cincinnati; University of Texas – Houston; Vanderbilt University Medical Center

1. Oregon Health and Sciences University Enrollment (OHSU)
- Total Enrollment: 2327
- Pre-Intervention: 486
- Washout: 152
- Post- Intervention: 1689* (*Graphs anticipated following fixes to O2 issues)

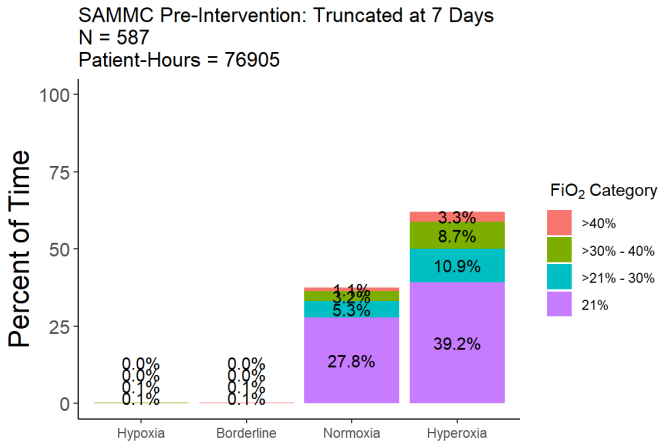
[site is missing many post-intervention oxygenation data points due to data transfer issues, therefore, we are unable to present unbiased graphs]

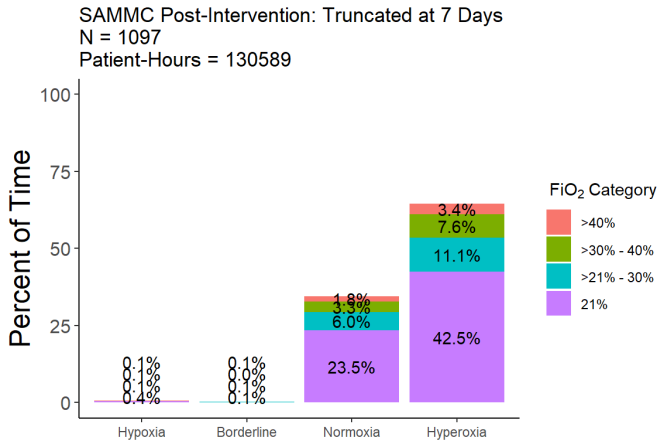
2. San Antonio Military Medical Center Enrollment (SAMMC)

- Total Enrollment: 1777
- Pre-Intervention: 587
- Washout: 93
- Post- Intervention: 1097

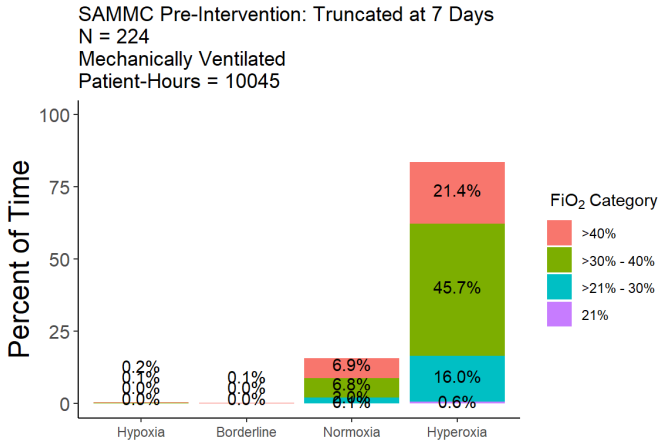
Pre/Post Intervention Graphs:

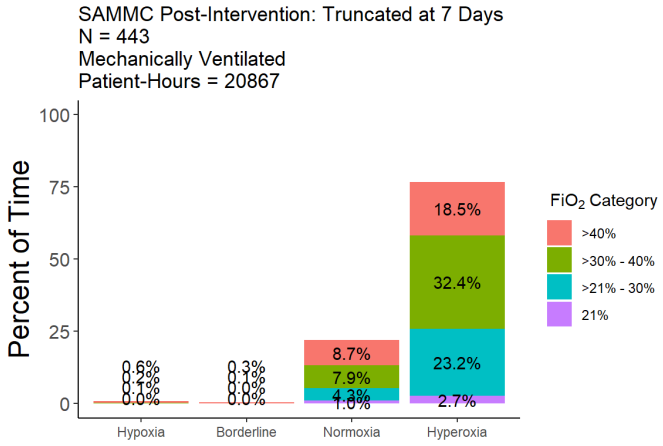
All Patients



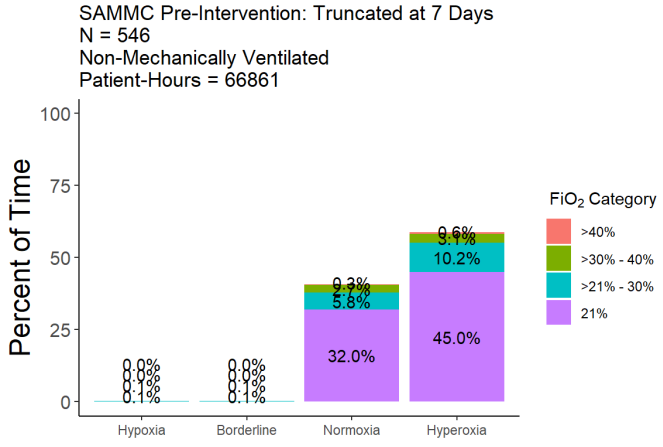


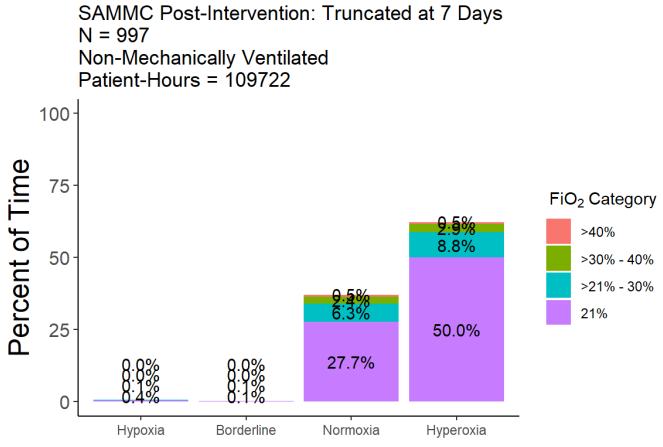
Mechanically Ventilated Patients





Nonmechanically Ventilated Patients



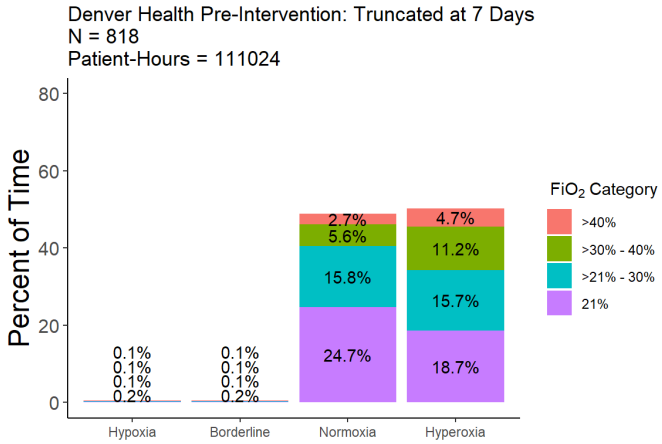


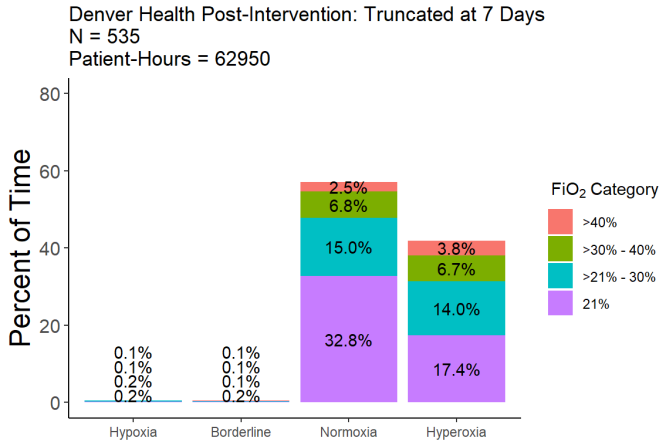
3. Denver Health

- Total Enrollment: 1561
- Pre-Intervention: 818
- Washout: 62
- Post- Intervention: 681

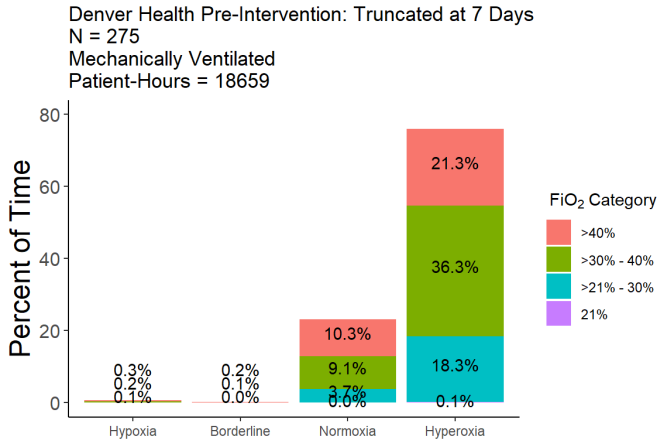
Pre/Post Intervention Graphs:

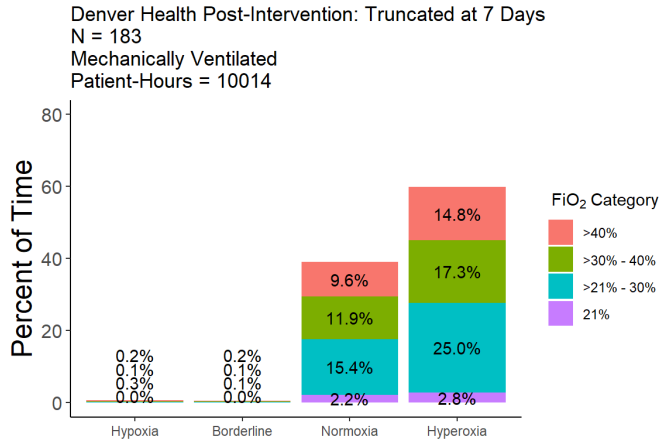
All Patients



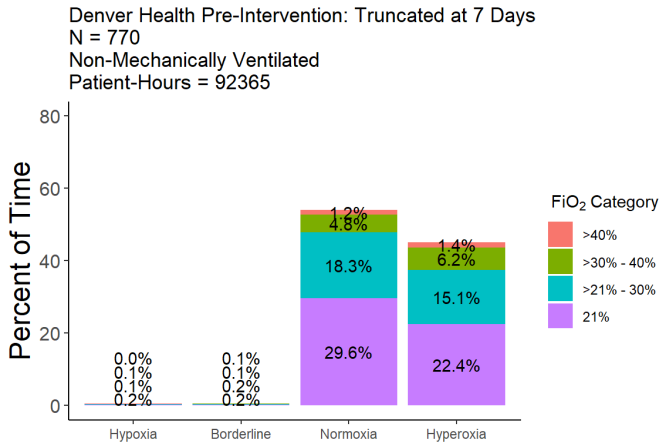


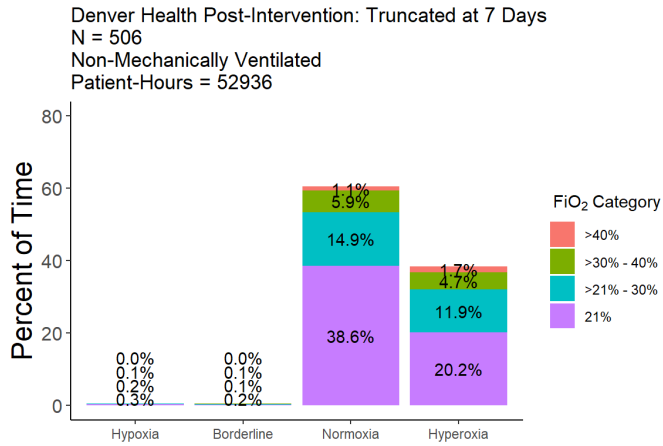
Mechanically Ventilated Patients





Nonmechanically Ventilated Patients



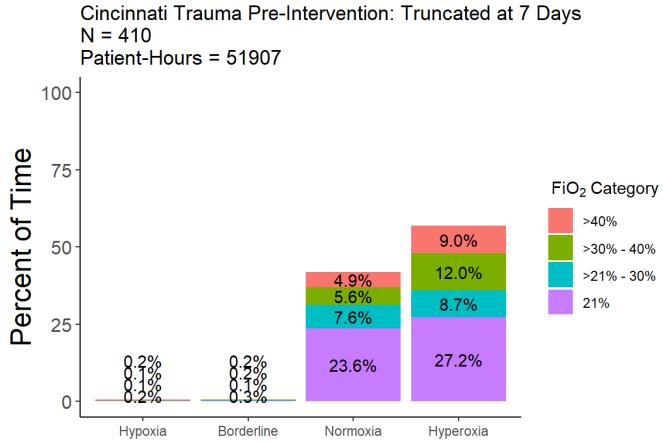


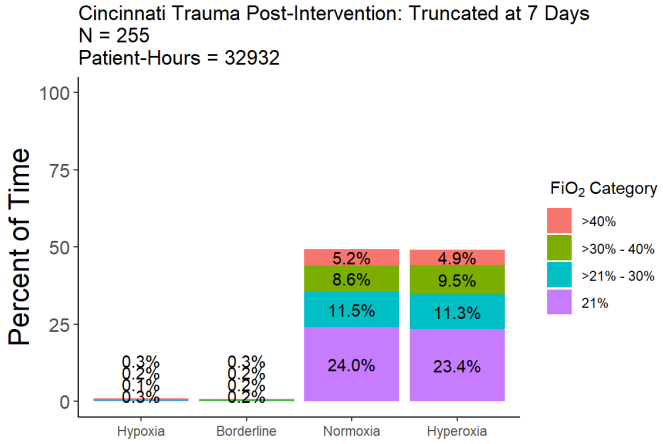
4. University of Cincinnati

- Total Enrollment: 727
- Pre-Intervention: 410
- Washout: 62
- Post- Intervention: 255

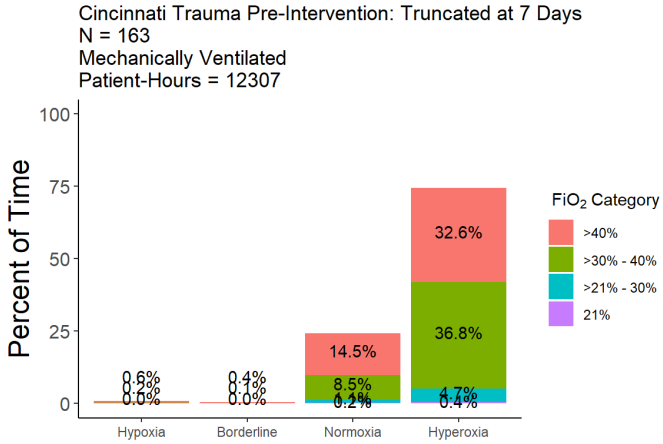
Pre/Post Intervention Graphs:

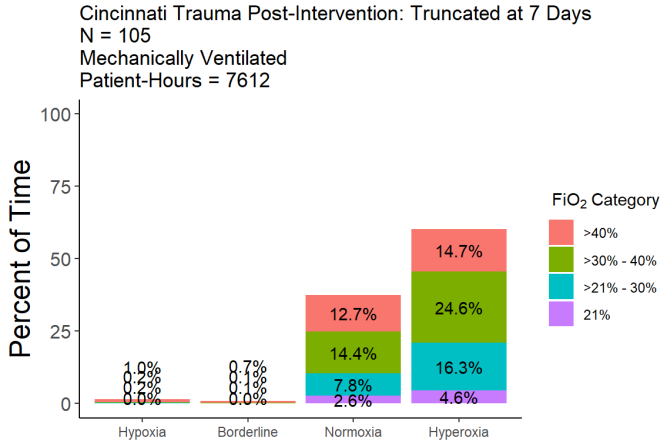
All Patients



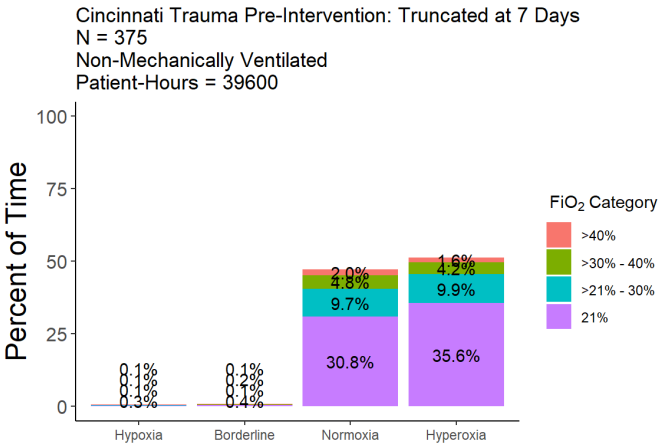


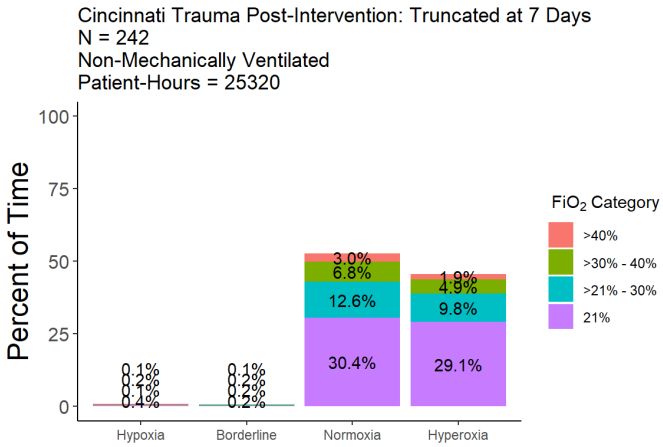
Mechanically Ventilated Patients





Nonmechanically Ventilated Patients



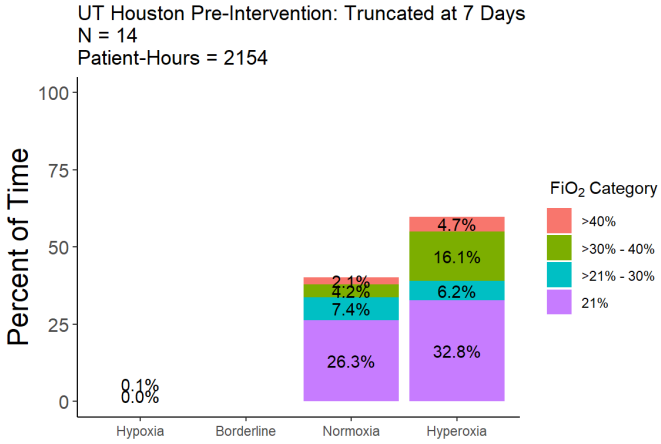


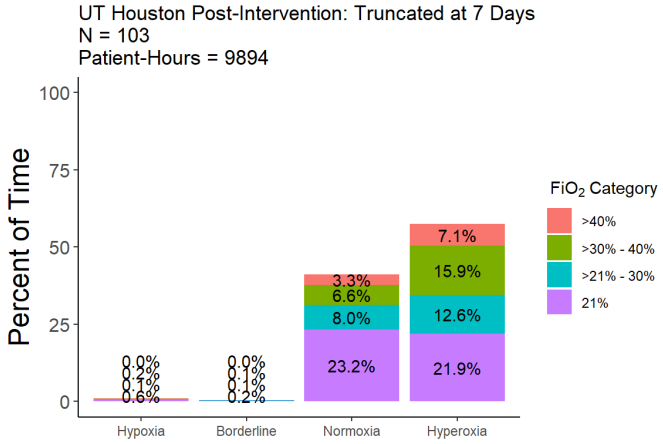
5. University of Texas – Houston

- Total Enrollment: 186
- Pre-Intervention: 14** (** Full data is missing)
- Washout: 54
- Post- Intervention: 118

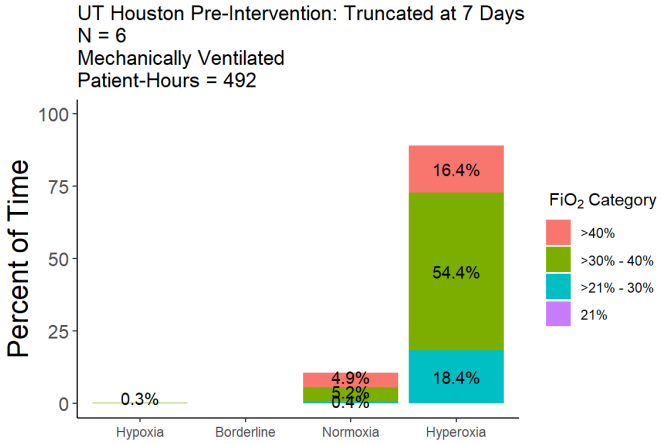
Pre/Post Intervention Graphs:

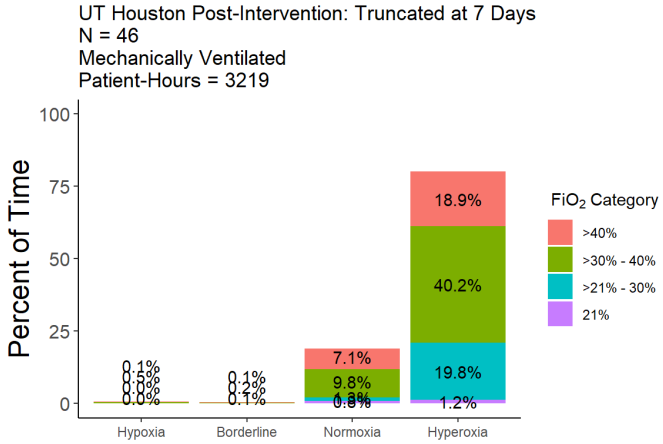
All Patients



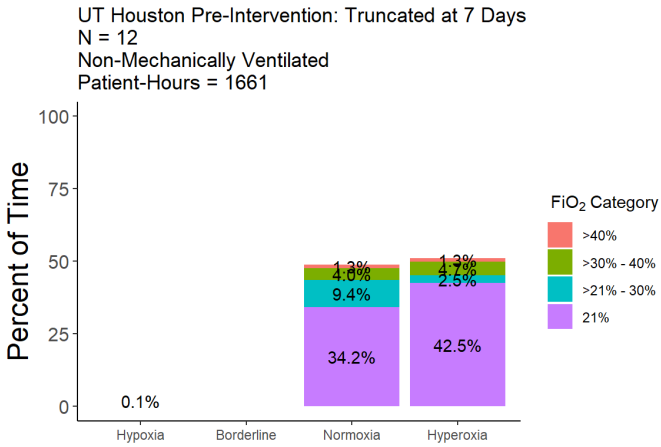


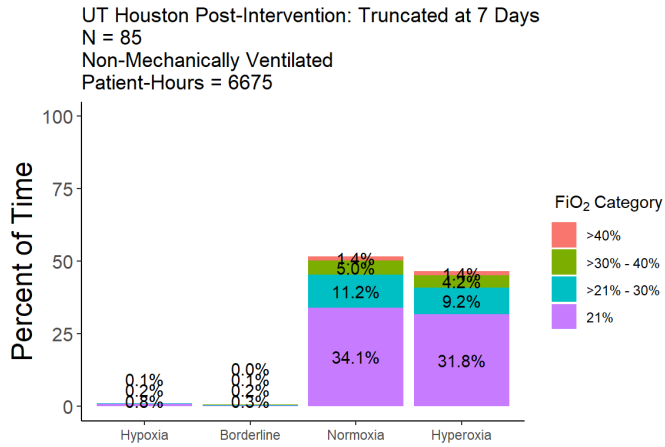
Mechanically Ventilated Patients





Nonmechanically Ventilated Patients



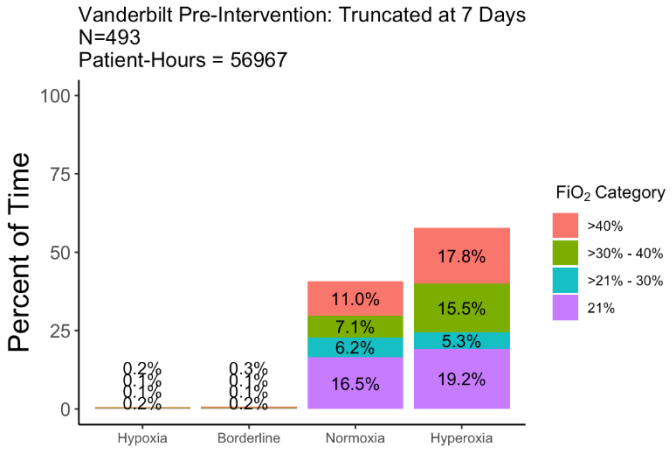


6. Vanderbilt University Medical Center

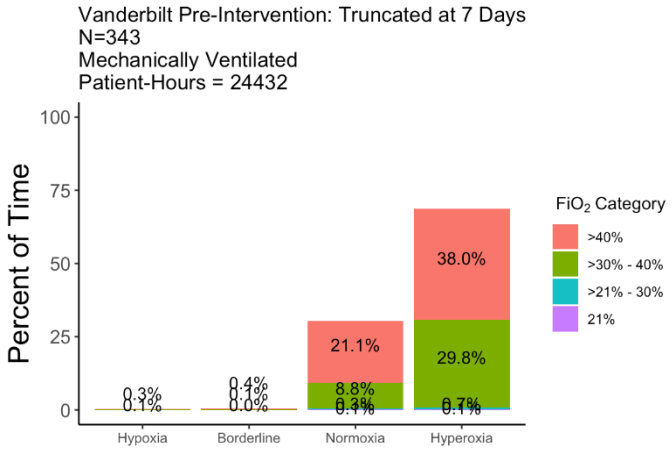
- Total Enrollment: 596
- Pre-Intervention: 493
- Washout: 58
- Post- Intervention: 45

Pre Intervention Graphs:

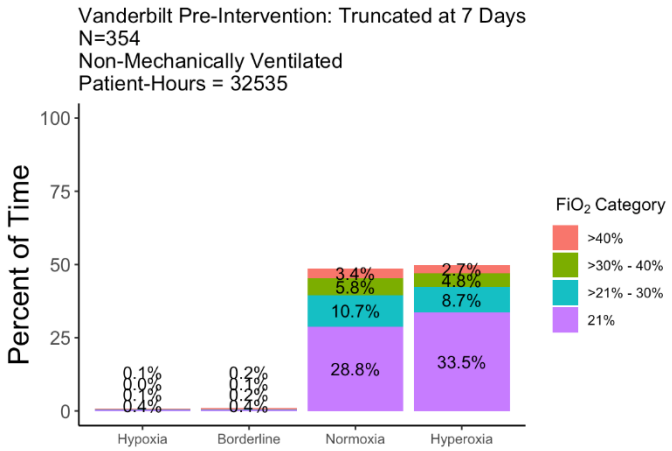
All Patients



Mechanically Ventilated Patients



Nonmechanically Ventilated Patients



-Continued Data Management/Cleaning at the Oregon Health and Sciences University and San Antonio Military Medical Center
-Began Data Management/Cleaning at the four sites launched between 15APR2021 to 15JAN2022: Denver Health; University of Cincinnati; University of Texas – Houston; Vanderbilt University Medical Center
-Continued on study reporting at Oregon Health and Sciences University and San Antonio Military Medical Center and began on study reporting at the four sites launched between 15APR2021 to 15JAN2022 – Denver Health; University of Cincinnati; University of Texas – Houston; Vanderbilt University Medical Center – to ensure compliance and review data for safety signals (please see attached most recent data reports)

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

During our monthly investigator meetings, we present relevant data and review areas in need of improvement to participating sites and military participants. We send each site extensive monthly data reports to review and disseminate to clinical and research staff. We presented the methods abstract for this trial at SOMSA 2021 and preliminary results at MHSRS 2021 (virtual conference). The University of Colorado and collaborating research team won the Best Research Presentation Award during SOMSA 2021. We plan to present secondary analysis results for TBI vs non-TBI patient population at SOMSA 2022 and preliminary results at MHSRS 2022.

- **What do you plan to do during the next reporting period to accomplish the goals?**

AIM 1:

- Complete site initiation visits for the final two enrolling sites (schedule TBD)
  - University of Alabama – Birmingham (Launch April 15, 2022)
  - University of Pittsburgh Medical Center (Launch July 15, 2022)

AIM 2:

- Continue the randomized implementation of the last two sites, University of Alabama-Birmingham and University of Pittsburgh
- Continue monitoring all sites that enter into the implementation phase of the trial
- Continue maintenance and retraining at sites that have entered into the implementation phase of the trial

AIM 3:

- Continue data collection
- Continue data management activities
- Continue data cleaning
- Continue analyzing on-study reporting compliance documents to ensure safety and compliance
- Start analysis of data

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

- Developed the core protocol to inform participating institutions of study design, multi-modal education and provided study materials to sites to ensure proper implementation at sites.

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:**

- **Changes in approach and reasons for change**

  Nothing to report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  UT-Houston accidentally sent MRNs instead of the auto-generated numbering used by REDCap for Record IDs, resulting in around 68 medical records being sent to the DCC Trauma Data Pool in REDCap at Vanderbilt. The University of Texas Houston has informed their compliance office of the breach of confidentiality and the following corrective action plan has been implemented:

  1. All identifiable information was deleted in the trauma data pool
  2. Vanderbilt requested that UT-Houston stop sending data until the Record IDs have been changed
  3. CCC's (Colorado) Statistician destroyed any code or processed datafiles that may have included these record IDs.
  4. Retrain on process of uploading data into sites REDCap (principal investigator, study coordinators, IT lead) with attestation from each confirming receipt and understanding of data transfer processes.

- **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**

  Nothing to report
- **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**

  1. Douin DJ, Anderson EL, Schauer, SG, et al. Strategy to avoid excessive oxygen (SAVE-O2) for critically ill trauma patients: A multicenter clinical trial to define oxygen requirements for combat casualty care. [Submitted to Special Operations Medical Scientific Assembly (SOMSA), June 2021; accepted; oral presentation

  2. Dylla L, Douin DJ, Anderson EL, et al. Strategy to avoid excessive oxygen (SAVE-O2) for critically ill trauma patients: A multicenter cluster randomized, stepped wedge trial for targeted normoxia. [Submitted to Military Health System Research Symposium (MHSRS), August 2021; accepted; poster presentation]

  3. Dylla L, Douin DJ, Anderson EL, et al. A multicenter cluster randomized, stepped wedge implementation trial for targeted normoxia in critically ill trauma patients: study protocol and statistical analysis plan for the Strategy to Avoid Excessive Oxygen (SAVE-O2) trial. *Trials*. 2021;22(1):784. Published 2021 Nov 8.

  4. Douin DJ, Dylla L, Anderson EL, et al. Hyperoxia is associated with a greater risk for mortality in critically ill traumatic brain injury patients than in critically ill trauma patients without brain injury. [Submitted to Special Operations Medical Scientific Assembly (SOMSA), May 2022; approval pending]

  5. Douin DJ, Dylla L, Anderson EL, et al. Strategy to avoid excessive oxygen (SAVE-O2) for critically ill trauma patients: A multicenter cluster-randomized, stepped wedge trial for targeted normoxia. [Submitted to Military Health System Research Symposium (MHSRS), August 2022; approval pending]

- **Other Products**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?** Please see below for University of Colorado personnel nearest month worked. Please see financial report for collaborating institutions (Oregon Health and Sciences University, San Antonio Military Medical Center, Denver Health, University of Cincinnati, University of Texas-Houston, Vanderbilt University, University of Alabama-Birmingham and University of Pittsburgh) personnel nearest month worked.

Name:	Dr. Adit Ginde, MD, MPH
Project Role:	Principle Investigator
Researcher Identifier:	Not Available
Nearest person month worked:	1.346
Name:	Vikhyat Bebarta, MD
Project Role:	C-Investigator
Researcher Identifier:	Not Available
Nearest person month worked:	0.220
Name:	Erin Anderson, RN
Project Role:	Project Manager
Researcher Identifier:	Not Available
Nearest person month worked:	5.645
Name:	Jessica Cwik
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	3.050
Name:	Aimee Steinwand
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	3.716
Name:	Conner Jackson, MS
Project Role:	Masters Biostatistician
Researcher Identifier:	Not Available
Nearest person month worked:	3.00
Name:	John Rice, PhD
Project Role:	PhD Analyst
Researcher Identifier:	Not Available
Nearest person month worked:	1.127

- **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, Current, and Pending Support

GINDE, ADIT A., MD

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: 06/17/14-04/30/22
Amount:
Time Commitment: 12.5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: National Center for Advancing Translational Sciences (NCATS)
Funding Agency: Colorado Clinical and Translational Sciences Institute
Role: Co-Investigator
Description/Aims: The CTSA to the University of Colorado Denver supports the institutional academic home for research and training in clinical and translational sciences.
Award Number: UL1TR002535 (Sokol)
Funding Period: 05/18/18-04/30/23
Amount:
Time: 10%
Agency Contact: Pablo Cure, 301-827-2014,pablo.cure@nih.gov
Overlap: None

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 (Thompson/Schoenfeld
Funding Period: 06/17/14-04/30/22
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

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:
Time Commitment: 1%
Agency Contact: Maria Mendoza-Puccini, 301-496-9135, maria.mendoza.puccini@nih.gov
Overlap: None

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:
Time Commitment: 5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

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:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Overlap: None

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
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.
Award Number: BA190054 (Mould-Millman)
Funding Period: 09/30/19-09/29/22
Amount:
Time Commitment: 5%
Agency Contact: Jennifer Shankle, 301-619-2193, Jennifer.e.shankle.civ@mail.mil
Overlap: None

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.
Award Number: MTEC-19-08-MuLTI-0043
Funding Period: 01/30/20-01/29/23
Amount:
Time Commitment: 10%
Agency Contact: Jenifer Ojeda, 301-619-0193, Jenifer.f.ojeda.civ@mail.mil
Overlap: None

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
Award Number: JW190515 (Ginde)
Funding Period: 03/01/20-02/28/23
Amount:
Time Commitment: 10%
Agency Contact: Sandy Snyder, 301-619-7047, sandy.j.snyder.civ@mail.mil
Overlap: None

Title: *Internationally Coordinating Center for ACTIV-3 Trial Initiative*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator/Site PI
Description/Aims: The goal of this project is to design and oversee the trial, drafting, and revising standard operating procedure documents and FAQs, interactions with DSMB, NHLBI, International Coordinating Center (ICC), running and attending meetings, and serving as an on-call PETAL Investigator for the ACTIV-3 COVID-19 protocol.
Award Number: 1OT2HL156812 (Thomas)
Funding Period: 06/15/20-05/31/22
Amount:
Time Commitment: 10%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *ACTIV-4 Host Targeting Therapies*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator/Site PI
Description/Aims: The goal of this platform phase III trial is to evaluate the efficacy and safety of host-directed interventions to improve outcomes for hospitalized COVID-19 patients.
Award Number: 1OT2HL156812 (Thomas)
Funding Period: 05/01/21-05/31/22
Amount:
Time Commitment:1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Epidemiology and Outcomes of Combat-Relevant Prolonged Trauma Care: A Prospective Multicenter Prehospital Study in South Africa*
Funding Agency: Department of Defense/U.S. Army
Role: Co-PI
Description/Aims: The goal of this project is to conduct a multicenter epidemiologic study that assesses the effect of prolonged durations of prehospital care, and key prehospital interventions, on morbidity and mortality of civilian patients with combat-like injuries.
Award Number: BA190049
Funding Period: 09/30/20 – 09/29/24
Amount:
Time Commitment: 3%
Agency Contact: Jennifer Shankle, 301-619-2193, Jennifer.e.shankle.civ@mail.mil
Overlap: None

Title: *An end-user assessment of the novel iView video laryngoscope*
Funding Agency: USAF/AFMC
Role: Site co-investigator
Description/Aims: The goal of this study to is to compare the use of the novel iView laryngoscope to traditional video laryngoscopy during acute airway management.
Award Number: FA8650-20-2-6227 (Schauer)

Funding Period: 08/01/20-09/30/22
Amount:
Time Commitment: 2%
Agency Contact: Vanessa Vazquez, 937-938-3192, Vanessa.vazquez.5@us.af.mil
Overlap: None

Title: *Adult Inpatient/Outpatient VE Case-Control Study*
Funding Agency: Centers for Disease Control and Prevention (CDC)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is to evaluate vaccine effectiveness of SARS-CoV-2 vaccination against symptomatic, medically attended SARS-CoV-2 infection by vaccine product.
Award Number: 75D30121F00002 (Self)
Funding Period: 02/05/21-02/14/22
Amount:
Time Commitment: 1%
Agency Contact: Tailee Tucker, ijk8@cdc.gov, 770-488-2812
Overlap: None

Title: *Implementation and Effectiveness of Monoclonal Antibodies to Treat High-Risk Outpatients with COVID-19*
Funding Agency: National Center for Advancing Translational Sciences (NCATS)
Role: Co-Investigator
Description/Aims: The goal of this project is to develop, implement, and evaluate strategies to optimize equitable nMAb access in Colorado and determine the effectiveness and safety of nMAb treatment in high-risk COVID-19 outpatients.
Award Number: UL1 TR002535-03S3 (Sokol/Ginde)
Funding Period: 03/15/21-04/30/22
Amount:
Time: 15%
Agency Contact: Pablo Cure, 301-827-2014,pablo.cure@nih.gov
Overlap: None

Title: *Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19 to Reduce the Burden of Illness for U.S. Service Members*
Funding Agency: FY20 BA 6.4 CARES Act Research and Development (RDT&E)
Role: Civilian PI
Description/Aims: The goal of this phase III trial is to test the efficacy and safety of the antiviral agent lopinavir/ritonavir to prevent disease progression and improve recovery in outpatients with COVID-19.
Award Number: ID07200010-301-2 (Ginde/Ng)
Funding Period: 05/03/21-09/30/22
Amount:
Time Commitment: 10%
Agency Contact: Mr. Ed Chagoy (59MDW), 210-292-2761, edward.a.chagoy.civ@mail.mil
Overlap: None

Title: *Human IFN Beta-1a In Severe CoronavirUS (HIBISCUS)*
Funding Agency: FY20 BA 6.4 CARES Act Research and Development (RDT&E)
Role: Civilian PI
Description/Aims: The goal of this phase III trial is to test the efficacy and safety of intravenous interferon beta-1a in the treatment of patients with severe hypoxemic respiratory failure/ARDS due to COVID-19
Award Number: ID07200010-301-5 (Ginde/Weitzel)
Funding Period: 10/01/21-09/30/22
Amount:
Time Commitment: 10%
Agency Contact: Mr. Ed Chagoy (59MDW), 210-292-2761, edward.a.chagoy.civ@mail.mil
Overlap: None

Title: *Randomized Trial of Fresh Frozen Plasma Versus Albumin in Acute Burn Resuscitation*
Funding Agency: Department of Defense/Military Burn Research Program
Role: Co-Investigator
Description/Aims: The goal of this study is to compare the safety and efficacy of fresh frozen plasma vs albumin for acute resuscitation of burn shock.
Award Number: MB200032 (Wiktor)
Funding Period: 09/01/21-08/30/24
Amount:
Time Commitment: 5%
Agency Contact: Eva Lai, eva.lai.ctr@mail.milrlap:
Overlap: None

Title: *Surveillance of Acutely Ill Adults with Respiratory Viruses, including SARS-CoV-2 (IVY 4)*
Funding Agency: Centers for Disease Control and Prevention (CDC)
Role: Subaward PI
Description/Aims: The goal of this study is to evaluate vaccine effectiveness of SARS-CoV-2 and influenza vaccination in preventing hospitalizations.
Award Number: 75D30122C12914 (Self)
Funding Period: 02/01/22-09/30/22
Amount:
Time Commitment:1%
Agency Contact: Lekeate Knox, Yvz3@cdc.com
Overlap: None

Title: *DirEct Versus VIdeo LaryngosCopE (DEVICE) Airway Trial*
Funding Agency: Department of Defense/FY21 Defense Health Agency (DHA) Restoral
Role: Subcontract PI
Description/Aims: The goal of this phase III trial is to compare the effect of video vs direct laryngoscope on first pass success of emergency tracheal intubation of critically ill adults in the acute care setting.
Award Number: pending
Funding Period: 02/01/22-09/30/22

Amount:
Time Commitment:6.967%
Agency Contact: Jennifer Trevino, Jennifer.Trevino@1stAmerican.com, 210.782.1319
Overlap: None

Title: *PRagmatic trial Examining OXygentation prior to Intubation (PREOXI)*
Funding Agency: Department of Defense/FY21 Defense Health Agency (DHA) Restoral
Role: Subcontract PI
Description/Aims: The goal of this phase III trial is to compare the effect of preoxygenation with non-invasive positive pressure ventilation to preoxygenation with a facemask on the incidence of hypoxemia, among critically ill adults undergoing emergency tracheal intubation.
Award Number: pending
Funding Period: 02/01/22-09/30/22
Amount:
Time Commitment:6.967%
Agency Contact: Jennifer Trevino, Jennifer.Trevino@1stAmerican.com, 210.782.1319
Overlap: None

PREVIOUS SUPPORT

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: 11/01/2015-06/30/2018
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

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 lead the conduct of a 3,000 patient, 48-institution randomized controlled trial.
Funding Period: 05/01/2016-01/31/2019
Amount:
Time Commitment: 10%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Overlap: None

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 are 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: 07/01/2016-06/30/2018
Amount:
Time Commitment: 1%
Agency Contact: Tim Lockie, 720-848-6660, tim.lockie@cuanschutz.edu
Overlap: None

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:
Time Commitment: 10%
Agency Contact: Douglas Simpson, douglas.simpson@socom.mil
Overlap: None

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: 09/05/18-08/31/19
Amount:
Time Commitment: 10%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

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:
Time Commitment: 2%
Agency Contact: Amanda Bistran-Hall, 410-361-7999, abistra1@jhmi.edu
Overlap: None

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:
Time Commitment: 1%
Agency Contact: Vallerie Redd, 770-488-2845
Overlap: None

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: 07/30/18-07/29/21
Amount:
Time Commitment: 1.75%
Agency Contact: Clifford Johnson, 937-713-9922, Clifford.johnson.4@us.af.mil
Overlap: None

Title: *Innovative Methods to Evaluate the Role of Influenza Vaccines in Attenuating Severe Disease in 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 and other viral infections including COVID-19 in critical illness, define and sub-phenotype severe influenza disease, and quantify the effectiveness of influenza vaccines for mitigating influenza-associated morbidity and mortality.

Award Number: 75D30120R67837 (Self)
Funding Period: 03/27/20-06/30/21
Amount: (est, depending on enrollment)
Time Commitment: 1%
Agency Contact: Vallerie Redd, 770-488-2845
Overlap: None

Title: *Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease (ORCHID)*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator/Site-PI
Description/Aims: This project will be a randomized controlled trial to compare the safety and efficacy of hydroxychloroquine versus placebo in hospitalized patients with laboratory-confirmed COVID-19
Award Number: 5U01HL123009-06S1 (Thompson)
Funding Period: 04/15/20-04/14/21
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *CORAL: PETAL COVID-19 Observational Study*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Site-PI
Description/Aims: Observational study of hospitalized patients with COVID-19 using both retrospective and prospective methods.
Award Number: 5U01HL123009-06S2 (Thompson)
Funding Period: 04/24/20-04/23/21
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO)*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Site PI
Description/Aims: The goal of this study to determine the efficacy and safety of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.
Award Number: 1OT2HL156812 (Korley)
Funding Period: 06/01/20-05/31/21
Amount: SubAward (est, depending on enrollment)
Time Commitment: 1%
Agency Contact: Maria Mendoza-Puccini, 301-496-9135, maria.mendoza.puccini@nih.gov
Overlap: None

Title: *Passive Immunity for Our Nation (PassItOn)*
Funding Agency: National Center for Advancing Translational Sciences (NCATS)

Role: Site PI
Description/Aims: The goal of this phase III trial is to compare the efficacy and safety of convalescent plasma versus placebo among adults hospitalized with COVID-19.
Award Number: 3UL1TR002243-04S3 (Bernard)
Funding Period: 08/18/20-08/31/21
Amount: (est, depending on enrollment)
Time Commitment: 1%
Agency Contact: Rashmi Gopal-Srivastava, gopalr@mail.nih.gov
Overlap: None

PENDING
None

OVERLAP
None

- **What other organizations were involved as partners?**
- Oregon Health and Sciences University
- San Antonio Military Medical Center
- Denver Health Medical Center
- University of Cincinnati
- University of Texas- Houston
- Vanderbilt University Medical Center
- University of Alabama-Birmingham
- University of Pittsburgh Medical Center

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:**

  Nothing to Report
- **QUAD CHARTS:**

  Attached

9. **APPENDICES:**

1. Methods Abstract: Submitted and approved for verbal presentation at SOMSA 2021 (PDF of PowerPoint attached)

2. 2021 Preliminary Results Abstract: Submitted and approved for poster presentation at MHSRS 2021 (Poster attached)

3. TBI vs Non-TBI Abstract: Submitted for SOMSA 2022, approval pending
4. 2022 Preliminary Results Abstract: Submitted for MHSRS 2022, approval pending
5. Study Protocol and SAP Abstract: Published in *Trials* 2021 Nov 8
6. Recent data reports provided to launched sites

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Critically Ill Trauma Patients: A Multicenter Clinical Trial to Define Oxygen Requirements for Combat Casualty Care

David J. Douin, MD[1]; Erin L. Anderson, RN[1]; MAJ Steven G. Schauer, DO, MS[3]; John Rice, PhD[2]; Layne Dylla, MD, PhD[1]; Conner Jackson, MS[2]; Alex Cheng, PhD[5]; Col Vikhyat S. Bebarta, MD[1,4,6]; Adit A. Ginde, MD, MPH[1,6]

[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
[5] Vanderbilt University Medical Center, Nashville, TN
[6] Center for COMBAT Research, University of Colorado School of Medicine, Aurora, CO

Background: Recent evidence supports targeting normoxia (SpO2 90-96% or PaO2 60-100mmHg) to avoid hyperoxia. Our objective is to determine the feasibility, safety, and effectiveness of targeted normoxia to conserve oxygen and improve clinical outcomes in critically injured patients.

Methods: This prospective multicenter clinical trial will enroll critically ill trauma patients at eight level 1 trauma centers in the United States (NCT04534959). We will follow patients from emergency department through hospital discharge or to day 90 - whichever comes first. Each hospital will contribute pre-implementation (control) and post-implementation (intervention) data. The start of the intervention period will be defined by randomized timing in a stepped wedge cluster randomized controlled trial design. All sites will begin in the control phase with usual care. When sites reach their randomly assigned time to transition, there will be a one-month training period, which does not contribute to data collection. Following the one-month training period, the site will remain in the intervention phase for the duration of the trial. The primary outcome is supplemental oxygen free days, defined as number of days alive and not on supplemental oxygen.

Results: The Colorado Multiple Institutional Review Board, the Single IRB for this trial, approved with a determination of minimal risk. This was subsequently approved by the Human Research Protections Office with the same determination. Vanderbilt University is serving as the data coordinating center. As of November 30, 2020, one site has transitioned into the intervention phase. The next site transition will occur on January 15, 2021. Preliminary results will be available for the 2021 SOMA conference.

Discussion/Conclusions: We hypothesize targeted normoxia will safely reduce the need for concentrated oxygen. These data will inform military stakeholders on oxygen requirements for critically injured warfighters, while reducing logistical burden in prolonged combat casualty care.

Disclosures: Funded by Joint Warfighter Medical Research Program (JWMRP) W81XWH-20-2-0001. 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.

Abstract Word Count: 293

Strategy to Avoid Excessive Oxygen in Critically Ill Trauma Patients

A Multicenter Clinical Trial to Define Oxygen Requirements for Combat Casualty Care

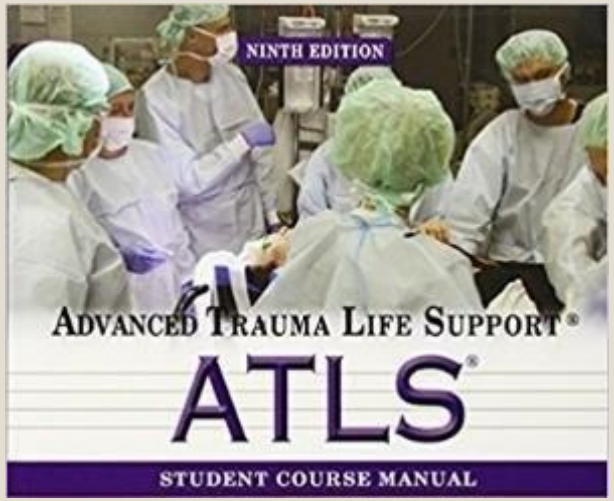
Presenter: David J. Douin, MD

Co-Authors: Erin L. Anderson, RN, MAJ Steven G. Schauer, DO, MS, John Rice, PhD, Layne Dylla, MD, PhD, Conner Jackson, MS, Alex Chang, PhD, Col Vikhyat S. Bebarta, MD, Adit A. Ginde, MD, MPH

Disclosures

- Authors have no conflicts of interest to report
- The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office
- Funding for SAVE-O2:
  - *Joint Warfighter Medical Research Program (JWMRP)*
- This work was supported by the Assistant Secretary of Defense for Health Affairs, through the Joint Warfighter Medical Research Program, under Award No. (W81XWH-20-2-0001). Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.
- Funding for Preliminary Work:
  - *DoD / US Special Operations Command W81XWH-17-C-0241*

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 is key to avoid morbidity from hypoxia

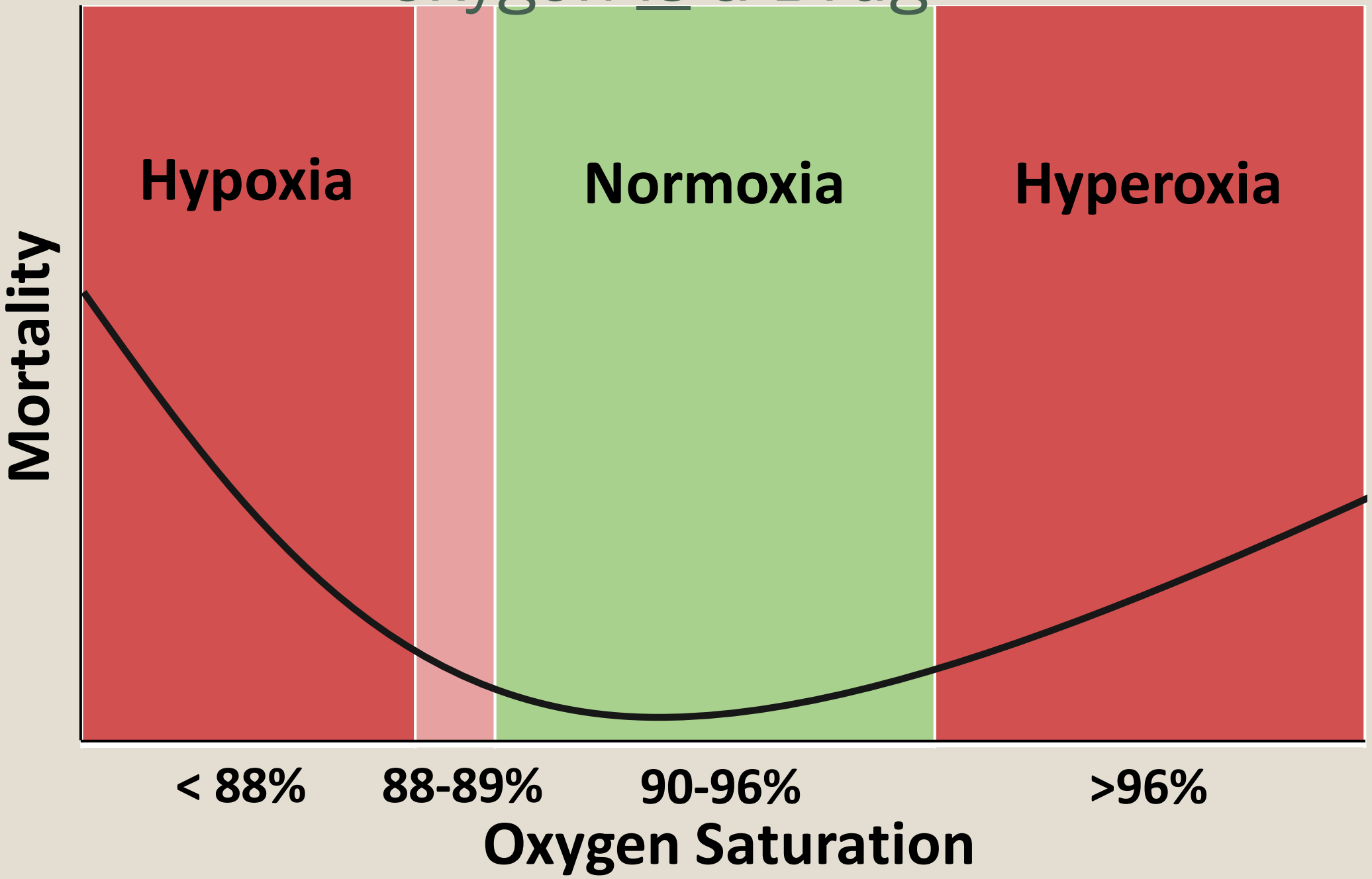
- Excessive oxygen in En-Route Care
  - *Common Practice*
  - *May cause harm*
  - *Increases mission weight, logistics/power; safety issues*

- Knowledge Gap: Limited data on optimal oxygen titration targets in critically injured pts

Rationale for Normoxia

Hypoxia	Hyperoxia
Anaerobic Metabolism	Vasoconstriction
Cell Death (necrosis)	Oxidative Stress
Brain = 20% O2 Consumption	Pro-Inflammatory
	Decreased Mucociliary Clearance in Lung

Oxygen is a Drug



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*

43 studies → 17 trauma & 26 non-trauma critical illness

Of 17 Trauma, 14 related exclusively to TBI

Association found between both hypoxia and hyperoxia with worse clinical outcomes suggesting normoxia is optimal

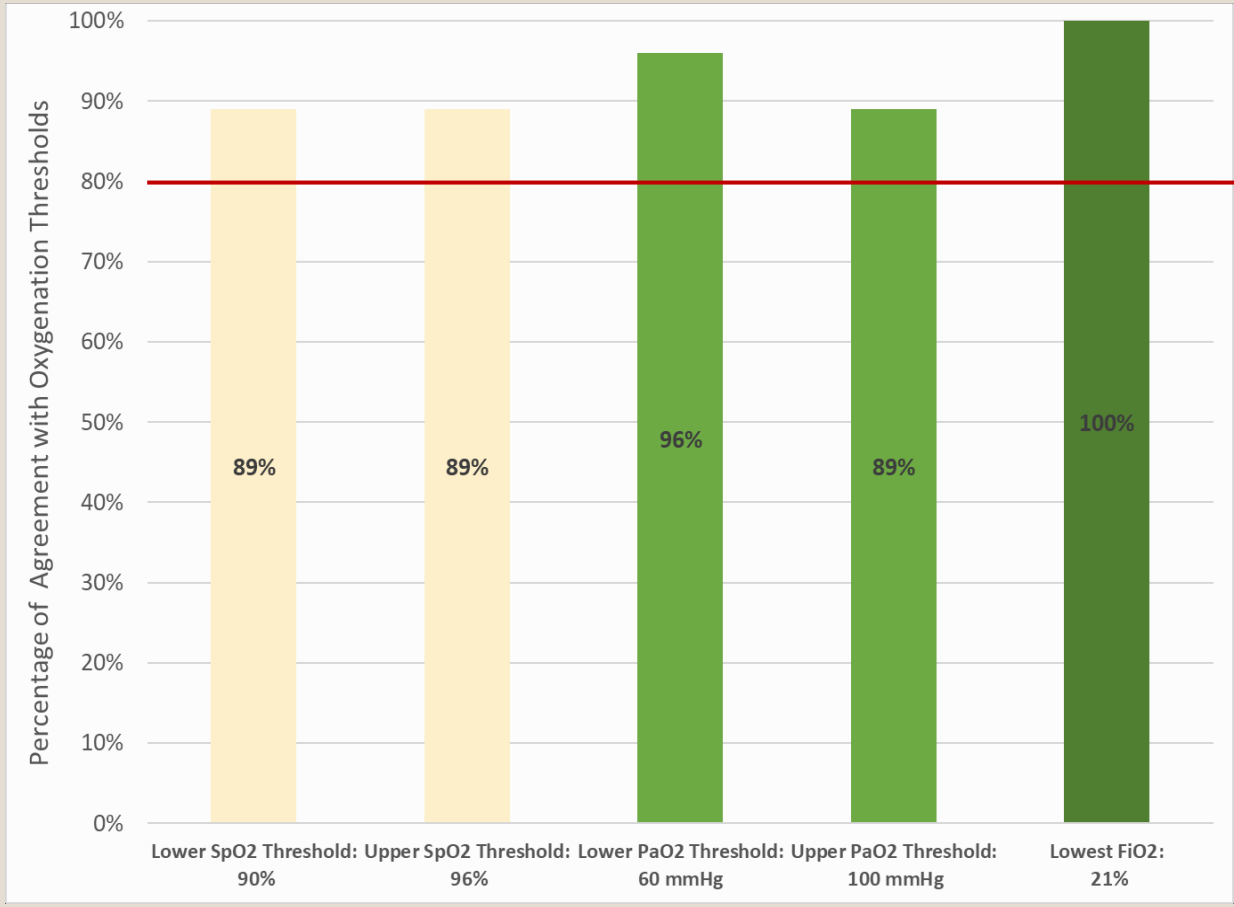
Supported needed for further Trauma-Specific Studies (particularly beyond TBI)

J Trauma Acute Care Surg, 2019

Delphi Consensus

- Support from 31 military and civilian experts for a <u>targeted normoxia strategy</u>

- Consensus Normoxia Definition:
  - SpO_2 90-96%
  - PaO_2 60-100mmHg



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

Multicenter Retrospective Observational Cohort

Critically Injured Patients (ICD Coding)

October 2015 – June 2018

Exposure: Oxygen Exposure during First 7 Days of Hospitalization

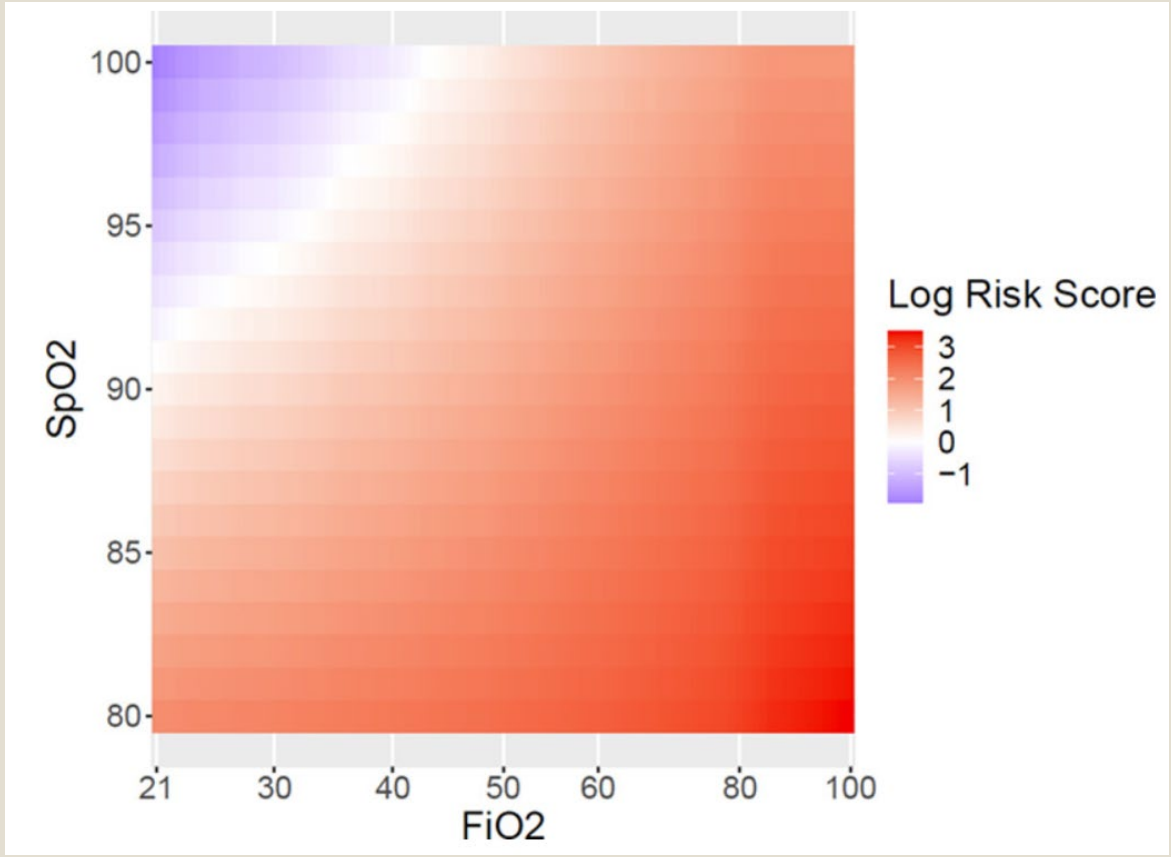
Primary Outcome: In-Hospital Mortality

Douin et al, Critical Care Explorations 2021

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

Hyperoxia (SpO_2>96%) present ~half of the time during first 7 days

During hyperoxia, greater FiO_2 associated with greater mortality risk



Douin et al, Critical Care Explorations 2021

A quasi-experimental study of targeted normoxia in critically ill trauma patients

Dylla, Layne MD, PhD[1]; Anderson, Erin L. RN[1]; Douin, David J. MD[2]; Jackson, Conner L. MS[3]; Rice, John D. PhD[3]; Schauer, MAJ Steven G. DO, MS[4,5,6]; Neumann, Robert T. MD[1]; Bebarta, Col Vikhyat S. MD[1,5,8]; Wright, Franklin L. MD[7]; Ginde, Adit A. MD, MPH[1,8] **Author Information**

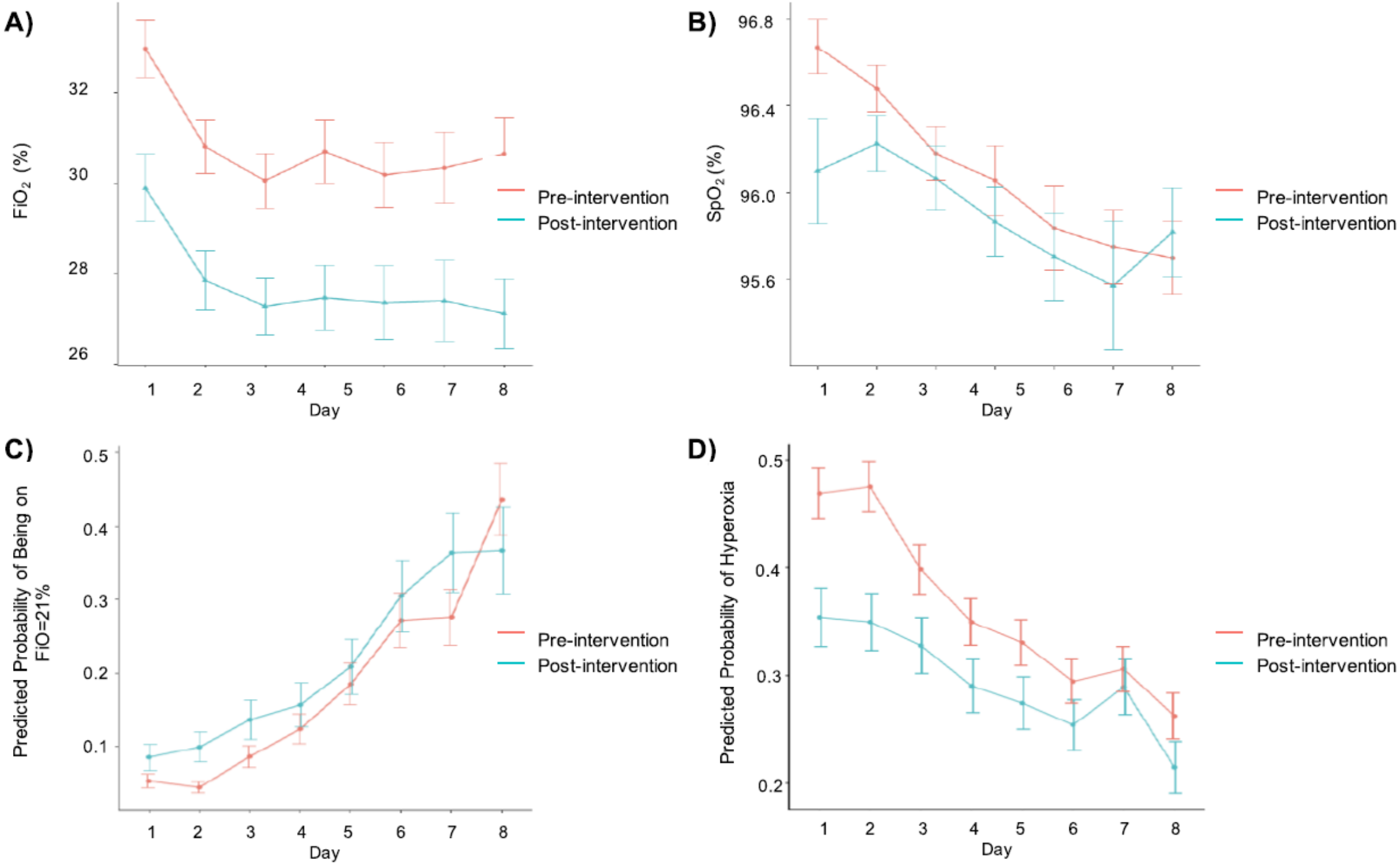
Design: Pre/Post Observational Pilot Study
12 Months "Pre" and 6 Months "Post" Implementation

Target: SpO_2 90-96% or PaO_2 60-100mmHg

Cohort: Adult Patients with Acute Injury requiring ICU Admission

Setting: University of Colorado Hospital

Dylla et al, J Trauma Acute Care Surg, 2021


A)
FiO_2 (%)
32
30
28
26
1 2 3 4 5 6 7 8
Day
Pre-intervention
Post-intervention
B)
SpO_2 (%)
96.8
96.4
96.0
95.6
1 2 3 4 5 6 7 8
Day
Pre-intervention
Post-intervention
C)
Predicted Probability of Being on FiO=21%
0.5
0.4
0.3
0.2
0.1
1 2 3 4 5 6 7 8
Day
Pre-intervention
Post-intervention
D)
Predicted Probability of Hyperoxia
0.5
0.4
0.3
0.2
1 2 3 4 5 6 7 8
Day
Pre-intervention
Post-intervention

Conclusions

Hyperoxia remains common in Critically Ill Trauma Patients

Changing practice in the ICU is difficult

Feasible to:

Significantly reduce Oxygen Consumption
Significantly increase time in Normoxia

No Increase in Hypoxia

Mortality, VFD, HFR → all similar in pre- and post- groups

Future Directions: Multicenter Interventional Trial…

Dylla et al, J Trauma Acute Care Surg, 2021

Strategy to Avoid Excessive Oxygen in Critically Ill Trauma Patients

NCT#04534959

SAVE-O2

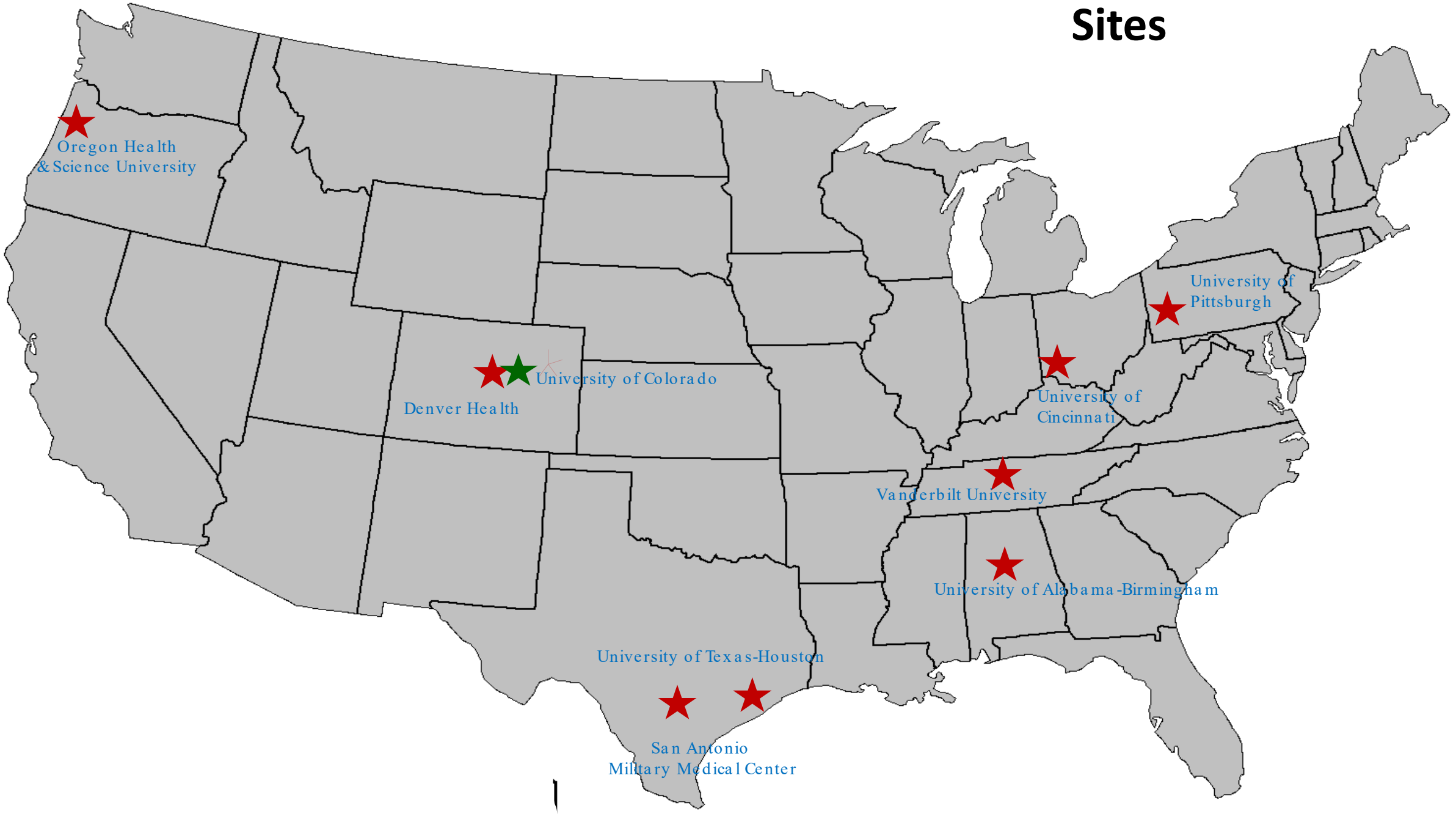
More oxygen isn’t always better

Objective: determine feasibility, safety & effectiveness of targeted normoxia to conserve oxygen and improve clinical outcomes in critically injured patients

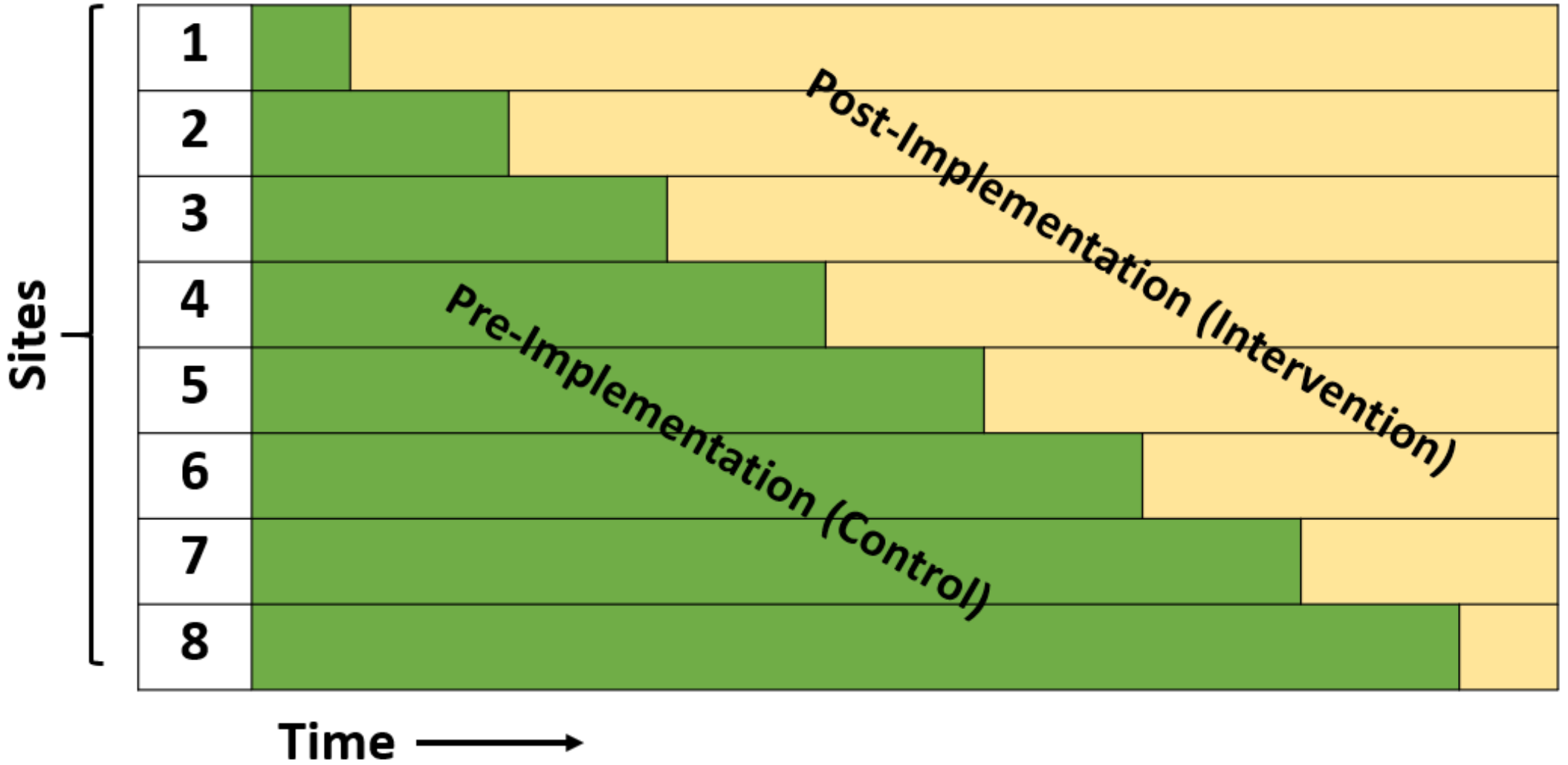
Design: Cluster Randomized, Stepped Wedge Implementation Trial

Human Subjects Issues: Minimal Risk, Waiver of Informed Consent (efficient & saves costs)

Sites


Oregon Health
& Science University
University of Colorado
Denver Health
University of
Pittsburgh
University of
Cincinnati
Vanderbilt University
University of Alabama-Birmingham
University of Texas-Houston
San Antonio
Military Medical Center

Stepped Wedge Cluster Randomized Trial



Inclusion

- Acutely injured patients & meet criteria for entry into national trauma registry
- Admission to Surgical/Trauma ICU within 24 hours of hospital arrival*

Exclusion

- Age <18 years
- Prisoners
- Pregnancy
- Transferred patients (Not admitted through the ED)

****All* patients on the unit will be included in the intervention, Inclusion/Exclusion criteria will be evaluated during data analysis**

Implementation in the ED & ICU

Oxygen Titration Goals

- SpO_2: 90-96%
- PaO_2: 60-100mmHg

*Patients will be followed from ED to Hospital Discharge or Day 90 (whichever comes first)

What if Patient is Hyperoxic?

SpO_2>96% or PaO_2>100mmHg

1) Down-Titrate FiO_2 or O_2 Flow Rate w/in ONE HOUR of identifying Hyperoxia
2) Intervention non-binding → can be overridden by clinician when in best interest of patient
3) Requires collaboration between RN, RT, MD and research team to maintain normoxia

SAVE-O2: Multicenter Normoxia RCT

Hypothesis: Targeted normoxia will limit exposure to hyperoxia and safely reduce the use of concentrated oxygen

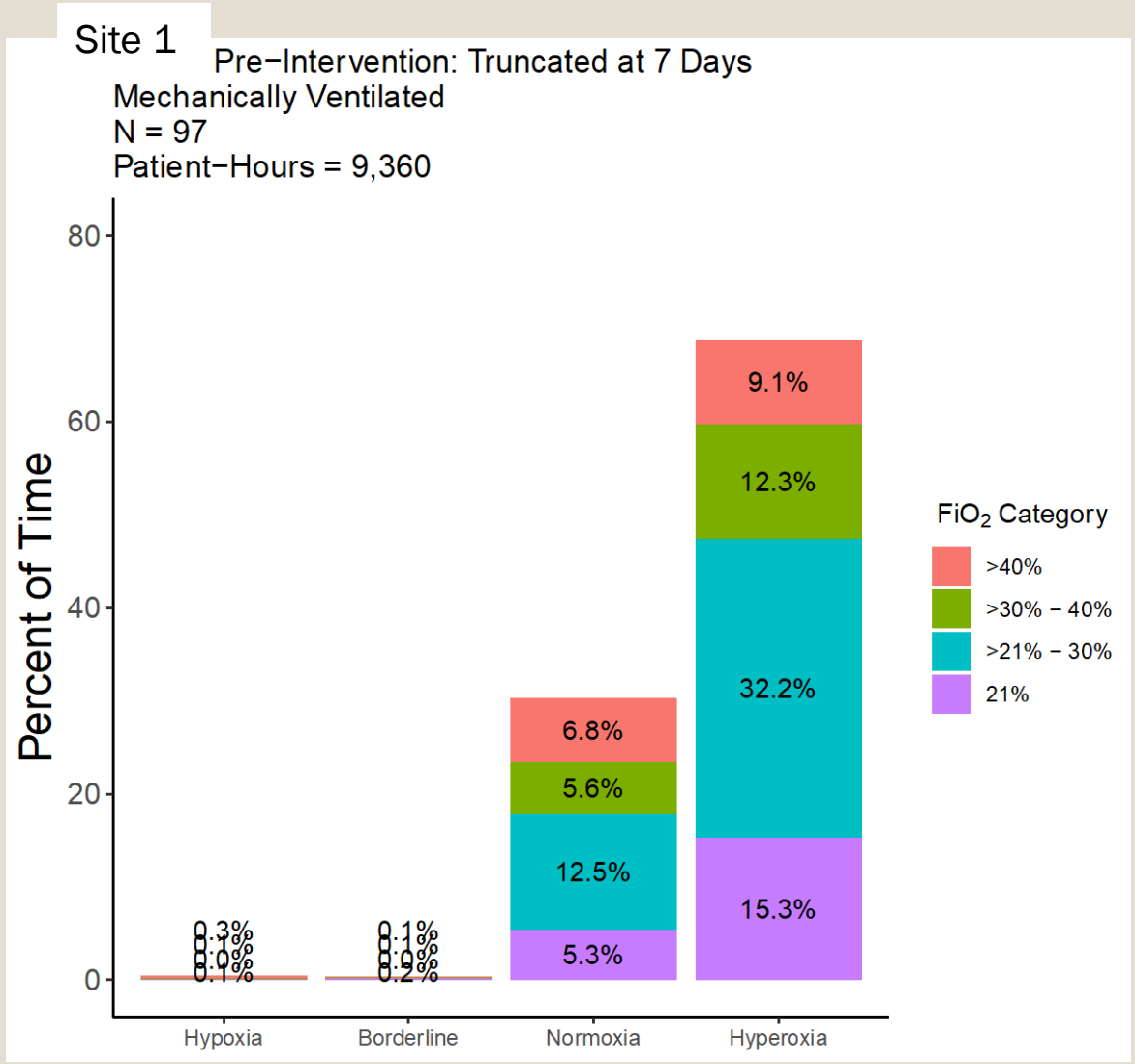
Primary Endpoint: Supplemental Oxygen Free Days (SOFD) to day 28

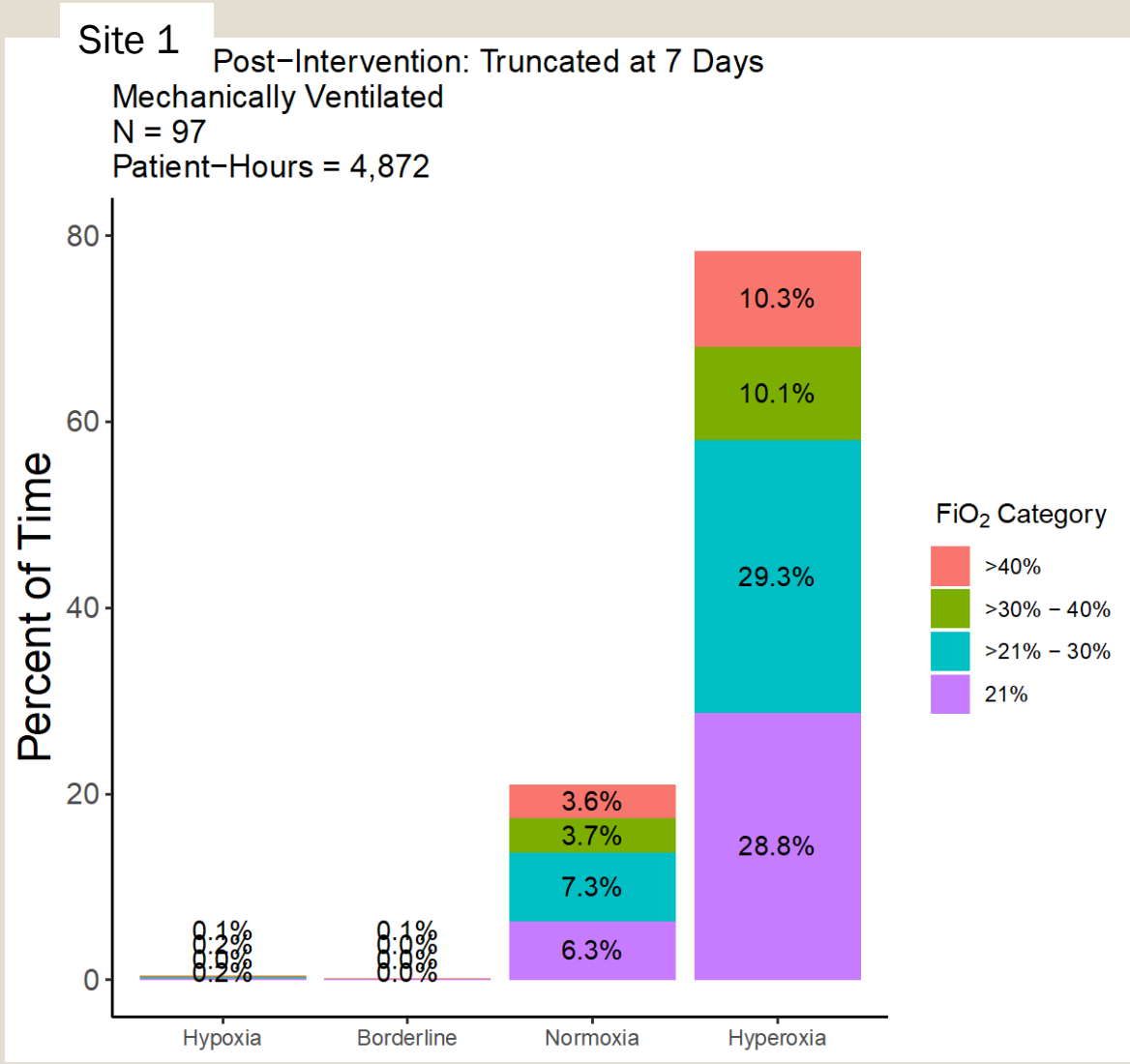
number of days alive and not on supplemental O_2

Trial Enrollment Numbers
(Enrollment through June 2021)

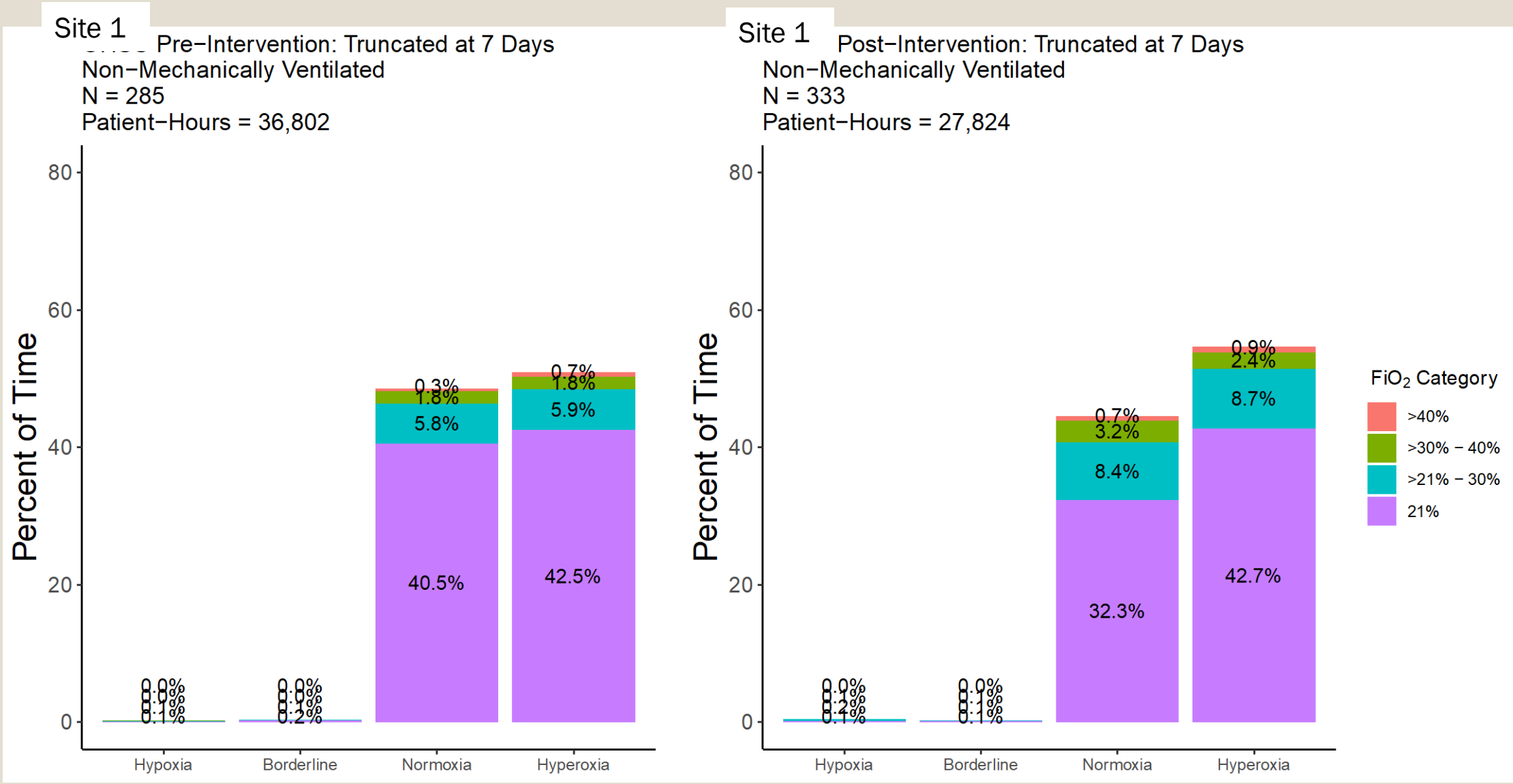
Trial Enrollment	N	Pre	Post
Total Enrollment	2937	1903	1034
Site 1	1204	487	717
Site 2	881	588	293
Site 3	852	828	24

Pre-Intervention/Post-Intervention: Mechanically Ventilated: Site 1



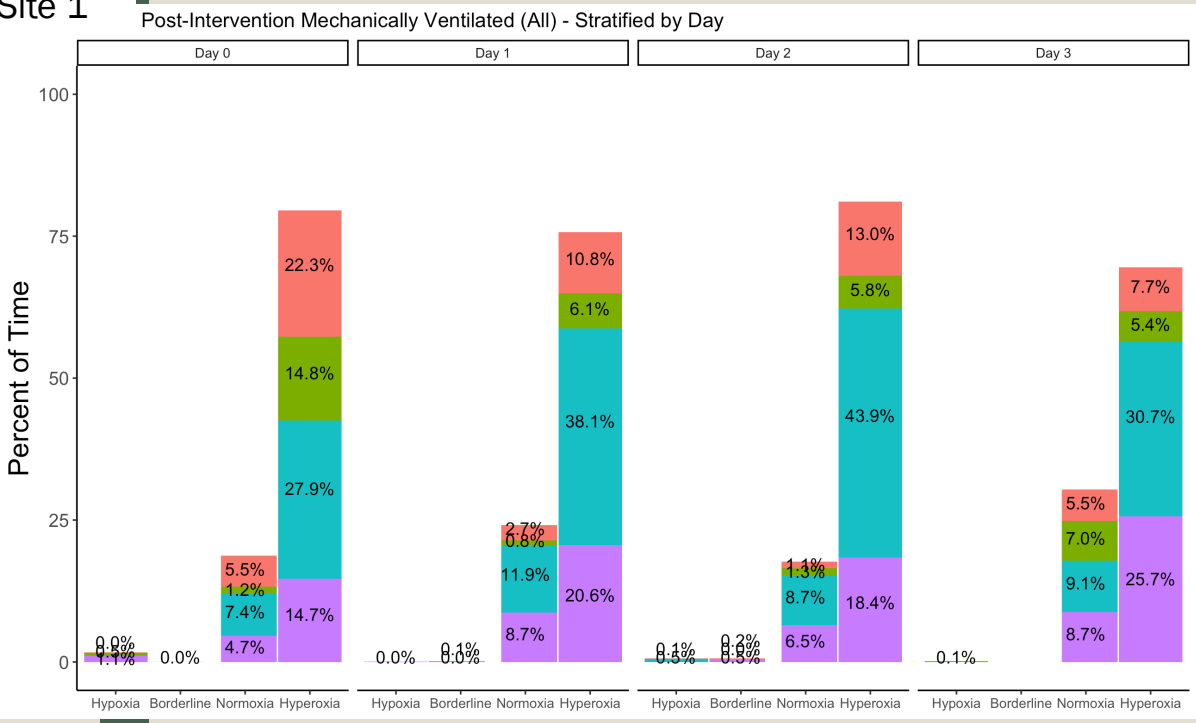


Pre-Intervention/Post-Intervention: Non-Mechanically Ventilated: Site 1

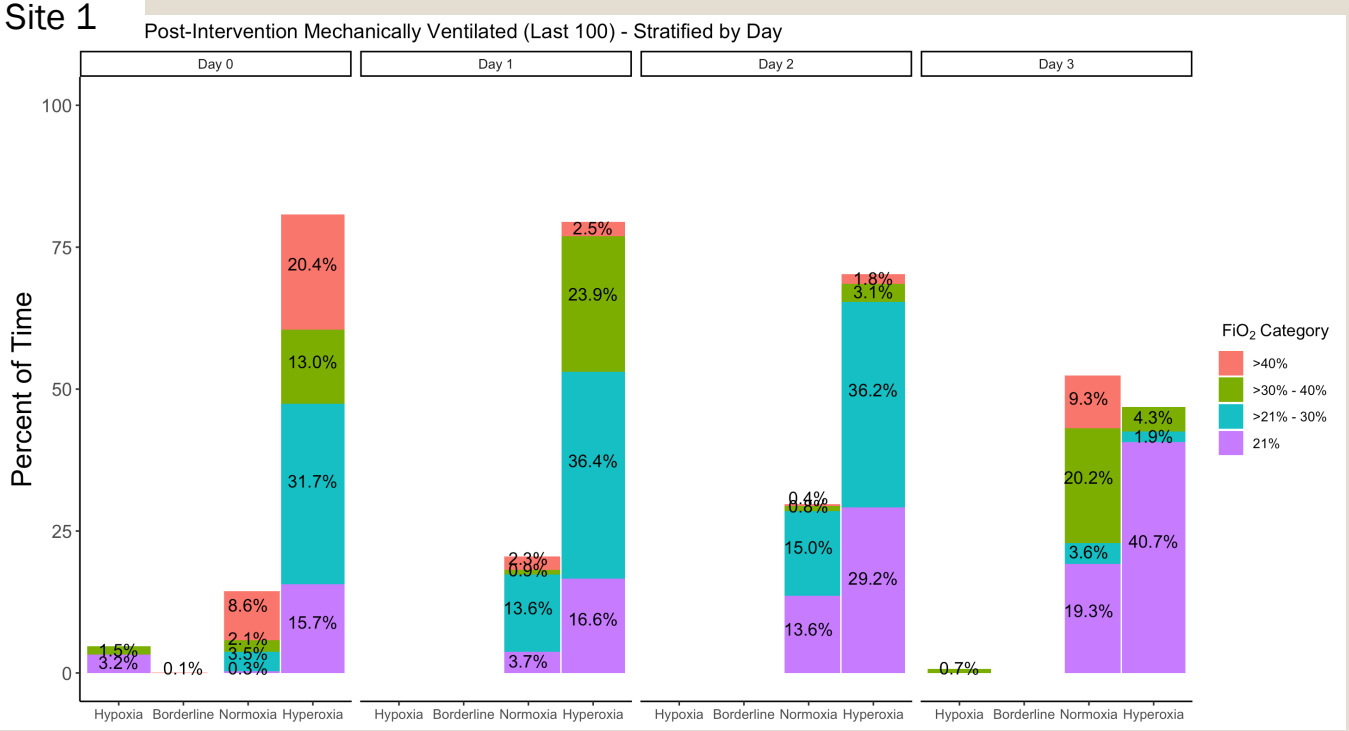


Post-Intervention Stratified by Day (all / last 100, MV only): Site 1

Site 1

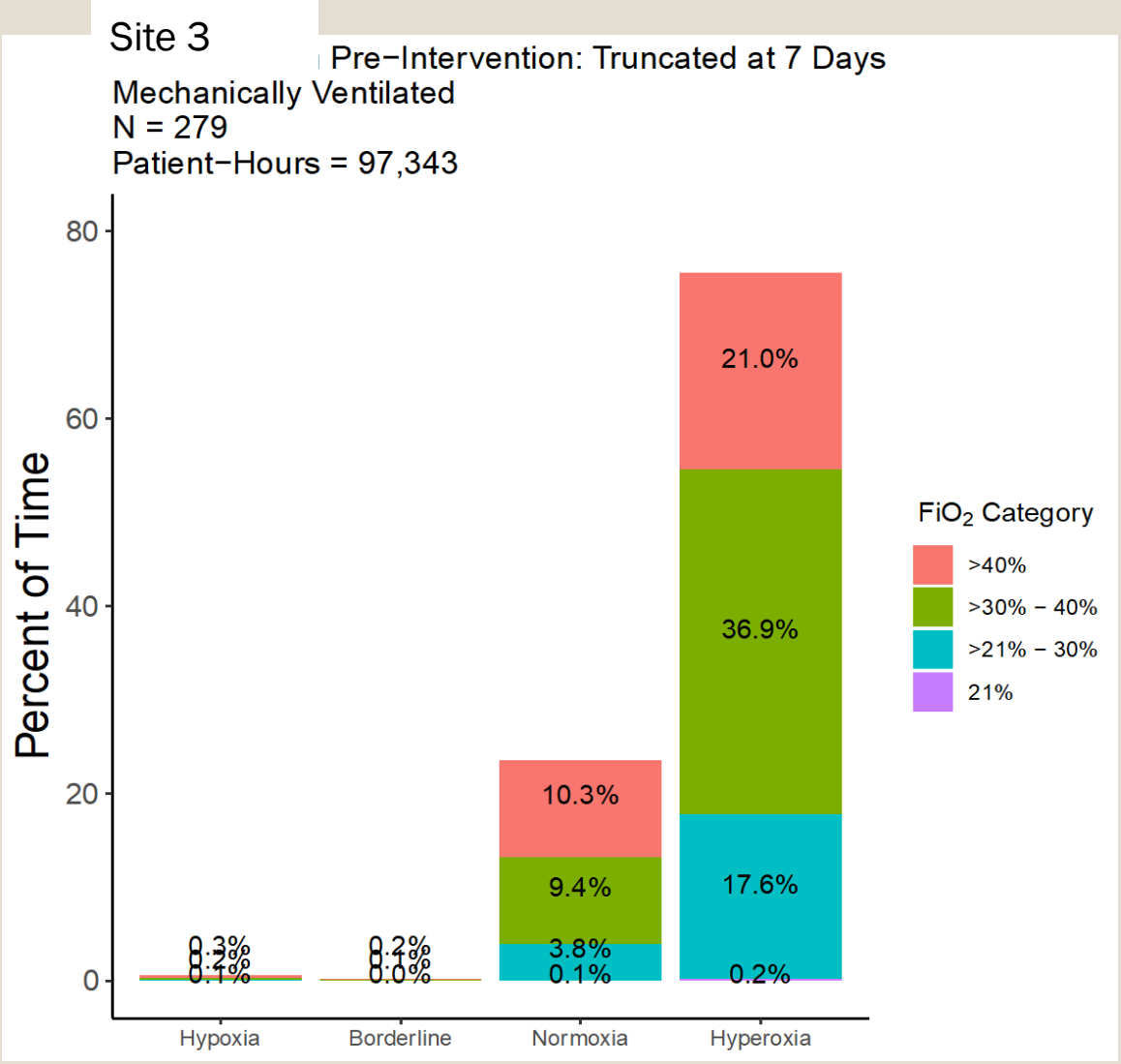


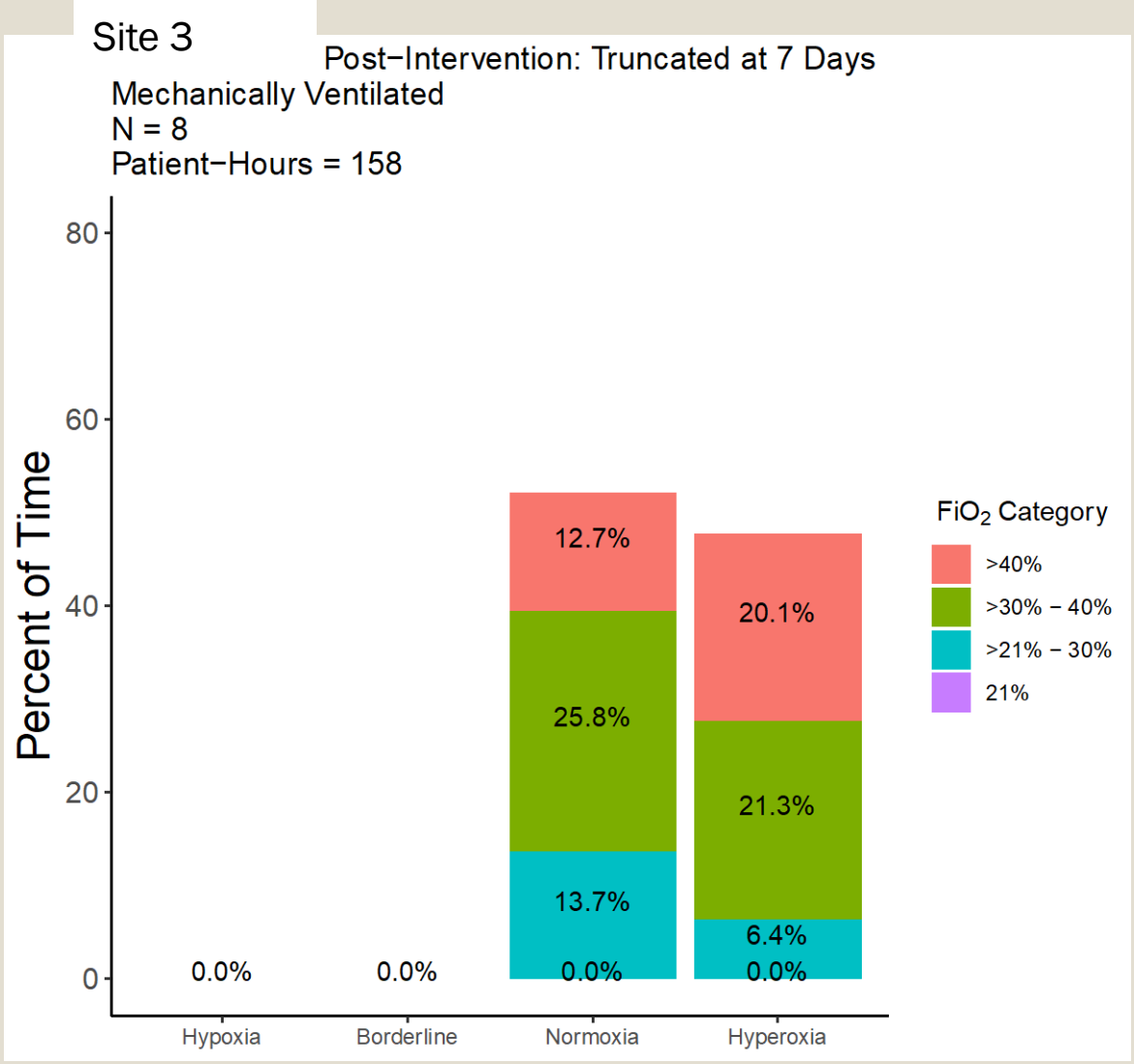
Site 1



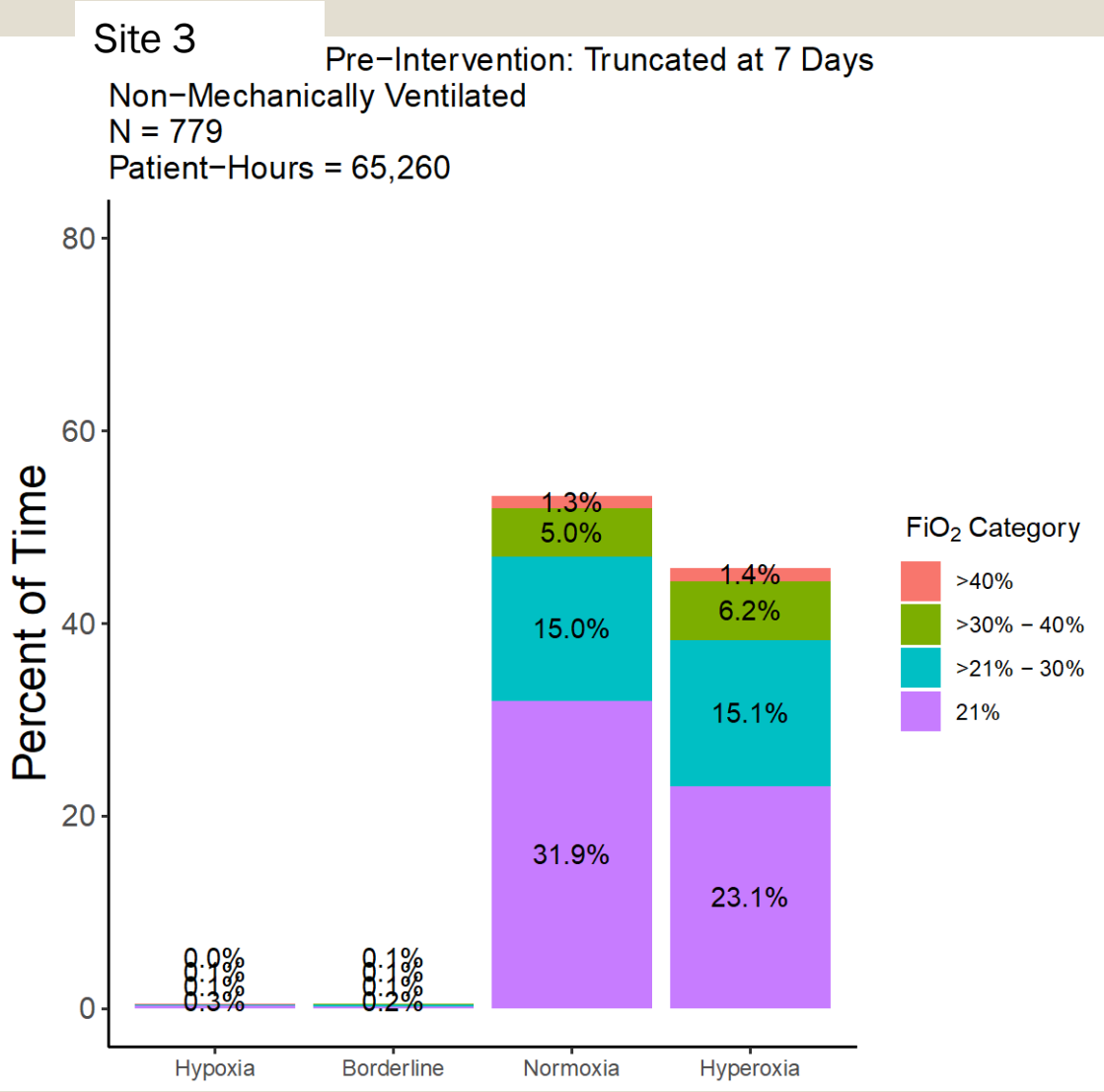
*Please note: ‘N value’ refers to the number of patients that contribute to the graph (ex: mechanically ventilated at any time, N=48) and not the total number of patients in each group. The “patient hours” value refers to the total number of patient hours for all patients in each group.

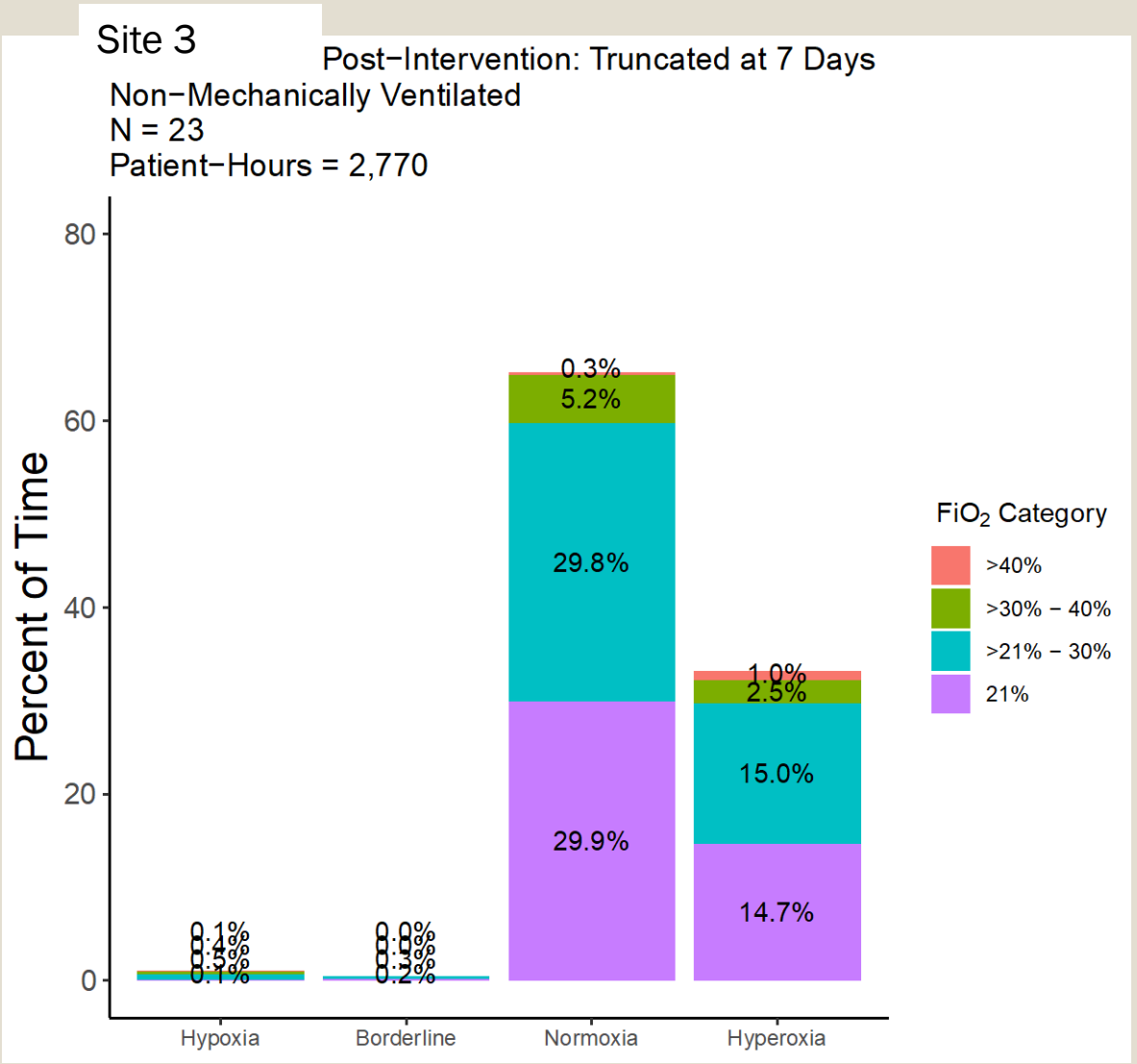
Pre-intervention/Post-intervention: Mechanically Ventilated: Site 3





Pre-intervention/Post-intervention: Non-Mechanically Ventilated: Site 3





Conclusion

- Trial is ongoing, due to complete in late 2022

Questions?

David J. Douin, MD

david.douin@cuanschutz.edu

Principal Investigator

Adit Ginde, MD, MPH

adit.ginde@cuanschutz.edu

Project Manager

Erin Anderson, RN

erin.l.anderson@cuanschutz.edu

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Critically Ill Trauma Patients: A Multicenter Cluster Randomized, Stepped Wedge Trial for Targeted Normoxia

Layne Dylla, MD, PhD[1]; David J. Douin, MD[1]; Erin L. Anderson, RN[1]; MAJ Steven G. Schauer, DO, MS[2,3]; John D. Rice, PhD[4]; Conner Jackson, MS[4]; Alex Cheng, PhD[5]; Martin A. Schreiber, MD[6]; Col Vikhyat S. Bebarta, MD[1,3,7]; Adit A. Ginde, MD, MPH[1]

[1] University of Colorado School of Medicine, Aurora, CO
[2] US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX
[3] US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA Lackland, TX
[4] Colorado School of Public Health, Aurora, CO
[5] Vanderbilt University Medical Center, Nashville, TN
[6] Oregon Health and Sciences University, Portland, OR
[7] Center for COMBAT Research, University of Colorado School of Medicine, Aurora, CO

Background: Prevention of hypoxia is critical to avoid secondary injury in critically ill trauma patients and often results in widespread supplemental oxygen use. Many patients are exposed to supraphysiological levels of oxygen, “hyperoxia”, which is also associated with increased mortality. The ability to safely conserve supplemental oxygen has many implications in terms of logistics, weight, and power requirements in combat casualty care and prolonged field care settings. Our objective is to determine the feasibility, safety, and effectiveness of targeting normoxia (pulse oximetry (SpO_2) of 90-96%) to conserve oxygen and improve clinical outcomes in critically ill patients.

Methods: This is a multicenter cluster randomized, stepped wedge implementation trial to determine the effectiveness of a multimodal intervention to target normoxia in critically ill trauma patients (NCT04534959). Eight Level 1 US trauma centers are randomized to cross over from a control pre-implementation phase (“control” - usual care) to the post-implementation (“intervention”) phase at three-month intervals in randomized order. During the one-month run-in phase for the intervention, we use a multimodal intervention tailored to each sight that includes multiple educational activities, electronic health record best practice alerts, recurring feedback regarding patient time in various oxygenation categories with and without supplemental oxygen, and/or protocols to down-titrate supplemental oxygen in hyperoxic patients (SpO_2>96% and on supplemental oxygen). Within a site, adults (aged 18 years or older), who meet criteria for inclusion into a state or national trauma registry and are admitted to a surgical or trauma intensive care unit (ICU) within 24 hours of arrival to a participating hospital are included in analysis. Prisoners and women with a known pregnancy are excluded. The primary outcome is supplemental-oxygen-free days, defined as the number of days a patient is alive and not on supplemental oxygen from time of presentation to day 28, with death assigned a value of -1. Additional secondary outcomes included ventilator-free days, hospital-free days, in-hospital mortality, and time to mortality. As of March 2021, one site has contributed preliminary data from both the pre- and post-implementation phase for review.

Results: Preliminary data from the first site to undergo cross-over to the post-implementation phase is complete; updated data will be provided at the time of presentation. The pre-implementation phase consisted of 311 patients, contributing 71,046 patient-hours of data. Pre-implementation patients had an average age of 55 years and were 28% female, 8% Hispanic, 4% non-Hispanic Black, 73% non-Hispanic White, and 14% other. The post-implementation phase consisted of 301 patients, contributing 44,470 patient-hours of data to date. Patients in the post-implementation population had an average age of 58 years and were 30% female, 6% Hispanic, 2% non-Hispanic Black, 70% non-Hispanic White, and 14% other.

Overall, there was a slight increase in the proportion of patient-time spent normoxic (SpO_2 90-96%) (32.5% pre-implementation and 37.8% post-implementation). Among patients who were hyperoxic (SpO_2>96%), there was an increase in the proportion of patient-time spent on supplemental oxygen (12.4% pre-implementation, 17.3% post-implementation). There was a similar proportion of patient-time spent hypoxic (SpO_2<88%) (0.2% pre-implementation, 0.3% post-implementation).

In non-mechanically ventilated patients, there was an increase in the proportion of patient-time spent normoxic (34.2% pre-implementation vs 40.5% post-implementation). However, among patients who were hyperoxic, there was an increase in the proportion of patient-time on supplemental oxygen (7.8% pre-implementation, 12.4% post-implementation). Again, there was a slight increase in the proportion of patient-time spent hypoxic (0.2% pre-implementation, 0.5% post-implementation).

In mechanically ventilated patients, there was a decrease in the proportion of patient-time spent normoxic (26.5% pre-implementation, 21.3% post-implementation), but also a reduction in supplemental oxygen use in this sub-group (23.6% pre-implementation, 14.2% post-implementation). Among those who were hyperoxic, there was also a reduction in supplemental oxygen use (60.3% pre-implementation, 46.6% post-implementation). This was also true of those patients found to be hyperoxic on high levels of FiO_2 (>40%) (9.1% pre-implementation, 8.2% post-implementation) and on moderate levels of FiO_2 (>30-40%) (19.6% pre-implementation, 11.1% post-implementation). Finally, there was a reduction in the proportion of patient-time spent hypoxic (0.3% pre-implementation, 0.1% post-implementation). Given that these are preliminary results, no assessment of statistical significance was made. Rather, trends are used to inform further multimodal interventions.

Conclusions: Preliminary data from the first site randomized to cross-over to the post-implementation phase of SAVE-O2 suggests that a multimodal intervention to target normoxia in critically ill trauma patients can increase the proportion of patient-time spent in normoxia. In non-mechanically ventilated patients, the total patient-time spent hyperoxic and on supplemental oxygen is minimal and close to our target of <10% total patient-time spent hyperoxic and on supplemental oxygen. The greatest improvement in oxygenation practices appears to be in mechanically ventilated patients where we reduced the amount the proportion of patient-time spent hyperoxic and on supplemental oxygen from 60.3% patient-time to 46.6% patient-time post-implementation. While doing

so, we did not observe a clinically significant difference in the proportion of patient-time spent in hypoxia overall. More attention is needed for mechanically ventilated patients who are hyperoxic to reduce supplemental oxygen use. We hypothesize that the final results will demonstrate that this intervention will reduce supplemental oxygen use, improve time spent in normoxia, and improve patient outcomes (with a primary endpoint: supplemental oxygen free days). This has many important implications for reduced supplemental oxygen use in the combat setting, including potentially reducing the amount of supplement oxygen required in remote and prolonged field care settings.

Disclosure: Funded by Joint Warfighter Medical Research Program (JWMRP) W81XWH-20-2-0001. 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.

Learning Objectives:
1. Describe the multimodal approach used by the SAVE-O2 trial to improve compliance with targeted normoxia
2. Analyze the preliminary data for the SAVE-02 trauma trial.
3. Discuss the potential implications of targeted normoxia in civilian and military critically ill trauma

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Critically Ill Trauma Patients: A Multicenter Cluster Randomized, Stepped Wedge Trial for Targeted Normoxia

Department of Emergency Medicine
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

Layne Dylla, MD, PhD[1]; David J. Douin, MD[1]; Erin L. Anderson, RN[1]; MAJ Steven G. Schauer, DO, MS[2,3,4]; John D. Rice, PhD[5]; Conner Jackson, MS[5]; Alex Cheng, PhD[6]; Martin A. Schreiber, MD[7]; Col Vikhyat S. Bebarta, MD[1,3,8]; Adit A. Ginde, MD, MPH[1]

[1] University of Colorado School of Medicine; [2] US Army Institute of Surgical Research, JBSA Fort Sam; [3] Brooke Army Medical Center, JBSA Fort Sam; [4] Uniformed Services University of the Health Sciences; [5] Colorado School of Public Health; [6] Vanderbilt University Medical Center; [7] Oregon Health and Sciences University; [8] Center for COMBAT Research, University of Colorado School of Medicine

WHAT WE LEARNED

Preliminary data suggests a multimodal intervention to target normoxia in critically ill trauma patients can increase the proportion of patient-time spent in normoxia

BACKGROUND

- Prevention of hypoxia in critically ill trauma patients results in widespread supplemental oxygen use
- Hypoxia and hyperoxia are associated with increased mortality
- Ability to safely conserve supplemental oxygen has implications for logistics, weight, and power requirements in combat

OBJECTIVE

- To determine the feasibility, safety, and effectiveness of targeting normoxia (pulse oximetry (SpO_2) of 90-96%) to conserve oxygen and improve clinical outcomes in critically ill patients

METHODS

- Multicenter cluster randomized, stepped wedge implementation trial (NCT04534959) (Figure 1)
- Multimodal Intervention – educational activities, electronic health record best practice alerts, recurring feedback, protocols to down-titrate supplemental O_2
- Analyze data from: adults (≥18yo), included in state/national trauma registry, admitted to ICU w/in 24hours arrival
  - Exclude: prisoners, known pregnancy
- Primary outcome: supplemental O_2 free days
- Secondary outcomes: ventilator-free days, hospital-free days, in-hospital mortality, time to mortality

RESULTS

- Overall, there was:
  - a slight increase in the proportion patient-time spent normoxic (32.5% pre vs 37.8% post) (Figure 2)
  - a similar proportion of patient-time spent hypoxic (0.2% pre vs 0.3% post) (Figure 2)

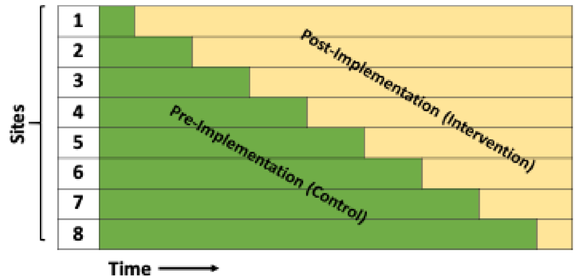


Figure 1: Cluster randomized stepped-wedge implementation design. Eight Level 1 trauma centers randomized at 3-month intervals to cross over from pre- to post-implementation phase with a 1-month run-in period

Table 1: Subject Demographics	Pre-Implementation (n=311)	Post-Implementation (n=301)
Age (years)– Mean (SD)	55.4 (21.5)	57.6 (21.9)
Female - n, (%)	137 (28.1%)	123 (29.7%)
Race/Ethnicity		
Hispanic	38 (7.8%)	24 (5.8%)
Non-Hispanic Black	18 (3.7%)	8 (1.9%)
Non-Hispanic White	356 (73.1%)	289 (69.8%)
Other	66 (13.6%)	59 (14.3%)

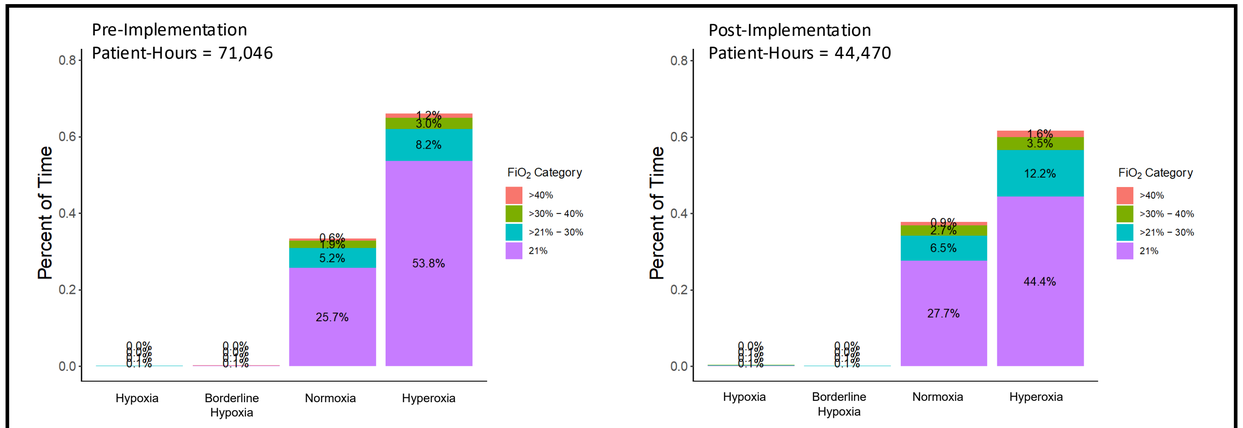


Figure 2: Pre- and Post-Implementation Patient-Time by Oxygenation Category (Hypoxia (SpO_2 <88%), Borderline Hypoxia (SpO_2 88-89%), Normoxia (SpO_2 90-96%), Hyperoxia (SpO_2 >96%) and FIO_2 Category

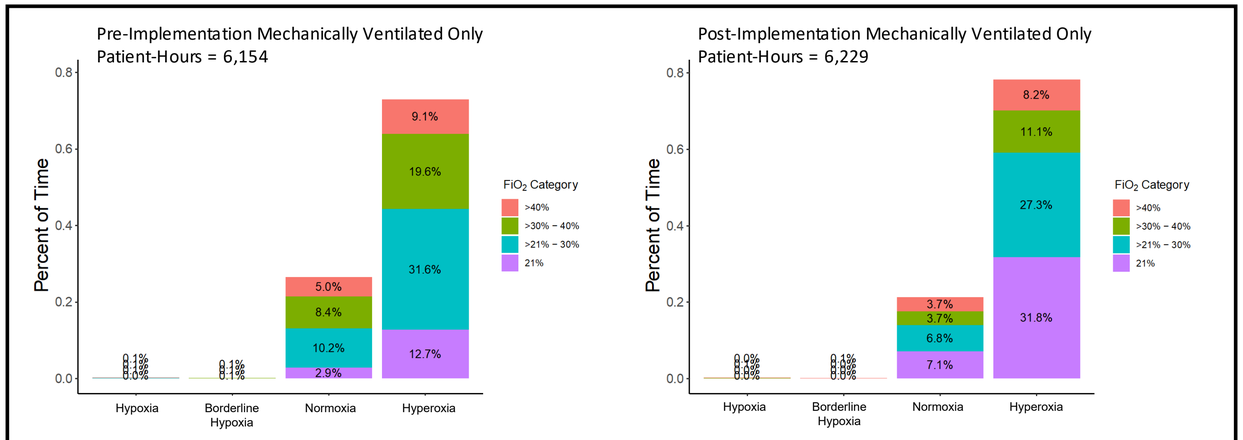


Figure 3: Mechanically Ventilated Pre- and Post-Implementation Patient-Time by Oxygenation Category (Hypoxia (SpO_2 <88%), Borderline Hypoxia (SpO_2 88-89%), Normoxia (SpO_2 90-96%), Hyperoxia (SpO_2 >96%) and FIO_2

RESULTS (Cont)

- In mechanically ventilated patients, there was: (Figure 3)
  - a decrease in the proportion of patient-time spent normoxic;
  - an increase in the proportion of patient-time on room air
  - a decrease in the proportion of patient-time spent hyperoxic and on supplemental O_2
- In non-mechanically ventilated patients, there was:
  - an increase in the proportion patient-time spent normoxic (34.2% pre vs 40.5% post)
  - an increase in proportion patient-time on supplemental oxygen among hyperoxic patients (7.8% pre vs 12.4% post)

CONCLUSIONS

- Preliminary data from the first site randomized to cross over to post-implementation phase suggests a multimodal intervention to target normoxia can increase the proportion of patient-time spent in normoxia
- In non-mechanically ventilated patients, the total patient-time spent hyperoxic and on supplemental O_2 is minimal (target <10% total)
- In mechanically ventilated patients, we reduced the proportion of patient-time spent hyperoxic and on supplemental
- There was little change in the proportion of patient-time spent hypoxic

FUTURE DIRECTIONS AND IMPLICATIONS

- Final analysis of patient outcomes (i.e. supplemental O_2 free days)
- Reduce supplemental O_2 required in remote and prolonged field care settings

Funding/Disclosures

This work was supported by the Assistant Secretary of Defense for Health Affairs, through the Joint Warfighter Medical Research Program, under Award No. (W81XWH-20-2-0001). Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

Title: Hyperoxia is Associated with a Greater Risk for Mortality in Critically Ill Traumatic Brain Injury Patients than in Critically Ill Trauma Patients Without Brain Injury

David J. Douin, MD[1*] david.douin@cuanschutz.edu
Layne Dylla, MD, PhD[2*] layne.dylla@cuanschutz.edu
Erin L. Anderson, RN[2] erin.l.anderson@cuanschutz.edu
John D. Rice, PhD[3] john.rice@cuanschutz.edu
Conner L. Jackson, MS[3] conner.jackson@cuanschutz.edu
Robert T. Neumann, MD[4] robert.neumann@cuanschutz.edu
Col Vikhyat S. Bebarta, MD[2,3,5] vikhyat.bebarta@cuanschutz.edu
MAJ Steven G. Schauer, DO, MS[6,7] steven.g.schauer.mil@mail.mil
Adit A. Ginde, MD, MPH[2,5] adit.ginde@cuanschutz.edu

[1] Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO
[2] Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO
[3] Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO
[4] Department of Neurological Surgery, University of Colorado School of Medicine, Aurora, CO
[5] Center for COMBAT Research, Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO
[6] US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA Lackland, TX
[7] US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX
May

Corresponding Author:
Adit A. Ginde, MD, MPH
Department of Emergency Medicine
University of Colorado School of Medicine
12401 E. 17th Avenue, B-215
Aurora, CO 80045
Phone: (720) 848-6777
Fax: (720) 848-7374
E-Mail: adit.ginde@cuanschutz.edu

Abbreviated Title: Oxygenation and Mortality in TBI

Funding/Support: This study was supported by the Department of Defense/SOCOM (W81XWH-17-C-0241).

Disclaimer: The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsements, either expressed or implied, of the Department of the Army, Department of the Air Force, Department of Defense, or the US Government.

Conflicts of Interest: The authors have no conflicts of interest to report.

ABSTRACT

Background: Both hypoxia and hyperoxia are associated with increased mortality among critically injured civilians and military personnel. However, the risks of hyperoxia in traumatic brain injury (TBI) patients relative to other critically ill trauma patients remain unknown.

Methods: We performed a secondary analysis of a multicenter retrospective cohort study of 3,464 critically injured adult patients presenting to three regional trauma centers (two level I and one level II) between October 1, 2015, and June 30, 2018. The primary outcome was in-hospital mortality. Secondary outcomes included proportion of time spent in hyperoxia (defined as SpO_2 >96%) and ventilator free days (VFD). We analyzed all available SpO2 values during the first seven ICU days.

Results: After adjusting for ICU length of stay and mechanical ventilation status, critically ill TBI patients spent a significantly greater amount of time in hyperoxia than critically ill non-TBI patients (49.2% vs 44.0%; $p<0.001$). A total of 163/1524 patients (10.7%) died in the TBI group, and 101/1940 patients (5.2%) died in the non-TBI group. The risk for mortality was significantly higher for TBI patients with hyperoxia than non-TBI patients with hyperoxia. At any fixed SpO_2 level, for both patients with and without TBI, the risk of mortality increased with increasing FiO_2. This trend was observed at all FiO_2 and SpO_2 levels but was more pronounced at lower FiO_2 and higher SpO_2 values where a greater number of patient observations were obtained.

Conclusion: Hyperoxia was more common and was associated with a greater risk for in-hospital mortality in critically ill TBI patients, compared to critically ill trauma patients without TBI. Prospective studies are needed to elucidate the mechanisms and clinical implications underlying these differences to inform oxygen-related clinical practice guidelines for military and civilian TBI patients.

Dylla et al. Trials (2021) 22:784
https://doi.org/10.1186/s13063-021-05688-6

Trials

STUDY PROTOCOL Open Access

A multicenter cluster randomized, stepped wedge implementation trial for targeted normoxia in critically ill trauma patients: study protocol and statistical analysis plan for the Strategy to Avoid Excessive Oxygen (SAVE-O2) trial

Layne Dylla[1†], David J. Douin[2†], Erin L. Anderson[1], John D. Rice[3], Conner L. Jackson[3], Vikhyat S. Bebarta[1,4,5], Christopher J. Lindsell[6], Alex C. Cheng[7], Steven G. Schauer[4,8,9] and Adit A. Ginde[1,5*]

Abstract

Background: Targeted normoxia (SpO_2 90–96% or PaO_2 60–100 mmHg) may help to conserve oxygen and improve outcomes in critically ill patients by avoiding potentially harmful hyperoxia. However, the role of normoxia for critically ill trauma patients remains uncertain. The objective of this study is to describe the study protocol and statistical analysis plan for the Strategy to Avoid Excessive Oxygen for Critically Ill Trauma Patients (SAVE-O2) clinical trial.

Methods: Design, setting, and participants: Protocol for a multicenter cluster randomized, stepped wedge implementation trial evaluating the effectiveness of a multimodal intervention to target normoxia in critically ill trauma patients at eight level 1 trauma centers in the USA. Each hospital will contribute pre-implementation (control) and post-implementation (intervention) data. All sites will begin in the control phase with usual care. When sites reach their randomly assigned time to transition, there will be a one-month training period, which does not contribute to data collection. Following the 1-month training period, the site will remain in the intervention phase for the duration of the trial.
Main outcome measures: The primary outcome will be supplemental oxygen-free days, defined as the number of days alive and not on supplemental oxygen. Secondary outcomes include in-hospital mortality to day 90, hospital-free days to day 90, ventilator-free days (VFD) to day 28, time to room air, Glasgow Outcome Score (GOS), and duration of time receiving supplemental oxygen.

* Correspondence: Adit.Ginde@cuanschutz.edu
†Layne Dylla and David J. Douin contributed equally to the drafting of this manuscript.
[1]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA
[5]Center for COMBAT Research, Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA
Full list of author information is available at the end of the article

Discussion: SAVE-O2 will determine if a multimodal intervention to improve compliance with targeted normoxia will safely reduce the need for concentrated oxygen for critically injured trauma patients. These data will inform military stakeholders regarding oxygen requirements for critically injured warfighters, while reducing logistical burden in prolonged combat casualty care.

Trial registration: ClinicalTrials.gov NCT04534959. Registered September 1, 2020.

Keywords: Oxygenation, Hyperoxia, Trauma, Injuries, Critical care, Intensive care units

Background

Oxygen therapy has undisputed importance in the care of critically ill patients to prevent morbidity associated with hypoxia and enhance oxygen delivery [1, 2]. Excessive oxygen supplementation to critically ill patients, resulting in hyperoxia, appears to be routine [3, 4] and may even be harmful [3, 5–8]. This practice also has critical consequences in terms of logistics during military operations, particularly in prolonged field care settings. A recent systematic review of 43 studies of oxygenation in critically ill patients identified few trauma-specific studies and none of high quality [8]. Therefore, there is ongoing uncertainty regarding the optimal use of oxygen therapy in critically ill trauma patients. Well-designed, trauma-specific trials are needed to guide oxygen targets in these patients.

To address this uncertainty, we are conducting the Strategy to Avoid Excessive Oxygen (SAVE-O2) for Critically Ill Trauma Patients clinical trial. The purpose of this trial is to determine the effectiveness of a multimodal educational intervention to safely reduce supplemental oxygen use in critically injured patients. Investigators will also evaluate the clinical effectiveness of the more targeted use of oxygen therapy. The pilot study for the SAVE-O2 trial demonstrated that the multimodal intervention is feasible and effective in reducing use of supplemental oxygen for critically ill trauma patients [9]. We convened an expert panel to develop consensus targets for oxygen saturation (SpO_2), which determined optimal range of 90–96%, partial pressure of arterial oxygen (PaO_2) range of 60–100 mmHg (when applicable), and fraction of inspired oxygen (FiO_2) of 0.21 for mechanically ventilated patients or room air for non-mechanically ventilated patients [10, 11]. These ranges will be utilized to titrate supplemental oxygen use. Here we describe the protocol and statistical analysis plan for SAVE-O2. By using a pre-specified statistical analysis plan, we aim to reduce the risk of bias arising from knowledge of study findings as they emerge during data analyses [12].

Methods

Trial design

SAVE-O2 is a multicenter cluster randomized, stepped wedge implementation trial to evaluate the superiority of a multimodal educational intervention to improve adherence to consensus-based normoxia compared to usual care in critically ill trauma patients. This pragmatic design allows for optimal evaluation of an intervention where benefits of targeted normoxia outweigh the alternative of potential increased frequency of hypoxia and/or hyperoxia [13]. Eight level 1 trauma centers will be randomized over time to crossover from a pre-intervention (control) phase of usual care to post-intervention phase (targeted normoxia). Intervention at the hospital level minimizes the potential from contamination between participants in the pre- versus post-intervention stage. We detail the SAVE-O2 study design here, with reference to the Standard Protocol Items: Recommendations for Interventional Trials checklist [14] (Fig. 1 and Appendix 1). University of Colorado serves as the Clinical Coordinating Center (CCC) for this trial.

Setting/Population

SAVE-O2 includes critically ill trauma patients from eight level 1 trauma centers geographically distributed throughout the United States. These hospitals have endorsed the consensus-based recommendation for normoxia (SpO_2 90–96%, PaO_2 60–100 mmHg) in critically ill trauma patients, but do not have existing protocols and/or resources to promote this oxygenation strategy. The target population includes adults aged 18 years or older who meet criteria for entry into state or national trauma registries and who are admitted to a surgical or trauma intensive care unit (ICU) within 24 h of arrival to a participating hospital. This includes patients who present directly to the emergency department of a participating hospital and those who are transferred into a participating hospital. Exclusion criteria include prisoners and known pregnancy. There is no selection for inclusion/exclusion based on mechanical ventilation status, injury severity, injury mechanism, or traumatic brain injury.

Ethics approval

SAVE-O2 has been approved with a waiver of informed consent by the Colorado Multiple Institutional Review Board (COMIRB #19-2153), which serves as the single IRB for this study. Each enrolling site has ceded review

Timepoint		Pre-intervention Data Collection	Post-intervention Data Collection
		T1	T2
Enrolment*	Eligibility Screen	X	X
	Waiver of Informed Consent	X	X
Interventions**	Multimodal Intervention of Targeted Normoxia		X
Assessments***	Demographics	X	X
	Injury Severity Score	X	X
	Elixhauser comorbidity Index	X	X
	Payer Status	X	X
	Mechanism of Injury	X	X
	Injury Severity Score	X	X
	Military Status	X	X
	Home supplemental oxygen use	X	X
	SpO_2	X	X
	PaO_2	X	X
	FiO_2	X	X
	Supplemental Oxygen Use	X	X
	Discharge from ICU	X	X
	Date of in-hospital death	X	X
	Discharge GOS	X	X

* Eligibility Screen – Intervention is applied at a "cluster" (hospital) level. Patient eligibility is determined continuously during data collection

** Intervention – see figure 1 for Cluster Randomized Stepped Wedge Schema

*** Assessments performed on a continuous basis throughout both the pre- and post-intervention period. See table 2 for full patient-level data to be collected

Fig. 1 SPIRIT diagram

to COMIRB under reliance agreements. Prior to the design of this study, we conducted a systematic review, Delphi consensus process, and pilot study. Together, these processes demonstrated preliminary safety evidence of targeted normoxia, identified consensus-based oxygenation targets, and provided a foundation to conduct this multicenter clinical trial with a waiver of informed consent under the Common Rule (45 CFR 46) that governs the ethical conduct and oversight of human subjects' research, section 116 (d). The COMIRB determined that this trial represents no more than minimal risk to participants – this multimodal educational intervention helps hospitals implement a consensus-based oxygenation target that is not binding and remains at the discretion of the treating physician to ensure optimal care of all critically ill trauma patients. The use of a waiver of consent does not adversely affect the rights and welfare of subjects—patient care remains at the discretion of the clinical team to act in the best interests of an individual patient and data collection occurs at a hospital unit-level to ensure that patient care and privacy is not compromised. Finally, the study conducts research that could not practicably be carried out without the waiver of consent—there is no interaction with patients or their surrogates as the intervention is conducted at the level of each hospital unit with subjects as a whole receiving either usual care in the pre-intervention period or education-enhanced usual care in the post-intervention phase. The full details of the ethical considerations of this trial are detailed in the full study protocol (Appendix 2).

Randomization

Randomization occurs at the hospital level ("cluster"). In randomly chosen order, each cluster will cross over from the pre-intervention phase of usual care to post-intervention targeted normoxia. This incorporates a 1-month run-in period during which the hospital engages staff in educational activities and trainings designed to increase familiarity and compliance with targeted normoxia protocols. These standardized activities and associated materials are part of the "intervention" provided by the clinical coordinating center. During this run-in period, patient-level data collected will not be used for the primary analysis. Cluster crossover occurs every 3 months for a total study duration of 27 months (Fig. 2).

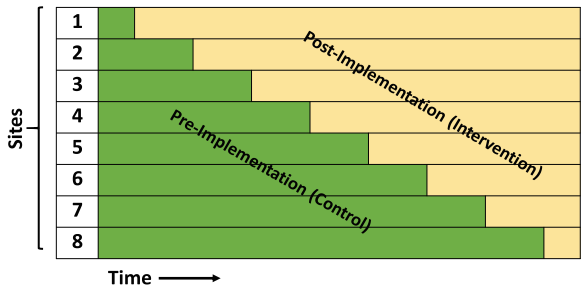


Fig. 2 Schematic of multicenter cluster randomized, stepped wedge design. An overview of the multicenter cluster randomized, stepped wedge implementation design. Each "step" represents the crossover at 3-month intervals from the pre-implementation period to the post-implementation period, with the first month of the crossover period considered a wash-out period

Study Intervention

This trial evaluates the effectiveness of a multimodal educational intervention to increase compliance with targeted normoxia in critically ill trauma patients. Normoxia is defined based on a modified Delphi consensus approach with 31 nationally recognized military and civilian experts from trauma surgery, emergency medicine, critical care, and military operational medicine as a SpO_2 of 90–96% or a PaO_2 of 60–100 mmHg. This expert consensus panel defined the following oxygenation ranges based on non-invasive SpO_2: hyperoxia as an SpO_2 of greater than 96%, normoxia as an SpO_2 of 90–96%, borderline as an SpO_2 of 88–89%m and hypoxia as an SpO_2 less than 88% [10, 11].

We take a multi-faceted approach to clinician and staff education at each site, starting with standardized educational presentations tailored to specific provider groups—physicians, nurses, and respiratory therapists. These presentations will (1) provide essential background information and stress the importance of avoiding both hypoxia and hyperoxia as a potential way to decrease patient morbidity and mortality, (2) give an overview of the SAVE-O2 trial, (3) provide potential protocols to down-titrate supplemental oxygen in hyperoxic patients, and (4) give instruction for reporting potential adverse events. In addition to these presentations, flyers will be placed strategically throughout sites reminding providers of the ongoing SAVE-O2 trial. Further education and reminders, led by local coordinators and investigators, will be conducted at staff meetings, floor rounds, and daily team meetings.

We will also provide monthly newsletters and feedback highlighting the pre- and ongoing post-intervention oxygenation practices. These will help guide sites in evaluating their progress toward a minimum goal of 90% of patient-hours spent within the targeted normoxia thresholds.

In addition to multiple educational activities, some sites will also include an electronic health record best practice alert (Fig. 3). These alerts are designed in accordance with local practices, but generally alert nurses and respiratory therapists when a patient falls in the hyperoxia range based on SpO_2 or PaO_2 measurements. They will make recommendations based on on-site practice patterns for oxygen titration which can be overridden by clinical judgments. In cases where a recommendation for down-titration of supplementation oxygen is overridden by clinical judgment, that patient remains in the trial. The educational component of this intervention is expansive and targets physicians, advanced practice providers, nurses, and respiratory therapists. However, in many cases, nurses and respiratory therapists will be primarily responsible for oxygen titration. Each site is free to follow its own practices for specific oxygen titration and the exact time frame in which titrations should be made. However, SAVE-O2 recommends down titration of supplemental oxygen in patients with sustained hyperoxia (30 minutes or greater) by FiO_2 increments of 0.1 until normoxia is reached, a mechanically ventilated patient is on an FiO_2 of 0.21 or until a non-mechanically ventilated patient is no longer on supplemental oxygen. In some cases, oxygen titration may not be possible, for example, patients who are hyperoxic with an $SpO_2 > 96\%$ but not on supplemental oxygen and those who are hypoxic but on an FiO_2 of 1.0. Treating physicians are also allowed to override study recommendations when determined to be in the best interest of the patients. Potential situations where it is anticipated that treating physicians may temporarily favor hyperoxia include carbon monoxide poisoning, untreated pneumothorax, and cyanide poisoning.

Oxygen titration is encouraged from the time that a patient enters the hospital through to his/her discharge from the ICU. While SAVE-O2 outcomes focus on oxygenation in the ICU, the intervention will also target emergency department providers who often establish post-acute injury therapeutic momentum. To further increase the success of the intervention, leadership from within each site's emergency department, trauma surgery teams, and the ICUs will work with study "champions" to reinforce intervention compliance. Oxygen titration is "encouraged" but not mandated because the primary study question focuses on the effectiveness of a multifaceted educational intervention to target normoxia in critically ill trauma patients. Thus, we focus on educating ICU providers and assess the effect of the education intervention on the ICU oxygenation of these patients. After a patient is discharged from the ICU or transferred to a floor bed, the patient's oxygenation status is no longer monitored for the purposes of this trial. Patients subsequently readmitted to the ICU from the

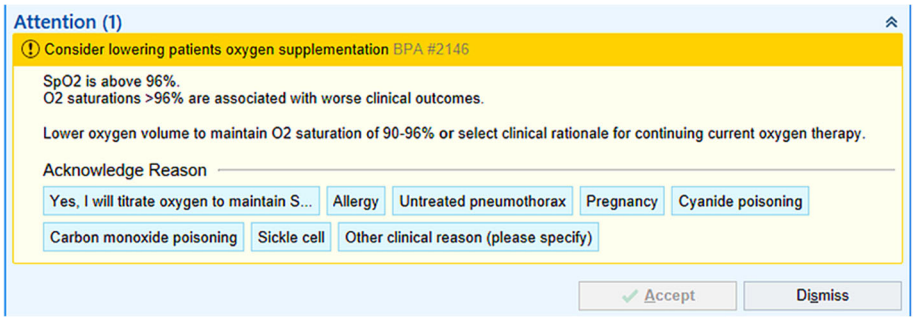


Fig. 3 Electronic health record alert

floor after 24 h may still experience the effects of the educational intervention which is deployed at the level of the ICU unit, but no further oxygenation data is collected for that patient during the ICU readmission.

Outcomes

Primary outcome

The primary outcome of SAVE-O2 is supplemental oxygen-free days (SOFD). This is defined as the number of days a patient is alive and not on supplemental oxygen from the time of presentation to day 28. SOFD is censored at hospital discharge. The score ranges from − 1 days (death) to 28 days (no supplemental oxygen use). Patients discharged from the hospital prior to day 28 are assumed to be maintained at the level of oxygenation they require on hospital discharge—i.e., if they are discharged on room air or the level of supplemental oxygen used prior to admission, it is assumed that they remained on no additional supplemental oxygen to day 28. When a patient receives the same level of supplemental oxygen as they require at home prior to admission, this will count as being free of supplemental oxygen. We will not count toward SOFD the amount of time patients are intubated and ventilated only for a surgical procedure and are immediately extubated upon completion of that procedure.

Secondary outcomes

There is no patient follow-up after hospital discharge in SAVE-O2 and all secondary outcomes are assessed at hospital discharge. However, variables will be censored at various intervals while hospitalized: hospital discharge, 28 days, or 90 days. SAVE-O2 will assess ventilator-free days to day 28 (VFD28) [10, 11, 15] as a secondary outcome. VFD28 is defined as 28 minus the number of days a patient is mechanically ventilated, censored at hospital discharge. Patients discharged on mechanical ventilation prior to 28 days are assumed to be maintained on mechanical ventilation to day 28 and will receive a score of zero if mechanical ventilation was initiated upon arrival. In cases of a failed extubation (reintubation in less than 48 h), this interval will count toward the number of days being ventilated. However, periods of mechanical ventilation lasting less than 24 h to facilitate surgical procedures or for sleep disordered breathing will not be counted toward ventilation days. Additionally, subjects who die prior to 28 days will be assigned a VFD28 score of − 1.

Secondary outcomes censored at 90 days include hospital-free days (HFD90), in-hospital mortality, and time to mortality. Hospital-free days is defined as the number of days a patient is alive and not hospitalized. The scores will range for − 1 days (worse outcome, patients who die in the hospital during the 90 days) or zero (patients who are hospitalized for more than 90 days) to 90 days (best outcome, patients who are discharged from the hospital alive to any location on the day of admission). In-hospital mortality is defined as alive or dead on the day of hospital discharge or day 90, whichever is first. Time to mortality is defined as the number of days from admission to death. Time to mortality is also censored at hospital discharge or day 90, whichever is first.

To better characterize oxygenation practices, we will collect data on multiple additional secondary outcomes. This includes the frequency and duration of ICU time a patient spends in the various oxygenation categories (hypoxia, borderline, normoxia, and hyperoxia) and the time spent compliant with targeted normoxia. For cases where a hyperoxic patient is ventilated on FiO_2 of 0.21 or is on room air, no further oxygenation adjustments can be made. This time will count toward compliance with the normoxia protocol. We will also assess the time to the first incidence of no supplemental oxygen use (room air in non-mechanically ventilated patients or FIO_2 of 0.21 in mechanically ventilated patients), censored at hospital discharge.

To characterize the potential reduction in the amount of supplemental oxygen used we will determine the total amount of supplemental oxygen administered. We will specifically examine the use of high levels of

supplemental oxygen, defined as an $FiO_2 > 0.40$ or more than 4 liters per minute. The proportion of participants on high levels of supplemental oxygen for more than 2 h in the ICU and the total duration of time receiving high levels of supplemental oxygen will be calculated.

The final patient-centered clinical outcomes include the discharge disposition and Glasgow Outcome Score (GOS) [16, 17]. Discharge disposition includes the following categories: expired, home, facility (i.e. long term care, rehabilitation facility, hospice, skilled nursing facility), long-term acute care facility, other (i.e., left against medical advice, missing). The GOS is a five-point scale rating the relative disability of patients from death to no disability that research staff will assign to a patient based on chart review. Limited independence due to orthopedic injuries and non-weight bearing status while fractures are healing will not count toward disability on the GOS scale.

Data collection and management

SAVE-O2 will leverage the expertise of the Data Coordinating Center (DCC) at Vanderbilt University Medical Center and the on-site informatics specialists to implement protocols that automatically extract variables directly from the electronic health record and state trauma registry data (Table 1), including all recorded SpO_2, PaO_2, FiO_2, and oxygen volume measurements. Many sites will also collect raw, unvalidated continuous SpO_2 measurements. Instances that require manual chart extraction by site coordinators (i.e., GOS, home supplemental oxygen use, and military status) will be minimized and obtained using standardized operating procedures with flow charts and detailed procedures for extraction.

SAVE-O2 uses the resources available at the DCC to provide specialized REDCap database development and management. REDCap is a secure, encrypted, HIPAA-compliant web application specifically designed for research data management with the ability for data capture and validation and data audits, and de-identified data export to common statistical packages [18]. Automated data extraction will take advantage of REDCap functionality that pulls data using electronic health record systems' application programming interfaces (API) that conform to the HL7 Fast Health Interoperability Resources (FHIR) standard [19]. Additional accuracy and consistency checks will be performed by trained project managers at each site. Once data have been uploaded into a site's REDCap database, REDCap deidentifies the data and sends it weekly to the DCC. The DCC assists with the automated feedback reports and shares these with the clinical coordinating center biostatistical core. Protected health information will only be accessible by the local site and not shared with other sites, the DCC or the CCC. Sites will be intermittently audited by the clinical coordinating center without notice to ensure both protocol compliance and data accuracy.

Data and safety monitoring

Under the guidance of the Department of Defense and COMIRB, an Independent Safety Officer was selected with expertise in acute and critical care to monitor participant safety, evaluate study progress, and suggest changes in design or conduct as needed to address potential safety issues. Adverse events and unanticipated problems will be reported to the Department of Defense Scientific Officer, the Independent Safety Monitor, COMIRB, and the Department of Defense Human Research Protection Office in accordance with their reporting policies. The CCC will provide both the Independent Safety Officer and the Department of Defense Scientific Officer quarterly reports to further monitor trial progress and safety events. No formal interim analyses are required.

Sample size and power

We estimate an approximate accrual rate of 30 patients per site per month for a total sample size of at least 6000 patients over the 27-month study duration. Based on pilot study data, we estimated a mean SOFD of 15.5 under control conditions with a standard deviation of 11.3 days and an interclass correlation coefficient of 0.04. The estimated sample size of 6000 patients will allow us to detect a difference of 1.42 days in the primary outcome SOFD at 80% power and 1.64 days at 90% power. This assumes that data is normally distributed and that each site contributes the same number of patients as all other sites. As pilot data suggested that some of these assumptions may be false (SOFD is restricted to a specific range, skewed, and bimodal), simulation studies were conducted to address the impact of their violation on power. The simulations, conducted under the less restrictive distributional assumption of SOFD as an ordinal outcome, included removing a fraction of patients during a site crossover period to account for run-in and using the relative trauma patient volume of each site (which varies between 500 and 1500 trauma ICU patients per year) to adjust its sample size relative to the total. These simulation studies demonstrated almost no difference in power estimates relative to traditional power calculations, so power calculations reported above reflect the simpler formula-based approach [20].

Statistical analysis plan

Overview of statistical analysis plan (Appendix 3)

We will use descriptive statistics to create summary tables for patient characteristics and outcome variables. We will report the sample size, mean, and standard

Table 1 Patient-level data collected

Source (extraction method)	Data collected
Trauma registry (automated extraction)	Date of presentation to the emergency department or hospital
	Date of ICU admission
	Age on day of admission
	Gender
	Race and ethnicity
	Payer status
	Elixhauser comorbidity index
	Mechanism of injury
	Injury Severity Score
Electronic health record (automated extraction)	Cigarette smoking status
	Body mass index
	Covid-19 status
	Shock Index
	All validated SpO_2 values in ICU
	Unvalidated SpO_2 values (continuous, recorded up to every minute when available) in ICU
	All PaO_2 values in ICU
	All FiO_2 values in ICU
	All PEEP values in ICU
	All oxygen volume measurements in ICU
	Date of discharge from ICU
	Date of in-hospital death
	Discharge disposition
Electronic health record (manual extraction)	Military status
	Home supplemental oxygen use
	Discharge GOS
Calculated outcomes	Supplemental Oxygen Free Day (SOFD) to day 28
	Ventilator-free days to day 28 (VFD28)
	Hospital-free days to day 90 (HFD90)
	In-hospital mortality to day 90
	Time to mortality to day 90
	Time to room air (or FiO_2=0.21)
	Frequency of hypoxic episodes
	Duration of hypoxic episode
	Frequency of hyperoxic episodes
	Duration of hyperoxic episodes
	Total duration of time on normoxia protocol
	Amount of supplemental oxygen administered (total estimated oxygen volume administered in ICU)
	Duration of time on normoxia protocol target (time with SpO_2 90-96% or receiving no supplemental oxygen while in ICU)
	Proportion of participants receiving high levels of supplemental oxygen ($FiO_2 > 0.4$ or more than 4LPM for more than 2 h while in ICU; excluding operating room time)
	Duration of time receiving high levels of supplemental oxygen
	Duration of time receiving no supplemental oxygen or $FiO_2 = 0.21$

Abbreviations: *COVID-19* coronavirus disease 2019, *FiO_2* fraction of inspired oxygen, *GOS* Glasgow Outcome Scale, *ICU* intensive care unit; *LPM* liters per minute; *PaO_2* partial pressure of arterial oxygen, *PEEP* positive end expiratory pressure, *SpO_2* saturation of oxygen

deviation for all continuous variables stratified by treatment condition (pre- vs post-intervention) and site. Descriptive statistics will exclude missing data. All analysis will be performed on the basis of intention to treat. We define a two-sided threshold for statistical significance of 5%. With a single primary outcome, we will not adjust for multiple comparisons; appropriate caution will therefore be used in interpreting the results of hypothesis testing for secondary analyses.

Primary outcome

We will analyze the primary outcome, SOFD, using a linear mixed-effects modeling framework. To account for possible temporal trends associated with intervention implementation at different times, a fixed effect for time will be included. We will account for clustering of patients within sites by including a random intercept term in all models. We will also adjust the model for the following patient-level covariates: age, sex, race and ethnicity, insurance type, Elixhauser Comorbidity Index [21], mechanism of injury, injury severity score, cigarette smoking status, body mass index, and COVID-19 status. We will consider alternative modeling approaches to avoid parametric assumptions while addressing the ordinal nature of these outcomes as needed.

Secondary outcomes

Continuous secondary outcomes (i.e., HFD90, VFD28, amount of supplemental oxygen administered, number of hyperoxic/hypoxic episodes) will be analyzed using a linear mixed modeling approach, similarly to the primary outcome. For dichotomous outcomes (i.e., whether or not a patient needed high levels of supplemental oxygen and 90-day in-hospital mortality), we will use a logistic mixed model. For time-to-event outcomes (i.e., time to room air, time to mortality), we will use a Cox proportional hazards regression model with a gamma-distributed random intercept for the site. Time zero will be taken to be the time of arrival in hospital. Kaplan-Meier plots of the time-to-event outcomes will be created to graphically compare distributions between treatment conditions. For ordinal outcomes (i.e., GOS), we will use a mixed-effects ordinal logistic regression model. The proportional odds assumption will be checked to assess if the relationship between the consecutive outcome levels is the same. If violated, a multinomial logit or

Table 2 Planned figures and tables

Proposed tables (stratified by treatment condition pre- vs post-intervention)	Table 1: Patient characteristics (stratified by treatment
	Table 2: Primary Outcome – SOFD - SOFD (Mean, SD) among survivors - In-hospital mortality (*n*, %) - Alive with 0 SOFD (*n*, %) - Alive with 28 SOFD (*n*, %)
	Table 3: Secondary clinical outcomes - HFD90 - In-hospital mortality to day 90 - VFD28 - Time to room air - GOS - Discharge disposition
	Table 4: Secondary oxygenation outcome - Amount of supplemental oxygen administered - Duration of time on normoxia protocol target - Proportion receiving high levels of supplemental oxygen while in ICU - Duration of time receiving high levels of supplemental oxygen - Duration of time receiving no supplemental oxygen - Incidence of hypoxic and hyperoxic events - Duration of hypoxic and hyperoxic evens
Proposed figures	Figure 1: CONSORT diagram
	Figure 2: Histogram of SOFD stratified by treatment conditions
	Figure 3: Time to mortality stratified by treatment condition (Kaplan-Meier Curve)
Supplemental Tables/Figures	Supplementary Table 1: Patient characteristics by site
	Supplementary Table 2: Primary Outcome – SOFD by site
	Supplementary Table 3: Secondary Outcomes by site
	Supplementary Table 4: Subgroup analysis by trauma subgroup
	Supplementary Table 5: Subgroup analysis by Injury Severity Score

Abbreviations: *GOS* Glasgow Outcome Score, *HFD90* hospital-free days to day 28, *ICU* intensive care unit, *SD* standard deviation, *SOFD* supplemental oxygen-free days, *VFD28* ventilator-free days to day 28

partially proportional odds mixed-effects model will be used.

Missing data

Based on pilot study data, some oxygen exposure and measurements are expected to be missing due to charting inconsistency. In mechanically ventilated patients, we assume that FiO_2 is maintained constantly until a patient is extubated or a new FiO_2 is entered. In non-mechanically ventilated patients, we will also assume that the level of supplemental oxygen provided will remain constant until a new value is entered up to 12 h later. However, after 12 h without a new measurement recorded, the patient will be assumed to be on room air. We will not assume an FiO_2 until the first recorded measurement in the first 12 h. If, after 12 h, a measurement is still not recorded, we will assume the patient is on room air. This will ensure that the primary outcome has no missing data.

Presentation of outcome data

Table 2 lists the proposed tables and figures for final trial reporting. The results of the trial will be published in peer-reviewed journals.

Discussion

SAVE-O2 is multicenter cluster randomized, stepped wedge implementation trial. This trial will determine if targeted normoxia will safely reduce the need for concentrated oxygen for critically ill trauma patients. The primary outcome will be supplemental oxygen-free days, defined as the number of days alive and not on supplemental oxygen. In addition to answering the primary scientific question, these data will inform military stakeholders on oxygen requirements for critically injured warfighters, while reducing logistical burden in prolonged combat casualty care. This protocol and statistical analysis plan article have been submitted for publication before recruitment was completed.

Trial status

This article is based on the SAVE-O2 Trauma protocol version 1.1 as of June 3, 2020. Pre-intervention data collection started on July 15, 2020. The first site began the 1-month run-in implementation period on October 15, 2020. The estimated study completion date is December 15, 2022.

Abbreviations

CCC: Clinical Coordinating Center; COMIRB: Colorado Multiple Institutional Review Board; DCC: Data Coordinating Center; FiO_2: Fractional inspired oxygen; GOS: Glasgow Outcome Score; HFD: Hospital-free days; ICU: Intensive care unit; PaO_2: Partial pressure arterial oxygen; SAVE-O2: Strategy to AVoid Excessive Oxygenation; SOFD: Supplemental oxygen-free days; SpO_2: Pulse oximetry; VFD: Ventilator-free days

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05688-6.

Additional file 1: Appendix 1: SPIRIT Checklist
Additional file 2: Appendix 2: Final Protocol
Additional file 3: Appendix 3: Statistical Analysis Plan

Acknowledgements

We would like to thank our collaborators and the following research staff for their hard work and dedication to the design and implementation of the SAVE-O2 study—the Clinical Coordinating Center at the University of Colorado School of Medicine: Jessica Cwik, Amanda Martinez, Jennifer Peers, Shelby Shelton, and Aimee Steinwand; the Data Coordinating Center at Vanderbilt University Medical Center: Francesco Delecqua, Kim Hart, Adam Lewis, Mark McEver, and Patrick Newman; and research staff at the eight enrolling sites in the SAVE-O2 network.

Authors' contributions

AAG conceived the study and led the proposal and protocol development. ELA, VSB, SGS, and AAG contributed to the design of the study. LD, DJD, ELA, JDR, CLJ, VSB, ACC, SGS, and AAG will implement the trial. JDR and CJL were responsible for the statistical analysis plan. JDR and CLJ are responsible for primary data analysis. LD and DJD contributed equally to the first draft of the manuscript. All authors contributed to the revisions and modifications of the manuscript and have approved the final version.

Funding

The US Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office. This work was supported by the Assistant Secretary of Defense for Health Affairs, through the Joint Warfighter Medical Research Program, under Award No. (W81XWH-20-2-0001). Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the Department of Defense. 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. The funder has no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Availability of data and materials

The materials generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

SAVE-O2 has been approved with a waiver of informed consent by the Colorado Multiple Institutional Review Board (COMIRB #19-2153), which serves as the single IRB for this study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA. [2]Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO, USA. [3]Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO, USA. [4]US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA, Lackland, San Antonio, TX, USA. [5]Center for COMBAT Research, Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA. [6]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA. [7]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA. [8]US Army Institute of Surgical Research,

JBSA Fort Sam, Houston, TX, USA. [9]Department of Emergency Medicine, Brooke Army Medical Center, San Antonio, TX, USA.

Received: 25 April 2021 Accepted: 6 October 2021
Published online: 08 November 2021

References

1. McMullan J, Rodriquez D, Hart KW, Lindsell CJ, Vonderschmidt K, Wayne B, et al. Prevalence of prehospital hypoxemia and oxygen use in trauma patients. Mil Med. 2013;178(10):1121–5. https://doi.org/10.7205/MILMED-D-13-00126.
2. Wetterslev J, Meyhoff CS, Jørgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database Syst Rev. 2015;6. https://doi.org/10.1002/14651858.CD008884.pub2.
3. Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood G, Young P, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. Am J Respir Crit Care Med. 2016;193(1):43–51. https://doi.org/10.1164/rccm.201505-1019OC.
4. Young PJ, Bailey M, Bellomo R, Bernard S, Bray J, Jakkula P, et al. Conservative or liberal oxygen therapy in adults after cardiac arrest: An individual-level patient data meta-analysis of randomised controlled trials. Resuscitation. 2020;157:15–22. https://doi.org/10.1016/j.resuscitation.2020.09.036.
5. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303(21):2165–71. https://doi.org/10.1001/jama.2010.707.
6. Smit B, Smulders YM, de Waard MC, Boer C, Vonk AB, Veerhoek D, et al. Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial. Crit Care. 2016;20(1):55. https://doi.org/10.1186/s13054-016-1240-6.
7. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA. 2016;316(15):1583–9. https://doi.org/10.1001/jama.2016.11993.
8. Douin DJ, Schauer SG, Anderson EL, Jones J, DeSanto K, Cunningham C, et al. Systematic Review of Oxygenation and Clinical Outcomes to Inform Oxygen Targets in Critically Ill Trauma Patients. J Trauma Acute Care Surg. 2019;87(4):961–77.
9. Dylla L, Anderson EL, Douin DJ, Jackson CL, Rice JD, Schauer SG, Neumann RT, Bebarta VS, Wright FL, Ginde AA. A quasi-experimental study of targeted normoxia in critically ill trauma patients. J Trauma Acute Care Surg. 2021;91:S169-S175. https://doi.org/10.1097/ta.0000000000003177.
10. Ginde A. Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces. Defense Technical Information Center. 2020;https://apps.dtic.mil/sti/pdfs/AD1101367.pdf:1-211.
11. Schauer SG, Anderson E, Cunningham C, Jones J, Bebarta VS, Ginde AA. Consensus-based recommendation for oxygenation targets in critically injured patients. Presented at Special Operations Medical Association Scientific Assembly. 2019. Available at: http://www.specialoperationsmedicine.org/Documents/2019%20SOMSA/Handouts/THURS-Research%20Schauer%20-%20Oxygen%20consensus.pdf.
12. Mackle DM, Bailey MJ, Beasley RW, Bellomo R, Bennett VL, Deane AM, et al. Protocol summary and statistical analysis plan for the intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX). Crit Care Resusc. 2018;20(1):22–32.
13. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol. 2006;6(1):54. https://doi.org/10.1186/1471-2288-6-54.
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.
15. Schoenfeld DA, Bernard GR, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002;30(8):1772–7. https://doi.org/10.1097/00003246-200208000-00016.
16. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1(7905):480–4. https://doi.org/10.1016/s0140-6736(75)92830-5.
17. McMillan T, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M. The Glasgow Outcome Scale - 40 years of application and refinement. Nat Rev Neurol. 2016;12(8):477–85. https://doi.org/10.1038/nrneurol.2016.89.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010.
19. Mandel JC, Kreda DA, Mandl KD, Kohane IS, Ramoni RB. SMART on FHIR: a standards-based, interoperable apps platform for electronic health records. J Am Med Inform Assoc. 2016;23(5):899–908. https://doi.org/10.1093/jamia/ocv189.
20. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials. 2007;28(2):182–91. https://doi.org/10.1016/j.cct.2006.05.007.
21. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying Increased Risk of Readmission and In-hospital Mortality Using Hospital Administrative Data: The AHRQ Elixhauser Comorbidity Index. Med Care. 2017;55(7):698–705. https://doi.org/10.1097/MLR.0000000000000735.

Publisher's Note

Targeted Normoxia in Trauma ICU for Cincinnati (Trauma Only)

Report Date: February 16th, 2022
Data from: July 2020-February 2022
Pre Intervention N= 219
Post Intervention N= 241

Quick things to mention:

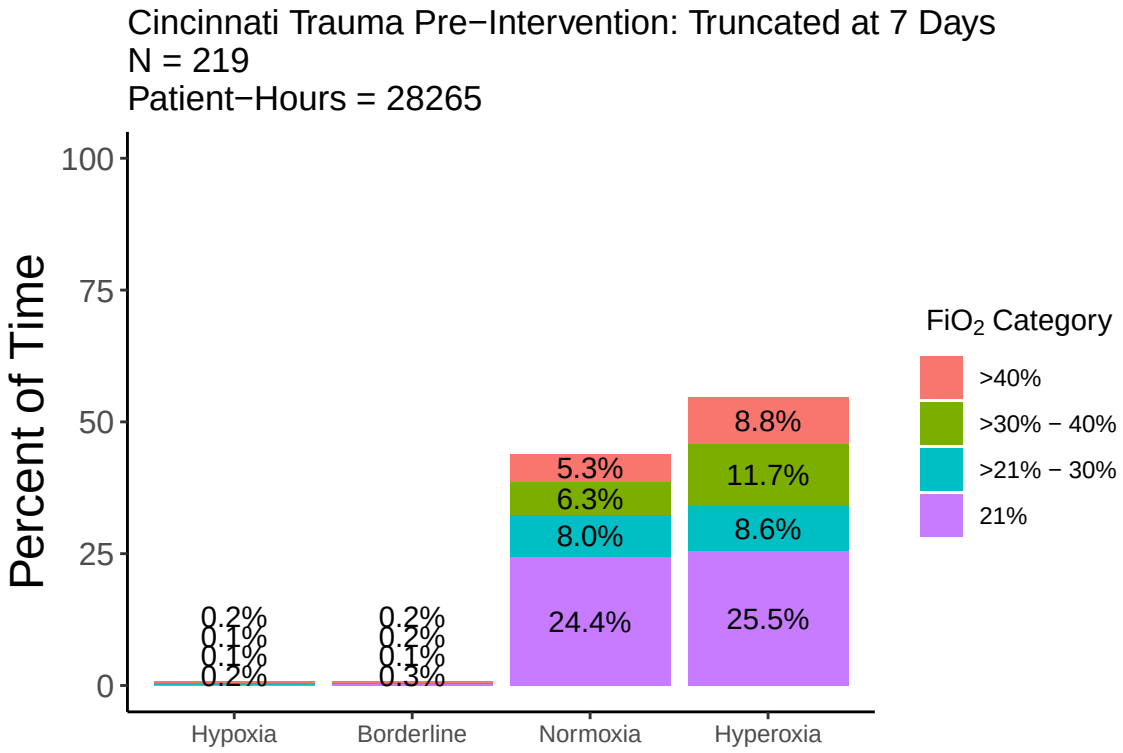
- Pre-Intervention data is static, meaning it cannot be changed
- Purple or FiO2 of 21% is considered "success" for patients in normoxia or hyperoxia (because the oxygen is as low as it can go)
- Main objective is to move patients with an FiO2 >21% and hyperoxia into the normoxia levels with less FiO2 administration or down to FiO2 21%
- Pay specific attention to FiO2 >30% and hyperoxia—every attempt should be made to minimize/eliminate this (unless there is a specific clinical indication)

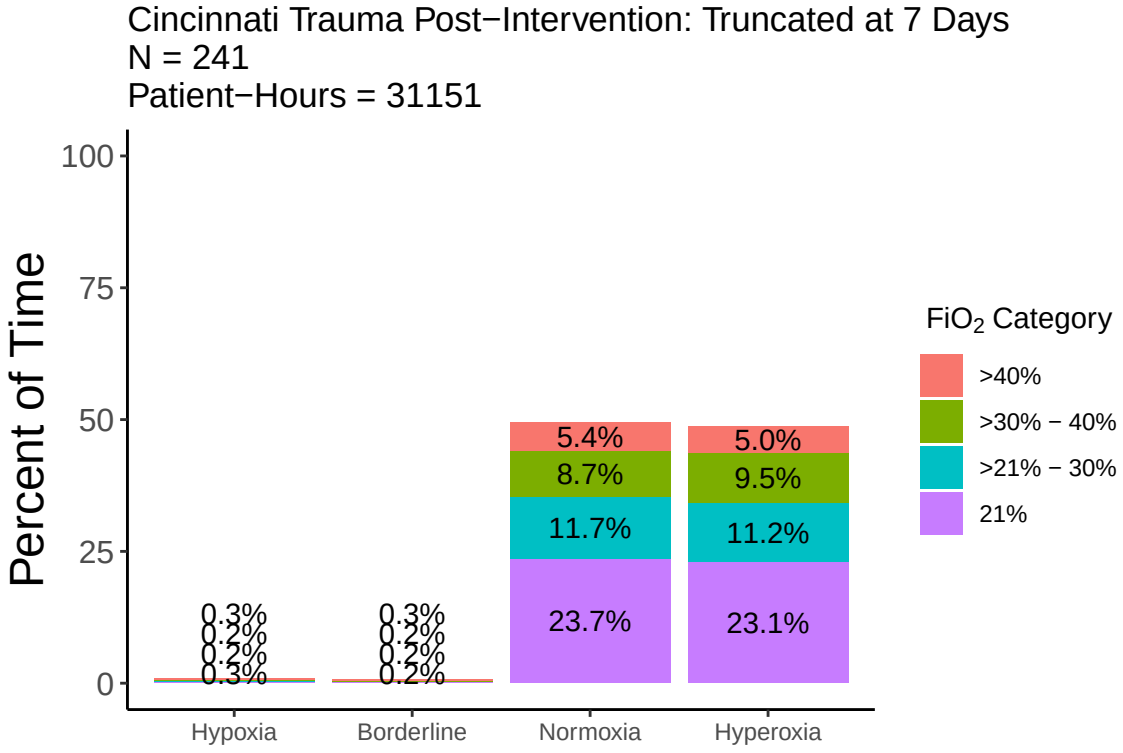
Quick tips for increased compliance (>90% of patient time spent in normoxia or at FiO2 = 21%)

- 1.Educate respiratory therapy, nurses and physicians on oxygenation strategy in ventilated patients and non-ventilated patients, attempting to reduce FiO2 and L/min to maintain an SpO2 of 90-96%.
- 2. Attend rounds on the unit to discuss why a patient is hyperoxic and is there the ability to down titrate FiO2, or is there a special circumstance as to why they remain at a higher FiO2.
- 3. Attend unit level meetings to remind clinicians of the oxygenation strategy

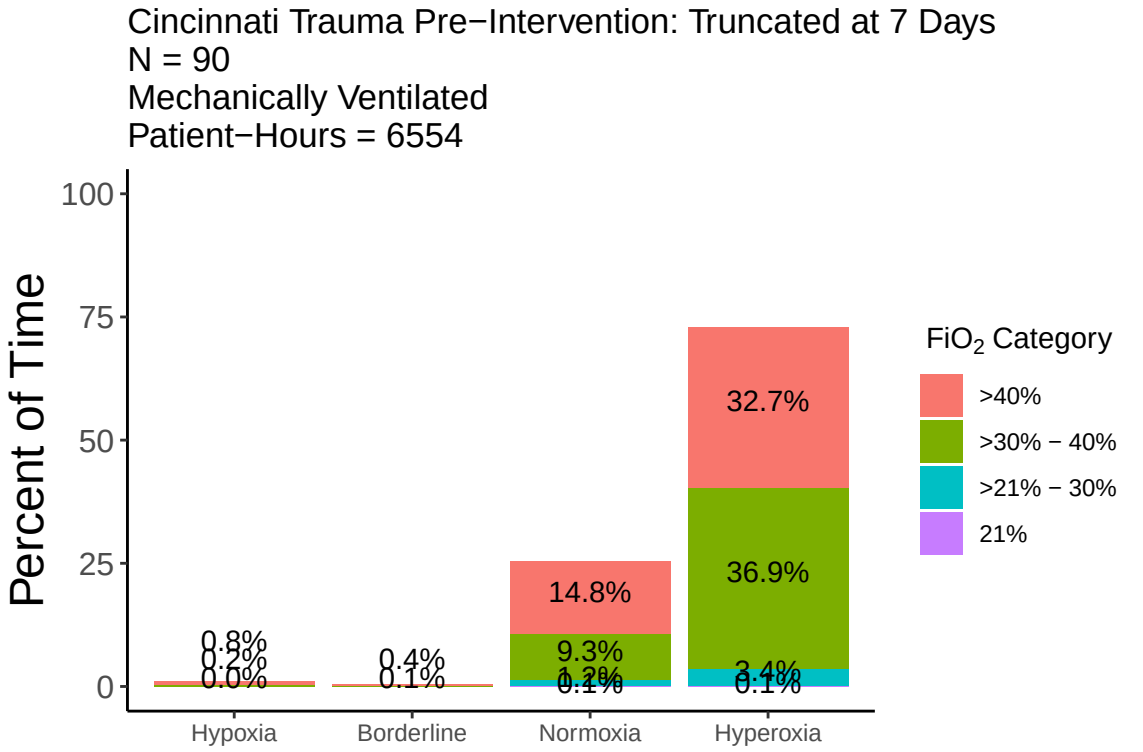
SAVE-O2 Cincinnati Trauma Report: 02/14/2022

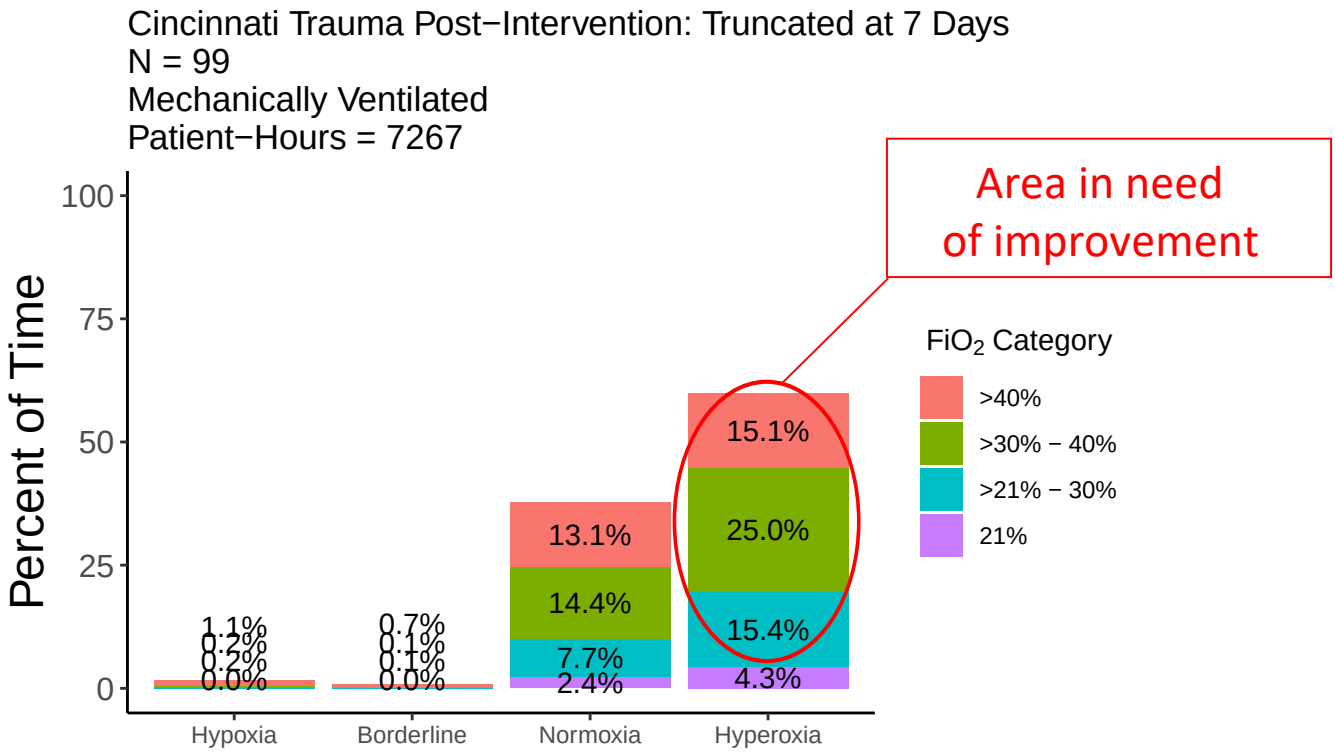
Overall Differences



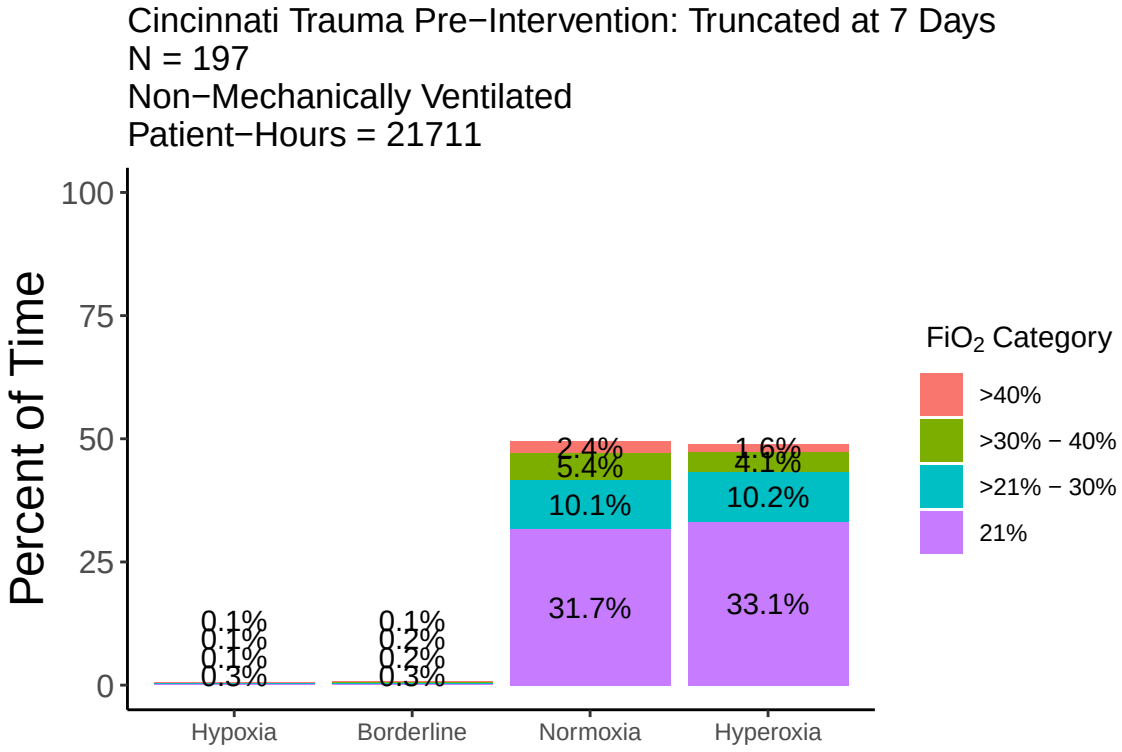


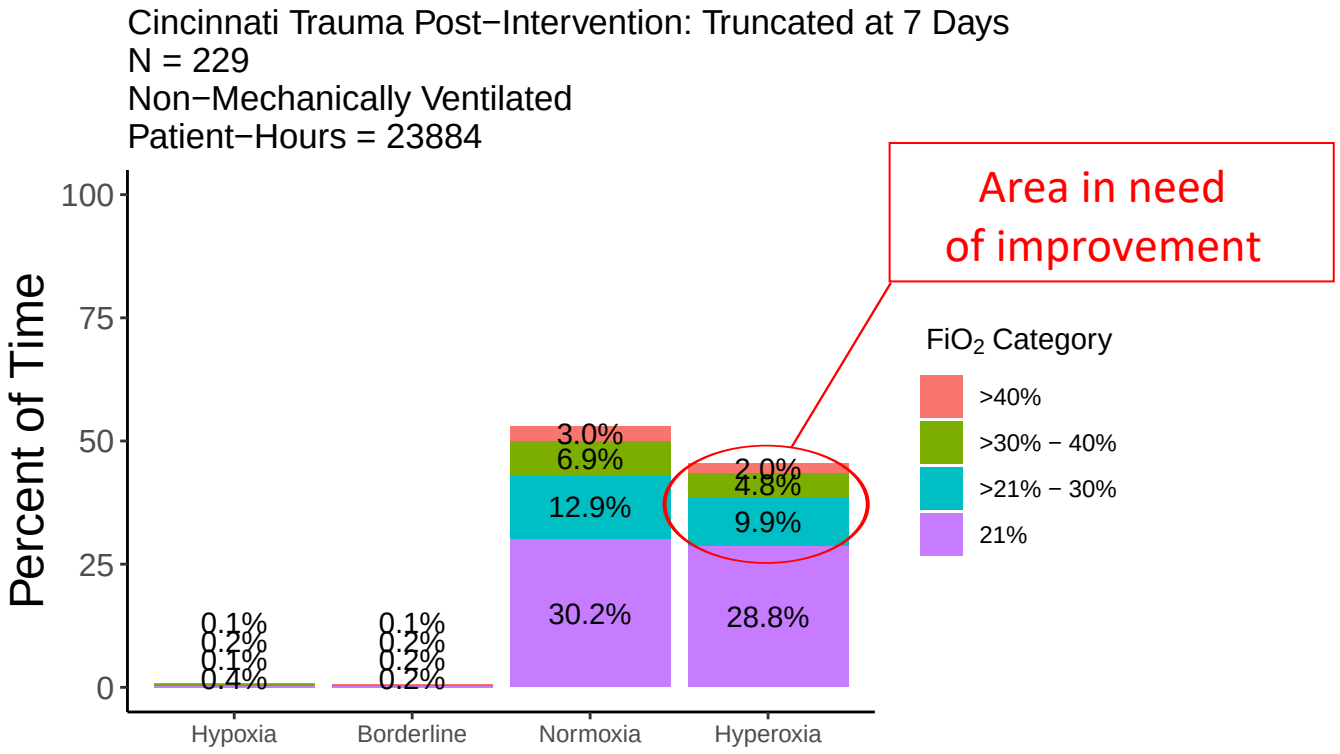
Mechanically Ventilated



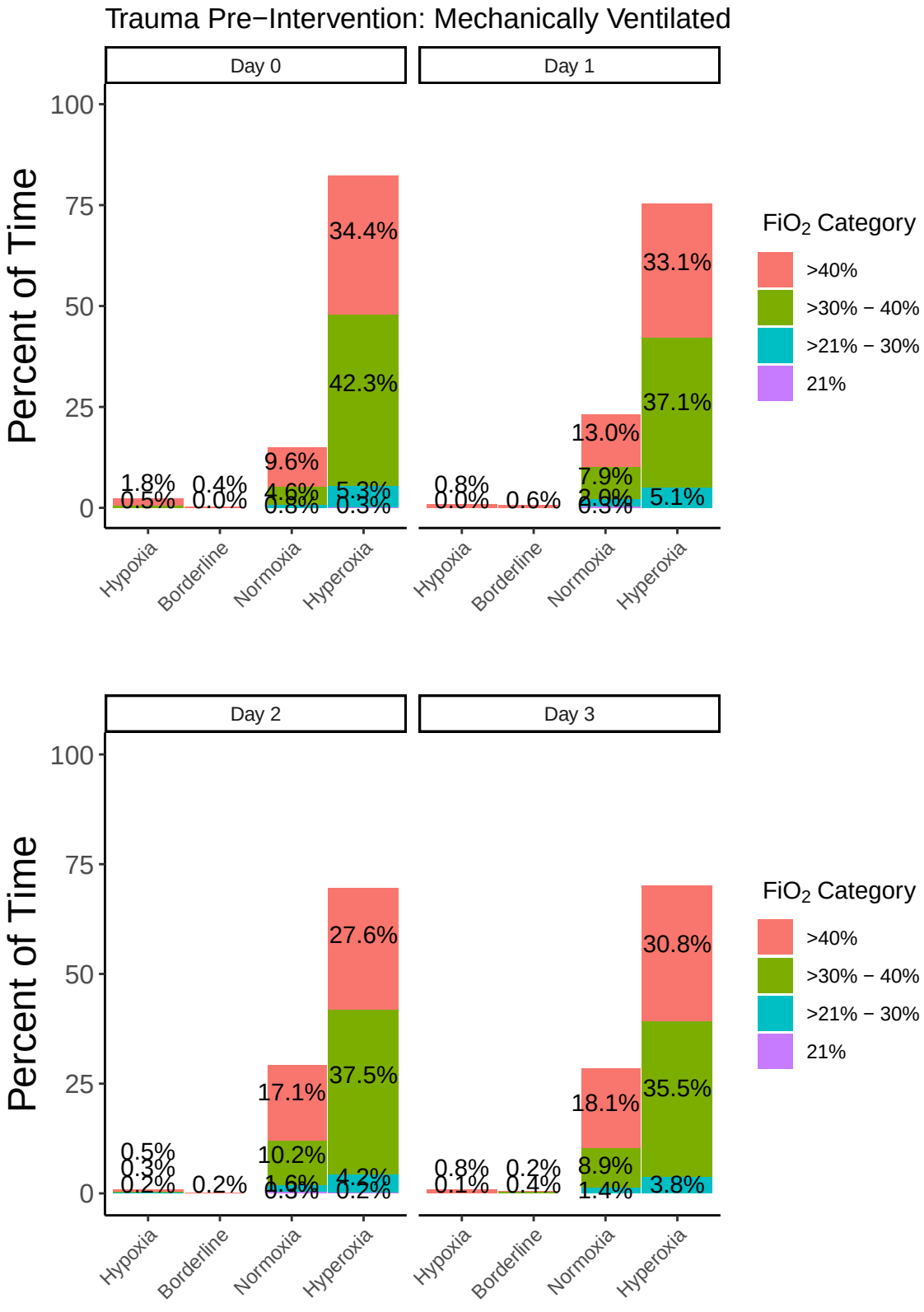


Non-Mechanically Ventilated

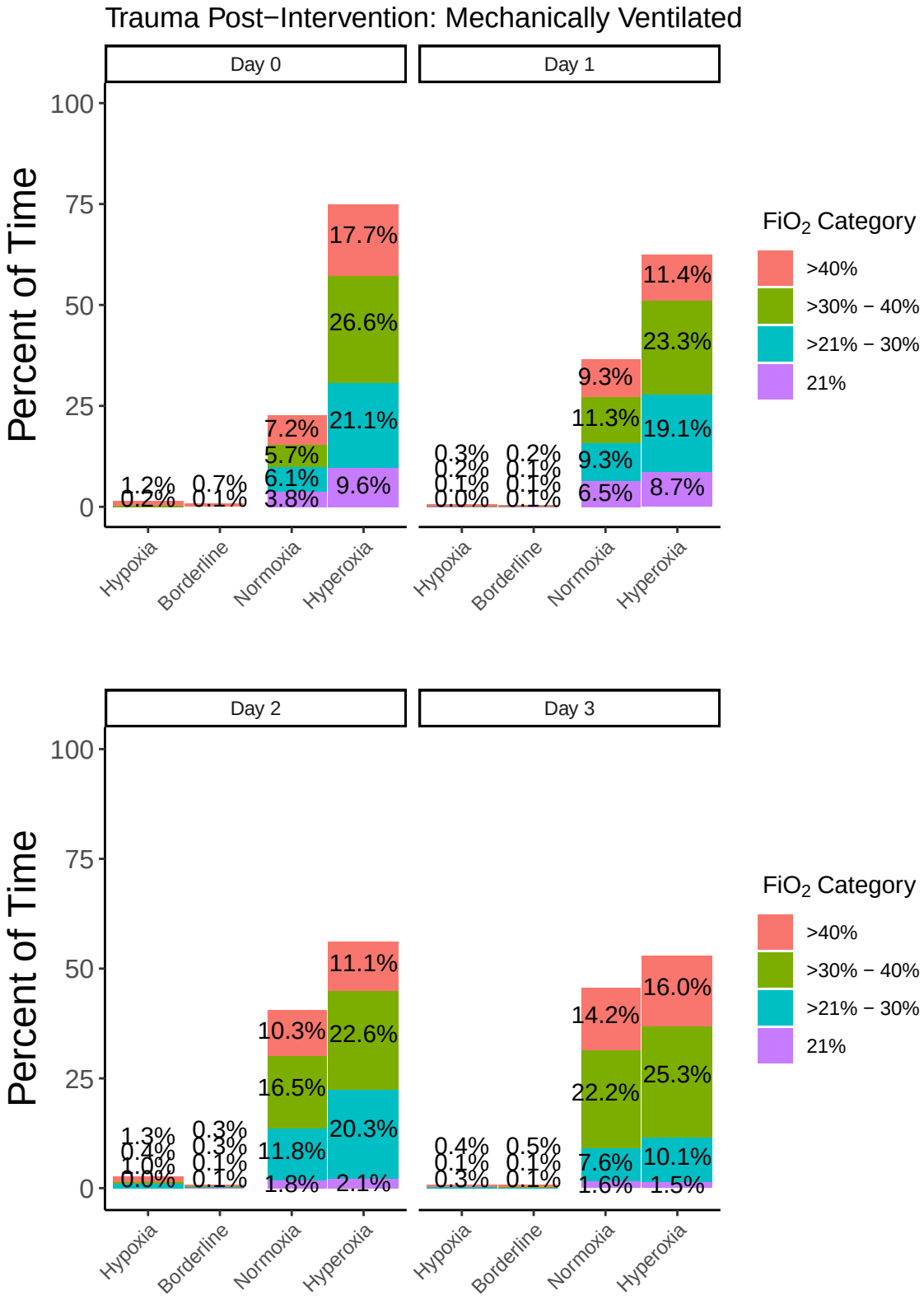




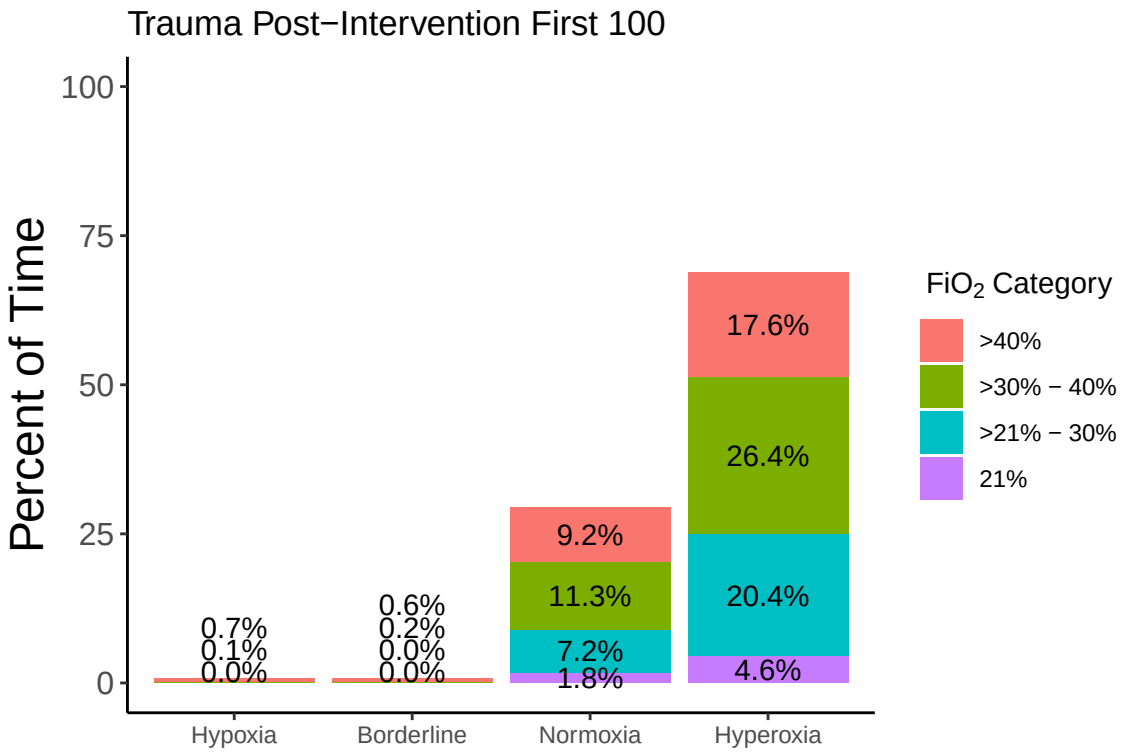
First 4 Days (Pre-Intervention)

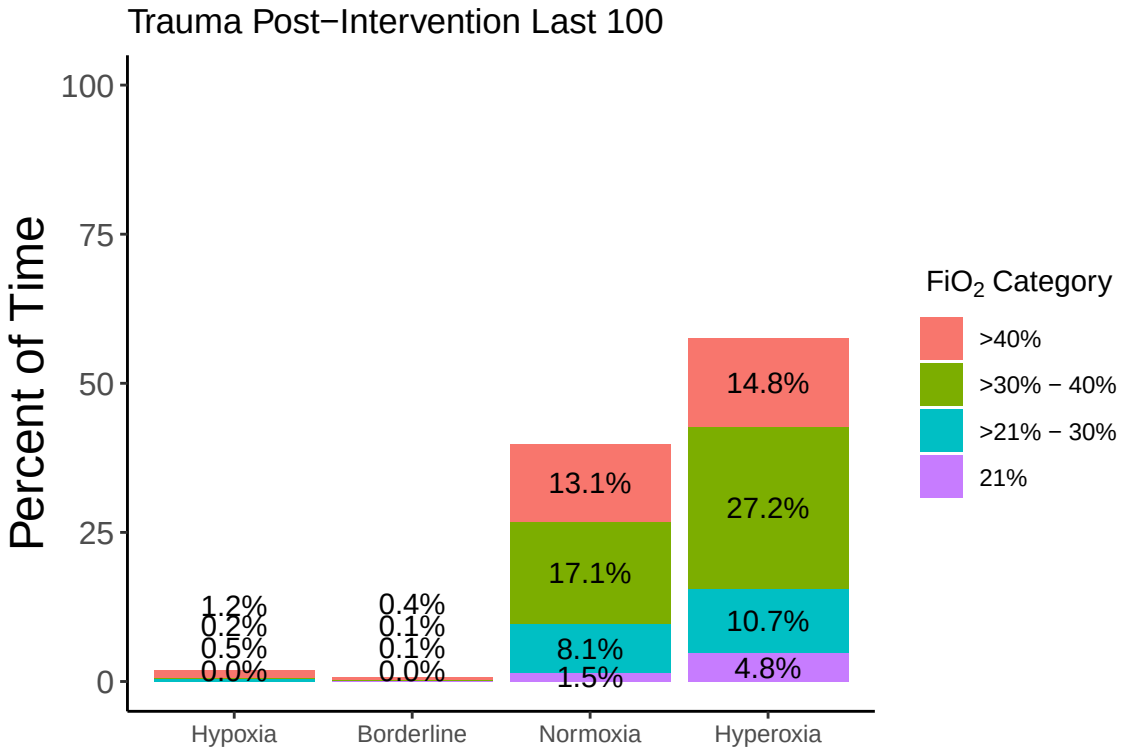


First 4 Days (Post-Intervention)

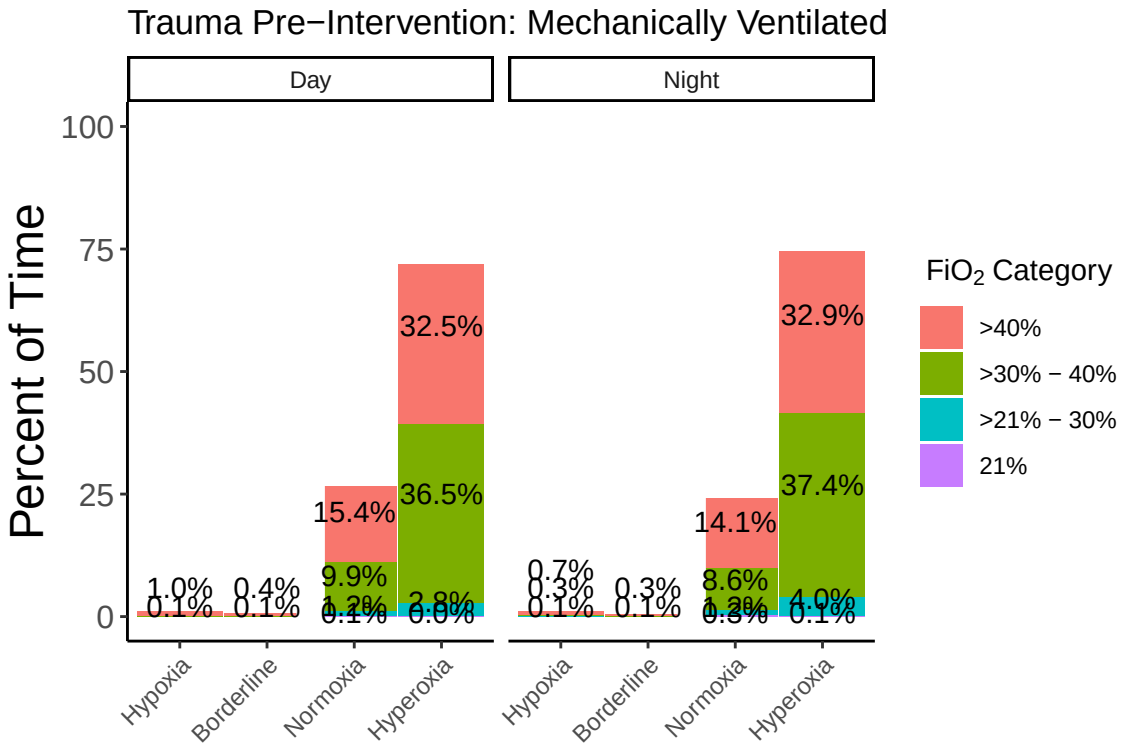


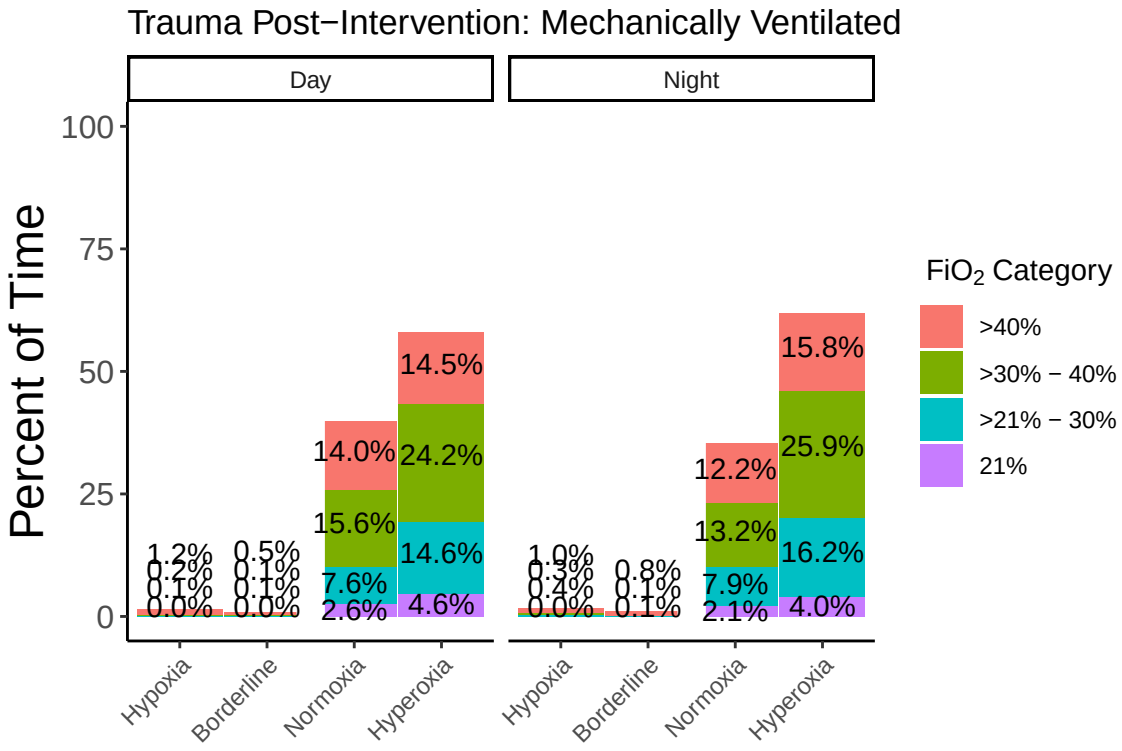
First and Last 100: Mechanically Ventilated





Day vs Night Shift (Post-Intervention)





Targeted Normoxia in Trauma ICU for Denver Health

Report Date: March 3rd, 2022
Data from: July 2020-February 2022
Pre Intervention N= 818
Post Intervention N= 535

Quick things to mention:

- Pre-Intervention data is static, meaning it cannot be changed
- Purple or FiO2 of 21% is considered "success" for patients in normoxia or hyperoxia (because the oxygen is as low as it can go)
- Main objective is to move patients with an FiO2 >21% and hyperoxia into the normoxia levels with less FiO2 administration or down to FiO2 21%
- Pay specific attention to FiO2 >30% and hyperoxia—every attempt should be made to minimize/eliminate this (unless there is a specific clinical indication)

Quick tips for increased compliance (>90% of patient time spent in normoxia or at FiO2 = 21%)

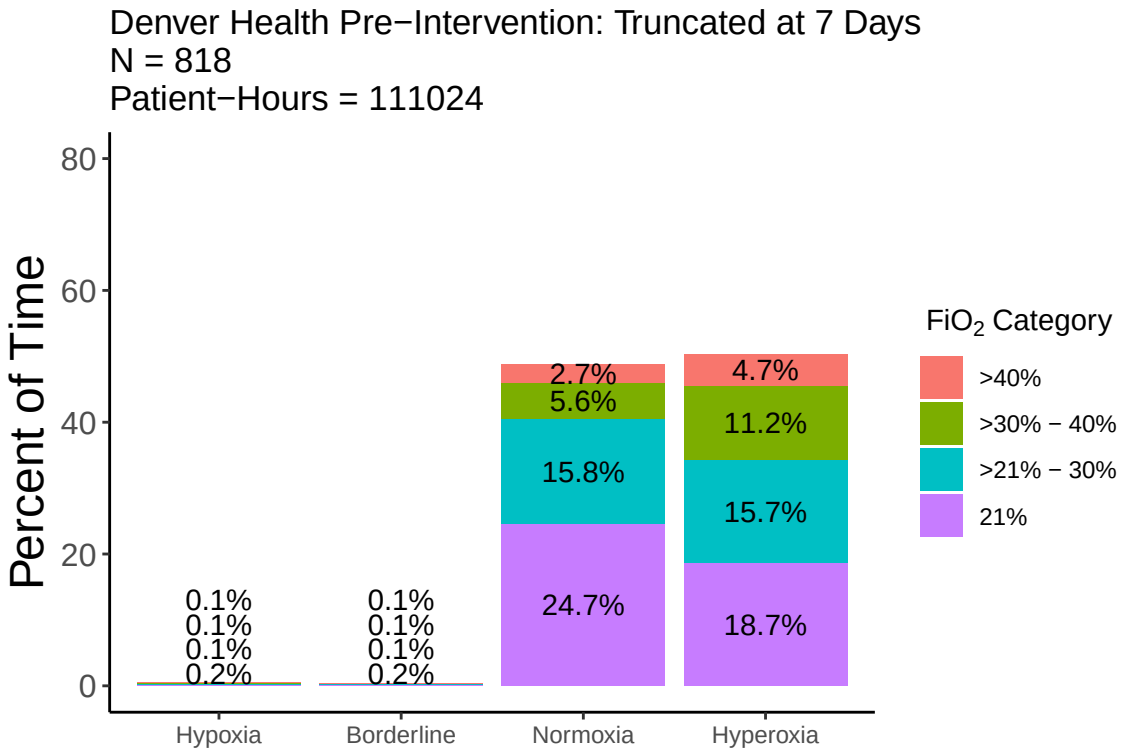
- 1. Provide data reports to clinical staff (respiratory therapy, RNs, and physicians) for information and educational purposes.

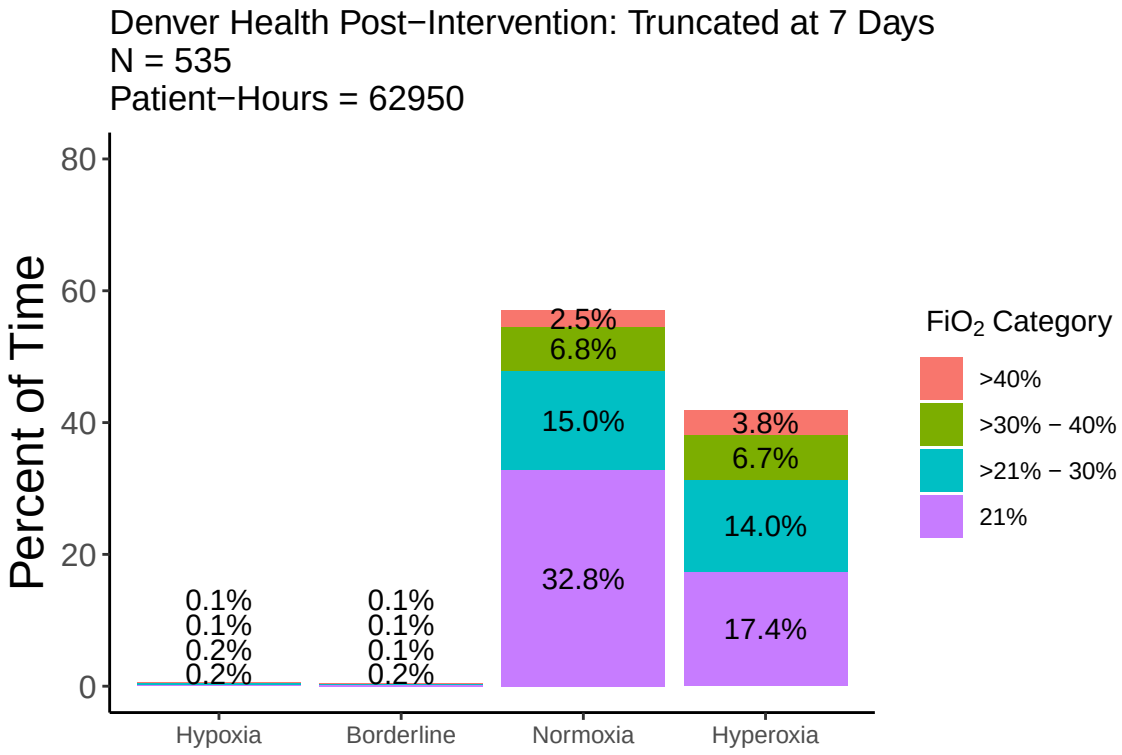
- 2. Provide re-education for clinical staff on oxygenation strategy in mechanically and non-mechanically ventilated patients (reduce FiO2 to 21%, reduce L/min to maintain an SpO2 of 90=-96%).

- 3. Attend huddles, rounds, and/or unit level meetings to remind clinical staff of the oxygenation strategy.

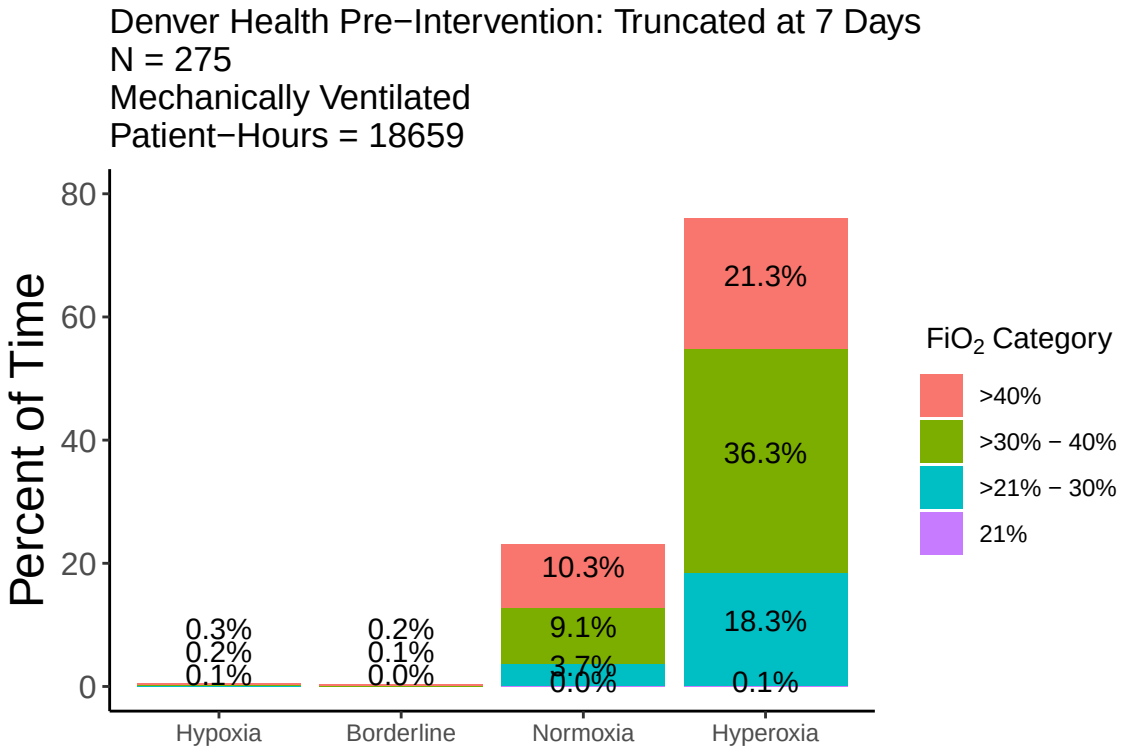
SAVE-O2 Denver Health Report: 03/01/2022

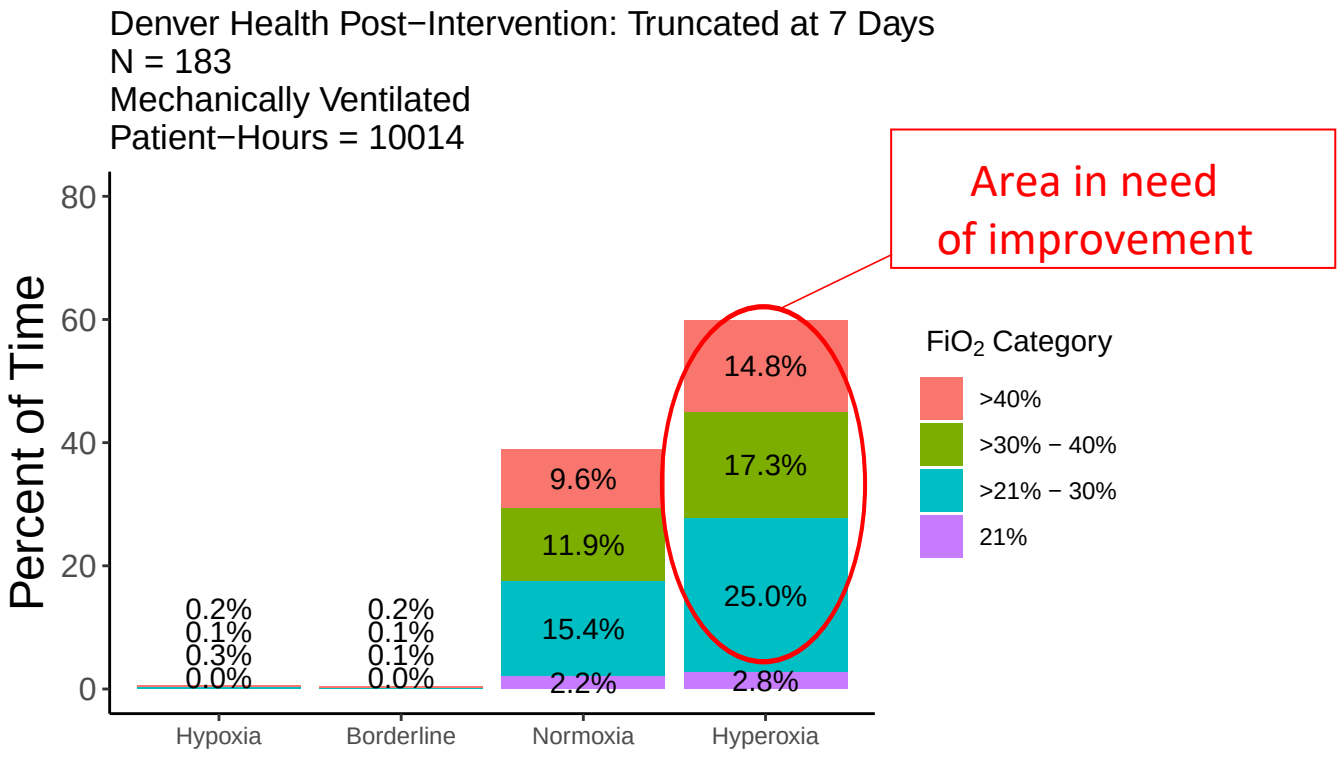
Overall Differences



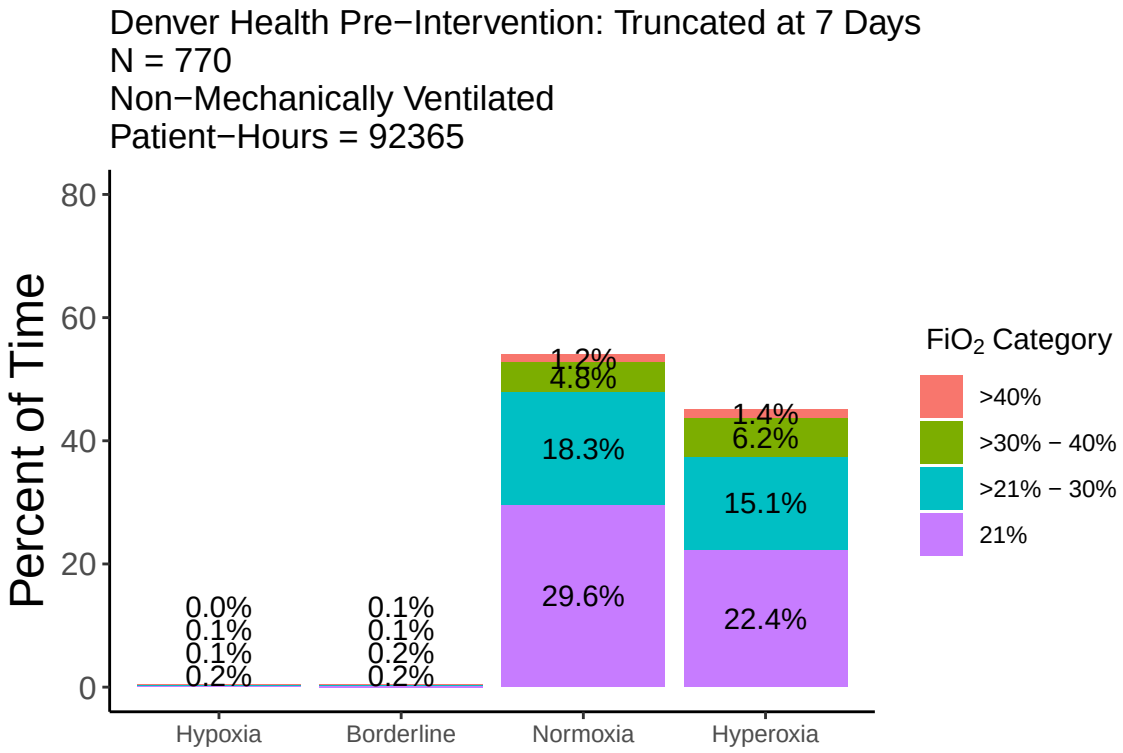


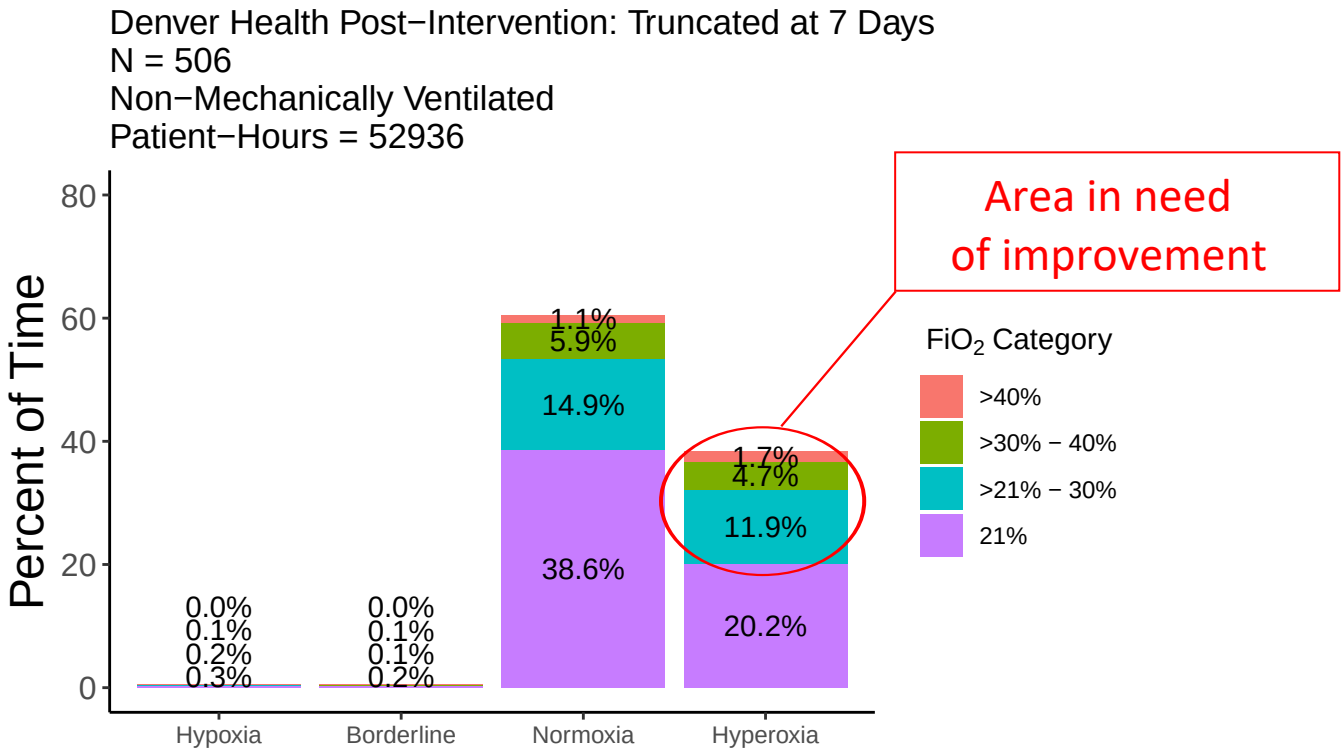
Mechanically Ventilated



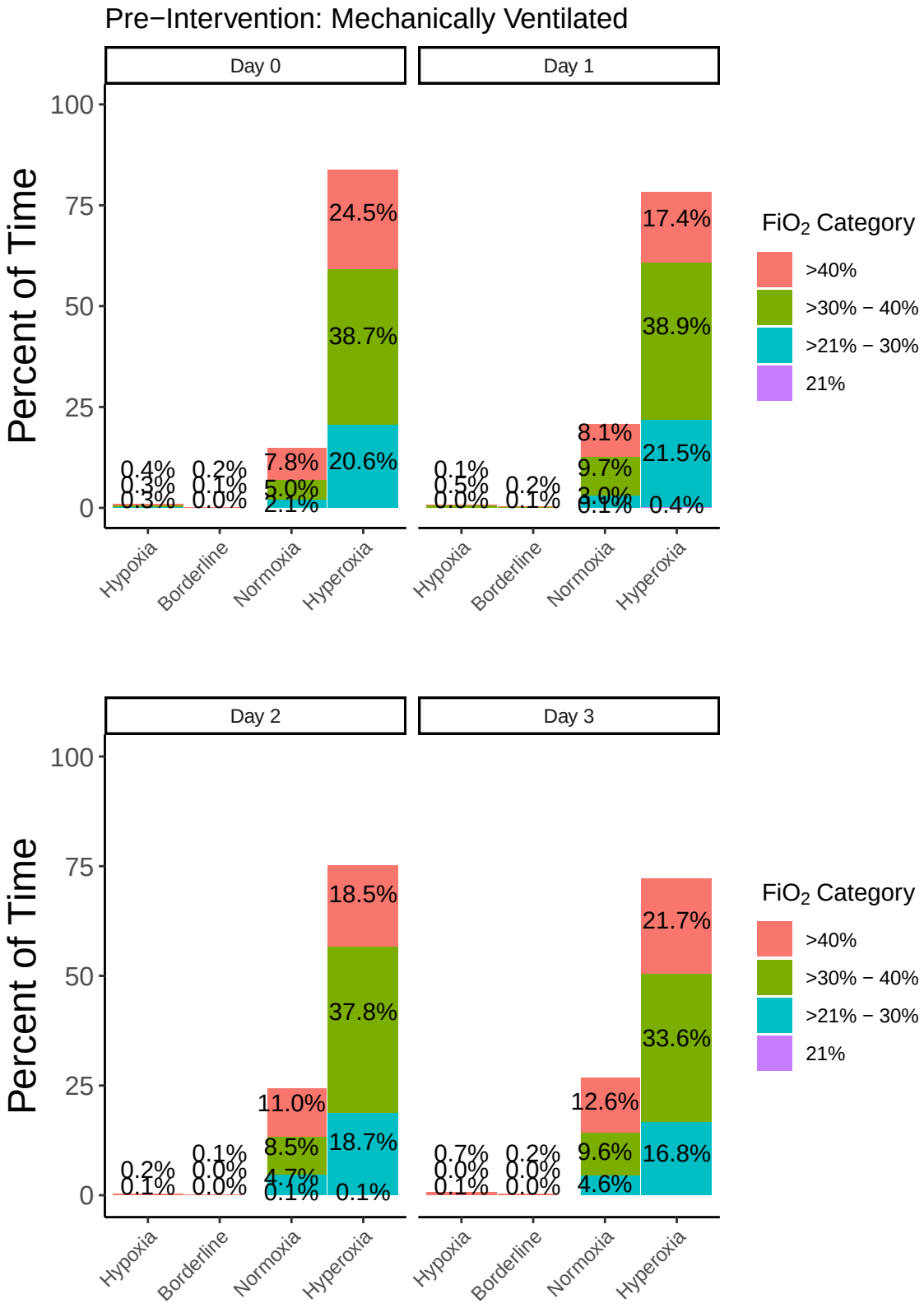


Non-Mechanically Ventilated

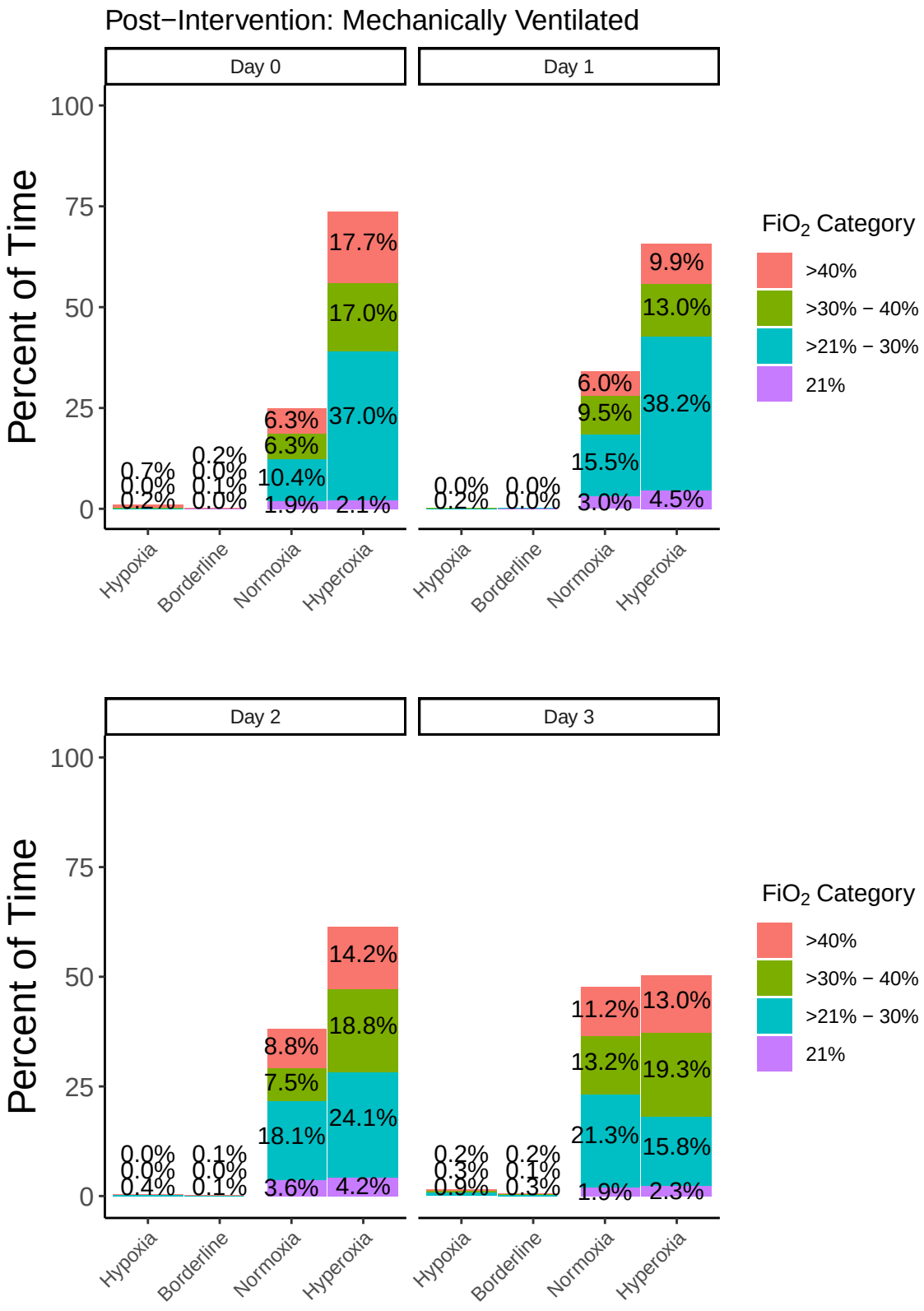




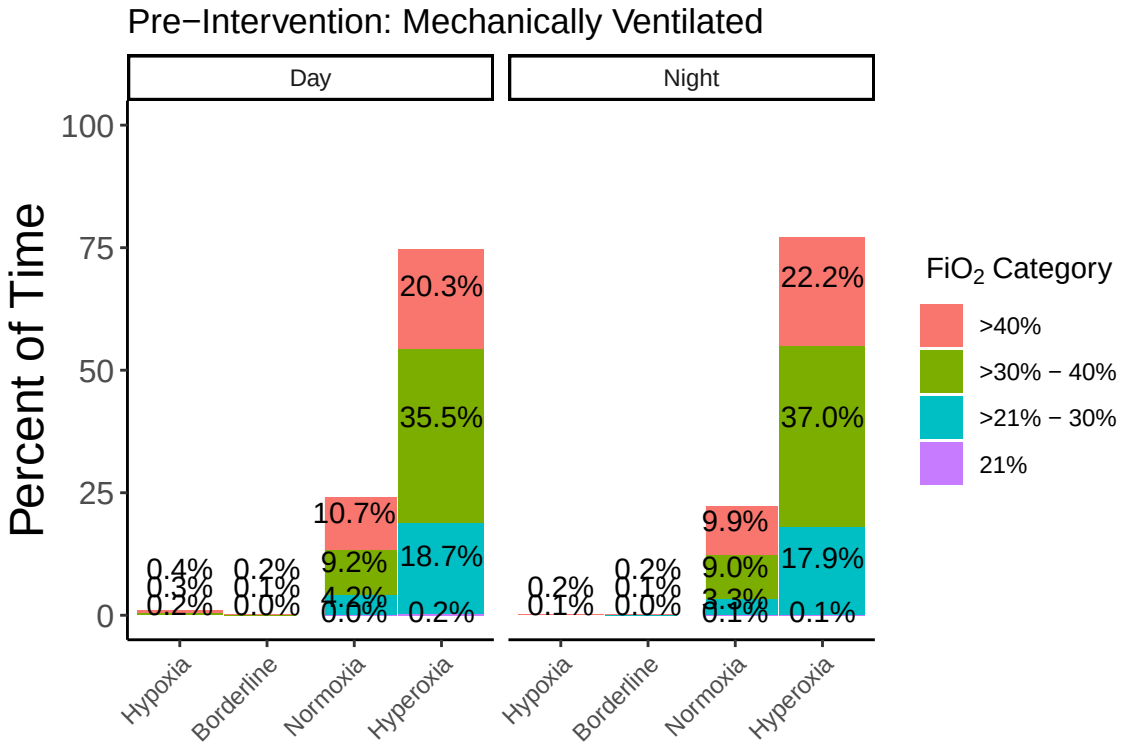
First 4 Days (Pre-Intervention)

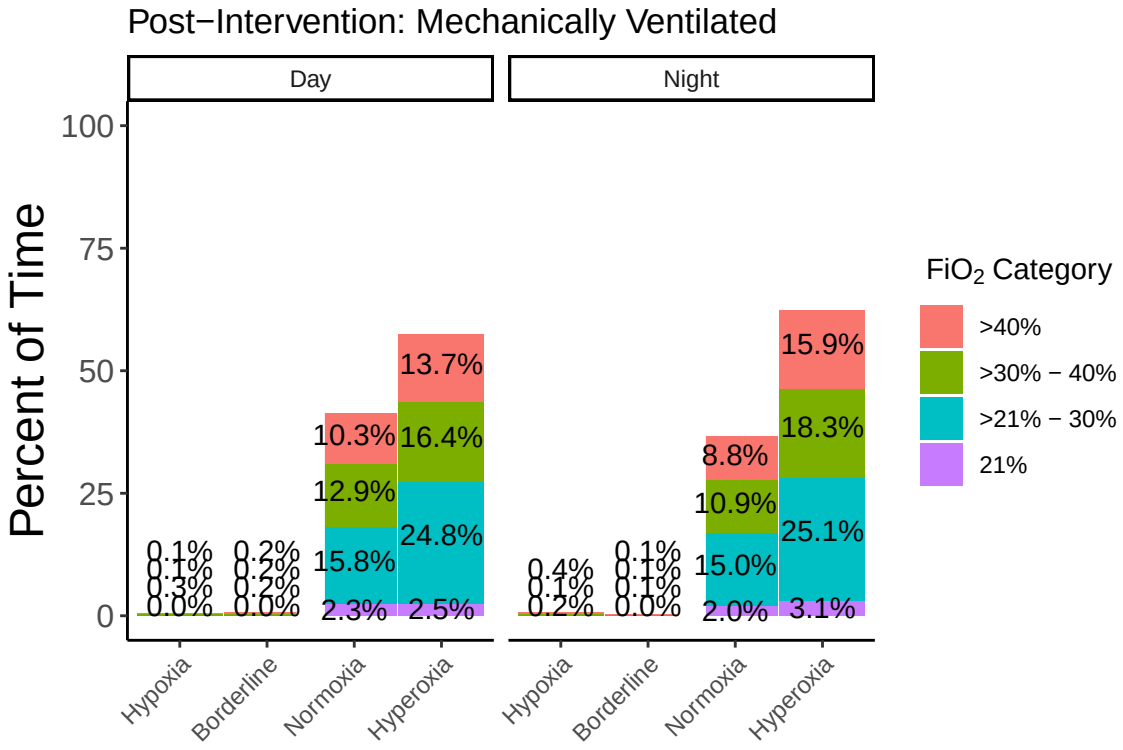


First 4 Days (Post-Intervention)



Day vs Night Shift (Post-Intervention)





Targeted Normoxia in Trauma ICU for SAMMC

Report Date: February 14th, 2022
Data from: July 2020-February 2022
Pre Intervention N= 587
Post Intervention N= 1097

Quick things to mention:

- Pre-Intervention data is static, meaning it cannot be changed
- Purple or FiO2 of 21% is considered "success" for patients in normoxia or hyperoxia (because the oxygen is as low as it can go)
- Main objective is to move patients with an FiO2 >21% and hyperoxia into the normoxia levels with less FiO2 administration or down to FiO2 21%
- Pay specific attention to FiO2 >30% and hyperoxia—every attempt should be made to minimize/eliminate this (unless there is a specific clinical indication)

Quick tips for increased compliance (>90% of patient time spent in normoxia or at FiO2 = 21%)

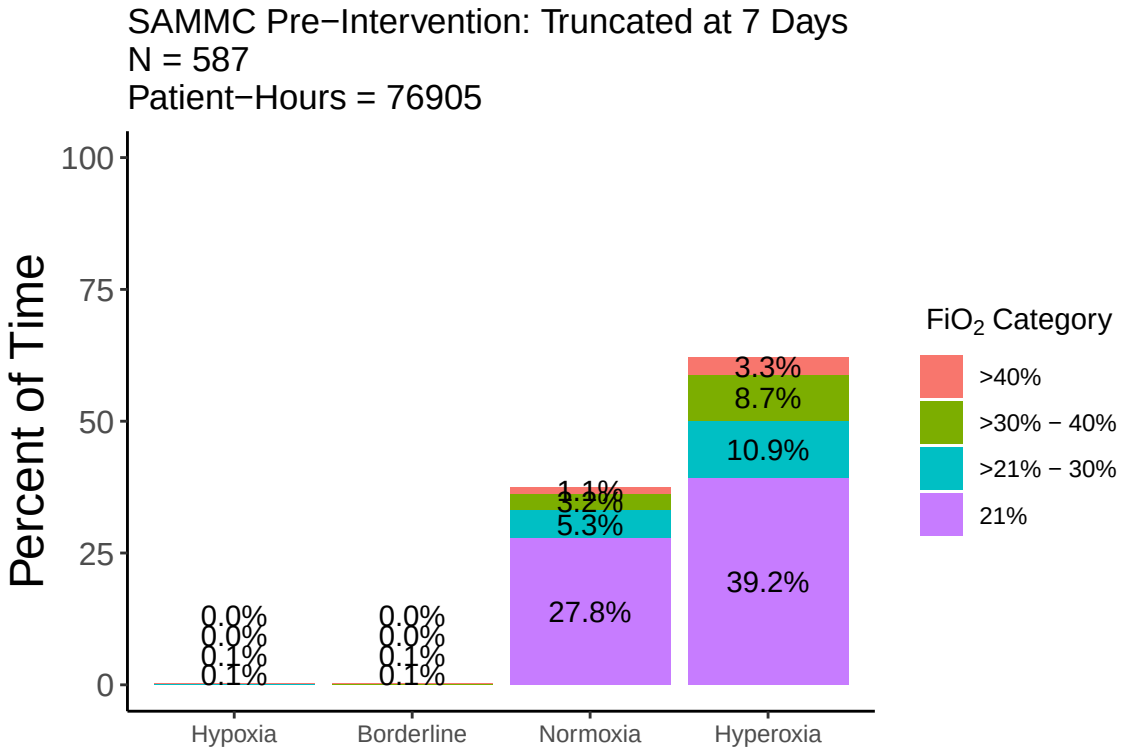
- 1. Provide data reports to clinical staff (respiratory therapy, RNs, and physicians) for information and educational purposes.

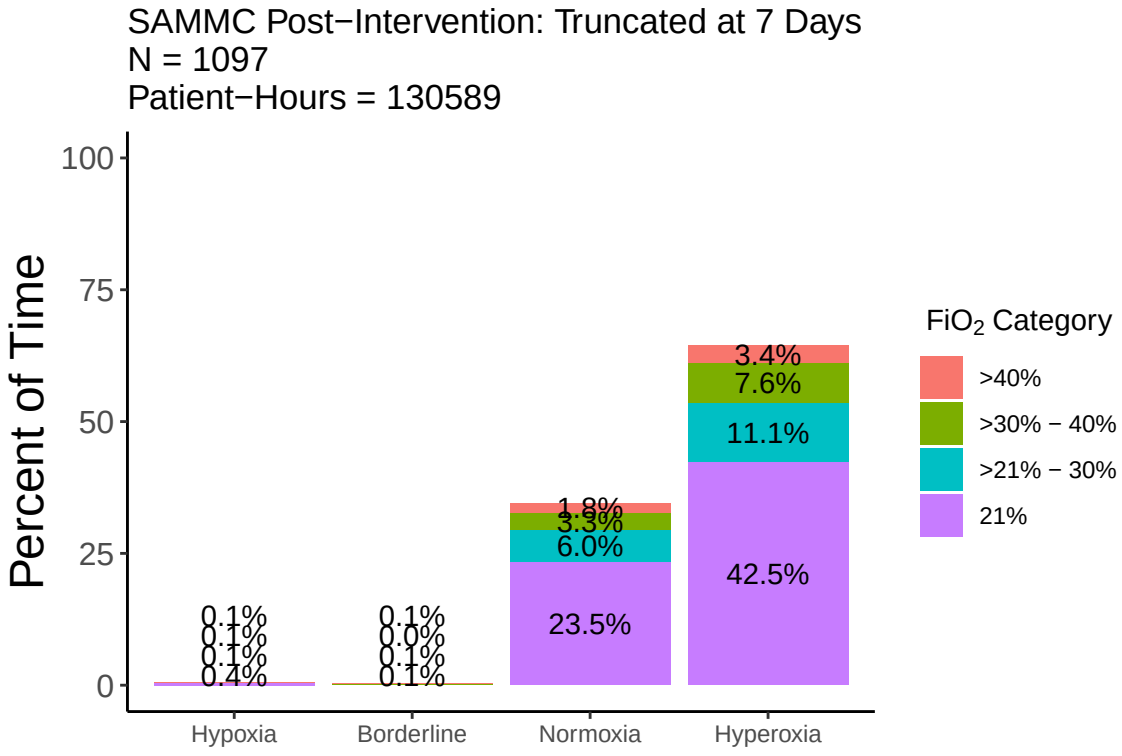
- 2. Provide re-education for clinical staff on oxygenation strategy in mechanically and non-mechanically ventilated patients (reduce FiO2 to 21%, reduce L/min to maintain an SpO2 of 90=-96%).

- 3. Attend huddles, rounds, and/or unit level meetings to remind clinical staff of the oxygenation strategy.

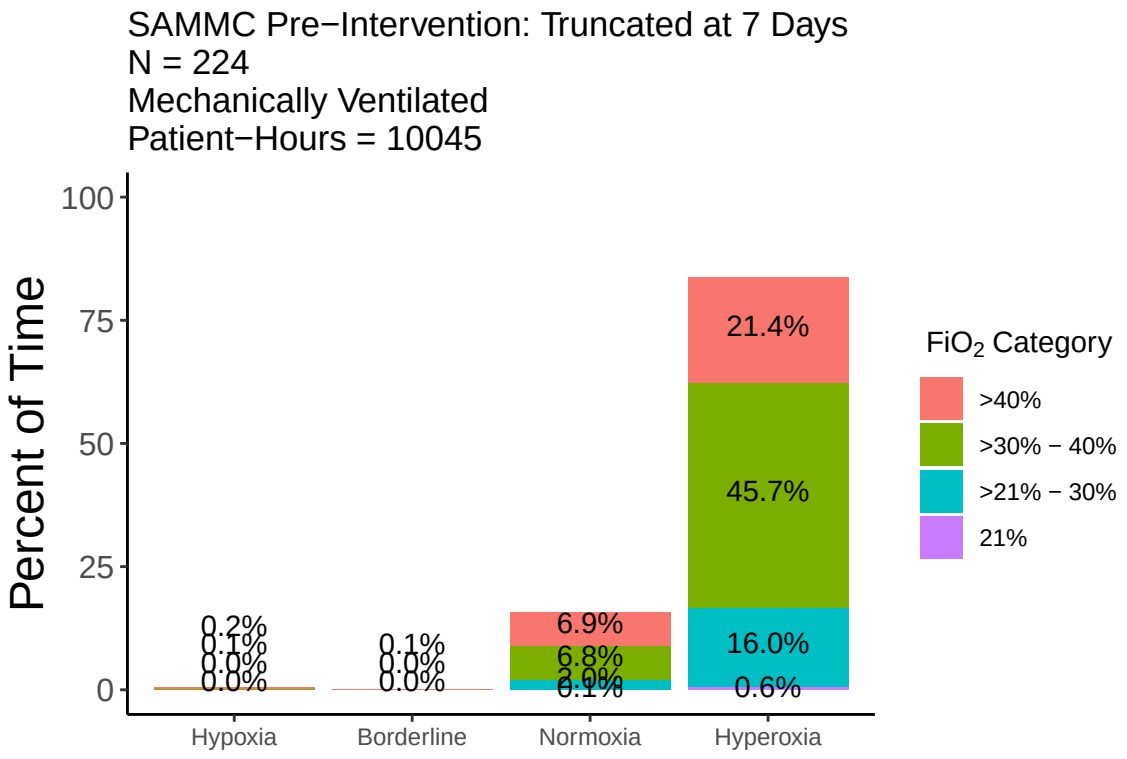
SAVE-O2 SAMMC Report: 02/11/2022

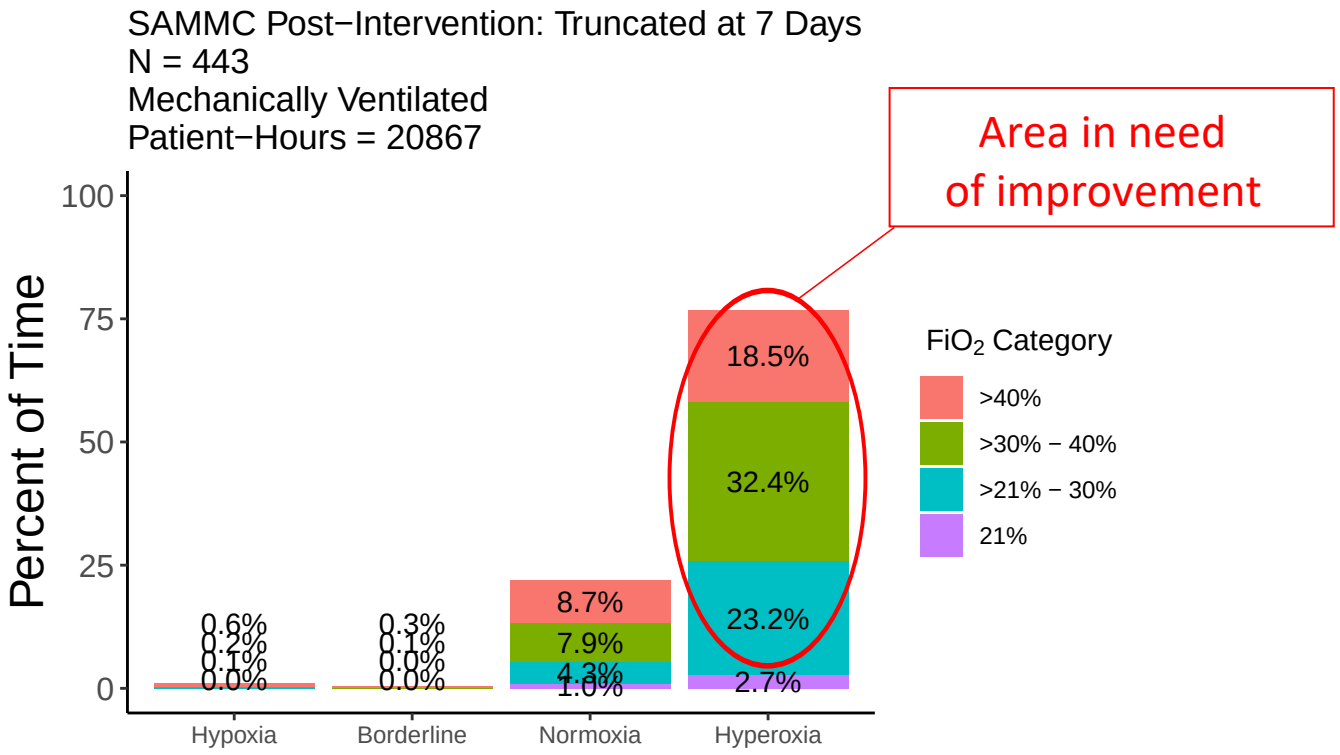
Overall Differences



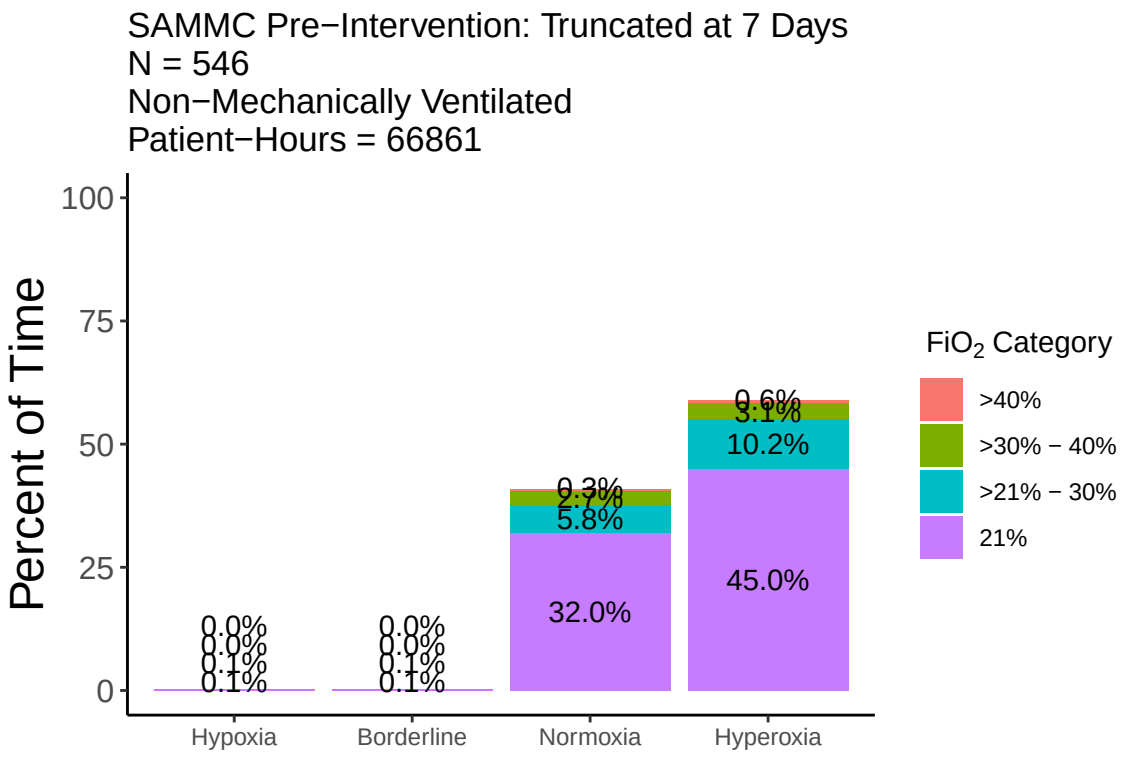


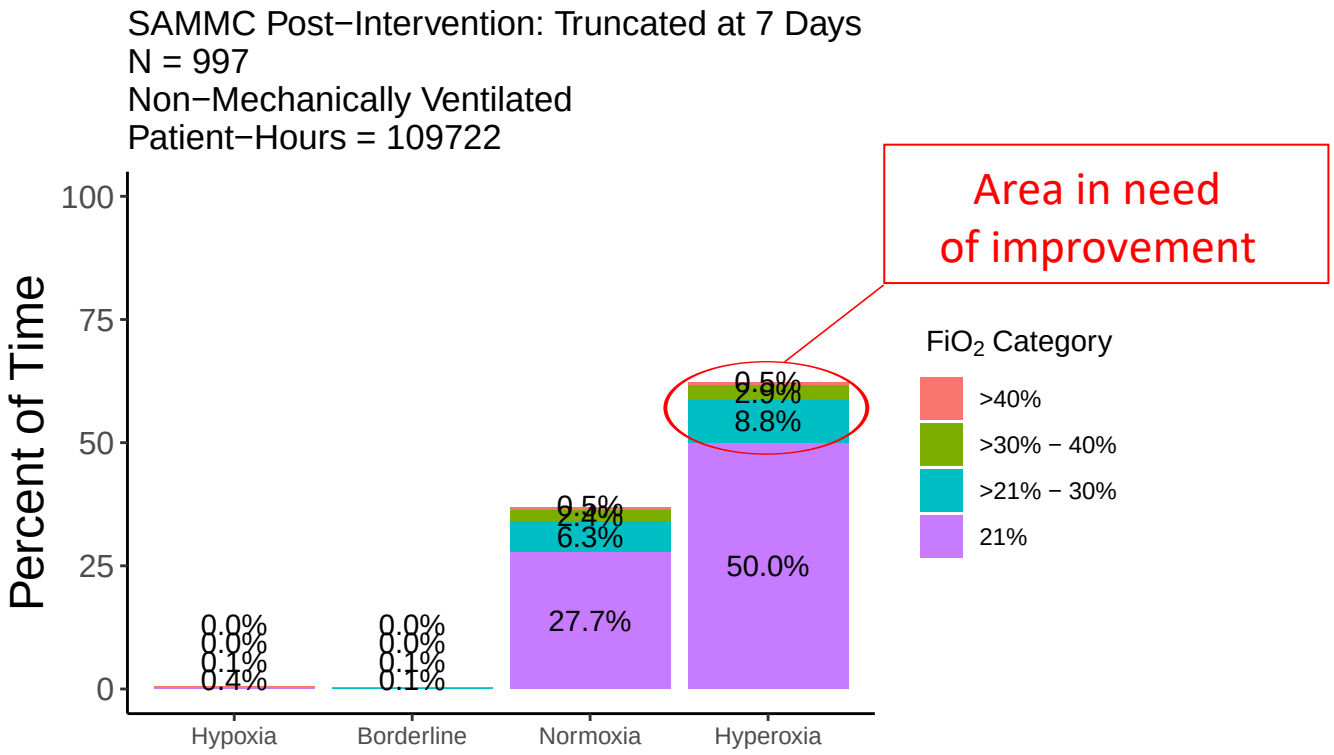
Mechanically Ventilated



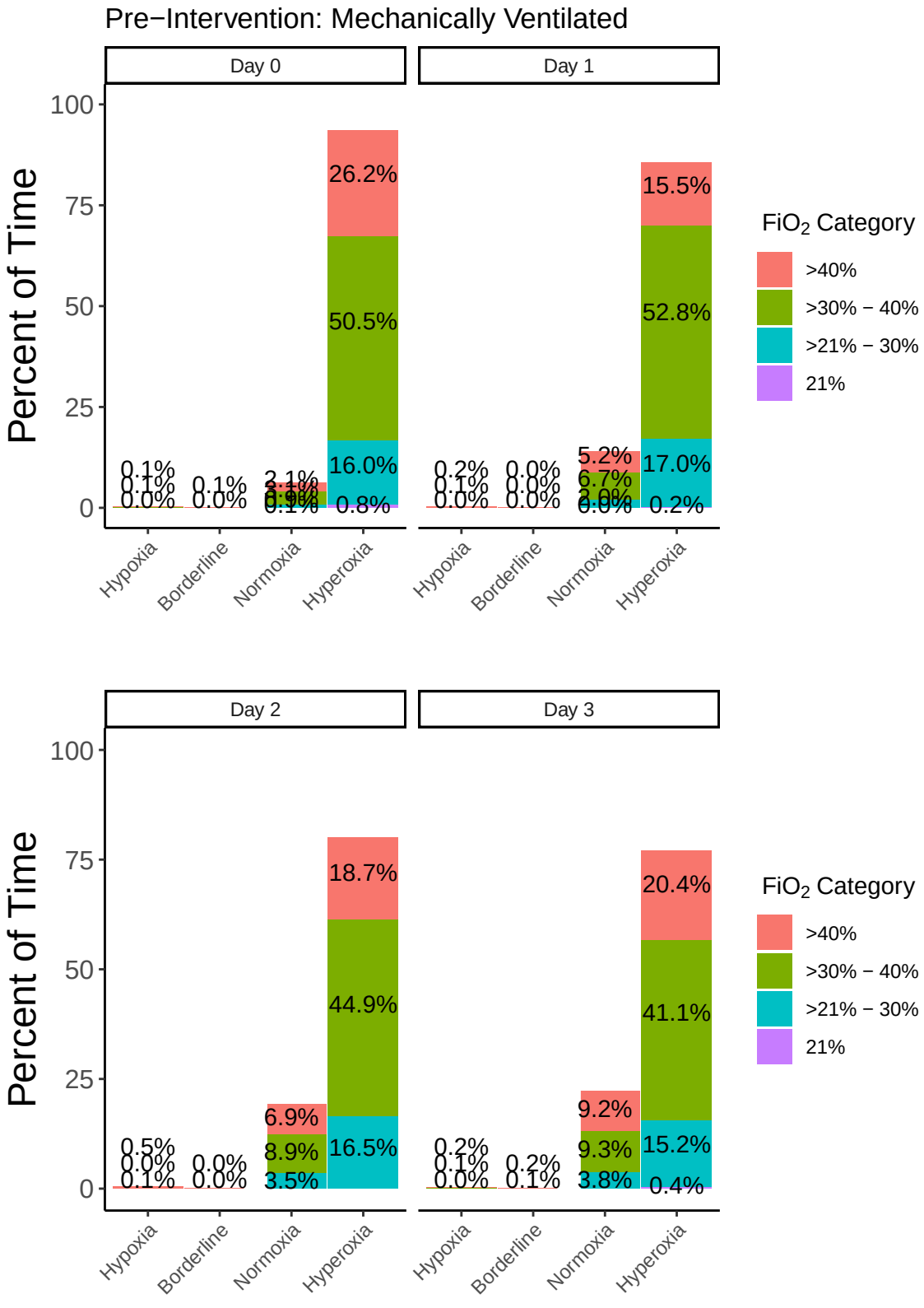


Non-Mechanically Ventilated

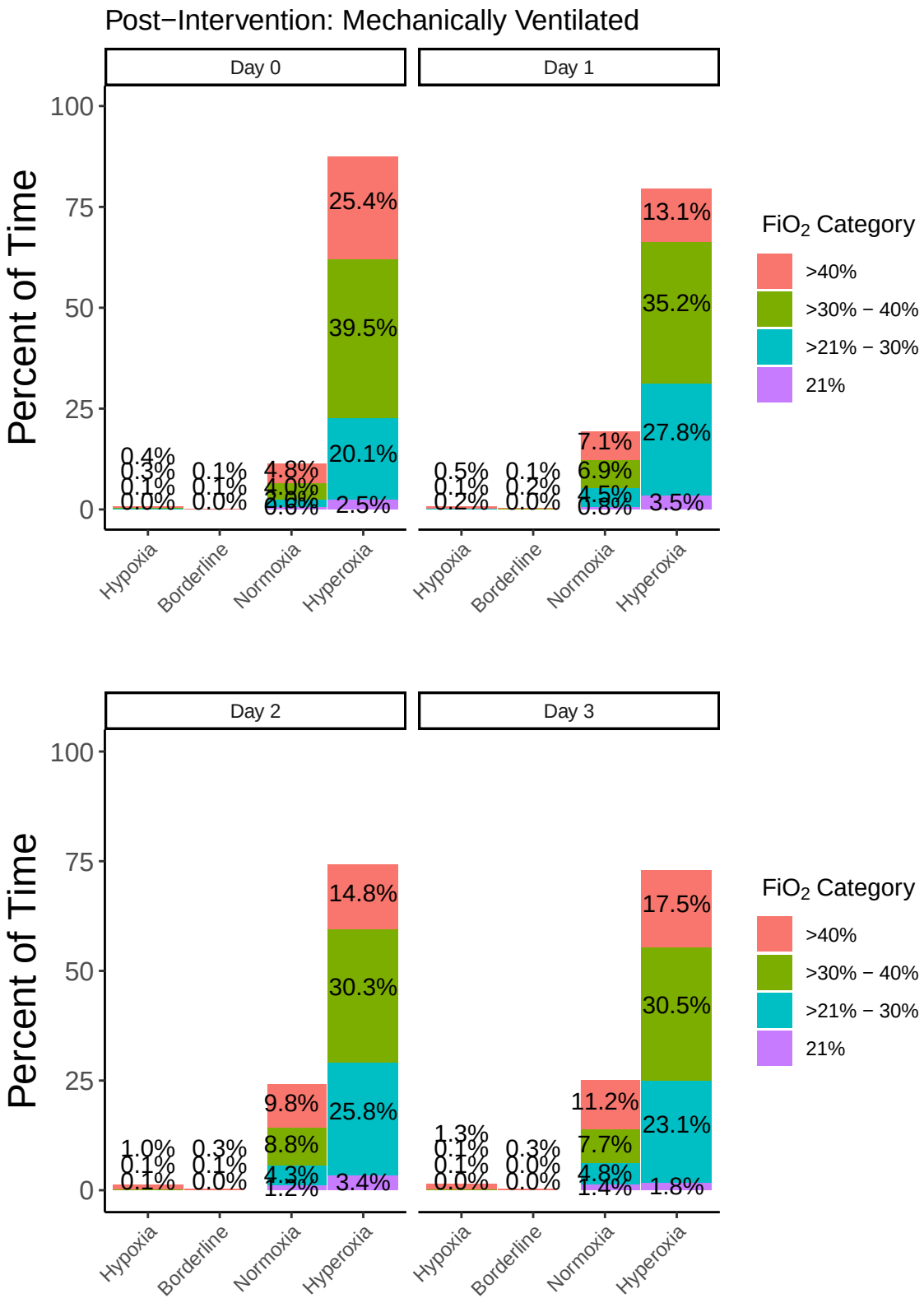




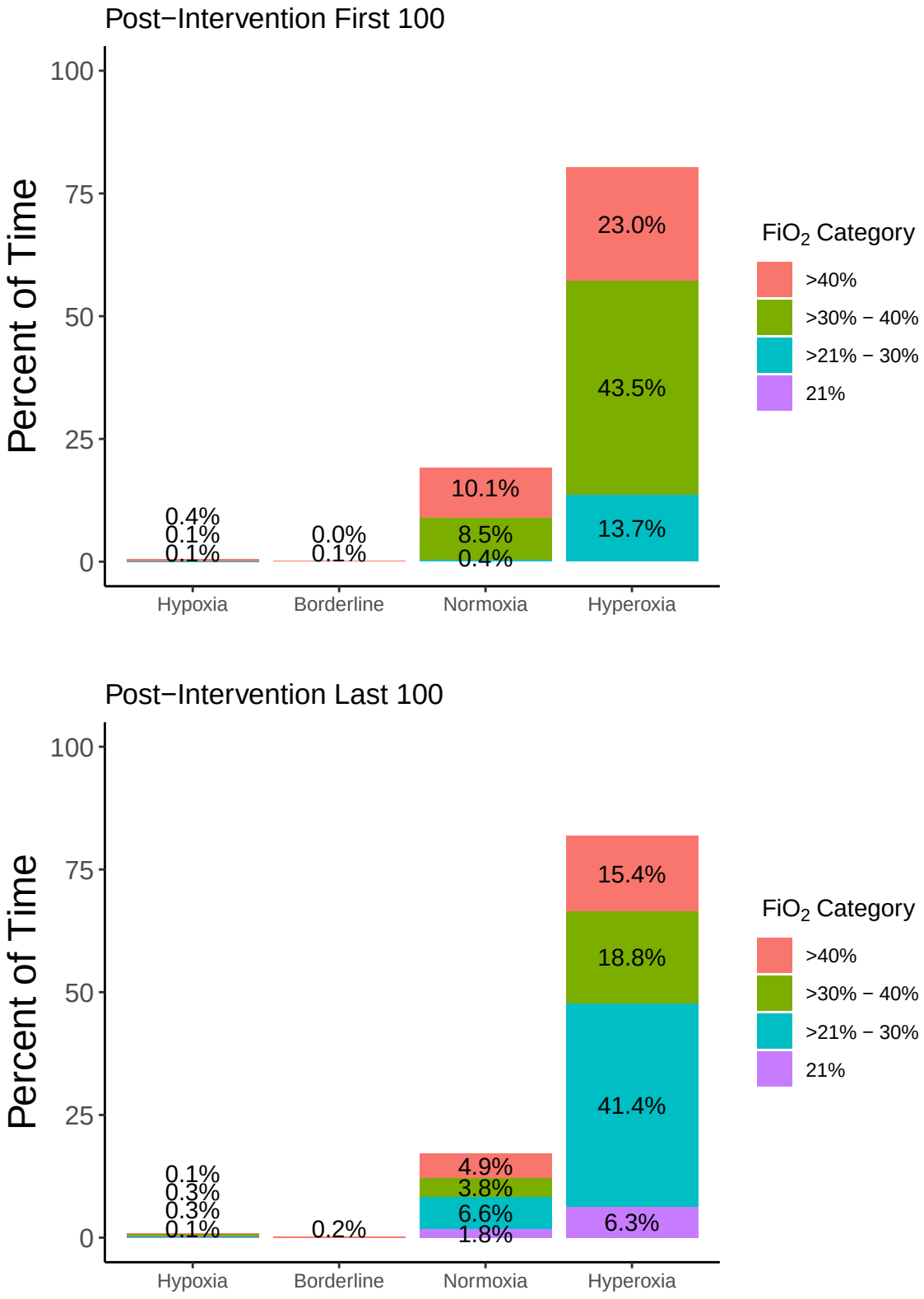
First 4 Days (Pre-Intervention)



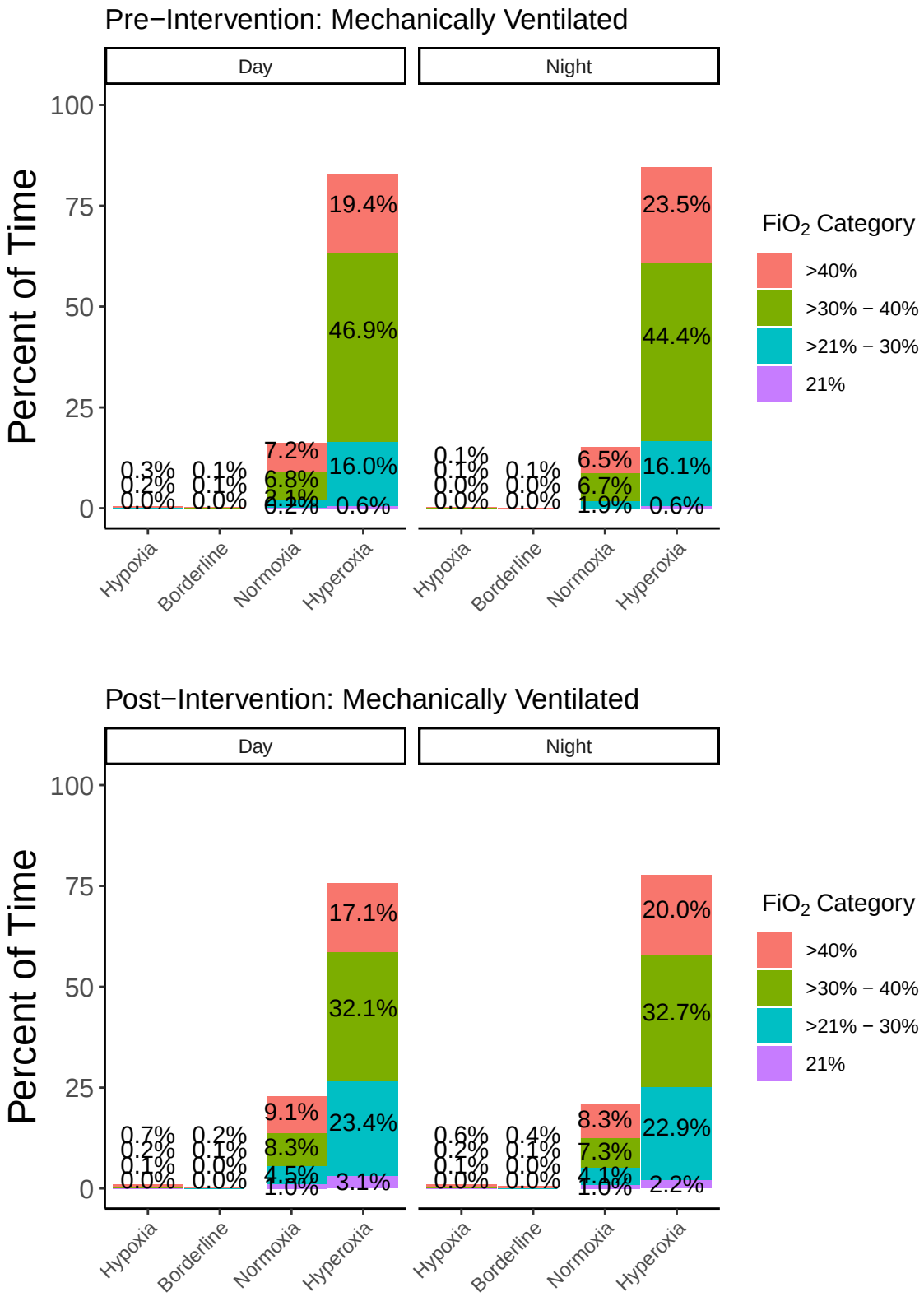
First 4 Days (Post-Intervention)



First and Last 100: Mechanically Ventilated



Day vs Night Shift (Post-Intervention)



Targeted Normoxia in Trauma ICU for UT-Houston

Report Date: February 14th, 2022
Data from: July 2020-February 2022
Pre Intervention N= 14
Post Intervention N= 103

Quick things to mention:

- Pre-Intervention data is static, meaning it cannot be changed
- Purple or FiO2 of 21% is considered "success" for patients in normoxia or hyperoxia (because the oxygen is as low as it can go)
- Main objective is to move patients with an FiO2 >21% and hyperoxia into the normoxia levels with less FiO2 administration or down to FiO2 21%
- Pay specific attention to FiO2 >30% and hyperoxia—every attempt should be made to minimize/eliminate this (unless there is a specific clinical indication)

Quick tips for increased compliance (>90% of patient time spent in normoxia or at FiO2 = 21%)

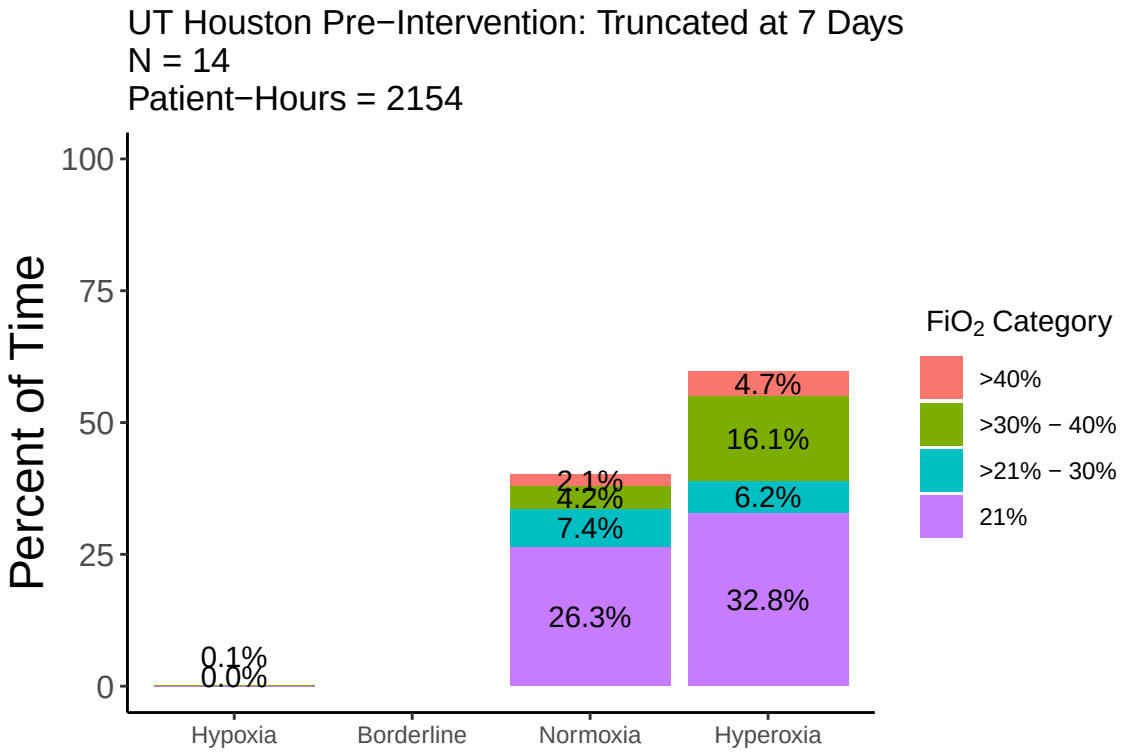
- 1. Provide data reports to clinical staff (respiratory therapy, RNs, and physicians) for information and educational purposes.

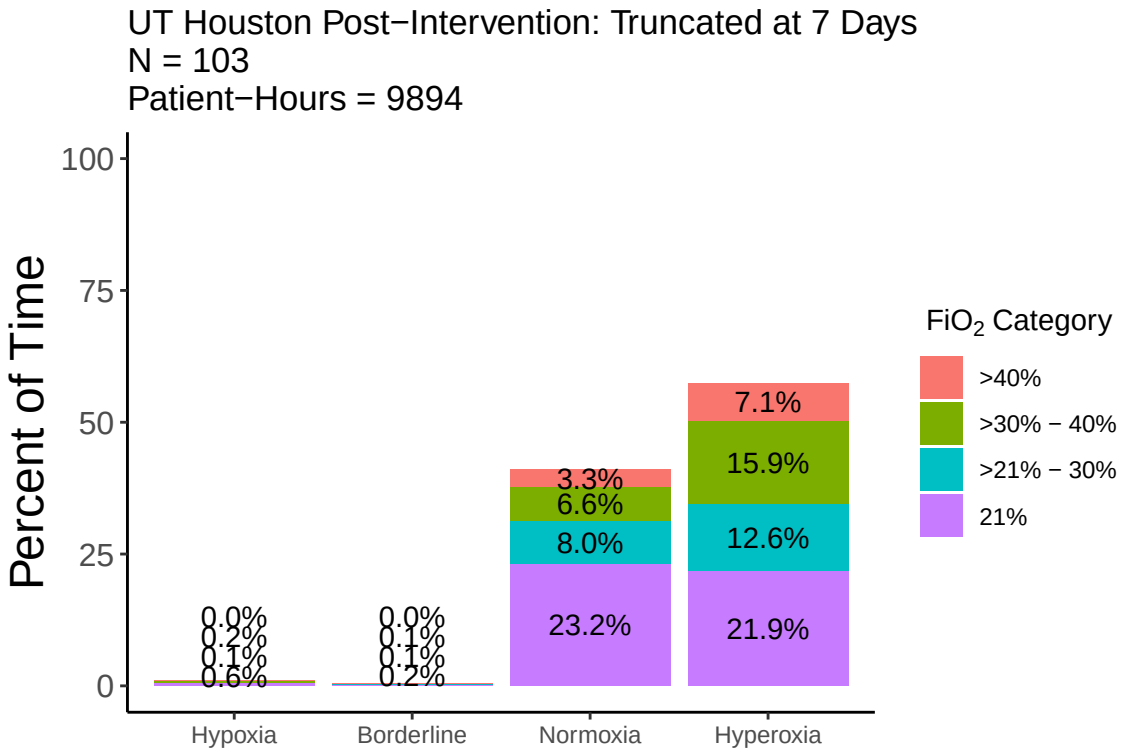
- 2. Provide re-education for clinical staff on oxygenation strategy in mechanically and non-mechanically ventilated patients (reduce FiO2 to 21%, reduce L/min to maintain an SpO2 of 90=-96%).

- 3. Attend huddles, rounds, and/or unit level meetings to remind clinical staff of the oxygenation strategy.

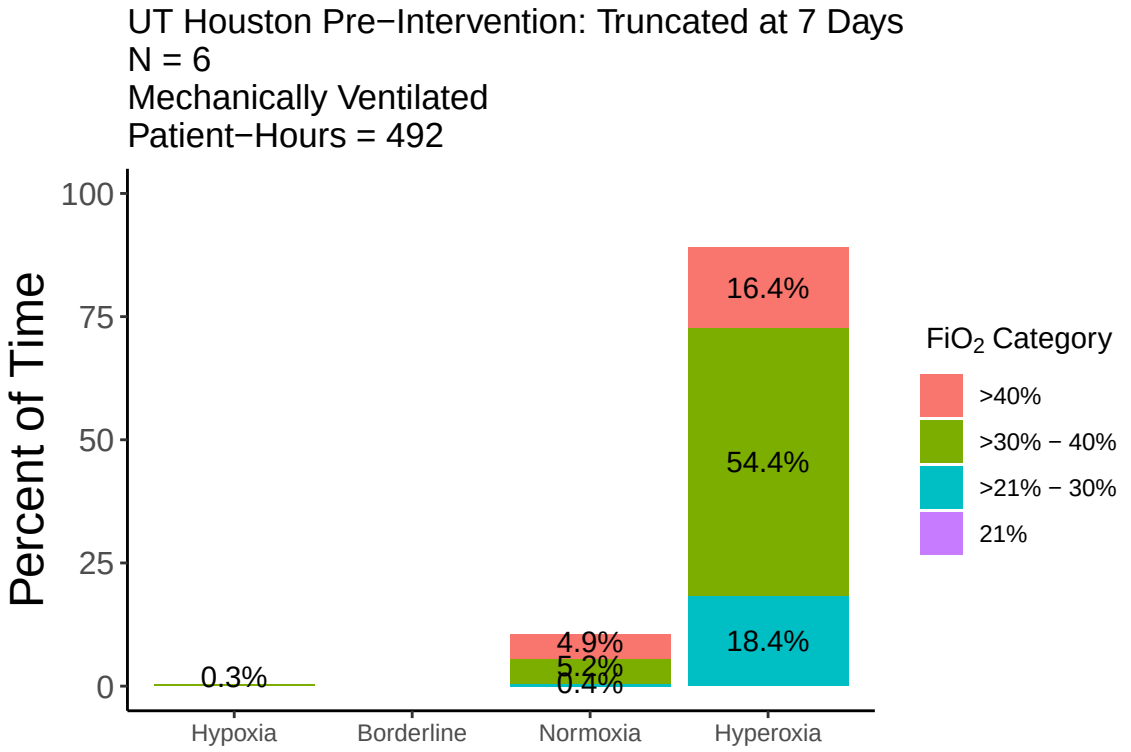
SAVE-O2 UT Report: 02/11/2022

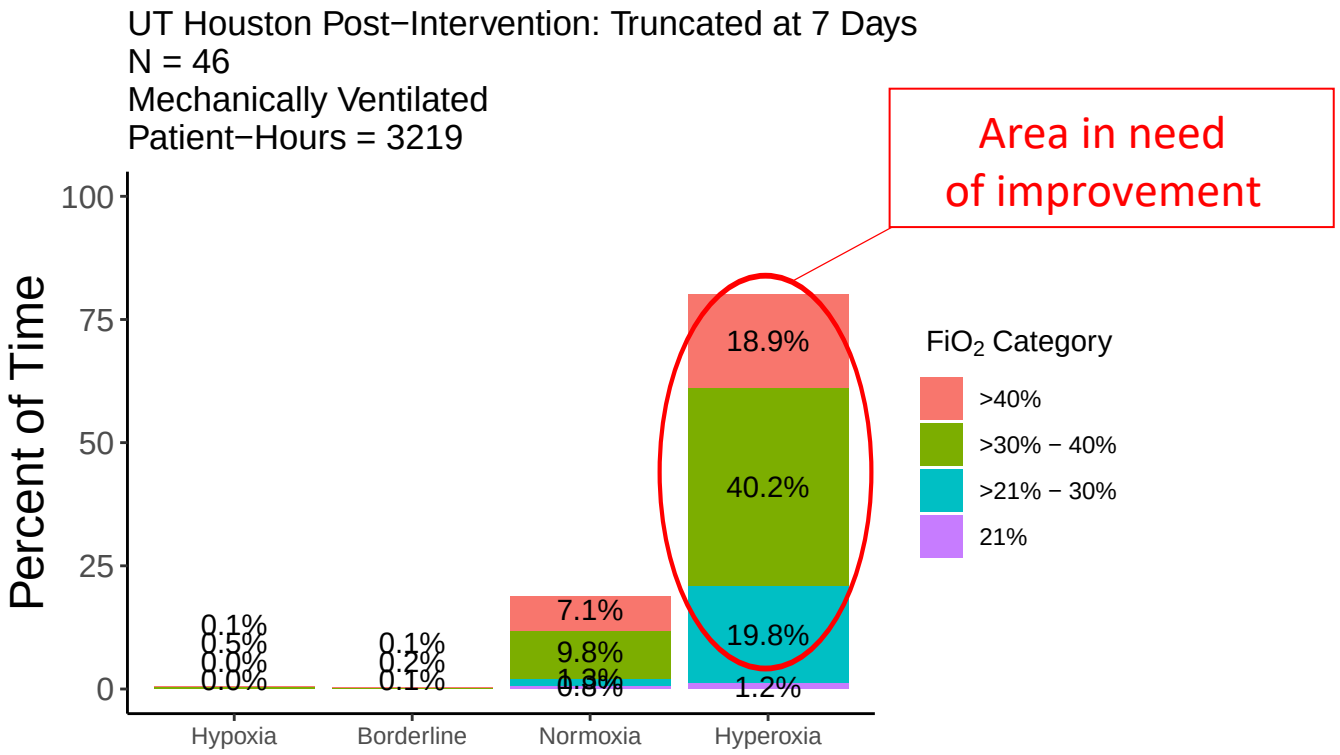
Overall Differences



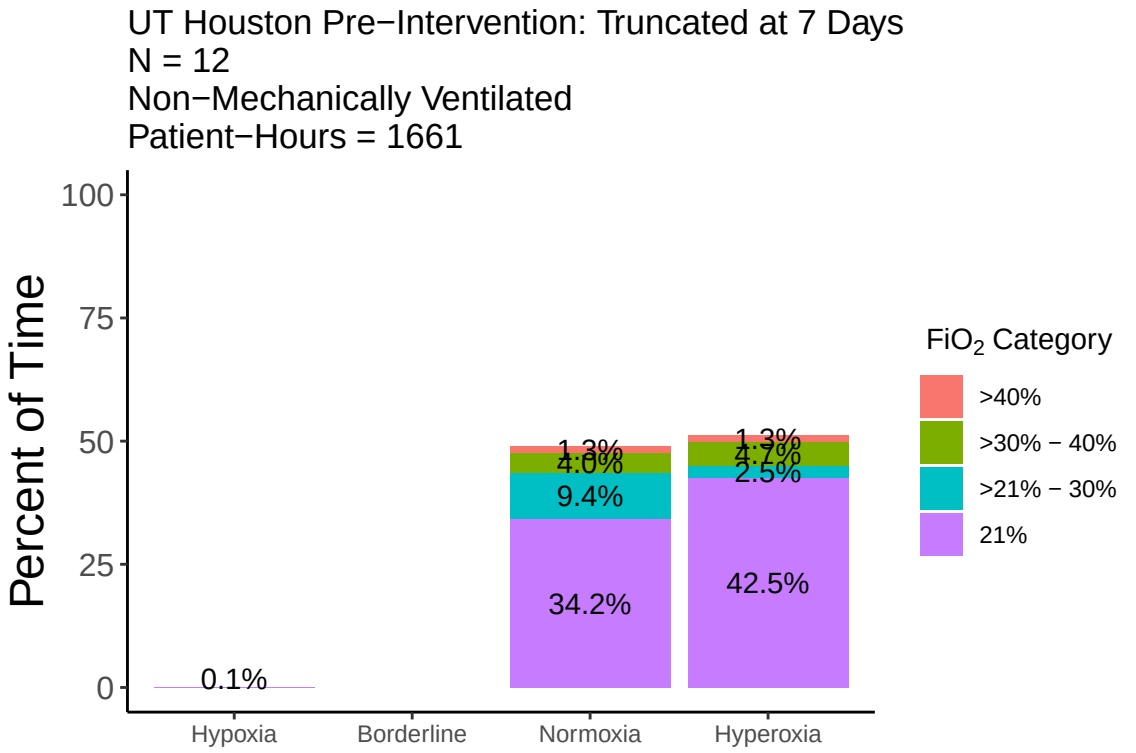


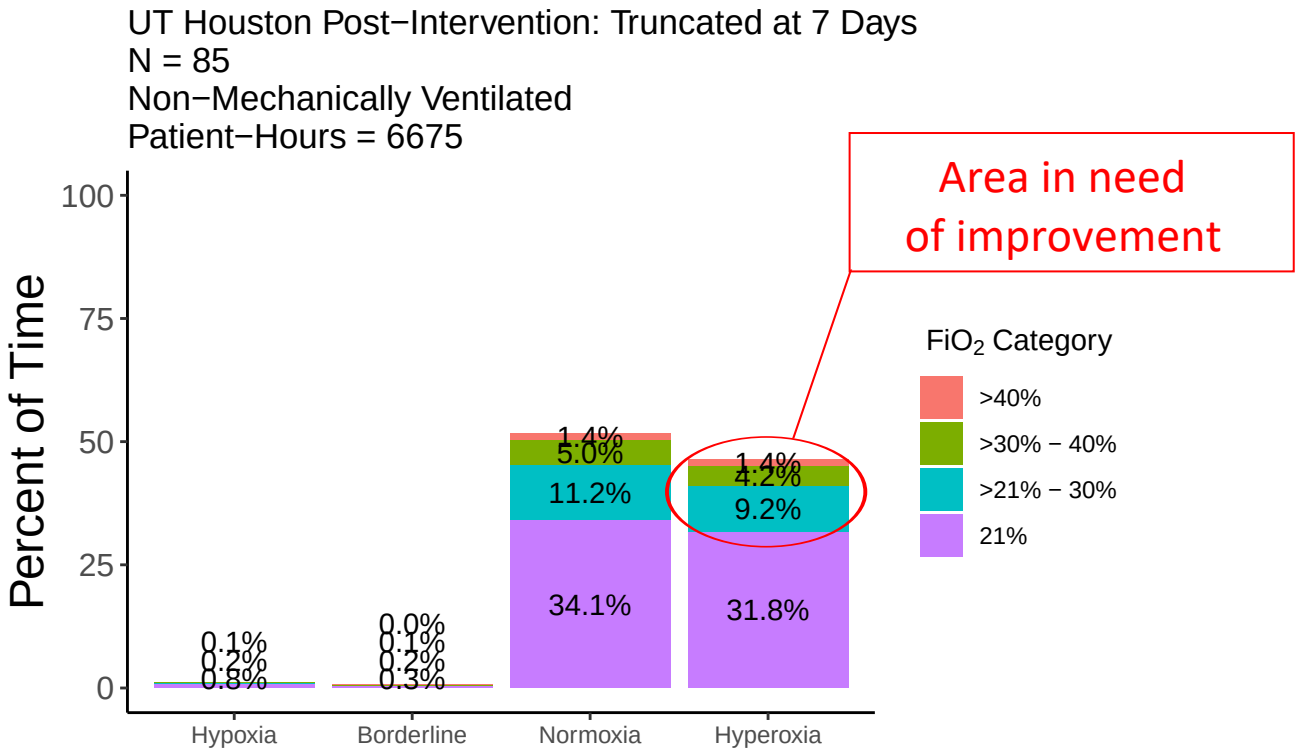
Mechanically Ventilated



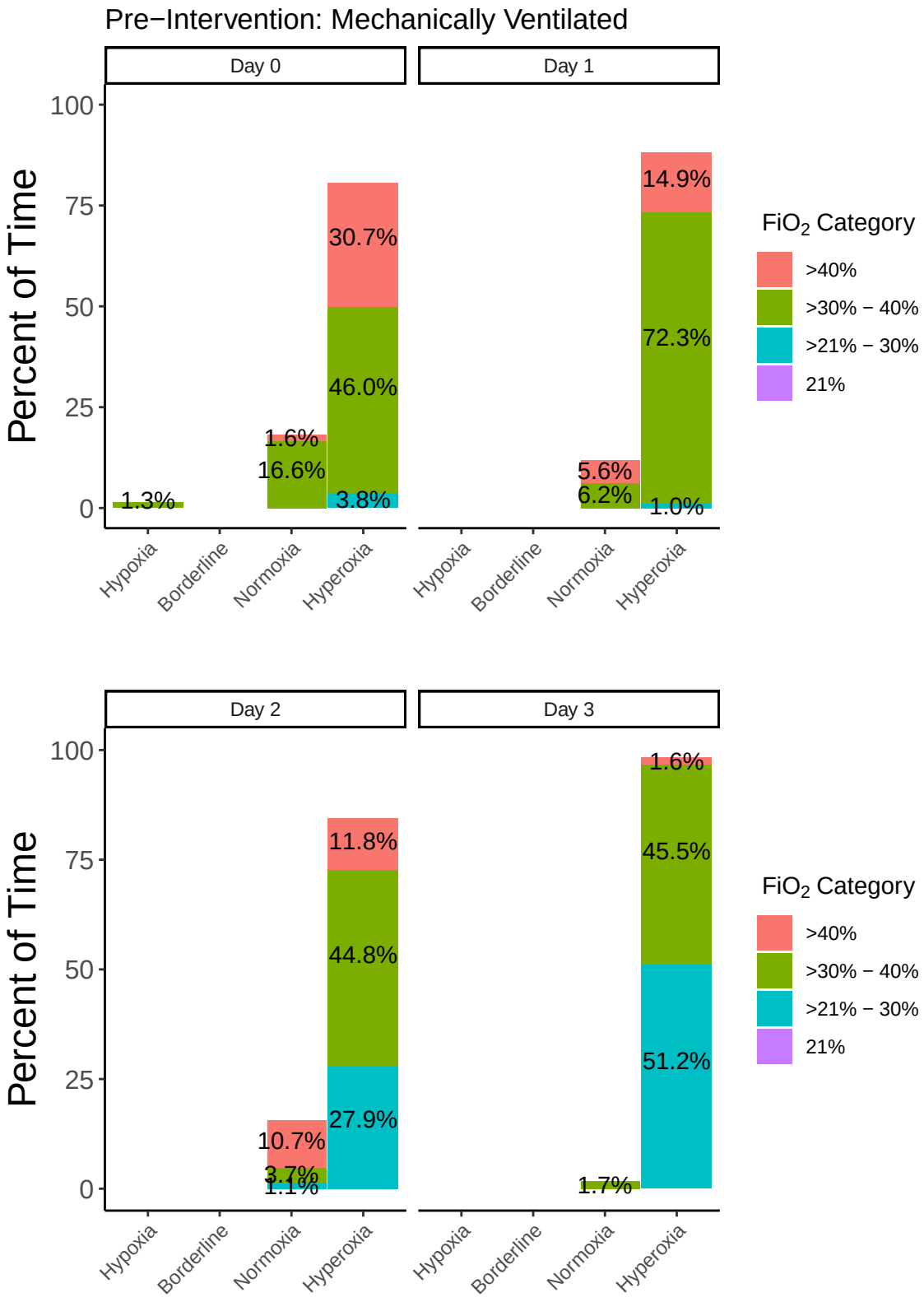


Non-Mechanically Ventilated

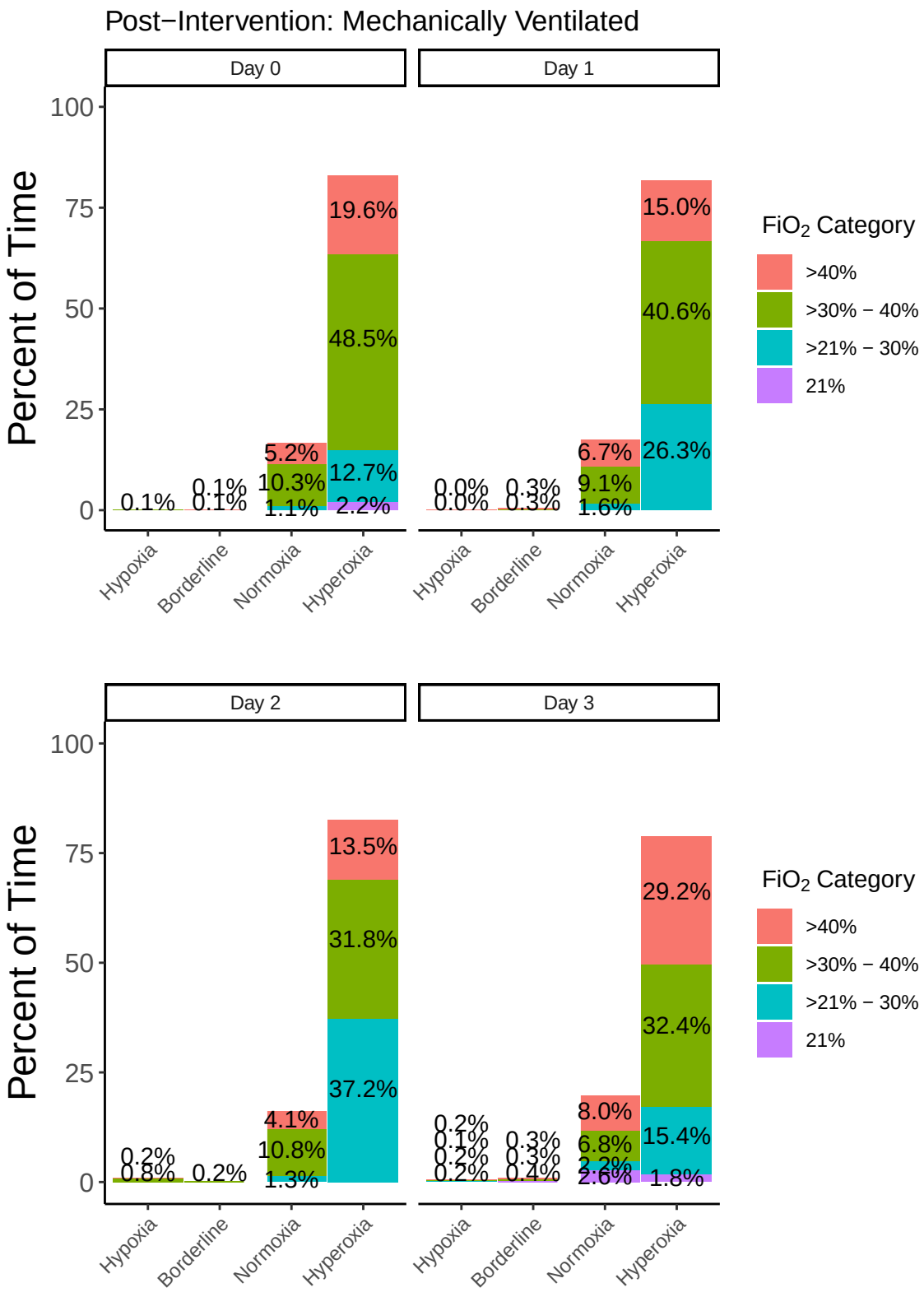




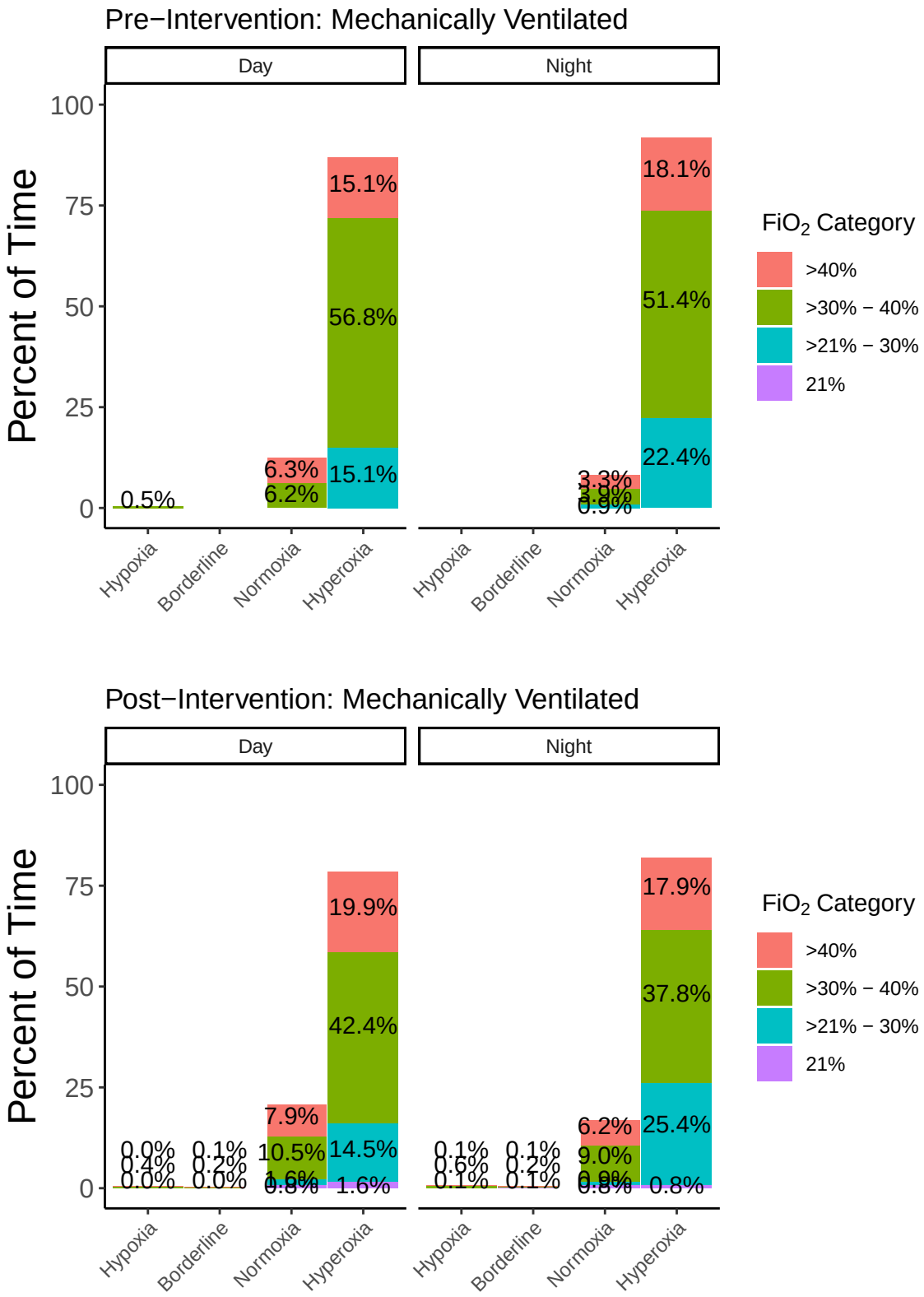
First 4 Days (Pre-Intervention)



First 4 Days (Post-Intervention)



Day vs Night Shift (Pre and Post-Intervention)



Targeted Normoxia in Trauma ICU for VUMC

Report Date: January 18th, 2022
Data from: July 2020-January 2022
Pre Intervention N= 493

Quick things to mention:

- Pre-Intervention data is static, meaning it cannot be changed
- Purple or FiO2 of 21% is considered "success" for patients in normoxia or hyperoxia (because the oxygen is as low as it can go)
- Main objective is to move patients with an FiO2 >21% and hyperoxia into the normoxia levels with less FiO2 administration or down to FiO2 21%
- Pay specific attention to FiO2 >30% and hyperoxia—every attempt should be made to minimize/eliminate this (unless there is a specific clinical indication)

Quick tips for increased compliance (>90% of patient time spent in normoxia or at FiO2 = 21%)

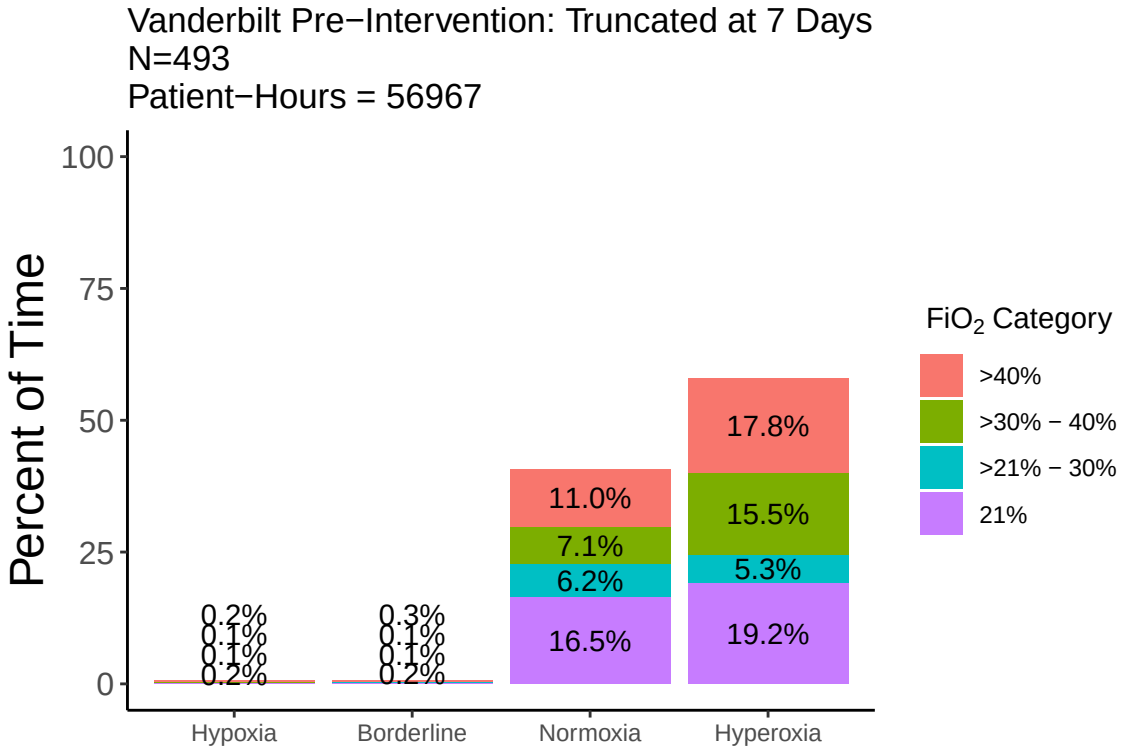
- 1. Provide data reports to clinical staff (respiratory therapy, RNs, and physicians) for information and educational purposes.

- 2. Provide re-education for clinical staff on oxygenation strategy in mechanically and non-mechanically ventilated patients (reduce FiO2 to 21%, reduce L/min to maintain an SpO2 of 90=-96%).

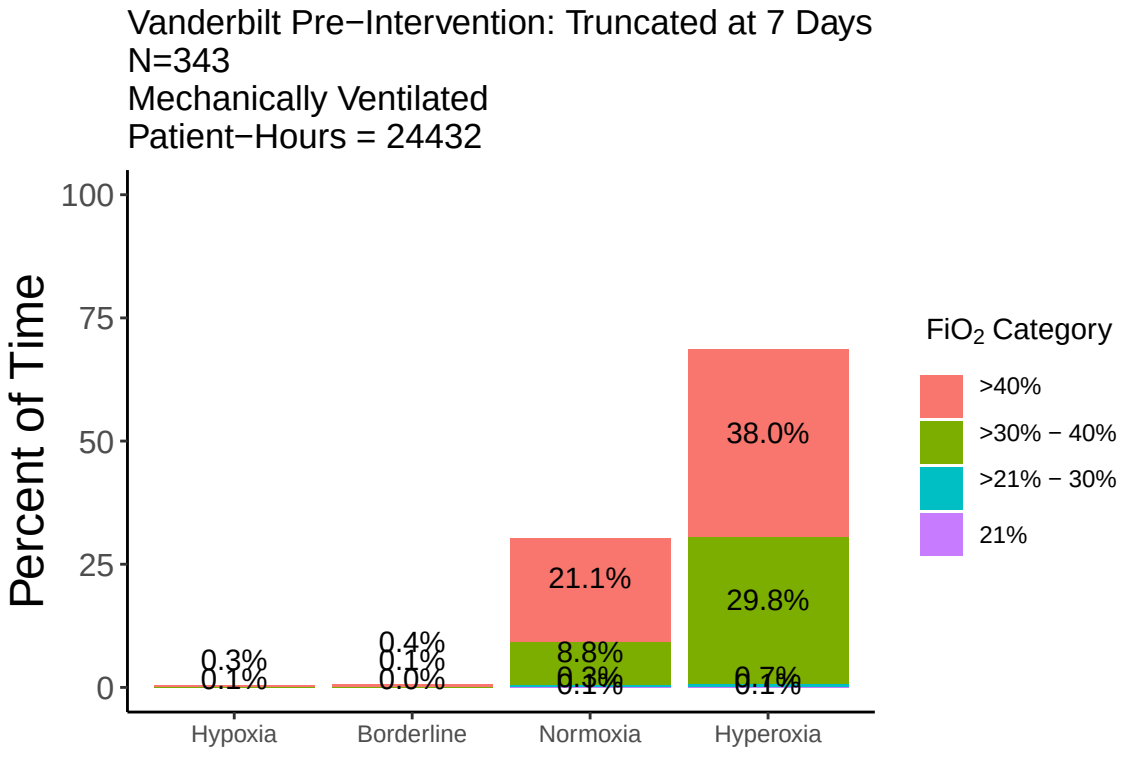
- 3. Attend huddles, rounds, and/or unit level meetings to remind clinical staff of the oxygenation strategy.

SAVE-O2 Vanderbilt Report: 01/18/2022

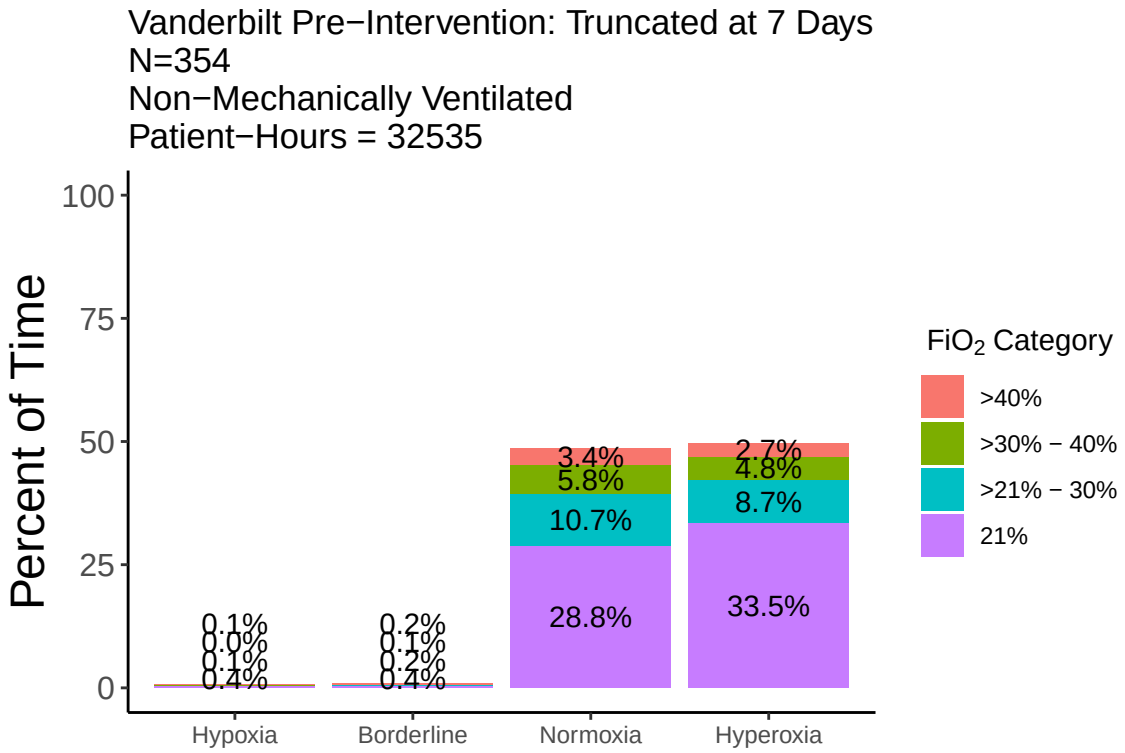
Overall



Mechanically Ventilated



Non-Mechanically Ventilated



First 4 Days (Pre-Intervention)