Patients with Traumatic Brain Injury Transported by Critical Care Air Transport Teams: The Influence of Altitude and Oxygenation During Transport

Lt Col Joseph K Maddry; Allyson A. Araña, PhD;
Lauren K. Reeves, MsPH; Alejandra G. Mora, MS;
Xandria E. Gutierrez; Crystal A. Perez, BSN, RN;
Capt Patrick C. Ng; Capt Sean A. Griffiths;
Col Vikhyat S. Bebarta

FINAL REPORT

Date: 30 Dec 2020

59th Medical Wing
Office of the Chief Scientist
1632 Nellis, BLDG. 5406
JBSA Lackland AFB, TX 78236-7517

DISTRIBUTION A. Approved for public release; distribution is unlimited.

DECLARATION OF INTEREST

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Air Force, Department of Defense, nor the U.S. Government. This work was funded by Project Code Number AC12EM01. Authors are military service members, employees, or contractors of the US Government. This work was prepared as part of their official duties. Title 17 USC §105 provides that 'copyright protection under this title is not available for any work of the US Government.' Title 17 USC §101 defines a US Government work as a work prepared by a military service member, employee, or contractor of the US Government as part of that person's official duties.

NOTICE AND SIGNATURE PAGE

Using Government drawings, specifications, or other data included in this document for any purpose other than Government procurement does not in any way obligate the U.S. Government. The fact that the Government formulated or supplied the drawings, specifications, or other data does not license the holder or any other person or corporation or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

Qualified requestors may obtain copies of this report from the Defense Technical Information Center (DTIC) (http://www.dtic.mil).

PATIENTS WITH TRAUMATIC BRAIN INJURY TRANSPORTED BY CRITICAL CARE AIR TRANSPORT TEAMS: THE INFLUENCE OF ALTITUDE AND OXYGENATION DURING TRANSPORT

TAVISH.MICHELE.F.1031059280 Digitally signed by TAVISH.MICHELE.F.1031059280 Date: 2021.03.08 15:45:22 -06'00'

Michele F. Tavish, DAF
Program Analyst
En route Care Research Program
59MDW Office of the Chief Scientist

MALLORY.AMBER.MELANIE.1471210206 Digitally signed by MALLORY.AMBER.MELANIE.1471210206 Date: 2021.03.08 15:15:51 -06'00'

Amber Mallory, Ph.D.
Director, Trauma & Clinical Care
59MDW Office of the Chief Scientist

This report is published in the interest of scientific and technical information exchange, and its publication does not constitute the Government's approval or disapproval of its ideas or findings.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202- 4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE 31 Dec 2020	**2. REPORT TYPE** Final Report	**3. DATES COVERED** 01 Oct 17 – 31 Dec 20

4. TITLE AND SUBTITLE
Patients with Traumatic Brain Injury Transported by Critical Care Air Transport Teams: The Influence of Altitude and Oxygenation during Transport

5a. CONTRACT NUMBER FA8650-19-2-6059

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Lt Col Joseph K Maddry; Allyson A. Araña, PhD; Lauren K. Reeves, MsPH; Alejandra G. Mora, MS; Xandria E. Gutierrez; Crystal A. Perez, BSN, RN; Capt Patrick C. Ng; Capt Sean A. Griffiths; Col Vikhyat S. Bebarta

5d. PROJECT NUMBER AC18EC03

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
United States Air Force, 59th Medical Wing (59MDW/ST)
1255 Wilford Hall Loop, Building 4430
Lackland Air Force Base, 78236-9980

8. PERFORMING ORGANIZATION REPORT NUMBER
FWH20180047H

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Air Force Medical Service (AFMS)

10. SPONSOR/MONITOR'S ACRONYM(S)
AMC

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

12. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution A: Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Introduction: Traumatic brain injuries (TBIs) are life threatening, and air transport of patients with TBI requires additional considerations. To mitigate the risks of complications associated with altitude, some patients fly with a cabin altitude restriction (CAR) to limit the altitude at which an aircraft's cabin is maintained. The goal of this study was to examine the effects of CARs on patients with TBI transported out of theater via Critical Care Air Transport Teams (CCATTs).

Materials and Methods: We conducted a retrospective chart review of patients with moderate-to-severe TBI evacuated out of combat theater to Landstuhl Regional Medical Center (LRMC) via CCATT. We collected demographics, flight and injury information, procedures, oxygenation, and outcomes (discharge disposition and hospital/ICU/ventilator days). We categorized patients as having a CAR if they had a documented CAR or maximum cabin altitude of 5,000 feet or lower in their CCATT record. We calculated descriptive statistics and constructed regression models to evaluate the association between CAR and clinical outcomes.

Results: We reviewed the charts of 435 patients, 31% of which had a documented CAR. Nineteen percent of the sample had a PaO_2 lower than 80 mm Hg, and 3% of patients experienced a SpO_2 lower than 93% while in-flight. When comparing preflight and in-flight events, we found that the percentage of patients who had a SpO_2 of 93% or lower increased for the No CAR group, whereas the CAR group did not experience a significant change. However, flying without a CAR was not associated with discharge disposition, mortality, or hospital/ICU/ventilator days. Further, having a CAR was not associated with these outcomes after adjusting for additional flights, injury severity, injury type, or preflight head surgery.

Conclusions: Patients with TBI who flew with a CAR did not differ in clinical outcomes from those without a CAR.

15. SUBJECT TERMS TBI, evacuation, military, altitude, oxygenation

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT:**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	UU	17	Lt Col Joseph K. Maddry **19b. TELEPHONE NUMBER** *(include area code)* 210-539-0936

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

Patients with Traumatic Brain Injury Transported by Critical Care Air Transport Teams: The Influence of Altitude and Oxygenation during Transport

Gaps and priority rank per AE Research Program of Record by Core Capability Area (CCA), including specific research objectives (RO):

1. Priority 4: Effects of flight on patients: CCA-Impact of Transport
   RO: Determine the impact of flight during patient transport
2. Priority 6: Advanced POI and ERC Resuscitation: CCA-Clinical ERC
   ROs: The effect of altitude on patients in the advanced POI and ERC resuscitation area, determine how much oxygen patients need.

Modified Abstract

Background: In the course of the Global War on Terror, the high prevalence of traumatic brain injury (TBI) has led to an intense focus on the effects of transport out of the combat zone on the injured.[1–4] Survivability of previously devastating injuries has been increased by bringing highly trained US Air Force Critical Care Air Transport Teams (CCATT) in theater to evacuate the warfighters.[5–7] However, the long-term effects of TBI can significantly impact the injured warfighter's quality of life. Management of TBI patients focuses on minimizing secondary cerebral insults, to include the prevention of hypoxia and hypotension.[2] Aeromedical evacuation brings into question multiple variables, such as altitude and oxygenation levels, and their effects on TBI patient outcomes.[2] Theoretically, patients may be at increased risk of secondary brain injury when transported at altitude.[1–4] The combat injured are moved within the continuum of military care on various platforms—often via air—and the threat this poses for secondary insult to patients with TBI is poorly understood.

We conducted a retrospective study evaluating the impact of CAR during fixed wing aeromedical evacuation on patient oxygenation and outcomes in patients with moderate to severe TBI.

Methods: We queried the Department of Defense Trauma Registry (DoDTR) to obtain a list of patients who suffered a moderate to severe TBI and were transported out of combat theater to Landstuhl Regional Medical Center (LRMC) between January 2007 and May 2014. We defined moderate to severe TBI as an Abbreviated Injury Scale (AIS) severity score of the head/neck body region of 3 or greater with an ICD-9-CM diagnosis code for TBI from the CDC's Barell Matrix classification scheme.[14]

We categorized patients as having a CAR if they had a documented CAR or maximum cabin altitude of 5000 feet or lower in their CCATT record. We calculated descriptive statistics as well as univariate comparisons between the CAR and No CAR groups on demographics, injuries, preflight and in-flight interventions, in-flight events, and outcomes.

Results:

- We received DoDTR data for 3867 patients with TBI who were transported to LRMC between January 2007 and May 2014, of which 477 patients fit the study inclusion criteria, when the greatest quantity of CCATT data was available.

- We excluded 39 patients with a catastrophic brain injury and 3 patients who were missing all CAR data, leaving a final sample of 435 patients for analysis (Fig. S1).
- Of the 435 patients, 136 (31%) were in the CAR group (had a CAR or maximum cabin altitude of 5,000 feet or less) and the remaining 299 (69%) were in the No CAR group.
- 90% US active duty men, median age of 25 (IQR 21–30).
- Blast was the most common mechanism of injury (70%), 65% of patients sustained a penetrating injury, and 60% of patients had polytrauma. The median ISS for the sample was 29 (IQR 21–35), 60% of all patients had a head/neck AIS severity score greater than 3, and 60% had a preflight GCS score of 8 or lower.
- The most common in-flight events were body temperatures higher than 99.5◦F (60% of sample), sodium levels lower than 145 mmol/L (46%), and SBP lower than 110 mm Hg (44%). Nineteen percent of the sample had a PaO2 lower than 80 mm Hg and 3% of patients experienced a SpO2 lower than 93% while in-flight.
- The overall survival rate for the sample was 96%. Most patients continued to receive medical care (89% of all patients) and 6% returned to duty or were discharged home.
- Thirteen percent of the sample was ventilated with a GCS score of 8 or lower at the time of discharge or transfer to another facility. Overall, survivors spent a median time of 15 days (IQR 6–33 days) in the hospital, 9 days (IQR 6–15 days) in the ICU, and 6 days (IQR 2–10 days) on a ventilator.
- We constructed Cox proportional hazards regression models to examine the independent association between CAR (yes versus no) and total hospital days, total ICU days, or total ventilator days while adjusting for possible confounds and censoring for mortality. Being flown with a CAR was not significantly associated with total hospital days, total ICU days, or total ventilator days in any of these models (Table SI). Similarly, CAR was not associated with returning to duty or discharge to home, mortality, and poor discharge disposition in multivariable logistic regression models.

Conclusions: Patients with moderate or severe TBI who were evacuated with a recorded CAR had a lower rate of hypoxia during transport; however, they did not significantly differ from those who flew without a CAR with regard to mortality rates, hospital days, ICU days, or ventilator days.

Evidence Based Recommendation:

- Based upon our findings, we cannot recommend all moderate to severe head injury patients be transported using CAR. Medical personnel will need to use their clinical judgment and surrounding circumstances to determine if CAR is appropriate.

2.0 INTRODUCTION

In the course of the Global War on Terror, the high prevalence of traumatic brain injury (TBI) has led to an intense focus on the effects of transport out of the combat zone on the injured.[1–4] Survivability of previously devastating injuries has been increased by bringing highly trained US Air Force Critical Care Air Transport Teams (CCATTs) in theater to evacuate the warfighters.[5–7] However, the long-term effects of TBI can significantly impact the injured warfighter's quality of life. Management of TBI patients focuses on minimizing secondary cerebral insults, to include the prevention of hypoxia and hypotension.[2] Aeromedical evacuation brings into question multiple variables such as altitude and oxygenation levels and their effects on TBI patient outcomes.[2] Theoretically, patients may be at increased risk of secondary brain injury when transported at altitude.[1–4] The combat injured are moved within the continuum of military care on various platforms often via air. The threat this poses for secondary insult to patients with TBI is poorly understood. In rat models with simulated TBI, hypobaria and hyperoxia were associated with worsened neurological outcomes.[8] Swine models with TBI have shown decreased cerebral perfusion pressure, mean arterial pressure, and brain oxygenation levels for subjects exposed to a hypobaric environment versus controls.[9] Civilian studies have evaluated the effects of oxygenation alone on the outcomes of patients with TBI. In one study of 1,547 patients with severe TBI, it was found that hyperoxia and hypoxia were equally harmful to short-term outcomes.[10] In a multi-center retrospective study (n = 1,212) of ventilated TBI patients, arterial hyperoxia was independently associated with higher in-hospital case fatality.[11] Our study of ventilated CCATT patients found few instances of hypoxia, but instead found that the majority of patients received oxygen in excess of the Joint Trauma System Clinical Practice Guidelines.[12]

During pressurized cabin fixed wing aeromedical evacuation, the standard practice is to transport with a cabin altitude pressure of 8,000 feet. Given the concern that this relative hypobaria and hypoxia may result in secondary brain injury, some patients are transported at a lower cabin altitude, referred to as a cabin altitude restriction (CAR), at the discretion of the CCATT, flight surgeon, and pilots.[13] Whether or not this practice impacts patient outcomes is unknown. We conducted a retrospective study evaluating the impact of CAR during fixed wing aeromedical evacuation on patient oxygenation and outcomes in patients with moderate to severe TBI.

3.0 METHODS, ASSUMPTIONS AND PROCEDURES

We performed a retrospective chart review of CCATT patients with TBI transported out of the combat theater between January 2007 and May 2014. This study was approved by the U.S. Air Force 59th Medical Wing Institutional Review Board. We queried the Department of Defense Trauma Registry (DoDTR), a database of medical charts of combat casualties treated in military medical treatment facilities (MTFs), to obtain a list of patients who suffered a moderate to severe TBI and were transported out of combat theater to Landstuhl Regional Medical Center (LRMC) between January 2007 and May 2014. We defined moderate to severe TBI as an Abbreviated Injury Scale (AIS) severity score of the head/neck body region of 3 or greater with an ICD-9-CM diagnosis code for TBI from the CDC's Barell Matrix classification scheme.[14] We excluded those patients who were younger than 18 years of age, did not have a CCATT medical record, or suffered a catastrophic brain injury (i.e., were on the levothyroxine/T4 protocol for organ donors, were being flown for organ donation, or were being flown home for family visitation). From the remaining patient CCATT medical records, trained research nurses abstracted demographics, flight information, injury description, oxygenation, medications, procedures, vital signs, and laboratory values. Routine quality control measures were implemented to ensure accuracy and consistency of data collection. These measures included set guidelines for data entry, regular meetings among abstractors to address questions about the data, and a thorough review of each patient record to identify discrepancies between abstractors, errors in data entry, and missing data. All data collected by the trained research nurses were based on provider documentation. Topography and starting altitudes before flight differ between Iraq and Afghanistan; therefore, we collected origination location. We excluded patients who did not have altitude or CAR data in their record. Data collected were based on provider documentation. We also queried the Theater Medical Data Store, a web-based platform containing electronic health records collected at theater-based MTFs, to obtain TBI-specific information for the eligible patients and to reconcile data.[16] The response to the initial DoDTR query provided additional injury information as well as outcome measures including mortality, discharge disposition, total days on a ventilator, total days in an intensive care unit (ICU), and total days in a hospital. The outcome measures obtained from DoDTR registry only captured patient data for the time period beginning from injury to the patient's discharge or transfer to the last MTF (Role IV or Role V).

Statistical Analysis

We categorized patients as having a CAR if they had a documented CAR or maximum cabin altitude of 5000 feet or lower in their CCATT record. We calculated descriptive statistics as well as univariate comparisons between the CAR and No CAR groups on demographics, injuries, preflight and in-flight interventions, in-flight events, and outcomes. We reported continuous variables as medians interquartile range (IQR), categorical variables as percentages with 95% confidence intervals, and univariate comparisons as median or proportional differences with 95% confidence intervals. Because of imperfect pairing of data (ie. not all patients had preflight and in-flight data for all variables), we used exact conditional logistic regression to determine changes in events from preflight to in-flight. Hospital, ICU, and ventilator days were compared between groups using Kaplan-Meier survival curves and log-rank tests while censoring for mortality. We extended these survival analyses to Cox proportional hazards regression models to determine the independent relationship of CAR with hospital, ICU, and ventilator days while controlling for possible confounds. We adjusted these models for preflight factors that were significantly associated with the outcomes or CAR grouping and clustered the analyses according to theater of operations (Iraq or Afghanistan). We also clustered analyses by the final MTF (Role IV or V) in the DoDTR record to account for the fact that this source of outcome data could differ for each patient. The final list of covariates included time to transport (defined as the days between injury and transport to the Role IV MTF), additional flights in theater, composite injury severity scores (ISS), polytrauma (defined as an AIS severity score greater than 2 in an additional body region), severe TBI (defined as a head AIS severity score greater than 3 and a preflight GCS score of 8 or lower), cranial or facial fractures, bone fragments or foreign bodies, pneumocephalus, ICP monitoring, and preflight head surgery. We evaluated the functional form of the covariates using Martingale and deviance residual plots with locally weighted scatterplot smoothing (LOWESS) and examined model fit using the likelihood ratio chi square and Akaike Information Criterion (AIC). Additionally, we constructed logistic regression models to examine the association between CAR and discharge disposition (mortality, return to duty or home, ventilated at discharge or transfer, and ventilated with a GCS score of 8 or lower at discharge or transfer). These models included the same covariates as the proportional hazards models and were clustered by theater of operations and final MTF. The set of predictors produced variance inflation factors, tolerance, and condition indices that were within the recommended limits to avoid collinearity (i.e., variance inflation factors <2.5, tolerance ≥0.5, and condition indices <15). We examined adjusted R2, chi-square p-values, and the area under the curve of the receiver operating characteristic (ROC AUC) as measures of model fit. We did not impute any missing data and excluded cases with missing data for any covariates by list wise deletion. We conducted all statistical analyses in SAS (version 9.4, SAS Institute, Inc., Cary, NC).

4.0 MAJOR EVENTS/MILESTONES/SUCCESS

For the execution of this project, the following milestones were met:

- Kick Off Meeting – 05/18
- IRB/IACUC Approval – 12/17
- All experimental procedures completed – 12/19
- Data Analysis – 03/20
- Poster presentation – MHSRS 2019
- Manuscript submitted to – Mil Med Sep/Oct 2020
- Dissemination of Results – 08/19

5.0 RISK ASSESSMENT

5.1 Risk Analysis:

This study presented no greater than minimal risks to the subjects. There were no interventions and no changes to the standards of care. The risk involved potential breaches of privacy and patient confidentiality had the data set been acquired by a person or agency outside of this research team. This risk was similar to basic patient care that would otherwise normally be carried out. The likelihood of that occurrence was mitigated by password protection of electronic files for identifiable information and de-identification of patient PHI prior to data being sent for analysis.

5.2 Technical Challenges

The study was retrospective, and therefore we were unable to determine causation. However, the data did not suggest an association between the use of CAR and patient outcomes. With the outcomes studied, multiple factors could be contributory; however, we attempted to correct for any confounding factors by using multivariable regression models. Second, the abstracted data were dependent on documentation within the medical records, leaving the potential for missing and inaccurate data because of imprecise documentation. We did not obtain data on the exact altitude of these flights or if any unplanned cabin altitude changes occurred during transport. As with any retrospective study, there was the potential for subjectivity in data abstraction. To limit such bias, we incorporated abstractor training and periodic quality reviews in our protocol to minimize this risk. With regard to the external validity of our findings, our patient population consisted predominately of young male adults who were not on anticoagulation therapy at their time of injury. Extrapolation of our findings to pediatric, female, and elderly patients was limited, but given the difficulty of obtaining a similarly large database, extrapolation of our findings to these populations may be prudent. Finally, detailed neurocognitive outcome data of our patient population were not available. Therefore, we were unable to determine the impact of CAR on neurocognitive function and quality of life.

6.0 TRANSITION PLAN

6.1 Military Relevance

The long-term effects of TBI can significantly impact the injured warfighter's quality of life. The main priority of TBI care is to prevent secondary insults. The combat injured are moved within the continuum of military care on various platforms and the threat this poses for secondary insult to patients with TBI is poorly understood. Determining the effects of hypobaria and hyperoxia on the injured brain may help inform decision making related to timing of transport and the care required during transport, thereby improving outcomes.

6.2 Transition Strategy

The results of this study provide knowledge about the influence of altitude during evacuation of combat casualties. Data collected was filtered into the database for Project Mercury, can be queried to conduct retrospective analysis to support and provide research to investigators, and allows for performance improvement initiatives. Lessons learned establish the groundwork for CPG development and standardization of care.

The results were also disseminated to the following:

1. The research community through national civilian and military academic conferences and meetings to include the Military Health Science Research Symposium (MHSRS).
2. Completed manuscripts submitted to peer-reviewed journals for publication.
3. The Defense Technical Information Center (DTIC) for publishing on their website.
4. Appropriate military leadership and training agencies.

7.0 RESULTS

We received DoDTR data for 3867 patients with TBI who were transported to Landstuhl Regional Medical Center between January 2007 and May 2014, of which 477 patients fit the study inclusion criteria, when the greatest quantity of CCATT data was available. We further excluded 39 patients with a catastrophic brain injury and 3 patients who were missing all CAR data, leaving a final sample of 435 patients for analysis (Fig. S1). Of the 435 patients, 136 (31%) were in the CAR group (had a CAR or maximum cabin altitude of 5,000 feet or less) and the remaining 299 (69%) were in the No CAR group. Recorded CARs ranged from "sea level" to 5,000 feet, with most patients having a CAR of 5,000 feet (n = 99; 73% of CARs). The sample consisted of over 90% US active duty men and had a median age of 25 (IQR 21–30). More than half of the patients had additional flights in theater, and most were transported within 2 days of injury (IQR 1–3 days). Seventy-eight percent of all patients were transported from Afghanistan, with the remaining 22% coming from Iraq.

Blast was the most common mechanism of injury (70%), 65% of patients sustained a penetrating injury, and 60% of patients had polytrauma. The median ISS for the sample was 29 (IQR 21–35), 60% of all patients had a head/neck AIS severity score greater than 3, and 60% had a preflight GCS score of 8 or lower. Patients with penetrating injuries, pneumocephalus, cranial or facial fractures, and bone fragments or foreign bodies present were more likely to be flown with a CAR (Table I). The most common preflight interventions were mechanical ventilation (72% of sample), blood products (50%), ICP monitoring (28%), ventriculostomy (21%), and supplementary oxygen (15%). Patients who had head surgery were more likely to be flown with a CAR (Table II). Most patients remained mechanically ventilated during flight (69% of all patients). Other common in-flight interventions included sedation (IV infusion; 72% of all patients), anti-seizure medications (36%), 3% saline infusion (26%), vasopressors (21%), and supplementary oxygen (17%). The CAR and No CAR groups did not differ in any of the in-flight interventions (Table II). Sodium levels below 145 mmol/L (49% of all patients), body temperatures above 99.5◦F (42%), and SBP lower than 110 mm Hg (21%) were among the most common preflight events.

The most common in-flight events were body temperatures higher than 99.5◦F (60% of sample), sodium levels lower than 145 mmol/L (46%), and SBP lower than 110 mm Hg (44%). Nineteen percent of the sample had a PaO_2 lower than 80 mm Hg and 3% of patients experienced a SpO_2 lower than 93% while in-flight. The CAR and No CAR groups did not significantly differ in rates of preflight or in-flight events (Fig. 1). When comparing preflight and in-flight rates of events, we found that the No CAR group experienced a significant increase in the percentage of patients who had a SpO_2 of 93% or lower and SBP higher than 160 mm Hg; the CAR group did not experience a significant change in these variables (Fig. 1). Both groups experienced significant increases in the proportion of patients who had an SBP lower than 110 mm Hg and body temperature higher than 99.5◦F. Neither group showed a change from preflight to in-flight in the percentage of patients with a PaO_2 lower than 80 mm Hg, sodium level lower than 145 mmol/L, or ICP greater than 20 mm Hg.

The overall survival rate for the sample was 96%. Most patients continued to receive medical care (89% of all patients) and 6% returned to duty or were discharged home. Thirteen percent of the sample were ventilated with a GCS score of 8 or lower at the time of discharge or transfer to another facility. Overall, survivors spent a median time of 15 days (IQR 6–33 days) in the hospital, 9 days (IQR 6–15 days) in the ICU, and 6 days (IQR 2–10 days) on a ventilator. The CAR and No CAR groups did not differ on any of these outcomes (Table III). We constructed Cox proportional hazards regression models to examine the independent association between CAR (yes versus no) and total hospital days, total ICU days, or total ventilator days while adjusting for possible confounds and censoring for mortality. Being flown with a CAR was not significantly associated with total hospital days, total ICU days, or total ventilator days in any of these models (Table SI). Similarly, CAR was not associated with returning to duty or being discharged home, mortality, and poor discharge disposition in multivariable logistic regression models.

8.0 CONCLUSION/DISCUSSION

We found no association between the use of CAR and patient outcomes, to include hospital stay, disposition, and mortality. There was also no significant difference in oxygenation between CAR and No CAR patients. Unlike previous animal research, our study evaluated human combat casualties, often with additional injuries. Based upon our findings, we cannot recommend all moderate to severe head injury patients be transported using CAR. Medical personnel will need to use their clinical judgment and surrounding circumstances to determine if CAR is appropriate. Previous research has demonstrated the adverse impact of hypoxia on TBI.[17,18] Furthermore, evaluation of aeromedically-evacuated patients has demonstrated a significant rate of hypoxia during transportation.[2] Our study confirms this finding, as nearly one in five patients experienced a PaO_2 lower than 80 mmHg and the No CAR group had a statistically significant higher rate of SpO_2 less than 94% in-flight compared to preflight. Despite this, we found no difference in clinical outcomes.

Our previous research has demonstrated similar findings: when evaluating the impact of the time to transport out of theater, we found that those patients transported over 72 h after their time of injury had higher rates of mild hypoxia during transport but superior outcomes compared to those evacuated earlier.[15] There is a growing body of evidence that hyperoxia can exacerbate TBI.[10,11] Our previous research evaluating ventilator management practices in CCATT patients found that a significant number of patients experienced hyperoxia during transport.[12] One could theorize that those patients transported at a CAR are at higher risk for developing hyperoxia because of the combined effect of a less hypoxic aircraft cabin and exogenous oxygen, potentially leading to secondary brain injury. However, we found no statistically significant difference in the percentage of patients with a PaO_2 greater than 150 mm Hg in the CAR and No CAR groups. Animal research aimed to determine if hypobaria alone exacerbates TBI has yielded conflicting results when evaluating histological evaluation.[9,19] Skovira et al found worsening cognitive deficits and neuronal loss with exposure to hypobaria.[20] Given the potential negative impact of hypobaria on intracranial pressure and cerebral perfusion pressure, it is conceivable that hypobaria may have a different impact on closed versus open skull injuries.

We intend to evaluate the association with hypobaria on closed versus open skull injuries in a future study. In a study by Boyd et al., 18% of the CCATT missions that involved patients with moderate-to-severe TBI had altitude restrictions.[21] Although CAR may be considered for patients with free air in a body cavity (i.e. pneumocephalus, ocular trauma, and arterial gas embolism), patients with severe lung disease and those at risk for decreased tissue oxygenation should have CAR determined by the flight surgeon. Unfortunately, we were unable to determine the rationale for CAR based on this record abstraction.[22–24] Hypotension and hyperthermia have also been associated with secondary brain injury.[2] In both the CAR and No CAR groups, there was a significant number of patients who had an SBP lower than 110 mm Hg and body temperature higher than 99.5 F.[25] Further research is warranted to determine the cause of these findings and prevent their occurrence in future CCATT operations.

Finally, we found no association between the use of CAR and patient outcomes, but the retrospective methodology of our study does not permit us to determine causation. Therefore, although we cannot recommend the use of CAR restriction, we are also unable to ascertain that CAR does not provide benefit to TBI patients. In addition, there may be other types of injury for which CAR may confer a benefit. A prospective study during future conflicts or in civilian aeromedical evacuation may provide a better answer. For now, we recommend that the clinician consider the findings of our study, use clinical judgement for CAR restriction, and take into account the circumstances of the mission.

CONCLUSION

Patients with moderate or severe TBI who were evacuated with a recorded CAR had a lower rate of hypoxia during transport; however, they did not significantly differ from those who flew without a CAR with regard to mortality rates, hospital days, ICU days, or ventilator days.

9.0 DELIVERABLES

9.1 Publications:

Maddry JK, Araña AA, Reeves LK, Mora AG, Gutierrez XE, Perez CA, Ng PC, Griffiths SA, Bebarta VS. Patients with Traumatic Brain Injury Transported by Critical Care Air Transport Teams: The Influence of Altitude and Oxygenation during Transport. Mil Med. 2020;185(9/10):e1562-e1568.

https://pubmed.ncbi.nlm.nih.gov/32515785/

9.2 Presentations:

Podium – Military Health System Research Symposium (MHSRS), Orlando, FL; 2019
Poster – American College of Emergency Physicians – Denver, CO; 2019
Poster – San Antonio Military Health System and Universities Research Forum – San Antonio, TX 2020

10.0 COST

This work was funded by an AFMS award. Total funding awarded for this Project Code Number, AC18EC03, in the amount of $293,000.00 were expended by September 29, 2020.

11.0 REFERENCES

1. Grocott M, Montgomery H, Vercueil A. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. Crit Care. 2007 Feb 1;11(1):203.

2. Dukes SF, Bridges E, Johantgen M. Occurrence of secondary insults of traumatic brain injury in patients transported by critical care air transport teams from Iraq/Afghanistan: 2003–2006. Mil Med. 2013 Jan 1;178(1):11-7.

3. McAllister TW. Neurobiological consequences of traumatic brain injury. Dialogues in clinical neuroscience. 2011 Sep;13(3):287.

4. Fang R, Markandaya M, DuBose JJ, Cancio LC, Shackelford S, Blackbourne LH. Early in-theater management of combat-related traumatic brain injury: A prospective, observational study to identify opportunities for performance improvement. J Trauma Acute Care Surg. 2015 Oct 1;79(4):S181-7.

5. Lairet J, King J, Vojta L, Beninati W. Short-term outcomes of US Air Force Critical Care Air Transport Team (CCATT) patients evacuated from a combat setting. Prehosp Emerg Care. 2013 Oct 1;17(4):486-90.

6. Carlton PK, Jenkins DH. The mobile patient. Crit Care Med. 2008 Jul 1;36(7):S255-7.

7. Galvagno SM, Dubose JJ, Grissom TE, et al. The epidemiology of Critical Care Air Transport Team operations in contemporary warfare. Mil Med. 2014 Jun 1;179(6):612-8.

8. Skovira JW, Kabadi SV, Wu J, et al. Simulated aeromedical evacuation exacerbates experimental brain injury. J of Neurotrauma. 2016 Jul 15;33(14):1292-302.

9. Scultetus AH, Haque A, Chun SJ, et al. Brain hypoxia is exacerbated in hypobaria during aeromedical evacuation in swine with traumatic brain injury. J Trauma Acute Care Surg. 2016 Jul 1;81(1):101-7.

10. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and worse outcomes after traumatic brain injury. Archives of Surg. 2012 Nov 1;147(11):1042-6.

11. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol Neurosurg Psychiatry. 2014 Jul 1;85(7):799-805.

12. Maddry JK, Mora AG, Savell SC, et al. Impact of Critical Care Air Transport Team (CCATT) ventilator management on combat mortality. J Trauma Acute Care Surg. 2018 Jan 1;84(1):157-64.

13. Butler WP, Steinkraus LW, Burlingame EE, et al. Clinical impact of cabin altitude restriction following aeromedical evacuation. Mil Med. 2018 Mar 1;183(suppl_1):193-202.

14. Barell V, Aharonson-Daniel L, Fingerhut LA, et al. An introduction to the Barell body region by nature of injury diagnosis matrix. Inj Prev. 2002 Jun 1;8(2):91-6.

15. Maddry JK, Arana AA, Perez CA, et al. Influence of time to transport to a higher level facility on the clinical outcomes of US combat casualties with TBI: A multicenter seven year study. Mil Med. 2019 Jul 23.

16. Daniele DO, Clark LL. Morbidity burdens attributable to various illnesses and injuries in deployed (per Theater Medical Data Store [TMDS]) active and reserve component service members, US Armed Forces, 2008-2014. Medical Surveillance Monthly Report. 2015 Aug;22(8):17-22.

17. Chi JH, Knudson MM, Vassar MJ, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: a prospective multicenter study. J Trauma Acute Care Surg. 2006 Nov 1;61(5):1134-41.

18. Chang JJ, Youn TS, Benson D, et al. Physiologic and functional outcome correlates of brain tissue hypoxia in traumatic brain injury. Crit Care Med. 2009 Jan 1;37(1):283-90.

19. Skovira JW, Wu J, Matyas JJ, et al. Cell cycle inhibition reduces inflammatory responses, neuronal loss, and cognitive deficits induced by hypobaria exposure following traumatic brain injury. J Neuroinflammation. 2016 Dec;13(1):299.

20. Skovira J, Fang R, Rosenthal R, Fiskum G, Faden AI. Prolonged hypobaria during aeromedical evacuation exacerbates cognitive deficits following traumatic brain injury. J Neurotrauma. 2013 Aug 1 (Vol. 30, No. 15, pp. A154-A154).

21. Boyd LR, Borawski J, Lairet J, Limkakeng AT. Critical Care Cir Transport Team severe traumatic brain injury short-term outcomes during flight for operation Iraqi freedom/operation enduring freedom. J Royal Army Med Corps. 2017 Oct 1;163(5):342-6.

22. Borden Institute: Walter Reed Medical Center. In: U.S. Department of the Army: Emergency War Surgery, ed 3, pp 47–59. Fort Sam Houston, TX, Military Bookshop, 2004.

23. Pollan WA, Fisher C: Hear ye, hear ye noble physicians! Anemia and air evac: how low can we go? TRAC2 ES Times 2006; 1(8): 5–6. 20.

24. Butler WP: Clinician’s corner – hemoglobin and air evacuation. TRAC2 ES Times 2007; 2(4): 7–12.

25. Van Wyck DO, Friedline N, Stephens D, et al. Traumatic Brain Injury Management in Prolonged Field Care (CPG ID: 63).

FIGURES AND TABLES:

Table 1. Patient characteristics and injuries

Variable	No CAR (n=299)	CAR (n=136)	Difference (95% CI)
Age	25 [21-30]	24 [21-29]	-1 (-2 to 0)
Male gender	97 (95-99)	99 (97-100)	-2 (-4 to 1)
US active duty	91 (88-95)	97 (94-100)	-6 (-10 to -1)*
Theater of operations			
Afghanistan	78 (74-83)	77 (69-84)	1 (-7 to 10)
Iraq	22 (17-26)	24 (16-31)	-2 (-10 to 7)
Additional flight(s) in theater	56 (51-62)	54 (45-62)	2 (-8 to 13)
Time to transport, days	2 [1-3]	2 [1-2]	0 (0 to 0)
Mechanism of injury			
Blast	69 (63-74)	74 (67-82)	-5 (-15 to 3)
GSW	14 (10-18)	13 (7-18)	1 (-5 to 8)
MVC	8 (5-12)	5 (1-9)	3 (-2 to 8)
Other	9 (6-12)	8 (3-13)	1 (-5 to 7)
Type of injury			
Penetrating	62 (56-67)	72 (64-80)	-10 (-20 to -1)*
Blunt	38 (32-43)	27 (20-35)	11 (1 to 20)*
Burn	1 (0-2)	1 (0-2)	0 (-2 to 2)
Polytrauma	59 (54-65)	60 (52-69)	-1 (-11 to 9)
Composite ISS	27 [21-35]	29 [21-38]	0 (-2 to 3)
Head/neck AIS severity score >3	59 (54-65)	62 (54-70)	-3 (-12 to 7)
Pre-flight GCS score ≤8	52 (46-58)	49 (41-58)	3 (-8 to 13)
Severe TBI†	33 (28-39)	35 (27-43)	-2 (-12 to 7)
Intracranial hemorrhage	47 (41-53)	47 (39-56)	0 (-10 to 10)
Cranial or facial fractures	61 (56-67)	79 (73-86)	-18 (-27 to -9)*
Pneumocephalus	15 (11-19)	31 (23-39)	-16 (-25 to -7)*
Bone fragments or foreign bodies present	17 (13-21)	32 (24-40)	-15 (-24 to -6)*
Contusion	19 (14-23)	15 (9-22)	4 (-4 to 11)
Midline shift	10 (7-13)	15 (9-22)	-5 (-12 to 2)
Mass effect	8 (5-11)	9 (4-14)	-1 (-7 to 5)

Values given are median [interquartile range] or column percent (95% confidence interval). Confidence intervals provide a range of likely values for the population parameter based on the values obtained from the data.

*The difference is significant if its confidence interval does not include or cross zero.

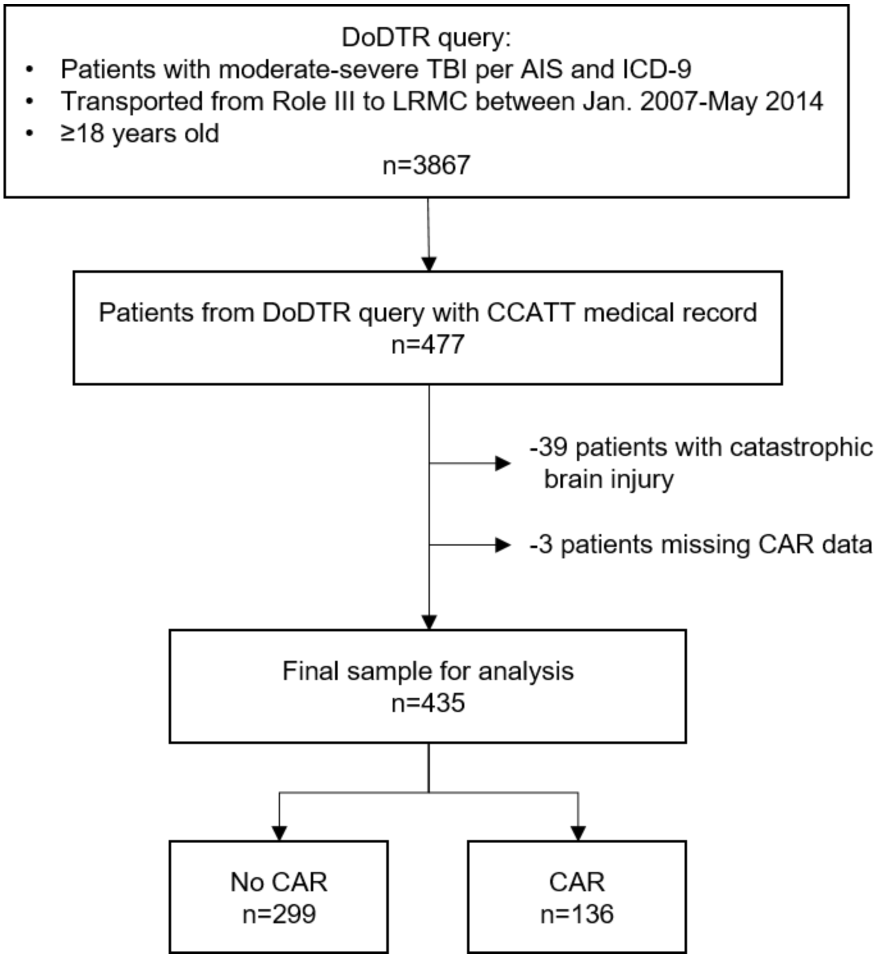
†Severe TBI is defined as head/neck AIS >3 and pre-flight GCS ≤8.

Table 2. Pre-flight and in-flight interventions

Variable	No CAR (n=299)	CAR (n=136)	Difference (95% CI)
Pre-flight			
Mechanical ventilation	72 (66-77)	73 (65-80)	-1 (-10 to 8)
Any blood products	51 (45-57)	49 (40-57)	2 (-7 to 13)
ICP monitoring	25 (20-30)	33 (25-41)	-8 (-17 to 1)
Ventriculostomy	20 (16-25)	24 (17-32)	-4 (-13 to 4)
Supplementary oxygen	14 (10-18)	16 (10-22)	-2 (-9 to 6)
Craniotomy	11 (7-15)	17 (11-23)	-6 (-13 to 1)
Craniectomy	9 (6-13)	13 (7-18)	-4 (-10 to 3)
Massive transfusion	9 (5-12)	8 (3-13)	1 (-5 to 6)
Globe repair	7 (4-10)	10 (5-15)	-3 (-9 to 3)
Hematoma evacuation	6 (4-9)	10 (5-15)	-4 (-10 to 2)
Fragment removal	5 (3-8)	8 (3-13)	-3 (-8 to 3)
Any surgery - head	51 (45-57)	68 (60-76)	-17 (-26 to -7)*
Any surgery - extremities	49 (43-55)	51 (42-59)	-2 (-12 to 9)
Any surgery - abdomen	21 (17-26)	26 (18-33)	-5 (-13 to 4)
Any surgery - neck	12 (8-15)	16 (10-22)	-4 (-12 to 3)
In-flight			
Sedation (IV drip)	72 (66-77)	74 (66-81)	-2 (-11 to 7)
Mechanical ventilation	69 (64-74)	71 (63-78)	-2 (-11 to 8)
Anti-seizure medications	34 (28-39)	42 (34-50)	-8 (-2 to 18)
Acetaminophen	30 (25-36)	23 (16-30)	7 (-1 to 16)
3% saline infusion	25 (20-30)	30 (22-38)	-5 (-15 to 4)
Vasopressors	21 (16-26)	21 (14-27)	0 (-8 to 9)
Any blood products	16 (12-20)	17 (11-23)	-1 (-9 to 6)
Supplementary oxygen	17 (13-21)	15 (9-22)	2 (-6 to 9)
Sedation (IV push)	16 (12-20)	11 (6-16)	5 (-2 to 11)
Paralytics	9 (5-12)	10 (5-15)	-1 (-7 to 5)
Mannitol	4 (2-6)	4 (1-8)	0 (-5 to 4)
Steroids	4 (2-6)	3 (0-6)	1 (-3 to 5)

Values given are column percent (95% confidence interval). Confidence intervals provide a range of likely values for the population parameter based on the values obtained from the data.
*The difference is significant if its confidence interval does not include or cross zero.

Figure S1. A flow diagram depicting study cohort and exclusions.



12.0 LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

AD	Active Duty
AE	Research Program of Record by Core Capability Area
AFMS	Air Force Medical Service
AIC	Akaike Information Criterion
AIS	Abbreviated Injury Scale
CAR	Cabin Altitude Restriction
CCA	Core Capability Area
CCATTs	Critical Care Air Transport Teams
CPG	Clinical Practice Guidelines
DoDTR	Department of Defense Trauma Registry
DTIC	Defense Technical Information Center
ERC	En route care
GCS	Glasgow Coma Scale
GSW	Gunshot wound
IA CUC	Institutional Animal Care and Use Committee
ICP	In-Flight Intracranial Pressure
ICU	Intensive Care Unit
IQR	Interquartile Range
IRB	Institutional Review Board
ISS	Injury Severity Scores
IV	Intravenous
LOWESS	Locally Weighted Scatterplot Smoothing
LRMC	Landstuhl Regional Medical Center
MAP	Mean Arterial Pressure
MHSRS	Military Health Science Research Symposium
Mil Med	Military Medicare
MTF	Medical Treatment Facility
OPE	Operation Enduring Freedom
POI	Point of Injury

PHI	Protected Health Information
RO	Research Objectives
ROC AUC	Receiver Operating Characteristic
SBP	Systolic Blood Pressure
TBI	Traumatic Brain Injury
VS	Vital Signs