59th Medical Wing Science and Technology

JBSA-Lackland, Texas 78236-5415

En route Care Research Center

SCIENTIFIC AND TECHNICAL REPORT

Impact of Critical Care Air Transport Team (CCATT) ventilator management on combat mortality

Joseph K. Maddry, MD
Alejandra G. Mora, BS
Shelia C. Savell, PhD, RN
Crystal A. Perez, BSN, RN
Phillip E. Mason, MD
James K. Aden, PhD
Vikhyat S. Bebarta, MD

September 2018

NOTICE AND SIGNATURE PAGE

The views expressed are those of the authors and do not reflect the official views of the Department of Defense or its Components.

The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402.

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).

TRADER.MICHAEL.W.1127754906 Digitally signed by TRADER.MICHAEL.W.1127754906 Date: 2018.12.04 11:47:09 -06'00'

MICHAEL W. TRADER, GS-12, DAF
Program Analyst, Medical Modernization
59th Medical Wing

MALLORY.AMBER.MELANIE.1471210206 Digitally signed by MALLORY.AMBER.MELANIE.1471210206 Date: 2018.12.11 08:08:29 -06'00'

AMBER MALLORY, Ph.D., GS-15, DAF
Director, Trauma and Clinical Care
59th Medical Wing

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

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
09-17-2018	Closeout	August 2015-August 2017

4. TITLE AND SUBTITLE
Mechanical Ventilation Methods in Transport of Critically Injured and Ill Patients by CCATT

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Joseph K. Maddry, MD
Alejandra G. Mora, BS
Shelia C. Savell, PhD, RN
Crystal A. Perez, BSN, RN
Phillip E. Mason, MD
James K. Aden, PhD
Vikhyat S. Bebarta, MD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
59th MDW/ST, En route Care Research Center
1100 Wilford Hall Loop, Bldg. 4554
JBSA Lackland AFB, TX 78236

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Air Force Medical Support Agency (AFMSA)

10. SPONSOR/MONITOR'S ACRONYM(S)

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

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

13. SUPPLEMENTARY NOTES

14. ABSTRACT

BACKGROUND: Aeromedical evacuation platforms such as Critical Care Air Transport Teams (CCATTs) play a vital role in the transport and care of critically injured and ill patients in the combat theater. Mechanical ventilation is used to support patients with failing respiratory function and patients requiring high levels of sedation. Mechanical ventilation, if not managed appropriately, can worsen or cause lung injury and contribute to increased morbidity. The purpose of this study was to evaluate the impact of ARDSNet protocol compliance during aeromedical evacuation of ventilated combat injured patients.
METHODS: We performed a retrospective chart review of combat injured patients transported by CCATTs from Afghanistan to Landstuhl Regional Medical Center (LRMC) in Germany between January 2007 and January 2012. After univariate analyses, we performed regression analyses to assess compliance and post-flight outcomes. Cox proportional hazard models were used to evaluate associations

between the risk factor of non-compliance with increased number of ventilator, ICU, or hospital days. Nominal logistic regression models were performed to evaluate the association between non-compliance and mortality.
RESULTS: Sixty-two percent (n = 669) of 1,086 patients required mechanical ventilation during transport. A total of 650 patients required volume-controlled mechanical ventilation and were included in the analysis. Of the 650 subjects, 62% (n = 400) were noncompliant per tidal volume and ARDSNet table recommendations. The groups were similar in all demographic variables, except the Non-compliant group had a higher Injury Severity Score compared to the Compliant group. Subjects in the Compliant group were less likely to have an incidence of acute respiratory distress, acute respiratory failure, and ventilator-associated pneumonia when combing the variables (2% vs. 7%, $p < 0.0069$). The Non-compliant group had an increased incidence of in-flight respiratory events, required more days on the ventilator and in the ICU, and had a higher mortality rate.
CONCLUSIONS: Compliance with the ARDSNet guidelines was associated with a decrease in ventilator days, ICU days, and 30-day mortality.

15. SUBJECT TERMS
En route care; ventilator settings; protective lung ventilation; ARDSNet; military; prehospital care

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Joseph K. Maddry, MD
U	U	U	SAR		19b. TELEPHONE NUMBER *(Include area code)* 210-539-4403

Contents

List of Figures

List of Tables

1.0 SUMMARY

Background: Aeromedical evacuation platforms such as Critical Care Air Transport Teams (CCATTs) play a vital role in the transport and care of critically injured and ill patients in the combat theater. Mechanical ventilation is used to support patients with failing respiratory function and patients requiring high levels of sedation. Mechanical ventilation, if not managed appropriately, can worsen or cause lung injury, as well as contribute to increased morbidity. The purpose of this study was to evaluate the impact of ARDSNet protocol compliance during aeromedical evacuation of ventilated combat injured patients. **Methods:** We performed a retrospective chart review of combat injured patients transported by CCATTs from Afghanistan to Landstuhl Regional Medical Center (LRMC) in Germany between January 2007 and January 2012. Following univariate analyses, we performed regression analyses to assess compliance and post-flight outcomes. Cox proportional hazard models were used to evaluate associations between the risk factor of non-compliance with increased number of ventilator, ICU, or hospital days. Nominal logistic regression models were performed to evaluate the association between non-compliance and mortality.

Results:

- Sixty-two percent (n=669) of 1086 patients required mechanical ventilation during transport. A total of 650 patients required volume controlled mechanical ventilation and were included in the analysis.
- Of the 650 subjects, 62% (n=400) were non-compliant per tidal volume and ARDSNet table recommendations. The groups were similar in all demographic variables, except the Non- compliant group had a higher ISS compared to the Compliant group.
- Ninety-two percent of in-flight spO2 values were above the ARDSNet target goal recommendation of 92-96%.
- Subjects in the Compliant group were less likely to have an incidence of acute respiratory distress, acute respiratory failure, and ventilator associated pneumonia when combing the variables (2% vs 7%, p=0.0069).
- The Non-compliant group had an increased incidence of in-flight respiratory events, required more days on the ventilator and in the ICU, and had a higher mortality rate.
- Mortality rate in Compliant group was 2%, compared to 7% in the Non-compliant group (p=0.0118). The odds of mortality were 2.75 times greater in the Non-compliant group.
- Inflight ventilator settings were similar to preflight ventilator settings; CCATT providers tended to maintain preflight ventilator settings established by the MTF providers and did not make adjustments as long as patients remained stable.

Conclusions:

- Over half of CCATT patients require mechanical ventilation
- Compliance with ARDSNet table recommendations is low
- Non-compliance is associated with more ventilator days and ICU days
- Non-compliance is associated with increased mortality

Note: The CCATT Mechanical Ventilation CPG, which is aligned with the ARDSNet protocol, was implemented in 2012**,** after this study period.

US Army, Joint Theater Trauma Systems Clinical Practice Guidelines. CCAT CPGs. CCAT Mechanical Ventilation. Updated 2013 Oct. Available from http://www.usaisr.amedd.army.mil/assets/cpgs/CCATCPGMechanicalVentilationOct2013.pdf

Evidence Based Recommendations:

- The results of this CCATT study, as well as related civilian studies should be incorporated into the training of military providers.
- Providers should be trained to provide ventilator management using the Mechanical Ventilation CPG.
- The CCATT Mechanical Ventilation CPG should be the basis for a joint en route care ventilator management CPG.
- Quality Assurance procedures should be implemented to ensure ongoing compliance with the CPG.
- Further research evaluating the impact of closed-loop ventilator management systems should be conducted.

2.0 INTRODUCTION

Aeromedical evacuation platforms such as Critical Care Air Transport Teams (CCATTs) play a vital role in the transport and care of critically injured and ill patients (1,2). CCATTs provide expedient transport within the combat theater and out of theater to higher echelons of care. CCATTs consist of highly trained doctors, nurses, and respiratory therapists who transport patients in several different modalities that include buses, aircrafts, and ambulances (1-3). We have previously shown the impact of blood transfusions and pain medications during CCATT missions (4,5). Mechanical ventilation in the delivery of en route care is used to support critically ill patients with respiratory failure. Mechanical ventilation is also used to support patients requiring high levels of sedation due to acuity of illness and severity of injury (6-9). Transporting patients on mechanical ventilation can present many challenges for providers.

Mechanical ventilation, if not managed appropriately, can worsen or cause lung injury such as Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), as well as contribute to increased morbidity (10-14). In civilian studies protective ventilation methods are associated with improved patient outcomes (12,14). The National Institutes of Health (NIH) and National Heart Lung and Blood Institute (NHLBI) have a mechanical ventilation protocol summary, ARDSNet, with established criteria for appropriate management of ventilator settings (15). The initial focus was on treatment of ARDS, but there is evidence to support use of protective ventilator settings to prevent ALI, ARDS, increased ventilator days, and death (10-14).This study protocol was developed using the ARDSNet trial data to provide guidelines for tidal volume and Positive End Expiratory Pressure (PEEP) settings (12,15).

The purpose of this study was to evaluate the impact of ARDSNet compliance during aeromedical evacuation of ventilated Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) combat injured patients. We hypothesized that ARDSNet compliance would shorten the duration of mechanical ventilation and decrease mortality.

3.0 METHODS

3.1 Study Design and Setting

We performed a retrospective chart review of patients with traumatic injuries transported from Iraq or Afghanistan to Germany between January 2007 and January 2012. This study was approved by the US Army Military Research Materiel Command Institutional Review Board.

3.2 Selection of Participants

We screened CCATT flight medical records to identify patients with trauma, requiring en route mechanical ventilation, departing the combat hospital and arriving at Landstuhl Regional Medical Center (LRMC) in Germany (approximately 7 hour flight). We excluded patients who did not require en route ventilation or were ventilated using pressure control mode. Patients who were ventilated using volume control mode were enrolled in the study.

3.3 Measurements

Using a study specific electronic database (Microsoft Excel 2010; Microsoft Corporation, Redmond, Washington) with pre-defined fields we abstracted data from records to include demographics, injury description, departure and arrival locations, clinical parameters, medications, procedures, laboratory measures, dates, and timestamps as available for pre-flight and in-flight data points. We included all available ventilator-related data such as mode, tidal volume, PEEP, fraction of inspired oxygen (FiO_2), and subject oxygenation measures along with timestamps. Using documented height, we calculated ideal body weight (IDW) and tidal volume. Abstractors were trained to interpret CCATT medical records and used standardized tools to determine medical events of interest (4). Data collected were based on provider documentation on the CCATT medical record (Air Force Form 3899). Routine quality control measures were implemented to ensure accuracy and consistency of data collection.

3.4 Outcomes

The Department of Defense Trauma Registry (DoDTR) was queried to provide post-flight and outcome data for our study subjects. Post-flight data included vital signs, hemodynamic parameters, laboratory values, oxygenation measures, and complications. Complications and adverse events were determined by trained coders and medical staff review of patient records per DoDTR definitions. Outcome data included total number of ventilator days, total number of intensive care unit days, total number of hospital days, and mortality through 30 days.

3.5 Analysis

Subjects were categorized based on ventilator setting compliance to ARDSNet recommendations with respect to tidal volume and PEEP to FiO_2 settings according to the low PEEP table (15). Subjects whose tidal volumes were ≤8 cc/kg IBW and PEEP to FiO_2 ratios were in accordance with the ARDSNet table recommendations were considered Compliant. Non-compliance with either parameter was considered Non-compliant for this study.

We conducted statistical analysis using JMP version 10 (SAS Institute Inc., Cary, NC). Initial descriptive analyses was performed followed by comparative tests such as t-tests (or Wilcoxon for non-parametric data) for continuous variables and chi-square (or

Fisher's Exact when appropriate) for categorical variables. Data were reported as percent (95% Exact Confidence Interval) or Mean±Standard Deviation; Median [Interquartile Range] as appropriate. The 95% confidence intervals were calculated using Poisson distribution based calculations. Following univariate analyses, we performed regression analyses to assess compliance and post-flight outcomes. Cox proportional hazards models were used to evaluate associations between the risk factor of non-compliance with likelihood of discharge from ventilator, ICU, or hospital. The Martingale residuals were examined to evaluate the assumption of proportional hazards across each covariate using regression smoothing fit techniques (locally weighted scatterplot smoothing-LOWESS) to ensure assumptions are maintained. Nominal logistic regression models were performed to evaluate the association between non-compliance and mortality.

In model analyses, as needed, baseline factors such as demographics, injury descriptions, and pre-flight variables were included in models to determine influence on outcomes or to adjust for relevant pre-flight differences between groups (covariates). Model significance, confidence intervals, Hosmer-Lemeshow goodness of fit, and Akiaike's information criterion were used as measures to determine the best-fit, optimal model. The Kaplan-Meier method was used to represent time to discharge from ventilator, ICU, and hospital. Log-rank statistics were used to report the difference between Compliant and Non-Compliant groups. Ventilator, ICU, and hospital day variables were censored for 30-day mortality.

4.0 RESULTS

4.1 Characteristics of Study Subjects

We reviewed 1086 CCATT records of trauma patients transported from theater to LRMC between January 2007 and January 2012. Sixty-two percent (n=669) of patients received mechanical ventilation during transport. We excluded 436 patients (417 were not ventilated and 19 received pressure controlled ventilation). A total of 650 patients received volume controlled mechanical ventilation. (Table 1) We were able to abstract preflight vital signs from 97% of records and at least seven in-flight vital sign entries from 83% of records. We had available preflight blood gases for 80% of records and at least two in-flight blood gas values for 67% of records.

Table 1: Demographics and Injury Description

	Overall Mean±SD; Median [IQR] or % (95% CI) n=650	**Tidal Volume and ARDSNet Table Compliant** Mean±SD; Median [IQR] or % (95% CI) n=250	**Tidal Volume and ARDSNet Table Non-compliant** Mean±SD; Median [IQR] or % (95% CI) n=400	**p-value**
Age	27±7.4; 25 [17-34]	26±6.2; 24 [21-28]	27±8.1; 24 [21-28]	0.0709
Gender, % male	98% (97-99%)	98% (95-99%)	98% (97-99%)	0.7573
Injury Description				
ISS	27±13.3; 25 [17-34]	25±13.3; 24 [17-30]	28±13.2; 25 [22-30]	0.0056
Blast	70% (67-74%)	69% (63-75%)	72% (68-77%)	0.4291
Penetrating	19% (16-22%)	20% (15-25%)	18% (14-22%)	0.5358
Blunt	8% (6-10%)	9% (6-13%)	7% (90-95%)	0.4539
Burn	2% (1-3%)	2% (<1-4%)	2% (96-99%)	0.5318
Head Injury	54% (5-58%)	57% (51-63%)	53% (48-58%)	0.2673
Inhalation Injury	11% (8-14%)	10% (6-16%)	11% (8-16%)	0.7193

Reflective of trauma patients on volume control mechanical ventilation during CCATT transport

4.2 Main Results

Oxygenation

Average oxygenation profile prior to flight: spO_2 99 %; paO_2 126 mmHg; pCO_2 41 mmHg; HCO_3 25 mEq/L (Table 2). Two subjects (<1%) had pre-flight spO_2 values <92% and eighty-eight (14%) had pre-flight paO_2 values <80 mmHg. In-flight average spO_2 was 99%, paO2 117 mmHg, pCO_2 42mmHg, HCO_3 25mEq/L (Table 3). Nine (1%) subjects had an in-flight spO_2 value <92% and three a value <90%. Ninety-two percent of in-flight spO2 values were above the ARDSNet target goal recommendation of 92-96%. Eighteen percent of subjects had an in-flight paO_2 <80 mmHg and of those 30% (36/119) had more than one documented paO_2 <80 mmHg. Four percent of subjects had documented in-flight paO_2 values >200 mmHg.

Tidal Volume

Prior to flight, tidal volume averaged 7.7 cc/kg IBW and 27% of subjects had a tidal volume greater than 8 cc/kg IBW. When comparing subjects with pre-flight tidal volume ≤8 cc/kg IBW versus >8 cc/kg IBW, subjects were similar in demographics, injury description, in-flight disposition, and outcomes. Pre-flight tidal volumes were associated with in-flight tidal volumes ($p<0.0001$). Subjects with initial tidal volume prior to flight greater than the recommended 6 to 8 cc/kg IBW had a higher likelihood of having an in-flight tidal volume >8 cc/kg IBW (22% vs 91%, $p<0.0001$) and >10 cc/kg IBW (1% vs 10%, $p<0.0001$).

Thirty percent of subjects had in-flight tidal volumes >8 cc/kg IBW and 4% had a tidal volume >10 cc/kg IBW. Subjects with in-flight tidal volumes ≤8 cc/kg IBW were also similar to those with tidal volumes >8 cc/kg IBW across demographic, injury description, in-flight disposition, and mortality. Subjects with in-flight tidal volume ≤8 cc/kg IBW were less likely to have an incidence of acute respiratory distress, acute respiratory failure, and ventilator associated pneumonia when combing the variables (2% vs. 7%, $p<0.0196$).

Tidal Volume and ARDSNet Table Compliance

Of the 650 subjects that received volume-controlled mechanical ventilation during transport, 62% (n=400) were Non-compliant per tidal volume or ARDSNet PEEP to FiO_2 table recommendations. The Non-compliant group had a higher ISS compared to the Compliant group. We did not identify any further differences in demographics or injury descriptions between the groups (Table 1).

Pre-flight, the Non-compliant group had a higher median ventilator rate, tidal volume, FiO_2, and PEEP values. While the Compliant group had a higher median spO_2, other oxygenation status and incidence rates of pre-flight events were similar between the groups (Table 2). In-flight, the Non-compliant group also had higher median tidal volume, FiO_2, and PEEP values; but ventilator rates were similar. Of the entire non-compliant PEEP to FiO_2 ratios, 84% of values were of FiO_2 values that were higher than recommended per ARDSNet table. Subjects with pre-flight PEEP to FiO_2 ratios that were within ARDSNet table recommendations were more likely to abide by ARDSNet table recommendations during flight (69% vs 14%, $p<0.0001$). The Compliant group had higher median spO_2 values. The Non-compliant group had an increased incidence in respiratory events during transport (Table 2). Respiratory events included parameters such as acidosis, significant changes in ventilator settings, significant decrease in oxygenation, and transport provider event documentation (4).

Post-flight, the Compliant group had higher median spO_2 values, however other oxygenation parameters did not differ between groups (Table 3). The Non-compliant group tended to have increased incidence of respiratory events. In addition, the Non-compliant group required more days on the ventilator and in the ICU. The subjects with compliant ventilator settings during flight had a higher survival rate (Table 3).

In our analyses we identified that ISS was a baseline factor in which the Compliant and the Non-compliant groups differed prior to transport; thus, regression models (Cox proportional hazards and nominal logistic regressions) were adjusted for ISS. During model development additional covariates ($p<0.20$ in univariate analyses) were included such as age and pre-flight spO_2. Subsequently, covariates were progressively eliminated due to insignificance ($p>0.05$) and lacking effect on outcome variable of interest. Per LOWESS fit and martingale residuals assumptions of proportional hazard analyses were maintained. All logistic regression models were valid per Hosmer-Lemeshow goodness of fit.

Table 2: Pre-flight and In-flight

	Overall Mean±SD; Median [IQR] or % (95% CI) n=650	**Tidal Volume and ARDSNet Table Compliant** Mean±SD; Median [IQR] or % (95% CI) n=250	**Tidal Volume and ARDSNet Table Non-compliant** Mean±SD; Median [IQR] or % (95% CI) n=400	**p-value**
Pre-flight				
Ventilator Settings				
Ventilator Rate	17±3.2; 18 [16-20]	18±3.0; 18 [16-20]	17±3.3; 18 [16-20]	<0.0001
Tidal Volume, ml	570±57.8; 550 [550-600]	556±45.2; 550 [530-600]	579±62.8; 570 [550-600]	<0.0001
FiO_2, %	43±9.6; 50 [40-50]	41±7.7; 40 [40-40]	44±10.3; 40 [40-50]	<0.0001
PEEP, cm H_2O	6±1.9; 5 [5-5]	5±1.3; 5 [5-5]	6±2.2; 5 [5-5]	0.0067
Oxygenation Status				
SPO_2, %	99±1.7; 100 [98-100]	99±1.4; 100 [99-100]	99±1.8; 99 [98-100]	0.0017
PaO_2, mmHg	126±54.4; 113 [90-147]	128±54.1; 115 [92-149]	124±54.7; 112 [88-146]	0.2640
PCO_2, mmHg	41±8.0; 40 [36-45]	40±6.5; 40 [36-44]	41±8.8; 41 36-45]	0.4768
HCO_3, mEq/L	25±3.2; 25 [23-27]	25±3.0; 25 [23-27]	25±3.4; 25 [23-27]	0.4148
Base Deficit/Excess, mEq/L	-0.2±3.44; 0.0 [-2.0-2.0]	-0.2±3.15; 0.0 [-2.0-2.0]	-0.2±3.6; 0.0 [-2.0-2.0]	0.8451
PaO_2/FiO_2	277±156; 268 [190-360]	285±166; 285[213-367]	271±150; 257 [183-353]	0.0821

Event				
Respiratory Event*	8% (6-11%)	6% (4-10%)	9% (7-13%)	0.2099
Cardiac Event	4% (2-5%)	2% (1-5%)	4% (3-7%)	0.1915
Neurologic Event	3% (3-4%)	3% (2-6%)	2% (1-4%)	0.4819
Infection Event	0% (0-1%)	1% (0-3%)	<1% (0-1%)	0.3281
In-flight				
Paralytic	7% (5-9%)	5% (3-8%)	8% (5-11%)	0.1546
Chest Tube	23% (20-26%)	21% (16-26%)	24% (20-29%)	0.2753
Ventilator Settings				
Ventilator Rate	18±3.2; 18 [16-20]	18±3.0; 18 [16-20]	18±3.3; 18 [16-20]	0.8383
Tidal Volume	576±59.7; 570 [550-600]	556±46.9; 550 [530-600]	588±63.1; 589 [550-632]	<0.0001
FiO_2, %	44±9.2; 40 [40-50]	40±5.8; 40 [40-40]	47±9.9; 46 [40-50]	<0.0001
PEEP, cm H_20	9±2.0; 5 [5-5]	6±1.4; 5 [5-5]	6±2.3; 5 [5-7]	0.0001
Oxygenation Status				
SPO_2, %	99±1.4; 100 [98-100]	99±1.1; 100 [99-100]	99±1.6; 99 [98-100]	0.0067
PaO_2, mmHg	117±33.5; 115 [91-134]	118±29.6; 117 [97-134]	116±35.7; 114 [88-135]	0.1484
PCO_2, mmHg	42±6.5; 41 [38-45]	41±5.4; 41 [38-44]	42±7.03; 41 [38-45]	0.3233
HCO_3, mEq/L	25±3.1; 25 [23-27]	25±2.8; 25 [23-27]	25±3.2; 25 [23-27]	0.5733
Base Deficit/Excess, mEq/L	0.1±3.46; 0.3 [-2.0-2.3}	-0.1±3.2; 0.0 [-2.0-2.0	0.1±3.6; 0.5 [-2.0-2.5]	0.4676
PaO_2/FiO_2	273±87; 270 [208-331]	299±80; 302 [245-349]	257±87; 250 [186-316]	<0.0001
Event				
Respiratory Event†	39% (35-43%)	27% (22-33%)	47% (42-52%)	<0.0001
Cardiac Event	0% (0-1%)	-	1% (<1-2%)	0.5247
Neurologic Event	1% (0-2%)	1% (<1-3%)	1% (<1-2%)	0.6429

*Pre-flight respiratory events inclusive of complications and diagnoses secondary to traumatic injuries; pneumothorax, pulmonary edema, acute hypoxemia, atelectasis, pulmonary embolism, pleural effusion, respiratory decompensation, pneumonia, and ARDS.

SD, standard deviation; IQR, interquartile range; CI, confidence interval; positive end-expiratory pressure, PEEP

Table 3: Post-flight and Outcomes

	Overall Mean±SD; Median [IQR] or % (95% CI) n=650	**Tidal Volume and ARDSNet Table Compliant** Mean±SD; Median [IQR] or % (95% CI) n=250	**Tidal Volume and ARDSNet Table Non-compliant** Mean±SD; Median [IQR] or % (95% CI) n=400	**p-value**
Post-flight				
Oxygenation Status				
SPO_2	99±1.3; 100 [99-100]	100±0.9; 100 [99-100]	99±1.5; 100 [99-100]	0.0007
PaO_2	121±39.6; 119 [95-138]	116±31.7; 40 [37-43]	123±43.6; 120 [95-143]	0.3329
PCO_2	41±6.0; 40 [37-44]	41±6.7; 40 [37-43]	41±5.6; 40 [37-44]	0.6591
HCO_3	25±3.1; 25 [23-27]	25±3.3; 25 [24-27]	25±3.0; 25 [23-27]	0.6235
Base Deficit/Excess	0.3±3.28; 0 [-2.0-2.3]	0.6±3.1; 0.5 [-1.0-2.0]	0.1±3.4; 0 [-2.0-3.0]	0.2927
Hgb	9.7±3.09; 9.2 [8.2-10.5]	9.8±4.3; 9.2 [8.4-10.5]	9.6±2.1; 9.2 [8.2-10.5]	0.5423
Events				
Respiratory Event*	31% (28-35%)	27% (22-33%)	34% (29-39%)	0.0513
ARDS	2% (2-4%)	<1% (0-2%)	4% (2-6%)	0.0025
ARF	1% (<1-2%)	-	2% (1-4%)	0.0089
VAP	2% (1-4%)	2% (1-5%)	3% (1-5%)	0.6768
ARDS/ARF/VAP	5% (4-7%)	2% (1-5%)	7% (5-10%)	0.0069
Cardiac Event	16 (13-19%)	16% (12-21%)	16% (13-20%)	0.9819
Neurologic Event	-	-	-	-
Infection Event	-	-	-	-
Outcomes				
Ventilator Days	7±9.0; 4 [3-7]	6±6.2; 4 [3-6]	7±10.4; 5 [3-8]	0.0118
ICU Days	11±20.9; 6 [4-11]	9±9.3; 5 [4-10]	12±25.6; 6 [4-13]	0.0201
Hospital Days	28±40.8; 10 [5-37]	27±39.5; 12 [5-36]	29±41.7; 13 [5-38]	0.6469
Mortality	5% (4-7%)	2% (1-5%)	7% (5-10%)	0.0118

*Post-flight respiratory events obtained from DoDTR; atelectasis, pulmonary embolism, pneumonia, pulmonary edema, pleural effusion, empyema ARDS, ARF, and VAP. SD, standard deviation; IQR, interquartile range; CI, confidence interval; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; VAP, ventilator-associated pneumonia; ICU, intensive care unit

Non-compliance as a risk factor for number of ventilator, ICU, or hospital days was not evident when ISS, age, and pre-flight spO_2 were included in models (Table 4a). However, after adjusting for ISS and evaluating adherence to ARDSNet table recommendations only, non-compliance with PEEP to FiO_2 ratios alone increased the risk of increased ventilator and ICU days by over 20% (Table 4b). Per hazard rates (<1) a higher ISS would decreases likelihood of discharge from ventilator, ICU, and hospital.

In logistic regression models, non-compliance was associated with increased mortality (Table 4c). The odds of mortality were 2.75 times greater in the Non-compliant group. Using the Kaplan-Meier methods, the Compliant group had a greater percentage of subjects with fewer ventilator and ICU days than the Non-compliant group (Figure 1).

Table 4: Regression Analyses

a.) Cox proportional hazards analysis for tidal volume and ARDSNet table Non-compliance

	Ventilator Days		ICU Days		Hospital Days	
	Hazard Ratio	**p-Value**	**Hazard Ratio**	**p-Value**	**Hazard Ratio**	**p-Value**
TV and ARDSNet Non-compliant	0.91 (0.76-1.08)	0.2698	0.90 (0.76-1.07)	0.2319	1.03 (0.87-1.23)	0.7259
ISS	0.97 (0.97-0.98)	<0.0001	0.97 (0.97-0.98)	<0.0001	0.98 (0.98-0.99)	<0.0001
Age	0.99 (0.98-1.00)	0.1071	0.99 (0.98-1.00)	0.0345	0.99 (0.98-1.00)	0.0312
Pre-flight spO_2	1.05 (1.00-1.10)	0.0693	1.05 (1.00-1.11)	0.0310	1.03 (0.98-1.10)	0.2258

b.) Cox proportional hazards analysis for ARDSNet table only Non-compliance

	Ventilator Days		ICU Days		Hospital Days	
	Hazard Ratio	**p-Value**	**Hazard Ratio**	**p-Value**	**Hazard Ratio**	**p-Value**
ARDSNet Non-compliant	0.83 (0.70-0.98)	0.0258	0.82 (0.70-0.97)	0.0209	0.98 (0.83-1.16)	0.8195
ISS	0.97 (0.97-0.98)	<0.0001	0.97 (0.97-0.98)	<0.0001	0.98 (0.98-0.99)	<0.0001

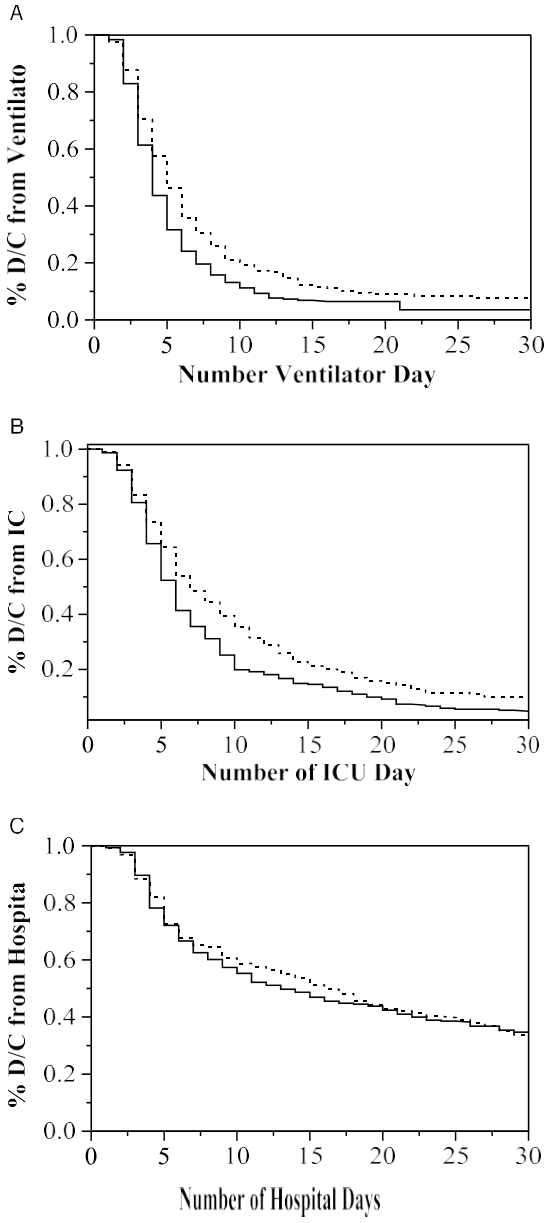
c. Nominal logistic regression analysis for 30-day mortality

	Model 1		Model 2		Model 3	
	Odds Ratio	**p-Value**	**Odds Ratio**	**p-Value**	**Odds Ratio**	**p-Value**
TV and ARDSNet Non-compliant	2.33 (0.97-6.47)	0.0579	2.40 (1.01-6.63)	0.0480	2.75 (1.17-7.54)	0.0.0187
ISS	1.04 (1.02-1.06)	0.0010	1.04 (1.02-1.06)	0.0009	1.04 (1.02-1.07)	0.0002
Age	1.01 (0.97-1.06)	0.5401	-	-	-	-
Pre-flight spO_2	0.90 (0.75-1.09)	0.2505	0.90 (0.76-1.10)	0.2823	-	-

ISS, injury severity score PF<=300; SF<=315

Mild 315; moderate 235; severe 144

Figure 1: Kaplan-Meier: TV and ARDS Compliance



— Compliant
..... Non-compliant

a. Discharge from Ventilator: Log-rank, p=0.0004
b. Discharge from ICU: Log-rank, p=0.0006
c. Discharge from Hospital: Log-rank, p=0.8742

5.0 DISCUSSION

In our study of CCATT ventilator patients, we found an association between compliance with the ARDSNet protocol and improved outcomes (decreased ventilator days, ICU days, and 30-day mortality) similar to civilian inpatient studies (9,11). We also found benefit in preventing ALI and ARDS, again similar to civilian inpatient studies (16).Ventilator management per the ARDSNet protocol during CCATT missions has the potential to decrease the morbidity and mortality of combat casualties.

According to the CCATT Pilot Unit Database (October 2016), over 4500 CCATT patients have been evacuated from theater during OEF and OIF. Appropriate mechanical ventilator management has the potential to minimize ALI and ARDS induced morbidity and mortality associated with combat injuries (16); however, little knowledge of the impact of mechanical ventilation methods during prolonged aeromedical evacuation is published.

The Air Force CCATT patients provide a unique population of patients, often suffering severe penetrating, blunt, and blast injuries. Similar injuries have occurred in previous conflicts but large-scale transcontinental aeromedical evacuation of ventilated patients within days of the initial injury had not occurred prior to 2001(1). Though fixed and rotary wing based aeromedical evacuation of ventilated patients occurs in the civilian setting, evaluation of the impact of this transportation is limited due to patients being transported by numerous aeromedical evacuation systems without a robust consolidated database (9,17,18).With limited prior experience and related published medical research, current military air transport ventilator management decisions are based upon the available intensive care literature. These civilian studies may not be applicable due to the unique aspects of combat injuries (blast injuries) and CCATT missions (altitude, non-intensivist physicians, etc.).

In our study, a subgroup analysis of patients with low TV was not associated with a statistically significant benefit in ventilator days, ICU days, or mortality. Previous studies have clearly demonstrated the benefit of low tidal volumes alone in the treatment of ARDS (12,14,19); however, studies evaluating the efficacy of low tidal volumes in preventing ALI and ARDS have yielded conflicting results. Previous studies have found a higher incidence of ALI and other pulmonary complications in those patients with larger tidal volumes when compared to those with a target tidal volume of 6 cc/kg (13,19). In patients undergoing major surgery, studies have found both benefit (20,21) and harm (22,23) associated with low tidal volume strategies. Furthermore, the increased lung compliance inherent in the younger patients evaluated in our study compared to previous ventilation studies, may alleviate the impact of increased tidal volumes.

Further analysis of our results demonstrates ARDSNet table compliance (a stepwise increase in PEEP and FiO2) was associated with a statistically significant benefit in ventilator days, ICU days, and mortality. Limited studies have evaluated the effect of PEEP and supplemental oxygen on the prevention of ARDS, especially in trauma patients. In our study, CCATT personnel would frequently increase FiO2 without increasing the PEEP. Theoretically, the increase in oxygen may result in a subsequent increase in free radical generation, inflammatory changes, and lung injury (24,25). There may be more benefit in using increased PEEP and decreased FiO2 in prevention of ALI/ARDS. Of note, the majority of patients had oxygen saturations above

96%, indicating that CCATTs were arbitrarily increasing oxygenation levels beyond those typically recommended (15). This excess oxygen may further exacerbate any potential lung injury (24,25).

We detected a substantial rate of non-compliance with the ARDSNet protocol by CCATTs. This finding should be interpreted in the context of other studies. Needham et al found that less than half of ventilator settings adhered to lung protective ventilation among a cohort of patients with acute lung injury (26). Similarly, Poole et al found compliance with 6-8 cc/kg IBW tidal volumes to be < 40% among patients enrolled in three large ARDS trials (27). The thresholds for defining non-compliance are different between these studies and ours. Needham et al defined tidal volume > 6.5 cc/kg IBW or plateau pressure > 30 cm H2O as non-compliant, while Poole et al, used a tidal volume threshold of 8 cc/kg IBW. Neither used adherence to the PEEP/FiO2 table as a criterion to identify non-compliance. Despite the differences, these studies are consistent with our findings that non-compliance with lung protective ventilator strategies is common. These studies were also limited to patients with ALI or ARDS while our study included all CCATT patients, some of which did not have ALI or ARDS. While it is still appropriate to manage this population using lung protective ventilation, the imperative to do so is certainly less.

While we did not aim to study the reasons for non-compliance, potential explanations include: 1) CCATT personnel maintained preflight ventilator settings established by the MTF providers and did not adjust these settings given the patient's ventilator status was stable, 2) providers empirically administered additional oxygen to prevent perceived altitude induced hypoxia, 3) providers assumed an oxygen saturation of 100% resulting from increased oxygen administration was better than 92-96% specified by the ARDSNet protocol, and 4) clinicians assumed that the ventilator settings during a 7-hour mission would not impact patient outcomes. In addition, a lack of familiarity with the ARDSNet protocol, particularly in providers not routinely exposed to ICU mechanical ventilation protocols, may have impacted compliance. Other factors we have not discussed may also have contributed. Future studies could evaluate potential causes of this non-compliance. The CCATT program has a rigorous and high performing quality improvement program. Dissemination of the findings of our study and incorporation of these findings into CCATT quality improvement/quality control measures will likely improve CCATT ARDSNet and CCATT CPG compliance to improve the outcomes of our patients.

Our study has several limitations. Given the study was retrospective in nature, tidal volumes used by providers may have been estimates (which should be calculated based upon ideal body weight); however, for this study we calculated ideal body weight based on documented height. Therefore, the tidal volumes may be estimates thereby limiting our ability to detect the impact of low tidal volume use. Furthermore, the data was abstracted from the CCATT record creating the potential for missing data due to a lack of documentation by the en route care teams. While all data abstractors were trained and periodic quality reviews occurred, there remains the potential for subjectivity in data abstraction from the CCATT patient care records (28,29). The mechanism of injury, severity of injury, young age of our population, and long transcontinental evacuation times may limit the generalizability of our findings to the civilian population.

Given these findings, ARDSNet guidelines should guide the management of CCATT mechanically ventilated patients. This study supports the CCATT leadership's decision to implement this practice in the 2012 CCATT Ventilator Management Clinical Practice Guideline CPG (30). Future studies and CCATT quality assurance measures should evaluate the impact of the CPG. The results of this study should be disseminated to improve CCATT practices and clinical outcomes in future combat en route care platforms. Furthermore, the findings of our study should be incorporated into ongoing efforts to develop automated closed loop and decision support based ventilator systems (8).

Conclusions In our study of CCATT ventilator patients, we found an association between compliance with the ARDSNet protocol and improved outcomes (decreased ventilator days, ICU days, and 30-day mortality) similar to civilian inpatient studies (9,11). We also found benefit in preventing ALI and ARDS, again similar to civilian inpatient studies (16).Ventilator management per the ARDSNet protocol during CCATT missions has the potential to decrease the morbidity and mortality of combat casualties.

6.0 REFERENCES

1. Ingalls N, Zonies D, Bailey JA, Martin KD, Iddins BO, Carlton PK, Hanseman, D, Branson R, Dorlac W, Johannigman, J. A. Review of the first 10 years of critical care aeromedical transport during operation Iraqi Freedom and Operation Enduring Freedom: The importance of evacuation timing. *JAMA Surg.* 2014;149(8):807-813.
2. 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;17(4):486-490.
3. Barnes SL, Branson R, Gallo LA, Beck G, Johannigman JA. En-route care in the air: snapshot of mechanical ventilation at 37,000 feet. *J Trauma*. 2008;64(2Suppl):S129-134; discussion S134-5.
4. Mora AG, Ganem VJ, Ervin AT, Maddry JK, Bebarta VS. En route use of analgesics in nonintubated, critically ill patients transported by U.S. Air Force Critical Care Air Transport Teams. *Mil Med.* 2016;181(5 Suppl):145-151.
5. Mora AG, Ervin AT, Ganem VJ, Bebarta VS. Aeromedical evacuation of combat patients by military critical care air transport teams with a lower hemoglobin threshold approach is safe. *J Trauma Acute Care Surg*. 2014;77(5):724-728.
6. Marini JJ. Mechanical ventilation: past lessons and the near future. *Crit Care*. 2013; 17(Suppl 1): S1.
7. Morris MJ. Acute respiratory distress syndrome in combat casualties: military medicine and advances in mechanical ventilation. *Mil Med*. 2006;171(11):1039-1044.
8. Johannigman JA, Branson R, Lecroy D, Beck G. Autonomous control of inspired oxygen concentration during mechanical ventilation of the critically injured trauma patient. *J Trauma.* 2009;66(2):386-92.
9. Rouse MJ, Branson R, Semonin-Holleran R. Mechanical ventilation during air medical transport: techniques and devices. *J Air Med Transp*. 1992;11(4):5-8.
10. Cordioli RL, Garelli V, Lyazidi A, Suppan L, Savary D, Brochard L, Richard JC. Cardiopulmonary resuscitation: risks and benefits of ventilation. *Rev Med Suisse*. 2013;9(410):2318-23.
11. Kashani KB, Farmer JC. The support of severe respiratory failure beyond the hospital and during transportation. *Curr Opin Crit Care*. 2006;12(1):43-9.
12. Brower, R G, Matthay, MA, Morris, A, Schoenfeld, D, Thompson, BT, & Wheeler, A. and the ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-08.
13. de Haro C, Martin-Loeches I, Torrents E, Artigas A. Acute respiratory distress syndrome: prevention and early recognition. *Ann Intensive Care* 2013;11.
14. Neto A, Cardosa S, Manetta J, Pereira V, Esposito D, Pasqualucci M, Damasceno M, Schultz M. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome. *JAMA.* 2012;24(31):1651-1659.

15. NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary. http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf. Accessed 10/26/2016.
16. Park PK, Cannon JW, Ye W, Blackbourne LH, Holcomb JB, Beninati W, Napolitano LM. Incidence, risk factors, and mortality associated with acute respiratory distress syndrome in combat casualty care. *J Trauma Acute Care Surg*. 2016 Nov; 81(5 Suppl 2 Proceedings of the 2015 Military Health System Research Symposium):S150-S156.
17. Wilcox SR, Richards JB, Fisher DF, Sankoff J, Seigel TA. Initial mechanical ventilator settings and lung protective ventilation in the ED. *Am J Emerg Med*. 2016; 34: 1446–1451.
18. Seymour CW, Kahn JM, Schwab CW, Fuchs BD. Adverse events during rotary-wing transport of mechanically ventilated patients: a retrospective cohort study. *Crit Care*. 2008; 12(3):R71.
19. Determann RM, Royakkers A, Wolthuis, EK, Vlaar AP,Choi G, Paulus F, Hofstra JJ, de Graaff MJ, Korevaar JC, Schultz MJ. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care*. 2010;14:R1.
20. Futier E, Pereira B, Jaber S . Intraoperative low-tidal-volume ventilation. N Engl J Med. 2013;369(19):1862-1863.
21. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, Dionigi G, Novario R, Gregoretti C, de Abreu MG, et.al. JAMA Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. *Anesthesiology.* 2013;118(6):1307-1321.
22. Levin MA, McCormick PJ, Lin HM, Hosseinian L, Fischer GW. Low intraoperative tidal volume ventilation with minimal PEEP is associated with increased mortality. *Br J Anaesth.* 2014;113(1):97-108.
23. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. High versus low positive end expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicenter randomised controlled trial. *Lancet.* 2014; 384 (9942):495-503.
24. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. *Intensive Care Med*. 2015;41:1118–1121.
25. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, Morelli A, Antonelli M, Singer M. 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):1583-1589.
26. Needham DM, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Sevransky JE, Himmelfarb CR, Desai SV, Shanholtz C, Brower RG, Pronovost PJ. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *Bmj*. 2012;344:e2124.
27. Poole J, McDowell C, Lall R, Perkins G, McAuley D, Gao F, Young D. Individual patient data analysis of tidal volumes used in three large randomized control

trials involving patients with acute respiratory distress syndrome. *British journal of anaesthesia*. 2017;118(4):570

28. Worster A, Bledsoe RD, Cleve P, Fernandes CM, Upadhye S, Eva K. Reassessing the methods of medical record review studies in emergency medicine research. *Ann Emerg Med.* 2005;45(4):448-51.

29. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: Where are the methods? *Ann Emerg Med.* 1996; 27(3):305-308.

30. US Army, Joint Theater Trauma Systems Clinical Practice Guidelines. CCAT CPGs. CCAT Mechanical Ventilation. Updated 2013 Oct. Available from http://www.usaisr.amedd.army.mil/assets/cpgs/CCATCPGMechanicalVentilationOct2013.pdf. Accessed 10 December 2014

APPENDIX: Publications and Presentations

A.1 Publications

Maddry JK, Mora AG, Savell SC, Perez CA, Mason PE, Aden JK, Bebarta VS. Impact of Critical Care Air Transport (CCATT) ventilator management on combat mortality. J Trauma Acute Care Surg. 2018;84(1):157-164.

https://www.ncbi.nlm.nih.gov/pubmed/28570350

A.2 Presentations

1. Maddry JK, Reeves LK, Mora AG, Savell SC, Bebarta VS. Mechanical Ventilation Methods in Transport of Critically Injured and Ill Patients by Critical Care Air Transport Teams (CCATT). Oral. MHSRS, August 2016
2. Savell SC, Mora AG, Paciocco JA, Perez CA, Maddry JK. The impact of Critical Care Air Transport Team (CCATT) ventilator management on combat mortality. Oral. TSNRP, April 2017
3. Maddry JK, Savell SC, Mora AG, Paciocco JA, Perez CA. The Impact of Critical Care Air Transport Team (CCATT) Ventilator Management on Combat Mortality. Poster, Oral. SURF, 2017
4. Perez C, Reeves L, Mora A, Lear J, Paciocco J, Medellin K, Savell S, Bebarta V, Maddry J. Mechanical ventilation practices during CCATT evacuation of non-trauma, medical patients. Poster. MHSRS, 2017
5. Perez C, Reeves L, Mora A, Lear J, Paciocco J, Medellin K, Savell S, Bebarta V, Maddry J. Mechanical ventilation practices during CCATT evacuation of non-trauma, medical patients. Poster. GSACEP, 2018

LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
CI	Confidence Interval
CCATT	Critical Care Air Transport Teams
CPG	Clinical Practice Guidelines
DODTR	Department of Defense Trauma Registry
FiO_2	Fraction of Inspired Oxygen
ICU	Intensive Care Unit
IDW	Ideal Body Weight
IQR	Interquartile Range
ISS	Injury Severity Score
LRMC	Landstuhl Regional Medical Center
MTF	Medical Treatment Facility
NHLBI	National Heart Lung and Blood Institute
NIH	The National Institutes of Health
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PEEP	Positive End Expiratory Pressure
SD	Standard Deviation
SpO_2	Peripheral Capillary Oxygen Saturation
TV	Tidal Volume
VAP	Ventilator Associated Pneumonia