AFRL-RH-WP-TR-2020-0001

The Practice and Clinical Impact of Two Theater Validating Flight Surgeons Employing the Tissue Oxygen Delivery Paradigm: A Three-Part Study

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January 2020

Final Report
for January 2015 to April 2019

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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 *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From – To)*
07-01-2020	Technical Report	2015 - 2019

4. TITLE AND SUBTITLE

The Practice and Clinical Impact of Two Theater Validating Flight Surgeons Employing the Tissue Oxygen Delivery Paradigm: A Three-Part Study

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N/A

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)

William Butler, Lawrence Steinkraus, Esther Burlingame, Danny Smith, Brittany Fouts, Anil Cherian, Kenneth Egerstrom, Justin Lovuolo, Jennifer Serres, David Burch

5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
N/A

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Air Force Research Lab (AFRL)
711th Human Performance Wing
711 HPW/RHMF
2510 Fifth St., Bldg. 840
Wright-Patterson AFB, OH 45433-7913

8. PERFORMING ORGANIZATION REPORT NUMBER

AFRL-RH-WP-TR-2020-0001

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

N/A

10. SPONSORING/MONITOR'S ACRONYM(S)

711 HPW/RHMF

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

DISTRIBUTION STATEMENT A. Approved for public release. Distribution is unlimited.

13. SUPPLEMENTARY NOTES

Cleared, 88PA, Case #88ABW-2020-0559, 14 Feb 20

14. ABSTRACT

This research is a first look at the clinical practice and clinical impact of the Theater Validating Flight Surgeon (TVFS). It documents two authors' (WPB and LWS) successive deployments as TVFSs where they developed/implemented the so-called tissue oxygen delivery (DO_2) paradigm. Calculation of DO_2 guided their evaluation/validation of evacuated patients. Part 1 was a descriptive analysis of their patients' clinical variety and severity as well as an accounting of the prescriptions employed by them, the most unique being the cabin altitude restriction (CAR). Part 2 was a population-level hypothesis-generating ecological study detecting a significant ($p = 0.034$) inverse relationship between the rates of CAR prescribing and postflight complications. As the rate of CAR prescribing rose, the rate of postflight complications dropped. Part 3 was a dual case-control study focusing on the CAR prescription. Although CAR patients were sicker, their postflight clinical outcomes were comparable to Non-CAR patients. At the same time, Non-CAR patients flown with a CAR appeared just as sick as Non-CAR patients; however, the Non-CAR patients flown with a CAR had clearly superior postflight clinical outcomes. It seemed that the CAR prescription normalized CAR patients into less sick Non-CAR patients and brought Non-CAR patients into a less morbid state. Specific flight stressors dropping DO_2 include hypoxia, vibration, and hypobaria. Hypoxia decreases oxygen availability; vibration and hypobaria increase intercapillary distance (aka tissue edema). A cut in oxygen and a greater tissue diffusion distance means DO_2 will drop. Using standard physiological equations, the TVFS can calculate DO_2 and then manipulate it by prescribing supplemental oxygen, transfusion, and/or CAR. In conclusion, this research is not only a first look at the clinical practice of the TVFS, but also documentation of the TVFSs' positive clinical impact. By employing the DO_2 paradigm, the TVFSs' prescriptions optimize DO_2 and, simultaneously, boost positive postflight clinical outcomes. Within this conceptual framework, CAR should be considered *strongly recommended* during movement of any seriously ill/injured patient.

15. SUBJECT TERMS
Aeromedical evacuation, AE, cabin altitude restriction, CAR, theater validating flight surgeon, TVFS, patient morbidity, tissue oxygen delivery, DO_2, DO_{2crit}, DO_2 paradigm

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					William P Butler
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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1.0 EXECUTIVE SUMMARY

During the recent conflicts in Iraq and Afghanistan, medical care of casualties has been outstanding. In fact, the lethality of injury, once in medical hands, has been among the lowest ever. There are a number of reasons for this: initial medical care is far forward, care is of the highest quality, and technological support of that care is the best it has ever been. In addition, aeromedical evacuation (AE) is more flexible than previously and Critical Care Air Transport Teams (CCATTs) routinely deliver intensive care level attention en route during AE.

Although much has been said and written about each of these factors, and rightfully so, little has been said or written about the Theater Validating Flight Surgeon (TVFS). This physician is generally a senior Aerospace Medicine specialist whose job it is to review a patient's clinical situation and warrant that he/she is clinically strong enough to weather the stressors of an AE flight. Indeed, the TVFS has final approval authority to manifest the patient.

The body of research reported here is essentially a first look at the TVFS's practice. It documents the deployment experience of two successive TVFSs (two of the authors, WPB and LWS). During their deployments, they employed a relatively novel approach to patient validation for flight, optimization of tissue oxygen delivery (DO_2). Although long a staple in intensive care units, DO_2 calculations entered the AE world only in late 2006/early 2007.

Factors affecting DO_2, within ready reach of the TVFSs' prescribing pen, include the fraction of inspired oxygen (FiO_2), hemoglobin level, and cabin altitude. The two author TVFSs embraced this DO_2 paradigm. The result was an aggressive prescribing regimen of supplemental oxygen, cabin altitude restriction (CAR), and, to some extent, transfusion. **Figure 1** illustrates the impact of this approach, a heightened use of CAR, and readily displays the makings for an unintentional natural experiment testing the clinical impact of the TVFSs' practices.

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This research looked at that unintentional natural experiment. Part 1 was a descriptive analysis of the two author TVFSs' operationally exigent worksheet, developed and implemented to streamline the AE queue during a particularly kinetic timeframe. The vast majority of patients were Army enlisted males out of Operation Iraqi Freedom. Slightly over half were Battle Injury and Priority precedence, while just over a quarter required a CCATT. The most common Battle Injury was an improvised explosive device associated extremity wound. On the other hand, the most common Disease, Non-Battle Injury was coronary artery syndrome. Among the most common prescriptions were CCATT, head of bed elevation, cardiac monitoring, no "remain overnights," supplemental oxygen, and CAR.

Part 2 was a hypothesis-generating ecological study that looked at the rate of CAR prescribing *vis a vis* the rate of postflight complications. A statistically significant ($p = 0.034$) inverse relationship was found. That is, as the monthly rates of CAR prescribing rose, the monthly rates of postflight complications dropped. This finding suggested that CAR, when prescribed within the DO_2 paradigm, might offer up clinical benefit.

Part 3 was a dual case-control study that compared CAR patients against Non-CAR patients and Non-CAR patients incidentally flown with a CAR against Non-CAR patients. Despite not being intentionally matched, demographic characteristics and clinical parameters were similar between groups. The only significant difference was injury severity. Both direct and indirect measures of severity suggested that the CAR patients were sicker than the Non-CAR patients. At the same time, there appeared to be no difference in severity between the Non-CAR patients flown with a CAR and the Non-CAR patients. Interestingly, although sicker, the CAR patients had postflight clinical outcomes similar to the Non-CAR patients while the Non-CAR patients flown with a CAR had clearly superior postflight clinical outcomes when compared to

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the Non-CAR patients. Thus, it appeared that the CAR prescription normalized the sicker CAR patients into Non-CAR patients and brought the Non-CAR patients into a less morbid state.

These salutary clinical effects appear to result from CAR prescribing as driven by the DO_2 paradigm. Specific flight stressors that will drop the DO_2 include hypoxia, vibration, and hypobaria. Hypoxia decreases oxygen availability; vibration and hypobaria increase intercapillary distance (aka tissue edema). Reduced amounts of oxygen and greater tissue diffusion distances mean DO_2 will drop. Using standard physiological equations, the TVFS can calculate and manipulate DO_2 by prescribing supplemental oxygen, transfusion, and/or CAR.

In conclusion, this research is not only a first look at the clinical practice of the TVFS, but also documentation of the TVFSs' positive clinical impact. By employing the DO_2 paradigm, the TVFSs' prescriptions will optimize DO_2 and, at the same time, boost positive postflight clinical outcomes. Within this conceptual framework, CAR should be considered *strongly recommended* during the movement of any seriously ill/injured patient.

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2.0 INTRODUCTION

During recent conflicts in Iraq and Afghanistan, combat medical care has been outstanding. Indeed, some of the lowest lethality rates, ranging from 9.6% to 10.2%, have been reported (U.S. Casualty Status, published February 12, 2015; department of Defense; http://defense.gov/news/casualty.pdf; accessed February 17, 2015; website no longer operable). (**Gawande, 2004; Goldberg, 2010**) This success is a consequence of care being farther forward than before, delivered with greater skill than before, and supported with better technology than before. (**Butler, 2016a**) In addition, CCATTs have made ICU (intensive care unit) level care routine in the AE of "stabilized," or clinically volatile, casualties. So good has CCATT care been that en route mortality has been reported less than 0.2%. (**Ingalls, 2014; Butler, unpublished, 2.5%**) Lastly, AE itself has become incredibly responsive and flexible, often returning the injured and ill to the United States within 24-36 hours.

Air Force AE is a regulated, fixed-wing logistic mission dedicated to the safe and swift transport of patients to the right level of care. Each such mission involves two flight surgeons --- the clearing flight surgeon and the theater validating flight surgeon (TVFS). The clearing flight surgeon, typically a junior flight surgeon, is on-site with the patient, examines the patient, and determines any requisite preflight and/or inflight needs. In contrast, the TVFS, typically a senior Aerospace Medicine specialty-trained physician, is off-site, regionally-based, and oversees patient evacuation for their given region. Notably, the TVFS has final oversight and approval authority for any patient transport. (**Hurd, 2006; Butler, 2017**)

Over the years, little research has targeted the TVFS's practice. In fact, a recent PubMed search on "theater validating flight surgeon" found only two relevant references with one directly related to this technical report. (**Hurd, 2006; Butler, 2017**) In order to fill this void, reporting

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the practice and clinical impact of two consecutively deployed TVFSs (authors WPB and LWS) was undertaken. There were three parts to this research: 1) a descriptive analysis of the TVFSs' practice; 2) a hypothesis-generating ecologic study examining the rates of postflight complications as a function of the rates of cabin altitude restriction; and, 3) a dual case-control study looking at the clinical impact of cabin altitude restriction. The findings from each part were previously published within the peer-reviewed literature. (**Butler, 2016a; Butler, 2017; Butler, 2018**) This technical report now brings all aspects of this research under a single account.

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3.0 BACKGROUND

Casualty transport is a well-honed system within the United States military. It begins with casualty evacuation, or CASEVAC, where a casualty is moved from the point of injury by any means (e.g., car, truck, boat, helicopter) and generally without dedicated medical personnel. CASEVAC brings the casualty to the medics (e.g., battalion aide station), where initial medical care begins. Medical evacuation, or MEDEVAC, is next. Here, an ambulance, bus, or helicopter takes the casualty (aka patient) to the next higher level of medical care, generally accompanied by earmarked medical personnel. Once the patient transitions from unstable to "stabilized," AE becomes viable. Whether it be intratheater (tactical) or intertheater (strategic), AE employing fixed-wing aircraft, transports injured and ill patients to definitive care. The ultimate final destination is the United States. Medics are always present during AE and consist of nurses, medical technicians, CCATTs, other specialty teams, and/or flight surgeons. (**Hurd, 2006**)

To manifest a patient on an AE flight, a Patient Movement Request (PMR) is entered into the TRANSCOM (Transportation Command) Regulating and Command and Control Evacuation System (TRAC^{2}ES) by the originating facility. Frequently, the clearing flight surgeon prepares the PMR, though attending physicians or patient administrative technicians may occasionally do it. Both administrative and clinical information are detailed in the PMR. Once submitted, the PMR undergoes both an administrative and clinical validation. The administrative validation, by a medical service corps officer, looks at the nonclinical aspects of transport (e.g., passports, diplomatic clearances for overflights, destination resources). At the same time, the clinical validation, by the TVFS, seeks to minimize patient vulnerability at altitude. This the TVFS does with patient prescriptions (e.g., supplemental oxygen, head-first loading, and assignment of CCATTs) and/or aircraft prescriptions (e.g., long, slow landing; no stops; cabin altitude

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restriction). (**Johnson, 1977a; Johnson, 1977b; Hurd, 2006**) **Table 1** depicts many of the interventions prescribed.

Table 1. Listing of prescriptions available to the TVFS. (Butler, 2016a)

CATEGORY	PRESCRIPTION
Medical Adjuncts	• Cardiac monitor; suction; pulse oximeter
	• Medical attendant (tech, nurse, doctor)
Medical Interventions	• Protected airway (nasotracheal/orotracheal intubation)
	• Supplemental oxygen and positive end-expiratory pressure
	• Sedation/restraints in flight
	• Deep venous thrombosis prophylaxis
	• Blood components and medications in flight
	• Further ground stabilizing—fluids, vasopressors, blood, tertiary survey
Middle Ear Interventions	• Equalization maneuvers (Valsalva, Toynbee, Frenzel, etc.)
	• Afrin™ and Neo-Synephrine for opening ostia
	• Myringotomy
Patient Paraphernalia	• Chest tube—suction or Heimlich valve (no clamping of tubing)
	• Jackson-Pratt™ drain—open on ascent and descent
	• Hemevac™ drain—open on ascent and descent
	• Colostomy bag—decompress on ascent (pinhole, "burp")
	• Bivalve casts; control air splints
Positioning Interventions	• Seizure precautions
	• Spine precautions
	• Head first loading
	• Headrest to elevate and protect head
	• Head-of-bed elevation (eye, face, and/or head injury, pulmonary dysfunction)
	• OWL™ litter (regular litter = 250 lb; overweight litter = 400 lb)
	• Stryker™ frame; vacuum spine board
	• Blankets
Aircraft Manipulations	• Cabin altitude restriction
	• Full use of runway length
	• Modify rate of climb and descent
	• Cabin airflow patterns
	• Aerial refueling
	• No RONs (remain overnights); no stops

A patient, as does any person, experiences physiological stressors during flight. Among these stressors are acceleration, low humidity, thermal instability, noise, vibration, hypoxia, and

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hypobaria. With the now routine evacuation of critically ill AE patients (Urgent [about 2%] and Priority [about 10%] precedence) over the past decade plus, ICU level care is no longer limited to ground-based treatment facilities. (**Butler, unpublished, 2001-2013**) Any one or any combination of flight stressors, in the face of an already seriously ill and/or injured patient, may well pose a *second hit* risk to the patient. The *first hit* being the initial injury (e.g., gunshot wound, myocardial infarction) and the *second hit* being an added physiological insult. (**Goodman, 2010**) This *second hit* most likely comes from the hypoxia and hypobaria associated with cabin altitude. Hypoxia results in reduced availability of oxygen. Vibration produces tissue edema. Hypobaria favors, through a number of potential mechanisms (e.g., Starling forces, vibration, inflammatory upregulation, bubble evolution and/or growth, and ischemia-reperfusion injury), fluid redistribution across the tissue space --- in other words, tissue edema --- which, in turn, provokes an increase in intercapillary distance and a relative increase in oxygen diffusion distance. The physiological result is a potential drop in tissue oxygen delivery and the clinical result is a potential rise in patient morbidity. (**Guyton, 1971; McDonald, 1999; Goodman, 2011; Skovira, 2016; Mashimo, 1980; Butler, 2013; Butler, 2016a; Fouts, 2017; Butler, 2018**)

Tissue oxygen delivery depends on a number of factors: fraction of inspired oxygen (FiO_2), blood oxygen content (hemoglobin level, hemoglobin saturation, and plasma oxygen content), and cardiac output. (**Constanzo, 2014**) Plasma oxygen content contributes minimally (only about 0.3 vol% oxygen), likewise hemoglobin saturation and cardiac output (as each is usually clinically maximized prior to AE). Consequently, only FiO_2 and hemoglobin level remain exploitable to the TVFS, via supplemental oxygen and transfusion, respectively. (**Earnest, 2012; Hannah, 2013**) However, CAR offers another means by which the TVFS may

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affect tissue oxygen delivery. By imposing a CAR, the TVFS essentially moves the patient atmospherically closer to ground level, moderating the impact of hypoxia and hypobaria while, simultaneously, boosting tissue oxygen delivery, and, presumably, lessening patient morbidity. (**Fouts, 2017; Butler, 2018**)

Cabin altitude is the pressure within an aircraft's hull. As an aircraft ascends, both the ambient pressure and cabin pressure drop. A certain level of cabin pressure is mandated to sustain crew and passenger, both for comfort and for performance (e.g., preventing effects of hypobaria and hypoxia, respectively). Standard military cabin altitude generally ranges from 8,000 to 10,000 feet while that in US commercial aircraft cannot exceed the federal mandate of 8,000 feet (14 CFR 25.841). (**Emergency War Surgery, 2004**) When a CAR is prescribed, the TVFS imposes a lower than normal cabin altitude, most commonly between 4,000 and 6,000 feet. (**Butler, 2017**) Notably, a drop in cruising altitude often accompanies the CAR. Conventional wisdom holds that the lower cruising altitude ups the potential for inflight turbulence and structural stress as well as operational risk (e.g., mountainous terrain and inclement weather), not to mention an increase in both flight time and fuel consumption. As a result, the TVFS does not blithely prescribe the CAR. (**Fouts, 2017**)

Traditionally, trapped gas, severe pulmonary disease, and decompression sickness prompted a CAR. (**Emergency War Surgery, 2004**) However, in late 2006/early 2007, the notion of tissue oxygen delivery, quite commonplace in the ICU, surfaced not only in pre-hospital tactical casualty combat care, but also within the TVFSs' practice. (**Grissom, 2006; Pollan, 2006; Butler, 2007; Butler, 2016a;**) While deployed in 2007, two of the authors (WPB and LWS) served as successive TVFSs over an eight-plus month period. During that time, they oversaw the AE transport of more than 8,600 patients. To minimize the physiologic impact of

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flight, they sought to optimize DO_2 prescribing supplemental oxygen, transfusion, and the non-traditional employment of CAR, all within the framework of the so-called DO_2 paradigm. Their goal for each patient was a DO_2 in excess of 7.3 ml O_2/kg/min, below which exists the human DO_{2crit} (DO_2 critical threshold). (**Lieberman, 2000**) To achieve this, they prescribed any combination of supplemental oxygen, transfusions, and CAR. **Figure 1** depicts the CAR rates from 2001 to 2013. It clearly depicts the "outlier" nature of their CAR prescribing. The rate of CAR missions averaged 10.2% annually, peaking in 2007 at 45.3%. At the same time, the rate at which TVFSs prescribed a CAR averaged 1.4% annually, again peaking in 2007 at 4.5%. Moreover, as CAR is uniquely the province of the TVFS, these rates highlight the coincidental natural laboratory for testing the effectiveness of the DO_2 paradigm within the clinical practice of the TVFS. This research takes advantage of that natural laboratory in three parts: 1) a descriptive analysis of the TVFSs' practice; 2) an ecologic study examining the rates of postflight complications as a function of the rates of CAR; and, 3) a dual case-control study looking at the clinical impact of CAR.

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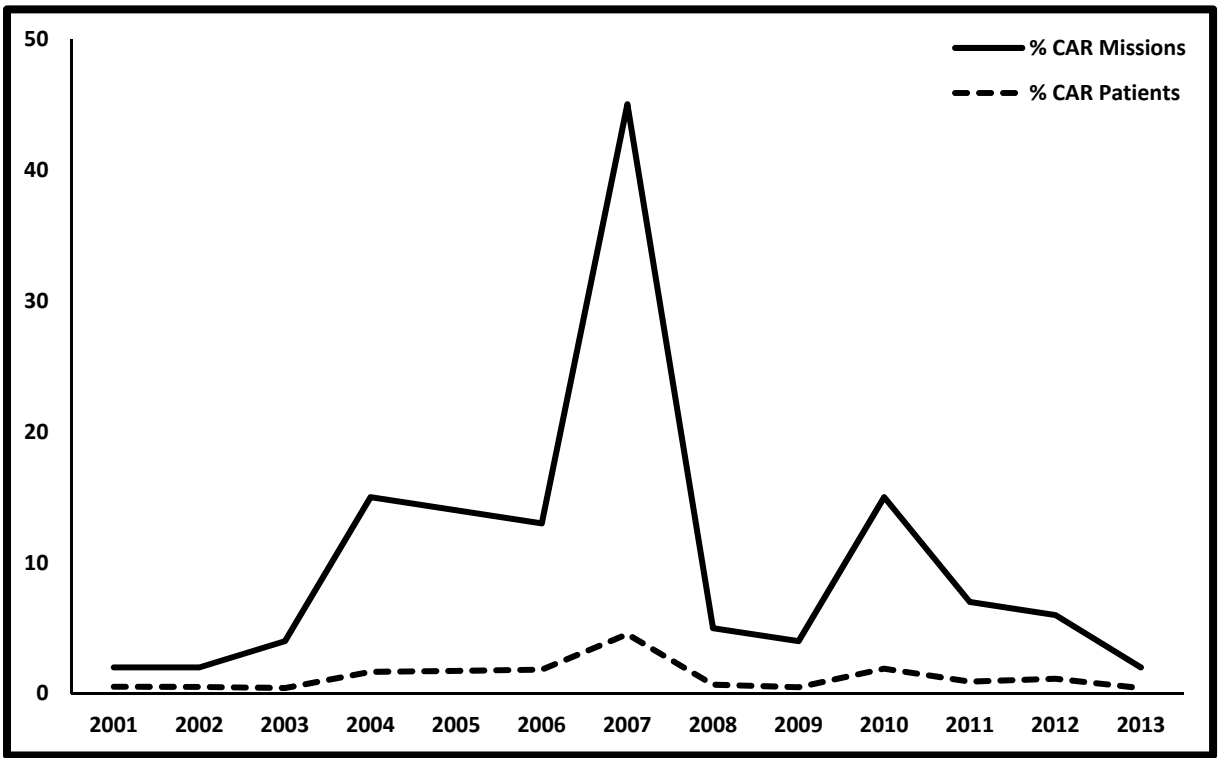
Figure 1. Annual incidence (percent) of CAR missions and annual incidence (percent) of patients prescribed a CAR --- note the spike in 2007. (Butler, 2018)



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4.0 METHODS

4.1 Institutional Review

This research was approved by the Air Force Research Laboratory Institutional Review Board (Parts 1 and 2 under FWR20100087E; Part 3 under FWR20150103H) and was conducted at the U.S. Air Force School of Aerospace Medicine at Wright-Patterson Air Force Base in Dayton, Ohio, with Defense Health Program funds.

This research involved a multi-phased approach to the clinical practice and clinical impact of the TVFS, covering the time when two of the authors (WPB and LWS) were successively deployed to Southwest Asia in 2007. The primary focus of this work is on the TVFS practices during their deployments. Part 1 was a descriptive analysis of their experience using an operational worksheet developed to facilitate patient validation. Part 2, using the hypothesis-generating epidemiological ecological study methodology, explored the population impact of the CAR, a uniquely TVFS prescription. Part 3 employed a dual case-control study to specifically look at the clinical impact of the CAR prescription on the individual patient.

4.2 Part 1: Theater Validating Flight Surgeon (TVFS) Practice (Butler, 2017)

Part I was a descriptive study of the two authors' successive deployments as Central Command's TVFS. Toward the end of the first deployment, patient volume surged. To facilitate management of the AE queue, the two authors employed a self-styled patient-tracking operational worksheet that streamlined the clinical validation process. This worksheet helped the TVFS keep track of the many patients and prescriptions concurrently being considered and was used for approximately five months. Consequently, it did not include all of the patients validated during the two TVFSs' tours. It was particularly void of the less ill/injured Routine precedence patients. The bulk of patients on the worksheet were Urgent and Priority precedence, marking

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their clinical acuity and serious need for higher level care. Entered patients often required additional laboratory and/or historical information and often were part of concomitant submissions of multiple patients. Recorded within the worksheet were 1,389 patients, the basis for this descriptive analysis.

Since the worksheet was a tool to accelerate clinical validation and decision-making, the TVFS entered patients and data fields as needed. As a result, only certain data from the PMR made the worksheet. This included some demographic characteristics, a few pertinent laboratory and physiological parameters, and the anatomic system(s) affected by the patient's clinical issue(s). In addition, there was a brief, less than one sentence, "reminder" clinical vignette and the prescriptions (patient and aircraft) levied by the TVFS. Notably, the worksheet, as opposed to the TRAC^{2}ES database, differentiated between the initial provisional PMR submission and the final validated PMR record in several data fields: Precedence, AE Classification, CCATT assignment, and FiO_2. This fact permitted an analysis of the agreement between the clearing flight surgeon and the TVFS.

Descriptive statistics analyzed basic demographic characteristics and laboratory/physiologic parameters using number and percent for categorical variables and median with interquartile range (Q_1,Q_3) for continuous variables. Since Battle Injury (BI) and Disease, Non-Battle Injury (DNBI) were recorded, this natural dichotomy of patients served as a logical platform for describing the clinical issues faced by the TVFS, their various etiologies, and the various prescribed interventions. Here, number and percent described categorical variables and median with interquartile range (Q_1,Q_3) described continuous variables while chi square statistics and Mann-Whitney U nonparametric statistics calculated comparisons, respectively. In addition, the kappa statistic for categorical variables and the Mann-Whitney U nonparametric

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statistic for the one continuous variable (FiO_2) tested agreement between the clearing flight surgeon and the TVFS. (**Viera, 2005**) Statistical significance was set *a priori* at $p < 0.05$. Data were analyzed using the Statistical Package for Social Sciences, version 22 (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, New York).

4.3 Part 2: Ecologic Study: Postflight Complications vs Cabin Altitude Restriction (Butler, 2016a)

Part 2 was an ecologic study --- an initial, exploratory, hypothesis-generating epidemiologic study of population characteristics. (**Morgenstern, 1995**) During their TVFS deployments, the two authors (WPB and LWS), employing the tissue oxygen delivery paradigm, liberally prescribed CAR for patients. See **Figure 1**. They felt that their prescribing, particularly with CAR, was more aggressive than either their predecessors or successors. Subsequently, an operationally driven investigation, using CAR as a surrogate for aggressive TVFS prescribing, confirmed this notion. Furthermore, they felt that being aggressive was "good" clinically. This ecological study looked at that.

There are two primary variables. The independent variable was the CAR rate, which is near unique to the TVFS and seldom prescribed by others. Not infrequently, it is also associated with some degree of organizational resistance. The resistance flows from the perception that a CAR has a cost --- longer flights, more structural stress, more turbulence, more fuel, and more refueling (either inflight or on the ground). Postflight complication rate served as the outcome, or dependent, variable. There were two ways of looking at this outcome. The first was the rate of patients with postflight complications (PFC) and the other was postflight complications per 100 patients (PFC-100). The former measure presented the more common way of looking at outcomes, while the latter, the less common. PFC looked directly at those patients who suffer

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postflight complications, while PFC-100 dealt with the complications themselves. Patients evacuated often have multisystem injuries. A flight-induced *second hit* may add insult to the injuries, making multisystem postflight complications possible in a single patient. PFC-100 captured this effect; PFC did not.

Data sourced from TRAC^{2}ES from January 2006 through February 2008 included the number of patients evacuated to Landstuhl Regional Medical Center (LRMC) each month along with the number of CARs prescribed each month (the CAR dataset). Monthly CAR rates (CAR prescriptions/total patients transported to LMRC) were calculated. Limited to Priority (requiring evacuation within 24 hours to preserve life, limb, or eyesight) and Urgent (requiring evacuation as soon as possible, but no later than 12 hours, to preserve life, limb, or eyesight) patients, the study sought only patients most vulnerable to the physiological impacts of flight.

Similarly, from January 2007 through June 2008, Landstuhl's Joint Theater Trauma Registry provided the number of patients arriving each month, the number of patients with postflight complications, and the specific complications suffered (the Complication dataset). The monthly complication rates, both PFC (number of patients with complications/total patients arriving at LRMC) and PFC-100 (number of complications/100 patients arriving at LRMC), were calculated.

In order to refute the notions of a delimited pair of "aggressive prescribing" TVFSs and resultant "good" clinical results, the CAR and postflight complication rates *before*, *during*, and *after* the TVFSs' deployments needed investigation and the relationship between the rates of CAR prescribing and the postflight complication rates needed exploration. The two datasets fully addressed both the *during* and *after* time frames; however, because Landstuhl's data were self-declared unreliable prior to January 2007 (personal communication), it was not possible to

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strictly assess the *before* time frame. However, the DO_2 paradigm, the basis for aggressive prescribing, largely came about during early 2007, specifically January through March. Consequently, that time became the *before*, giving the study a small cadre of postflight complication rates that could be considered *before*. Thus, January 2006 through March 2007 defined *before*, April 2007 through September 2007 *during*, and October 2007 through February 2008 *after*. See **Figure 2**.

Some basic demographics were described within the two datasets --- categorical variables with number and percent, continuous variables with median and interquartile range (Q_1,Q_3). Comparisons used the chi square statistic and Mann-Whitney U nonparametric statistic, respectively. Next explored was the CAR and postflight complication rates *before*, *during*, and *after* the two TVFSs' deployments using means with standard deviation and the independent t-statistic. Lastly, the monthly CAR rates were examined relative to the postflight complication rates employing the Spearman correlation. Statistical significance was set *a priori* at $p < 0.05$. Data were analyzed using the Statistical Package for Social Sciences, version 20 (IBM SPSS Statistics 20, IBM Corp., Somers, New York).

4.4 Part 3: Dual Case-Control Study of Outcomes *vis a vis* Cabin Altitude Restriction (Butler, 2018)

Part 3 consisted of a two-pronged, or dual, case-control study encompassing the two TVFSs' deployments. After merging data sourced from TRAC^{2}ES (January 2007 through February 2008) with LRMC trauma data (January 2007 through June 2008), the common time period (January 2007 through February 2008) was extracted. Only Priority and Urgent patients were included, thus limiting the study to 1,114 patients most vulnerable to AE's physiological stressors.

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These patients fell into thee natural groupings: 442 patients prescribed and flown with a CAR (CAR); 436 patients not prescribed a CAR, flown without a CAR (Non-CAR); and, 236 patients not prescribed a CAR, incidentally flown with a CAR (Non-CAR flown with a CAR). The Non-CAR patients flown with a CAR define those patients not prescribed a CAR, but evacuated on the same mission as a patient prescribed a CAR. Indeed, any patient flown with a CAR patient was *de facto* a CAR patient. Homogeneity between groups was tested with demographic characteristics (e.g., age and gender), clinical parameters (e.g., vital signs and arterial blood gases), and injury severity indicators. Direct injury severity indicators consisted of injury severity score (ISS: <9, mild; 9-15, moderate; 16-25, severe; >25, critical) and pulmonary shunt ratio (PaO_2/FiO_2: <200, acute respiratory distress syndrome (ARDS); < 300, acute lung injury. (**Baker, 1974; Bolorunduro, 2011; Rice, 2007**)

As CAR prescribing during the deployments was well outside baseline, any potential impact on clinical outcome should best be detected then. Thus, two CAR-related case-control studies were performed --- CAR versus Non-CAR and Non-CAR flown with a CAR versus Non-CAR. Clinical outcome differences were determined using time-related variables (e.g., ventilator, intensive care unit, and length of stay days) and morbidity variables (e.g., postflight procedures and postflight complications), as recorded into the trauma dataset by the treating physicians during the patients' LRMC stay. Notably, postflight procedures derived from ICD-9 codes and descriptors, whereas postflight complications came as explicitly logged.

Rates for both CAR missions and CAR prescriptions were calculated. In addition, descriptive statistics were applied to patients' basic demographic characteristics, clinical parameters, injury severity indicators, and clinical outcomes using number and percent for categorical variables and median with interquartile range (Q_1,Q_3) for continuous variables, with

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deciles (D_1,D_9) when data skewness demanded further clarity. Comparisons employed the chi square statistic for categorical variables and the Mann-Whitney U statistic for continuous variables. Statistical significance was set *a priori* at $p < 0.05$. Data were analyzed using the Statistical Package for Social Sciences (SPSS), IBM Corp., released 2013 (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, New York).

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5.0 RESULTS

5.1 Part 1: Theater Validating Flight Surgeon (TVFS) Practice (Butler, 2017)

The two TVFSs', in their successive rotations, validated 8,634 patients for AE (Urgent = 303, Priority = 1,500, Routine = 6,831). Comparing precedence in the overall 8,634 patients to the worksheet's 1,389 patients demonstrated a statistically significant difference (chi square = 1,726; $p < 0.00001$), suggesting the worksheet unrepresentative of the entire deployment.

Characterizing the worksheet cohort of 1,389 patients, the majority was male (94%) and the median age was 30 years (22,35; range 1 day to 67 years). Army comprised 71%, much more than the Marines (6%), Air Force (4%), or Navy (2%); most were enlisted (90%). Also, regularly flown were contractors (8%) and allies (2%).

Patient evacuations mainly originated from Operation Iraqi Freedom (77%) and BI (55%) transports surpassed those for DNBI (45%). Priority precedence (63%) dominated, as did AE Classification 2a/2b (inpatients on a litter, 84%). Of note, prior to transport, only a few patients cancelled and only a few patients died. En route, only one patient died (0.01%). See **Table 2** for further details.

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Table 2. Worksheet demographics extracted from PMRs (N = 1389). (Butler, 2017)

Characteristic	Number	Percent
Gender (n = 1388)		
Male	1308	94.2
Female	80	5.8
Status (n = 1387)		
USA	981	70.7
USMC	87	6.3
USAF	58	4.2
USN	29	2.1
US Civilian	131	9.4
Non-US	101	7.3
Grade (n = 1157)		
Enlisted	1037	89.4
Officer	105	9.1
Warrant Officer	15	1.3
Theater (n = 1387)		
Operation Iraqi Freedom	1071	77.2
Operation Enduring Freedom	308	22.2
Horn of Africa	8	0.6
Medical Class (n = 1388)		
Battle Injury	762	54.9
Disease, Non-Battle Injury	626	45.1
Precedence (n = 1387)		
Urgent	166	12.0
Priority	875	63.0
Routine	346	25.0
Classification (n = 1386)[a]		
1a-psychiatric, litter, sedation, restraints	1	0.1
1b-psychiatric, litter, sedation, opt. restraints	11	0.8
2a-immobile inpatient litter	821	59.2
2b-mobile inpatient litter	346	24.9
3a-ambulatory inpatient	90	6.5
5a-ambulatory outpatient	98	7.1
5d-outpatient, litter for comfort	19	1.4
Critical Care Air Transport Team (n = 1387)	380	27.4
Cancelled Transport (n = 1389)	7	0.5
Died Prior to Transport (n = 1389)	10	0.7

[a]Brief descriptions of AE Classification categories abridged from AFI 41-307.

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The worksheet logged several key laboratory and physiological parameters. Among them were hemoglobin (Hgb) level (median = 13.0 g/dL; 11.0, 14.7; range 5.0–20.0), Hgb saturation (median = 98%; 98,99; range 29–100), FiO_2 (median = 40.0%; 21, 50; range 21–100), positive end expiratory pressure (PEEP, median = 5.0 cm H_2O; 5,5; range 0–40), and arterial oxygen partial pressure (PaO_2, median = 128.0 mmHg; 97,201; range 37–467). Interestingly, BI exhibited significantly lower Hgb, higher FiO_2, and higher PaO_2 when compared to DNBI. See **Table 3** for further details.

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Table 3. Worksheet laboratory/physiologic parameters extracted from PMRs (N = 1389) (Butler, 2016a)

Parameter	Number (%)	Battle Injury Median (Q_1,Q_3) (n = 762)	Disease, Non-Battle Injury Median (Q_1,Q_3) (n = 626)	p-value
Hemoglobin, g/dl (n = 1184)		12.6 (10.6, 14.0)	14.0 (13,0, 15.0)	< 0.0001*
≤ 8.0	21 (1.8)			
8.1 – 9.0	75 (6.3)			
9.1 – 10.0	104 (8.8)			
10.1 – 15.0	856 (72.3)			
> 15.0	128 (10.8)			
Hemoglobin Saturation, % (n = 1276)		98.0 (98.0, 100.0)	98.0 (97.0, 99.0)	< 0.0001*†
< 90	7 (0.6)			
91 – 94	33 (2.6)			
95 – 100	1236 (98.8)			
Fraction of Inspired Oxygen, % (n = 357)		40.0 (28.0, 50.0)	28.0 (21.0, 36.0)	< 0.0001*
21	95(26.6)			
22 – 30	45 (12.6)			
31 – 40	108 (30.3)			
41 – 50	55 (15.4)			
51 – 60	28 (7.9)			
61 – 99	13 (3.6)			
100	13 (3.6)			
Positive End Expiratory Pressure, cm H_2O (n = 186)		5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	0.967
≤ 5	143 (76.9)			
6 – 10	36 (19.3)			
> 10	7 (3.8)			
Arterial Oxygen Partial Pressure, mmHg (n = 227)		143.0 (98.3, 204.8)	99.0 (80.0, 128.0)	0.006*
≤ 50	3 (1.3)			
51 – 60	3 (1.3)			
61 – 70	8 (3.6)			
71 – 80	15 (6.6)			
81 – 90	14 (6.2)			
91 – 100	47 (20.7)			
> 100	137 (60.3)			

*Denotes statistical significance based on independent-samples Mann-Whitney U analysis

† Hemoglobin saturations were significantly different despite identical medians, the difference having more mathematical than clinical relevance.

Extremity issues dominated with 48% of worksheet transports followed by face-neck (18%), head (15%), chest (13%), abdomen (13%), spine (8%), and pelvis (6%). Six percent were burns and 14% were cardiac. BI predominated in all anatomic systems except the cardiac where DNBI held sway (98%). In fact, Army soldiers (59%) and U.S. civilians (25%) had most of the

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cardiac issues and, generally, they proved older (Army soldier median = 38 years of age; 30,45; range 19–58 while U.S. civilian median = 50 years of age; 47,59; range 28-67). Indeed, the Army cardiac patients proved significantly older than the worksheet's Army population ($p < 0.00001$). Similarly, the U.S. Civilian cardiac patients proved significantly older than the worksheet's U.S. Civilian population ($p < 0.0001$). BI etiologies were relatively limited, the top four being improvised explosive device (IED, 52%), gunshot wound (GSW, 21%), rocket propelled grenade (RPG, 3%), and mortar (3%). With DNBI, however, the etiologies were much more varied, the top four being coronary artery syndrome (CAS, 29%), infection (9%), fall (5%), and seizure (3%). Of note, multi-anatomic system involvement was not uncommon (median = 1.0; 1.0,2.0; range 1-6), the exceptions being extremity (51%) and cardiac (91%) where a single system was more commonly implicated. **Table 4** gives further details, emphasizing the top two etiologies and CCATT assignments for each anatomic system.

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Table 4. Worksheet anatomic categories of injury/illness with most frequent etiologies associated with BI and DNBI along with CCATT assignment as prescribed by the TVFS (N = 1389) (Butler, 2017)

Anatomic System[a]		Injury Source[b]	Battle Injury (n = 762) N (%)	Illness/Injury Source[c]	Disease, Non-Battle Injury (n = 626) N (%)
Head (n = 208)			126 (60.6)		82 (39.4)
		IED	77 (61.1)	Seizure	20 (24.4)
		GSW	20 (15.9)	Stroke	18 (22.0)
	CCATT assignment		65 (51.6)		20 (24.4)
Spine (n = 112)			88 (78.6)		24 (21.4)
		IED	59 (67.1)	MVA[d]	4 (16.7)
		GSW	12 (13.6)	Fall	4 (16.7)
	CCATT assignment		45 (51.1)		6 (25.0)
Face-Neck (n = 256)			232 (90.6)		24 (9.4)
		IED	155 (66.8)	Fall	7 (29.2)
		GSW	28 (12.1)	Fight	2 (8.3)
	CCATT assignment		95 (41.0)		2 (8.3)
Extremity (n = 666)			560 (84.1)		106 (15.9)
		IED	315 (56.3)	Fall	18 (17.0)
		GSW	91 (16.3)	Infection	16 (15.1)
	CCATT assignment		156 (27.9)		9 (8.5)
Chest (n = 176)			130 (73.9)		46 (26.1)
		IED	59 (45.4)	Infection	14 (30.4)
		GSW	32 (24.6)	Pneumothorax[d]	5 (10.9)
	CCATT assignment		67 (51.5)		12 (26.1)
Abdomen (n = 176)			119 (67.6)		57 (32.4)
		IED	58 (48.7)	Cholecystitis	12 (21.1)
		GSW	29 (24.4)	Appendicitis	7 (12.3)
	CCATT assignment		70 (58.8)		6 (10.5)
Pelvis (n = 88)			74 (84.1)		14 (15.9)
		IED	36 (48.7)	Genitourinary	4 (28.6)
		GSW	22 (29.7)	Fall	2 (14.3)
	CCATT assignment		31 (41.2)		3 (21.4)
Burns (n = 79)			65 (82.3)		14 (17.3)
		IED	45 (69.2)	Electrical	2 (14.3)
		RPG	3 (4.6)	JP8 Trash Fire[d]	2 (14.3)
	CCATT assignment		41 (63.1)		6 (42.9)
Cardiac (n = 196)			4 (2.0)		192 (98.0)
		IED	3 (75.0)	CAS	178 (92.7)
		RPG	1 (25.0)	Peri/Myocarditis	8 (4.2)
	CCATT assignment		4 (100.0)		75 (39.1)

[a]More than one system may be involved in any given patient.
[b]Two most commonly recorded etiologies for each anatomic system's BI patients.
[c]Two most commonly recorded etiologies for each anatomic system's DNBI patients.
[d]MVA = motor vehicle accident; JP8 = jet plane #8 fuel.
[e]Spontaneous pneumothorax.

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The TVFS prescriptions fell into six categories: Preventive Actions (16%), Positioning Actions (20%), Medicinals (13%), Equipment Actions (7%), Aircraft Actions (42%), and Miscellaneous Actions (2%). Excepting Equipment Actions, the most often used prescription in both BI and DNBI was the same for each category: Preventive Actions, CCATT assignment (39%); Positioning Actions, head of bed elevation (91%); Medicinals, supplemental oxygen (41%); and Aircraft Actions, no "remain overnights" (44%). Interestingly, CCATTs were assigned to just over a quarter (27%) of the worksheet's patients, most being assigned to BI (BI = 231 (30%), DNBI = 149 (24%); chi square = 6.54, $p = 0.01$).

Further analysis of the BI/DNBI dichotomy demonstrated significantly different prescriptive patterns. BI prescriptions dealt with the aftermath of trauma and surgery --- most notably, spine precautions ($p < 0.0001$), C-collar ($p < 0.0001$), neurovascular checks ($p < 0.0001$), head-first loading ($p < 0.0001$), long landing ($p = 0.013$), supplemental oxygen ($p < 0.0001$), transfusion ($p < 0.0001$), and postsurgical tube maintenance ($p \leq 0.004$). On the other hand, DNBI prescriptions focused on infection and cardiac illness as seen with infectious precautions ($p < 0.0001$), N-95 mask ($p < 0.0001$), medical attendants ($p < 0.0001$), and cardiac monitoring ($p < 0.0001$). See **Table 5** for further details.

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Table 5. Worksheet prescriptions levied by the TVFS (N = 1389) (Butler, 2017)

Prescriptions	Battle Injury (n = 762) N (%)	Disease, Non-Battle Injury (n = 626) N (%)	p-value[b]
Preventive Actions (n = 975)			
Spine precautions	76 (7.8)	9 (0.9)	< 0.0001*
C-collar	50 (5.1)	11 (1.1)	< 0.0001*
Infectious precautions	---	47 (4.8)	< 0.0001*
N-95 mask	---	14 (1.4)	< 0.0001*
Seizure precautions	1 (0.1)	21 (2.2)	< 0.0001*
Neurovascular checks	161 (16.5)	36 (3.7)	< 0.0001*
Medical attendant	3 (0.3)	49 (5.0)	< 0.0001*
CCATT assignment	231 (23.7) [a]	149 (15.3) [a]	0.091
Wire-cutters	16 (1.6)	3 (0.3)	0.018*
Saline lock	5 (0.5)	67 (6.9)	< 0.0001*
No or gentle Valsalva maneuver	17 (1.7)	9 (0.9)	0.406
Total	560 (57.4)	415 (42.6)	0.417
Positioning Actions (n = 1176)			
Forward loading	---	22 (1.9)	< 0.0001*
Head first loading	61 (5.2)	15 (1.3)	< 0.0001*
Head of bed elevation	569 (48.1) [a]	507 (42.9) [a]	0.052
Extremity elevation	2 (0.2)	---	0.099
Total	632 (53.7)	544 (46.3)	0.0002*
Medicinals (n = 750)			
Supplemental oxygen	242 (32.3) [a]	68 (9.1) [a]	< 0.0001*
Transfusion	79 (10.5)	8 (1.1)	< 0.0001*
Promethazine	134 (17.9)	64 (8.5)	0.493
Oxymetazoline	29 (3.9)	13 (1.7)	0.920
Enoxaparin	11 (1.5)	28 (3.7)	< 0.0001*
Morphine	14 (1.9)	23 (3.1)	< 0.0001*
Antibiotics	8 (1.1)	5 (0.7)	0.549
Other	5 (0.7)	19 (2.5)	< 0.0001*
Total	522 (69.6)	228 (30.4)	< 0.0001*
Equipment Actions (n = 417)			
Chest tube suction	77 (18.5)	13 (3.1)	0.004*
Nasogastric tube suction	142 (34.1) [a]	27 (6.5)	< 0.0001*
Ostomy/drain maintenance	64 (15.4)	6 (1.4)	0.0002*
Overweight litter	24 (5.8)	6 (1.4)	0.410
Cardiac monitoring	---	58 (13.9) [a]	< 0.0001*
Total	307 (73.6)	110 (26.4)	< 0.0001*
Aircraft Actions (n = 2530)			
Cabin altitude restriction	463 (18.3)	324 (12.8)	0.098
No “remain overnights”	608 (24.0) [a]	494 (19.5) [a]	0.273
No stops	329 (13.0)	277 (11.0)	0.229

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Long landing	27 (1.2)	8 (0.3)	0.013*
Total	1427 (56.4)	1103 (43.6)	0.003*
Miscellaneous Actions (n = 127)	54 (42.5)	73 (57.5)	0.0002*
TOTAL Prescriptions = 5975	**3,502 (59.0)**	**2,473 (41.0)**	

Note: Chi-square and Fisher's exact tests were used when appropriate.
[a]Denotes most prevalent prescription in a given category of intervention for BI or DNBI.
*Denotes statistical significance.

The decisions of the clearing flight surgeon *vis a vis* the TVFS could be seen with four prescriptions: Precedence, Classification, CCATT assignment, and FiO_2 level (aka supplemental oxygen). Kappa statistic demonstrated moderate agreement in Precedence (kappa = 0.54, standard error [SE] = ± 0.02, 95% confidence interval [CI] 0.50–0.58) and substantial agreement in both Classification (kappa = 0.67, SE = ± 0.02, 95% CI 0.63–0.71) and CCATT assignment (kappa = 0.74, SE = ± 0.02, 95% CI 0.70–0.78). In contrast, a close examination of FiO_2 demonstrated a significant difference between that prescribed by the clearing flight surgeon and the TVFS ($p < 0.0001$). Indeed, the TVFS prescribed a higher level FiO_2 (median difference between the TVFS and clearing flight surgeon = 10%; 9,15; range −54 to + 64).

5.2 Part 2: Ecologic Study: Postflight Complications vs Cabin Altitude Restriction (Butler, 2016a)

The CAR dataset included 2,329 patients, while the Complication dataset had 2,722. Median age for the CAR dataset was 24.0 years (21.0,29.0; range 5-63) and median age for the Complication dataset was 24.0 years (21.0,30.0; range 6-65); they were not statistically different ($p = 0.59$). Men made up 98.1% of the CAR dataset and 97.7% of the Complication dataset; however, factoring the small numbers of women and unknowns into the mix demonstrated the two datasets statistically different (chi square = 16.48, $p = 0.0003$). Despite the statistical difference, there appeared to be no practical clinical consequence.

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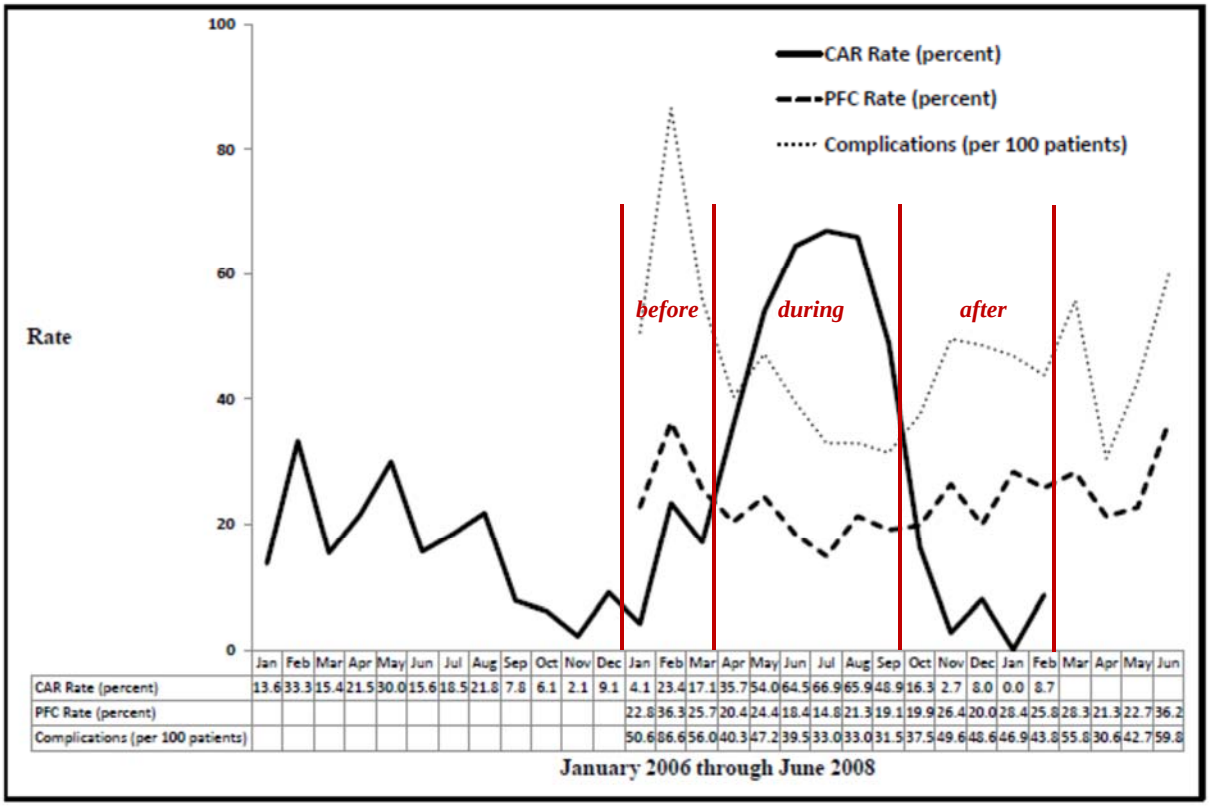
The CAR rate ranged from 0 – 67% per month (mean = 23.5%, standard deviation [SD] = ± 20.2); the most prescribed CAR was 5000 ft (1524 m) (48%, peaking June 2007) followed by 4000 ft (1219 m) (27%, peaking May 2007) and 6000 ft (1829 m) (22%, peaking August 2007). The PFC rate ranged from 15 – 36% per month (mean = 24.0%, SD = ± 5.6) and the monthly PFC-100 rate ranged from 31-87 complications per 100 patients (mean = 46.3/100 patients, SD = ± 13.0). The tabular portion of **Figure 2** depicts the specific monthly rates.

Figure 2. Graphic depiction of the relationship of CAR rates to PFC and PFC-100 rates. (Butler, 2016a)



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
CAR Rate (percent)	13.6	33.3	15.4	21.5	30.0	15.6	18.5	21.8	7.8	6.1	2.1	9.1	4.1	23.4	17.1	35.7	54.0	64.5	66.9	65.9	48.9	16.3	2.7	8.0	0.0	8.7				
PFC Rate (percent)													22.8	36.3	25.7	20.4	24.4	18.4	14.8	21.3	19.1	19.9	26.4	20.0	28.4	25.8	28.3	21.3	22.7	36.2
Complications (per 100 patients)													50.6	86.6	56.0	40.3	47.2	39.5	33.0	33.0	31.5	37.5	49.6	48.6	46.9	43.8	55.8	30.6	42.7	59.8

January 2006 through June 2008

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Four categories of complication dominated: pulmonary, infectious, resuscitative, and coagulation. See **Table 6** for further details.

Table 6. Postfllight patient complications as recorded at LRMC. (Butler, 2016a)

CATEGORY	n	%
Pulmonary		**29**
Atelectasis	177	
Pleural Effusion	85	
Pneumothorax	23	
Pulmonary Edema	18	
Pulmonary Embolus	17	
Aspiration/Aspiration Pneumonia	13	
Acute Respiratory Distress Syndrome	12	
Acute Respiratory Failure	8	
Hemothorax	7	
Infectious		**20**
Acinetobacter	73	
Pneumonia	49	
Wound Infection	46	
Cellulitis	20	
Sepsis	20	
Bacteremia	12	
Urinary Tract Infection	8	
Disseminated Fungal Infection	5	
Clostridial Difficile Colitis	5	
Line Sepsis	4	
Intraabdominal Abscess	2	
CNS Infection	2	
Soft Tissue Infection	1	
Empyema	1	
Resuscitative		**19**
Anemia/Blood Loss	232	
Hypovolemia	4	
Shock (traumatic)	2	
Blood Transfusion Reaction	2	
Postoperative Hemorrhage	1	
Coagulation		**18**
Coagulopathy	189	
Deep Vein Thrombosis	36	
Acute Arterial Occlusion	4	
Gastrointestinal		**4**
Ileus	28	
Dehiscence/Evisceration	11	
Pancreatitis	3	
Jaundice	2	
Small Bowel Obstruction	1	
Orthopedic		**2**
Compartment Syndrome	18	
Fat Embolus Syndrome	2	
Renal		**2**
Acute Renal Failure	17	
Renal Failure	2	
Metabolic		**1**
Hyperkalemia	11	
Hypothermia	6	
Dermatologic		**1**
Decubitus/Skin Breakdown	15	
Neurologic		**1**
Progression of Original Insult	10	
Seizures	2	
Cardiac		**<1**
Cardiopulmonary Arrest	2	
Major Arrhythmia	2	
Miscellaneous		**3**
Other	29	
Adverse Drug Reaction	3	
Total Complications	1242	**100**

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Looking at the CAR rates *before*, *during*, and *after* found TVFSs' CAR prescribing differed significantly from their predecessors [$t(19) = 8.2$, $p < 0.0001$] and successors [$t(9) = 8.0$, $p < 0.0001$]; the TVFSs' predecessors and successors did not differ statistically [$t(18) = 2.0$, $p = 0.063$]. Likewise, the PFC rates *during* the TVFSs' deployment were significantly different from those *before* [$t(7) = 2.6$, $p = 0.036$] or *after* [$t(13) = 2.4$, $p = 0.033$]; the *before* and *after* PFC rates did not differ statistically [$t(10) = 0.8$, $p = 0.471$]. Interestingly, the PFC-100 rates during the TVFSs' deployment were significantly different from those *before* [$t(7) = 3.3$, $p = 0.013$], but not those *after* [$t(13) = 2.1$, $p = 0.057$]; the *before* and *after* PFC-100 rates did differ statistically [$t(10) = 2.3$, $p = 0.042$].

Over the January 2007 through February 2008 time-frame, the datasets aligned making correlational analysis possible. As the monthly rates over time did not appear linear (see **Figure 2**), analysis mandated the Spearman correlation. This assessment demonstrated a statistically significant inverse relationship between the CAR and PFC rates (Spearman rho = - 0.587, $p = 0.027$). Also demonstrated was a statistically significant inverse relationship between CAR and PFC-100 rates (Spearman rho = - 0.568, $p = 0.034$). In other words, as the rate of CAR prescribing rose, the rate of patients with postflight complications as well as the rate of postflight complications per 100 patients dropped.

To ensure the recorded postflight complications were indeed "postflight," patient length of stay at Landstuhl demanded examination. If the length of stay took the patient sufficiently distant from the flight, then a postflight complication could well be unrelated to the flight and the prescribed CAR. Overall mean length of stay was 3.5 days (SD, $\pm$ 4.5; range 1-113) --- with no statistical difference among the *before*, *during*, or *after* time-frames --- intimating existence of a postflight complication-CAR relationship.

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5.3 Part 3: Dual Case-Control Study of Outcomes *vis a vis* Cabin Altitude Restriction (Butler, 2018)

Within the 2007 cadre of 1,114 patients (Urgent and Priority precedence), the prototypical patient was a 26-yr-old male, deployed in support of Operation Iraqi Freedom. Most commonly, he was battle injured from the explosive energy of a blast. The vast majority of patients flew as immobile litter patients on board a C-17. Notably, both demographic and clinical factors demonstrated great similarity between all three groups (CAR, Non-CAR, and Non-CAR flown with a CAR). Indeed, the only relevant and significant difference between groups was the higher percent suffering burns found in the CAR group. See **Table 7** for the specific demographic characteristics and clinical parameters.

Table 7. Demographic characteristics and clinical parameters of patients evacuated between January 2007 and February 2008. (Butler, 2018)

Demographic Characteristics	CAR (n = 442)	Non-CAR (n = 436)	p-value	Non-CAR flown with a CAR (n = 236)	Non-CAR (n = 436)	p-value
Age (years),[a] Median (Q1, Q3)	24 (21, 29)	24 (22, 28)	0.829	24 (21, 28)	24 (22, 28)	0.234
Gender,[b] N (%)						
Male	437 (98.9)	428 (98.2)	0.388	233 (98.7)	428 (98.2)	0.583
Female	5 (1.1)	8 (1.8)		3 (1.3)	8 (1.8)	
Weight (pounds),[a] Median (Q1, Q3)	190 (180, 195)	189 (176, 200)	0.835	190 (180, 190)	189 (176, 200)	0.854
Theater,[b] N (%)						
Operation Iraqi Freedom	368 (83.4)	358 (82.1)	0.600	209 (88.6)	358 (82.1)	**0.028**
Operation Enduring Freedom	73 (16.6)	78 (17.9)		27 (11.4)	78 (17.9)	
Casualty Event,[b] N (%)						
Battle Injury	438 (99.3)	431 (98.9)	0.467	234 (99.2)	431 (98.9)	0.715
Disease, Non-Battle Injury	3 (0.7)	5 (1.1)		2 (0.8)	5 (1.1)	
Mechanism of Injury,[b] N (%)						
Blunt	318 (22.2)	270 (20.6)	0.281	143 (23.6)	270 (20.6)	0.131
Penetrating	322 (22.5)	281 (21.4)	0.474	137 (22.6)	281 (21.4)	0.546
Burns	58 (4.1)	28 (2.1)	**0.004**	14 (2.3)	28 (2.1)	0.803
Blast	732 (51.2)	735 (55.9)	**0.013**	312 (51.5)	735 (55.9)	0.069
Injury Etiology,[b] N (%)						
Projectile Energy	144 (30.7)	147 (31.2)	0.867	83 (32.3)	147 (31.2)	0.778
Explosive Energy	290 (62.0)	283 (60.2)	0.582	139 (54.1)	283 (60.2)	0.110
Blunt Energy	22 (4.7)	27 (5.8)	0.473	27 (10.5)	27 (5.8)	**0.019**
Thermal Energy	11 (2.4)	12 (2.6)	0.841	7 (2.7)	12 (2.6)	0.890
Other	1 (0.2)	1 (0.2)	0.998	1 (0.4)	1 (0.2)	0.664

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Classification,[b] N (%)						
5A – ambulatory patient	1 (0.2)	4 (0.9)	0.174	6 (2.5)	4 (0.9)	0.097
2A – immobile litter patient	408 (92.3)	353 (81.0)	**<0.001**	171 (72.5)	353 (81.0)	**0.011**
2B – mobile litter patient	33 (7.5)	79 (18.1)	**<0.001**	59 (25.0)	79 (18.1)	**0.035**
Aircraft,[b] N (%)						
C-17	401 (94.8)	405 (93.7)	0.509	223 (97.8)	405 (93.7)	**0.021**
C-130	0 (0)	6 (1.4)	**0.015**	0 (0)	6 (1.4)	0.074
KC-135	22 (5.2)	21 (4.9)	0.820	5 (2.2)	21 (4.9)	0.094
Calculated Flight Hours,[a] Median (Q1, Q3)	4.9 (4.7, 5.2)	5.0 (4.8, 5.4)	**<0.001**	4.8 (4.7, 5.1)	5.2 (4.8, 7.4)	**<0.001**
[sans outliers, N (%)]	412 (93.2)	350 (80.3)		232 (98.3)	350 (80.3)	
Clinical Parameters	**CAR (n = 442)**	**Non-CAR (n = 436)**	**p-value**	**Non-CAR flown with a CAR (n = 236)**	**Non-CAR (n = 436)**	**p-value**
Vital Signs,[a] Median (Q1, Q3)						
Temperature (°C)	37.4 (36.9, 37.9)	36.7 (36.5, 37.7)	**0.008**	37.6 (36.6, 38.8)	36.7 (36.5, 37.7)	0.138
Systolic BP (mm Hg)	124 (107, 139)	129 (112, 139)	**<0.001**	108 (101, 119)	129 (112, 139)	**<0.001**
Diastolic BP (mm Hg)	63 (55, 74)	65.5 (59, 79.5)	**<0.001**	57 (51, 68)	66 (59, 80)	**<0.001**
Heart Rate (per min)	108 (87, 124)	104 (87, 115)	**0.001**	113 (71, 126)	104 (87, 115)	**<0.001**
Respiratory Rate (per min)	16 (16, 18)	16 (16, 18)	0.075	16 (16, 18)	16 (16, 18)	0.343
Pulmonary Status,[a] Median (Q1, Q3)						
pH	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	0.825	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	**<0.001**
PaO_2 (mm Hg)	169 (99, 230)	135 (97, 194)	0.419	174 (142, 318)	135 (97, 194)	**0.001**
$PaCO_2$ (mm Hg)	42 (37, 45)	36.9 (35, 45)	0.387	40 (35, 46)	37 (35, 45)	**0.009**
SpO_2 (%)	100 (98, 100)	100 (98, 100)	0.357	100 (98, 100)	100 (98, 100)	**0.002**
FiO_2 (%)	50 (40, 60)	50 (40, 62)	**<0.001**	45 (40, 58)	50 (40, 62)	**0.012**
Laboratory Values,[a] Median (Q1, Q3)						
Glucose (mg/dl)	124 (109, 142)	122 (108, 145)	0.149	121.5 (109, 143)	122 (108, 145)	**0.477**
WBC (cells/ml)	11 (7.8, 15)	11.5 (6.6, 14.8)	0.813	6.5 (5.0, 9.3)	11.5 (6.6, 14.8)	**0.046**
Hemoglobin (g/dl)	11 (9, 13)	11 (10, 12)	0.099	10.7 (10, 12)	11 (10, 12)	**0.001**
Hematocrit-preflight (%)	34 (28, 40)	32 (28, 37)	0.956	32 (29, 36)	32 (28, 37)	**<0.001**
Hematocrit-postflight (%)	29 (27, 34)	30 (28, 36)	0.856	30 (26, 33)	30 (28, 36)	**<0.001**

Bold denotes statistical significance.
[a]Values calculated using the independent samples Mann-Whitney U test.
[b]Values calculated using the Chi-square statistic.
Note: BP = Blood Pressure; PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; SpO_2 = oxygen saturation per pulse oximetry; FiO_2 = fraction of inspired oxygen

The CAR patients had significantly higher injury severity scores (ISS) than the Non-CAR patients. Both fell into the ISS "moderate" injury category, but the upper quarter of CAR patients displayed a much greater degree of "critical" injury than the upper quarter of Non-CAR patients. Furthermore, CAR patients had significantly lower pulmonary shunt ratios (PaO_2:FiO_2) than Non-CAR patients, both exhibiting the "acute lung injury" criterion. Strikingly, a full quarter of the CAR patients met ARDS criterion. Moreover, the CAR patients manifested greater ventilator use and more CCATT assignments. Indeed, CAR patients were classified

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more commonly 2A (immobile litter patient) and less commonly 2B (mobile litter patient). In fact, the TVFSs more commonly declared CAR patients Urgent precedence and "remain overnight" restricted, meaning an immediate need for aircraft reassignment from operational to AE missions and the direct non-stop routing of the AE flight, respectively. See **Table 8** for specific injury severity indicators.

Table 8. Injury severity indicators of patients evacuated between January 2007 and February 2008. (Butler, 2018)

Injury Severity Indicators	CAR (n = 442)	Non-CAR (n = 436)	p-value	Non-CAR flown with a CAR (n = 236)	Non-CAR (n = 436)	p-value
Direct Indicators			**<0.001**			**<0.001**
ISS,[a] Median (Q1, Q3)	14 (9, 25)	13 (6, 20)		9 (4, 14)	13 (9, 17)	
[D1, D9]	[5, 34]	[4, 26]		[2, 22]	[4, 26]	
ISS Clinical Injury Severity Group	moderate	moderate		moderate	moderate	
PaO_2/FiO_2 Shunt Ratio,[a] Median (Q1, Q3)	250 (172, 348)	278 (227, 411)	**0.004**	275 (269, 309)	278 (227, 411)	0.460
[D1, D9]	[135, 529]	[137, 554]		[198, 398]	[137, 554]	
Clinical Severity Descriptor	acute lung injury	acute lung injury		acute lung injury	acute lung injury	
Indirect Indicators						
Precedence,[b] N (%)	330 (75)	387 (89)	**< 0.001**	220 (93)	387 (89)	0.062
Priority	112 (25)	49 (11)		16 (7)	49 (11)	
Urgent						
Classification,[b] N (%)						
2A – immobile litter patient	408 (92.3)	353 (81.0)	**<0.001**	171 (72.5)	353 (81.0)	**0.011**
2B – mobile litter patient	33 (7.5)	79 (18.1)	**<0.001**	59 (25.0)	79 (18.1)	**0.035**
Remain Overnight Restriction,[b] N (%)						
Yes	387 (88)	179 (41)	**< 0.001**	113 (48)	179 (41)	0.088
No	55 (12)	257 (59)		123 (52)	257 (59)	
CCATT Assignment,[b] N (%)						
Yes	223 (53)	148 (34)	**< 0.001**	37 (16)	148 (34)	**< 0.001**
No	209 (47)	288 (66)		199 (84)	288 (66)	
On Ventilator,[b] N (%)						
Yes	159 (36)	93 (21)	**< 0.001**	13 (6)	93 (21)	**< 0.001**
No	283 (64)	343 (79)		223 (94)	343 (79)	
Tidal Volume (ml),[a] Median (Q1, Q3)	580 (550, 628)	600 (550, 650)	0.570	550 (500, 610)	600 (550, 650)	0.153
PEEP (mm Hg),[a] Median (Q1, Q3)	5 (5, 6)	5 (5, 8)	0.337	5 (5, 5)	5 (5, 8)	0.411

Bold denotes statistical significance.
[a]Values calculated using the independent samples Mann-Whitney U test.
[b]Values calculated using the Chi-square statistic.

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Note: CCATT = critical care air transport team; PaO_2 = partial pressure of oxygen in arterial blood; FiO_2 = fraction of inspired oxygen; PEEP = positive end expiratory pressure; ISS = Injury Severity Score

Clinical outcomes between CAR and Non-CAR patients were quite similar. Analyses detected no difference in length of stay, number of postflight procedures, the number of patients undergoing postflight procedures, or the postflight procedure profiles (e.g., the number of major and minor procedures). There was, however, a significant difference in ventilator days, intensive care unit days, and number of postflight complications, though the decile examination showed the difference to be nominal. There was a lesser number of patients with postflight complications in the Non-CAR group. See **Table 9** for outcome particulars.

Table 9. Clinical outcomes of patients evacuated between January 2007 and February 2008. (Butler, 2018)

Clinical Outcomes	CAR (n = 442)	Non-CAR (n = 436)	p-value	Non-CAR flown with a CAR (n = 236)	Non-CAR (n = 436)	p-value
Intensive Care Unit Days,[a] Median (Q1, Q3) [D1, D9]	1 (0, 3) [0, 4]	0 (0, 2) [0, 3.4]	**0.010**	0 (0, 2) [0, 3]	0 (0, 2) [0, 3.4]	**<0.001**
Ventilator Days,[a] Median (Q1, Q3) [D1, D9]	0 (0, 2) [0, 3]	0 (0, 1) [0, 2.6]	**0.002**	0 (0, 0) [0, 1]	0 (0, 1) [0, 2.6]	**0.002**
Length of Stay Days,[a] Median (Q1, Q3) [D1, D9]	3 (2, 4) [1, 6]	3 (2, 4) [1, 6]	0.287	3 (2, 5) [2, 6]	3 (2, 4) [1, 6]	**<0.001**
Number of Postflight Procedures,[a] Median (Q1, Q3) [D1, D9]	2 (0, 4) [0, 6]	2 (0, 4) [0, 6]	0.658	1 (0, 3) [0, 5]	2 (0, 4) [0, 6]	**0.004**
Patients with Postflight Procedures,[b] N (%)						
Yes	349 (79)	355 (77)	0.448	160 (68)	355 (77)	**0.011**
No	93(21)	101 (23)		76 (32)	101 (23)	
Procedure Profile,[b] N (%)						
Major	672 (61)	642 (59)	0.262	259 (56)	642 (59)	0.254
Minor	431 (39)	454 (41)		208 (44)	454 (41)	
Number of Postflight Complications,[a] Median (Q1, Q3) [D1, D9]	0 (0, 1) [0, 2]	0 (0, 1) [0, 2]	**0.018**	0 (0, 0) [0, 1]	1 (0, 1) [0, 2]	**<0.001**
Patients with Postflight Complications,[b] N (%)						
Yes	177 (40)	139 (32)	**0.012**	44 (19)	139 (32)	**<0.001**
No	265 (60)	297 (68)		192 (81)	297 (68)	

Bold denotes statistical significance.
[a]Values calculated using the independent samples Mann-Whitney U test.
[b]Values calculated using the Chi-square statistic.

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The severity comparison between Non-CAR flown with a CAR and Non-CAR patients demonstrated mixed results. Although the Non-CAR group had higher ISS scores, both groups fell into the "moderate" ISS injury category. In addition, there was no difference in pulmonary shunt ratios between the groups, both falling into the "acute lung injury" category; however, a full quarter of the Non-CAR group had ratios exceeding the less severe score of 400. Despite a significantly greater number 2A classified patients, ventilated patients, and CCATT assignments in the Non-CAR group, precedence and remain overnight restrictions exhibited no between-group differences. See **Table 8** for specific injury severity indicators.

Though severity between groups was equivocal, clinical outcomes were not, favoring the Non-CAR flown with a CAR group. There were significantly fewer patients with postflight procedures (odds ratio = 0.833, Non-CAR flown with a CAR to Non-CAR) as well as a lesser number of postflight procedures. In addition, there were fewer patients with postflight complications (odds ratio = 0.585) as well as a lesser number of postflight complications. Moreover, there were significantly fewer ventilator, intensive care unit, and length of stay days. See **Table 9** for outcome particulars.

Curiously, postflight procedure profiles proved to be relatively uniform between groups. In fact, there was no significant difference detected when looking at the distribution of major and minor procedures. See **Table 9**. Notably, wound surgeries predominated followed by orthopedic, abdominal, and neurological surgeries. The most common major procedures in CAR patients were excisional debridement, debridement of open fractures, spine/cord surgery, and exploratory laparotomy; in Non-CAR patients, excisional debridement, debridement of open fractures, internal fixation, and exploratory laparotomy; and, in Non-CAR patients flown with a CAR, excisional debridement, debridement of open fractures, internal fixation, and spine/ cord

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surgery. The most common minor procedures consisted of x-rays, upper/lower endoscopy, local/regional analgesia, and bronchoscopy. See **Table 10** for the entire spectrum of postflight procedures.

Table 10. Postflight patient procedures recorded between January 2007 and February 2008. (Butler, 2018)

CATEGORY	CAR		Non-CAR		Non-CAR flown with a CAR	
	n	%	n	%	n	%
Wound (44%)						
Major		**34**		**30**		**14**
Excisional Debridement	400		354		164	
Other	5		3		3	
Minor		**9**		**8**		**5**
Non-excisional Debridement	44		40		20	
Skin Closure	29		31		21	
Porcine Dressing	14		10		6	
Other	19		10		5	
Orthopedic (13%)						
Major		**35**		**42**		**19**
Debridement, Open Fracture	52		75		29	
Internal Fixation	13		29		12	
Amputation	12		6		2	
External Fixator	6		10		3	
Open Reduction	5		9		4	
Fasciotomy	9		2		1	
Other	27		16		15	
Minor		**1**		**2**		**1**
Closed Reduction	3		3		3	
Other	1		4		1	
Abdominal (5%)						
Major		**44**		**52**		**1**
Exploratory Laparotomy	19		19		2	
Colon	8		8		0	
Intestine	10		3		0	
Stomach	1		1		0	
Other	25		44		0	
Minor		**2**		**1**		**0**
Other	3		1		0	
Neurological (3%)						
Major		**41**		**34**		**23**
Spine and Cord	21		10		11	
Intracranial	8		14		4	
Peripheral Nerve	0		0		1	
Minor		**2**		**0**		**0**
Peripheral Nerve	1		0		0	
Vascular (1⁺%)						
Major		**49**		**41**		**8**
Vena Cava Interruption	19		13		1	
Other	0		3		2	
Minor		**2**		**0**		**0**
Vessel	1		0		0	
Otolaryngological (1⁺%)						
Major		**50**		**18**		**13**
Jaw Complex	9		1		4	
Tracheostomy	7		6		0	
Facial Bones	3		0		1	
Minor		**13**		**3**		**3**
Jaw Complex	4		1		1	
Nose	1		0		0	
Thoracic (< 1%)						
Major		**17**		**4**		**0**
Exploratory Thoracotomy	1		1		0	
Other	3		0		0	

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Minor	**48**	**22**		**9**
Chest Tube Insertion/Removal	11	5	2	
Ophthalmological (< 1%)				
Major	**43**	**0**		**0**
Globe and Orbit	3	0	0	
Minor	**43**	**14**		**0**
Globe and Orbit	1	1	0	
Other	2	0	0	
Genitourinary (< 1%)				
Major	**33**	**67**		**0**
Urinary Tract	2	2	0	
Genital	0	2	0	
Endoscopy (10%)				
Major	**1**	**4**		**0**
Cystoscopy	2	4	0	
Percutaneous Endoscopic Gastro/Jejunostomy	1	4	0	
Arthroscopy	0	1	0	
Minor	**52**	**37**		**6**
Upper and Lower GI Endoscopy	77	55	6	
Bronchoscopy	56	39	10	
Radiological (9%)				
Major	**1**	**1**		**0**
Angiography	1	1	0	
Myelography	0	1	0	
Minor	**17**	**45**		**36**
Plain X-rays	27	88	56	
Computer-Assisted Tomography	15	19	32	
Magnetic Resonance Imagery	0	3	2	
Sonography	1	4	1	
Miscellaneous (11^{+}%)				
Minor	**40**	**46**		**14**
Local/Regional Analgesia	40	81	34	
Enteral Feeding	44	41	2	
Vaccination	16	9	2	
Monitoring	8	4	2	
Other	13	5	2	
Total Procedures (100%)	**1,103**	**1,096**	**467**	

Lastly, postflight complications most commonly found were pulmonary, infectious, resuscitative, or coagulopathic origin; in fact, a full 87% fell into those four categories. The CAR patients most frequently suffered from coagulopathy, anemia/blood loss, atelectasis, and pleural effusion; Non-CAR patients endured anemia/blood loss, atelectasis, coagulopathy, and *Acinetobacter* infection; and Non-CAR patients flown with a CAR bore atelectasis, anemia/blood loss, pleural effusion, and coagulopathy. See **Table 11** for the entire spectrum of postflight complications. Interestingly, postflight hematocrit was significantly lower than preflight hematocrit in all three groups (CAR: 31.3 [27.1, 36.7] versus 37.0 [31.0, 42.0], $p < 0.001$; Non-CAR: 29.9 [24.9, 35.6] versus 36.0 [30.0, 41.0], $p < 0.001$; Non-CAR flown with a CAR: 35.2 [19.0, 41.3] versus 40.0 [34.0, 43.0], $p < 0.001$).

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Table 11. Postflight patient complications recorded between January 2007 and February 2008. (Butler, 2018)

CATEGORY	CAR		Non-CAR		Non-CAR flown with a CAR	
	n	%	n	%	n	%
Pulmonary (32%)		**44**		**35**		**21**
Atelectasis	52		44		22	
Pleural Effusion	23		22		15	
Pneumothorax	11		6			
Pulmonary Edema	6		4		4	
Pulmonary Embolus	6		2		5	
Aspiration/Aspiration Pneumonia	1		3		2	
Acute Respiratory Distress Syndrome	3		1		1	
Acute Respiratory Failure	3		2			
Hemothorax	1		2		1	
Infectious (20%)		**45**		**44**		**11**
Acinetobacter	12		21		5	
Pneumonia	16		20		1	
Wound Infection	20		8		3	
Cellulitis	7				2	
Sepsis	5		5		2	
Bacteremia	3		4		2	
Urinary Tract Infection	1		1			
Disseminated Fungal Infection	2					
Clostridium Difficile Colitis	2		1			
Line Sepsis			2			
Intraabdominal Abscess			2			
CNS Infection			1			
Empyema					1	
Resuscitative (18%)		**40**		**46**		**14**
Anemia/Blood Loss	54		62		18	
Hypovolemia	1		1		1	
Shock (traumatic)	1					
Postoperative Hemorrhage			1			
Coagulation (17%)		**58**		**35**		**7**
Coagulopathy	59		34		7	
Deep Vein Thrombosis	14		8		2	
Acute Arterial Occlusion	1		2			
Gastrointestinal (3%)		**63**		**33**		**4**
Ileus	8		4		1	
Dehiscence/Evisceration	4		4			
Pancreatitis	1					
Jaundice	1					
Small Bowel Obstruction	1					
Renal (2%)		**56**		**31**		**13**
Acute Renal Failure	9		4		1	
Renal Failure			1		1	
Orthopedic (1^{+}%)		**36**		**55**		**9**
Compartment Syndrome	4		4		1	
Fat Embolus Syndrome			2			
Metabolic (1^{+}%)		**82**		**18**		
Hyperkalemia	7		1			
Hypothermia	2		1			
Dermatologic (1^{+}%)		**36**		**64**		
Decubitus/Skin Breakdown	4		7			
Neurologic (1%)		**50**		**38**		**12**
Progression of Original Insult	4		1		1	
Seizures			2			
Cardiac (< 1%)				**50**		**50**
Cardiopulmonary Arrest			1			
Major Arrhythmia					1	
Miscellaneous (3%)		**39**		**35**		**26**
Other	9		7		5	
Adverse Drug Reaction			1		1	
Total Complications (100%)	**358**		**299**		**106**	

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6.0 DISCUSSION

6.1 Tissue Oxygen Delivery Paradigm

Up until this research effort, there has been no systematic appraisal of the TVFS practice or clinical impact. This study focused on the experience of two successively deployed Aerospace Medicine specialists as TVFSs (authors WPB and LWS). The reason for this focus rests with the development and implementation of a DO_2 paradigm as applied to AE.

In late 2006, Grissom et al suggested prehospital supplemental oxygen be added to tactical casualty combat care during mountain operations based on DO_2 modelling. (**Grisson, 2006**) Around the same time, Pollan and Fisher followed by Butler independently addressed hemoglobin levels during AE using similar DO_2 modelling. (**Pollan and Fisher, 2006; Butler, 2007**)

Although DO_2 had long been part of the critical care world, its incorporation into pre-hospital care and AE was pioneering. The two author TVFSs employed this paradigm to optimize AE patient DO_2. And, DO_2-related factors, within the ready purview of the TVFS, include FiO_2, hemoglobin level, and cabin altitude translating to prescriptions for supplemental oxygen, transfusion, and CAR. When examining the prescriptive practice of CAR, there was a clear bump during the two TVFSs' deployments. See **Figure 1**. This bump created an unintentional natural experiment. If the DO_2 paradigm and the TVFS's use of it were to demonstrate clinical benefit, it would be apparent here. Hence, the execution of this research.

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6.2 Study Results

The research had three parts --- a descriptive analysis of the two TVFSs' practices, a hypothesis-generating ecological study looking at the CAR prescription, and a dual case-control study examining the clinical impact of the CAR prescription.

The descriptive analysis, Part 1, dissected their operational worksheet, a locally created spreadsheet designed to streamline the validation queue during a particularly kinetic timeframe within Operation Iraqi Freedom. From a total of 8,634 patients validated, 1,389 patients were entered into the worksheet. Most of the patients were enlisted male Army soldiers; most were evacuated Urgent (12%) and Priority (63%) precedence; and, most were BI (55%). The contrast between BI and DNBI served as a useful platform for examining the TVFSs' practice.

Recapitulating previous experience, BI was mostly extremity injury (48%), the result of IEDs. (**Bridges, 2009; Belmont, 2010; Mason, 2011; Galvagno, 2014**) On the other hand, coronary artery syndrome (28%) dominated DNBI. Of note, not dissimilar from Bridges' experience, those patients suffering coronary artery syndrome were generally around 10 years older than their peers, whether they be military or civilian. (**Bridges, 2009**) A large number of both BI (30%) and DNBI (24%) were very sick, attended by CCATTs.

Though the CCATT need was often self-evident, making the formal requirement fell to the TVFS. In fact, this was the most frequent Preventive Action prescribed by the TVFS. Head of bed elevation was the most frequent BI/DNBI Positioning Action. Supplemental oxygen, the most frequent BI/DNBI Medicinal. Interestingly, the TVFS routinely prescribed a higher FiO_2 (~10% higher) than the clearing flight surgeon. At the same time, the Medicinal transfusion was relatively frequent, though largely limited to BI. These two prescriptions, supplemental oxygen and transfusion, reflect the concerted effort to boost DO_2. And, although no "remain overnight"

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was the most frequent Aircraft Action, CAR was imposed on 57% of the patients (BI = 61%; DNBI = 52%). (**Butler, 2017**)

The two author TVFSs advanced their post-deployment impression that CAR, the TVFS's most quintessential prescription, when aggressively employed would proffer clinical benefit. Part 2 of this research investigated whether this impression had any validity via a hypothesis-generating ecological study.

Data from TRAC^{2}ES (CAR dataset) and LRMC Joint Theater Trauma Registry (Complications dataset), January 2007 through February 2008, were studied. The rate of CAR prescribing was significantly higher during the two author TVFSs' deployments than before or after. Postflight complications demonstrated the opposite relationship, higher postflight complication rates before and after the two author TVFSs' deployments.

Formal correlation analysis detected a statistically significant inverse relationship. That is, as the rate of CAR prescribing rose, the rate of postflight complications dropped. This relationship was extant for both the rate of patients with postflight complications and the number of postflight complications per 100 patients. (**Butler, 2016a**)

Having confirmed the notion that CAR might well benefit the AE population of patients, Part 3, designed for a more in depth look at individual patient clinical impact, employed a dual case-control methodology. The CAR and Complications datasets were merged, generating 1,114 patients eligible for study. These patients fell into three natural groups --- CAR patients, Non-CAR patients, and Non-CAR patients incidentally flown with a CAR --- and two natural comparisons --- CAR versus Non-CAR and Non-CAR flown with a CAR versus Non-CAR. Demographic characteristics and clinical parameters were similar between groups, not so, however, with injury severity indicators. Both direct and indirect markers of injury severity

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suggested that CAR patients were sicker than Non-CAR patients. At the same time, no such clear-cut dichotomy of severity could be detected between the Non-CAR flown with a CAR and Non-CAR patients.

Clinical outcomes were essentially the same between CAR and Non-CAR patients; whereas, Non-CAR patients flown with a CAR demonstrated clearly superior outcomes over the Non-CAR patients. The data showed that the Non-CAR flown with a CAR group had 17% better odds of having fewer patients with postflight procedures and 41% better odds of having fewer patients with postflight complications than the Non-CAR group. All told, it appeared that the CAR prescription normalized the sicker CAR patients into Non-CAR patients and brought the Non-CAR patients into a less morbid state. (**Butler, 2018**)

In toto, this three-part research program ratified the notion that TVFSs' clinical practice can have a salutary clinical impact on AE patients. This impact is prominently seen via the CAR prescription, but, most likely, results from employment of the DO_2 paradigm during the clinical validation of these patients.

6.3 Inflight Stressors and the Second Hit

Tissue oxygen delivery is all about getting the right amount of oxygen to the right tissues without interruption. Interruption of DO_2 delivery produces hypoxia, ischemia, and tissue injury. In AE patients, this means a *second hit*. The *first hit* being the initial injury/illness and the *second hit* being an added physiological insult that aggravates the *first hit* --- the result: a potential rise in patient morbidity and mortality. Indeed, Ritenour et al, retrospectively examined 336 AE patients focused on extremity compartment syndrome. There were 643 fasciotomies and, of those requiring a fasciotomy revision after evacuation, there was a significantly higher rates of muscle excision, amputation, and mortality. (**Ritenour, 2008**) These findings suggest a

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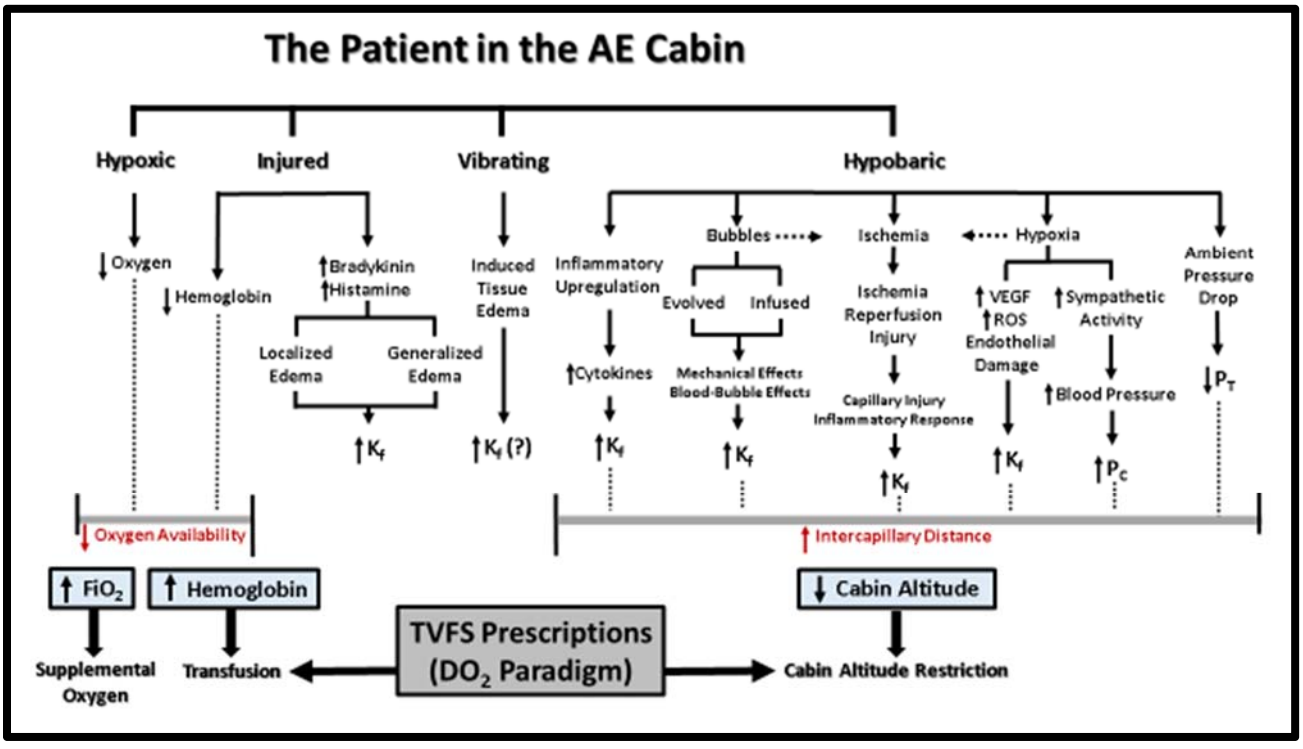
second hit mediated by an AE flight environment rife with potential *second hit* physiological stressors.

The most commonly discussed flight stressors include accelerations/decelerations, reduced humidity, reduced environmental temperature, elevated noise levels, significant ongoing vibration, reduced oxygen partial pressure (hypoxia), and reduced ambient pressure (hypobaria). Pertinent to the discussion of CAR and the DO_2 paradigm are vibration, hypoxia, and hypobaria. Hypoxia and vibration make for reduced oxygen availability while vibration and hypobaria favor fluid movement into the interstitial space (aka tissue edema). Follow the ensuing discussion with **Figure 3**.

Figure 3. Graphic depiction of inflight stressors' physiological impact on the AE patient with TVFS prescriptive countermeasures.



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6.4 Hypoxia and Vibration Reduce Oxygen Available to Tissues

6.4.1 Oxygen

Hypoxia is a function of both the amount of oxygen present and the amount of hemoglobin present, oxygen to support tissue respiration and hemoglobin to carry it to the tissues. As military cabin altitude generally ranges between 8,000-10,000 feet, at best the ground level equivalent FiO_2 is around 16%, well below the standard ground level FiO_2 of 21%. (**Emergency War Surgery, 2004**) Cottrell et al, looking at 38 commercial airline pilots, found an average drop in SpO_2 of 8.4% and 20 of the pilots' SpO_2 fell below 90%. (**Cottrell, 1995**) Bendrick et al studied 24 coronary artery disease AE patients; the median SpO_2 was 91% (range 85%-96%). A full 21% dropped SpO_2 below 90%, fortunately without symptoms. (**Bendrick, 1995**) Similarly, Johannigman et al followed the evacuation of the so-called "walking wounded." Of 61 patients, 90% exhibited "hypoxemia" ($SpO_2 < 90\%$), while 56% exhibited "critical hypoxemia" ($SpO_2 < 85\%$). Most concerning were the durations of hypoxemia and critical hypoxemia, 4 seconds to 3.9 hours and 6 seconds to 42 minutes, respectively. (**Johannigman, 2015**) Most importantly, Henry et al examined inflight PaO_2 in 201 patients evacuated from Vietnam to Japan. Without supplemental oxygen, they found PaO_2 dropped to $\leq$ 60 mmHg in 47% and $\leq$ 50 mmHg in 31%. In addition, the higher the cabin altitude the greater the drop in PaO_2 --- cabin altitudes between 6,700-7,500 feet produced a 33% drop while cabin altitudes between 3,000-3,500 feet generated only a 19% drop. (**Henry, 1973**) Thus, altitude and its concomitant drop in FiO_2, SpO_2, and PaO_2 demand an increased need for oxygen.

Add into the mix hours of ongoing aircraft vibration. Here, the Tonic Vibration Reflex, the physiological counter to external vibration, produces increased muscle contraction and osteoarticular rigidity, upping both muscle activity and energy expenditure. (**Wollersheim,**

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2017) At the same time, exercise (aka muscle activity), when taken to altitude (9,186 feet), promotes a simultaneous drop in both SpO_2 and PaO_2, 12% and 30%, respectively. (**Schacke, 2007**) Thus, vibration with its concomitant escalation in energy expenditure produces an additional increased need for oxygen.

Such a drop in oxygen can have clinical impact. Earnest et al demonstrated, in a complex wounded/infected caprine model, that supplemental oxygen significantly inhibited *Pseudomonas aeruginosa* growth during a simulated 7-hour AE flight to 8,800 feet, thus abrogating an infectious *second hit*. (**Earnest, 2012**) Thus, to deliver adequate oxygen (optimize DO_2), in the face of altitude-induced hypoxia and flight-associated vibration, supplemental oxygen must be prescribed, at least to ground equivalent levels.

6.4.2 Hemoglobin

Unfortunately, supplemental oxygen is of limited value without adequate hemoglobin levels. At ground level, it appears that DO_2 is unaffected until hemoglobin levels drop below 7 g/dl. (**Madjdpour, 2006**) At the same time, lowered hemoglobin is akin to being at altitude --- 8 g/dl being like 8,400 feet and 11 g/dl being like 4,800 feet. (**Alaska Air Medical Escort Training Manual, 2006**) These two observations make low hemoglobin states at altitude problematic. Indeed, in patients with hemoglobin levels < 7 g/dl (chronic anemias) and < 8 g/dl (acute anemias), Air Force oxygen requirement guidance instructs, "As directed by the AE Validating FS." (**AFI 48-307v1**) Currently, the Air Force Instruction does not provide any further guidance to the TVFS.

The clinical impact of hemoglobin levels during AE has been studied. Mora et al demonstrated in CCATT patients that hemoglobin levels $\leq$ 8 g/dl were associated with increased inflight transfusions and Hamilton et al demonstrated in CCATT burn patients that hemoglobin

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levels $\leq$ 10 g/dl were associated with increased ventilator days and mortality. Both studies, however, when subjected to regression analytics, were unable to discern a negative impact to lower hemoglobin levels. (**Mora, 2014; Hamilton, 2015**) In contrast, Hannah and Rice studied 90 Canadian orthopedic casualties. They found postflight revisions of proximal amputations were required in 46% of those with hemoglobin levels below 8.0 g/dl versus 15% in those at or above 8.0 g/dl. Logistic regression analytics demonstrated a dose-response relationship. At a hemoglobin of 6.4 g/dl, 55% required revision; at 8 g/dl, 37%; and, at 10 g/dl, 20%. (**Hannah, 2013**) Thus, to minimize tissue ischemia (aka optimize DO_2), an adequate level of hemoglobin must be present. To make this happen, the TVFS can transfuse the patient; however, the potential untoward infectious and immunologic effects demand caution. (**Madjdpour, 2006**) As yet, a specific threshold value for transfusion remains undetermined. Consequently, a methodology for balancing both supplemental oxygen and transfusion is requisite. The DO_2 paradigm offers just such a methodology.

6.5 Hypobaria and Vibration Exacerbate Tissue Edema

6.5.1 Injury Response Edema

Before manifesting casualties on an aircraft, the TVFS must consider tissue edema. This is particularly the case with BI. The body's initial healing response includes localized tissue edema. (**Hunt, 1988; McDonald, 1999**) In addition, its response to major systemic injuries (e.g., large burns, major trauma) is generalized body edema. (**Barillo, 2003**) Both phenomena result from leaky capillaries and fluid movement into the interstitial tissues. (**Rippe, 1994; McDonald, 1999; Hettiaratchy, 2004; Persson, 2006**)

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6.5.2 Vibration Edema

Once airborne, besides the increased muscle and metabolic activity, vibration appears to be associated with tissue edema. Lundborg et al demonstrated sciatic epineural edema in rats with 82 Hz at 0.21 mm. (**Lundborg, 1987**) Mittermayr et al, in an unrelated publication, reported rapid leg edema with exposures to 30-50 Hz. (**Mittermayr, 2003**) No etiologic basis for this effect is forthcoming.

6.5.3 Hypobaria Edema

Superimposed upon this milieu is hypobaria. Edema at altitude is not a novel observation. Indeed, peripheral edema (hands, ankles, periorbital, and face) is not uncommon (up to 18% in one study). (**Sheridan, 1970; Pines, 1974; Hackett, 1979**) In fact, such edemas have been seen under varied study environments to include mountains, inflight, and altitude chambers. (**Gunga, 1995; Mittermayr, 2003; Iblher, 2013; Pescosolido, 2015**) As first suggested by Shuster, then later by Mittermayr et al and Butler et al, the Starling forces best describe the physiology governing the movement of fluid into the interstitial space (aka edema formation) at altitude. (**Shuster, 1996a, 1996b; Mittermayr, 2003; Butler, 2016a**) Indeed, Starling's fluid flux equation is expressed as:

$$J_v = K_f * [(P_C - P_T) - (\pi_C - \pi_T)], \quad \text{where}$$

J_v is the driving force for fluid movement

($J_v > 0$ → denotes filtration into the interstitial space;

$J_v < 0$ denotes reabsorption into the vascular space),

K_f is the capillary permeability factor,

P_C is the capillary hydrostatic pressure,

P_T is the interstitial tissue hydrostatic pressure,

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π_C is the capillary osmotic pressure, and

π_T is the interstitial tissue osmotic pressure. (**Costanzo, 2010**)

Edema formation is most commonly seen with an increased K_f, increased P_C, and/or decreased π_C. (**Costanzo, 2010**) However, a rise in π_T or drop in P_T could potentially produce edema. It is instructive to examine each of these factors in the AE setting of reduced ambient pressure. See **Figure 3** offers a graphic overview of this discussion. Let's approach each factor in order:

a) Increased Capillary Permeability (K_f) --- A rise in K_f secondary to hypobaric hypoxia was first implicated in 1932. Since that time, altitude-associated mechanisms for such capillary dysfunction have included both oxygen radicals and adhesion molecules. (**Richalet, 1995**) In addition, studies into acute mountain sickness have implicated cytokines, hypoxia inducible factor-1 alpha, vascular endothelial growth factor, and inducible nitric oxide synthetase. (**Hackett, 2012; Luks, 2015**) Indeed, movement of albumin into the interstitial space has confirmed the leaky capillaries. (**Gunga, 1995**) Add to this recent animal studies that suggest altitude itself upregulates inflammatory activity (**Goodman, 2010; Skovira, 2016**), capillary dysfunction caused by infused and/or evolved bubbles (**Richalet, 1995; Roach, 1995; Butler, 2016a**), and high levels of histamine and bradykinin released in traumatized and/or burned patients (**Richalet, 1995; Costanzo, 2010**); all effectively upping K_f. Plus in the fact that reperfusion of altitude-related ischemic tissue, upon landing, may well set the stage for the leukocyte-mediated tissue injury, with its associated leaky capillaries, common to the ischemia-reperfusion phenomenon. (**Carden, 2000**)

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Lastly, vibration appears associated with tissue edema; the mechanism, though unclear, may involve capillary dysfunction. (**Lundborg, 1987; Mittermayr, 2003**) In sum, K_f almost certainly rises in the evacuated patient and is a key to fluid movement into the interstitium.

b) Increased Capillary Hydrostatic Pressure (P_C) --- A rise in P_C is expected. A consistent finding at altitude is a rise in blood pressure, both in animals and humans. (**Scultetus, 2015; Torlasco, 2015; Parati, 2015**) This is especially realized in the lung where pulmonary artery pressure rises with altitude. (**Ballmer, 1995**) Couple that with dilated arterioles and constricted venules (seen with trauma/burn-mediated release of histamine and bradykinin) and P_C is bound to rise. (**Richalet, 1995; Costanzo, 2010**) In toto, P_C most likely rises in the evacuated patient and is a key to fluid movement into the interstitium.

c) Decreased Capillary Osmotic Pressure (π_C) --- A drop in π_C is an unlikely primary consequence of altitude. Most commonly, fluid movement into the interstitium due to decreased π_C is from significant medical maladies (e.g., nephrotic syndrome, hepatic failure). (**Costanzo, 2010**) On the other hand, as a secondary effect from rises in K_f and/or P_C, π_C may well drop. After all, movement of albumin from the intravascular space into the extravascular space has been observed with altitude. (**Gunga, 1995**) So, a drop in π_C may occur, but cannot be considered a key to fluid movement.

d) Increased Interstitial Tissue Osmotic Pressure (π_T) --- A rise in π_T is an unlikely primary consequence of altitude. It would be the consequence of albumin movement into the interstitial space associated with rises in K_f and P_C. (**Gunga, 1995**) So, an increase in π_T may occur, but cannot be considered a key to fluid movement.

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e) Decreased Interstitial Tissue Hydrostatic Pressure (P_T) --- A drop in P_T is a potential primary consequence of altitude. Lundvall et al studies employing lower body negative pressure suggest lowered ambient pressure favors fluid movement into the interstitial tissues. (**Lundvall, 1989a, 1989b, 1993**) Others have similarly suggested that with a drop in ambient pressure (P_B), interstitial pressure (P_T) "…will fall towards the value of the applied pressure [Pippard]." (**Brace, 1977; Pippard, 1989**) Generally, P_T, is considered to be around -3 mmHg relative to atmospheric pressure (which is considered zero pressure). (**Guyton, 1971; Hall, 2011**) Flying at 8,000 feet will reduce P_B by almost 200 mmHg. In order for the microcirculation to equilibrate, P_T must drop. To our knowledge, there is no specific literature addressing this question. However, there seems to be abundant indirect evidence to include: increased pulmonary lymph flow with normoxic hypobaria (**Roach, 1995**); hypobaria without associated albumin movement (**Ballmer, 1995**); increased forehead tissue thickness with long haul commercial flights unassociated with albumin movement (**Mittermayr, 2003**); increased corneal thickness associated with normoxic hypobaria (**Pescosolido, 2015**); subtle cerebral edema on maganetic resonance imagery (MRI) with Inside Observers (on oxygen) following altitude chamber training (**Sherman, 2015**); and worsening of rat TBI with normoxic hypobaria (**Hsieh, 2015**). Consequently, decreased P_T may well be a key to fluid movement into the interstitium.

With the movement of fluid into the interstitial space, interstitial hydrostatic pressure rises. As it climbs from around -3 mmHg to and beyond 0 mmHg, there is a sudden drop in tissue resistance to fluid influx accompanied by a sudden rise in tissue conductance of fluid influx.

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This makes for a rapid high-volume fluid accumulation in the interstitium producing tissue edema. (**Guyton, 1966; Guyton, 1968**) With such edema, plus the injury response and vibration edemas, a widened intercapillary distance is likely which, in turn, would impede oxygen diffusion. (**Miserocchi, 2011**) The overall result is a potential drop in DO_2. To counter this effect, the TVFS can only affect altitude and, therefore, must prescribe a CAR.

6.6 Tissue Oxygen Delivery (DO_2)

As seen above, three flight stressors --- hypoxia, vibration, and hypobaria --- when conjoined with serious patient injury and/or illness, create an environment where oxygen availability is decreased and intercapillary distance is increased (aka edema). An environment fraught with potential for DO_2 impairment, second hit insult, and upped patient morbidity/mortality.

This research suggests that coherent application of the DO_2 paradigm may well avert AE-associated morbidity in the evacuated patient. Within this paradigm, the TVFS has three tools (supplemental oxygen, transfusion, and CAR) with which to effect a *good* DO_2 inflight.

Good DO_2 is any oxygen delivery exceeding the critical DO_2, or DO_{2crit}. The DO_{2crit} is the level of DO_2 below which tissues suffer ischemia and injury. Certain healthy animal (e.g., rats, dogs, pigs, baboons) critical DO_{2crit} thresholds have been defined, not so for the human. (**Lieberman, 2000**) Despite this, the DO_{2crit} has been determined in small populations of critically ill patients (e.g., septic patients, anesthetized cardiac surgical patients, immediately postoperative cardiac patients), ranging from 4.5 ml O_2/kg/min to 8.2 ml O_2/kg/min. (**Shibutani, 1983; Komatsu, 1987; Ronco, 1993**) But, outside of these very specific patient populations, the healthy human DO_{2crit} threshold remains elusive. Lieberman et al have the closest estimate to date, that being < 7.3 ml O_2/kg/min. (**Lieberman, 2000**)

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Using several well-established physiological equations --- the alveolar gas equation, Kelman's oxygen dissociation model equation, the blood oxygen content equation, and the tissue oxygen delivery equation --- DO_2 can be calculated. (**Contanzo, 2014; Kelman, 1966**) Manipulating the FiO_2, hemoglobin level, and cabin altitude within the framework of these equations, the TVFS can assure a *good* DO_2, a DO_2 in excess of 7.3 ml O_2/kg/min. (**Pollan, 2006; Butler, 2007**) In fact, Butler et al found that patients with *good* DO_2 (> 7.3 ml O_2/kg/min) were associated with significantly fewer postflight procedures when compared to patients with *bad* DO_2 (< 7.3 ml O_2/kg/min). (**Butler, 2016b**) Thus, attention to DO_2 has the potential to minimize patient morbidity and the DO_2 paradigm offers a coherent means of optimizing DO_2 with supplemental oxygen, transfusion, and CAR.

6.7 Limitations

This research focused on two specific TVFSs deployment experience. Since they aggressively employed the DO_2 paradigm (most noticeable with the CAR), arguably, the findings may not be generalizable. However, their experience (**Figure 1**) made for an unintentional natural experiment testing the clinical impact of the DO_2 paradigm. The findings suggest that CAR, as applied within the DO_2 paradigm, is associated with reduced postflight patient morbidity.

In addition, this research employed retrospective data from databases that could be incomplete, inconsistent, inaccurate, and/or duplicative. In fact, LRMC self-declared its database inadequate prior to January 2007 (personal communication). No LRMC data prior to January 2007 were employed and care was taken to minimize retrospective data pitfalls.

The DO_2 paradigm presupposes aggressive use of all prescriptions available to the TVFS. Consequently, other interventions (e.g., supplemental oxygen, transfusion) with or without the

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CAR may be responsible for the findings. The research was not designed nor had the breadth of data to address this differentiation.

Positive postflight outcomes could result from preflight clinical care/ground transport, inflight clinical care, and/or postflight ground transport/clinical care; however, patient management within the Joint Theater Trauma System was mostly standardized via widely distributed/implemented clinical practice guidelines. Essentially, system variation existed primarily with the TVFS and flight environment, highlighting the impact of TVFS interventions. Moreover, the relatively short stay at LRMC (~3.5 days) further highlighted the TVFS impact.

Specific to Part 1, the descriptive analysis did not utilize a systematic collection of data from a well-maintained database. Rather, it employed an operational extraction of real-time data, the so-called "worksheet." This worksheet was designed to expedite TVFS decision-making and streamline the validation queue. As a result, the recorded patients were not necessarily representative of the entire deployments, but they were a cohort of high acuity patients that offered up a good snapshot of the two TVFSs' clinical practice.

Specific to Part 2, the ecological study made two assumptions: CAR being a good surrogate for aggressive TVFS prescribing within the DO_2 paradigm and postflight complications being a good surrogate for postflight clinical morbidity. Almost certainly, CARs were undercounted, as patients not prescribed a CAR flew with patients prescribed a CAR, and postflight complications were probably over-counted, as some were likely unrelated to the flight. Overall, however, the non-systematic nature of such discrepancies coupled with the large number of patients tend to minimize this limitation. Unique to ecological studies is the ecological fallacy (applying population findings wrongly to individuals). To avoid the ecologic fallacy, a study must exhibit both internal and construct validity. (**Schwartz, 1994**) In this study, internal

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validity appeared good. Construct validity, on the other hand, appeared not-as-good. (**Butler, 2016a**) Thus, while the findings might well apply to the patient population as a whole, extrapolating to individual patients could not be done.

Lastly, specific to Part 3, the dual case-control study was not a matched case-control study. Without matching, which removes potential confounding variables, outcome comparisons could be suspect. However, detailed between-group comparisons with demographic characteristics and clinical parameters strongly suggested overall group homogeneity. The only significant difference lay with injury severity. Patients prescribed a CAR appeared sicker than Non-CAR patients. Since CAR promotes a better DO_2, abrogating, to some extent, injury severity, CAR should normalize the severity between groups. Indeed, it could be argued the singular difference being injury severity strengthened, rather than weakened, the outcome comparison between groups.

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7.0 CONCLUSION

This research presents an initial look at the practice and clinical impact of two TVFSs who employed the DO_2 paradigm when making validation decisions. Described are the breadth of clinical variety and clinical severity seen in evacuated patients as well as an accounting of the many prescriptions employed by the TVFSs, the most unique being the CAR. Also appreciated is an early insight into the clearing flight surgeon versus TVFS approach to inflight patient packaging.

In addition, the population-level ecological findings suggest a significant inverse relationship between CAR prescribing and postflight complications. In other words, as the rate of CAR prescribing rose, the rate of postflight complications dropped.

Moreover, the dual case-control findings suggest that these patients were either "more severely injured" (CAR patients) or "not so severely injured" (Non-CAR patients). It appeared that the CAR prescriptions normalized the "more severely injured" outcomes to those of the "not so severely injured" and significantly improved the outcomes of the "not so severely injured."

In conclusion, it seems that the CAR, when prescribed within the framework of the DO_2 paradigm, may well have a salutary clinical impact on patients and should be considered *strongly recommended* during movement of any seriously ill/injured patient.

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9.0 ACKNOWLEDGEMENTS

This technical report contains many of the figural and tabular results found in three previously published articles. The authors have appropriately cited each figure and table. The Reference section lists the three publications. The articles are as follows:

Butler WP, Steinkraus LW, Burlingame EE, Fouts BL, Serres JL. Complication rates in altitude restricted patients following aeromedical evacuation. Aerosp Med Hum Perform. 2016a; 82(4):352-359.

Butler WP, Steinkraus LW, Fouts BL, Serres JL. A retrospective cohort analysis of battle injury versus disease, non-battle injury – two validating flight surgeons' experience. Mil Med. 2017; 182(3/4):155-161.

Butler WP, Steinkraus LW, Burlingame EE, Smith DE, Fouts BL, Serres JL, Burch DS. Clinical impact of cabin altitude restriction following aeromedical evacuation. Mil Med. 2018; 183(3/4):193-202.

Notably, this research was developed, funded, executed, and authored under the auspices of the USAF School of Aerospace Medicine. Consequent to its government origin, there are no separate copyrights associated with it.

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10.0 ABBREVIATIONS AND ACRONYMS

AE	aeromedical evacuation
ARDS	acute respiratory distress syndrome
BI	battle injury
BP	blood pressure
CAR	cabin altitude restriction
CAS	coronary artery syndrome
CASEVAC	casualty evacuation
CCATT	Critical Care Air Transport Team
C-collar	cervical collar
CI	cervical collar
D_1, D_9	interdecile range
DNBI	disease, non-battle injury
DO_2	tissue oxygen delivery
FiO_2	fraction of inspired oxygen
GSW	gunshot wound
Hgb	hemoglobin
ICD-9	International Classification of Diseases, Ninth Revision
ICU	intensive care unit
IED	improvised explosive device
ISS	Injury Severity Score
JP8	jet plane #8 fuel
LRMC	Landstuhl Regional Medical Center
M	mean
MEDEVAC	medical evacuation
MRI	magnetic resonance imagery

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MVA motor vehicle accident

OWL™ overweight litter

$PaCO_2$ arterial carbon dioxide pressure

PaO_2 arterial oxygen partial pressure

PEEP positive end expiratory pressure

PFC rate of patients with postflight complications

PFC-100 postflight complications per 100 patients

PMR Patient Movement Request

Q_1, Q_2 interquartile range

RON remain overnight

SD standard deviation

SE standard error

SpO_2 peripheral arterial oxygen saturation (pulse oximetry)

TBI traumatic brain injury

$TRAC^2ES$ Transportation Command Regulating and Command and Control Evacuation System

TRANSCOM Transportation Command

TVFS theater validating flight surgeon

Vol % volume percent

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