AFRL-RH-WP-TR-2020-0002

Employing Tissue Oxygen Delivery Calculations to Predict Aeromedical Evacuation Patient Outcomes --- A Pilot Study

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January 2020

Final Report
for March 2014 to June 2019

Air Force Research Laboratory
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From – To)*
08-01-2020	Technical Report	March 2014 – June 2019

4. TITLE AND SUBTITLE
Employing Tissue Oxygen Delivery Calculations to Predict Aeromedical Evacuation Patient Outcomes --- A Pilot Study

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N/A

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
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Susan Connor, PhD, RN; Jennifer Serres, PhD;
Susan Dukes, PhD, RN (Col, USAF, NC); David Burch, PhD

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-2020-0002

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 PA 88ABW-2020-0706, 9 Mar 20

14. ABSTRACT

In late 2006/early 2007, the notion of tissue oxygen delivery (DO_2) was introduced into the aeromedical evacuation (AE) arena. This so-called DO_2 paradigm offered up a coherent approach for Theater Validating Flight Surgeons (TVFS) prescribing supplemental oxygen, transfusions, and cabin altitude restriction (CAR). Research into CAR suggested superior postflight outcomes, which, in turn, suggested that "good" DO_2 (> 7.3 ml O_2/kg/min) might be a contributing factor. Using data obtained from a retrospective case-control study where a random sample of 50 CAR patients were matched with 50 Non-CAR patients, the DO_2-GUI calculated DO_2. Independent variables were DO_2 and CAR status with postflight procedures, the dependent variable. While the case-control study demonstrated that CAR was associated with significantly fewer postflight procedures, this pilot study likewise found that "good" DO_2 was associated with significantly fewer postflight procedures ($p = 0.002$). Additionally, DO_2 and the number of postflight procedures exhibited a significant dose-response, inverse relationship ($p = 0.045$). As DO_2 rose, the number of postflight procedures fell. Lastly, tests of the DO_2-GUI construct suggested it a valid DO_2 calculator. In summary, this pilot study is a first look at DO_2 and the DO_2 calculator (DO_2-GUI). It suggested that "good" DO_2 had a salutary impact on postflight patient morbidity. It also suggested the DO_2-GUI a valid means for calculating DO_2. Further research looking at both DO_2 and the DO_2-GUI is justified.

15. SUBJECT TERMS
aeromedical evacuation, AE, cabin altitude restriction, CAR, theater validating flight surgeon, TVFS, patient morbidity, tissue oxygen delivery, DO_2, critical DO_2, DO_2crit, DO_2-GUI, fit to fly

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			William P Butler
U	U	U	SAR	42	19b. TELEPHONE NUMBER *(include area code)* 804-909-1803

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1.0 EXECUTIVE SUMMARY

The United States military has seen a gradual drop in wound lethality over the years until, today, it is at its lowest ever. Air Force aeromedical evacuation (AE) has had no small part in this historic era. Its speed and agility as well as its Critical Care Air Transport Teams (CCATTs) have contributed mightily, not to mention the Theater Validating Flight Surgeons (TVFS).

Over the past decades, there have been thousands of AE missions and, literally, tens of thousands of patients transported, with each patient having been cleared for flight, or validated, by the TVFS. To optimize patient resiliency while at altitude, the TVFS prescribes for both the patient and the aircraft. Patient prescriptions include such interventions as supplemental oxygen, head-first loading, and assignment of CCATT teams, while aircraft prescriptions include long slow landings, limiting of overnight stops, and cabin altitude restriction (CAR). (**Butler, 2017a**)

To examine the clinical and operational implications of the CAR, Fouts et al merged patient records from four different databases. From the U.S. Transportation Command Regulating and Command and Control Evacuation System (TRAC^{2}ES) database, 1,207 CAR patients were identified and 50 patients with relatively complete records were randomly selected. These 50 CAR patients were matched with 50 Non-CAR patients by injury using ICD-9 codes and, to some extent, aircraft. All patients were CCATT accompanied and all Non-CAR patients were confirmed to have flown without a CAR. (**Fouts, 2017**)

Overall, these patients were young, mostly Army service members, and, for the most part, suffering orthopedic trauma caused by improvised explosive devices (IEDs). In addition, most were flown on C-17s under the Priority precedence. Excepting a few differences --- preflight surgeries, preflight blood product use, systolic blood pressure, 24-hour fluid intake, and initial

hemoglobin --- the CAR and Non-CAR groups were comparable suggesting that any differences in clinical or operational outcomes might well relate to the CAR prescription.

Looking at the clinical outcomes between groups, no difference was detected in length of stay, days in the ICU, postflight transfusions, or discharge status. However, a significantly fewer number of major and minor postflight procedures was found with the CAR patients ($p = 0.032$). (**Fouts, 2017**)

These results suggested that the AE flight may pose a "second hit" risk to patients' initial "first hit" injury. (**Goodman, 2010**) This was most likely due to the hypoxia, vibration, and hypobaria encountered during the AE flight, creating a milieu where reduced oxygen availability and increased intercapillary distance favor impaired oxygen diffusion with a concomitant drop in tissue oxygen delivery (DO_2). (**Butler, 2020**) And, any drop in DO_2 can set up the AE patient for such a "second hit." The result --- added morbidity.

In late 2006/early 2007, first Pollan et al and then Butler recognized the importance of DO_2 in the AE patient. (**Pollan, 2006; Butler, 2007**) Furthermore, two of the authors (WPB and LWS) began calculating DO_2 to better prescribe supplemental oxygen, transfusions, and CAR. In this way, they optimized patient DO_2.

By hand, these calculations proved challenging. Tables, though unwieldy and not-too-user-friendly, proved easier. (**Pollan, 2006; Butler, 2007**) Later, an Excel spreadsheet graphic user interface (DO_2-GUI) was developed by Egerstrom with Cole and Butler (unpublished, 2009). (**Butler, 2016b; Butler, 2017b**) This tool proved much more practical.

By bringing DO_2 calculations into the validation process, the so-called DO_2 paradigm sought to optimize clinical status while, at the same time, minimizing postflight morbidity.

Indeed, studies focused on CAR, the most visible TVFS prescription affecting DO_2, suggest just that. (**Henry, 1973; Butler, 2016a; Fouts, 2017; Butler, 2018; Butler, 2020**)

This effort, a pilot study, investigated DO_2 and tested the utility of the DO_2-GUI. The DO_2-GUI calculated DO_2 in individual patients and that value, when applied within the DO_2 paradigm, coupled with a critical DO_2 (DO_{2crit}) cut-point of < 7.3 ml O_2/kg/min offered critical validation information to the TVFS. If below the DO_{2crit} cut-point, the TVFS prescribed supplemental oxygen, transfusions, and/or CAR, bringing the predicted DO_2 above the DO_{2crit} cut-point. Once in the "good" DO_2 range, patients were expected to have less morbidity postflight. In fact, "good" DO_2 patients suffered significantly fewer postflight procedures than those patients with "bad" DO_2, on average almost two fewer procedures ("bad" = 7.42; "good" = 5.73; $p = 0.002$). Moreover, despite the limitation of a data ceiling for postflight procedures, DO_2 levels demonstrated a significant inverse dose-response relationship with postflight procedures ($R = - 0.18$, $p = 0.045$). As the DO_2 rose, the number of postflight procedures fell.

At the same time, the DO_2-GUI proved internally consistent with highly significant correlations between 1) DO_2 calculated with and without arterial blood gases (ABGs) ($R = 0.98$, $p < 0.0001$), 2) predicted and actual inflight DO_2 ($R = 0.98$, $p < 0.0001$), and 3) PaO_2/FiO_2 ratio and calculated A-a gradient ($R = - 0.59$, $p < 0.0001$).

These results suggest that the DO_2 paradigm not be limited to CAR prescribing. Rather, they suggest a more general application aimed at the well-being and validation of the AE patient. These results also support the utility of the DO_2-GUI. Lastly, these results justify further investigations into DO_2 and the DO_2-GUI.

2.0 INTRODUCTION

Over the past decade plus, the medical care of military casualties has been consistently remarkable, recording some of the lowest lethality rates in US history. (**Gawande, 2004**) One of the reasons for this stunning record is the agility of AE. (**Hurd, 2006; Butler, 2016a**)

Patients undergo both administrative and clinical clearance (aka validation) in order to appear on a flight's manifest. The TVFS executes the clinical validation, ensuring that the patient is "fit to fly." (**Hurd, 2006; Butler, 2017a**) To accomplish this, the TVFS employs both patient (e.g., supplemental oxygen) and aircraft prescriptions (e.g., long slow landing).

The CAR, an aircraft prescription, is nearly specific to the province of the TVFS. Traditional indications include penetrating eye injuries with intraocular air, free air in any body cavity, decompression sickness/air gas embolism, and severe pulmonary disease. (**Borden Institute, 2004**) Recent practice and recent research strongly suggest an additional indication for CAR: enhancement of DO_2. (**Butler, 2016a; Butler, 2016b; Butler, 2017b; Fouts, 2017; Butler, 2018; Butler, 2020**)

In order to consider DO_2, the TVFS had to calculate it. Although not difficult, it was time consuming and not practical for each patient. As a result, DO_2 tables and eventually the DO_2-GUI were created. (**Pollan, 2006; Butler, 2007; Butler, 2016b; Butler, 2017b**) The empiric use of calculated DO_2 proved useful in prescribing supplemental oxygen, transfusion, and CAR. (**Butler, 2018; Butler, 2020**)

While prescribing patients supplemental oxygen and transfusions is relatively straightforward for the TVFS, not so prescribing an aircraft CAR. Conventional wisdom suggested that CAR was costly in flight time and extra fuel costs. Consequently, there was

organizational resistance to liberal CAR prescribing, particularly if the CAR did not offer clear benefit to the patient. (**Butler, 2016a; Butler, 2016b; Fouts, 2017**)

This prompted a matched case-control study investigating the clinical outcomes of patients flown with and without a CAR. The findings suggested that CAR patients underwent significantly fewer major and minor postflight procedures than Non-CAR patients ($p = 0.032$). (**Fouts, 2017**) It appeared that the CAR might well offer patient benefit and it appeared that TVFS decision-making using DO_2, the so-called DO_2 paradigm, might well offer a systematic approach to prescribing CAR. Studies examining the impact of CAR, specifically prescribed within the DO_2 paradigm, affirmed this notion. (**Butler, 2016a; Butler, 2018; Butler, 2020**) However, to date, the direct clinical impact of DO_2 itself remains unstudied.

The goal of this pilot study was to calculate DO_2 within an extant dataset, the previously mentioned matched case-control study dataset (**Fouts, 2017**), and test whether patients with a "good" DO_2 fared better than patients with a "bad" DO_2.

3.0 BACKGROUND

During flight, the healthy human experiences physiological stressors that routinely affect performance and safety. (**McFarland, 1959**) These stressors include acceleration/deceleration forces, reduced ambient humidity, thermal instability (both hypothermia and hyperthermia), noise, hypoxia, vibration, and hypobaria. Likewise, during AE, the ill or injured human (aka patient) faces these same stressors. In the patient, however, these stressors potentially effect a "second hit." The first hit being the initial injury/illness, the second being an added physiological insult. (**Goodman, 2010**) This second hit most likely comes from the hypoxia, hypobaria, and, to some extent, the vibration associated with an AE flight. (**Butler, 2020**)

At standard military cabin altitudes of 8,000-10,000 feet, the ground equivalent oxygen fraction of inspired air (FiO_2) is around 16%, an almost 25% drop from normal. (**Borden Institute, 2004**) A concomitant fall in arterial oxygen partial pressure (PaO_2), often into the 50-60 mmHg range, accompanies this drop. (**Henry, 1973**)

Conjoined to this reduced oxygen availability is an increase in intercapillary distance associated with tissue edema. Depending on the extent of tissue injury, both localized and generalized edema may follow. (**Hunt, 1988; Barillo, 2003**) In addition, vibration itself may directly provoke tissue edema. (**Lundborg, 1987; Mittermayr, 2003**) At the same time, hypobaria may well affect the Starling equilibrium in favor of intravascular fluid movement into the extravascular interstitium. (**Shuster, 1996a; Shuster, 1996b; Mittermayr, 2003; Butler, 2016a; Butler, 2020**) A number of potential mechanisms have been highlighted: upregulation of histamine and bradykinin (**Richalet, 1995; Constanzo, 2010**), inflammatory upregulation (**Goodman, 2011; Skovira, 2016**), bubble evolution/infusion (**Richalet, 1995; Roach, 1995;**

Butler, 2016a), ischemia-reperfusion phenomenon (**Carden, 2000**), and altitude itself (**Hackett, 2011; Luks, 2015**). Butler et al offers a recent more detailed review. (**Butler, 2020**)

This increased intercapillary distance and reduced capillary oxygen create a milieu rife with potential for impaired oxygen diffusion. The overall result being a drop in DO_2. Indeed, adequate DO_2 is critical to the health and well-being of any patient, especially the critically ill/injured. Without adequate DO_2, healthy tissues can fail and compromised tissues can fail even more quickly and more extensively, even to the point of patient morbidity and mortality. (**Butler, 2016a; Fouts, 2017; Butler, 2018; Butler, 2020**)

In late 2006/early 2007, the notion of DO_2 expanded from the intensive care unit (ICU) into both the pre-hospital care and AE of casualties. (**Grissom, 2006; Pollan, 2006; Butler, 2007**) It was recognized that AE had fully transitioned from moving only stable patients to the frequent movement of the clinically volatile "stabilized" patients. The TVFS, whose job it is to warrant that a patient is "fit to fly," began to incorporate DO_2 into the decision-making process. To do so, the TVFS considered a number of factors --- FiO_2, hemoglobin level, hemoglobin saturation, plasma oxygen content, and cardiac output. (**Contanzo, 2014**) Factors easily manipulated by the TVFS were FiO_2, hemoglobin level, and altitude --- prescribing supplemental oxygen, transfusion, and CAR, respectively.

To ensure adequate, or "good," DO_2, the TVFS must manipulate these three factors to exceed 7.3 ml O_2/kg/min, below which lies the DO_{2crit} for the healthy human. (**Lieberman, 2000**) Initially, TVFSs calculated DO_2 manually on each individual patient, but this quickly became impractical. As a result, first Pollan et al and then Butler created DO_2 reference tables. (**Pollan, 2006; Butler, 2007**) Unfortunately, these tables were limited and not altogether user-friendly. See **Figure 1**.

Figure 1. The Late 2006/Early 2007 DO_2 Tables

A. Solitary DO_2 Table Created by Pollan & Fisher
B. One of Several DO_2 Tables Created by Butler

Effects of Anemia					**A.**
% O2 Delivered	Altitude (Ft)	Hb Level (g/dL)	CaO2	DO2/kg if Cardiac Output = 5.5 (normal) in 80 kg	DO2 (if Cardiac = 4.5 (impaired))/kg in 80 kg man
21%	1	2	2.97	2.04	1.67
21%	1	4	5.62	3.86	3.16
21%	1	6	8.27	5.69	4.65
21%	1	8	10.93	7.51	6.15
21%	1	10	13.58	9.34	7.64
21%	1	12	16.23	11.16	9.13
21%	1	14	18.89	12.99	10.62
50%	1	2	4	2.48	2.03
50%	1	4	6	4.31	3.52
50%	1	6	9	6.13	5.02
50%	1	8	11.43	7.86	6.43
50%	1	10	14.22	9.78	8.00
50%	1	12	16.88	11.60	9.49
50%	1	14	19.53	13.43	10.98
100%	1	2	5	3.24	2.65
100%	1	4	7	5.07	4.14
100%	1	6	10	6.89	5.64
100%	1	8	12.39	8.52	6.97
100%	1	10	15.33	10.54	8.62
100%	1	12	17.98	12.36	10.11
100%	1	14	20.63	14.19	11.61
21%	8000	2	2.56	1.76	1.44
21%	8000	4	4.91	3.38	2.76
21%	8000	6	7.27	5.00	4.09
21%	8000	8	9.63	6.62	5.42
21%	8000	10	11.99	8.24	6.74
21%	8000	12	14.35	9.86	8.07
21%	8000	14	16.71	11.48	9.40
50%	8000	2	3.33	2.29	1.87
50%	8000	4	5.98	4.11	3.36
50%	8000	6	8.63	5.94	4.86
50%	8000	8	11.29	7.76	6.35
50%	8000	10	13.94	9.58	7.84
50%	8000	12	16.59	11.41	9.33
50%	8000	14	19.25	13.23	10.83
100%	8000	2	4.15	2.85	2.33
100%	8000	4	6.80	4.68	3.83
100%	8000	6	9.46	6.50	5.32
100%	8000	8	12.11	8.32	6.81
100%	8000	10	14.76	10.15	8.30
100%	8000	12	17.42	11.97	9.80
100%	8000	14	20.07	13.80	11.29

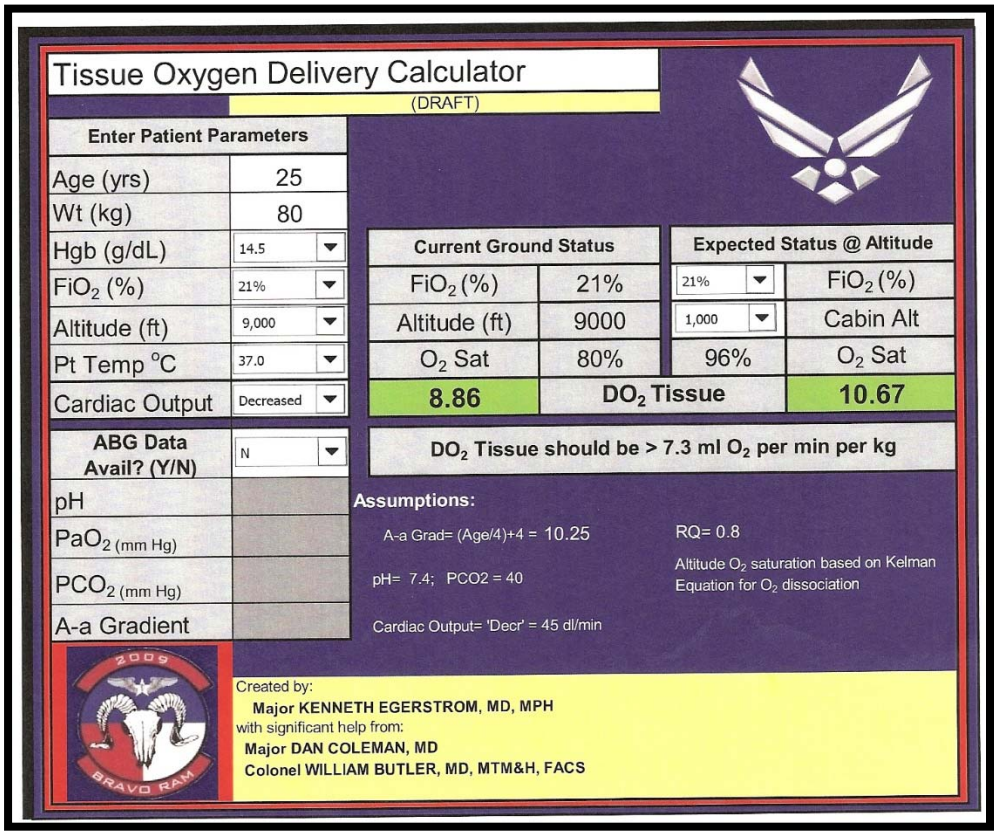
(Pollan, 2006)

Effects of Lowered Hemoglobin on Tissue Oxygen Delivery											
B. Hgb (g/dl)	% O2 Delivered	Altitude (Ft)	Atmospheric Pressure (mmHg)	Moist (37C) O2 (mmHg)	RQ	Alveolar O2 (mmHg) w/ typical PCO2 40 mmHg	Arterial O2 (mmHg) w/ A-a = 8	O2 %Sat (from dissociation curve)	CaO2	DO2 w/ nl CO	DO2 w/ abn CO
7.0	21%	0	760	150	0.85	103	95	0.98	9.5	6.5	5.3
7.0	21%	1000	733	144	0.85	97	89	0.97	9.4	6.4	5.3
7.0	21%	2000	707	139	0.86	92	84	0.96	9.3	6.4	5.2
7.0	21%	3000	681	133	0.86	87	79	0.95	9.2	6.3	5.1
7.0	21%	4000	656	128	0.87	82	74	0.95	9.1	6.3	5.1
7.0	21%	5000	633	123	0.87	77	69	0.93	8.9	6.1	5.0
7.0	21%	6000	609	118	0.88	73	65	0.91	8.7	6.0	4.9
7.0	21%	7000	587	113	0.88	68	60	0.90	8.6	5.9	4.9
7.0	21%	8000	565	109	0.89	64	56	0.86	8.2	5.7	4.6
7.0	21%	9000	543	104	0.89	59	51	0.83	7.9	5.5	4.5
7.0	21%	10000	522	100	0.90	55	47	0.79	7.6	5.2	4.3
7.0	**50%**	**0**	**760**	**357**	0.85	**309**	**301**	**0.99**	**10.2**	**7.0**	**5.7**
7.0	**50%**	**1000**	**733**	**343**	0.85	**296**	**288**	**0.99**	**10.2**	**7.0**	**5.7**
7.0	**50%**	**2000**	**707**	**330**	0.86	**283**	**275**	**0.99**	**10.1**	**7.0**	**5.7**
7.0	**50%**	**3000**	**681**	**317**	0.86	**270**	**262**	**0.99**	**10.1**	**6.9**	**5.7**
7.0	**50%**	**4000**	**656**	**305**	0.87	**259**	**251**	**0.99**	**10.1**	**6.9**	**5.7**
7.0	**50%**	**5000**	**633**	**293**	0.87	**247**	**239**	**0.99**	**10.0**	**6.9**	**5.6**
7.0	**50%**	**6000**	**609**	**281**	0.88	**236**	**228**	**0.99**	**10.0**	**6.9**	**5.6**
7.0	**50%**	**7000**	**587**	**270**	0.88	**225**	**217**	**0.99**	**10.0**	**6.8**	**5.6**
7.0	**50%**	**8000**	**565**	**259**	0.89	**214**	**206**	**0.99**	**9.9**	**6.8**	**5.6**
7.0	50%	9000	543	248	0.89	203	195	0.99	9.9	6.8	5.6
7.0	50%	10000	522	238	0.90	193	185	0.99	9.9	6.8	5.5
7.0	100%	0	760	713	0.85	666	658	0.99	11.3	7.8	6.4
7.0	100%	1000	733	686	0.85	639	631	0.99	11.2	7.7	6.3
7.0	100%	2000	707	660	0.86	613	605	0.99	11.2	7.7	6.3
7.0	100%	3000	681	634	0.86	587	579	0.99	11.1	7.6	6.2
7.0	100%	4000	656	609	0.87	563	555	0.99	11.0	7.6	6.2
7.0	100%	5000	633	586	0.87	540	532	0.99	10.9	7.5	6.2
7.0	100%	6000	609	562	0.88	517	509	0.99	10.9	7.5	6.1
7.0	100%	7000	587	540	0.88	495	487	0.99	10.8	7.4	6.1
7.0	100%	8000	565	518	0.89	473	465	0.99	10.7	7.4	6.0
7.0	100%	9000	543	496	0.89	451	443	0.99	10.7	7.3	6.0
7.0	100%	10000	522	475	0.90	431	423	0.99	10.6	7.3	6.0

(Butler, 2007)

Consequently, the DO_2-GUI was developed by Egerstrom with Cole and Butler (unpublished, 2009). (**Butler, 2016b; Butler, 2017b**). See **Figure 2**. The DO_2-GUI employed standard physiological equations --- alveolar gas equation, arterial oxygen content equation, and the DO_2 equation --- along with Kelman's oxyhemoglobin-dissociation-curve model (adjusted for temperature and pH). (**Kelman, 1966; Contanzo, 2014**) See the **Methods** section for the equation specifics. This DO_2-GUI simplified the calculations and TVFSs employed it as needed.

Figure 2. The DO_2-GUI



(**Egerstrom with Cole and Butler, 2009, unpublished; Butler, 2016b; Butler, 2017b**)

This research effort is a pilot study designed to test the efficacy of the DO_2 paradigm and the utility of the DO_2-GUI for TVFS validation of AE patients. Data for this study came from a retrospective matched case-control study that examined clinical outcomes in patients prescribed a CAR. (**Fouts, 2017**) Calculations of DO_2 employing the DO_2-GUI were the bases for the analyses reported here.

4.0 METHODS

4.1 Institutional Review

The Air Force Research Laboratory Institutional Review Board approved this pilot study (FWR20140077H) as part of a multi-phased research effort conducted entirely at the United States Air Force School of Aerospace Medicine at Wright-Patterson Air Force Base in Dayton, Ohio.

The overall goal was to compare post-flight clinical outcomes in aeromedically evacuated service members who were prescribed a CAR to those who were not. Phase I looked at clinical outcomes, Phase II explored inflight patient events as reported in the Patient Movement Quality event reports (PMQR), and Phase III examined mission cost parameters. (**Fouts, 2017**) Specific to this report, Phase IV, the DO_2 pilot study, performed DO_2 calculations, employing the DO_2-GUI, and compared the number of postflight procedures observed in patients with "good" DO_2 versus the number with "bad" DO_2.

4.2 Methodology

Patients flown on AE missions between 2007 and 2013 were studied using a retrospective matched case-control records review methodology. The TRAC^{2}ES database, which tracks regulated patient movement throughout the AE system and contains pertinent clinical history as well as information recorded by the TVFS specific to the patient's inflight needs, was used to identify patients who were transported with a CAR. Out of a total of 1,207 CAR patients found within the TRAC^{2}ES database, 50 patients with relatively complete records were randomly selected. No record was missing more than 1% of its data fields and those records missing data fields were a heterogeneous mix (greatly reducing the chance for error bias). These 50 CAR patients were then matched with 50 Non-CAR patients by injury using ICD-9 codes and, to some

extent, aircraft. All patients were CCATT accompanied and all Non-CAR patients were confirmed to have flown without a CAR. (**Fouts, 2017**)

Patients identified in the TRAC^{2}ES system as CAR (cases) and Non-CAR (controls) subjects were cross-referenced with records from three clinical databases (Theater Medical Data System [TMDS], Department of Defense Trauma Registry [DoDTR], Military Health System Data Mart [M2]) in order to access in-flight and in-theater medical care data. Preflight, inflight, and postflight variables were collected. Postflight outcome metrics --- intensive care unit (ICU) days, ventilator days, hospitalization days, discharge status, postflight transfusions, and postflight procedures --- were considered valid if they occurred before the patient departed Landstuhl Regional Medical Center (LRMC) or within 7 days post-flight, whichever was shorter. Of the outcome variables, only postflight procedures demonstrated a statistically significant difference, that being fewer major and minor postflight procedures in CAR patients vis a vis Non-CAR patients. (**Fouts, 2017**)

To understand better the contribution of CAR to the number of postflight procedures, outcome data underwent regression analyses employing the conditional inference tree methodology. (**Hothorn, 2006**) Independent variable rank importance was then determined with the conditional random forest methodology. (**Hapfelmeier, 2012**) CAR was the sixth most influential variable.

Because of these findings, the DO_2 pilot study limited its outcome, or dependent variable, to postflight procedures. Independent variables, as calculated by the DO_2-GUI, were preflight, inflight, and postflight DO_2. The DO_2-GUI calculated DO_2 employing four well-accepted physiological equations --- the alveolar gas equation, the blood oxygen content equation, the tissue oxygen delivery equation, and Kelman's oxygen dissociation curve model (equation) ---

with or without ABG values. All reported DO_2 calculations utilized ABGs. The DO_2-GUI equations are as follows:

Alveolar Gas Equation (**Constanzo, 2014**) →

$$P_AO_2 = [(P_B - P_{H2O}) * FiO_2] - PaCO_2/RQ$$

Arterial Oxygen Content Equation (**Constanzo, 2014**) →

$$CaO_2 = (SaO_2 * HgbCC * Hgb) + (0.0031 * PaO_2)$$

Tissue Oxygen Delivery Equation (**Constanzo, 2014**) →

$$DO_2 = (CaO_2 * CO)/Wt$$

Kelman's Oxygen Dissociation Curve Model (equation) (**Kelman, 1966**) →

$$SaO_2 = [100 * (a_1x + a_2x^2 + a_3x^3 + x^4)] / (a_4 + a_5x + a_6x^2 + a_7x^3 + x^4)$$

Note: See **Appendix B** for equation specifics.

These equations were incorporated into an Excel (Microsoft Office Suite) spreadsheet coupled to a graphic user interface, the DO_2-GUI, to facilitate data entry and calculation. Adjustments for body temperature and pH were made as well as certain assumptions (bicarbonate renal compensation and 100% humidified respired air). The alveolar-arterial gradient (A-a gradient), when not calculated with patient ABGs, was assumed to be A-a gradient = (age/4) + 4 (mmHg). (**Petersson, 2014**)

Once the DO_2-GUI calculated the DO_2, the number of postflight procedures in patients with "good" DO_2 was compared against the number in those with "bad" DO_2. Tissue oxygen delivery was considered "good" if > 7.3 ml O_2/kg/min and "bad" if < 7.3 ml O_2/kg/min. (**Leiberman, 2000**) Since several studies suggested that very ill patients might have a higher DO_{2crit}, testing was also performed with "good" DO_2 valued at > 8.0 ml O_2/kg/min. (**Shibutani, 1983; Komatsu, 1987; Ronco, 1993**) Lastly, a dose-response effect was sought testing DO_2 against the number of postflight procedures.

Construct validation was then examined looking at DO_2 with and without ABGs along with predicted versus actual inflight DO_2. In addition, pulmonary status using the PaO_2/FiO_2 pulmonary shunt ratio was checked against the DO_2-GUI's calculated-with-ABG A-a gradient.

Continuous variables were described by mean (standard deviation) while categorical variables, number (percent). Comparison between groups used t-tests, Mann-Whitney U-tests, and Chi-square tests as appropriate. Dose-response effect was tested with Pearson correlation and linear regression. *Construct validation* employed both the Pearson correlation and linear regression. Analyses underwent *post hoc* power calculations where sample size deemed appropriate. Statistical significance was set *a priori* at $p < 0.05$. Throughout the study, data were cleaned, merged, and analyzed using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp).

5.0 RESULTS

5.1 *Preflight and Inflight Characteristics*

The prototypic patient in this sample of 100 patients was an Army male, around 25 years old, suffering orthopedic trauma from an IED. This prototypic patient was usually evacuated Priority precedence aboard a C-17. Three different airframes predominated: C-130 (Urgent 15, Priority-19, Routine-0), C-17 (Urgent-25, Priority-31, Routine-1), and KC-135 (Urgent-3, Priority-6, Routine-0). The homogeneity between CAR and Non-CAR groups reflected the matched nature of the data. See **Table A1** for further details.

Pre-flight characteristics between groups were also very similar. Time from injury to flight, Injury Severity Score (ISS), number of patients either transfused or massively transfused were not significantly different between groups. Indeed, the ISS exceeded 25 (critical) in both groups, substantiating CCATT assignment to all the patients. (**Baker, 1974**) Of note, there were a higher number of preflight procedures and preflight blood products in the Non-CAR group, suggesting perhaps a sicker Non-CAR group. See **Table A2** for further details.

Inflight physiological characteristics similarly demonstrated between group homogeneity. The only parameters proved statistically different were a lower systolic blood pressure and a higher 24-hour fluid intake in the CAR group, suggesting perhaps a sicker CAR group. Despite CAR patients having a higher initial hemoglobin, there was no difference in the final hemoglobin and no difference in inflight transfusion characteristics between CAR and Non-CAR groups. In addition, there was no significant difference in S_pO_2/F_iO_2 (< 300, acute lung injury) ratios, again substantiating CCATT assignment to all the patients. (**Rice, 2007**) Of note, altitude restrictions on CAR missions ranged from 2,500 to 6,000 feet above sea level (M = 4,696 feet, *SD* = 669 feet). See **Table A3** for further details.

In-depth discussion of all these findings can be found in an earlier report. (**Fouts, 2017**)

5.2 *Postflight Patient Outcomes*

Length of stay, number of ICU days, postflight transfusions, and discharge status proved not statistically different between groups; however, there was a significant difference in the number of postflight procedures performed at the debarkation site. Those transported with a CAR had significantly fewer major and minor postflight procedures compared to those transported without a CAR. See **Table A4** for further details.

Regression analysis using the conditional inference tree methodology examined the influence of variables on the number of postflight procedures. Since the mean hospital stay for both groups was 3.7 days, time indexing was not employed. Thirteen independent variables were selected --- type of injury, location of injury, flight precedence, ISS, number of preflight surgeries, injury-to-flight time, flight duration, systolic blood pressure, ventilated or not, SpO_2/FiO_2 initial ratio (Ratio 1), SpO_2/FiO_2 final ratio (Ratio 2), 24-hour fluid intake, Hgb initial (Hgb 1), Hgb final (Hgb 2), and CAR. The covariate showing the greatest influence over the number of postflight procedures was whether a patient was ventilated or not ($p = 0.036$). With conditional inference trees, not every independent variable necessarily appears in the model, so it is often valuable to rank the variables in terms of their importance. The conditional random forest method was employed to rank the 13 independent variables' strength of association with the number of postflight procedures. The variable with the highest association was whether or not the patient was ventilated. The second and third variables of most import were the two SpO_2/FiO_2 ratios and ISS. CAR was the sixth most influential variable. See **Figure A1**.

In-depth discussion of all these findings can be found in an earlier report. (**Fouts, 2017**)

5.3 *Tissue Oxygen Delivery (DO_2) Analyses*

The distribution of "good" DO_2 versus "bad" DO_2 patients was not significantly different whether flying with or without a CAR, though the number of "good" DO_2 patients consistently trended higher in the CAR group. At the same time, patients with "good" DO_2 dominated both the CAR and Non-CAR groups.

"Good" DO_2 patients (preflight, inflight, and postflight) demonstrated no difference in the number of postflight procedures whether CAR or Non-CAR, though the CAR group consistently trended lower numbers. Likewise, "bad" DO_2 patients (preflight, inflight, and postflight) demonstrated no difference in number of postflight procedures whether CAR or Non-CAR; however, here, the trend was not as consistent. Interestingly, independent of CAR status, the "good" DO_2 patients appeared to have fewer postflight procedures.

Post hoc power evaluation demonstrated underpowered analyses, suggesting that a larger study would be required to detect significant differences. See **Table 1** for further details.

Table 1. Calculated Tissue Oxygen Delivery (DO_2) Metrics

Variable	CAR	Non-CAR	*p-value*	*Power*
Preflight DO_2 (ml O_2/kg/min)				
Bad DO_2 < 7.3 ml O_2/kg/min	4 (15%)	8 (26%)		
Good DO_2 > 7.3 ml O_2/kg/ml	23 (85%)	23 (74%)	0.480[a]	17%
	n = 27	n = 31		
Inflight DO_2 (ml O_2/kg/min)				
Bad DO_2 < 7.3 ml O_2/kg/min	2 (17%)	12 (40%)		
Good DO_2 > 7.3 ml O_2/kg/ml	10 (83%)	18 (60%)	0.147[a]	30%
	n = 12	n = 30		
Postflight DO_2 (ml O_2/kg/min)				
Bad DO_2 < 7.3 ml O_2/kg/min	3 (30%)	7 (41%)		
Good DO_2 > 7.3 ml O_2/kg/ml	7 (70%)	10 (59%)	0.561[a]	8%
	n = 10	n = 17		
Bad DO_2 Postflight Procedures, Mean (*SD*)				
Preflight	6.75 (2.50)	8.00 (0.00)	0.166[b]	17%
Inflight	8.00 (0.00)	7.17 (1.99)	0.578[b]	30%
Postflight	8.00 (0.00)	6.86 (2.27)	0.424[b]	26%
Good DO_2 Postflight Procedures, Mean (*SD*)				
Preflight	5.22 (2.59)	6.26 (1.55)	0.163[b]	38%
Inflight	4.70 (3.02)	6.28 (2.45)	0.144[b]	29%
Postflight	5.14 (2.85)	7.30 (1.64)	0.066[b]	44%

Note: [a]Values calculated using Chi-square test. [b]Values calculated using independent samples t-test. Mann-Whitney U not applicable for variables with less than five values. *Denotes statistical significance (bold). Percentages may not add up to 100% due to rounding.

When specifically examined, "good" DO_2 patients consistently underwent fewer postflight procedures. In fact, preflight, "good" DO_2 patients had significantly fewer postflight procedures (effect size: Hedges' g = 0.78, large effect) while, inflight, "good" DO_2 patients closely approached significance. These findings marked "bad" DO_2 at the healthy male DO_{2crit} described by Lieberman et al, that is < 7.3 ml O_2/kg/min. (**Lieberman, 2000**)

In contrast, taking the "bad" DO_2 at an estimated DO_{2crit} < 8.0 ml O_2/kg/min, as derived from several DO_2 studies of the very sick (**Shibutani, 1983; Komatsu, 1987; Ronco, 1993**), patients with "good" DO_2, preflight and inflight, fared better with significantly fewer postflight procedures (preflight effect size: Hedges' g = 0.62, high medium effect; inflight effect size: Hedges' g = 0.79, large effect).

When combining the two phases of AE flight within the purview of the TVFS, preflight and inflight, "good" DO_2 patients suffered significantly fewer postflight procedures than the "bad" DO_2 patients ($DO_{2crit} < 7.3$ effect size: Hedges' $g = 0.71$, large effect; $DO_{2crit} < 8.0$ effect size: Hedges' $g = 0.64$, high medium effect). At the same time, the two DO_{2crit} cut-points demonstrated no postflight procedure difference.

Postflight, at either DO_{2crit}, no difference was seen in the number of postflight procedures. See **Table 2** for further details.

Table 2. "Bad" and "Good" DO_2 as Relates to AE Flight Status and Postflight Procedures

AE Flight Status	Number of Postflight Procedures with Bad DO_2, M (SD)	Number of Postflight Procedures with Good DO_2, M (SD)	*p-value*	*Power*
**** Good DO_2 > 7.3 ml O_2/kg/min & Bad DO_2 < 7.3 ml O_2/kg/min ****				
Preflight	7.58 (1.44) n = 12	5.74 (2.52) n = 46	**0.019***	91%
Inflight	7.29 (1.86) n = 14	5.71 (2.39) n = 28	0.059	65%
Postflight	7.20 (1.93) n = 10	6.41 (2.40) n = 17	0.386	15%
TVFS Impact (Preflight & Inflight)	7.42 (1.65) n = 26	5.73 (2.58) n = 74	**0.002***	97%
**** Good DO_2 > 8.0 ml O_2/kg/min & Bad DO_2 < 8.0 ml O_2/kg/min ****				
Preflight	7.11 (1.82) n = 19	5.64 (2.59) n = 39	**0.031***	71%
Inflight DO_2	7.05 (2.06) n = 22	5.35 (2.31) n = 20	**0.030***	71%
Postflight	7.23 (1.74) n = 13	6.21 (2.58) n = 14	0.245	23%
TVFS Impact (Preflight & Inflight)	7.07 (1.93) n = 41	5.54 (2.64) n = 59	**0.002***	92%

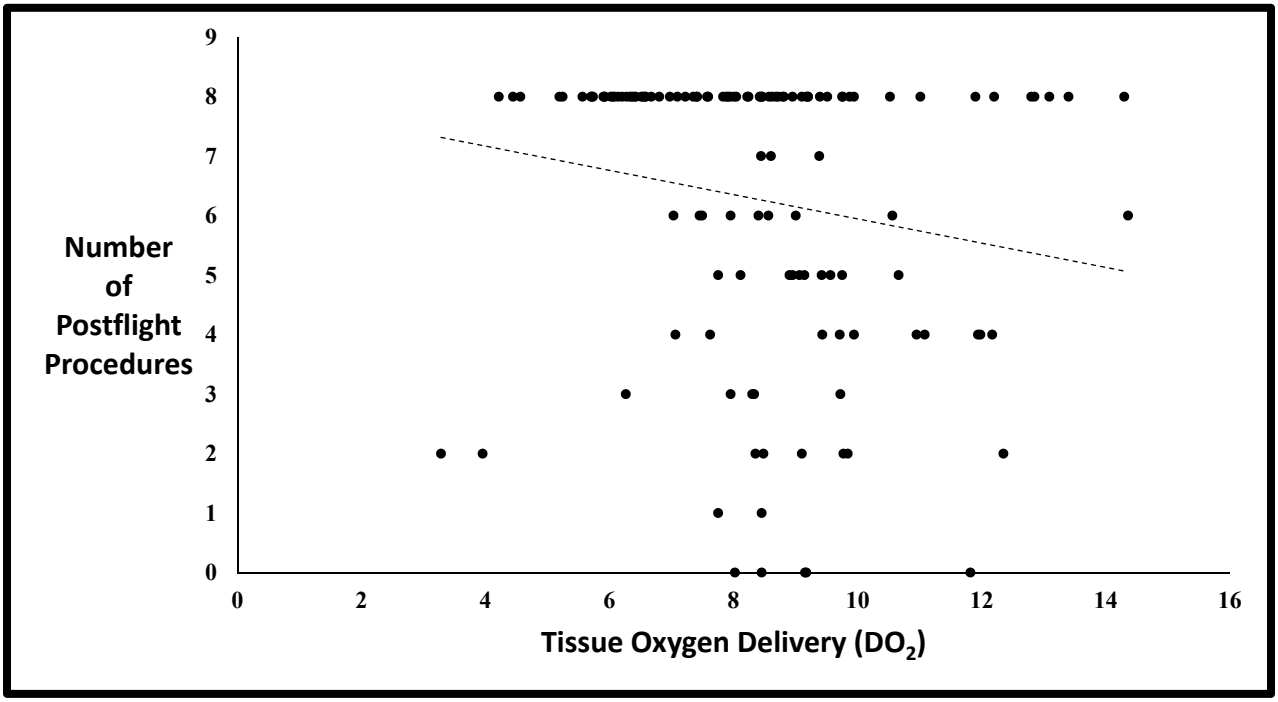
Note: Values calculated using independent samples t-test (results replicated with Mann-Whitney U test). *Denotes statistical significance (bold).

Lastly, with a drop in DO_2, a rise in the number of postflight procedures might well be expected; in short, a dose-response relationship. In fact, this proved to be the case. There was a significant inverse correlation between DO_2 and postflight procedures ($R = - 0.1786$, $p = 0.0454$). In other words, as the DO_2 rose the number of postflight procedures fell. See **Figure 3**. The applicable regression equation was:

$$y = - 0.20x + 7.98$$

But for the postflight procedure recording ceiling, well depicted in the figure, this inverse relationship would almost certainly have been stronger.

Figure 3. Relationship between the Number of Postflight Procedures and Calculated DO_2

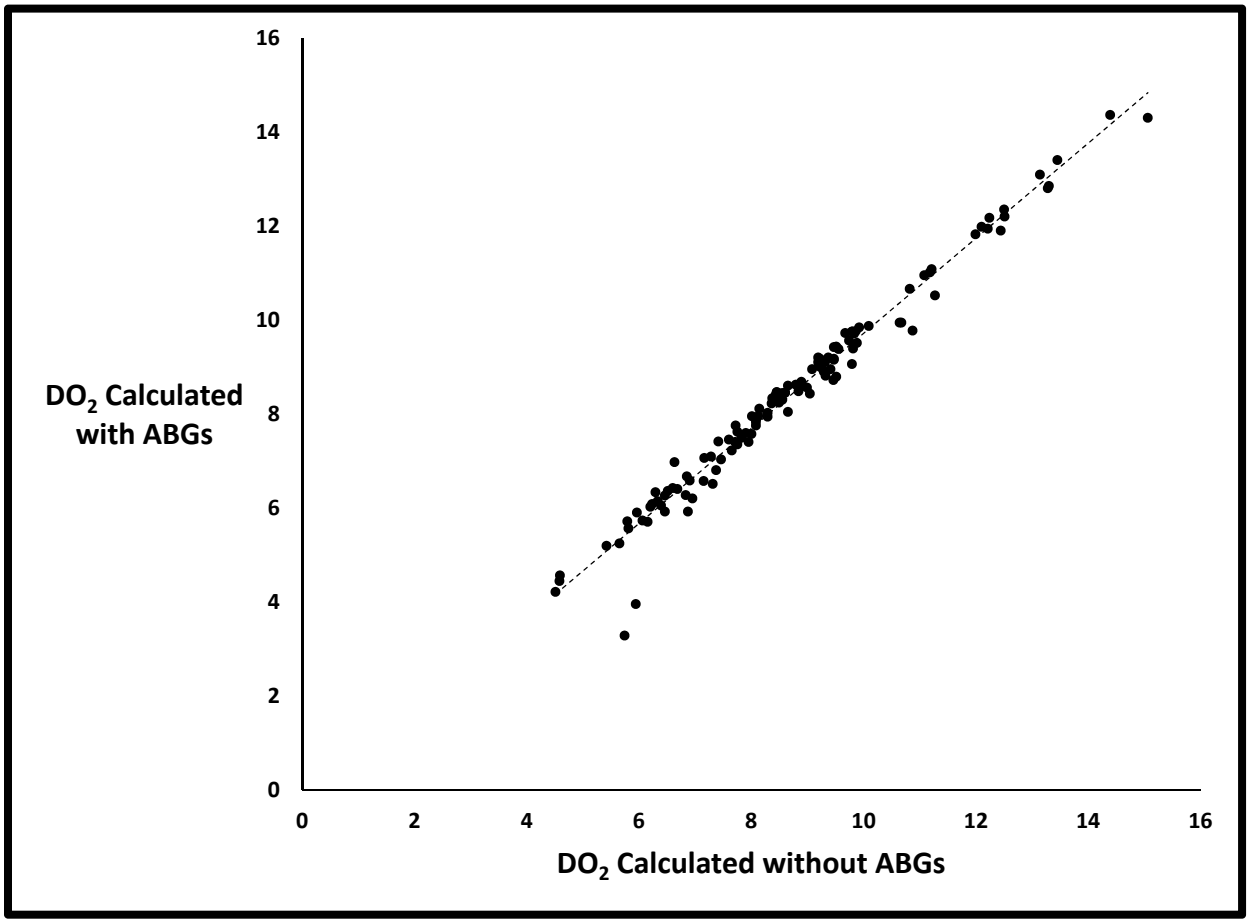


5.4 Construct Validation

The DO_2-GUI calculated DO_2 employing the previously described standard physiological equations. These equations presuppose access to relatively current ABGs. Unfortunately, that is not always the case. It was important to determine whether the DO_2 calculated without ABGs was a reasonable estimate of that calculated with ABGs. Indeed, DO_2 calculated with ABGs was highly correlated to DO_2 calculated without ABGs ($R = 0.9871$, $p < 0.0001$). See **Figure 4**. In fact, the regression equation demonstrated how close the two calculations actually were:

$$y = 1.01x - 0.40.$$

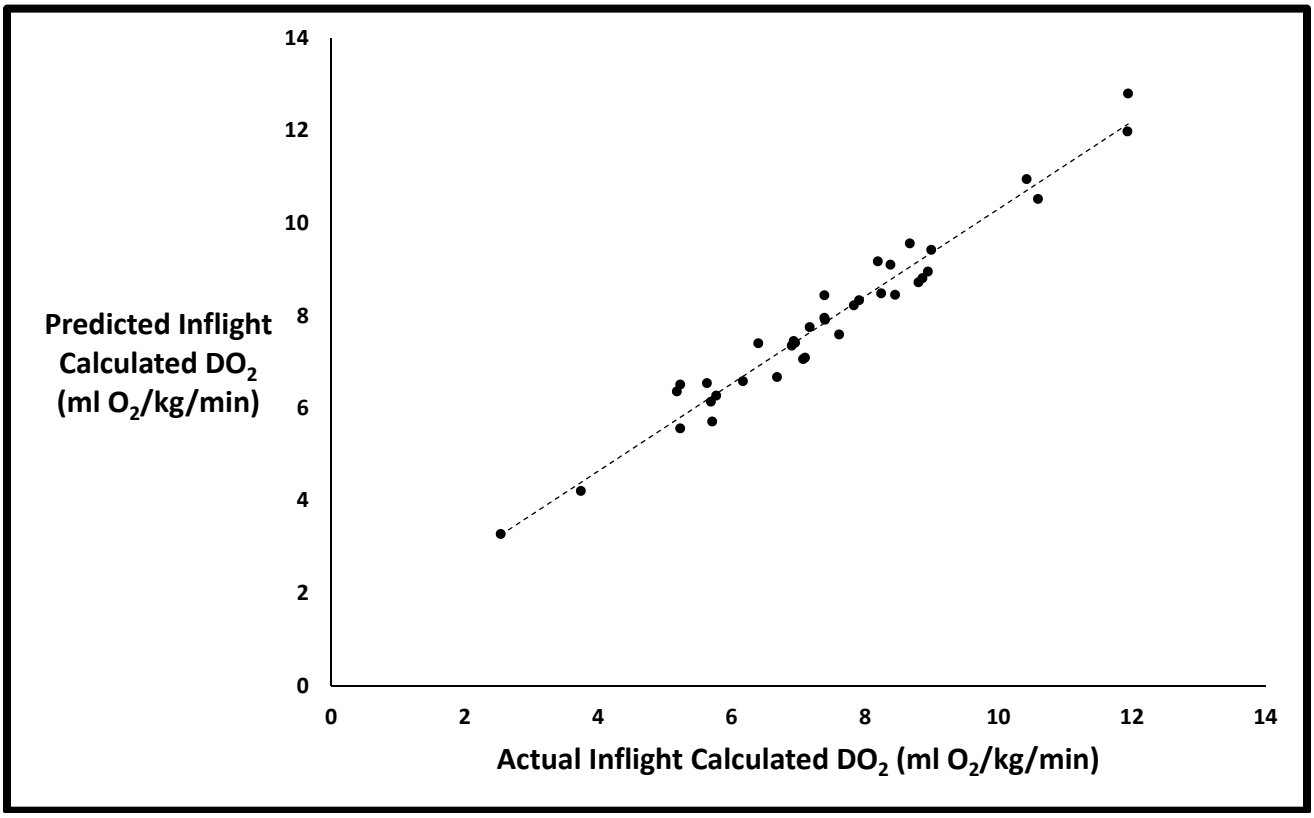
Figure 4. Relationship between Calculated DO_2 with and without ABGs



It was also important that the DO_2-GUI be able to take preflight data and reliably predict actual inflight DO_2. Able to do this, the TVFS could individualize supplemental oxygen, transfusion, and CAR prescriptions. This would be analogous to the PaO_2 nomogram developed by Henry et al during the Vietnam War. (**Henry, 1973**) What was found was no significant difference between the predicted and actual inflight calculated DO_2 ($t = -1.2561$, $p = 0.2129$). Moreover, a significant correlation was discovered ($R = 0.9809$, $p < 0.0001$). See **Figure 5**. Once again, the regression equation demonstrated how close the two calculations were:

$$y = 0.95x + 0.86.$$

Figure 5. Relationship between Predicted and Actual Inflight DO_2

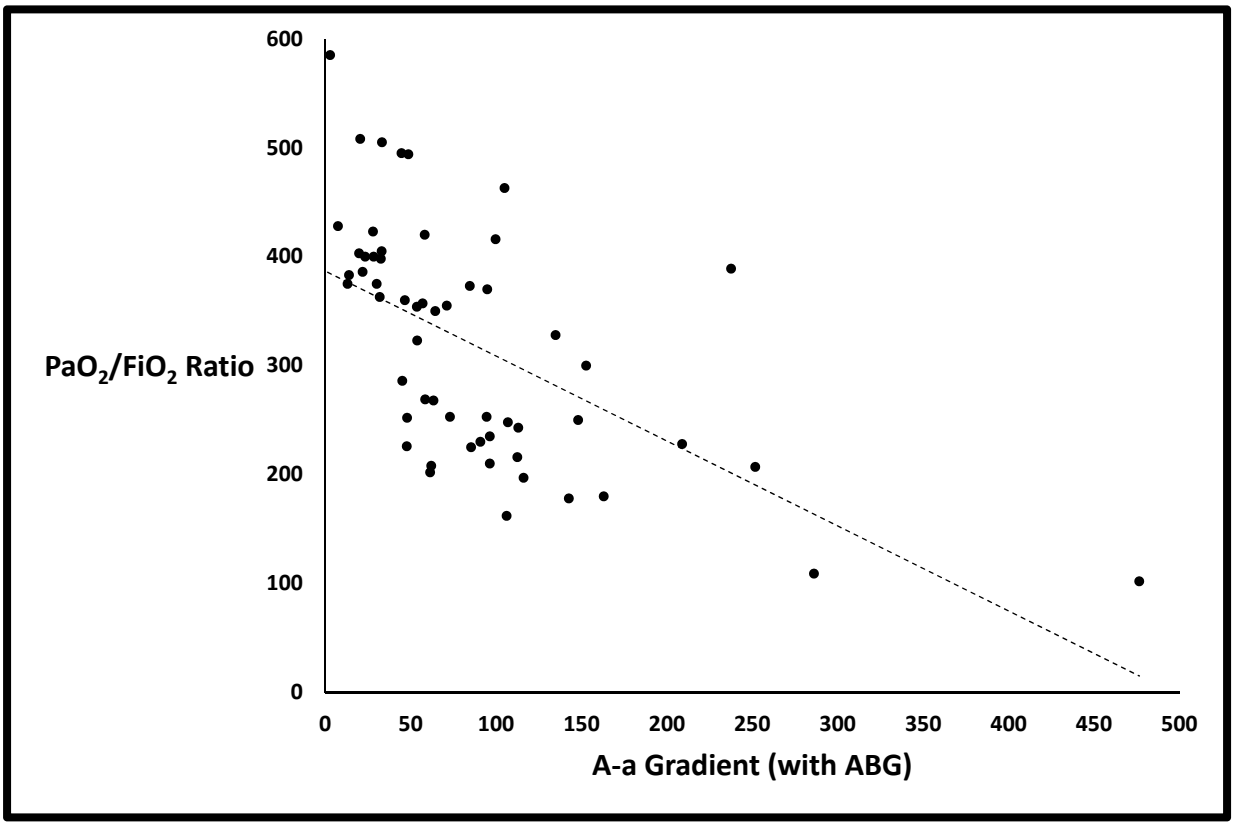


Another DO_2-GUI utility test was its ability to discern a very sick patient from the data, more specifically the patient's pulmonary status. One easy bedside measure is the PaO_2/FiO_2 pulmonary shunt ratio. The lower it gets, the sicker the patient is (normal > 400). (**Pandharipande, 2009**) With the DO_2-GUI, the A-a gradient can be determined. As the patient's pulmonary status worsens, the A-a gradient rises (normal < 30). (**Petersson, 2014**) As expected, when correlated, the PaO_2/FiO_2 ratio and A-a gradient demonstrated a significant inverse relationship ($R = - 0.5908$, $p < 0.0001$). See **Figure 6**. The describing regression equation was:

$$y = - 0.78x + 387.$$

The A-a gradient calculated with ABGs significantly differed from that calculated without ABGs, independent of CAR status (CAR, $p < 0.0001$; Non-CAR, $p < 0.0001$), this being predictable with the no ABG A-a gradient assumption.

Figure 6. Relationship between PaO_2/FiO_2 Ratio and Calculated A-a Gradient



6.0 DISCUSSION

This pilot study was a late add-on component of a multi-phased retrospective matched case-control study dedicated to examining the postflight clinical outcomes of AE patients flown with and without a CAR. (**Fouts, 2017**) It was designed to look at both the clinical impact of DO_2 on the AE patient and the utility of the DO_2-GUI for calculating DO_2.

Fifty randomly selected CAR patients were matched to 50 Non-CAR patients. As expected, demographic, clinical, and physiological characteristics proved comparable. What few differences detected suggested sicker Non-CAR patients preflight and sicker CAR patients inflight, serving only to highlight the clinical volatility of these "stabilized" patients. Postflight, however, the CAR patients underwent significantly fewer major and minor procedures than the Non-CAR patients.

At the same time, regression analyses found five variables with greater influence over the number of postflight procedures than CAR (**Figure A1**). Each of the five --- mechanical ventilation, SpO_2/FiO_2 ratio, ISS, number of preflight surgeries, and flight duration --- offer little opportunity for TVFS modulation. Fortunately, the TVFS wields the sixth most influential factor.

The potential for a salutary effect of CAR has been shown in a number of animal studies. (**Goodman, 2011; Earnest, 2012; Skovira, 2016; Proctor, 2017**) Likewise, a number of human studies have demonstrated a positive clinical impact from the imposition of a CAR. (**Henry, 1973; Butler, 2016a; Fouts, 2017; Butler, 2018; Butler, 2020**) All these studies suggest a place for prescribing a CAR beyond its traditional indications (i.e., trapped air, decompression illness, and severe pulmonary disease). (**Borden Institute, 2004**) However, a

systematic means for evaluating for and prescribing of the non-traditional CAR remained elusive.

In late 2006/early 2007, the notion of DO_2 expanded from the ICU into both casualty pre-hospital care and AE. (**Grissom, 2006; Pollan, 2006; Butler, 2007**) Five patient factors and one aircraft factor affect DO_2. The patient factors are FiO_2, hemoglobin level, hemoglobin saturation, plasma oxygen content, and cardiac output and the aircraft factor is cabin altitude. (**Constanzo, 2014; Pollan, 2006; Butler, 2007; Butler, 2016a; Fouts, 2017; Butler, 2018; Butler, 2020**) Factors easily wielded by the TVFS are FiO_2 (via supplemental oxygen), hemoglobin level (via transfusion), and cabin altitude (via CAR).

A patient at altitude feels a number of physiologic stressors. Those pertinent to DO_2 include hypoxia, vibration, and hypobaria. Hypoxia means decreased oxygen availability, while hypobaria, in conjunction with vibration, favors fluid movement into the interstitium (aka tissue edema) making for an increased intercapillary distance. Decreased oxygen availability and increased intercapillary distance make for a potential drop in DO_2, a "second hit" added onto the initial "first hit." This drop in DO_2, particularly below the healthy human DO_{2crit} of < 7.3 ml O_2/kg/min, makes for a potential rise in patient morbidity (e.g., added postflight procedures). Avoiding this drop in DO_2, this "second hit," demanded the prescription of the non-traditional CAR. (**Goodman, 2010; Butler, 2016a; Fouts, 2017; Butler, 2018; Butler, 2020**)

Calculating DO_2 by hand proved cumbersome and, though easier, tables were not especially user-friendly. (**Pollan, 2006; Butler, 2007**) Thus, the DO_2-GUI came about. Its graphic user interface offered the TVFS a relatively straightforward means to manipulate FiO_2, hemoglobin level, and cabin altitude. (**Butler, 2016b; Butler, 2017b**)

This pilot study found that the CAR group of patients trended toward higher numbers of "good" DO_2 patients than the Non-CAR group. In addition, the CAR group of patients trended toward fewer postflight procedures than the Non-CAR group. Unfortunately, these analyses were underpowered to detect a significant difference.

"Good" DO_2 patients were then compared to "bad" DO_2 patients, using a DO_{2crit} cut-point first of < 7.3 ml O_2/kg/min (< 7.3) after Lieberman et al and then of < 8.0 ml O_2/kg/min (< 8.0) as inferred from several other studies. (**Lieberman, 2000; Shibutani, 1983; Komatsu, 1987; Ronco, 1993**) The preflight < 7.3 cut-point "good" DO_2 patients experienced significantly fewer postflight procedures than the "bad" DO_2 patients. Likewise, both the preflight and inflight < 8.0 cut-point "good" DO_2 patients had significantly fewer postflight procedures.

As the TVFS can affect preflight and inflight DO_2, it was reasonable to combine the data. The result: with either DO_{2crit} cut-point, the "good" combined-preflight-inflight DO_2 patients underwent significantly fewer postflight procedures. In addition, there was no difference in the number of postflight procedures between the two DO_{2crit} cut-points. And, even in the face of some power limitations, the effect size throughout ranged from high medium to large.

Moreover, despite a database-imposed ceiling on the number of recorded postflight procedures (maximum = 8), there was a significant inverse dose-response relationship between DO_2 and postflight procedures. In other words, as the DO_2 rose, the number of postflight procedures fell.

Concurrently, the DO_2-GUI proved internally consistent with highly significant correlations between DO_2 calculated with and without ABGs, predicted and actual inflight DO_2, and PaO_2/FiO_2 ratio and calculated A-a gradient.

Thus, it appears that by ensuring a "good" DO_2, the TVFS promoted less patient morbidity and by ensuring an even better "good" DO_2, the TVFS might well promote an even greater reduction in patient morbidity. Being able to do this with internal consistency and without the user-unfriendly nature of hand- and/or table-calculated DO_2 affirms the utility of the DO_2-GUI.

7.0 LIMITATIONS

Although the CAR and Non-CAR groups were carefully matched on ICD-9 codes and, to some extent airframes, this retrospective case-control study relied on the accuracy and completeness of patient information in the various electronic medical record keeping systems. Any generalizations presented bear cautious interpretation, as there were no assurances that all of the recorded patient information was accurate. The TMDS database imposed a recording ceiling on the diagnoses, preflight surgeries, and postflight procedures data; the number of diagnoses was restricted to a maximum of eight, preflight surgeries a maximum of ten, and postflight procedures a maximum of eight. Consequently, there could be an incomplete clinical characterization of some patients. More specifically, the postflight procedure ceiling may well have limited the DO_2-postflight procedure dose-response effect, making the significant finding reported here even more convincing. Additionally, provider notes and surgical reports were both outside the scope of the study and not readily available to the research team, which precluded the researchers from either gathering more or confirming clinical data. Lastly, all the patients were under the care of a CCATT team, which may have independently abrogated some of the possible adverse effects of the AE environment.

8.0 CONCLUSION

This study continued the investigation into the TVFS's impact on patient outcome. It was a pilot study designed to test both the clinical effect of DO_2 and the utility of the DO_2-GUI. The DO_2-GUI calculates DO_2 in individual patients, with or without ABGs. That value, when applied within the DO_2 paradigm, coupled with a DO_{2crit} cut-point of < 7.3 ml O_2/kg/min (or maybe as high as 8.0 ml O_2/kg/min) offers critical validation information to the TVFS. If below the DO_{2crit} cut-point, the TVFS can prescribe supplemental oxygen, transfusions, and/or CAR to bring the DO_2 above the DO_{2crit} cut-point. Once in the "good" DO_2 range, a patient can expect potentially less morbidity postflight. In fact, "good" DO_2 patients suffered significantly fewer postflight procedures than those patients with "bad" DO_2, on average almost two fewer procedures. Moreover, despite the limitation of a data ceiling for postflight procedures, DO_2 levels demonstrated an inverse dose-response relationship with postflight procedures. As the DO_2 rose, the number of postflight procedures fell.

At the same time, the DO_2-GUI proved internally consistent with highly significant correlations between 1) DO_2 calculated with and without ABGs, 2) predicted and actual inflight DO_2, and 3) PaO_2/FiO_2 ratio and calculated A-a gradient.

These results suggest that the DO_2 paradigm not be limited to CAR prescribing, rather they suggest a more general application to the well-being and validation of the AE patient. That said, this pilot study is just the beginning. Further research into the DO_2 paradigm and utility of the DO_2-GUI must follow.

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10.0 ACKNOWLEDGEMENTS

This technical report contains some of the tabular and figure results found in a previously published technical report. See **Appendix A**. The authors have appropriately cited each figure and table. The Reference Section lists the publication. It is as follows:

Fouts BL, Butler WP, Connor S, Smith DE, Maupin G, Greenwell B, Serres JL, Dukes S. Assessment of aeromedical evacuation transport patient outcomes with and without cabin altitude restriction. August 2017; AFRL-SA-WP-TR-2017-0016.

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11.0 APPENDICES

11.1 APPENDIX A: Supplemental Figure & Tables

In the Results section, Preflight and Inflight Characteristics (Section 5.1) and Postflight Patient Outcomes (Section 5.2) from a previously published Defense Technical Information Center (DTIC) technical report are cited. (**Fouts, 2017**) Cited Figure and Tables are provided here for the readers' convenience.

Table A1. Demographics of CAR and Non-CAR Patients

Variable	CAR (*n* = 50)	Non-CAR (*n* = 50)	*p-value*
Age, Mean (*SD*)	25.74 (5.30)	25.78 (5.76)	0.971[a]
Range	19 - 40	18 - 42	
Service Component, *n* (%)			
USA	38 (76%)	42 (84%)	0.223[b]
USN	1 (2%)	3 (6%)	
USAF	1 (2%)	1 (2%)	
USMC	10 (20%)	4 (8%)	
Type of Injury, *n* (%)			
Blunt	2 (4%)	1 (2%)	0.740[b]
Trauma	34 (68%)	38 (76%)	
Penetrating	12 (24%)	10 (20%)	
Burns	2 (4%)	1 (2%)	
Injury Location, *n* (%)			
Head/Neurologic	19 (38%)	13 (26%)	0.088[b]
Orthopedic	12 (24%)	24 (48%)	
Torso	16 (32%)	12 (24%)	
Eye	1 (2%)	0 (0%)	
Other	2 (4%)	1 (2%)	
Mechanism of Injury, *n* (%)			
IED[c]/Blast	35 (70%)	42 (84%)	0.109[b]
GSW[c]	10 (20%)	8 (16%)	
NBI[c]	1 (2%)	0 (0%)	
Other	4 (8%)	0 (0%)	
Flight Precedence, *n* (%)			
Urgent	23 (46%)	20 (40%)	0.687[b]
Priority	27 (54%)	29 (58%)	
Routine	0 (0%)	1 (2%)	
Airframe, *n* (%)			
C-130	17 (34%)	17 (34%)	0.999[b]
C-17	29 (58%)	28 (56%)	
KC-135	4 (8%)	5 (10%)	

Note: [a]Values calculated using independent samples t-test. [b]Values calculated using Fisher's exact probability test. Percentages may not add up to 100% due to rounding. [c]IED = improvised explosive device, GSW = gunshot wound, NBI = non-battle injury.

Table A2. Preflight Clinical Characteristics of CAR and Non-CAR Patients

Characteristics (as taken from TMDS)	**CAR (*n* = 50)**	**Non-CAR (*n* = 50)**	***p-value***
Injury to Flight Time (hr), M (*SD*)	31.97 (36.21) n=49	35.49 (26.34) n=50	0.581
Injury Severity Scores (ISS), Mean (*SD*)	28.74 (14.12) n=46	25.82 (12.10) n=50	0.441[a]
Embarkation Site Pre-Flight Surgeries, Mean (*SD*)	3.10 (2.53)	4.22 (2.25)	***0.007[a]**
Embarkation Site Pre-Flight Surgeries Profile			
Major Surgeries	99 (62%)	116 (54%)	0.119[b]
Minor Surgeries	60 (38%)	98 (46%)	
Pre-Flight Blood Product Use (Units), Mean (SD)	6.62 (13.74)	15.98 (28.16)	***0.037[c]**
Massive Transfusion Patients (≥ 10 units blood), n (%)			
Yes	10 (20%)	14 (28%)	0.349[b]
No	40 (80%)	36 (72%)	
Patients Transfused, n (%)			
Yes	13 (26%)	19 (38%)	0.198[b]
No	37 (74%)	31 (62%)	

Note: *****Denotes statistical significance (bold). [a]Values calculated using Mann-Whitney U-test. [b]Values calculated using the Chi square test. [c]Values calculated using independent samples t-test. Percentages may not add up to 100% due to rounding.

Table A3. Inflight Physiological Characteristics of CAR and Non-CAR Patients

Characteristics (as taken from TMDS)	CAR (*n* = 50) M (*SD*)	Non-CAR (*n* = 50) M (*SD*)	*p-value*
Flight Time (hr), M (*SD*)	5.72 (3.30) n=49	6.09 (3.03)	0.565
Systolic Blood Pressure (mmHg)			
Lowest	107.50 (18.19)	115.10 (15.47)	***0.027**
Highest	130.78 (19.30)	137.62 (18.32)	0.072
Mean	119.14 (17.04)	126.36 (15.61)	***0.029**
Heart Rate (bpm)			
Lowest	86.32 (19.32)	91.72 (19.71)	0.170
Highest	101.04 (21.99)	104.28 (18.75)	0.430
Mean	93.68 (20.23)	98.00 (18.85)	0.272
Ventilated, *n* (%)			
Yes	33 (66%)	39 (78%)	0.181[a]
No	17 (34%)	11 (22%)	
Ventilator Setting, M *(SD)*			
Tidal Volume (ml)	573.59 (70.78) n=32	546.84 (55.02) n=38	0.080
Positive End Expiratory Pressure (cm H_20)	5.47 (1.02) n=32	5.97 (2.15) n=39	0.197
FiO2 (%)			
Initial	41.22 (16.62)	39.62 (9.60)	0.557
Final	45.10 (20.15)	39.42 (10.16)	0.079
SpO2 (%)			
Initial	98.72 (1.85)	98.94 (1.30)	0.493
Final	98.86 (1.80)	101.02 (14.34)	0.293
SpO2/ FiO2 Ratio			
Initial	269.99 (88.94)	264.34 (70.05)	0.725
Final	255.15 (94.69)	272.70 (85.01)	0.332
Fluctuation in SpO2/FiO2 Ratio	22.15 (45.59)	20.45 (45.91)	0.853
SpO2 (%)			
Lowest	98.70 (1.63)	97.82 (2.64)	0.102
Highest	99.70 (0.64)	99.72 (0.61)	0.887
Mean	99.20 (1.08) n=33	98.77 (1.41) n=39	0.160
24 hr Fluid Intake (ml)	5855.19 (5005.65)	4338.98 (1959.33)	***0.049**
24 hr Fluid Output (ml)	4134.58 (4129.33) n=48	2826.86 (2100.73)	0.054
HgB (g/dL)			
Initial	10.25 (2.55) n=35	9.03 (1.76) n=33	***0.025**
Final	9.92 (2.28) n=21	8.65 (1.86) n=20	0.058
Inflight Blood Product Use (Units), M (SD)	0.16 (0.55)	0.30 (0.97)	0.378
Patients Transfused, n (%)			
Yes	5 (10%)	7 (14%)	0.538[a]
No	45 (90%)	43 (86%)	

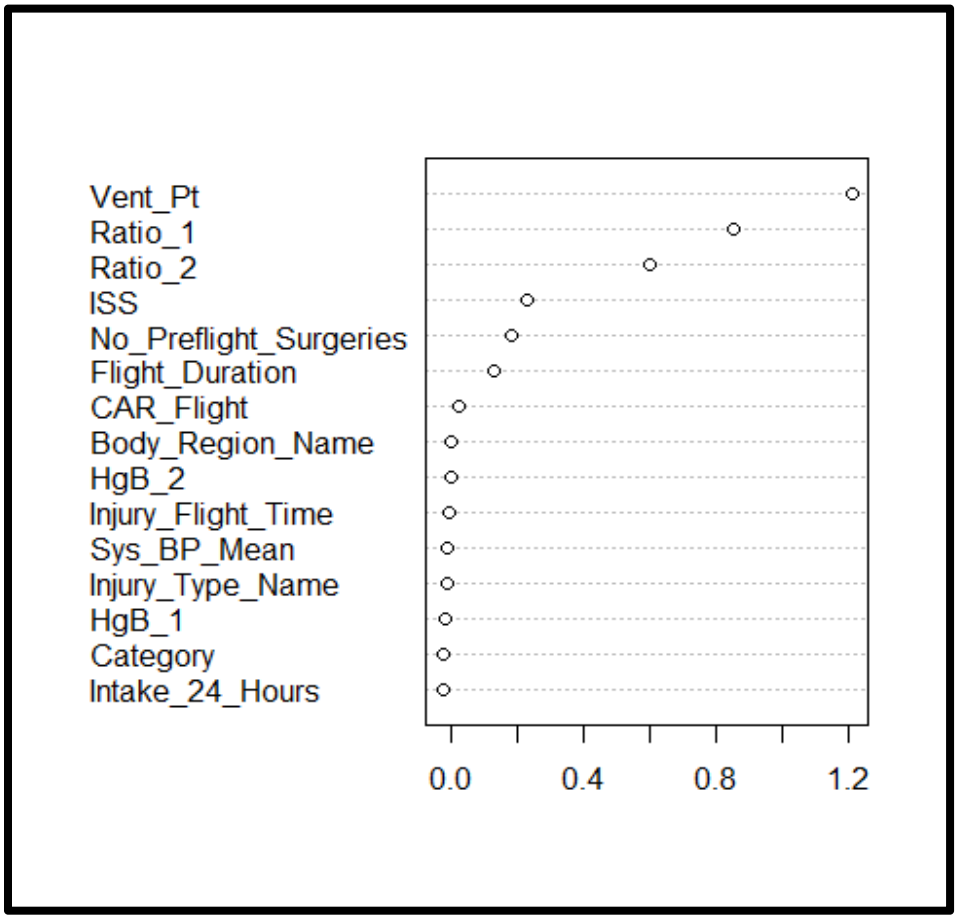
Note: *Denotes statistical significance (bold). [a]Values were calculated using Chi-square test. All other values were calculated using an independent samples t-test.

Table A4. Postflight Outcomes of CAR and Non-CAR Patients

Outcomes (as taken from TMDS)	CAR (*n* = 50)	Non-CAR (*n* = 50)	*p-value*
Length of Stay (days), M (*SD*)	3.70 (4.08) n=47	3.70 (2.54)	0.998[a]
Number ICU Days, M (*SD*)	2.34 (2.20) n=47	3.08 (2.63)	0.138[a]
Postflight Blood Product Use (Units), M (SD)	1.86 (9.50)	0.88 (3.73)	0.499[a]
Patients Transfused, n (%)			
Yes	6 (12%)	6 (12%)	1.000[b]
No	44 (88%)	44 (88%)	
Debarkation Site Postflight Procedures, M (*SD*)	4.98 (2.77)	6.08 (2.49)	***0.032[c]**
Postflight Procedure Profile			
Major Surgeries	57 (23%)	95 (31%)	
Minor Surgeries	63 (25%)	80 (26%)	***0.047[b]**
Other Procedures	129 (52%) n=249	129 (43%) n=304	
Discharge Status, n (%)			
Home/Self-Care	8 (17%)	6 (12%)	
Transfer to Short Term Facility	38 (81%)	43 (86%)	0.342[b]
Death	1 (2.1%)	1 (2%)	
Unknown	3 (6.4%)	0 (0%)	

Note: *Denotes statistical significance (bold). [a]Values calculated using independent samples t-test. [b]Values were calculated using the Chi-square test. [c]Values calculated using the Mann-Whitney U-test.

Figure A1. Rank Importance of Variables to Number of Postflight Procedures



11.2 APPENDIX B: Notations from the Equations

Alveolar Gas Equation (*Constanzo, 2014*) →

$$\mathbf{P_AO_2 = [(P_B - P_{H2O}) * FiO_2] - PaCO_2/RQ}$$

P_AO_2: alveolar oxygen partial pressure (mmHg)
P_B: ambient barometric pressure (mmHg)
P_{H2O}: water vapor partial pressure (generally considered 47 mmHg)
FiO_2: oxygen fraction of inspired air
$PaCO_2$: arterial carbon dioxide partial pressure (mmHg)
RQ: respiratory quotient ($CO_{2\ eliminated}/O_{2\ consumed}$)

Arterial Oxygen Content Equation (*Constanzo, 2014*) →

$$\mathbf{CaO_2 = (SaO_2 * HgbCC * Hgb) + (0.0031 * PaO_2)}$$

CaO_2: arterial oxygen content (ml O_2/dl)
SaO_2: arterial hemoglobin oxygen saturation (%)
HgbCC: hemoglobin carrying capacity (1.34 ml O_2/g)
Hgb: hemoglobin level (g/dl)
PaO_2: arterial oxygen partial pressure (mmHg)

Tissue Oxygen Delivery Equation (*Constanzo, 2014*) →

$$\mathbf{DO_2 = (CaO_2 * CO)/Wt}$$

DO_2: tissue oxygen delivery (ml O_2/kg/min)
CaO_2: arterial oxygen content (ml O_2/dl)
CO: cardiac output (heart rate x stroke volume, ml/min)
Wt: weight (kg)

Kelman's Oxygen Dissociation Curve Model (equation) (*Kelman, 1966*) →

$$\mathbf{SaO_2 = [100 * (a_1x + a_2x^2 + a_3x^3 + x^4)] / (a_4 + a_5x + a_6x^2 + a_7x^3 + x^4)}$$

SaO_2: arterial hemoglobin oxygen saturation (%)
x: oxygen tension (aka arterial oxygen partial pressure, mmHg)
a_1: -8.5322289×10^3
a_2: 2.1214010×10^3
a_3: -6.7073989×10^1
a_4: 9.3596087×10^5
a_5: -3.1346258×10^4
a_6: 2.3961674×10^3
a_7: -6.7104406×10^1

12.0 ABBREVIATIONS AND ACRONYMS

A-a gradient: alveolar-arterial gradient

AE: aeromedical evacuation

ABG: arterial blood gas

CAR: cabin altitude restriction

CCATT: Critical Care Air Transport Team

cm: centimeter

dl: deciliter

DoDTR: Department of Defense Trauma Registry

DO_2: tissue oxygen delivery

DO_{2crit}: critical tissue oxygen delivery

DO_2-GUI: Tissue Oxygen Delivery Graphic User Interface Calculator

F_iO_2: oxygen fraction of inspired air

g: gram

hgb: hemoglobin

hr: hour

ICU: intensive care unit

IED: improvised explosive device

ISS: Injury Severity Score

kg: kilogram

LRMC: Landstuhl Army Regional Medical Center

M2: Military Health System Data Mart

min: minute

ml: milliliter

mmHg: millimeters of Mercury

PaO_2: arterial oxygen partial pressure

PaO_2/FiO_2: pulmonary shunt ratio

SpO_2/FiO_2: pulmonary shunt ratio (alternative)

SaO_2: arterial oxygen saturation

SpO_2: peripheral oxygen saturation (pulse oximetry)

SD: standard deviation

PMQR: Patient Movement Quality Report

TMDS: Theater Medical Data Store

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

TVFS: Theater Validating Flight Surgeon