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Do Intravenous Gas Bubbles Formed from Blood Products Infuse in the Aeromedical Evacuation Environment Influence Outcomes in Traumatic Brain Injuries (TBI)

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14. ABSTRACT
Background: The combined injury of traumatic brain injury (TBI)/hemorrhagic shock has been shown to worsen coagulopathy/systemic inflammation thereby increasing post-traumatic morbidity/mortality. Aeromedical evacuation (AE) to definitive care may exacerbate post-injury morbidity due to inherent hypobaric hypoxic environment. We hypothesized that blood product resuscitation may mitigate adverse physiologic effects of flight post-injury. **Methods:** An established porcine model of controlled cortical injury was used to induce TBI. Intracerebral monitors were placed to record intracranial pressure (ICP), brain tissue oxygenation, and cerebral perfusion. Each of the 42 models were bled while under general anesthesia to a goal mean arterial pressure of 40±5 mmHg for 1 hour. Models were grouped according to resuscitation strategy utilized - Lactated Ringer's (LR) or shed whole blood (WB) - then placed into an altitude chamber for 2 hours at ground, 8,000ft, or 22,000ft, and observed for 4 hours. Hourly blood samples were analyzed for pro-inflammatory cytokines and lactate. Internal jugular vein blood flow was monitored continuously for microbubble formation with altitude changes. **Results:** Cerebral perfusion, tissue oxygenation, and ICP were unchanged among the 6 groups. No internal jugular venous microbubbles were observed with differing altitude or resuscitation strategy. Serum lactate levels from hour-2 of flight to the end of the 4-hour observation were significantly elevated in 22,000+LR compared to both 8,000+LR and 22,000+WB. Serum IL-6 levels were significantly elevated in 22,000+LR compared to 22,000+WB, 8,000+LR and ground+LR hour-1 of observation. Serum TNF-α was significantly elevated hour-2 of flight in 8,000+LR vs ground+LR, and 22,000+LR vs 22,000+WB hour-1 observation. Serum IL-1β levels were significantly elevated hour-1 flight between 8,000+LR and ground+LR. **Conclusions:** Crystalloid resuscitation during AE transport may cause a prolonged lactic acidosis/pro-inflammatory response that can predispose polytrauma patients to secondary injury. This physiologic insult may be prevented by utilizing blood product resuscitation strategies.

15. SUBJECT TERMS
whole blood, aeromedical evacuation, inflammation, cytokine, Traumatic Brain Injury, Microbubble

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1.0 BACKGROUND

Currently, there are limited consensus guidelines regarding the optimal resuscitation strategy for traumatic brain injury (TBI) patients, especially those who have experienced polytrauma. It has previously been shown that the combined injury of TBI with hemorrhagic shock leads to significant coagulopathy and an increased risk of mortality[1]. The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) and Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trials studied and supported the concept of balanced component transfusion with the goal of recreating whole blood resuscitation for patients presenting with hemorrhagic shock[2]. More recently, the role of whole blood to not only correct coagulopathy, but also to mitigate systemic inflammation has become a topic of interest and increasingly common post-injury treatment standard. Therefore, we aimed to investigate the role of whole blood resuscitation in mitigating the systemic inflammatory response experienced secondary to TBI at altitude.

TBI has been shown to cause acute disruptions in coagulation homeostasis, induce hemodynamic compromise, and initiate a profound systemic inflammatory response that may contribute to secondary brain injury post flight[3-4]. Due to the potentially devastating effects of secondary brain injury, rapid evacuation to head injured patients to tertiary care facilities has become an essential component in management. Previous work from Maddry et al. revealed the importance of early aeromedical transport with flight durations of less than 90 minutes to tertiary care facilities decreased patient 30-day mortality and improved patient quality of life[5]. The aeromedical evacuation of TBI patients has been a subject of increased investigation due to the potential exacerbation of hemodynamic and cellular effects experienced by both patients and medical care teams while in flight[3-4].

One of the main concerns with aeromedical evacuation is the effect of hypobaria on TBI physiology. Hypobaria has been shown to cause significant neurophysiologic changes including reduced cerebral blood flow, cerebral perfusion pressure, and tissue oxygenation[6]. Decreases in perfusion and oxygenation to the brain subsequent to traumatic injury may lead to the development of ongoing cerebral injury causing acute and persistent effects on overall neurologic recovery and function. The proposed mechanism of secondary brain injury involves the recruitment and activation of circulating inflammatory cells such as neutrophils and astrocytes[4]. TBI patients with elevated levels of circulating inflammatory markers post injury have been shown to have poor clinical outcomes[4]. Various resuscitation strategies have been employed to help alleviate the systemic inflammation of TBI including hypertonic saline and plasma. Hypertonic saline administration has been shown to decrease the inflammatory insult of TBI with notable increases in anti-inflammatory cytokines with decreases in pro-inflammatory cytokines[7]. Gruen et al provided evidence for early plasma administration for TBI patients by acting to attenuate the endothelial damage and inflammation of the initial TBI preventing further inflammatory insult[8]. TBI patients who received plasma resuscitation early in clinical course were shown to have a 44 percent (%) decreased risk of mortality suggesting a possible survival benefit with early blood component resuscitation in TBI injured patients[8].

Blood first and whole blood resuscitation have recently been shown to be beneficial in early resuscitation of polytrauma patients in the correction of hemodynamic and underlying cellular parameters. The role of whole blood resuscitation in mitigating the systemic inflammatory response to TBI and early post-traumatic flight has yet to be investigated. We hypothesized that the use of whole blood resuscitation during altitude exposure following polytrauma would have protective effects on systemic inflammation and end-organ function, thereby decreasing the risk for post-traumatic secondary brain injury.

2.0 METHODS

2.1 Animal Model

This study was reviewed and approved by University of Cincinnati Institutional Animal Care and Use Committee and the Air Force Medical Support Agency Office of Research Oversight and Compliance. Animals were cared for by a program approved by the Association for Assessment and Accreditation of Laboratory Animal Care International and in compliance with the National Research Council's 2011 Guide for the Care and Use of Laboratory Animals as well as Department of Defense Instruction 3216.1. Forty-two female domestic Yorkshire swine with a mean weight of 40.7 ± 3.0 kg were obtained from Isler Genetics (Prospect, OH) and were acclimated for 48-72 hours prior to utilization. The animals were housed alone or in pairs and provided unlimited food and water except for the night prior to investigation.

Studies were performed at the surgical facility in the University of Cincinnati Center for Surgical Investigation. Swine were sedated with 5mg/kg tiletamine hydrochloride (Telazol) and 5mg/kg xylazine hydrochloride by intramuscular injection (Henry Schein Animal Health, Dublin, OH). Subsequent to induction, pigs were placed in a supine position, orotracheally intubated and maintained on mechanical ventilation during ground-level portions of experimentation (Ohmeda, Madison, WI). Swine were transferred onto the Impact 731 Series Ventilator (IMPACT Instrumentation, West Caldwell, NJ) and maintained on intravenous propofol for simulated flight.

Hemodynamic monitoring and GAMPT placement for detection of intravascular microbubbles

All animals were prepped and shaved using clean technique. Prior to arterial and central line placement, pigs were randomized to one of six resuscitation and altitude exposure (simulated

flight) groups with 5 animals in each group: Lactated Ringer's (LR) at ground level, whole blood resuscitation (WB) at ground level, LR at 8000 feet altitude, WB at 8000 feet altitude, LR at 22,000 feet altitude, or WB at 22,000 feet altitude (Figure 1).

Figure 1

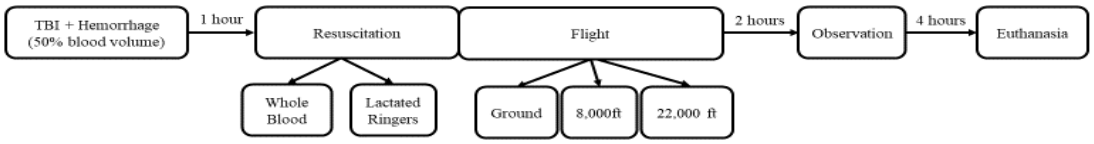

Figure 1: Timeline of animal studies

All animals underwent the following procedures for monitoring instrumentation. The right internal jugular vein was cannulated with an 8 Fr introducer for central venous access. The left internal jugular vein was used for placement of a GAMPT ultrasonic microbubble counter (GAMPT Ultrasonic Solutions, Merseburg, Germany). Gas bubbles have been shown to form within hypobaric environments due to the associated pressure reduction leading to many deleterious mechanical, embolic and biochemical manifestations that can range from minor to possibly fatal[9]. The goal of using the GAMPT ultrasonographic microbubble counter was to measure circulatory microbubbles and provide a comprehensive assessment of the venous gas load and the consequences of operationally relevant hypobaric exposures and high-volume crystalloid and blood product resuscitation. After achieving proximal and distal internal jugular

vein control, a small venotomy was created and a 4 centimeters (cm) portion of a clear 20 Fr chest tube was placed as an interposition within the vessel and secured (Figure 2A). The GAMPT ultrasound probe was then placed around the plastic interposition graft (Figure 2B). Continuous monitoring of microbubble detection occurred via the BCC300 GAMPT monitor (Figure 2C). In order to preliminarily confirm the functionality of the GAMPT probe, we introduced both a 3mL bolus of air as well as agitated saline proximal to the probe and observed the results. The GAMPT device was able to accurately detect the presence of induced microbubbles and was therefore subsequently used in all test subjects for further investigation. Intravascular ultrasound could not be utilized because it is designed for characterization of the vessel wall rather intraluminal contents.

Figure 2

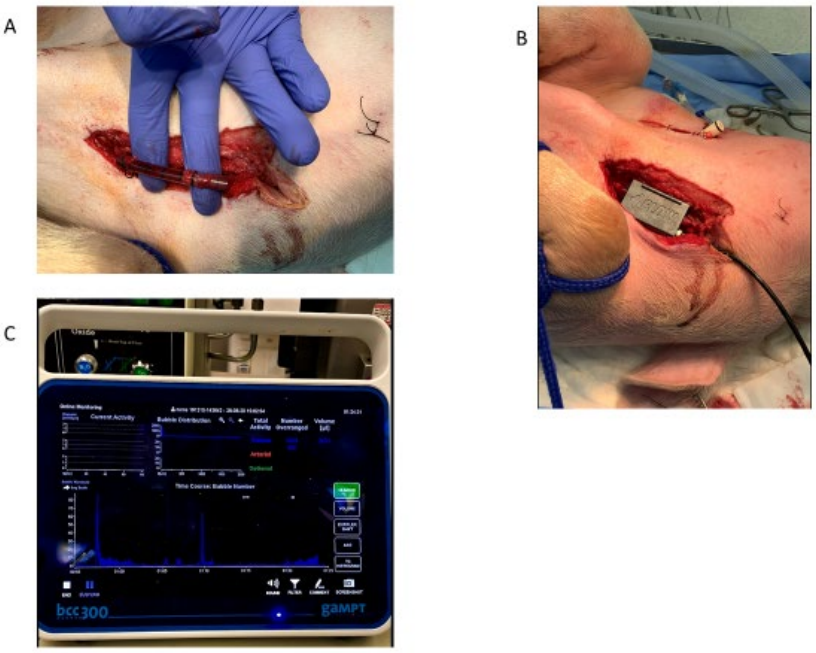

Figure 2. GAMPT probe insertion technique and microbubble detection

A: Interposition tubing in place around internal jugular vein

B: GAMPT probe in place around interposition tubing

C: GAMPT continuous recording device

Bilateral femoral arterial access was obtained via surgical cut-down. The left femoral artery was cannulated with a 20-gauge arterial catheterization set (Teleflex, Wayne, PA) and used for continuous arterial pressure monitoring. The right femoral artery was cannulated with a 7 Fr introducer sheath and used for controlled hemorrhage.

TBI Model and Neuromonitoring

After arterial and central venous line placement, animals were repositioned prone and the head was manipulated and stabilized between the stage base parallel rails of a controlled cortical impactor (Stoelting Co, IL). An elliptical incision was made in the midline skin between bilateral pinna down to cranium. Exposure of both sagittal and coronal sutures was completed as previously described[10]. A 2 cm burr hole was created in right parietal bone, centered 16 millimeter (mm) anterior to coronal suture and 12 mm lateral to the sagittal suture with dura left intact. Another 2 cm burr hole was subsequently created in the left parietal bone, similarly centered 16mm anterior to coronal suture and 12 mm lateral to sagittal suture. The dura was opened in the left sided burr hole and an intracranial pressure monitor was placed into the cerebral parenchyma. Intracranial pressure monitoring was performed utilizing a Raumedic Neuromonitoring apparatus (Raumedic, Mills River, NC). A controlled cortical injury was induced using Precision Cortical Impactor (Hatteras Instruments, Cary, NC) at a speed of 400 m/s, depth of 14 mm, and dwell time of 4 milliseconds.

Multimodal intracranial monitoring was accomplished with the addition of three intracranial probes measuring intracranial pressure (ICP), brain tissue oxygenation (Licox probe Integra, Saint Priest, France), and brain perfusion (Bowman Perfusion probe, Hemedex,

Cambridge, MA, USA). All data was recorded by a CNS monitor (Moberg Research INC, Ambler, PA, USA) for further evaluation.

Hemorrhagic shock model

After TBI, the pigs underwent controlled hemorrhage by removal of blood from the right femoral arterial access sheath. Hemorrhage began with 100 milliliters (mL/minute (min) to a target mean arterial pressure (MAP) of 40 millimeter of mercury (mmHg) (+/- 5 mmHg) or up to 50% of calculated total blood volume for 1 hour of persistent hypotension. Animals that were to receive whole blood for resuscitation were given shed blood that was collected during hemorrhage returned in citrated coated blood bags (Terumo Corporation Imuflex, Tokyo, Japan). After 15 minutes at ground level, animals were placed into an altitude chamber. The altitude chamber used is a custom-built chamber located within Center for Surgical Innovation at University of Cincinnati (Abbess Instruments and Systems, Ashland, MA) (Figure 3). Ground level pigs remained in the open chamber without altitude increase and simulated flight pigs were taken to altitude - 8000 (8K) or 22,000 (22K) feet - for a 2 hour simulated flight. A maximum altitude of 22,000 feet (ft) was chosen as some aeromedical evacuation aircraft such as C21 and V-22 Osprey jets fly above this altitude[11]. Also, with the development of drone technology for the medical evacuation of military casualties, investigation of altitudes of 15,000 to max 22,000 ft are warranted as these are the altitudes flown by current and future medical evacuation drones[12]. Pigs were resuscitated to a goal MAP of 65 mmHg, with either two thirds of the volume of shed citrated whole blood or LR up to a maximum of three times the total shed blood volume. Resuscitation was initiated with onset of flight and the remainder of the blood/LR was given 1 hour into flight. Pigs then underwent a 4-hour observation with goal MAP greater than 50mmHg.

Figure 3. Altitude Chamber

Vital signs (heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate and temperature) were measured at baseline, TBI induction, during hemorrhagic shock, after 2/3 resuscitation, simulated flight hours 1 and 2, and hourly post flight during the 4-hour observation period.

Serum Analysis

Arterial blood was collected at each of the time points stated above and an iSTAT point of care analyzer (Abaxis, Union City, CA) was used to measure an arterial blood gas and electrolytes. Whole blood was then placed in serum separator tubes (BD Bioscience, San Diego, CA) and centrifuged at 1000 gram (g)for 10 min. Serum was collected and subsequently analyzed for pro-inflammatory cytokines interleukin IL-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α using a Qplex Porcine Chemokine High Sensitivity enzyme linked immunosorbent assay according to manufacturer protocol (Quansys Bioscience, Logan, UT). Serum was also analyzed for the presence of neuron specific enolase (NSE) using an enzyme linked immunosorbent assay according to manufacturer protocols (human and porcine ELISAs) (MyBiosource, San Diego, CA).

Statistical Analysis

A p-value of < 0.05 was considered statistically significant. Student's t tests were used when comparisons are made between two treatment groups. One-way analysis of variance (ANOVA) was used to compare multiple populations. Experiments that contain multiple data points were used to calculate means and standard errors of the mean. All statistical analyses were performed with Prism 6 (GraphPad Software, La Jolla, CA).

3.0 RESULTS

Hemodynamic effects of TBI + hemorrhage at altitude

Hemorrhagic shock was adequately induced in all groups with decreasing MAP and subsequent elevated HR that was otherwise improved with resuscitation (Figure 4C). The average change in MAP and HR from baseline to end of observation were not statistically significant between groups, however, groups resuscitated with WB had an average change in MAP of 16.7 mmHg compared to 27.6 mmHg in LR treated groups from baseline to end of 4-hour observation, and an average change in HR of 19.5 bpm in WB groups compared to 94 bpm in LR treated groups (Figure 4B, D).

Animals resuscitated with whole blood trended towards increased MAP during and after altitude compared to those given LR (Figure 4C). MAP was significantly decreased in animals resuscitated with LR during simulated flight at 22K compared to those that received WB post resuscitation (61.2±14.6 mmHg 22K+LR vs 93.4±20 mmHg 22K+WB), after 2-hours altitude (54.2±9.36 mmHg 22K+LR vs 91±11.08 mmHg 22K+WB), and after 2-hour observation (57.2±5.8 mmHg 22K+LR vs 80.4 ±7.1 mmHg 22K+WB) ($p<0.05$) (Figure 4C).

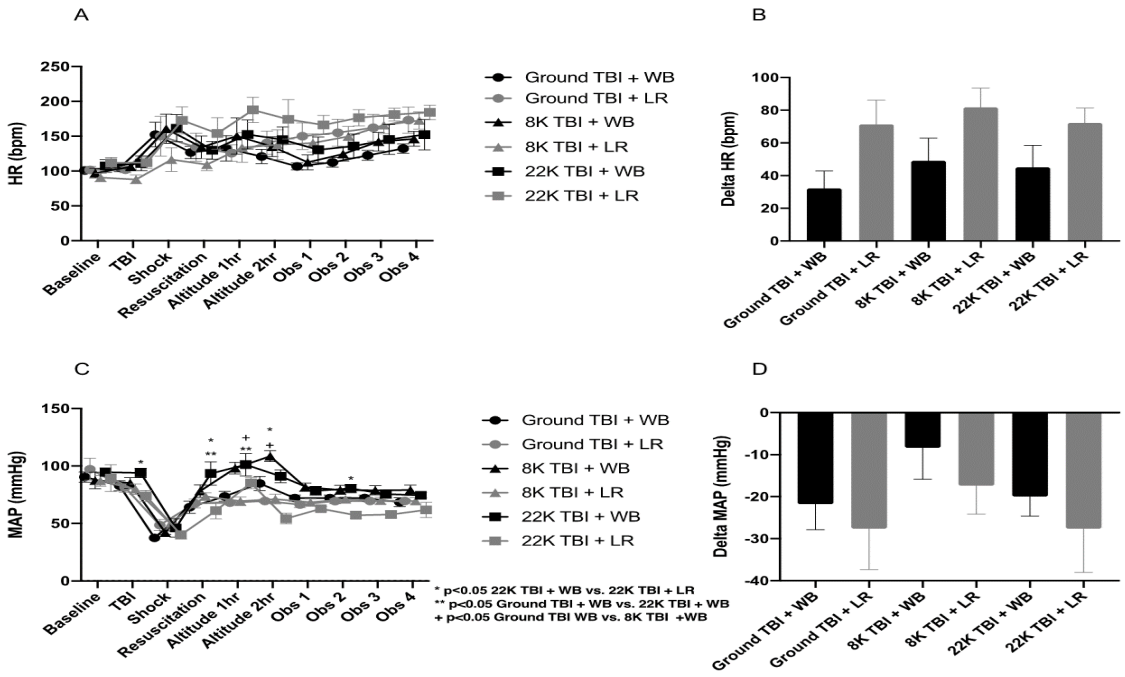

Figure 4. Hemodynamic effects of TBI and hemorrhagic shock during and after flight

Neurophysiologic effects of TBI at altitude

Intracranial pressure increased from baseline to the end of 4-hour observation in all groups but was not statistically significant given the variability (Figure 5A). Notably, ICP was not sustained over the clinically relevant cutoff of 20 mmHg in any experimental group. There was no change in brain tissue oxygenation amongst treatment groups from baseline to end of 4-hour observation (Figure 5C). Cerebral perfusion pressure (CPP) was noted to be increased among WB-treated groups with the largest increase noted during altitude exposure (Figure 5D). CPP differed significantly in ground and 8K exposed animals resuscitated with whole blood at 1 (61± 13.4 mmHg ground+WB vs. 85.8 ±12.7 mmHg 8K+WB) and 2 hours (67.8 ± 14.5 mmHg ground+WB vs 93.8 ±10.7 mmHg 8K+WB) of flight ($p<0.05$, Figure 5D). Notably, the CPP did not fall below the critical clinical value of 60 mmHg. CPP also differed between ground and 22K WB-treated animals during resuscitation (49.2 ± 15.2 mmHg ground+WB vs. 76.6 ±19.3 mmHg 22K+WB, $p<0.05$, Figure 5D). Changes in ICP and CPP were not statistically significant in each

group from baseline to end of experimentation (Figure 5B). Importantly, there were no differences in CPP between resuscitation strategy groups at any of the three altitudes studied. The Hemedex probe was found to be unreliable and provided inconsistent data for cerebral blood flow in porcine cerebral parenchyma; instead we calculated the CPP based upon the ICP and MAP.

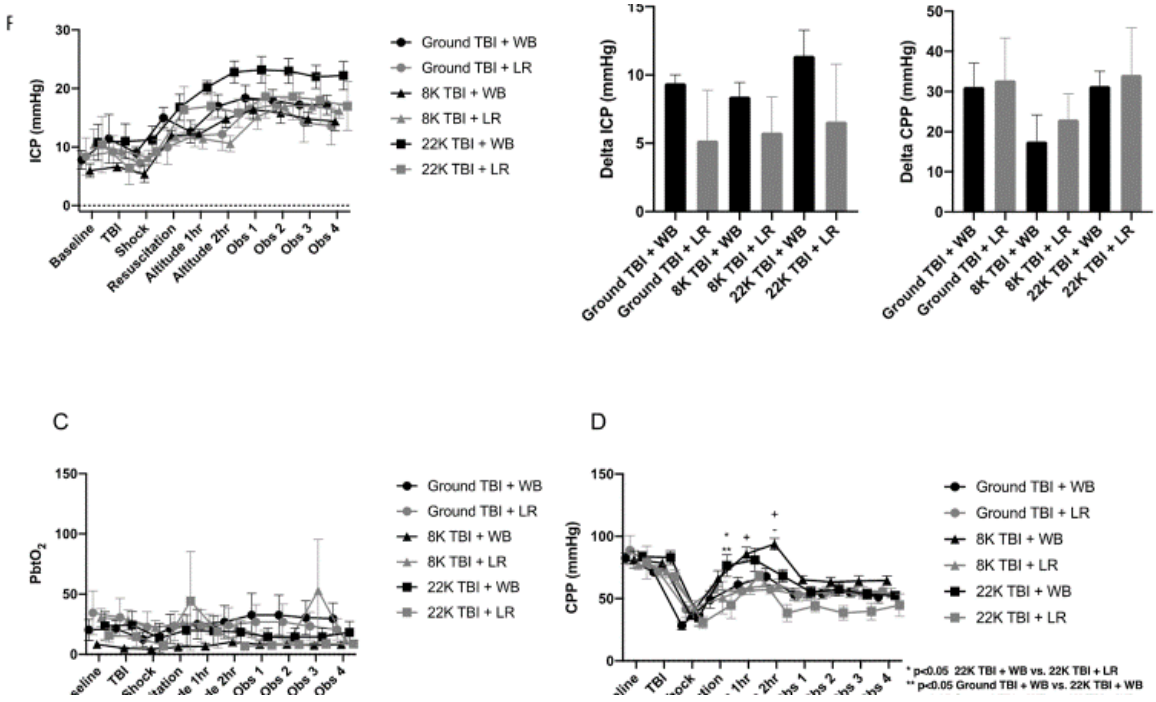

Figure 5. A. Mean arterial pressure B. LiCox C. Intracranial pressure D. Cerebral Perfusion Pressure

Effect of altitude on inflammation and stress hormone production

With increasing altitude from ground to 22K elevation there was an increase noted in physiologic biomarkers of stress and pro-inflammatory cytokines. Lactate elevation noted during hemorrhagic shock persisted following exposure to extremes of altitude (Figure 6A). Lactate levels from 2 hours in flight to the end of 4-hour observation remained elevated in 22K group given LR compared to both 8K LR and 22K WB groups, $p<0.05$ (Figure 6A). pH was also noted

to be significantly decreased in the 22K LR group compared to ground and 8K LR groups during hours 1 and 2 of simulated flight, $p<0.05$ (Figure 6B). Hemoglobin was shown to be lower in those animals receiving LR compared to those resuscitated with WB after 1 hour of observation (Figure 6C). Potassium levels were also significantly elevated after 2 hours of observation in 22K LR group compared with 22K WB $p<0.05$ (Figure 6D).

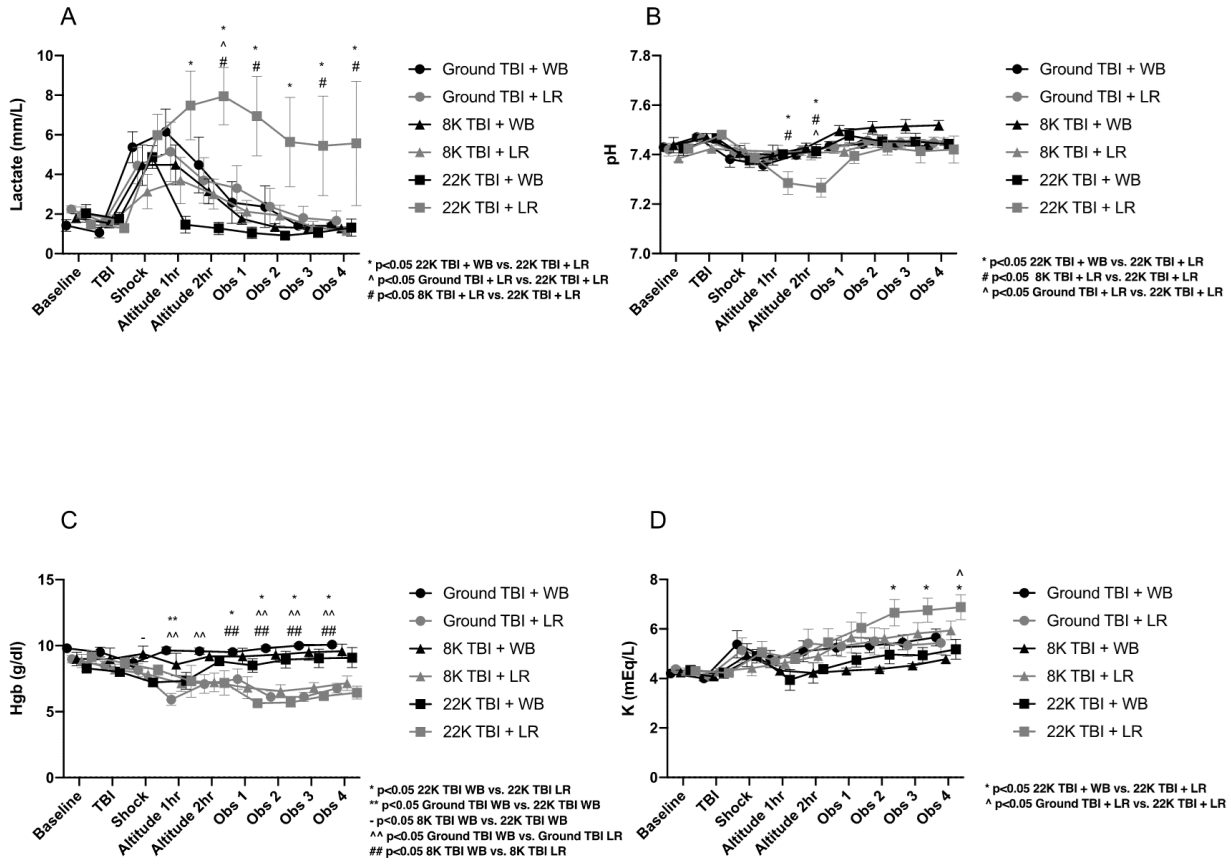

Figure 6. Physiologic markers of resuscitation A. Lactate, B. pH, C. Hgb, D. K

Whole blood resuscitation and the effect on systemic inflammation

Serum IL-1β levels were significantly elevated in 8K+LR compared to ground+LR at 1 hour of flight (4.08± 1.04 pg/mL 8K+LR vs 2.12± 0.85 pg/mL ground+LR) and 3 hours into observation (4.11± 1.08 pg/mL 8K+LR vs 2.10 ± 0.85 pg/mL ground+LR) ($p<0.05$, Figure 7A). Serum IL-6 levels were significantly elevated in 22K+LR compared to ground+LR after 2 hours of altitude, and observation hours1 and 3 ($p<0.05$, Figure 7B). IL-6 levels were also noted to be elevated in 8K+LR compared to ground+LR during hour 2 of flight, along with 22K+LR compared to 8K+LR and 22K WB 1 hour into observation ($p<0.05$, Figure 7B). Serum IL-8 levels were significantly elevated in 22K+LR group vs ground+ LR 2 hours into flight ($p<0.05$, Figure 7C). TNFα expression was significantly elevated in 8K+LR compared to ground+LR 2 hours into flight (50.67± 3.8 pg/mL 8K+LR vs 15.05±9.17 pg/mL ground+LR) and after hour 1 of observation (50.35±35 pg/mL 8K+LR vs 13.28 ±10.24 pg/mL ground+LR) ($p<0.05$, Figure 7D). TNFα was also noted to be elevated amongst 22K+LR and 22K+WB groups along with 22K+LR and ground+LR at observation hour 1($p<0.05$, Figure 7D).

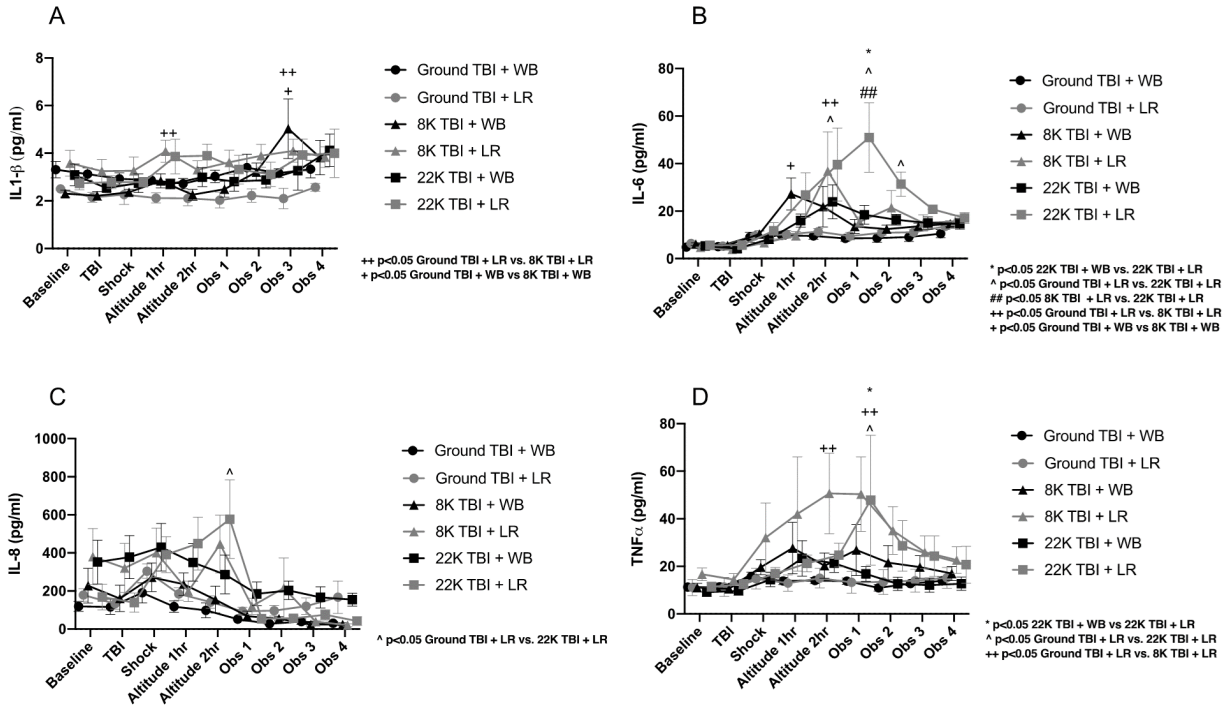

Figure 7. Inflammatory Markers at Altitude

Microbubble Formation

Neither the presence nor formation of venous microbubbles was detected in this model. Preliminary analysis demonstrated that the GAMPT device functioned to show induced microbubbles, but no group was observed to have systemic (internal jugular venous) microbubbles at any time point, in either altitude exposure setting, or with resuscitation strategy.

NSE evaluation

Upon the use of various NSE ELISA kits, the presence of NSE was undetectable or significantly low in all cohorts. This result was likely due to the difficulty of the ELISA kit rather than the extent of the TBI experienced by all subjects, as this injury has been shown to induce significant cerebral parenchymal damage even with lower demonstrable NSE levels[10].

4.0 DISCUSSION

The goal of our study was to investigate the role of whole blood resuscitation in a TBI polytrauma model assessing the overall effect on the acute physiologic and systemic inflammatory responses. Aeromedical evacuation to levels of 22K according to our study may lead to increasing levels of various inflammatory markers, including IL-1 β, IL-6, IL-8 and TNF-α, which could cause long term effects for severely wounded warriors or civilian patients undergoing aeromedical evacuation to regional trauma centers. Animal cohorts resuscitated with whole blood at extremes of altitude demonstrated improvements in metabolic stress including decreased lactate, normalization of pH and maintenance of physiologic levels of potassium compared to those receiving LR. Whole blood resuscitation was also shown to prevent the exacerbation of the systemic pro-inflammatory markers as noted by IL-6 and TNF-α compared to crystalloid resuscitation.

Hypoxia and hypotension remain concerning mechanisms of secondary brain injury after TBI and are of foremost concern in the acute care of the head injured patient. A majority of the current literature surrounding aeromedical evacuation and TBI focuses on the physiologic effects of hypoxia and hypobaria. Johannigman et al. presented evidence that hypoxia is a prevalent side effect of aeromedical evacuation and that keen attention to TBI patients during transport is needed to prevent further secondary insult[3]. Lopez et al. described the role of hypobaria and cardiac dysfunction during aeromedical evacuation[13]. They found that cardiac output and stroke volume decrease 8 hours after traumatic injury, along with notable increases in endothelial cell damage secondary to a hypobaric environment[13]. A study by Scultetus et al. revealed that swine exposed to altitudes of 8000 ft have decreased brain tissue oxygenation, MAP and CPP compared to ground control cohorts[6]. In our study there were no significant differences in systemic or

cerebral hypotension which differs from the study described above. We also did not observe induced cerebral hypoxia from post-traumatic altitude exposure in this model, even at altitudes of 22000 feet. Therefore, further investigation into the role of systemic inflammation and physiologic alterations induced by flight is warranted, since the classic bedside hemodynamic parameters are grossly unchanged.

Early exposure to hypobaria in TBI patients has been shown to increase the severity of secondary brain injury via an increase in the overall neuroinflammatory response[4]. Tamm et al. have shown that in general, hypoxic conditions cause a systemic release of inflammatory cytokines such as IL-6 and IL-8 which cause subsequent end organ damage [14]. Skovira et al. evaluated the role of hypobaria and TBI in aeromedical evacuation and observed distinct changes in hippocampal cell loss, secondary brain inflammation and worsened cognitive outcomes in subjects with TBI exposed to hypobaria[15]. In our study we similarly observed an increase in pro-inflammatory cytokines at elevations of altitude; however, our goal was to then evaluate if whole blood resuscitation could mitigate this inflammatory response thereby preventing secondary brain injury. With the initiation of whole blood resuscitation, we observed significant improvements in various metabolic and inflammatory derangements raising questions into which component of whole blood is able to mitigate such effects.

Another aim of our study was to evaluate for the presence of microbubble formation with elevations in altitude and high-volume fluid resuscitation. Decompression sickness is a known disease process that occurs typically with deep water diving or with changes in altitude chamber pressures. In this study we were unable to detect the presence of central venous microbubble formation with descent from altitudes of maximum 22,000 ft. A study in humans by Powell et al. revealed evidence that out of 150 deep water dives 70% of divers experienced decompression

illness symptoms without the formation of gas microbubble formation[16]. Overall the formation of gas microbubble formation does not appear to cause clinically relevant changes with ascent to or descent from extremes of altitude.

Our study did present some limitations, the first being that although hypobaria of flight was replicated, the gravitational forces of take-off and landing were not included in evaluation. Previous work has shown that the positioning of TBI patients, along with the vibration and noise during aeromedical evacuation may cause changes in patients ICP leading to possible deleterious outcomes post flight if not continuously monitored[17]. Another limitation to the study is that all swine were hemorrhaged to a shock state and subsequently resuscitated to goal MAP. Scultetus et all revealed that hypobaria of flight causes significant changes in MAP and CPP[6]. Due to our hemorrhagic shock model we may have masked the possible hemodynamic effects of hypobaria that would be expected with extremes of altitude.

5.0 CONCLUSION

In conclusion, whole blood resuscitation may mitigate the systemic inflammatory effects experienced during aeromedical evacuation. Inflammatory markers such as IL-1 β, IL-6, IL-8, and TNF- α may be induced by acute exposure to high altitude, and subsequently reduced with initiation of whole blood resuscitation which has not previously been demonstrated. Our study has shown that the combination of exposure to extremes of altitude and crystalloid resuscitation may cause a prolonged lactic acidosis and acute phase inflammatory response that may predispose TBI patients to secondary injury with delayed morbidity and mortality. These deleterious effects may be mitigated by the initiation of blood product resuscitation strategies. Further evaluation into the components of whole blood and the contribution each may play on systemic inflammation will need to be performed in future studies.

The stated authors have no conflicts of interest to disclose

The views published in this article are those of the authors and do not necessarily reflect the official policy or position of the United States Air Force, the Department of Defense or the U.S. Government.

6.0 REFERENCES

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

%	percent/percentage
+	meaning “and”
<	Less-than
>	Greater-than
±	plus or minus
22K	22000
8K	8000
ANOVA	Analysis of Variance
bpm	beats per minute
CPP	Cerebral perfusion pressure
cm	centimeter(s)
CNS	Central Nervous System
DBP	diastolic blood pressure
iSTAT	an in vitro whole-blood analyzer that uses single-use cartridges for critical care tests at the point of care
ELISA	enzyme-linked immunoassay
Fr	French Size (medical tubing unit of measurement)
ft	feet (unit of distance measurement)
g	gram(s)
GAMPT	Company for Applied Medical Physics and Techniques
HR	Heart Rate
ICP	Intracranial Pressure
IL-1β	Interleukin 1-beta cytokine
IL-6	Interleukin 6 cytokine
IL-8	Interleukin 8 cytokine
LR	lactated ringer
m/s	meter per second
MAP	mean arterial pressure
mL	milliliter
mL/min	milliliter per minute
mm	millimeter(s)
mmHg	millimeter of mercury
NSE	Neuron-specific enolase
p	power
pg/mL	picograms per milliliter
pH	power of Hydrogen
PROMMTT	Prospective Observational Multicenter Major Trauma Transfusion
PROPPR	Pragmatic Randomized Optimal Platelet and Plasma Ratios
RR	respiration rate
SBP	Systolic Blood Pressure
TBI	Traumatic Brain Injury
TNF-α	tumor necrosis factor alpha (multifunctional cytokine)
vs	verses
WB	Whole blood