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Physiologic Impact of In-Flight Stress Following Traumatic Brain Injury

Andrew D. Jung, MD; Mackenzie C. Morris, MD; Rosalie Veile, BS; Lou Ann Friend, RVT; Sabre Stevens-Topie; Timothy A. Pritts, MD, PhD; Amy T. Makley, MD; Michael D. Goodman, MD; Lt Col Daniel Cox, MD

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Air Force Research Laboratory
711th Human Performance Wing
U.S. Air Force School of Aerospace Medicine
Aeromedical Research Department
2510 Fifth St., Bldg. 840
Wright-Patterson AFB, OH 45433-7913

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Chief, En Route Care Research Division	Chair, Aeromedical Research Department

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14. ABSTRACT

Traumatic brain injury (TBI) is a growing concern in both the military and civilian populations. Explosive devices used in military combat commonly result in a blast-induced TBI. Warfighters participating in combat operations have a reported 8-22% incidence of TBI. Those with the most severe TBI often require emergency medical evacuation, first by helicopter then by fixed wing aircraft. During aeromedical transport, wounded warfighters and pilots experience whole body vibration characterized by common frequencies of 16 and 100 Hz due to the movement of the rotors. The effect of this ongoing vibration on patients with TBI is currently unknown. In addition, transported patients may also experience a mild hypoxia in flight, which has been associated with increased morbidity and mortality following TBI. Secondary brain injury can occur by exposure to posttraumatic insults, exacerbating the primary brain injury and contributing to poor outcomes. For this study, we developed a porcine model of traumatic brain injury to investigate the effects of the continuous vibration and hypoxia of simulated aeromedical evacuation on the injured brain. We hypothesized that the combination of vibration and hypoxia would contribute to secondary brain injury following TBI, as evidenced by serum biomarkers or neuroimaging. We used serum biomarkers, neurologic monitoring, blood gas analysis, imaging, and histology to evaluate the effects of vibration and hypoxia following TBI. Serum biomarkers, magnetic resonance imaging, and histology demonstrated changes following TBI but were similar between groups with or without vibration after TBI. Our study demonstrated that pigs subjected to post-TBI vibration, hypoxia, or both did not demonstrate any detectable differences by 6 hours after injury.

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Traumatic brain injury, vibration, porcine model

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1.0 SUMMARY

Traumatic brain injury (TBI) is a growing concern in both the military and civilian populations. Explosive devices used in military combat commonly result in a blast-induced TBI. Warfighters participating in combat operations have a reported 8-22% incidence of TBI. Those with the most severe TBI often require emergency medical evacuation, first by helicopter then by fixed wing aircraft. During aeromedical transport, wounded warfighters and pilots experience whole body vibration characterized by common frequencies of 16 and 100 Hz due to the movement of the rotors. The effect of this ongoing vibration on patients with TBI is currently unknown. In addition, transported patients may also experience a mild hypoxia in flight, which has been associated with increased morbidity and mortality following TBI. Secondary brain injury can occur by exposure to posttraumatic insults, exacerbating the primary brain injury and contributing to poor outcomes. For this study, we developed a porcine model of traumatic brain injury to investigate the effects of the continuous vibration and hypoxia of simulated aeromedical evacuation on the injured brain. We hypothesized that the combination of vibration and hypoxia would contribute to secondary brain injury following TBI, as evidenced by serum biomarkers or neuroimaging. We used serum biomarkers, neurologic monitoring, blood gas analysis, imaging, and histology to evaluate the effects of vibration and hypoxia following TBI. Serum biomarkers, magnetic resonance imaging, and histology demonstrated changes following TBI but were similar between groups with or without vibration after TBI. Our study demonstrated that pigs subjected to post-TBI vibration, hypoxia, or both did not demonstrate any detectable differences by 6 hours after injury.

2.0 INTRODUCTION

Traumatic brain injury (TBI), defined as alteration of brain function as a result of external force, is a growing concern in both the military and civilian populations. TBI can categorized as mild, moderate, or severe based on initial Glasgow Coma Scale, duration of unconsciousness, and duration of amnesia [1]. It is estimated that 1.7 million people annually present for evaluation of TBI associated symptoms in the United States alone [2]. Observational studies estimate the mortality rate of severe TBI to be up to 30-40%, with nearly 60% of survivors experiencing long term neurological impairment [3]. Unfortunately, the incidence of TBI is likely underreported, as the numbers reported by the Center for Disease Control and Prevention do not include injuries sustained without receiving medical treatment and military casualties.

Explosive devices used in military combat commonly result in a blast-induced TBI. With the use of improvised explosive devices seen in Operation Iraqi Freedom/Operation Enduring Freedom, TBI has been designated a signature injury of soldiers deployed during these and ongoing international conflicts [4]. Warfighters participating in combat operations have a reported 8-22% incidence of TBI [5]. Those with the most severe TBI often require emergency medical evacuation, first by helicopter then by fixed wing aircraft. During aeromedical transport, wounded warfighters and pilots experience whole body vibration characterized by common frequencies of 16 and 100 Hz due to the movement of the rotors [6]. The effect of this ongoing vibration on patients with TBI is currently unknown. In addition, transported patients may also experience a mild hypoxia in flight, which has been associated with increased morbidity and mortality following TBI [7-9]. Secondary brain injury can occur by exposure to posttraumatic insults, exacerbating the primary brain injury and contributing to poor outcomes.

For this study, we developed a porcine model of traumatic brain injury in order to investigate the effects of the continuous vibration and hypoxia of simulated aeromedical evacuation on the injured brain. We hypothesized that the combination of vibration and hypoxia would contribute to secondary brain injury following TBI, as evidenced by serum biomarkers or neuroimaging.

3.0 METHODS

3.1 Animal Model

Female pigs with an average weight of 40 kg were obtained from Isler Genetics (Prospect, OH) and used for all experiments. The pigs were fed a diet of standard chow and allowed water *ad libitum*. Housing was provided by the Laboratory Animal Medical Services facility at the University of Cincinnati, maintaining a climate-controlled environment with a 12 hour light-dark cycle. Pigs were housed for 2-7 days prior to experimental use to allow for acclimatization to the new environment. The study protocol was reviewed and approved by the University of Cincinnati's Institutional Animal Care and Use Committee and the Air Force Medical Supporty Agency Office of Research Oversight and Complaince. Animals were handled and studies were conducted under a program of animal care accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International and in accordance with the National Research Council's 2011 *Guide for the Care and Use of Laboratory Animals* (in compliance with Department of Defense Instruction 3216.1).

Porcine Model for TBI: Prior to intervention, anesthesia was induced using intramuscular injection of a mixture of telazol, xylazine and atropine. Pigs were then orotracheally intubated and anesthesia was maintained using inhaled 2% isofluorane for the duration of the experiment. Two peripheral intravenous catheters were placed in the ears for fluid administration. The femoral artery was cannulated via a cut-down technique and a catheter was placed for continuous blood pressure monitoring. The anesthetized pigs were then placed prone on a table and the scalp was removed to expose the skull. A 20 mm burr hole was made overlying the right hemisphere and centered 16 mm anterior to the coronal suture and 10 mm lateral to the sagittal suture. The dura was left intact. A 6 mm burr hole was placed in the skull overlying the left hemisphere and centered similarly to the right side, creating mirrored craniotomies. This model is depicted in Figure 1. The dura was opened in the 6 mm burr hole and an intracranial pressure monitor was placed into the cerebral parenchyma just below the dura. Intracranial pressure was monitored by a Raumedic Neuromonitoring apparatus (Raumedic, Mills River, NC, USA). Controlled cortical injury was achieved using an automated pneumatic piston with 15 millimeter diameter set to induce a consistent force delivered into the intact dura at 400 meters/second with a depth 15 millimeters and a dwell time of 4 milliseconds (Hatteras Instruments, Inc. Cary, North Carolina). Preliminary experiments demonstrated these settings to maximize cerebral injury without inducing an immediately lethal injury.

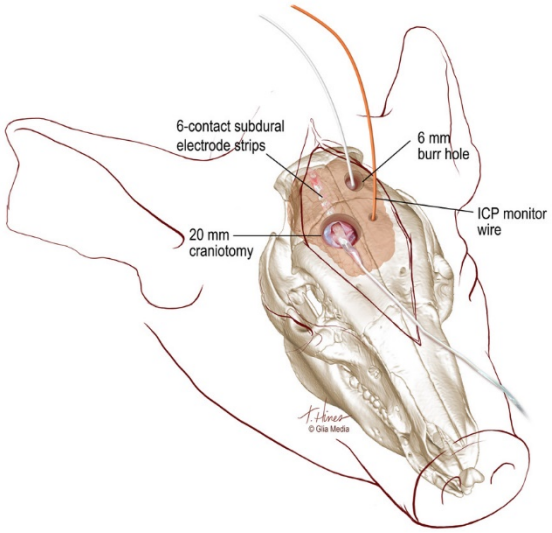

Figure 1. Porcine model for TBI.

3.2 Neuromonitoring

Following TBI but prior to vibration, several neuromonitoring devices were placed. A 6 lead electroencephalogram monitor was placed in a subdural position through the 20mm burr hole. Four electroencephalogram leads were placed posterior to the site of injury, and two electrodes were placed anterior to the injury. Brain tissue oxygenation was monitored via a Licox probe (Integra, Saint Priest, France) placed in uninjured grey matter in a gyrus adjacent to the site of injury. In the same gyrus, a Bowman Perfusion probe (Hemadex, Cambridge, MA, USA) was placed to monitor brain tissue perfusion. All data was monitored and recorded by a CNS Monitor (Moberg Research INC, Ambler, PA, USA).

3.3 Vibration and Hypoxia Model

A customized vibration table was purchased from Cleveland Vibrator Company (Cleveland, OH, USA). Following TBI, the pig was placed on a standard military stretcher and secured to the vibration table. The vibration table was set to vibrate at a consistent frequency of 16 Hz for the entire duration of the experiment. Pigs underwent 2 hours of vibration or sham vibration, lying on the stretcher on the table without the vibration. During the vibration period, pigs also underwent concomitant exposure to hypoxic conditions titrated to a peripheral oxygen saturation of 88%, or were maintained in a normoxic state. Following the simulated transport period including vibration/hypoxia exposure, pigs were observed and monitored for an additional 4 hours, for a total experimental duration of 6 hours post-injury.

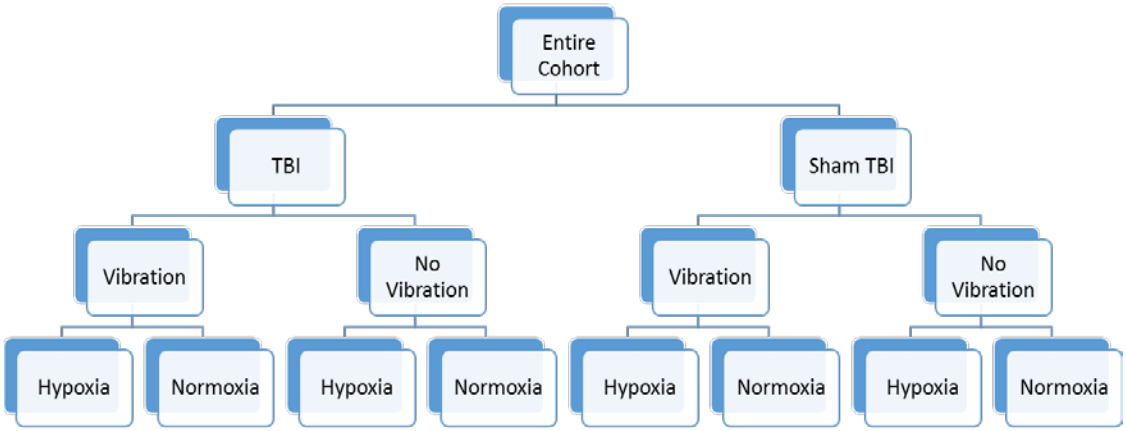

Figure 2. Experimental groups.

3.4 Electrolyte and Physiologic Monitoring

Blood samples were obtained at baseline prior to TBI, and every hour thereafter. Whole blood samples were analyzed with an iSTAT (Abaxis, Union City, CA) to determine hemoglobin, hematocrit, blood urea nitrogen, glucose, chloride, sodium, potassium, pH, partial pressure of carbon dioxide, bicarbonate, anion gap, lactate, and base excess.

Serum and Tissue Analysis

Whole blood samples obtained via arterial catheter were centrifuged at 8000 rpm for 15 min in serum separator tubes. All samples were stored at -80°C. Serum was then analyzed for multiple pro-inflammatory cytokines and chemokines by a multiplex enzyme-linked immunosorbent assay (Quansys, Logan, UT), including interleukin 1 beta (IL-1β), IL-6, IL-8, tumor necrosis factor alpha (TNFα). Additionally, hypoxia inducible factor 1 alpha (HIF1α) was analyzed as a marker of hypoxic injury and syndecan-1 was measured as a marker of endothelial glycocalyx injury. Serum biomarkers of TBI were also analyzed, including S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP) and neuron specific enolase (NSE).

3.5 Brain Imaging

Six hours after the traumatic brain injury, pigs were converted from isofluorane anesthesia to intravenous propofol for transport to magnetic resonance imaging (MRI). The pigs were then transported with propofol sedation to obtain a brain MRI. Initial MRI imaging was performed following pig euthanasia and decapitation, but the protocol was modified to be performed in a live, sedated animal for the second half of the study to optimize the quality of the MRI. Standard non-contrast MRI images were obtained in order to assess blood flow and tissue damage. MRI images were then read and analyzed by a radiologist blinded to the experimental groups.

3.6 Brain Extraction and Histology

Following euthanasia, the brain was extracted via craniotomy and preserved in 10% buffered formalin. Sections were preserved and stained with cresyl violet and FluoroJade C to analyze the extent of cerebral tissue damage.

4.0 RESULTS

4.1 Arterial Blood Gas Analysis and Electrolytes

The pH and pO2 were similar in both the pigs that were vibrated versus the pigs that were not vibrated and the pigs that underwent TBI versus those undergoing sham injury only. In the hypoxia group, the mean pO2 during the two-hour period of hypoxia was significantly lower than the normoxia group (Figure 3). The pCO2 was also similar in all groups. However, the hypoxic, sham TBI with vibration group did seem to have a trend towards increased levels compared to the hypoxic, sham TBI without vibration group (Figure 4). There were no other differences appreciated in the ABG or electrolyte results.

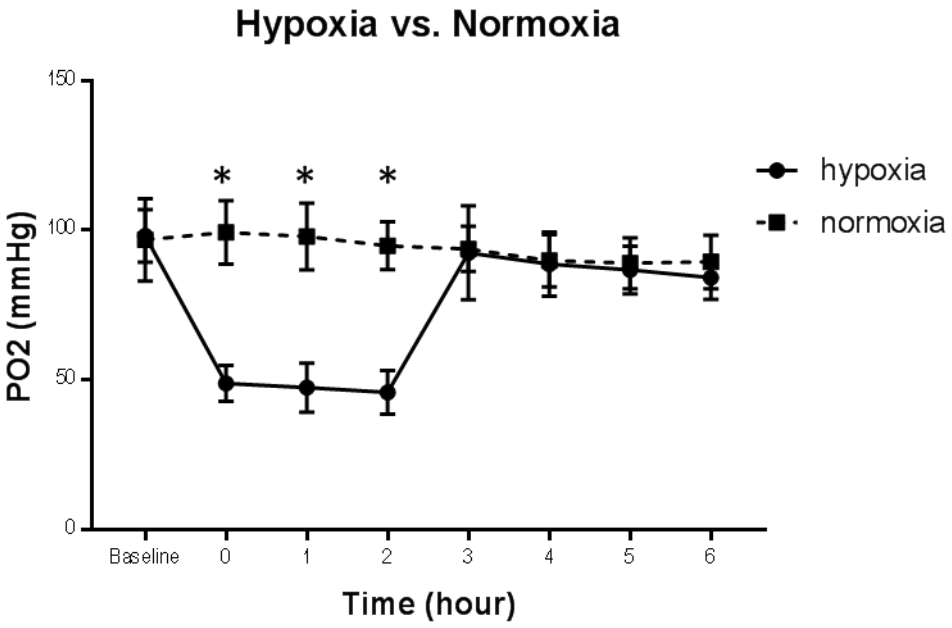

Figure 3. Hypoxia versus normoxia groups over study period.

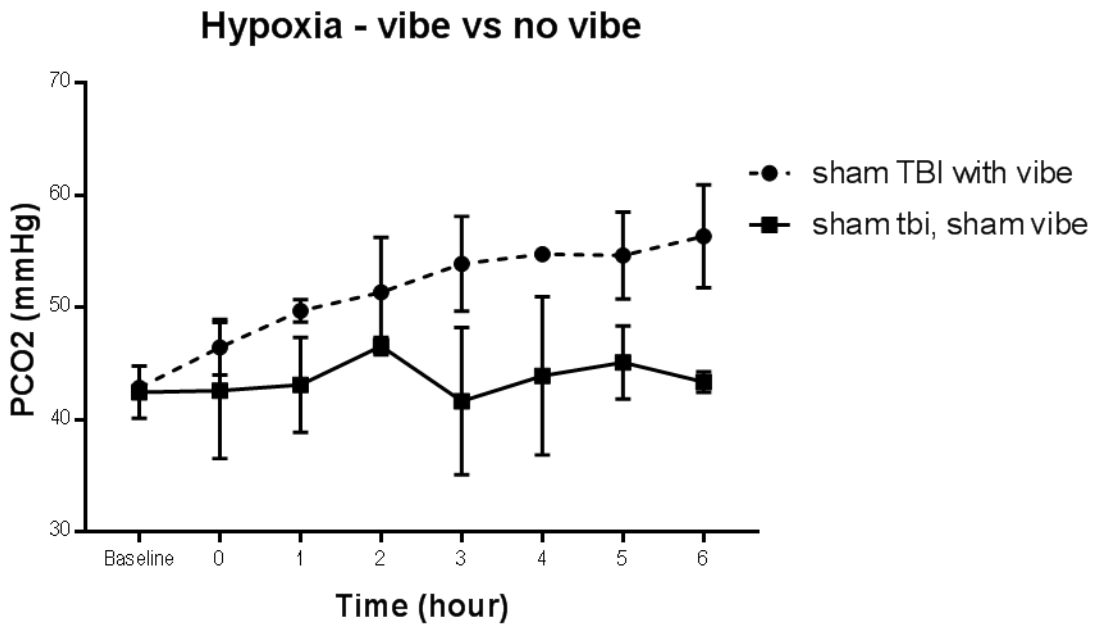

Figure 4. Hypoxia, sham TBI with vibration versus hypoxia, sham TBI without vibration.

4.2 Neuromonitoring

The mean ICP during cerebral impact in the TBI group was 279.8 ± 56.2 mmHg. The brain oxygenation levels (PbtO2) were similar between the TBI hypoxia versus normoxia groups.

4.3 Serum Biomarkers

There were no differences in HIF1α, Syndecan-1, or S100B levels in the TBI, vibration or hypoxia groups compared to their respective controls (n=4-5 in TBI and n=2 in sham TBI groups). There were also no differences in IL-1β, IL-6, IL-8, TNFα or GFAP in the TBI, vibration or hypoxia groups compared to their respective controls (n= 9-11 in TBI groups and 2-7 in sham TBI groups).

Human NSE levels were similar between vibration and hypoxia groups compared to their controls. The levels were also similar between TBI groups, but the TBI group did significantly increase over time (Figure 5). The levels did not change when adding hypoxia or vibration to the TBI group (Figures 6 and 7). The sham TBI groups did not show this increase over time. The porcine NSE multiplex enzyme-linked immunosorbent assay was attempted, but did not work (n= 9-11 in TBI groups and 2-7 in sham TBI groups).

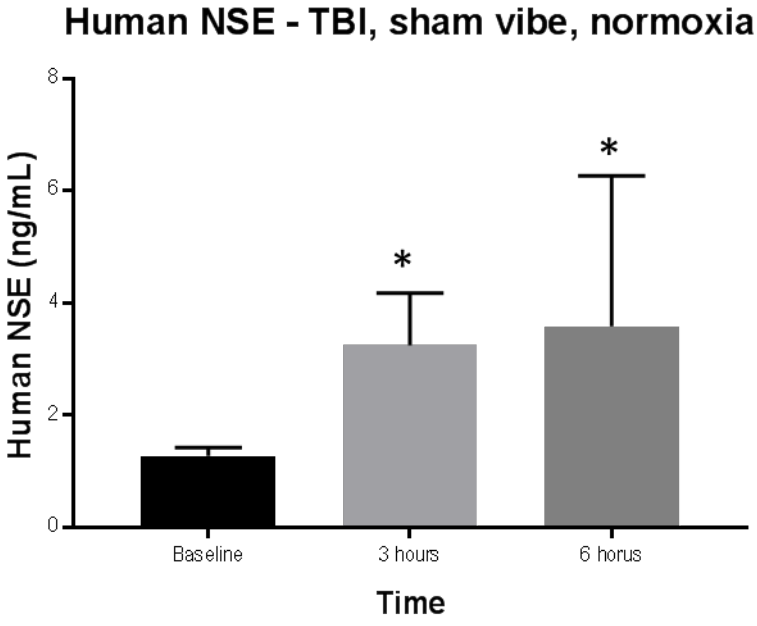

Figure 5. NSE levels over time in the TBI group.

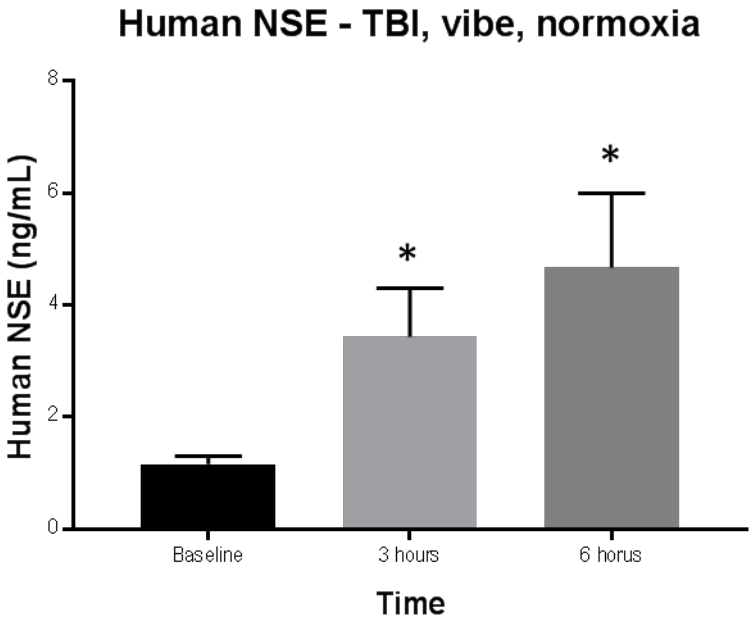

Figure 6. NSE levels in TBI with vibration.

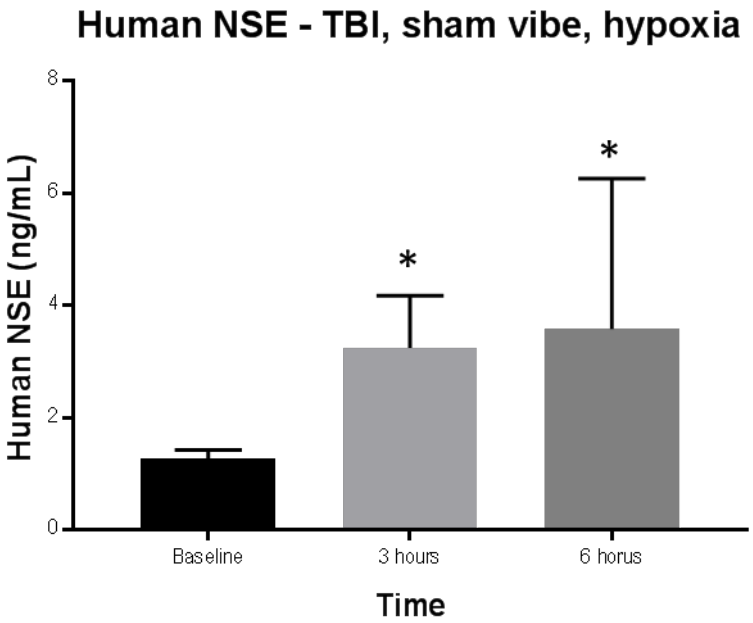

Figure 7. NSE levels in TBI with hypoxia.

4.4 Magnetic Resonance Imaging and Histology

The TBI was able to be imaged by MRI and histology. The addition of vibration and/or mild hypoxia did not lead to MRI detectable or histologic changes compared to TBI alone by 6 hours following the primary injury (Figures 8-10)**.**

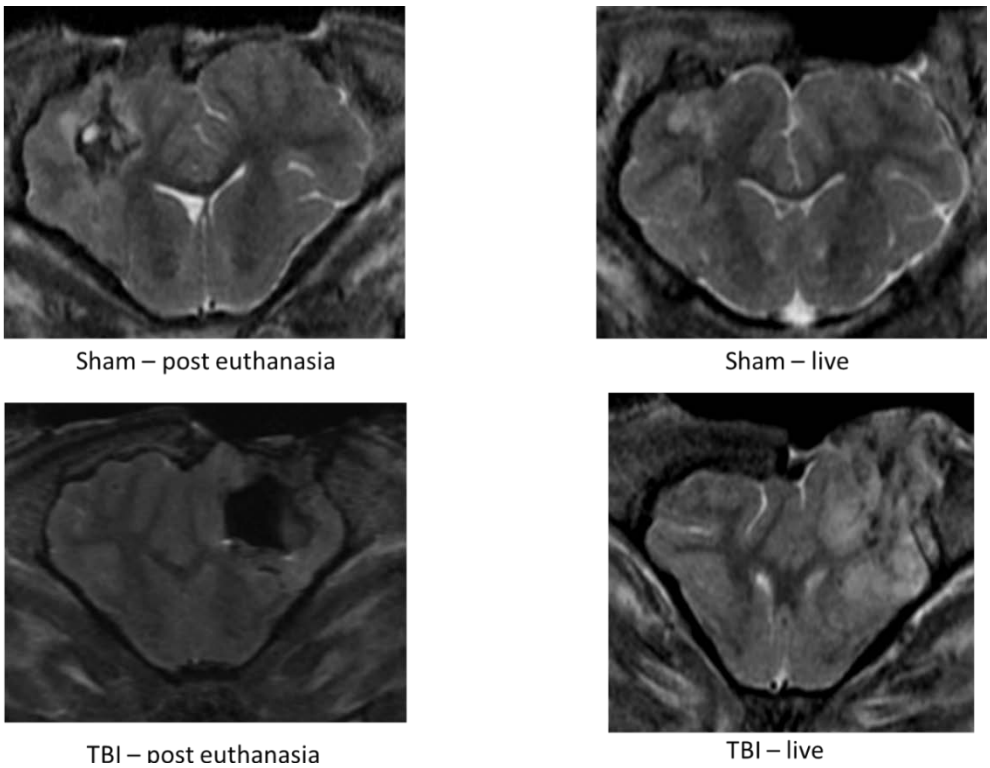

Figure 8. MRI results with post-euthanasia and live protocols.

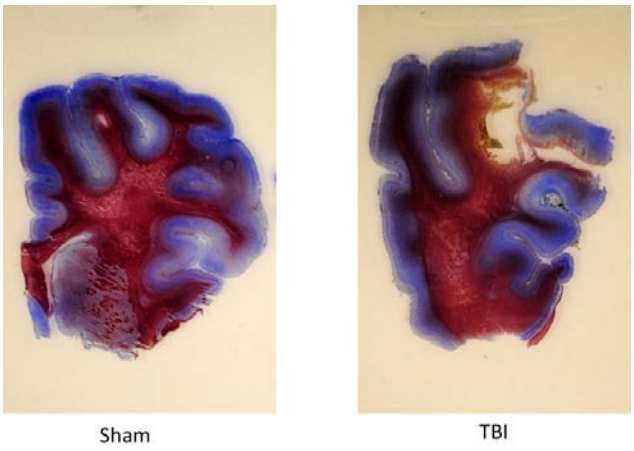

Figure 9. Histological analysis – cresyl violet stain.

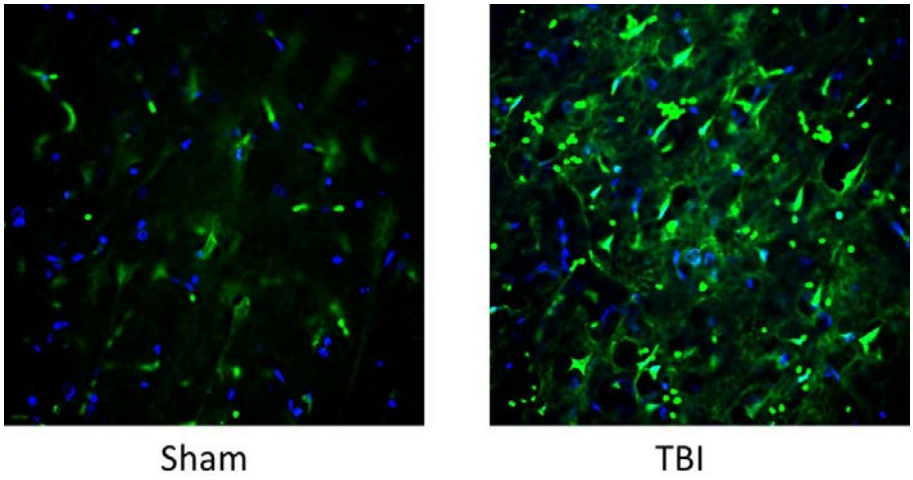

Figure 10. FluoroJade C.

5.0 DISCUSSION

Traumatic brain injury is a common injury both in military and civilian sectors. Aeromedical transport following injury in both settings is common, and although it may expedite definitive care, the transport environment includes inherent factors such as vibration and hypoxia that may contribute to secondary brain injury, thus potentially exacerbating the effects of TBI [7, 10]. Although hypoxia has been shown to be associated with worsened outcomes after TBI, the effects of vibration alone or in combination with hypoxia have not been studied. These effects are important for injured patients and wounded warriors who are evacuated by either rotary or fixed wing transport following a traumatic injury.

In this study, we used serum biomarkers, neurologic monitoring, blood gas analysis, imaging and histology to evaluate the effects of vibration and hypoxia following TBI. Serum biomarkers, MRI and histology demonstrated changes following TBI but were similar between groups with or without vibration after TBI. Schulte et al. previously demonstrated a lack of vibration effect on S100B levels following exercise to exhaustion [11]. However, to our

knowledge, this is the first study that demonstrates that vibration does not have an acute, independent effect on TBI.

Serum biomarkers have been utilized in humans to supplement the diagnosis and support the prognosis of traumatic brain injury, with GFAP, NSE, S100B and ubiquitin carboxy-terminal hydrolase-1 being the most commonly studied [12]. Although biomarkers have been reliably used in rodent models of TBI as well, there are few studies that have demonstrated early biomarker differences following TBI in large animal models [13]. While our data demonstrate a significant increase in NSE over time in the TBI group that was not found in the sham group, the absolute NSE level was not significantly different between TBI and sham at any time point. Costine et al. studied serum biomarker elevation in piglets following TBI and found a significant increase in NSE post-injury [14]. Additionally, Korley et al. recently demonstrated increased serum GFAP and neurofilament light chain levels after TBI in a porcine model that improved at 24 hours after early treatment with valproic acid [15]. Both of these prior studies noted that serum biomarker levels peaked at 24 hours following injury, potentially explaining why the NSE levels in this study were not significantly higher in the TBI group during the limited six hour observation time post-injury.

Hypoxia has been associated with adverse outcomes in patients with TBI. However, our study did not demonstrate any deleterious effects of hypoxia on pigs following TBI. However, there is a paucity of data studying serum biomarkers in TBI and hypoxia. Yan et al. showed an increase in cytokines and serum biomarkers in hypoxic TBI patients, but they did not show an elevation in NSE in the hypoxia compared to the normoxia group [16]. In addition, Thelin et al. found that serum biomarkers including HIF1α and vascular endothelial growth factor were increased in rats following a controlled cortical impact TBI but not in those subjected to a 30 minute period of hypoxia following TBI [17]. Scultetus et al. demonstrated that hypobaric conditions might worsen TBI outcomes in a porcine model [9]. Our group has previously shown the effect of hypobaric conditions on secondary brain injury in a murine model and Skovira et al. also demonstrated similar findings in a rat model [8, 18]. Future investigations into the combined effects of hypobaric conditions and vibration on TBI may be of benefit. In addition, studies continuing to search for a reliable serum biomarker for secondary brain insults after TBI may be beneficial.

There are several limitations of this study. First, the sham TBI groups only had two pigs per group which may be the cause for us not finding a significant difference when comparing sham TBI and TBI cohorts. The decision was made to limit utilizing additional control animals when we did not observe a difference in the pigs that underwent vibration. Second, we utilized only a single frequency of vibration. A more complex vibration scheme to model that of aeromedical transport flights may provide additional data, but the 16 Hz chosen was a starting point for a recognized vibration frequency experienced in the common aircraft used that may contribute to neurological symptoms. Third, the dose and time effect of hypoxia after TBI is not known, thus the depth and duration of hypoxia after TBI in a porcine model may need further evaluation to demonstrate acute effects. Lastly, our study is limited to outcomes in the first 6 hours following injury. Based on recent literature, additional differences may have been observed if the study was performed over a longer time course.

In conclusion, this is a novel study evaluating the combined and independent effects of hypoxia and vibration on short-term outcomes following traumatic brain injury. Our study demonstrated that pigs subjected to post-TBI vibration, hypoxia, or both did not demonstrate any detectable differences by six hours after injury.

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LIST OF ABBREVIATIONS AND ACRONYMS

GFAP glial fibrillary acidic protein

MRI magnetic resonance imaging

NSE neuron specific enolase

S100B S100 calcium-binding protein B

TBI traumatic brain injury