NAVAL MEDICAL RESEARCH UNIT SAN ANTONIO

UTILIZING SPECTRAL TRANSCRANIAL DOPPLER TO CHARACTERIZE CEREBRAL HEMODYNAMICS IN A NON-HUMAN PRIMATE (RHESUS MACAQUE)

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EXPEDITIONARY AND TRAUMA MEDICINE DEPARTMENT
COMBAT CASUALTY CARE AND OPERATIONAL MEDICINE DIRECTORATE

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Declaration of Interest

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Abbreviations

AALAC	Association for Assessment and Accreditation for Laboratory Animal Care International
ACA	Anterior Cerebral Artery
CTA	Computed Tomography Angiography
EDV	End Diastolic Velocity
EEG	Electroencephalography
ET	Endotracheal Tube
$ETCO_2$	End-Tidal Carbon Dioxide
IACUC	Institutional Animal Care and Use Committee
ICA	Internal Carotid Siphon
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MFV	Mean Flow Velocity
MHz	Megahertz
MTF	Medical Treatment Facility
NHP	Non-human Primate
OA	Ophthalmic Artery
PI	Pulsatility Index
PSV	Peak Systolic Velocity
RI	Resistance Index
SD	Standard Deviation
SECNAVINST	Secretary of the Navy Instruction
StO_2	Tissue Oxygen Saturation
TBI	Traumatic Brain Injury
TCD	Transcranial Doppler

Executive Summary

Background: Hemodynamic resuscitation methods are employed to attenuate tissue hypoxia and maintain circulatory homeostasis during hemorrhagic shock. There is increasing advocacy for 'permissive hypotension' resuscitative methods to prevent exsanguination. While data supports this strategy to decrease hemorrhage, questions remain regarding its physiologic effect on the brain. Transcranial Doppler (TCD) ultrasonography is a non-invasive modality that can be used to monitor cerebral perfusion during resuscitation. Utilizing a non-human primate (NHP) model, our goal was to use TCD ultrasonography to characterize normal cerebral hemodynamics, allowing for future comparative analyses of cerebral hemodynamics in animal models of polytraumatic hemorrhagic shock. **Materials and Methods:** Concurrent with an ongoing NHP protocol, the ophthalmic artery (OA) was insonated to establish baseline TCD values. A transorbital acoustic window was used, imaging was obtained with a 2.0 MHz transducer probe. OA was chosen because the transtemporal window for middle cerebral artery (MCA) resulted in suboptimal waveforms. **Results:** The following TCD results represent the mean ± standard deviation, n = 10. Pulsatility index (1.66±0.33), mean flow velocity (MFV) (21.64±5.48 cm/s), peak systolic velocity (45.46±5.48 cm/s), end diastolic velocity (9.84±3.91 cm/s) and resistance index (0.79±0.08). **Conclusions:** We discovered that Rhesus macaques are absent of an adequate transtemporal acoustic window for MCA insonation, and normal resting OA MFV pressure in NHPs mimics reported OA MFV in humans. This data is foundational for our future studies to evaluate cerebral hemodynamics during hemorrhage and the degrees of severity in hemorrhagic shock. Our future goals include the utilization of TCD technology to elucidate a safety threshold for permissive hypotensive resuscitation or aggressive fluid resuscitation as it pertains to cerebral blood flow.

INTRODUCTION

In the United States, injury accounts for one third of deaths under the age of 44[1]. Of these injuries, hemorrhage is a major cause of death[1-3] second only to traumatic brain injuries[1]. A retrospective analysis by Eastridge *et al*. 2012 evaluated the outcomes of wounded military personnel who died of injuries prior to reaching a medical treatment facility (MTF). Of those pre-MTF deaths, hemorrhagic shock accounted for 90% of potentially survivable deaths in the battlefield[4]. Hemodynamic resuscitation methods are employed to attenuate tissue hypoxia and maintain circulatory homeostasis thereby protecting end organ function[5], and medical standard of care for volume replacement is rapid infusion of crystalloid solution or blood products[6]. There is gaining advocacy for 'permissive hypotension' resuscitative methods, the strategy of which is to administer fluid to maintain a systolic pressure of 90 mmHg or below until definitive hemostasis is obtained, most often surgically. The intent of this strategy is to reduce ongoing bleeding due to loss of thrombus (ie. prevent 'popping of the clot') attributed to increased vascular hydrostatic pressure[5, 7]. Questions remain regarding the safety of this strategy, specifically the effects of prolonged hypotension on the brain and neurologic outcomes. This strategy is not recommended in the setting of traumatic brain injury (TBI), but animal models suggest cerebral derangements even in the absence of direct TBI. Defining the limits of cerebral blood flow is critical to the safe implementation of a permissive hypotension strategy.

Transcranial Doppler (TCD) ultrasonography is an FDA approved non-invasive modality utilized to evaluate real-time cerebral hemodynamics. Spectral Doppler waveforms are visual displays of blood flow velocities within a specified cross-sectional area of blood vessel as a time-velocity (i.e. cm/s)[16]. The technology employs the Doppler Effect and the Bernoulli principal to determine vessel blood flow velocities[16, 17]. Low frequency transducers (≤ 2 MHz) insonate

intracranial vessels through cerebral 'acoustic windows' to offer real-time evaluation of cerebral hemodynamics[16-18]. Rune Aaslid et al. (1982) first demonstrated the clinical utility of TCD to assess arterial flow velocities in patients[19]. Currently, TCD is clinically utilized in hemorrhagic stroke, ischemic stroke, and traumatic brain injury[20]. It has been utilized in numerous non-human primate (NHP) studies as a non-invasive modality to evaluate blood flow velocity, structure and function of organs such as brain, lung and heart[13-15]. During hemorrhagic shock, compensatory and auto-regulatory mechanisms are activated to preserve cerebral perfusion[21], and changes in cerebral blood flow due to hypotension can have permanent deleterious effects[22]. TCD is an ideal modality to track these changes real time.

There are no reported spectral TCD characterizations of cerebral indices during profound hemorrhagic shock. Utilizing non-human primate Rhesus macaques from an ongoing study of polytrauma and hemorrhagic shock (Sheppard et al. submitted for publication), our goal was to employ a non-invasive TCD ultrasound system to characterize normal cerebral hemodynamics for the following cerebral indices prior to traumatic injury and hemorrhagic shock: mean flow velocity (MFV), peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI) and resistance index (RI). Establishing normal values of cerebral perfusion in our NHP model would facilitate defining baseline values for future comparative analyses of cerebral hemodynamics at various time points of polytraumatic hemorrhagic shock. This data does not exist in the literature and represents a critical gap in translational research knowledge.

MATERIALS AND METHODS

Ethical Approval and Accreditation:

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the 711th Human Performance Wing, Joint Base San Antonio-Fort Sam Houston, and conducted in accordance with the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animals Resources, National Research Council, National Academy Press, 2011. All procedures were performed in facilities accredited by the Association for Assessment and Accreditation for Laboratory Animal Care International (AAALAC).

Animal protocol:

Rhesus Macaques utilized in this study were housed in compliance with the Secretary of the Navy Instruction (SECNAVINST) 3900.38C regulations. Ten male Rhesus Macaques (n=10) weighing 8-12 kilograms and aging 5-12 years were utilized, all of which were undergoing other approved research protocols at this institution.

Food and water was restricted for 12 hours prior to surgery. NHPs were sedated with Telazol (3.0mg/kg), pre-medicated with an analgesic (Buprenex 0.03mg/kg) and weighed. Airway was intubated and animals were placed on a Dräger Apollo Anesthesia Workstation (Dräger Medical Inc., Telford, PA, USA) with volume-controlled respiration (10mL/kg) at 12-15 breaths per minute, FiO_2 of 21-25% and isoflurane (1.0-2.0%) inhalational anesthesia. Core body temperature was monitored continuously and maintained between 36.0-38.0°C.

The right femoral artery and vein were cannulated to facilitate blood sampling and continuous blood pressure monitoring. The left femoral artery was cannulated to facilitate the trauma protocol hemorrhage.

Systemic perfusion monitoring was also conducted via end-tidal carbon dioxide ($ETCO_2$) and tissue oxygen saturation (StO_2). Deltoid StO_2 was monitored continuously using an InSpectra™ StO_2 Tissue Oxygenation Monitor (Hutchinson Technology Inc., Hutchinson, MN, USA).

Transcranial ultrasonography:

Initially, the middle cerebral artery (MCA) was chosen for cerebral monitoring through the transtemporal acoustic window. However, MCA insonation yielded inconsistent and suboptimal spectral waveforms. To monitor cerebral perfusion, the ophthalmic artery (OA) was insonated through the orbital acoustic window using a ROBOTOC2MD TCD (Multigon Industries Inc., Yonkers, NY) ultrasound system. To maintain reproducibility, 2 researchers who have both performed over 270 TCD scans were tasked for this study. Utilizing a 2.0 MHz transducer probe, placed over the closed eyelid and angled slightly medially, the ophthalmic artery was identified by waveform. Conductive ultrasound gel was utilized to enhance Doppler signal. Acoustic signal was recorded using ROBOTOC2MD TCD system software package. After identifying and acquiring adequate waveforms, acoustic signals were recorded continuously for 30 seconds. Continuous per second data for the following indices were recorded, calculated and displayed by the ROBOTOC2MD TCD system software: MFV, PSV, EDV and PI. Resistance index was calculated as: $RI = (PSV - EDV)/PSV$[23]. Concurrent

systemic hemodynamics were recorded to allow for comparative analysis. Data is presented for each index as the mean of 30 seconds of continuous data ± standard deviation (SD), n = 10.

RESULTS

Cerebral and Systemic Perfusion Indices at Rest

In a cohort of 10 healthy anesthetized male Rhesus macaques, spectral TCD ultrasonography was employed to characterize normal cerebral hemodynamics. The ophthalmic artery (OA) was insonated through the transorbital window. Blood flow of the ophthalmic artery travels towards the transducer and is represented as a Doppler shift that is displayed as peaks of sinusoidal like waveforms (Figure 1). TCD ultrasonography demonstrated the following outcomes for these cerebral perfusion indices as normal rates or values for Rhesus macaques: PI (1.66±0.33), MFV (21.64±5.48 cm/s), PSV (45.46±5.48 cm/s), EDV (9.84±3.91 cm/s) and RI (0.79±0.08) (Table 1A, Figures 2A-F). Systemic perfusion was monitored by tissue oxygen saturation (StO_2) and end tidal CO_2 ($ETCO_2$). Normal resting values for StO_2 was (89.56±8.28 %) with an $ETCO_2$ pressure of (43.00±2.87 mmHg) (Table 1B). Attenuation of blood pressure (Table 1B) is a common characteristic of anesthesia and fasting restrictions imposed 12 hours preceding surgical procedure. However, invasive continuous blood pressure monitoring demonstrated normal values of systolic pressure (83.56±14.67 mmHg), diastolic pressure (54.33±7.94 mmHg) and mean arterial pressure (MAP) (70.65±5.33 mmHg) (Table 1B).

DISCUSSION

Animal models of hemorrhage and shock are employed to develop new therapies and resuscitative adjuncts that are translatable to human trauma patients. In this study, concurrent with other ongoing protocols, NHPs were selected for their phylogenetic and anatomic similarity to humans, with consistent anatomic analogy in cerebral vasculature. The use of hypotensive resuscitation[24, 25] has steadily increased over the last 20 years. The rapid infusion of fluids has contributed to an increase in blood pressure that can lead to the loss of formed thrombi, 'popping the clot,' in addition to hemodilution of coagulation products within the blood[26, 28]. In contrast, hypotension increases morbidity and mortality in trauma patients with traumatic brain injury (TBI) [29, 30], and it has been reported that intraoperative hypotension is a common secondary insult with TBI victims[31]. According to the guidelines by the Brain Trauma Foundation, hypotension must be avoided and systolic pressure must remain above 90 mmHg[32] with some groups suggesting systolic pressure of >110 mmHg is necessary for improved overall patient outcome[33].

It has been shown that the quality of systemic perfusion is not always indicative of the quality of cerebral perfusion. The monitoring of patients in shock requires the use of invasive techniques such as arterial line placement to evaluate circulatory pressure and signs of hypoperfusion[22, 34, 35]; but generally only changes in systemic hemodynamics are monitored to guide therapy[35, 36], without regard to real time cerebral flow dynamics. Utilizing non-invasive spectral TCD offers real-time continuous monitoring of cerebral perfusion that could be implemented in pre- and interim-phases of care as well as post-surgical intensive care[18, 37, 38].

We discovered that Rhesus macaques of this size are absent of an adequate transtemporal acoustic window for middle cerebral artery (MCA) insonation, a limitation seen in

approximately 10 – 20% of humans[39-41]. Previous investigations have demonstrated the efficacy and utility of transorbital insonation of the OA in the absence of a transtemporal window to evaluate cerebral hemodynamics[42-44] and our data is comparable to these human data.

We have established values for normal cerebral OA flow velocities in NHPs which are comparable to human OA MFV of (21±5 cm/s)[16, 23, 45].

These data provide a baseline data set to compare against, within the same species, during research on cerebral hemodynamics in shock and TBI. Given the comparable values to human data, this data is highly translatable to human trauma patients, and may allow for more targeted resuscitation protocols from the translational data obtained during animal shock protocols.

CONCLUSION

The results of this study established normal flow velocities and vascular indexes of healthy Rhesus macaques. Additionally, it elucidated the limitations of MCA insonation through the transtemporal acoustic window and validated the contingent approach of OA insonation through the transorbital window. This data is foundational for our future studies to evaluate the hemodynamics of cerebral perfusion during hemorrhage across varying degrees and severity of hemorrhagic shock. This data also establishes baseline values for NHP cerebral blood flow that can be capitalized upon in a multitude of research arenas. Our future perspective is to utilize TCD technology to elucidate a threshold value that can better determine when it is most appropriate to employ permissive hypotensive resuscitation or aggressive fluid resuscitation in the setting of hemorrhage and trauma.

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Table 1. Normal Baseline NHP Cerebral and Systemic Characteristics. Table data values are expressed as the mean, (n = 10).

A.

Baseline OA Cerebral Indices NHP

Clinical Index	Value		+/- (STDEV)
Pulsatility Index	1.66	-	0.33
Mean Flow Velocity	21.64	cm/s	5.48
Peak Systolic Velocity	45.46	cm/s	5.48
End Diastolic Velocity	9.84	cm/s	3.91
Resistance Index	0.79	-	0.08

B.

Baseline Systemic Indices NHP

Clinical Index	Value		+/- (STDEV)
StO_2	89.56	%	8.28
$ETCO_2$	43.00	mmHg	2.87
Systolic	83.56	mmHg	14.67
Diastolic	54.33	mmHg	7.94
MAP	70.65	mmHg	5.33

Figure 1: Transcranial Doppler spectral Doppler insonation of the intracranial ophthalmic artery. Ultrasound beam with a transmission frequency of ≤ 2.0 MHz through the transorbital window insonates the ophthalmic artery.

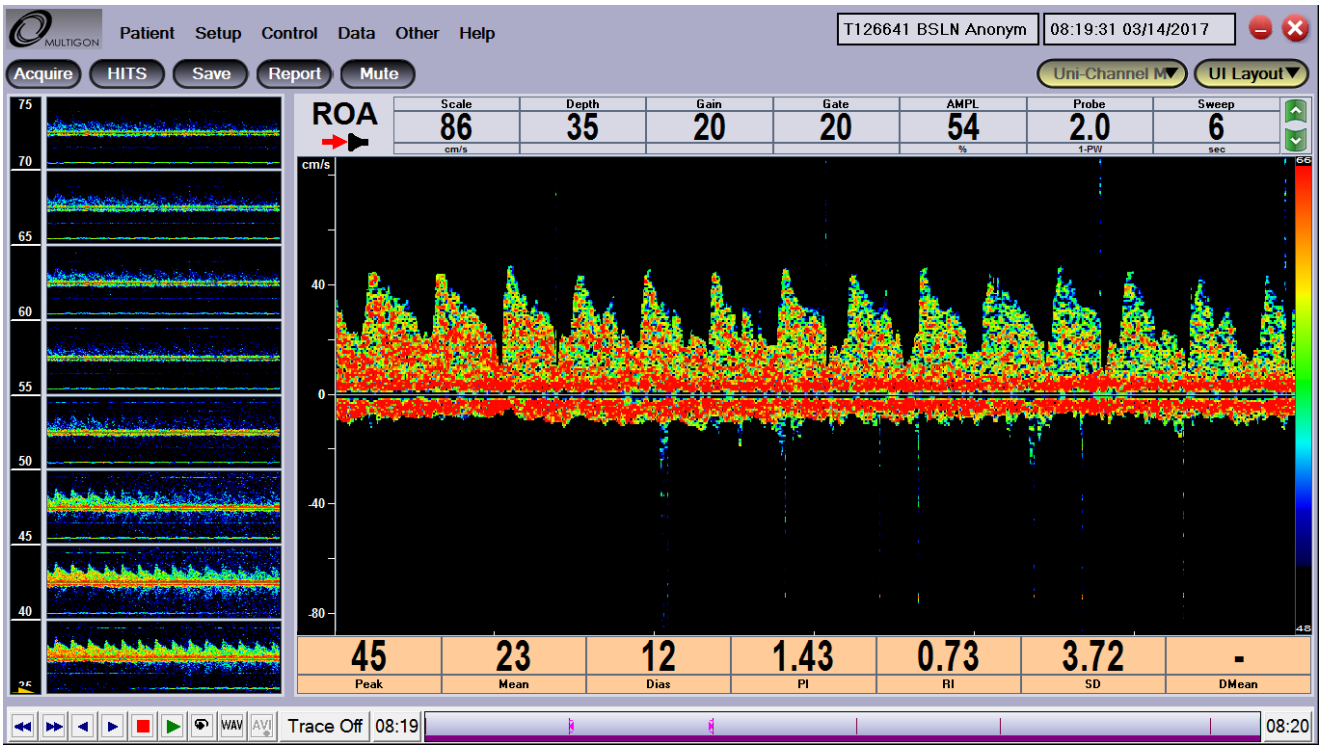
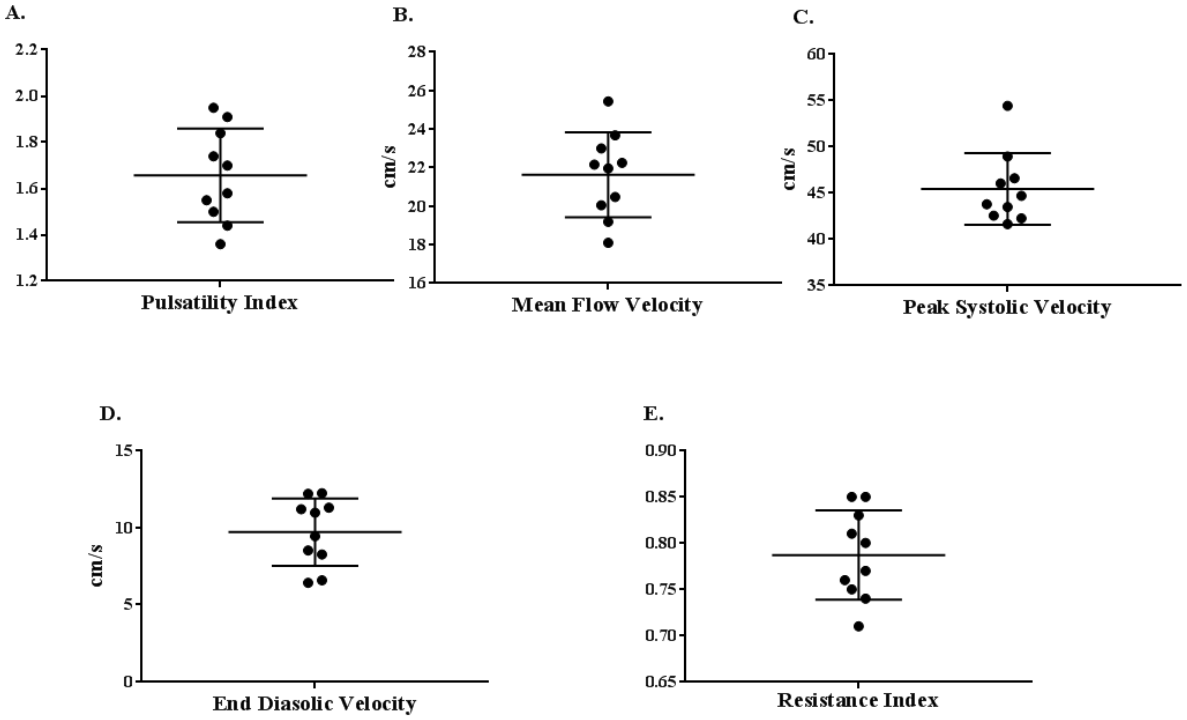


Figure 2. Normal cerebral indices at rest for Rhesus macaques. The ophthalmic artery was insonated through the transorbital window. The x-axis identifies the cerebral index, the y-axis values corresponds to flow velocities or a calculated vascular index. Flow velocities are presented in centimeters per second (cm/s), index values are calculated values and are represented numerically. Dot plots represent the population and display the mean ± standard deviation (n = 10).



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14. ABSTRACT

Background: Hemodynamic resuscitation methods are employed to attenuate tissue hypoxia and maintain circulatory homeostasis during hemorrhagic shock. There is increasing advocacy for 'permissive hypotension' resuscitative methods to prevent exsanguination. While data supports this strategy to decrease hemorrhage, questions remain regarding its physiologic effect on the brain. Transcranial Doppler (TCD) ultrasonography is a non-invasive modality that can be used to monitor cerebral perfusion during resuscitation. Utilizing a non-human primate (NHP) model, our goal was to use TCD ultrasonography to characterize normal cerebral hemodynamics, allowing for future comparative analyses of cerebral hemodynamics in animal models of polytraumatic hemorrhagic shock. **Materials and Methods:** Concurrent with an ongoing NHP protocol, the ophthalmic artery (OA) was insonated to establish baseline TCD values. A transorbital acoustic window was used, imaging was obtained with a 2.0 MHz transducer probe. OA was chosen as the transtemporal window for middle cerebral artery (MCA) resulted in suboptimal waveforms. **Results:** The following TCD results represent the mean ± standard deviation, n = 10. Pulsatility index (1.66±0.33), mean flow velocity (MFV) (21.64±5.48 cm/s), peak systolic velocity (45.46±5.48 cm/s), end diastolic velocity (9.84±3.91 cm/s) and resistance index (0.79±0.08). **Conclusions:** We discovered that Rhesus macaques are absent of an adequate transtemporal acoustic window for MCA insonation, and normal resting OA MFV pressure in NHPs mimics reported OA MFV in humans. This data is foundational for our future studies to evaluate cerebral hemodynamics during hemorrhage and the degrees of severity in hemorrhagic shock. Our future goals include the utilization of TCD technology to elucidate a safety threshold for permissive hypotensive resuscitation or aggressive fluid resuscitation as it pertains to cerebral blood flow.

15. SUBJECT TRMS
Cerebral perfusion, transcranial Doppler (TCD), ultrasonography, polytrauma, hemorrhagic shock, non-human primate (NHP), Rhesus macaque

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