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Cerebral blood flow in polytrauma: transcranial Doppler analysis in a nonhuman primate shock model

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ABSTRACT

Background: In combat-related trauma, resuscitation goals are to attenuate tissue hypoxia and maintain circulation. During hemorrhagic shock, compensatory and autoregulatory mechanisms are activated to preserve cerebral blood flow. Transcranial Doppler (TCD) ultrasonography may be an ideal noninvasive modality to monitor cerebral hemodynamics. Using a nonhuman primate (NHP) model, we attempted to characterize cerebral hemodynamics during polytraumatic hemorrhagic shock using TCD ultrasonography.

Materials and methods: The ophthalmic artery was insonated at multiple time points during varying stages of shock. Hemorrhage was controlled and pressure targeted to 20 mmHg to initiate and maintain the shock period. Mean flow velocity (MFV), peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI), and resistance index (RI) were recorded. Results represent mean ± standard deviation; statistical significance is $P < 0.05$; $n = 12$.

Results: Compared to baseline, MFV, PSV, EDV, and RI show significant changes after 60 min of hemorrhagic shock, (9.81 ± 3.60 cm/s; $P < 0.01$), (21.15 ± 8.59 cm/s; $P < 0.01$), (5.15 ± 0.21 cm/s; $P < 0.01$), (0.70 ± 0.11; $P < 0.05$), respectively. PI did not change during hemorrhagic shock. At end of prehospital care (T30), cerebral flow recovers for MFV, PSV, and RI while EDV remained decreased at T30 (6.15 ± 1.13 cm/s; $P < 0.01$) and 1 h of simulated transport (T90) (5.87 ± 0.62 cm/s; $P < 0.01$). Changes in PI at T30 and T90 were not significant. MFV diminished (16.45 ± 3.85 cm/s; $P < 0.05$) at T90.

Conclusions: This study establishes baseline and hemorrhagic shock values for NHP cerebral blood flow velocities and cerebrovascular indices. TCD ultrasonography may represent an important area of research for targeted resuscitation investigations using a hemorrhagic shock model in NHPs.

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Introduction

Hemorrhage accounts for up to 90% of potentially survivable deaths on the battlefield in wounded military personnel.[1] Thus, the goals of resuscitation in combat-related trauma are to attenuate tissue hypoxia and maintain circulatory homeostasis thereby protecting end organ function.[1] Rapid volume replacement is critical, and the standard of care includes blood component and/or crystalloid infusion.[2] There is increasing advocacy for "permissive hypotension" resuscitation, which is the strategy of administering fluid to a goal systolic pressure of 90 mmHg until definitive hemostasis is obtained. The intent of this strategy is to reduce ongoing bleeding from loss of thrombus (i.e., prevent "popping of the clot") attributed to increased vascular hydrostatic pressure.[1,3]

Questions remain regarding the safety of this strategy, specifically the effects of this strategy on the brain and neurologic outcomes. This strategy is not recommended in the setting of traumatic brain injury (TBI). Work form our group and others have previously shown that cerebral derangements from hemorrhagic shock, despite the absence of a direct TBI, lead to diminished cerebral blood flow; this may result in deleterious cerebral outcomes.[4-7] Defining the acceptable limits of cerebral blood flow is critical to the safe implementation of a permissive hypotension strategy, in particular, in the setting of prolonged field care.

Transcranial Doppler (TCD) ultrasonography is approved by the Food and Drug Administration as a non-invasive modality 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 expressed as a time-velocity value (i.e., cm/s).[8] The technology uses the Doppler Effect and the Bernoulli principle to determine vessel blood flow velocities.[8,9] Low-frequency transducer probes (≤2 MHz) insonate intracranial vessels through cerebral "acoustic windows" to offer real-time evaluation of cerebral hemodynamics.[8-10] Blood flow traveling toward or away from the transducer probe results in a Doppler shift represented as peaks of sinusoidal like waveforms (Fig. 1A). Rune Aaslid *et al.*[11] (1982) first demonstrated the clinical utility of TCD ultrasonography to assess arterial flow velocities in patients. Currently, TCD ultrasonography is clinically used in hemorrhagic stroke, ischemic stroke, and TBI.[12] It has been used in nonhuman primate (NHP) studies as a noninvasive modality to evaluate blood flow velocity, structure and function of organs such as brain, lung, and heart.[13-15] During hemorrhagic shock, compensatory and autoregulatory mechanisms are activated to preserve cerebral perfusion, and changes in the cerebral blood flow due to hypotension can have permanent deleterious effects.[16,17] TCD ultrasonography is an ideal modality to track these changes in real time.

Currently, there are no reported spectral TCD ultrasonography characterizations of cerebral indices in NHPs during profound hemorrhagic shock. These data represent a critical gap in current translational research knowledge and can provide insight into the limits of cerebral autoregulation in trauma and the safety profile of a prolonged hypotensive resuscitation strategy. Using NHPs (rhesus macaques) from an ongoing study of polytrauma and hemorrhagic shock, we hypothesized that TCD ultrasonography could characterize cerebral hemodynamics during shock.

Materials and methods

Ethical approval and accreditation

The study protocol was reviewed and approved by the 711th Human Performance Wing, Joint Base San Antonio-Fort Sam Houston the Institutional Animal Care and Use Committee, in compliance with all applicable Federal regulations governing the protection of animals in research. All procedures were performed in facilities accredited by AAALAC International.

Animal protocol

As an ancillary study to a previously approved protocol addressing hemorrhage, polytrauma, and resuscitation, male rhesus macaques ($n = 6$/group, 12 total) weighing 8-12 kg were used.

Anesthetized NHPs were intubated, placed on a ventilator, and instrumented as previously described by our group.[4] Core body temperature was monitored continuously and maintained between 36.0°C and 38.0°C. Continuous systemic monitoring, including end-tidal carbon dioxide ($ETCO_2$), and tissue oxygen saturation (StO_2) was performed. StO_2 was monitored via InSpectra StO_2 sensor placed on the tricep and InSpectra Tissue Oxygenation Monitor (model 650, Hutchison Technology Inc. Hutchinson, MN, USA).

A polytrauma model with a pressure-controlled hemorrhage was implemented (Fig. 2), including a soft tissue injury (15 cm laparotomy) and musculoskeletal injury (femur fracture) previously described by our group.[4] Hemorrhage was performed by cannulation of the left femoral artery using a 14-guage Abbocath-T IV catheter (Hospira, Lake forest, IL, USA). The right femoral artery was cannulated with 18-guage polyvinyl pressure tubing for continuous blood pressure monitoring. Pressure-targeted controlled hemorrhage was initiated by opening a stopcock in-line with the left arterial catheter, allowing free bleeding to the target mean arterial pressure (MAP) of 20 mmHg, marking the beginning of shock. Hemorrhaged blood was collected in a blood bag containing a 1:10 ratio of anticoagulant citrate phosphate dextrose adenine solution (Sigma–Aldrich, St. Louis, MO, USA) on a rocking scale. Decompensatory shock (an inability to maintain compensatory hemodynamics) was defined as a decline in an NHP's MAP of 25% from the average MAP over 60 min in the shock period. In other words, after animals maintained a minimum of 60 min of shock, and then dropped their MAP by an additional 25% ("decompensation"), this ended the shock period and initiated the beginning of prehospital resuscitation.[4]

The left femoral vein was also cannulated using a 14-guage Abbocath-T IV catheter (Hospira, Lake forest, IL, USA) for intravenous resuscitation fluid infusion during the prehospital resuscitation period. NHPs were randomly assigned to one of two prehospital treatment cohorts to receive either intravenous whole blood (WB) or Hextend (Hospira Inc. Lake