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Traumatic Brain Injury May Worsen Clinical Outcomes After Prolonged Partial Resuscitative Endovascular Balloon Occlusion of the Aorta (pREBOA) in Severe Hemorrhagic Shock Model

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Abstract

Background: The use of partial resuscitative endovascular balloon occlusion of the aorta (pREBOA) in combined hemorrhagic shock (HS) and traumatic brain injury (TBI) has not been well studied. We hypothesized that the use of pREBOA in the setting of TBI would be associated with worse clinical outcomes.

Methods: Female Yorkshire swine were randomized to the following groups: HS + TBI; HS + TBI + pREBOA; and HS + pREBOA, (n=5/cohort). Animals in the HS + TBI group were left in shock for a total of 2 hours, whereas animals assigned to pREBOA groups were treated with supraceliac pREBOA deployment (60 minutes) 1 hour into the shock period. All animals were then resuscitated, and physiologic parameters were monitored for six hours. Further fluid resuscitation and vasopressors were administered as needed. At the end of the observation period, brain hemispheric swelling (%) and lesion size (mm³) were assessed.

Results: Mortality was highest in the HS + TBI + pREBOA group (40% [2/5] vs 0% [0/5] in the other groups, $p = 0.1$). Severity of shock was greatest in the HS + TBI + pREBOA group, as defined by peak lactate levels and pH nadir ($p < 0.05$). Fluid resuscitation and norepinephrine requirements were significantly higher in the HS + TBI + pREBOA group ($p < 0.05$). No significant differences were noted in brain hemispheric swelling and lesion size between the groups.

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Conception and design – AMW, JE, HBA. Data acquisition – AMW, UFB, ISD, NG, VCN, KC, PC, RO, JL, JZ, PG, BEB; Data interpretation – AMW, UFB, ISD, NG, VCN, KC, PC, RO, JL, JZ, PG, BEB, JE, YL, HBA; Manuscript preparation – AMW, UFB, ISD, NG, VCN, KC, PC, RO, JL, JZ, PG, BEB, JE, YL, HBA; Critical revisions – all authors. Grant funding – AMW, HBA.

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Conclusions: Prolonged application of pREBOA in the setting of TBI does not contribute to early worsening of brain lesion size and edema. However, the addition of TBI to HS + pREBOA may worsen the severity of shock. Providers should be aware of the potential physiologic sequelae induced by TBI.

Level of Evidence: not applicable (preclinical study).

Keywords

traumatic brain injury; hemorrhagic shock; partial aortic occlusion; non-compressible torso hemorrhage; trauma; swine model

Background

Hemorrhagic shock (HS) and traumatic brain injury (TBI) remain leading causes of immediate and early death in trauma patients.(1, 2) HS accounts for the majority of trauma deaths during the first hour of care, while TBI is responsible for a large segment thereafter.(3) In traumatic settings, TBI is often accompanied by other insults, including vascular injury and hemorrhage. When HS and TBI are found in combination, the likelihood of early death is approximately 80%.(4) Although TBI contributes to significant morbidity and mortality, the priority in these patients is hemorrhage control to prevent early deaths due to exsanguination.(5, 6)

Within recent years, resuscitative endovascular balloon occlusion of the aorta (REBOA) has gained attention as a technique for the management of non-compressible torso hemorrhage (NCTH).(7–9) Use of REBOA has been shown to confer early survival advantages in HS; however, concerns have been raised regarding the risk of end-organ ischemia with complete REBOA (cREBOA).(10, 11) As a result, alternative endovascular strategies, like partial REBOA (pREBOA), have been devised to overcome this limitation.(12, 13) Although early in its adoption, pREBOA may afford better distal perfusion, more physiologic proximal aortic mean arterial pressures (MAP), and less reperfusion injury following balloon deflation.(12, 13) However, despite promising early data, further studies are required to fully define the consequences of pREBOA deployment in the setting of severe hemorrhage.

Although REBOA has been widely believed to be useful in NCTH, its utility in the setting of concurrent TBI has not been well studied. Some have reported exacerbation of TBI following REBOA deployment, raising concerns about guidelines for use and patient selection.(14, 15) Moreover, preclinical studies of both cREBOA and pREBOA have been limited to mild trauma models of HS and TBI with several clinical limitations.(16) In this study, we sought to investigate the effects of pREBOA deployment in a swine model of severe HS and TBI with limited resuscitation strategies. We hypothesized that the use of pREBOA in the setting of TBI would be associated with worse clinical outcomes.

Materials and Methods

The study protocol was approved by the University of Michigan Institutional Animal Care and Use Committee. Experiments were conducted in compliance with all guidelines and

regulations regarding animal welfare and research. Figure 1 provides a schematic representation of the model used in this experiment.

Animal Selection and Acclimation

Female Yorkshire swine (40–50 kg; Michigan State University, East Lansing, MI) were used for this study. All animals underwent an acclimation period of 5 days.

Induction and Maintenance of Anesthesia

Animals were induced with Telazol (0.5 mg/kg intramuscular injection; Pfizer, New York, NY) and inhaled isoflurane (2–4%). Following endotracheal intubation (7.0mm tube), anesthesia was maintained with isoflurane (1–3%) for the duration of the procedure.

Instrumentation and Monitoring

Bilateral groin incisions were made, and femoral vessels exposed using a cut-down technique. Both femoral arteries were dissected and isolated. The right femoral artery was cannulated with a 7F 13-cm sheath (Cook Medical, Bloomington, IN) for the placement of pREBOA. A 5F 11-cm catheter (Super Sheath, Boston Scientific Corporation, Marlborough, MA) was placed into the left femoral artery for distal MAP monitoring, hemorrhage, and blood collection for laboratory analysis. An 8F 11-cm catheter (Super Sheath) was inserted into the left femoral vein for drug and fluid administration during the case.

Bilateral neck incisions were made to expose both carotid arteries and external jugular veins. A 5F 11-cm catheter (Super Sheath) was inserted into the left common carotid artery to allow measurement of proximal aortic MAP. An 8F 11-cm catheter (Super Sheath) was placed in the left external jugular as additional access for fluid and drug administration. A 9F 10-cm catheter (Arrow International, Cleveland, OH) was placed in the right external jugular for pulmonary artery catheterization using a Swan-Ganz catheter.

A laparotomy was performed to access to the supra-celiac aorta (zone I). After proper exposure, the diaphragm was partially divided. A 32-mm aortic balloon occlusion catheter (pREBOA-PRO[®]™, Prytime Medical, Lakewood, CO) was advanced in the right femoral artery to the descending thoracic aorta (Figure 2). Targeted placement in the supraceliac aorta was confirmed via manual palpation. Following appropriate placement, balloon catheters were secured using a 5F catheter clamp (REBOA Convenience Kit, Prytime Medical). Positioning of all balloon catheters was validated at the conclusion of the experiment prior to removal. A suprapubic cystostomy tube was also placed into the bladder and secured temporarily with a purse-string suture at the time of laparotomy.

The animal was then placed in the prone position and the head fixed in a custom-made stereotactic frame. Two skull pegs were affixed to the zygoma to prevent movement during cortical impact. A U-shaped scalp incision was made to expose the skull. A 21-mm burr hole was made anterolateral to the coronal and sagittal sutures on the right side of the skull, and a 6-mm burr hole was made 10-mm anterolateral to the bregma on the left side. The 21-mm burr hole was used for brain injury, and the 6-mm burr hole was used for intracranial pressure (ICP) and oxygenation monitoring.

Following instrumentation, animals were block randomized to three groups: 1) HS + TBI; 2) HS + TBI + pREBOA; 3) HS + pREBOA (n=5/cohort).

Traumatic Brain Injury and Hemorrhage

Animals were then subjected to their respective randomized injury patterns, including HS, or HS + TBI. 40% estimated total blood volume (ETBV (ml) = weight (g) x 0.06 + 0.77) was hemorrhaged over 12.5 minutes using a Masterflex pump (Cole-Palmer, Vernon Hills, IL). Blood was collected in standard blood collection bags containing anticoagulants (CPDA, AS-5; Terumo, Ann Arbor, MI). If randomized to undergo TBI, a computer-controlled cortical impact (CCI) device (University of Michigan Innovation Centre, Ann Arbor, Michigan) was used to create an impact concurrently (20mm cylindrical impactor, 4m/s velocity, 100 millisecond dwell time, 12mm cortical penetration depth). This insult has been shown to reliably produce a severe TBI.(17, 18)

During the hemorrhage period, if MAP decreased below 30mm Hg, hemorrhage was held, isoflurane was turned off, and a 50–100ml bolus of 0.9% normal saline (NS) was administered. Hemorrhage was restarted when MAP returned above 30mmHg. The bone fragment from the 21-mm Burr hole was replaced, and bone wax was used to seal the hole. This prevented CSF-leakage and ensured accurate ICP monitoring. The scalp incision was temporarily closed following TBI using silk suture.

Hemorrhagic Shock, Treatment, and Resuscitation

Once hemorrhage was complete, animals were subjected to shock (MAP goal of 30–35 mmHg). Following 60 minutes of shock, HS + TBI animals were kept in shock for an additional 60 minutes, while HS + TBI + pREBOA and HS + pREBOA animals underwent 60 minutes of supraceliac (zone I) partial aortic balloon occlusion. For animals randomized to pREBOA deployment, a distal MAP of 20–25 mmHg was targeted, achieving a 60–70% systolic-to-diastolic pressure gradient. Aortic balloons were inflated with normal saline and manually adjusted as needed to meet this target. A standard balloon titration device (Encore Advantage Kit, Boston Scientific Corporation, Natick, MA) was used for balloon volume titration. In the HS + TBI group, pREBOA catheters were maintained in the supraceliac aorta during the 60-minute shock period, but balloons were not inflated.

At the end of the 60-minute pREBOA deployment period, aortic occlusion balloons were deflated manually at a rate of 0.5 mL/min using the balloon titration device until completely deflated. pREBOA catheters were then withdrawn following balloon deflation. Concurrently, all animals were resuscitated with NS (3x hemorrhage volume) over a 1-hour period.

Critical Care Monitoring

Animals were observed for 6 hours following resuscitation with continuous monitoring of physiological and laboratory parameters. Maintenance intravenous fluids were administered at a rate of 50 mL/hr of NS. Additional fluids and vasopressor therapy were administered according to objective thresholds. Animals received a 500 mL NS fluid bolus if the CVP was less than 6 mmHg and were reassessed. Fluid boluses were repeated as needed to a maximum volume of 100 ml/kg. A norepinephrine (24 μ g/mL) infusion was initiated and

titrated to maintain a MAP of 55–60 mmHg. Electrolyte abnormalities, including hypoglycemia and hyperkalemia, were corrected throughout the critical care monitoring phase. A Bair Hugger (Arizant Healthcare, Inc., Eden Prairie, MN) was used to maintain physiologic temperature.

Intraoperative Hemodynamic and Laboratory Monitoring

Physiologic parameters were measured continuously as previously described.(19–21) Parameters measured included heart rate; proximal and distal systolic, diastolic, and MAP; central venous pressure (CVP); cardiac output (CO); core body temperature; pulse oxygenation; and ICP.

Arterial blood gases (ABGs; Nova Biochemical, Waltham, MA) and whole blood samples were obtained at baseline, post-shock, post-resuscitation, and at the end of the observation phase. Additional ABGs were performed as needed throughout the experiment. Whole blood samples were withdrawn into vacuum-sealed tubes, centrifuged for separation into serum and plasma, and flash frozen for future analysis. All laboratory samples were included in the calculation of hemorrhage volume.

Tissue Collection

Animals were euthanized with Euthasol® (Virbac, Fort Worth, TX) at the end of the 6-hour observation period. Brains were harvested and sliced into 5-mm coronal sections using a sectioning block (University of Michigan Medical Innovation Center, Ann Arbor, MI). Sections were then stained with 2% 2,3,5-triphenyltetrazolium chloride (TTC; SigmaChemical Co., St. Louis, MO) to detect viable tissue. Brain lesion size (mm³) and hemispheric volumes were calculated using ImageJ analysis software (National Institutes of Health, Bethesda, MD). Hemispheric swelling ipsilateral to the brain lesion was calculated using the following equation: ipsilateral hemispheric swelling = (volume of ipsilateral hemisphere/volume of contralateral hemisphere – 1) x 100%.(22, 23)

Statistical Analyses

Primary endpoints involved clinical outcomes (laboratory parameters and resuscitation requirements) following pREBOA deployment. Pilot experiments, which were not included in this study, were used to conduct an *a priori* power analysis by a biostatistician. Using pilot data comparing the primary endpoints for the HS + TBI + pREBOA and HS + pREBOA groups, effect size (*d*) was determined. Sample sizes were then planned with 90% power and 95% confidence for each variable following pREBOA deployment: lactate levels (*d*=5; *n*=2), pH levels (*d*=2.6; *n*=4), total fluid resuscitation (*d*=3; *n*=3), and vasopressor requirements (*d*=10; *n*=2). The HS + TBI group is used for reference.

All statistical analyses were performed using GraphPad Prism v6.00 (GraphPad Software, San Diego, CA). Survival rates were compared using Kaplan-Meier method with log-rank testing. One-way analysis of variance (ANOVA) with Tukey post-hoc testing was utilized for all discrete time points. The Brown-Forsythe test was used to check for differences in variance between groups. Data are expressed as mean ± standard deviation (SD), unless specified otherwise. Statistical significance was defined as *p* < 0.05.

Results

To achieve the primary endpoints, n=5 was required for each cohort.

Survival

The HS + TBI + pREBOA group had increased mortality (40%; 2/5) compared to the HS + TBI and HS + pREBOA groups (0%; 0/5), although this did not reach statistical significance ($p = 0.1$) (Figure 3). The animals in the HS + TBI + pREBOA group that died, did so at 4 and 5 hours following pREBOA balloon deflation.

Intraoperative Hemodynamics and Physiology

Baseline hemodynamics and physiology were similar between groups. All animals experienced tachycardia and a predictable decrease in MAP, CO, and CVP immediately following injuries (Figure 4 and 5).

Following the 60-minute shock period, pREBOA deployment resulted in a significantly higher average proximal MAP for HS + TBI + pREBOA (64.4 ± 11.1 mmHg; $p = 0.002$) and HS + pREBOA (66.6 ± 14.7 mmHg; $p = 0.003$) groups compared to the HS + TBI group (33.4 ± 2.2 mmHg) (Figure 4A, B). There was a trend towards a lower proximal MAP for the HS + TBI + pREBOA group compared to the HS + pREBOA group, although not statistically significant. As expected, pREBOA deployment resulted in a significantly lower average distal MAP for HS + TBI + pREBOA (22.1 ± 3.1 mmHg; $p = 0.001$) and HS + pREBOA (23.1 ± 2.1 mmHg; $p = 0.001$) groups compared to the HS + TBI group (33.4 ± 2.2 mmHg) (Figure 4C, D). Following pREBOA deflation, aortic pressure gradients quickly dissipated, returning to baseline MAP with fluid resuscitation and vasopressors (Figure 4A, C).

Following resuscitation, no significant differences were noted in intraoperative hemodynamics and physiologic responses between the groups, although several trends were noted (Figure 5). Heart rate was elevated in the HS + TBI + pREBOA group compared to other groups during the critical care phase. CVP was elevated in the HS + pREBOA group following fluid resuscitation, while CVP was decreased in the HS + TBI + pREBOA group during the early critical care phase. CO was elevated in the HS + TBI + pREBOA group during the early hours of the critical care phase compared to other groups. Lastly, the ICP values were higher in the two TBI groups, but the difference between the three groups did not reach statistical significance.

Laboratory Parameters

Severity of shock was greatest in the HS + TBI + pREBOA group (Figure 6). At the end of the critical care phase, lactate level was significantly higher in the HS + TBI + pREBOA group (lactate level, mmol/L: HS + TBI + pREBOA, 15 ± 2 mmol/L; HS + pREBOA, 2 ± 1 mmol/L; HS + TBI, 3 ± 2 mmol/L; $p = 0.001$) (Figure 6A). The pH nadir was also significantly lower for the HS + TBI + pREBOA (pH, mmol/L: HS + TBI + pREBOA, 7.16 ± 0.04 ; HS + TBI, 7.26 ± 0.04 ; HS + pREBOA, 7.31 ± 0.03 ; $p = 0.007$) (Figure 6B).

Resuscitation and Vasopressor Requirements

Total fluid requirement during the critical care phase was significantly higher in the HS + TBI + pREBOA group (3360 ± 706 mL) compared to the HS + TBI (300 ± 0 mL; $p = 0.001$) and HS + pREBOA (660 ± 371 mL; $p = 0.004$) groups (Figure 7A). Norepinephrine requirement was also significantly higher in the HS + TBI + pREBOA group compared to the other groups (norepinephrine, mg/kg/hr: HS + TBI + pREBOA, 0.14 ± 0.02 mg/kg/hr; HS + pREBOA, 0.014 ± 0.001 mg/kg/hr; HS + TBI, 0 ± 0 mg/kg/hr; $p < 0.01$) (Figure 7B).

Brain Hemispheric Swelling and Lesion Size

Compared with the HS + pREBOA group, ipsilateral hemispheric swelling was significantly increased in the HS + TBI and HS + TBI + pREBOA groups (ipsilateral hemispheric swelling, %: HS + TBI = 32.5 ± 6.5 ; HS + TBI + pREBOA = 26.5 ± 8.5 ; HS + pREBOA, 1.1 ± 2.1 ; $p = 0.001$) (Figure 8A); however, no significant differences were noted between the HS + TBI and HS + TBI + pREBOA groups. No significant differences were noted between brain lesion sizes in the HS + TBI and HS + TBI + pREBOA groups (mean lesion size, mm³: HS + TBI = 3107 ± 999 ; HS + TBI + pREBOA: 3084 ± 619.7 , $p = 0.99$) (Figure 8B).

DISCUSSION

Although REBOA use has gained wide attention for NCTH, its deployment in the setting of TBI has not been well studied. With an increasing use of pREBOA, a better understanding of pREBOA deployment in polytrauma and rigorous patient selection guidelines are required. In this study, we found that prolonged application of pREBOA does not contribute to early worsening of brain lesion size or swelling. However, the degree of circulatory shock is significantly increased when pREBOA is deployed in the presence of severe TBI. As such, providers should be aware of the potential physiologic sequelae induced by TBI in the setting of pREBOA deployment.

Traumatic brain injury (TBI) remains a leading cause of death and disability worldwide.(24, 25) In both civilian and military traumatic settings, TBI is frequently associated with other traumatic insults, including vascular injury and HS, which are the leading cause of preventable death in trauma.(26) Because hypo- or hypertension can affect clinical outcomes of TBI, providers must be well-versed in the management of concurrent injuries.

Concerns exist regarding REBOA deployment in patients with TBI. Supraphysiologic blood pressure and flow in the proximal aorta may exacerbate intracranial hemorrhage and increase cerebral edema by destabilizing intracerebral clots, ultimately worsening TBI.(14, 27, 28) Several studies have demonstrated that patients with TBI and a low GCS were more likely to die following REBOA deployment compared to patients without TBI.(29) Furthermore, several reports demonstrate that REBOA deployment may lead to death secondary to exacerbation of TBI progression.(15) However, these studies have had several limitations regarding patient selection and lack of cerebral flow monitoring. Also, these studies used the traditional REBOA with complete aortic occlusion, and it remains unclear whether pREBOA would have the same impact on TBI progression.

Studies assessing the effects of REBOA in clinically realistic, large animal models of TBI are lacking. A previous pre-clinical study used a mild model of concurrent HS and TBI, involving 25% total blood volume hemorrhage and a 1200 mm³ CCI-induced brain lesion. (16) That particular study involved an early deployment of c- and pREBOA immediately following hemorrhage, and external automated devices to ensure optimal proximal perfusion. These circumstances may not reflect clinical scenarios and current practices. Our study decided to use a model of severe HS (40% total blood volume hemorrhage) and TBI (2400 mm³ CCI-induced brain lesion). We also simulated a delay in pREBOA deployment and had a resuscitation schedule designed to represent a clinically realistic timeline with limited resuscitation to mimic prehospital settings. Furthermore, we elected to test the concept of partial aortic occlusion as there has been an increasing use of pREBOA clinically and in pre-clinical large animal studies.(12, 13, 16, 30–33) The pREBOA-PRO catheter, which facilitates ease of transition from complete to partial to no aortic occlusion, is currently being evaluated in numerous studies.(30)

The optimal duration of aortic balloon occlusion remains a matter of investigation. Well-described porcine models have demonstrated that cREBOA deployment in zone 1 is tolerated for approximately 30 minutes.(13, 34, 35) In an attempt to maintain distal perfusion and prolong aortic occlusion, several strategies have been devised, including the development of pREBOA that involves partially occluding aortic flow.(12, 13) In this study, we used pREBOA to target a distal MAP goal of 20–25 mmHg, which achieved a 60–73% systolic-to-diastolic pressure gradient, similar to other studies.(12, 16, 30, 32, 36) This was well tolerated as all animals subjected to pREBOA following HS recovered toward baseline physiology with minimal fluid resuscitation and vasopressor requirements. Furthermore, pREBOA was successfully deployed for twice as long (60 minutes) in isolated HS compared to cREBOA.(13, 34, 35) Several other preclinical large animal studies using partial REBOA have demonstrated successful deployment for up to 60 and 90 minutes; however, these have mainly involved non-survival studies with milder insults (25% total blood volume hemorrhage) and immediate pREBOA deployment following hemorrhage. (12, 16) The upper limit of pREBOA deployment time remains unknown, but is likely much longer (4–6 fold) compared to cREBOA based on our and others' preliminary studies.

In this study, we observed severe cardiovascular dysfunction and an increased degree of shock following pREBOA deployment in the setting of TBI. During pREBOA deployment, animals subjected to HS and TBI were unable to sustain an elevated proximal MAP, which decreased during the last 30 minutes of the balloon inflation period compared to animals without TBI. This is consistent with prior studies demonstrating a degree of cardiac dysfunction and endotheliopathy with REBOA deployment.(16) Furthermore, animals with TBI subjected to pREBOA required significantly more fluid resuscitation and had higher vasopressor requirements, lactate levels, and acidosis.

Cardiovascular complications are common following severe TBI and are linked to increased morbidity and mortality.(37, 38) Immediately following TBI, a systemic catecholamine-storm can massively increase sympathetic outflow, inducing severe systemic vasoconstriction.(39) This can increase cardiac afterload, inducing myocardial ischemia, impairment of ventricular function, and even systemic hypotension in severe cases.(39) As

the catecholamine surge diminishes, the early hyperdynamic response is blunted and significant hypotension can ensue secondary to unopposed peripheral vasodilation and ventricular dysfunction.(39) In this study, high-dose norepinephrine was required to improve systemic vasodilation; however, we suspect that the increased $\beta 1$ adrenergic activity may have also worsened existing cardiac dysfunction, promoting ventricular dysfunction and cardiogenic shock. However, we did not use intraoperative echocardiography to confirm this.

We suspect several additional reasons played a role in the development of cardiovascular shock following TBI. Neurogenic stunned myocardium (NSM), which results from an excessive norepinephrine release from cardiac sympathetic nerve terminals, may lead to prolonged $\beta 1$ activity and cardiac mitochondrial dysfunction, resulting in hypotension.(39) We suspect that animals subjected to TBI exhibited a degree of ventricular dysfunction and NSM. In addition, TBI can activate a massive neuroinflammatory response leading to widespread release of cytokines into systemic circulation.(38, 39) We also suspect the presence of TBI may have worsened the inflammatory cytokine release causing circulatory shock and organ dysfunction in the setting of pREBOA deployment. Overall, these reasons may have led to high-dose norepinephrine requirements, causing significant systemic vasoconstriction contributing to intestinal ischemia with worsening acidosis, increased lactate levels, and even death. Mechanistic studies are currently underway to elucidate the impact of TBI on the cardiovascular system and how it contributes to an increase in mortality.

In addition, pREBOA deployment did not appear to worsen early brain lesion size and swelling following TBI. Comparisons between HS + TBI and HS + TBI + pREBOA groups revealed similar hemispheric brain swelling and lesion sizes, suggesting that there was no further extension of the TBI following pREBOA deployment. This is consistent with prior studies where no change in brain lesion size was observed using serial computed tomography imaging following c- and pREBOA deployment compared to controls.(16) Furthermore, no significant increase in ICP was observed with pREBOA deployment in the setting of TBI compared to the HS + TBI group.

Several reasons may explain why pREBOA deployment did not worsen brain lesion size and swelling. First, supraphysiologic proximal MAP during pREBOA deployment may not be as extreme as that observed with cREBOA; furthermore, the proximal MAP may be higher in milder HS models due to decreased hemorrhage volumes. In this study, however, we focused on the effects of pREBOA deployment in a severe HS model. Second, the increase in proximal MAP following pREBOA deployment may help maintain an appropriate cerebral perfusion pressure (CPP) despite an increase in ICP; this may have minimized any exacerbation of TBI. Third, only a subset of patients demonstrate TBI progression during the first 24 hours following injury; therefore, detection of TBI progression is difficult early following injury as was the case in this experiment.(40, 41) Despite the absence of early worsening in brain lesion size and swelling following pREBOA deployment seen in this study, survival studies are required to further assess the effects of pREBOA deployment on neurologic outcomes and mortality following TBI and HS.

Although the presence of TBI is not a contraindication for pREBOA in HS, it is crucial for providers to be aware of the potential physiologic sequelae induced by TBI. The presence of TBI may significantly affect patient physiology, hemodynamics, and clinical outcomes following pREBOA deployment. For example, patients may require more fluid resuscitation, vasopressors, and pharmacologic therapies. Ultimately, this may translate into more utilization of resources, which is especially relevant for far-forward and other austere settings.

There are several limitations to this study. First, sample size in this study was limited by ethical considerations and costs and therefore the results may be prone to a type II error. Furthermore, there were unbalanced groups at the completion of the study given the increased mortality observed in the HS + TBI + pREBOA group; this finding may also affect the statistical analyses. Second, although swine are commonly utilized for human translation, they serve as an imperfect surrogate for human subjects. Studies of pREBOA application in patients with TBI are needed to confirm the results of this study. Third, we used a controlled-hemorrhage model for proof-of-concept testing of pREBOA in the setting of TBI and to minimize variability; however, uncontrolled hemorrhage models (from vascular injuries in the abdomen and pelvis) are more clinically realistic and optimal for testing pREBOA deployment. Fourth, objective thresholds were used to guide fluid resuscitation and vasopressor requirements even though resuscitation is often guided by 'fluid responsiveness' in the clinical setting. Fluid responsiveness as a benchmark for resuscitation is highly subjective and operator dependent. Therefore, we used pre-defined thresholds to minimize investigator bias. Fifth, animals were not transfused blood during the study. We realize this may not reflect clinical practice in urban centers; however, we sought to attain a worst case scenario with limited resuscitation and vasopressors, reflecting military or austere settings with delayed evacuation where blood products may not be available. Further studies should be done in the application of these findings to other types of brain injury. Lastly, this study involved a short-term non-survival model. In the future, the effects of pREBOA deployment on long-term TBI progression and neurologic outcomes should be tested. Our team is planning follow-up studies to address many of these issues.

Conclusions

In conclusion, this study demonstrates that prolonged application of pREBOA in the setting of TBI does not contribute to early worsening of brain lesion size and swelling. However, the addition of TBI to HS + pREBOA may worsen the severity of shock and create a situation that is difficult to reverse with resuscitation. Although the presence of TBI is not a contraindication for pREBOA in HS, it is crucial for providers to be aware of the potential physiologic sequelae induced by TBI. Overall, the findings of this study support continued evaluation of pREBOA deployment in pre-clinical models of polytraumatic injuries, including HS, TBI, and multi-organ injuries.

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Figure 1. Visual representation of experimental model.

Injury consisting of 40% total blood volume hemorrhage with and without concurrent traumatic brain injury (TBI). Animals in the HS + TBI group were left in shock for a total of 2 hours, whereas animals assigned to pREBOA groups underwent supraceliac pREBOA deployment 1 hour into the shock period for 60 minutes. All animals receive resuscitation with normal saline (3 x volume of shed blood) over 1 hour. Animals then undergo critical care monitoring for 6 hours. BL – baseline; S – shock; R – resuscitation; PR – post-resuscitation; E – end; TBI – traumatic brain injury; MAP – mean arterial pressure.

Figure 2. pREBOA-PRO Catheter.

pREBOA-PRO catheter inflated demonstrating spine and occlusion balloons (A). Illustration of aorta in cross section with pREBOA-PRO catheter deployed allowing partial aortic flow through dual flow channels (B).

Figure 3. Survival curve following injuries.

Animals subjected to hemorrhagic shock (HS) and traumatic brain injury (TBI) with pREBOA deployment had increased mortality compared to other groups (40% [2/5] vs 0% [0/5] vs 0% [0/5]; $p = 0.1$). HS – hemorrhagic shock; TBI – traumatic brain injury; pREBOA – partial resuscitative endovascular balloon occlusion of the aorta; BL – baseline; S – shock; R – resuscitation; PR – post-resuscitation; E – end.

Figure 4. Hemodynamic response to injury and pREBOA deployment.

Intraoperative measurements of (A) proximal mean arterial pressure (MAP), (B) proximal MAP during balloon inflation, (C) distal MAP, and (D) distal MAP during balloon inflation. pREBOA deployment resulted in a significantly higher proximal MAP for HS + TBI + pREBOA and HS + pREBOA groups compared to the HS + TBI group. pREBOA deployment resulted in a significantly lower distal MAP for HS + TBI + pREBOA and HS + pREBOA groups compared to the HS + TBI group. Data are presented as group mean $\pm$ SE. Asterisks indicate time points which were significantly different ($p < 0.05$). MAP – mean arterial pressure; HS – hemorrhagic shock; TBI – traumatic brain injury; pREBOA – partial resuscitative endovascular balloon occlusion of the aorta; BL – baseline; S – shock; R – resuscitation; PR – post-resuscitation; E – end.

Figure 5. Physiologic response to injury and pREBOA deployment.

Intraoperative measurements of (A) heart rate (HR), (B) central venous pressure (CVP), (C) cardiac output (CO), and (D) intracranial pressure (ICP). No significant differences were noted in intraoperative physiologic responses between groups. Data are presented as group mean $\pm$ SE. HR – heart rate; CVP – central venous pressure; CO – cardiac output; ICP – intracranial pressure; HS – hemorrhagic shock; TBI – traumatic brain injury; pREBOA – partial resuscitative endovascular balloon occlusion of the aorta; BL – baseline; S – shock; R – resuscitation; PR – post-resuscitation; E – end.

Figure 6. Laboratory parameters in response to injuries and pREBOA deployment.

Intraoperative measurements of (A) lactate and (B) pH. Severity of shock was greatest in the HS + TBI + pREBOA group, as defined by peak lactate levels and pH nadir ($p < 0.05$), compared to other groups. Data are presented as group mean $\pm$ SE. Asterisks indicate time points which were significantly different ($p < 0.05$). HS – hemorrhagic shock; TBI – traumatic brain injury; pREBOA – partial resuscitative endovascular balloon occlusion of the aorta; BL – baseline; S – shock; R – resuscitation; PR – post-resuscitation; E – end.

Figure 7. Resuscitation requirements in response to injuries and pREBOA deployment. Total (A) additional fluid resuscitation and (B) norepinephrine administration during the critical care phase. Data are presented as group mean $\pm$ SD. Asterisks indicate significant differences ($p < 0.05$). HS – hemorrhagic shock; TBI – traumatic brain injury; pREBOA – partial resuscitative endovascular balloon occlusion of the aorta.

Figure 8. Brain ipsilateral hemispheric swelling volume (A) and lesion size (B) following injuries. Data are presented as group mean $\pm$ SD. Asterisks indicate significant differences ($p < 0.05$). HS – hemorrhagic shock; TBI – traumatic brain injury; pREBOA – partial resuscitative endovascular balloon occlusion of the aorta.