Safe and Effective Escalating Strategies to Treat Occult Non-Compressible Torso Hemorrhage

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FINAL REPORT

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14. ABSTRACT-
Hemorrhage is associated with the majority of potentially survivable deaths on the battlefield. Most of these injuries are due to non-compressible torso hemorrhage (NCTH), which includes injuries to the lungs, solid organs, pelvis, and major blood vessels. Injuries at junctional sites, such as the neck, groin (inguinal), and underarm (axillary) areas, also contribute significantly to the total number of these injuries. Two methods of controlling pelvic and inguinal hemorrhage are the Abdominal Aortic and Junctional Tourniquet (AAJT) and Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). The AAJT can be applied quickly, but prolonged use may damage the bowel, inhibit ventilation, and obstruct surgical access. REBOA requires technical proficiency, but has fewer complications. REBOA involves introducing a balloon catheter into the descending aorta in a specific occlusion region (Zone 1, 2, or 3) and acts as a hemorrhage control adjunct with resuscitative support. The balloon is placed in Zone 3 in the infrarenal aorta for high junctional or pelvic injuries and in Zone 1 proximal to the diaphragm for torso hemorrhage. Zone 1 REBOA provides more resuscitative support than Zone 3; however, the potential for ischemia and reperfusion injuries is greater with Zone 1 than with Zone 3 REBOA placement. This study aimed to determine the benefit and feasibility of transitioning from less invasive hemorrhage control adjuncts to more resource intensive interventions.

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1.0 EXECUTIVE SUMMARY

Hemorrhage is associated with the majority of potentially survivable deaths on the battlefield. Most of these injuries are due to non-compressible torso hemorrhage (NCTH), which includes injuries to the lungs, solid organs, pelvis, and major blood vessels. Injuries at junctional sites, such as the neck, groin (inguinal), and underarm (axillary) areas, also contribute significantly to the total number of these casualties. Two methods of controlling pelvic and inguinal hemorrhage are the Abdominal Aortic and Junctional Tourniquet (AAJT) and Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). The AAJT can be applied quickly, but prolonged use may damage the bowel, inhibit ventilation, and obstruct surgical access. REBOA requires technical proficiency but has fewer complications. REBOA involves introducing a balloon catheter into the descending aorta in a specific occlusion region (Zone 1, 2, or 3) and acts as a hemorrhage control adjunct with resuscitative support. The balloon is placed in Zone 3 in the infrarenal aorta for high junctional or pelvic injuries and in Zone 1 proximal to the diaphragm for torso hemorrhage. Zone 1 REBOA provides more resuscitative support than Zone 3; however, the potential for ischemia and reperfusion injuries is greater with Zone 1 than with Zone 3 REBOA placement. This study aimed to determine the benefit and feasibility of transitioning from less invasive hemorrhage control adjuncts to more resource intensive interventions. Experiment 1 was designed to test the possibility and physiologic effects of converting a patient with AAJT applied to one with Zone 3 REBOA. Experiment 2 was designed to test the potential benefit of converting Zone 3 REBOA to Zone 1 REBOA in a patient with continued, occult hemorrhage.

Yorkshire male swine were used in all studies. In experiment 1, the animals underwent a 40% controlled hemorrhage. Subsequently, the AAJT was placed on the abdomen and inflated. After an hour, animals were treated with either an additional 30 minutes of AAJT inflation, Zone 3 REBOA placement with AAJT inflated, or REBOA placement following AAJT removal. Observation lasted 3.5 hours. In experiment 2, the animals underwent injury to the femoral artery that was subsequently controlled with hemostatic gauze, and Zone 3 REBOA. Additionally, a controlled venous bleed was carried out until a mean arterial pressure (MAP) of 30 mmHg was reached to create an impending cardiovascular collapse. The animals were then randomized into either continued Zone 3 REBOA or transition from Zone 3 to Zone 1 REBOA. after 30 minutes, deflation of the REBOA balloon was performed followed by a two-hour observation period. In each experiment, survival, hemodynamics, and blood chemistries were compared among groups.

No significant differences were seen in blood pressure or laboratory values at baseline in either experiment. Conversion to REBOA was largely successful in all animals but one. No animal had observable intestinal injury. In experiment 2, survival was significantly longer in animals transitioned into Zone 1 REBOA (log ranks analysis, $p = 0.012$). The average time of survival was 14 ± 10 min for Zone 3 animals vs. 65 ± 59 min for Zone 1 animals ($p=0.064$). No animals in the Zone 3 group survived to the hospital phase. Zone 1-treated animals showed immediate hemodynamic improvement after transition, with maximum blood pressure reaching near baseline values compared to those in the Zone 3 group.

Overall, these results can be interpreted to show that conversion of AAJT to infrarenal REBOA is safe and effective, but access may be difficult while the AAJT is applied. Additionally, hemodynamics and survival were improved when the REBOA balloon was transitioned from Zone 3 to Zone 1 during an impending cardiovascular collapse. Both results support the pursuit of additional research into mitigating ischemia-reperfusion insult to the abdominal viscera while still providing excellent resuscitative support, such as intermittent or partial REBOA.

2.0 INTRODUCTION

Hemorrhage is associated with the majority of potentially survivable deaths and is responsible for 22.2 % of all deaths on the battlefield.[1] The liberal use of tourniquets has been successful in treating extremity injuries, but non-compressible torso hemorrhage (NCTH) and junctional hemorrhage remain difficult areas to treat. Recently, specialized products including expandable foams, XSTAT, and junctional tourniquets have been developed to treat these types of injuries.[2–4] Unfortunately, no product or therapy has yet to gain widespread success and adaptation.

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a technique using an inflated intravascular balloon that stops blood flow in order to create hemostasis. The balloon catheter can be inserted into the femoral artery and positioned in the descending aorta between the subclavian and celiac arteries (Zone 1) or inserted between the renal artery and the aortic bifurcation (Zone 3) depending on the site of hemorrhage.[5] Current clinical practice guidelines from the Joint Trauma System suggests that Zone 1 REBOA may be placed for 30-60 minutes and Zone 3 REBOA may potentially stay up for a longer period of time if necessary. However, shorter times are advisable to minimize complications. One of REBOA's advantages is that its' use allows for the escalation of vessel occlusion more proximal to the heart, Zone 1, in case of unrecognized hemorrhage in the torso.

The Abdominal Aortic and Junctional Tourniquet (AAJT), a device with a wedge-shaped bladder, is designed to occlude blood flow at junctional sites (axilla and groin) or the lower abdomen. When placed around the abdomen, the AAJT occludes blood flow through the abdominal aorta at the site of bifurcation. The product has been previously tested and shown to be effective in both laboratory and patient care settings.[6–9] However, some complications have been observed with the product including producing pain, respiratory arrest in swine, and the potential for ischemic damage.[10,11] Application of AAJT and implementation of REBOA in Zone 3 are aimed at occluding blood at the same anatomical site with both treating pelvic and junctional hemorrhage. Each product has advantages and disadvantages that imply different usage scenarios.

The AAJT is a more user-friendly product that can be applied with minimal training and is effective as a standalone device. REBOA requires more proficient expertise in arterial access and uses additional equipment including arterial sheaths, stopcocks, syringes, ultrasound, and other surgical supplies. The AAJT can also be applied fairly quickly compared to REBOA and can be used in an austere environment at the point of injury. In some situations, arterial access can prove difficult or impossible, making REBOA unachievable. However, if access is achieved, REBOA poses little risk to the patient beyond the ischemic damage which can result from extended application (longer than current clinical practice guidelines recommendation of less than one hour).

This study was undertaken to evaluate the benefits and risks of each of the hemorrhage adjuncts and in what scenario escalation to a higher level of intervention (i.e. conversion of AAJT to REBOA or conversion of Zone 3 REBOA to Zone 1 REBOA) is beneficial to the patient. The first experiment 1 assessed the possibility and physiologic effects of converting a patient with AAJT applied to one with Zone 3 REBOA after undergoing a controlled hemorrhage. Experiment 2 was designed to test the potential benefit of converting Zone 3 REBOA to Zone 1 REBOA in a patient with continued, occult hemorrhage with impending cardiovascular collapse.

3.0 METHODS, ASSUMPTIONS AND PROCEDURES

3.1 Experiment 1: AAJT to Zone 3 REBOA Conversion

3.1.1 Hypothesis

The hypothesis tested in Experiment 1 is that conversion of AAJT to Zone 3 REBOA is safe and effective compared to leaving the AAJT in place in a setting of hemorrhagic shock. Amount of blood loss following conversion, blood vessel damage, and molecular markers of damage were compared between groups.

3.1.2 Methods

The study was approved by the Institutional Animal Care and Use Committee for the Bridge PTS (Preclinical Testing Services) Research Facility (Brooks City Base, TX). This facility's animal care and use program is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. All animals were treated in accordance with The Guide for the Care and Use of Laboratory Animals.[12] All products utilized were commercially purchased.

Animal preparation

Yorkshire cross castrated male swine were procured from a local USDA registered vendor. The animals were housed at the facility vivarium for 3-5 days prior to their use in the study. Animals weighing 70-90 kg were fasted overnight with free access to water. Animals were pre-medicated with an initial intramuscular injection of 0.02-0.05 mg/kg of Atropine for 15-30 minutes followed by Tiletamine-Zolazepam (4-8 mg/kg, IM). Anesthesia was induced with a facemask and 2-4% isoflurane. Once intubated, isoflurane was adjusted to 1-3% during procedures. Overall experimental design for Experiment 1 is shown in Figure 1.

Vascular access was accomplished via cutdown except as otherwise noted. The right carotid artery was accessed for blood pressure measurement and blood sampling. The left external jugular vein was accessed for infusion of resuscitation fluids. The right femoral artery was percutaneously accessed for blood withdrawal and monitoring distal pressure. Near Infrared Spectroscopy (NIRS) pads were placed over the left pectoralis muscle, the left flank (overlying the kidney), and the medial thigh muscle of both legs. NIRS technology allows for increased non-invasive tissue penetration allowing for monitoring of regional tissue oxygenation.[13,14] Finally, the AAJT (Compression Works, Birmingham, AL) was pre-positioned under the animal in order to minimize disturbing the animal during the experiment.

Hemorrhage

Blood was withdrawn from the femoral artery in a multi-rate fashion to more physiologically simulate uncontrolled hemorrhage compared to a single constant rate.[15] Up to 40% (27 mL/kg) of estimated blood volume was withdrawn over 30 minutes, divided in two phases: half of this volume was withdrawn over 10 minutes and the remaining over the last 20 minutes. However, hemorrhage was paused if the MAP dropped below 30 mmHg and resumed once it rose above 30 mmHg resulting in less hemorrhage than the goal of 40% EBV.

Intervention

Immediately after the 30-minute hemorrhage, the AAJT was applied to the animal's waist at the midline, ~2 cm superior to the ilium, and inflated to 300 mmHg according to the manufacturer's instructions. Correct AAJT placement was confirmed by the absence of an arterial pressure waveform from the right femoral artery. Five minutes following application, 500 mL of shed blood was administered at 100 mL/min. During the application period, the AAJT would be further inflated if pulse fluctuations reappeared.

Animals were randomly allocated to one of three experimental groups 55 minutes following AAJT inflation: the first group had the AAJT left in place and inflated (continuous AAJT occlusion, CAO), the second had the AAJT completely deflated prior to REBOA insertion (sequential aortic occlusion, SAO), and the third group had the REBOA inserted while the AAJT was still inflated, after which the AAJT was deflated (overlapping aortic occlusion, OAO). In both REBOA groups, the left femoral artery was percutaneously catheterized with a 5 French micropuncture set using ultrasound guidance followed by upsizing to a 7 French sheath. The ER-REBOA (Prytime Medical Devices Inc., Boerne, TX) was then inserted 25 cm into the artery (based on fluoroscopic catheter depth measurements taken during model development) and inflated with 5 mL of normal saline either prior to or following AAJT deflation, depending on group allocation. Once the balloon was fully inflated and no femoral arterial waveform was observed, the time was set as T=0 and a 30-minute period of Zone 3 REBOA began. For the CAO group, the 30-minute period began immediately following the initial 60-minute AAJT application for a total of 90 minutes of AAJT occlusion. In all groups, five minutes before the end of the intervention period, a second 500 mL of shed blood was infused at 100 mL/min.

Intervention removal and observation

The REBOA catheter and AAJT were deflated slowly over three minutes in all cases. Following deflation of the intervention, up to one liter of Hextend and one liter of lactated Ringers were administered as needed to maintain a MAP greater than 60 mmHg. Animals were observed for an additional 3.5 hrs without further interventions. Arterial blood samples were taken at baseline, following hemorrhage, after the initial AAJT period (T0), then 30, 60, 120, 180, and 240 minutes after randomized intervention. Animals were euthanized using IV Pentobarbital, 100 mg/kg (Euthanasia solution) and in accordance with the 2013 AVMA Guidelines for the Euthanasia of Animals. Immediate laparotomy with inspection of the small and large bowel for signs of compression damage was performed.

3.1.3 Data Analysis

Primary outcomes of this study were ability to correctly place the REBOA and time of REBOA deployment. Other outcomes included survival, hemodynamics (blood pressure, $EtCO_2$, HR, etc), and markers of tissue damage (lactate, BUN, Creatinine, pH, potassium, myoglobin).

Data are presented as mean ± standard deviation for continuous variables. One-way analysis of variance (ANOVA) was used for baseline comparisons and two-way repeated measures ANOVA was utilized for continuous variables over a time course. Survival was analyzed using log-rank analysis. Fisher's exact test was used for categorical variables. Statistical analysis and data management were performed using Excel 2019 (Microsoft, www.microsoft.com) and Sigmaplot 12 (Grafiti LLC, Palo Alto, CA).

3.2 Experiment 2: Zone 3 to Zone 1 REBOA

3.2.1 Hypothesis

The conversion from Zone 3 to Zone 1 REBOA would provide the additional resuscitative support needed for survival despite ongoing occult hemorrhage.

The experiments in this protocol will address the following objectives:

1. Determine if Zone 1 REBOA confers a survival advantage compared to control in a model of occult hemorrhage.
2. Determine the possibility, safety, and contraindications for transitioning Zone 3 to Zone 1 in a model of occult hemorrhage.

3.2.2 Methods

We conducted a prospective, randomized, blindly allocated, large animal model study. Experiment 2 was approved by the Institutional Animal Care and Use Committee for the U.S. Air Force 59th Medical Wing Clinical Investigation and Research Support Facility (Lackland Air Force Base, TX). This facility's animal care and use program is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. All animals were treated in accordance with The Guide for the Care and Use of Laboratory Animals.[12] All products utilized were commercially purchased.

Instrumentation

Yorkshire-cross castrated male swine (75.3 ± 4.6 kg) were procured from a local USDA-registered vendor. The animals were housed at the facility vivarium for at least five days prior to their use in the study. Animals were fasted overnight with free access to water. Sedation was performed with Tiletamine-Zolazepam (4-8 mg/kg intramuscular (IM)) and 2.2 mg/kg ketamine subcutaneously. Preemptive analgesia was accomplished with buprenorphine at 0.01 mg/kg IM. Anesthesia was induced with a facemask and 2-4% isoflurane. Once intubated, isoflurane was adjusted to 1-3% during procedures. The overall experimental design is shown in Figure 4.

Vascular access was accomplished using the modified Seldinger technique. The right carotid artery was accessed for continuous blood pressure measurement and blood sampling. The left external jugular vein was accessed for infusion of resuscitation fluids, while the right jugular vein was utilized for pulmonary catheter introduction. The left femoral artery was accessed percutaneously for REBOA (ER-REBOA, Prytime Medical, Boerne, TX) placement, and the left femoral vein was accessed percutaneously and used for controlled hemorrhage. Celiotomy and splenectomy were performed due to the swine's contractile spleen and potential red blood cell sequestration.[16] A tube cystostomy was then performed to drain the bladder continuously. The abdomen was closed using skin staples. Finally, the REBOA catheter was positioned in Zone 3 and confirmed using fluoroscopy.

Experimental Procedure

Following instrumentation, the right femoral artery was isolated for planned arteriotomy to create uncontrolled hemorrhage, as previously described.[17,18] Briefly, the right femoral artery was surgically isolated and bathed in lidocaine for 10 minutes to induce vasodilation and prevent vasospasm. Next, bulldog clamps were placed proximal and distal to the target area. A 6 mm arteriotomy was created using an aortic punch, and the clamps were released. Concurrently, blood removal from the left femoral vein was initiated at 0.3 mL/kg/min using a peristaltic pump (Masterflex II; Cole-Parmer, Vernon Hills, IL). The wound was allowed to bleed freely for 60 seconds, after which QuickClot Combat Gauze (Teleflex, Wayne, PA) was packed into the wound, followed by three minutes of manual compression. The artery was then ligated using a silk suture, and the REBOA balloon was inflated. After five minutes, 500 mL of warmed Hextend (6% hetastarch in Lactated Electrolyte Injection, Hospira, Lake Forest, Illinois) was infused at 100 mL/min through the left external jugular vein.

Once the MAP reached 30 mmHg (Defined as time zero, T0) due to the continued venous hemorrhage, the animals were randomly selected to undergo continued Zone 3 REBOA or transition from Zone 3 to Zone 1 REBOA using the sealed envelope method.[19] For animals randomized to Zone 1 placement, the balloon was deflated and placed into Zone 1 at the level of the diaphragm (Zone 1c) using fluoroscopic guidance.[20] Concurrently, animals were switched from room air to supplemental oxygen (100%) ventilation.

Resuscitation observation

Thirty minutes after either the transition of REBOA to Zone 1 or allowing the REBOA balloon to remain in Zone 3, the balloon was slowly deflated over 5 minutes. During the balloon deflation, all animals received one unit (450 mL) of warmed autologous whole blood stored in sodium citrate infused at 100 mL/min. If the MAP was < 60 mmHg, normal saline was administered. Additionally, a norepinephrine drip was initiated at four µg per hour in 5% dextrose and titrated to maintain MAP > 60 mmHg. This observation period was allowed to proceed for two hours or until death criteria (MAP < 20 mmHg for two minutes) were reached.

3.2.3 Data Analysis

The primary outcome of this study was survival, where death was defined as a MAP < 20 mmHg for two minutes. Secondary outcomes analyzed included animal hemodynamics (blood pressure, heart rate, end-tidal carbon dioxide ($EtCO_2$)) and lab values (blood gases, chemistry panels). The required sample size to achieve 80% power of a test of difference in two exponential survival functions with hazard rates of 1.61 (control group: 20% survival) and 0.36 (treatment group: 70% survival) was 14 (7 per group). Data are presented as mean ± standard deviation for continuous variables. Kaplan-Meier Survival curves and log-rank analysis were used to compare survival between groups. Student's t-test was used to compare groups at baseline and after hemorrhage. Repeated-measures ANOVA was used to compare variables over time. Fisher's exact test was used for categorical variables. Statistical analysis and data management were performed using Excel 2019 (Microsoft, Redmond, Washington) and Sigmaplot 12 (Grafiti LLC, Palo Alto, CA).

4.0 MAJOR EVENTS/MILESTONES/SUCCESS

- IACUC Approval of Experiment 1 –Nov 2018
- Full Experimental Matrix Initiated – Oct 2019
- All experimental procedures completed – Dec 2019

- Data analysis completed – Mar 2020
- Manuscript published in Journal of Special Operations Medicine – Aug 2020
- Full Experimental Matrix Initiated – Jun 202
- IACUC Approval of Experiment 2 –Jul 2020
- All experimental procedures completed – Aug 2021
- Data analysis completed – Mar 2022
- Manuscript published in Military Medicine – Aug 2023

5.0 RISK ASSESSMENT

5.1 Risk Analysis

Scheduling delays during the project:

- Project start day delayed due to contracting actions with BridgePTS.
- Experiment 2 significant delay due to COVID-19. IACUC approval delay, supplies procurement delay, and animal subjects delivery delays all contributed to almost a yearlong postponement in experimentation.

5.2 Technical Challenges

None.

6.0 TRANSITION PLAN

6.1 Military Relevance

More than 90% of potentially survivable battlefield deaths are associated with hemorrhage. This effort is designed to address the most common source of potentially survivable hemorrhage associated injuries: non-compressible torso hemorrhage. This proposal focuses on treatment strategies for wound management to extend the golden hour. It is aimed to address the following 2017 AFMS capability gaps: AFMS CBA #137: Research on Advanced Point of Injury Through En Route Care and AFMS CBA #186 Detection and Treatment of Occult Hypovolemia.

6.2 Transition Strategy

The outcome of this project is primarily a knowledge product. The studies involved in this effort use FDA-approved products currently in use by service members. This effort is designed to address potentially survivable prehospital deaths on the battlefield: non-compressible torso hemorrhage and focuses on treatment strategies for wound management to extend the golden hour. The results of this study will be used to inform clinical practice guidelines such as Joint Trauma System (JTS) and Tactical Combat Casualty Care (TCCC) guidelines.

KRL at the beginning of project was KRL 4 and will end at KRL 6.

7.0 RESULTS

7.1 Experiment 1: AAJT to Zone 3 REBOA Conversion

Baseline characteristics

A total of 17 animals weighing 82.2 ± 7.4 kg were included for analysis: CAO (n=5), OAO (n=6), SAO (n=6). One animal was removed from analysis in the CAO group due to iatrogenic injuries during surgical preparation. The groups were similar at baseline (Table 1).

Hemorrhage and intervention

At baseline, animals had a mean MAP of 63.2 ± 5.9 mmHg, a HR of 94 ± 11 bpm, and an $EtCO_2$ of 40.6 ± 3.2 mmHg with no statistically significant difference among groups (Table 1). All animals except one required temporary suspension of hemorrhage resulting in an average loss of 35.9 ± 4.2% of the estimated blood volume. Hemorrhage resulted in a MAP of 41.8 ± 11.0 mmHg, a HR of 155 ± 31 bpm, and an $EtCO_2$ of 36.6 ± 4.5 mmHg. Inflation of the AAJT resulted in an absence of waveform in the femoral arteries with a MAP of 26.2 ± 15.7 mmHg and a pulse pressure of 2.5 ± 5.8 mmHg after ten minutes. Most animals required some additional inflation to maintain the required 300 mmHg inflation pressure in the air bladder. At the end of the initial 60-minute period of AAJT inflation, MAP was 67.7 ± 17.4 mmHg, HR was 174 ± 34 bpm, and $EtCO_2$ was 42.2 ± 4.3 mmHg (Table 1).

In the REBOA groups, catheterization was attempted using ultrasound guidance. All femoral arteries in the SAO group were successfully cannulated and the REBOA correctly placed. One artery in the OAO group was improperly cannulated with the REBOA inserted into the femoral vein. This was noted as a failure of REBOA insertion and the animal was excluded from further analysis. Time to REBOA inflation (including arterial access, introducer sheath placement, and advancement of REBOA catheter) was 4.2 ± 2.2 min for all REBOA animals and did not differ between the two REBOA groups (Table 2). The two-step conversion of AAJT to REBOA in the SAO group resulted in various acute effects including a drop in carotid blood pressure, decrease in pectoralis NIRS, increase in both left and right thigh NIRS, and increased end tidal CO_2 during the conversion. Additionally, an increase in carotid MAP and $EtCO_2$ was observed after balloon inflation (Table 2, Figure 2).

Post treatment

Hemodynamic values during the observation period were not different between the groups (Figure 2). All groups experienced a modest increase in MAP of about 15 mmHg in response to the administration of 500 mL of shed blood prior to intervention deflation. After AAJT or REBOA deflation, all groups had a return of femoral arterial waveform within five minutes. All groups also had an acute increase in $EtCO_2$ five minutes following removal, with values remaining above baseline for the remainder of the observation period. Biochemical markers of shock and tissue injury were assessed throughout the protocol (Figure 3). No differences were observed among groups in any of the lab values assessed at any time point. A sharp drop in blood pH and a corresponding increase in lactate were observed in all groups following intervention removal. Potassium, BUN, creatinine, IL-6, and myoglobin were all elevated throughout the observation period in all groups with no significant differences among groups. However, creatinine and myoglobin were persistently higher in the CAO group following intervention removal, but these differences did not reach stastical significance. At

necropsy, no evidence of intestinal injury was observed in any animal and no abdominal tissue damage was noted on inspection.

7.2 Experiment 2: Zone 3 to Zone 1 REBOA

Baseline and initial injury

A total of 17 pigs were used in this study. Three were used for model development and refinement. Two were excluded from the analysis: one with an iatrogenic injury and one due to early administration of norepinephrine. Twelve animals weighing 75.3 ± 4.6 kg, six in each group, were included for analysis. Groups were similar at baseline (Table 3).

The femoral artery punch injury with a 60-second free bleed resulted in hypotension in both groups with an average drop of MAP to 36 ± 10 mmHg with no significant differences between groups ($p = 0.376$, Table 1). Blood loss from this injury was 1490 ± 441 mL or 29.7 ± 7.5% EBV ($p = 0.532$). Immediate resuscitation with a single unit of Hextend resulted in a near return to baseline blood pressure despite the continued venous controlled hemorrhage (Figure 5).

The mean time from initial uncontrolled hemorrhage injury to a MAP of 30 mmHg (impending cardiovascular collapse) was 86 ± 24 min with no significant differences between groups. The volume of venous blood withdrawn to reach this severe state of hypovolemia was 2182 ± 484 mL or 44.3 ± 11.4% EBV, with no significant differences between groups. This amount of blood loss substantially affected the blood chemistry measurements, resulting in elevated serum potassium and lactate (6.1 ± 1.7 mmol/L and 6.1 ± 3.8 mmol/L, respectively; $p = 0.811$ and $p = 0.795$).

Survival

The Kaplan-Meier survival curve comparing the transition of REBOA to Zone 1 versus remaining in Zone 3 is shown in Figure 3. The average survival time was 14 ± 10 min for Zone 3 animals vs. 65 ± 59 min for Zone 1 animals ($p=0.064$), with 50% of animals reaching death criteria at 12 min vs. 32 min for Zone 3 and Zone 1 animals, respectively. The log-rank analysis resulted in a significant difference in survival with transitioning the balloon to Zone 1 during continued venous bleeding ($p=0.012$). None of the animals in the Zone 3 group survived to the end of the 30-minute experimental period with continued femoral venous bleeding. Additionally, hemodynamics appeared to be improved in the Zone 1, group but repeated measures ANOVA was not performed due to the limited survival in the Zone 3 group. However, the animals that were transitioned to Zone 1 demonstrated a return to near preinjury blood pressures above the balloon, near-normal venous oxygen saturation (SVO_2), and improved $EtCO_2$ (Figure 5).

8.0 CONCLUSION/DISCUSSION

Traumatic injury and the resultant hemorrhagic shock are the leading cause of mortality in people under 46 years old and in military settings.[1,21] Injuries to the torso and junctional sites are difficult to treat with few good options. The AAJT and REBOA are two such treatments that are currently in use, and each technology has their benefits and drawbacks. This study addressed the unanswered questions: 1) Is conversion of AAJT to Zone 3 REBOA possible and beneficial? 2) In cases of ongoing venous hemorrhage with impending circulatory collapse, is it better to keep the REBOA in Zone 3 or move it to Zone 1?

In regards to the first question, we have demonstrated that conversion from AAJT to Zone 3 REBOA is technically feasible in a swine model of severe controlled hemorrhage and that transition between the two devices can be accomplished with or without prior deflation of the AAJT device. Initiation of REBOA prior to AAJT deflation mitigated BP, HR, and EtCO2 variability compared to advancement and inflation after AAJT deflation but was associated with increased difficulty in obtaining and confirming transfemoral access to the infrarenal aorta.

After induction of class IV shock and placement of the AAJT device, proximal aortic MAP returned to pre-hemorrhage values while the decrease in femoral artery MAP was consistent with prior studies.[22,23] In each of the three groups (CAO, OAO, SAO) no sustained significant hemodynamic differences were observed with respect to carotid MAP, femoral MAP, EtCO2, and heart rate (Figure 2). However, SAO was found to yield significantly different hemodynamic effects within the time periods during and shortly after conversion of AAJT to REBOA. These differences include a drop in carotid MAP, decreased pectoralis NIRS, increased left and right leg NIRS, and increased EtCO2 (Table 2). These changes are consistent with hemodynamic effects seen directly following cessation of aortic occlusion. The variations can be attributed to the temporary lapse in aortic occlusion during SAO placement which allows for transient reperfusion of the bilateral lower extremities likely resulting in a washout of built-up lactate and carbon dioxide. These effects are seen in the rise of EtCO2 (Table 2) and indirectly by the trend towards lower lactate in the SAO group. Additionally, the lapse of occlusion could allow for the potential for continued hemorrhage during that time.

While both AAJT and REBOA occlude antegrade major pelvic arterial flow, their methods of occlusion are drastically different. The AAJT produces extrinsic compression across the lower abdomen resulting in occlusion of both arterial and venous flow and affects collateral as well as major vessels. In comparison, Zone 3 REBOA specifically occludes the infrarenal aorta. This allows for continued collateral arterial circulation and preserves venous outflow. Despite these major methodologic differences and the transient hemodynamic variation seen with SAO, we observed no significant physiologic differences between groups. The hyperkalemia and lactic acidosis observed in this study are consistent with the metabolic derangements noted in prior studies and are associated with the severity of hemorrhage and the length of ischemic time produced by the intervention.[24,25]

Transfemoral placement of a REBOA device in the presence of an inflated AAJT presents a unique challenge in accessing the artery and inflating the balloon. While no difference was noted in the time to REBOA deployment with the AAJT inflated or deflated, one REBOA in the OAO group was inaccurately placed into the femoral vein. This error can be attributed to the lack of arterial pulsatility on exam and lack of Doppler flow visualized on ultrasound secondary to AAJT-mediated arterial occlusion. Additionally, confirmation of intra-arterial needle placement is difficult due to the lack of pulsatile pressure and the appearance of deoxygenated distal arterial blood. Inflation of a REBOA must be done “blindly” while the AAJT is in place as the typical signs of complete aortic occlusion are not present (rise in proximal MAP and/or loss of contralateral pulse). The volume of REBOA inflation must therefore be based on the recommended volume for Zone 3 deployment and adjusted if needed once the AAJT is removed. Finally, introduction and inflation of the REBOA catheter into the infrarenal aorta was met with little or no resistance from the inflated AAJT, likely due to the AAJT’s occlusion occurring more cranial than the placement of the REBOA catheter.

The increased hemodynamic variability within the SAO group and the overall feasibility of AAJT to REBOA transition we observed is concordant with the findings of a similar study by Brannstrom, et al.21 We expanded upon their findings by assessing 60 minutes of AAJT prior to intervention (compared to 30

minutes) and by investigating the practicality of AAJT conversion to REBOA without deflation of the AAJT bladder and temporary loss of aortic occlusion.

Bowel ischemia is a known complication after prolonged AAJT application, specifically after 240 minutes as noted by Brannstrom, et al.[26] Current guidelines call for AAJT placement for no more than 60 minutes. Another study utilizing the AAJT to control pelvic bleeding observed small bowel injury in half of the animals subjected to AAJT treatment.6 In the current study, no evidence of gross intestinal ischemia was noted at the time of necropsy for all groups, including the CAO group which underwent 90 minutes of AAJT placement. The source of the discrepancy between the two studies is not known, but may be due to the larger swine used in our experiments (70-90 kg) compared to the previous study that had a mean weight of 44 kg. This disparity in animal size likely results in differing pressure distribution generated by the AAJT on the abdomen and underlying organs.

Transition from AAJT to Zone 3 REBOA is feasible. While no metabolic advantages are evident, early transition to REBOA would allow for avoidance of prolonged AAJT morbidities such as bowel ischemia,[27] difficulty ventilating,[28] and poor access to abdominopelvic surgical sites.[29] Furthermore, Zone 3 REBOA can be placed immediately without the need to deflate the AAJT device. This technique may increase the difficulty of femoral artery access but avoids the hemodynamic fluctuation seen with REBOA placement after deflation of an AAJT device.

In regards to the second question regarding transition of REBOA from Zone 3 to Zone 1, the results presented here show that the transition of REBOA from Zone 3 to Zone 1 improved hemodynamics and survival in this swine model of hemorrhagic shock with ongoing venous bleeding. The deterioration of hemodynamics is seen in the animals that had REBOA remain in place in Zone 3. In contrast, the animals that had the escalation of REBOA to Zone 1 immediately increased blood pressure to near preinjury values, implying improved perfusion to the brain, lungs, and heart. This group succeeded in the main purpose of REBOA, which is a bridge to hemorrhage control through surgical therapy. The restoration of near-normal physiology in the Zone 1 group occurred despite the ongoing venous bleeding and combined loss of almost 70% of the animal's estimated blood volume. The resuscitative response of moving the REBOA to Zone 1 is beneficial and may also be similar in patients not in extremis.

Various studies have shown that Zone 1 REBOA provides more resuscitative support than Zone 3 REBOA.[27,30] This effect is seen following hemorrhage and during chest compressions following cardiac arrest. However, there is a difference in time sensitivity between Zone 1 and Zone 3, given the inability to have prolonged visceral ischemia. Studies have shown a clear resuscitative benefit from using Zone 3 REBOA to treat pelvic hemorrhage compared to pelvic packing.20,21 The current study adds to this body of work by demonstrating that as the patient nears hemodynamic collapse, the REBOA should, at least in the first 30 minutes, be moved to Zone 1 and not left in Zone 3, even if the bleeding is isolated to an area controlled by the Zone 3 REBOA.

This study demonstrates the superiority of Zone 1 REBOA compared to Zone 3 REBOA in a model of ongoing hemorrhage and recognizes several limitations. First, our model produced a severe hypovolemic shock that did not allow for comparison after balloon deflation due to low survival. This critical information is important due to the additional ischemic insult produced by the Zone 1 REBOA and should be the subject of further study. Additionally, extrapolating the results presented here to human anatomy should be taken with caution because the swine has a different distribution of mass below and above the various REBOA zones discussed in this study. Despite these limitations, this study did demonstrate a reproducible model for studying controlled arterial hemorrhage with ongoing, unrecognized venous bleeding.

These results indicate that transitioning REBOA from Zone 3 to Zone 1 is superior to leaving the REBOA balloon in Zone 3 in cases of impending circulatory collapse in the setting of an occult bleed despite the original observation of a pelvic or a high junctional wound. Zone 1 placement of the catheter resulted in the restoration of near-normal physiology, even beyond the recommended time for Zone 1 placement. This study suggests that further studies should determine whether partial REBOA provides the same benefit, allowing for prolonged Zone 1 placement, and the need for possible future protocols or catheters that allow inflation in both Zone 1 and Zone 3 simultaneously. This would initially give the advantage of resuscitative response with Zone 1 and then possible transition to hemorrhage control in Zone 3.

This study has several limitations worth noting. First, although the animals were observed for several hours following treatments, true long-term consequences of the interventions may have arisen had the observation period been prolonged. Second, the injuries utilized here are contrived and not typical of true battlefield injuries. Finally, there are notable anatomic differences between swine and humans (primarily with regard to AAJT application) that may affect the applicability of these findings in human care. Swine have a more developed collateral system compared to humans including the well-developed subclavian-to-iliac mammary collateral system that likely provides to abdominal wall and perfusion below the REBOA.[31,32] These collaterals are likely occluded with the AAJT making a direct comparison to responses in a human patient not ideal.

9.0 DELIVERABLES

9.1 Publications

- Stigall K, Blough PE, Rall JM, Kauvar DS. Conversion of the Abdominal Aortic and Junctional Tourniquet (AAJT) to Infrarenal Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) Is Practical in a Swine Hemorrhage Model. *J Spec Oper Med.* 2021;21(1):30-36. doi:10.55460/V5UD-1SVF
- Rall JM, Baker KJ, Sandoval ML, Flinn AN, Causey MW. Transition of Resuscitative Endovascular Balloon Occlusion of the Aorta from Zone 3 to Zone 1 to Treat Hemodynamic Collapse during Continued Hemorrhage. *Mil Med*. Published online August 8, 2023. doi:10.1093/milmed/usad313

9.2 Presentations

- Poster presentation at the 2022 Military Health System Research Symposium (MHSAOS)
- Poster presentation at the 2022 San Antonio Military and Universities Research Forum (SURF)
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10.0 COST

This work was funded by the Air Force Medical Service. FY19 funding under project code number AC19EM05 was $389,000 for FY19 and $185,000 for FY20.

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12.0 TABLES AND FIGURES

12.1 Tables

12.2 Figures

Table 1. Baseline, post hemorrhage, and post AAJT Values

	CAO	OAO	SAO	p-value
n	5	6	6	
Weight (kg)	81.0 ± 10.4	84.6 ± 5.6	81.0 ± 6.5	0.523
Baseline				
MAP (mmHg)	61.0 ± 8.2	62.0 ± 5.0	66.3 ± 3.4	0.278
HR (bpm)	97± 9	92 ± 11	95 ± 13	0.728
$EtCO_2$ (mmHg)	41.6 ± 3.2	42.0 ± 3.5	38.5 ± 2.2	0.125
pH	7.508 ± 0.058	7.492 ± 0.053	7.539 ± 0.042	0.374
K (mmol/L)	4.03 ± 0.51	3.85 ± 0.26	3.76 ± 0.23	0.586
Lactate (mmol/L)	1.79 ± 0.21	1.72 ± 0.70	2.07 ± 0.62	0.871
Post Hemorrhage				
MAP (mmHg)	43.0 ± 10.5	41.8 ± 12.2	40.8 ± 12.1	0.955
HR (bpm)	167 ± 36	139 ± 31	161 ± 26	0.303
$EtCO_2$ (mmHg)	37.8 ± 2.7	37.2 ± 5.1	35.0 ± 5.3	0.577
pH	7.499 ± 0.022	7.506 ± 0.033	7.536 ± 0.049	0.178
K (mmol/L)	4.30 ± 0.57	4.00 ± 0.50	4.14 ± 0.25	0.746
Lactate (mmol/L)	2.53 ± 0.58	2.05 ± 0.82	2.46 ± 0.49	0.960
Hemorrhage (%EBV)	34.7 ± 7.1	35.9 ± 4.2	35.3 ± 4.0	0.532
Post 60-min AAJT				
MAP (mmHg)	65.8 ± 21.4	67.1 ± 17.9	69.8 ± 16.4	0.933
HR (bpm)	180 ± 40	161 ± 42	181 ± 17	0.566
$EtCO_2$ (mmHg)	42.8 ± 2.4	42.5 ± 6.2	41.3 ± 4.0	0.852
pH	7.478 ± 0.042	7.450 ± 0.079	7.460 ± 0.059	0.868
K (mmol/L)	4.30 ± 0.48	4.30 ± 0.50	4.08 ± 0.41	0.966
Lactate (mmol/L)	3.29 ± 1.3	4.03 ± 1.1	3.88 ± 1.5	0.688

CAO, Continuous AAJT Occlusion; OAO, Overlapping Aortic Occlusion; SAO, Sequential Aortic Occlusion; MAP, Mean Arterial Pressure; HR, Heart Rate; Data is mean ± s.d.

Table 2. Select values during and shortly after conversion to REBOA

	CAO	OAO	SAO	p-value
Success n (%)	-	5/6 (83%)	6/6 (100%)	0.999
Time (min)	-	4.3 ± 2.9	4.1 ± 1.8	0.909
Values obtained proximal to occlusion				
Carotid MAP (mmHg) - Nadir	63.4 ± 21.2	60.8 ± 19.1	43.6 ± 6.6	0.172
$EtCO_2$ (mmHg) - Peak	42.8 ± 2.4	44.2 ± 8.3	57.5 ± 6.5	0.003†
Pectoralis StO_2 (%)	67.8 ± 4.6‡	71.0 ± 12.9‡	53.8 ± 5.3	0.010*
Left Flank StO_2 (%)	53.2 ± 10.5	56.2 ± 13.8	43.3 ± 8.3	0.153
Values obtained distal to occlusion				
Femoral Artery Pressure(mmHg) - Peak	26.2 ± 7.2§	34.5 ± 16.6§	60.7 ± 12.4	0.0014†
Left Thigh StO_2 (%)	16.5 ± 3.0‡	22.5 ± 10.9	39.7 ± 18.5	0.0380*
Right Thigh StO_2 (%)	15.6 ± 1.3§	21.8 ± 8.2§	48.3 ± 15.1	0.0002†
Values obtained shortly after conversion				
$EtCO_2$ (mmHg) - Peak	46.2 ± 2.0§	51.0 ± 6.7§	61.5 ± 5.4	0.0008†
Carotid MAP (mmHg) - Peak	66.8 ± 20.7‡	77.5 ± 22.0	105.6 ± 21.4	0.0343*

CAO, Continuous AAJT Occlusion; OAO, Overlapping Aortic Occlusion; SAO, Sequential Aortic Occlusion; MAP, Mean Arterial Pressure; StO_2, Skeletal Muscle Tissue Oxygenation. Data is mean ± s.d.; *, $p < 0.05$; †, $p < .01$; ‡, $p < 0.05$ vs SAO; §, $p < 0.01$ vs SAO

Table 3. Baseline and Post-Hemorrhage Values

	Zone 3 (n=6)	Zone 1 (n=6)	p-value
Weight (kgs)	74.8 ± 4.8	75.8 ± 4.8	0.726
Length (cm)	158 ± 7	160 ± 8	0.757
MAP (mmHg)	67.2 ± 5.9	65.0 ± 5.0	0.509
$EtCO_2$ (mmHg)	42.3 ± 1.9	44 ± 1.9	0.159
Potassium (mmol/L)	3.9 ± 0.4	3.9 ± 0.2	0.919
Lactate (mmol/L)	1.9 ± 0.8	1.7 ± 0.6	0.566
After Arterial Injury			
Blood Loss (% EBV)	28.2 ± 7.2	31.1 ± 8.2	0.532
MAP (mmHg)	38.2 ± 9.5	32.8 ± 10.4	0.376
$EtCO_2$ (mmHg)	36.0 ± 1.3	37.2 ± 5.9	0.647
Potassium (mmol/L)	3.7 ± 0.3	3.8 ± 0.2	0.489
Lactate (mmol/L)	2.2 ± 0.6	2.1 ± 1.0	0.868
At T_0 (MAP = 30 mmHg)			
Venous Blood Loss (% EBV)	48 ± 15	41 ± 4.6	0.299
Time After Artery Injury (min)	90 ± 29	81 ± 20	0.554
$EtCO_2$ (mmHg)	31.5 ± 3.0	33.5 ± 6.3	0.498
Potassium (mmol/L)	6.2 ± 2.3	6.0 ± 1.1	0.811
Lactate (mmol/L)	5.8 ± 3.6	6.4 ± 4.4	0.795

MAP, Mean Arterial Pressure; EBV, Estimated Blood Volume; $EtCO_2$, End-Tidal CO_2

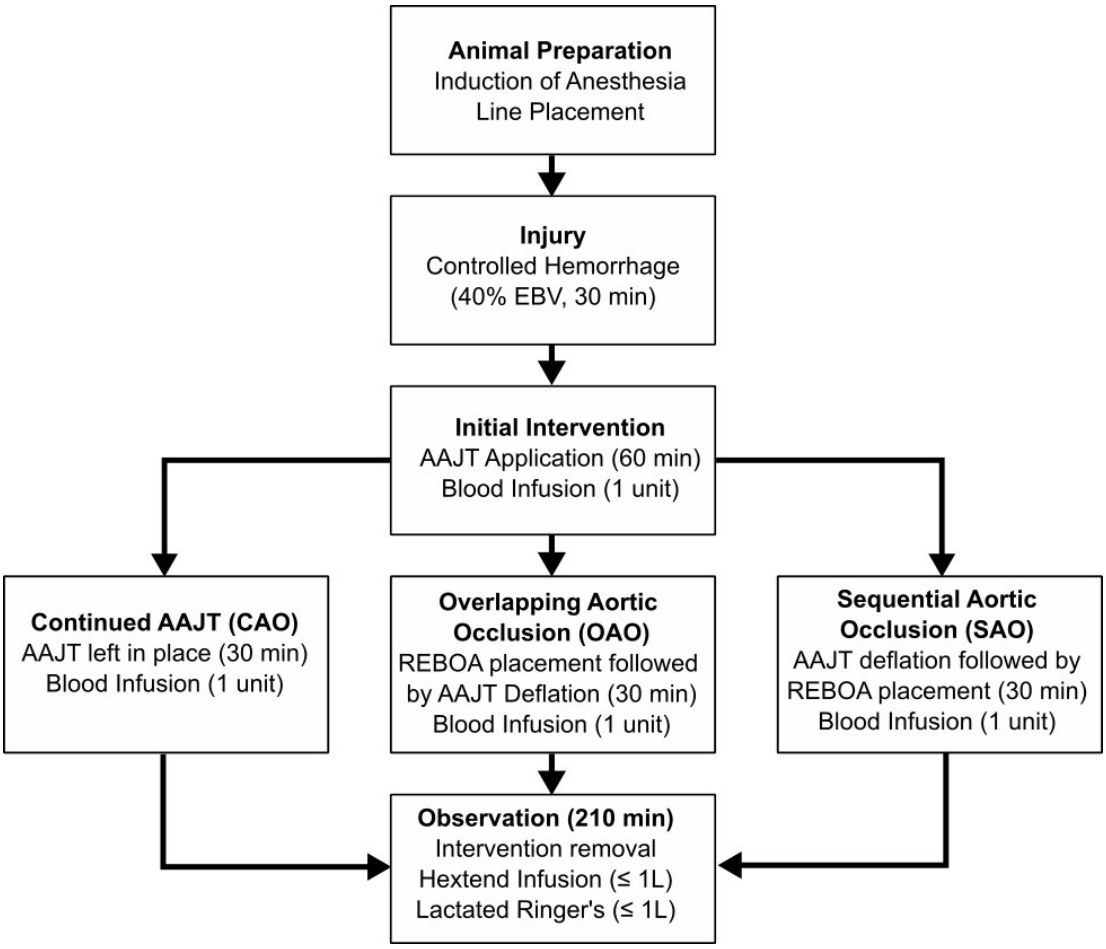

Figure 1. Experimental timeline showing the progression of experimentation. EBV – Estimated Blood Volume

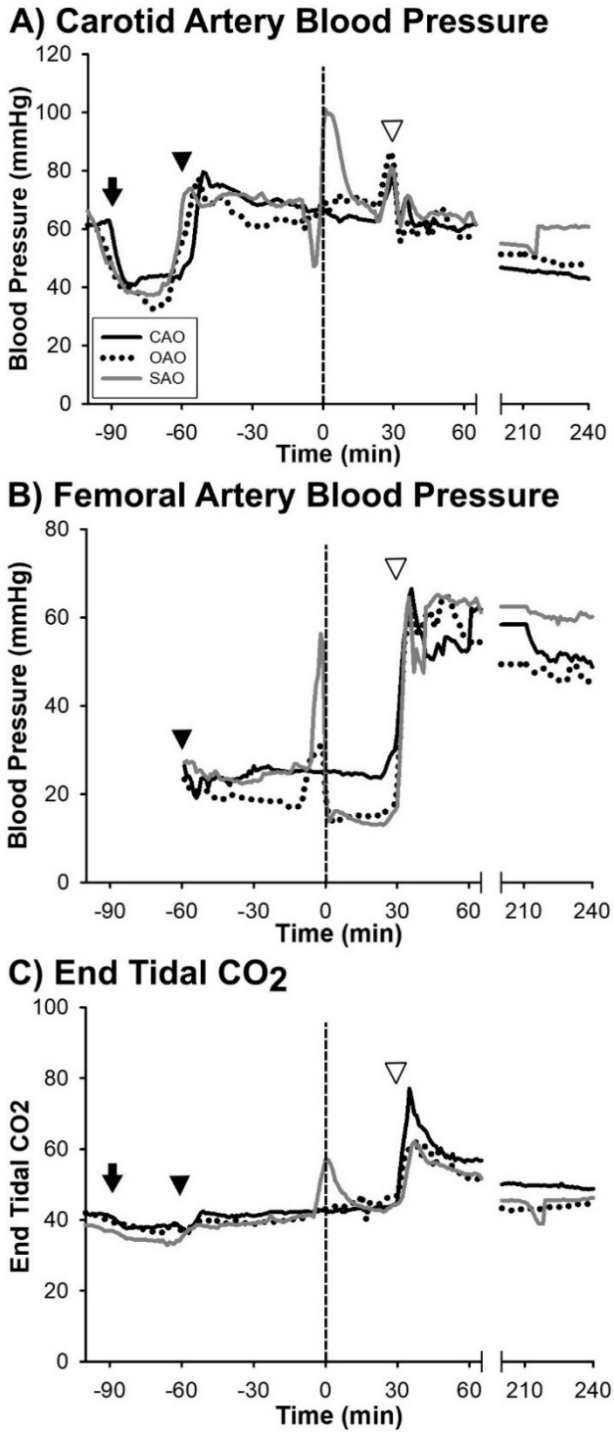

Figure 2. Blood pressure and end tidal CO_2 A) Carotid artery blood pressure B) Femoral artery blood pressure C) End-tidal CO_2. Arrow indicates start of hemorrhage. Solid arrowhead indicates application of AAJT in all groups. Dashed line is start of REBOA or continued AAJT. Open arrowhead is removal of occlusion. Error bars not shown for clarity. CAO, Continuous AAJT Occlusion; OAO, Overlapping Aortic Occlusion; SAO, Sequential Aortic Occlusion.

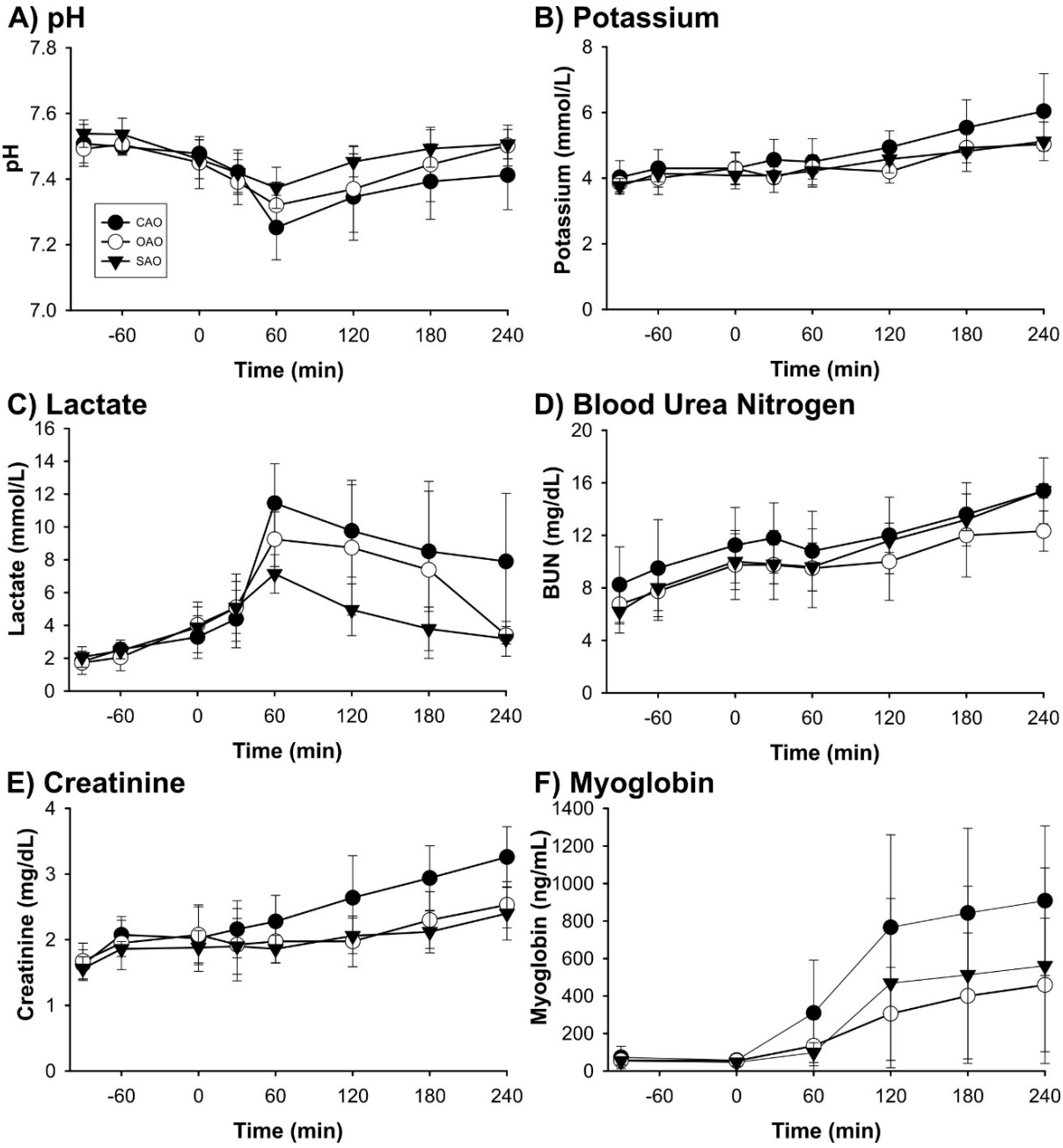

Figure 3. Lab Values A) pH B) Potassium C) Lactate D) Urea Nitrogen E) Creatinine F) Myoglobin. T0 is start of randomized aorta occlusion. CAO, Continuous AAJT Occlusion; OAO, Overlapping Aortic Occlusion; SAO, Sequential Aortic Occlusion.

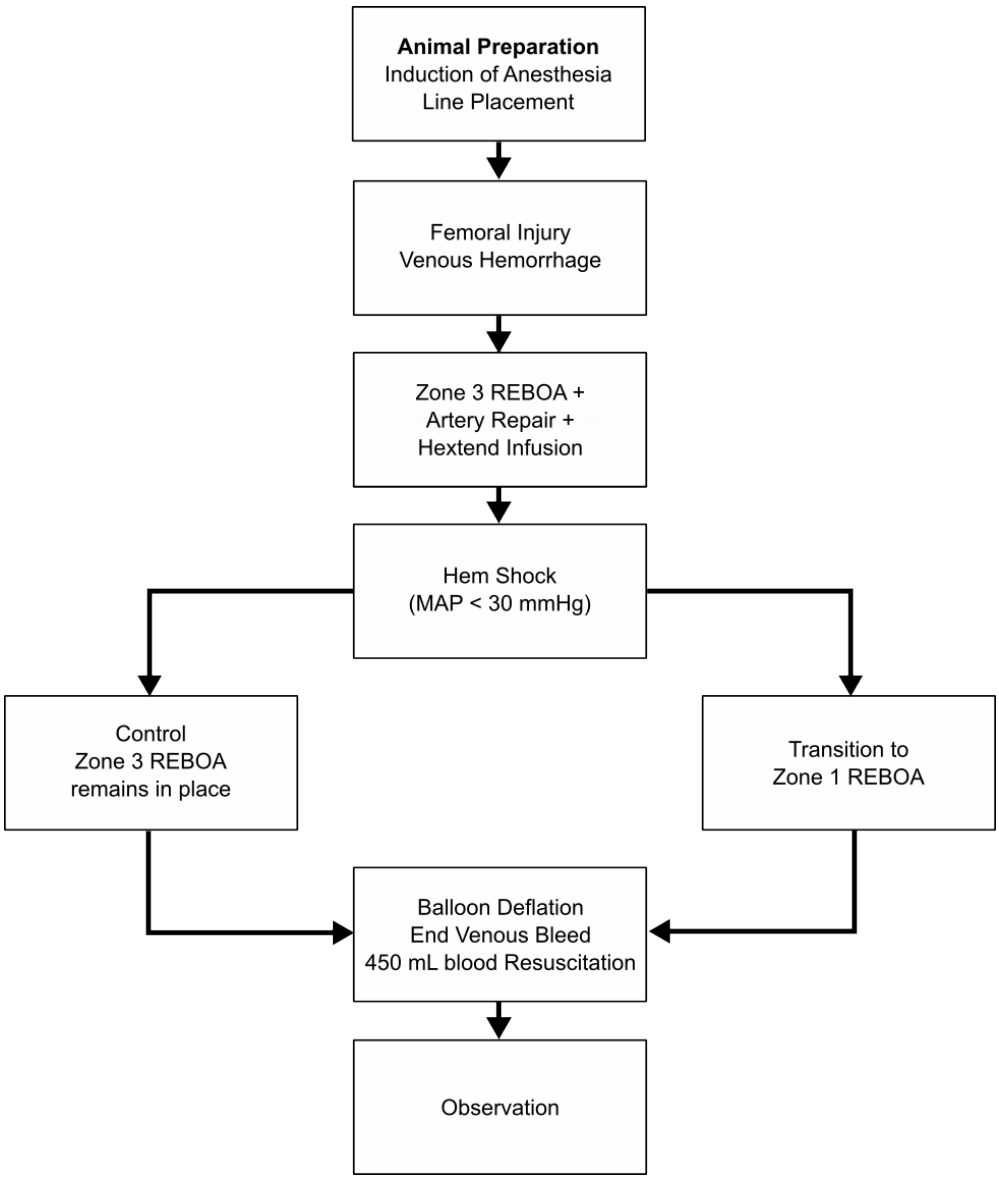

Figure 4. Experimental timeline for Experiment 2**.** Flow diagram of the experimental procedures from instrumentation until the end of the experiment. REBOA, Resuscitative Endovascular Occlusion of the Aorta; Hem, hemorrhage; MAP, Mean Arterial Pressure.

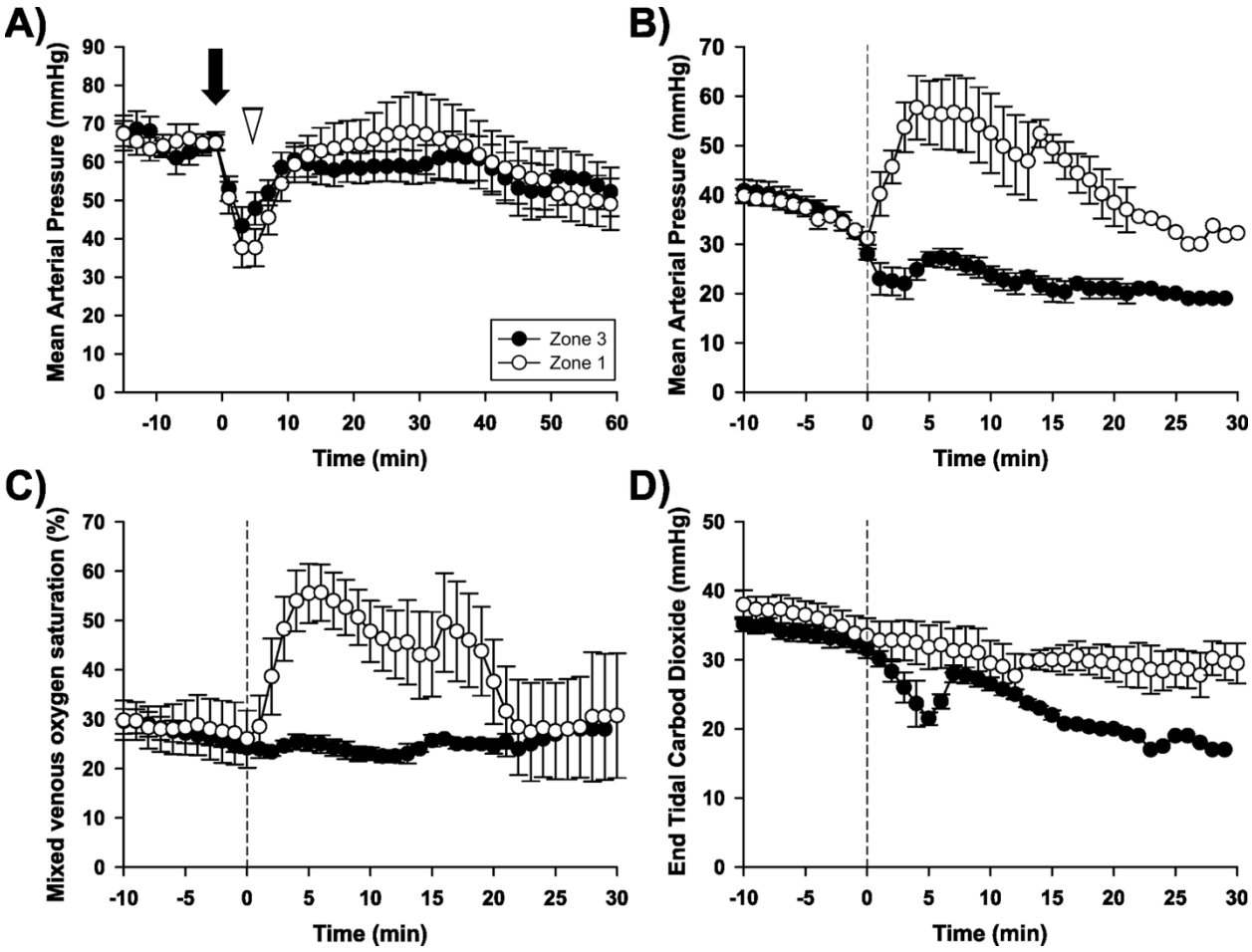

Figure 5. Carotid Mean Arterial Pressure (MAP) throughout the experiment **A)** Initial injury and resuscitation. Arrow indicates point of injury. The white arrowhead marks balloon inflation and the start of the Hextend administration. **B-D)** Cardiovascular collapse and randomization. T_0 is at the point when MAP is at 30 mmHg, and REBOA was moved to Zone 1 or remained in Zone 3, showing **B)** MAP **C)** Mixed venous oxygen saturation (SvO_2 and **D)** End Tidal Carbon Dioxide ($EtCO_2$).

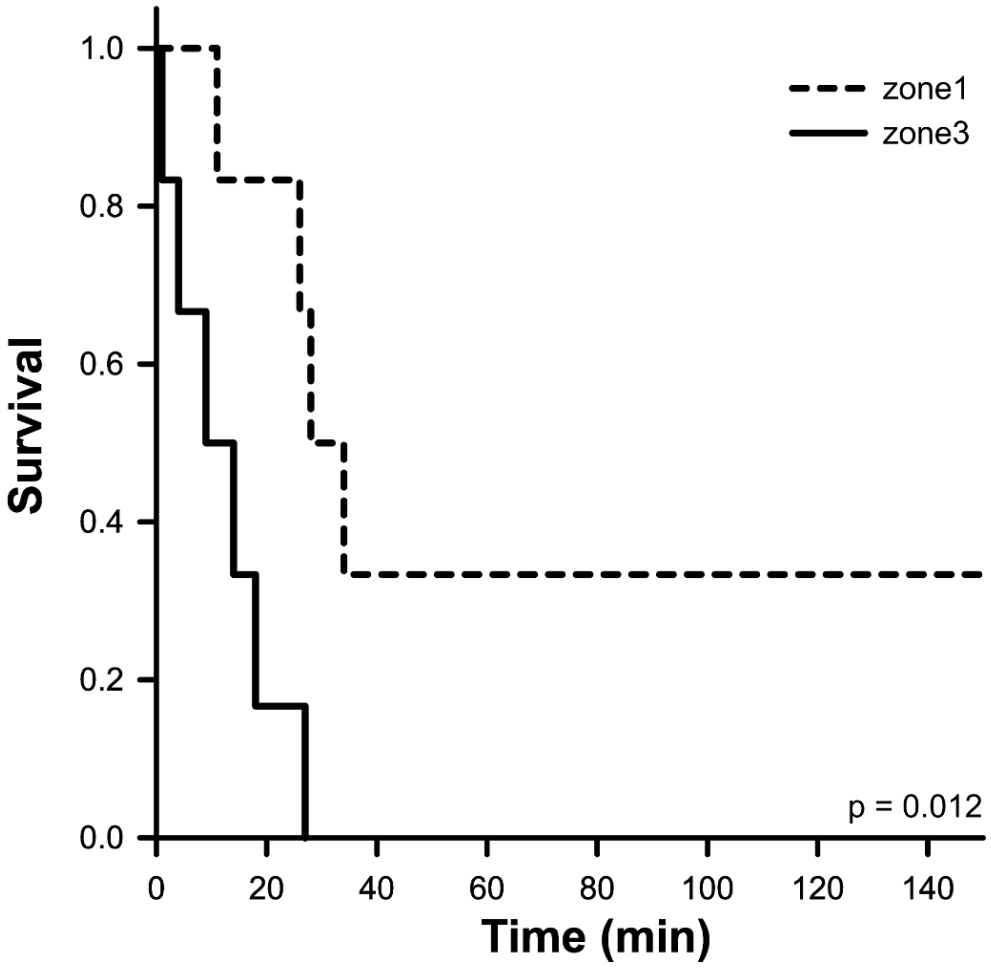

Figure 6. Kaplan – Meier Survival Curve. T_0 is when MAP reaches 30 mmHg. The dotted line (T_{30}) represents the end of controlled hemorrhage and balloon deflation. Groups were compared using log-rank analysis.

13.0 LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

AAJT	Abdominal Aortic and Junctional Tourniquet
ANOVA	ANalysis Of VAriance
CAO	Continuous AAJT Occlusion
EBV	Estimated Blood Volume
$EtCO_2$	End-Tidal Carbon Dioxide
HR	Heart Rate
IM	IntraMuscular
JTS	Joint Trauma System
MAP	Mean Arterial Pressure
NCTH	Non-Compressible Torso Hemorrhage
NIRS	Near Infrared Spectroscopy
OAO	Overlapping Aortic Occlusion
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
SAO	Sequential Aortic Occlusion
SBP	Systolic Arterial Blood Pressure
SVO_2	Mixed Venous Oxygen Saturation
TCCC	Tactical Combat Casualty Care