Conversion of Abdominal Aortic and Junctional Tourniquet (AAJT) to Infrarenal Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is Safe and Practical in a Swine Hemorrhage Model

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Short Title: Conversion from AAJT to REBOA

Abstract

Background. 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. Safe conversion of AAJT to REBOA would allow for field hemorrhage control with mitigation of the morbidity associated with prolonged AAJT use. **Methods:** Yorkshire male swine (n=17, 70-90kgs) underwent controlled 40% hemorrhage. Subsequently, AAJT was placed on the abdomen and inflated. After one hour, animals were allocated to an additional 30 minutes of AAJT inflation, (continuous AAJT, CA), REBOA placement with the AAJT inflated, (immediate REBOA; IR), or REBOA placement following AAJT removal (subsequent REBOA; SR). Following removal, animals were observed for 3.5 hours. **Results.** No significant differences in survival, blood pressure, or laboratory values were found following intervention. Conversion to REBOA was successful in all animals but one in the IR group. REBOA placement time was 4.3±2.9 min for IR and 4.1±1.8 min for SR (p=0.909). No animal had observable intestinal injury. **Conclusions.** Conversion of AAJT to infrarenal REBOA is safe and effective, but access may be difficult while the AAJT is applied.

Introduction

Hemorrhage is responsible for a quarter of all deaths in combat and is the leading cause of potentially survivable battlefield deaths.[1] The liberal use of tourniquets has been successful in preventing exsanguination from extremity injuries, but noncompressible torso hemorrhage (NCTH) and junctional hemorrhage are particularly difficult to treat due to the inability to rapidly and safely compress the site of injury. Recently, specialized products including expandable foams, injectable compressed sponges, and various junctional tourniquets have been developed to manage hemorrhage from such injuries.[2,3] Unfortunately, none of these has been uniformly successful or gained widespread adoption. Two therapies that have shown promise in the treatment of pelvic and junctional bleeding are the Abdominal and Aortic and Junctional Tourniquet (AAJT) and Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA).

The AAJT consists of a belt with a wedge-shaped inflatable bladder that can be applied to occlude blood flow at junctional sites (axilla and groin) or occlude the distal aorta and iliac vessels in the lower abdomen. When placed around the abdomen, the AAJT applies pressure at the level of the aortic bifurcation. The product has been shown to be effective in limiting femoral artery blood flow in both laboratory and clinical settings.[4–6] One of the main benefits of the AAJT is that it can be applied quickly and accurately by prehospital personnel with minimal training.[6,7] Complications of AAJT application include increased pain, respiratory arrest, obstruction of surgical access sites, and the potential for ischemic bowel damage with extended inflation times.[8–11] REBOA is a technique which uses an inflated intravascular balloon that stops blood flow in order to achieve hemostasis. The balloon catheter is introduced via the femoral

artery and can be positioned in the descending aorta between the subclavian and the celiac arteries (Zone 1) or inserted between the renal artery and the aortic bifurcation (Zone 3) depending on the site of hemorrhage.[12] Current clinical practice guidelines from the American College of Surgeons recommend an aortic occlusion time less than 15 minutes if positioned in zone 1 and less than 60 minutes if positioned in zone 3.[13] Initiation of REBOA requires significant training and technical proficiency. Its use is currently limited to the hospital environment and to situations in which expeditious surgical hemostasis can be obtained.[13] Several translational studies have demonstrated broad equivalence between REBOA and AAJT for the control of femoral hemorrhage.[14–16] In simple controlled hemorrhage, and polytrauma models, similar hemostatic, hemodynamic, and metabolic profiles were observed.

The ability to safely convert an AAJT to a zone 3 REBOA would allow for rapid control of pelvic and lower extremity junctional hemorrhage in the field while minimizing the morbidity associated with prolonged AAJT application. As the AAJT is a stand-alone device that can be applied rapidly by prehospital personnel, it is uniquely suited for use by first responders, especially in austere environments. Upon escalation of care, transition to a zone 3 REBOA would avoid the adverse outcomes seen with prolonged AAJT application and allow for continued hemorrhage control. A recent study examined the transition from AAJT to zone 3 REBOA, but did not include realistic conversion, examination of laboratory parameters, or an extended period of observation.[17] This study was designed to rigorously explore the consequences of conversion of AAJT to zone 3 REBOA in a clinically relevant translational model of severe hemorrhagic shock.

Methods

Animal preparation

The study was approved by the Institutional Animal Care and Use Committee for the U.S. Air Force 59th Medical Wing Clinical Investigation and Research Support (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.[18] Overall experimental design is shown in Figure 1.

Male Yorkshire swine 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.

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 to monitor regional tissue oxygenation. 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 an exponential fashion to simulate uncontrolled hemorrhage.[19] 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. Hemorrhage was paused when the mean arterial pressure (MAP) dropped below 30 mmHg and resumed once it rose above 30 mmHg.

Intervention

Immediately after the 30-minute hemorrhage, the AAJT was applied 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 100mL/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, CA), the second had the AAJT completely deflated prior to REBOA insertion (Subsequent REBOA, SR), and the third group had the REBOA inserted while the AAJT was still inflated, after which the AAJT was deflated (Immediate REBOA, IR). In both REBOA groups, the left femoral artery was percutaneously catheterized with a 5 French micropuncture set using ultrasound guidance and a 7 French sheath was inserted. 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 CA 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.

Outcomes and 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, EtCO2, 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 2010 (Microsoft, www.microsoft.com) and Sigmaplot 12 (Systat Software, https://systatsoftware.com).

Results

Baseline characteristics

A total of 17 animals weighing 82.2 ± 7.4 kg were included for analysis: CA (n=5), IR (n=6), SR (n=6). One animal was removed from analysis in the CA 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 EtCO2 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 EtCO2 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 EtCO2 was 42.2 ± 4.3 mmHg.

In the REBOA groups, catheterization was attempted using ultrasound guidance. All femoral arteries in the SR group were successfully cannulated and the REBOA correctly placed. One artery in the IR 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 SR 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 CO2 during the conversion. Additionally, an increase in carotid MAP and EtCO2 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 EtCO2 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 all were elevated throughout the observation period in all groups with no differences among groups. However, creatinine and myoglobin were persistently higher in the CA group following intervention removal, but these differences did not reach significance. At laparotomy, no evidence of intestinal injury was observed in any animal and no abdominal tissue damage was noted on inspection.

Discussion

We have demonstrated that conversion from AAJT to Zone 3 REBOA is safe and 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.[14,15] In each of the three groups (CA, IR, SR) no sustained significant hemodynamic differences were observed with respect to carotid MAP, femoral MAP, EtCO2, and heart rate (Figure 2). However, SR 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 $EtCO_2$ (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 SR 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 SR 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 SR, 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.[4,6]

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 IR

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 SR 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.[17] We expanded upon their findings by assessing 60 minutes of AAJT prior to intervention (compared to 30 minutes) and by investigating the practicality and safety 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.[10] 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.[11] In the current study, no

evidence of gross intestinal ischemia was noted at the time of necropsy for all groups, including the CA 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 safe and feasible. While no metabolic advantages are evident, early transition to REBOA would allow for avoidance of prolonged AAJT morbidities such as bowel ischemia,[11] difficulty ventilating,[8] and poor access to abdominopelvic surgical sites.[17] 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.

This study has several limitations worth noting. First, although the animals were observed for four hours, true long-term consequences of the interventions may have arisen had the observation period been prolonged. Second, a controlled hemorrhage model was utilized in this study as opposed to an uncontrolled model and we therefore not cannot comment on blood loss differences between the groups. Finally, there are notable anatomic differences between swine and humans (primarily vis-à-vis AAJT application) that may affect the applicability of these findings in human care.

Conclusion

Conversion of AAJT to infrarenal REBOA is safe and effective with each technique having physiologic advantages and disadvantages. Placement of a REBOA catheter in the presence of an inflated AAJT can make accessing the femoral artery difficult, potentially resulting in improper cannulation. Further studies are needed to define clear guidelines for managing NCTH in the austere environment.

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

	CA	IR	SR	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

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

	CA	IR	SR	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
EtCO2 (mmHg) - Peak	42.8 ± 2.4	44.2 ± 8.3	57.5 ± 6.5	0.003**
Pectoralis StO2 (%)	67.8 ± 4.6$^{\#}$	71.0 ± 12.9$^{\#}$	53.8 ± 5.3	0.010*
Kidney StO2 (%)	53.2 ± 10.5	56.2 ± 13.8	43.3 ± 8.3	0.153
Values obtained distal to occlusion				
Femoral MAP (mmHg) - Peak	26.2 ± 7.2$^{\#\#}$	34.5 ± 16.6$^{\#\#}$	60.7 ± 12.4	0.0014**
Left Thigh StO2 (%)	16.5 ± 3.0$^{\#}$	22.5 ± 10.9	39.7 ± 18.5	0.0380*
Right Thigh StO2 (%)	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*

*, $p < 0.05$; **, $p < .01$; #, $p < 0.05$ vs SR; ##, $p < 0.01$ vs SR;

Figure 1. Flow Chart showing the progression of experimentation

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 CO2. Dashed line is start of REBOA or continued AAJT. Open arrowhead is removal of occlusion. Error bars not shown for clarity.

Figure 3. Lab Values A) pH B) Potassium C) Lactate D) Urea Nitrogen E) Creatinine F) Myoglobin. T0 is start of variable occlusion. CA – continuous AAJT, IR – Immediate REBOA, SR – Subsequent REBOA. No significant differences were observed in factor.

Figures 1. Flow Chart

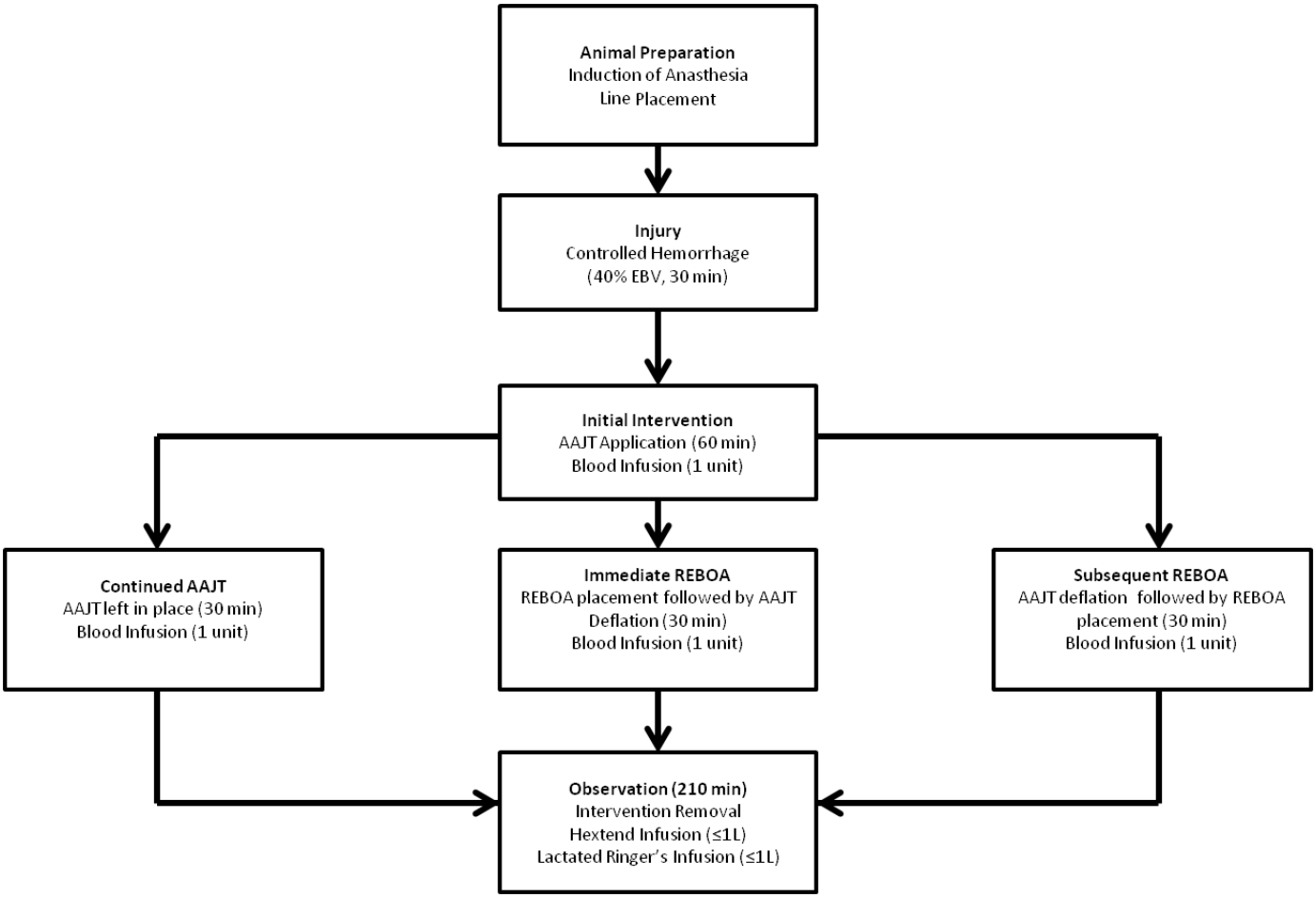

Figure 1. Experimental design and timeline for occlusion and resuscitation experiments. EBV=estimated blood volume (66mL/kg)

Figure 2.

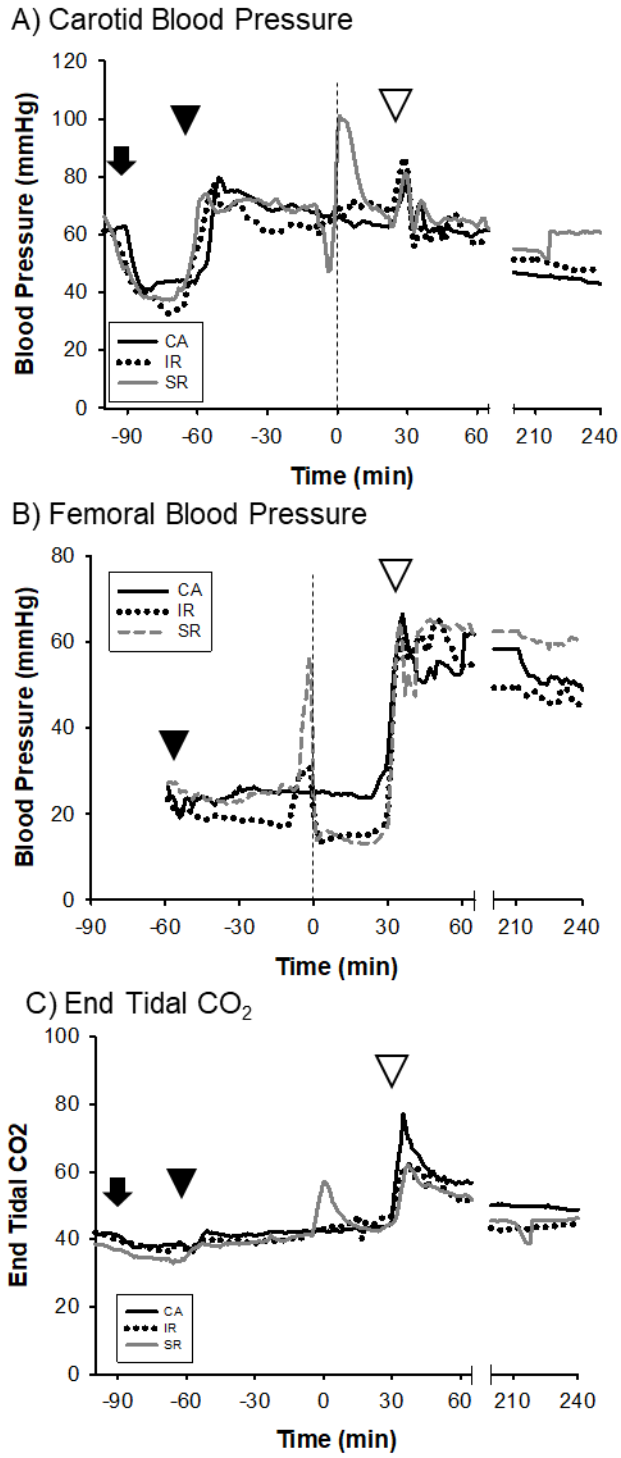
A) Carotid Blood Pressure
Blood Pressure (mmHg)
120
100
80
60
40
20
0
CA
IR
SR
-90
-60
-30
0
30
60
210
240
Time (min)
B) Femoral Blood Pressure
Blood Pressure (mmHg)
80
60
40
20
0
CA
IR
SR
-90
-60
-30
0
30
60
210
240
Time (min)
C) End Tidal CO_2
End Tidal CO2
100
80
60
40
20
0
CA
IR
SR
-90
-60
-30
0
30
60
210
240
Time (min)

Figure 3. Lab values