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Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is an emerging technique in trauma; however, the physiological sequelae are un-quantified. The objectives of this study are to characterize the burden of reperfusion and organ dysfunction of REBOA incurred during 30 or 90 minutes of class IV shock in a survivable porcine model of hemorrhage. REBOA in shock improves MCAP and is associated with a higher lactate burden, however, this returned to control levels within the study period. Ultimately, prolonged REBOA is a survivable and potentially life-saving intervention in the setting of hemorrhagic shock and cardiovascular collapse.

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Final Report

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Physiologic Tolerance of Descending Thoracic Aortic Balloon Occlusion in a Swine Model of Hemorrhagic Shock.

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ABSTRACT

Background: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is an emerging technique in trauma; however, the physiological sequelae are un-quantified. The objectives of this study are to characterize the burden of reperfusion and organ dysfunction of REBOA incurred during 30 or 90 minutes of class IV shock in a survivable porcine model of hemorrhage.

Methods: Following the induction of shock, animals were randomized into 4 groups (n=6): 30 minutes of shock alone (30-Shock) or REBOA (30-REBOA) and 90 minutes of shock (90-Shock) or REBOA (90-REBOA). Cardiovascular homeostasis was then restored with blood, fluid and vasopressors for 48 hours. Outcomes included mean central aortic pressure (MCAP), lactate, organ dysfunction, histological evaluation and resuscitation requirements.

Results:

Both REBOA groups had a higher MCAP throughout their shock phase compared to controls ($p<0.05$), but accumulated a significantly higher lactate burden, which returned to control levels by 150 mins in the 30-REBOA groups and 320 mins in the 90-REBOA group. There was a greater level of renal dysfunction and evidence of liver necrosis seen in the 90-REBOA group compared to the 90-Shock group. There was no evidence of necrosis in cerebral or spinal cord tissue in any group. The 90-REBOA group required significantly more fluid resuscitation than the 90-Shock group ($p=0.049$).

Conclusion: REBOA in shock improves MCAP and is associated with a higher lactate burden, however, this returned to control levels within the study period. Ultimately, prolonged REBOA is a survivable and potentially life-saving intervention in the setting of hemorrhagic shock and cardiovascular collapse.

INTRODUCTION

Vascular disruption within the torso with concomitant hemorrhage remains a leading cause of death in military and civilian trauma.[1–5] Patients often present *in extremis* with profound cardiovascular collapse. Occlusion of the thoracic aorta can be used to improve after-load, supporting the myocardial and cerebral circulations,[6] while controlling arterial inflow to the distal circulation where vascular disruption has occured. This is most commonly performed via a thoracotomy and aortic cross-clamp; however, this technique requires significant resources and yields few survivors.[7–9] Recognition of these limitations has motivated investigators to explore other methods of achieving aortic occlusion earlier and by less invasive means.[10–12]

One such alternative is endovascular balloon occlusion, which is practiced by vascular surgeons to control the inflow of abdominal aortic aneurysm's during the placement of stent-grafts.[13,14] Interestingly, the use of balloon occlusion of the aorta in trauma is not a new concept having been reported as early as the 1950's during the Korean War,[15] but has never gained widespread acceptance. With refinements in surgical technology and improved critical care, this technique is now being revisited clinically.[12]

A recent publication from our group has characterized the method of insertion of resuscitative endovascular balloon occlusion of the aorta (REBOA) for trauma patients.[10] The authors described 3 aortic zones: I - left subclavian to celiac trunk, II - celiac trunk to the lowest renal artery and III - the infrarenal aorta. Zone I occlusion was described as optimal for torso hemorrhage and zone II for pelvic and lower extremity hemorrhage. However, while REBOA appears to have clear application for hemorrhage control in patients *in extremis*, the physiological sequelae following balloon deflation after extended periods of aortic occlusion

remain un-quantified. The aim of this study was to assess the physiological tolerance of Zone I REBOA for 30 and 90 minutes compared to untreated class IV shock in a survivable porcine model of controlled hemorrhage.

MATERIALS AND METHODS

Study Approval and Overview.

Institutional Animal Care and Use Committee (IACUC) approval was obtained in accordance with all applicable laws, regulations and policies. Procedures were performed at an accredited facility (Lackland Air Force Base, San Antonio, TX) in compliance with IACUC policies and under the supervision of a licensed veterinary staff. Female Yorkshire–Landrace crossbred swine (John Albert, Cibolo, TX) (age range, 5–6 months; weight range 70-90 kg) were housed at the facility 7 days before the protocol to allow for quarantine and acclimation.

There were 4 study groups, each with 6 animals: 30 mins of shock and Zone I REBOA (30-REBOA), 30 mins of shock alone (30-Shock), 90 mins of shock and Zone I REBOA (90-REBOA) and 90 mins of shock alone (90-Shock). Animals were exposed to 5 study phases: surgical preparation, hemorrhage, intervention, resuscitation and critical care phases (Fig 1). Physiological and biochemical parameters were recorded throughout the protocol and animals were euthanized at the end of the 48 hour critical care phase where necropsy was performed, gross pathology assessed and tissue was taken for histology.

Preparation of Animals

Following cannulation of an ear vein, anesthesia was induced with intravenous Ketamine to facilitate oro-tracheal intubation and mechanical ventilation where anesthesia was maintained with Isoflurane (range: 2 - 4%). All animals underwent cannulation of the common carotid artery, and the internal and external jugular veins by midline surgical exposure using a modified Seldinger technique. This permitted transduction of the carotid arterial catheter to enable cartoid-

flow monitoring, intra-venous fluid replacement via the internal-jugular catheter and measurement of cardiovascular indices via a Swan-Ganz catheter in the external-jugular.

The right brachial artery was operatively exposed and a cannula was fluoroscopically guided into the aortic arch to measure central aortic pressure. The right iliac artery was exposed via retroperitoneal approach and cannulated with a 15 fr sheath to permit a controlled hemorrhage and access for endovascular aortic balloon placement. The animals' cranium was also trephined to permit the placement of a brain oximeter (Licox; Integra NeuroSciences, Plainsboro, NJ).

At the conclusion of surgical procedures and catheter placements, baseline laboratory and physiological recordings were performed. Throughout the protocol, heart rate (HR), mean central aortic pressure (MCAP), brain oxygenation ($PbrO_2$), carotid flow (CF), end tidal carbon dioxide (CO_2), core temperature (rectal), and urine output (UOP) were continuously monitored.

Hemorrhage (30 minutes)

To achieve a controlled hemorrhage and class IV shock, a method for blood and volume estimation and rate of hemorrhage was used as previously described.[16] In brief, over 20 mins, 35% of total blood volume (total porcine intravascular volume: 66 ml/kg) was withdrawn through the sheath in the iliac artery; half of this volume was taken over 7 mins and the remaining over 13 mins. As swine possess a contractile spleen and can readily autotransfuse in response to hemorrhagic shock, animals were subjected to ongoing hemorrhage at a rate of 0.15ml/kg/min for an additional 10 minutes to ensure class IV shock was maintained. Shed blood was stored in citrated bags (Terumo, Japan) for later transfusion during the resuscitation phase. If mean arterial pressure (MCAP) decreased below 30 mm Hg, hemorrhage was stopped until

arterial pressure was consistently greater than 30 mmHg, and then the hemorrhage was resumed until completion.

The start of the hemorrhage phase was considered time zero; the reference points for all other experimental timings. The 30 min time period also served to simulate the pre-hospital time, prior to admission to a trauma center. At the conclusion of the hemorrhage phase, labs were drawn and physiological recordings made.

Intervention (30 or 90 minutes)

Following the hemorrhage phase, animals were randomized into one of four groups: 30-Shock, 30-REBOA, 90-Shock or 90-REBOA. Animals in either REBOA group underwent aortic occlusion with an endovascular balloon (Coda Balloon; Cook Medical Inc, Bloomington, IN), inflated distal to the left subclavian artery orifice under fluoroscopic guidance. Successful occlusion was confirmed by loss of an arterial waveform from a catheter transduced distal to the balloon. Animals in the shock groups were observed throughout their study period (30 or 90 minutes) without any intervention taking place.

Resuscitation (6 hours)

A 6 hour resuscitation phase began immediately subsequent to the intervention phase with animals receiving transfusion of previously shed whole blood. Following withdrawal of the iliac arterial sheath (with or without balloon), the artery was ligated and the midline incision closed. The resuscitation strategy differed slightly between the REBOA groups and the shock groups.

Resuscitation in the REBOA groups was initiated 10 minutes prior to the end of 30 or 90 minute intervention period. Whole blood was slowly infused until the MCAP was raised by 25%, to avoid precipitous cardiovascular collapse, prior to deflation of the aortic balloon. The aortic balloon deflation was accomplished incrementally over a 3-minute period and the remainder of the blood was given after complete deflation. The resuscitation in the shock groups began immediately upon completion of the 30 or 90-minute period of shock with whole blood.

Blood pressure was titrated to a goal mean pressure of 60 mm Hg using 1 liter intravenous fluid boluses once the previously collected whole shed blood was exhausted. When animals failed fluid challenges, norepinephrine was administered for hemodynamic support. Norepinephrine doses were titrated to maintain the targeted MCAP.

Critical Care (48 hours)

The final component of the protocol was a 48 hour critical care phase where the animals remained sedated (Isofluane, Ketamine and Midazolam) and mechanically ventilated. The hemodynamic support commenced during the resuscitation phase was continued and was designed to replicate the support that trauma patients would receive in the intensive care unit post damage control surgery. Blood samples were taken and physiological parameters recorded throughout this phase. At conclusion of the ICU phase, the animals were euthanized and underwent necropsy and gross pathology. Tissue samples from brain, spinal cord, liver, lung, heart and kidney were collected for histological analysis.

Study End Points

Study end-points were separated into three categories: perfusion, organ dysfunction and resuscitation requirements. Markers of perfusion included mean central aortic pressure (MCAP), cerebral oxygen partial pressure ($PBrO_2$) and lactate measurements. These samples were taken from the brachial arterial line at Q15 minutes until 2 hours and then Q30 minutes until the end of the resuscitation phase, then at 24 and 48 hours.

Markers of cardiac, renal, hepatic and muscle dysfunction were analyzed at 24 and 48 hours and included cardiac Troponin I (cTnI), Aminotransferases, Blood Urea Nitrogen (BUN), Creatinine, Potassium and Creatine Kinase. Brain, spinal cord, heart, lung, kidney and liver were also examined histologically at the conclusion of the study. Tissues were examined by a Veterinary Pathologist and subjectively graded as having no, minimal, mild, moderate, marked or severe necrosis using a nominal scale of zero to five. Resuscitation requirement consisted of total norepinepherine dose and total volume of intra-venous fluid (blood and crystalloid) administered over 48 hours.

Statistical Analysis

Statistical analyses were performed using SAS Version 9.2 for Windows (SAS Institute, Cary, North Carolina) and R Version 2.13.1 (R Foundation for Statistical Computing). Continuous data were tested with a mixed effect repeated measures analysis of variance (ANOVA). Nominal data was tested with contingency tables using Fisher's exact test and ordinal data were tested with the Kruskal-Wallis test. The Bonferroni method was used to correct the level of significance for post hoc multiple comparison tests to investigate effects.

RESULTS

Baseline Characteristics and Mortality

The baseline characteristics of the 4 study groups (n = 6 / group), are shown in table 1. Time zero occurred at the start of the hemorrhage phase, and serves as the reference point for all reported time points and values. There was no significant difference in weight or volume of hemorrhage (per kg) used to induce shock. Measures of perfusion and organ function were also similar amongst the groups. There were two deaths: one animal died in the 30-Shock group during the hemorrhage phase and another animal in the 90-Shock group died during the resuscitation phase. Necropsy did not identify an obvious cause of death, although cardiovascular collapse was thought likely.

Measures of Organ Perfusion

Immediately post hemorrhage, all four groups had a similar mean MCAP (±SD) of 33±8 mmHg, indicating class IV shock had been attained (figure 2). In the 30 minute arm, the 30-REBOA group had a significantly greater MCAP upon initiation of aortic occlusion (91±16 vs 31±4; $p<0.001$) compared to the 30-Shock group. The MCAP remained significantly elevated throughout the intervention phase in the 30-REBOA group compared to the 30-Shock group. This observation was also recorded in the 90 minute group where the MCAP was significantly greater in the 90-REBOA compared to the 90-Shock group (89±22 vs 38±13; $p=0.001$). This increased MCAP was maintained throughout the 90 minute intervention phase in the REBOA group. In all groups, the MCAP's returned to their respective baselines during the resuscitation and critical care phases.

The partial pressure of brain tissue oxygenation ($PBrO_2$) was noted to increase significantly from post-hemorrhage levels in both the REBOA groups ($p<0.001$), but not in

either of the shock only groups. There was a significantly greater PBrO2 in the 90-REBOA compared to the 90-Shock group (66±35 vs 30±14; p=0.042); however, despite a rise in the 30-REBOA PBrO2 compared to the 30-Shock, there was no statistically significant difference (45±37 vs 22±17; p=0.225) (figure 3).

There was a significantly elevated lactate concentration measured in the REBOA groups compared to the shock alone groups at 15 minutes into the intervention phase (figure 4). This rise in lactate peaked at 75 minutes in the 30-REBOA and at 150 minutes in the 90-REBOA group. Lactate levels were no longer elevated, when compared to the shock only groups, by 150 minutes in the 30-REBOA and 320 minutes in the 90-REBOA group.

Measures of Organ Dysfunction

There was no difference in cTnI measurements across all four groups at either 24 or 48 hrs (tables 2 and 3).We observed a statistically significant rise in AST level in the 30-REBOA group compared to the 30-Shock at 24 hrs, although there was no detectable difference by 48 hrs (table 2). The 90-REBOA group had a greater AST level at both 24 and 48 hours, although it was not statistically significant (table 3). LDH was noted to rise in all groups at 24 hours but began to decrease by 48 hrs. The reduction in LDH between the 24 and 48 hr time points was significantly greater in the Shock groups than in the REBOA groups.

There were no significant differences detected in Creatinine level amongst all groups; however, BUN was noted to be significantly higher in the 30-Shock group than the 30-REBOA group by 48 hrs. This trend was reversed by 90 minutes group, where the 90-REBOA group had a significantly greater BUN than the 90-Shock by 48 hrs. There was no difference in potassium or CK measurements by 48 hrs in either group.

Histologically, there was no significant difference in the numerical rates of necrosis, inflammatory infiltrates or edema observed in cerebral, spinal cord or myocardial tissue amongst the four groups (figure 5). There was a suggestion of greater renal damage and regeneration in the 90-REBOA group compared with the 90-Shock group, though neither achieved statistical significance. There was, however, significantly higher observed rate of centrilobular liver necrosis in the 90-REBOA group compared with the 90-Shock group. Significant necrosis was not observed in any other group's organs (figure 5).

Resuscitation Requirements

Cumulative intravenous fluids (IVF) and vasopressor requirements during the resuscitation and critical care phases are shown in table 4. The 90-REBOA group required a greater mean total fluid (ml) resuscitation than the 90-Shock group (2667±931 vs 1000±1225; p = 0.034). The total mean dose of Norepinepherine (mg) was also greater in the 90-REBOA group (2381.2±2316.3 vs 494.2±1171.7; p=0.068), although this only trended towards significance. There was no difference in IVF and norepinepherine dose between the 30 minute groups.

DISCUSSION

This study characterizes the physiological sequelae of Zone 1 REBOA in the setting of class IV shock compared to shock alone for either 30 or 90 minutes. Following the controlled hemorrhage, both REBOA groups had a significantly greater central aortic pressure and cerebral oxygen delivery than in shocked animals alone. This was achieved at the expense of a greater lactate rise observed following balloon deflation, as a consequence of visceral and lower extremity reperfusion. However, lactate measurements returned to control level by 150 mins in the 30-REBOA group and 320 mins in the 90-REBOA group. There was also evidence of limited organ dysfunction following 90 minutes of REBOA which manifested as an elevated indices of renal dysfunction and histological evidence of centilobular liver necrosis.

This study confirms and extends the findings of earlier work performed by our group and by others.[17,18] White et al, demonstrated that the physiological burden of Zone I REBOA was significantly less than that of resuscitative thoracotomy in a porcine model of 50 minutes of hemorrhagic shock.[18] Animals treated with REBOA were less acidotic with a lower serum lactate, requiring less resuscitation than animals treated with thoracotomy and aortic cross clamping.

Avaro et al, examined the role of Zone I REBOA in a porcine model of uncontrolled splenic hemorrhage compared to resuscitation with normal saline in combination with damage control surgery (DCS). The use of REBOA, followed by DCS, significantly increased mean arterial pressure and the proportion of 2 hour survivors while reducing overall hemorrhage and resuscitation volumes. When examining the REBOA groups that underwent either 40 or 60 minutes of occlusion, 40 minutes appeared to be optimal by incurring a lower lactate and potassium than the 60 minute group.

These studies prompted the current study to examine the temporal profile of the physiological burden incurred with REBOA. Ultimately, while there are physiological penalties, as also described by other investigators, the current study demonstrates that these can be ameliorated with proficient resuscitation and critical care, yielding zero mortality from re-perfusion injury in the REBOA groups by 48 hours.

The physiological burden must be weighed against the improvements seen in central aortic pressure and brain oxygenation - indices of vital importance in trauma patients presenting *in extremis.* This is especially important in patients who have sustained concomitant traumatic brain injury (TBI). REBOA may be able to preserve cerebral perfusion in the context of hemorrhage, although it is unclear whether this would reduce the effects of secondary brain injury, or dangerously raise intra-cranial pressure.

Clinical experience with Zone I REBOA is currently limited despite the concept's genesis over half a century ago. The first published report was by Hughes who deployed it in two combat casualties during the Korean War.[15] Despite both patients succumbing to their wounds, he felt it effective in restoring blood pressure and controlling intra-abdominal hemorrhage. Interestingly, this report pre-dated Ledgerwood's original description of the pre-laparotomy thoracotomy and aortic clamping in patients with a tense hemoperitoneum and shock.[19]

The largest case series of Zone I REBOA comes from Gupta and co-workers who in 1989 deployed the technique in 21 patients in cardiac arrest or profound shock.[11] Hemorrhage control was achieved in 11 patients, although ultimately only seven survived to be discharged. Failure was most commonly seen in major venous injuries and patients in cardiac arrest - challenging injury complexes for any surgeon.

The current study demonstrates the importance of resuscitation and organ support post REBOA use; however, there are a number of limitations to note. The animal model of shock consisted of a controlled hemorrhage; rather than an organ injury *per se*. This may reduce the inflammatory component and sequelae seen in trauma patients immediately post-injury. However, the study was designed to examine the physiological response to shock, thus a survivor model was essential where the volume of hemorrhage could be precisely controlled. While the study was able to demonstrate a difference in measures of perfusion; it could not demonstrate a statistical difference in organ dysfunction, which may relate to insufficient study power.

Furthermore, there were also important differences in the methods of resuscitation between the REBOA and shock alone groups. The "pre-loading" of blood, ten minutes prior to balloon deflation was essential to avoid precipitous cardiovascular collapse following balloon deflation, as noted in the model development phase of the study. While this may appear to favor the REBOA group, it is important to note that the balloon remained inflated for the full duration of the intervention phase and as already noted, a survival model was essential in order to study the physiological changes. As shed blood was the only oxygen carrying fluid available, it is also likely that animals were under resuscitated and the use of further blood would have reduced the inotropic support required.

Conclusion

Zone I REBOA can be used for up to 90 minutes in a porcine model of class IV shock without mortality as a consequence of the reperfusion injury. REBOA incurs a significant physiological burden, although this can be ameliorated with resuscitation and critical care. Central aortic pressure and cerebral oxygen delivery is significantly improved by the use of REBOA. Further study is required in a model of torso trauma to better understand the clinical potential of REBOA.

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TABLES AND FIGURES

Figure 1: Flow diagram of the study protocol

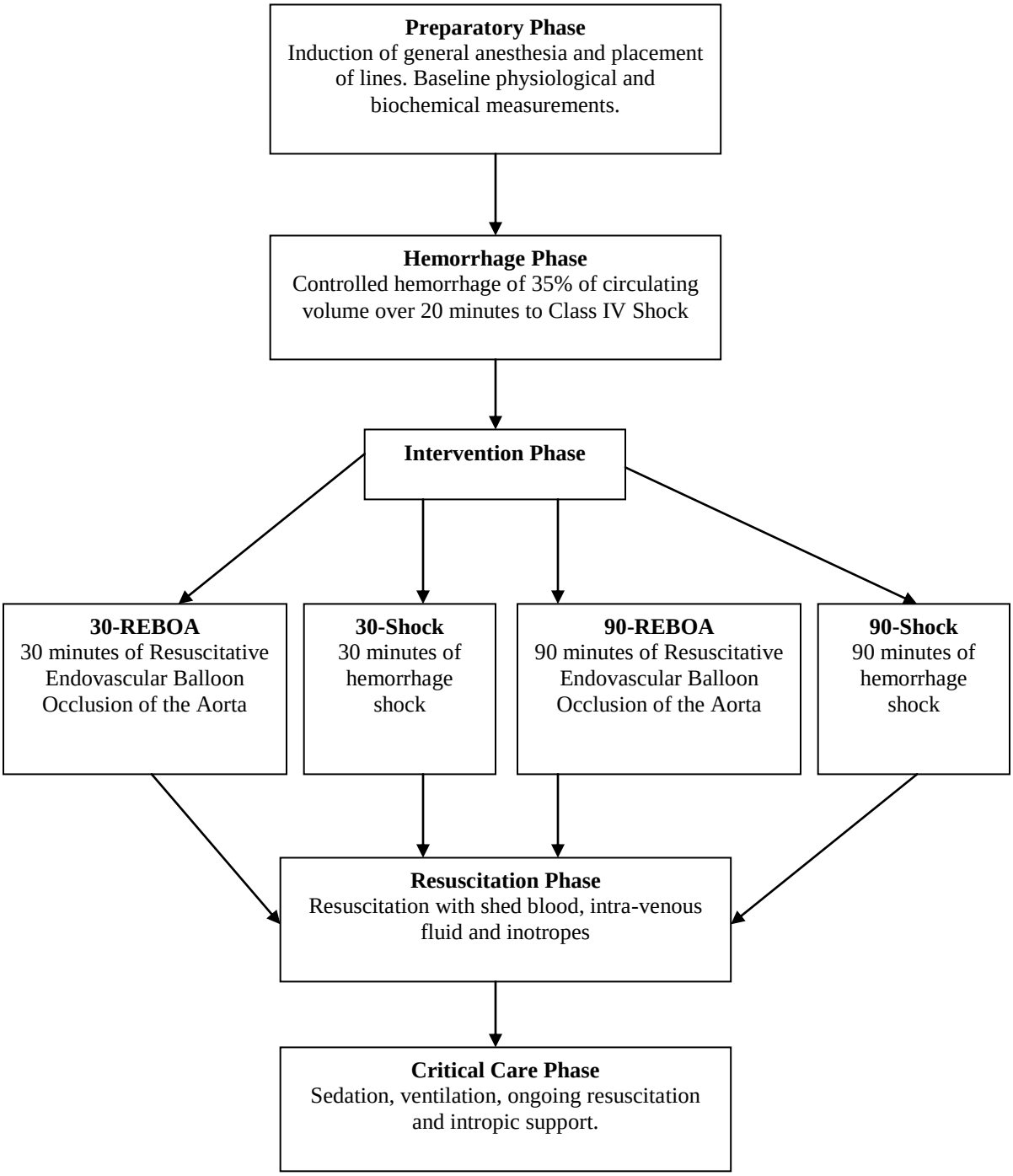
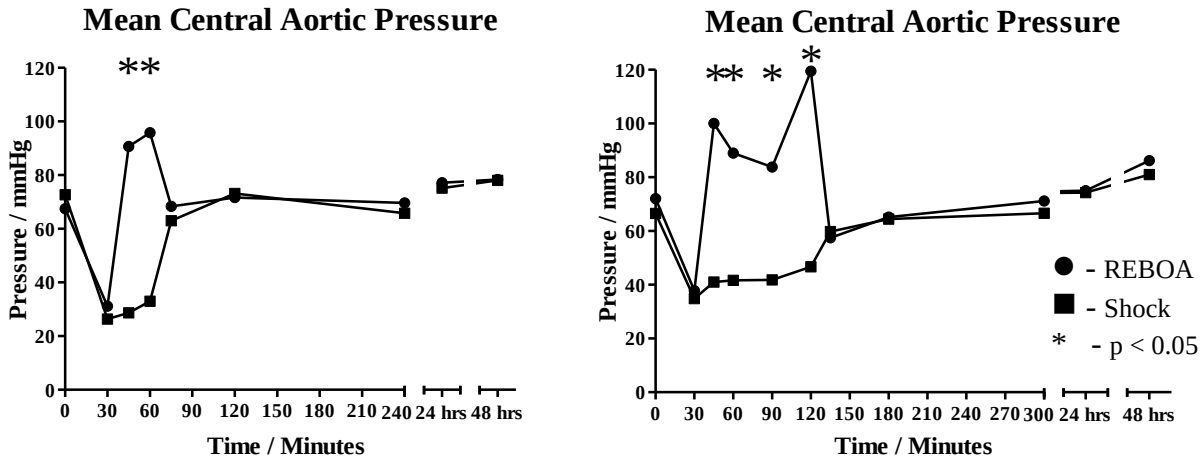


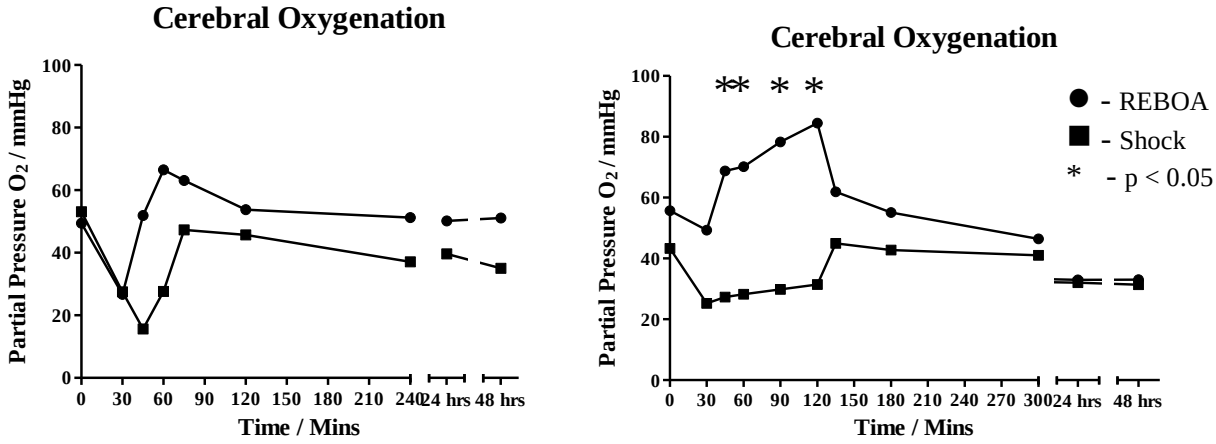
Figure 2: Mean Central Aortic Pressure measurements against time



30 Minute Groups

90 Minute Groups

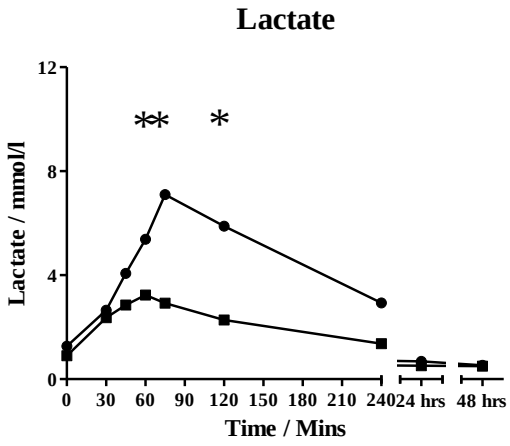
Figure 3: Cerebral Oxygenation measurements against time



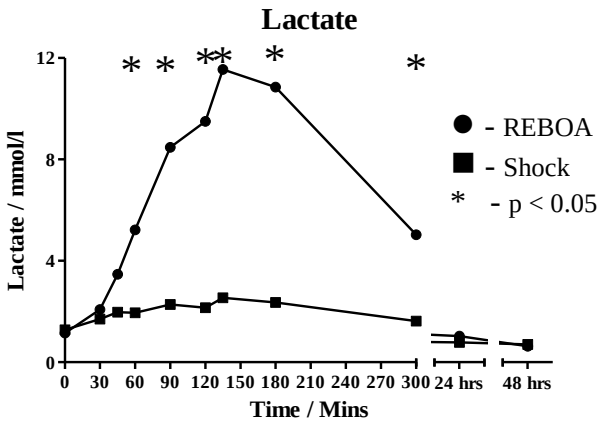
30 Minute Groups

90 Minute Groups

Figure 4: Lactate measurements against time



30 Minute Groups



90 Minute Groups

Figure 5: Representative histological samples of brain, spinal cord, liver and kidney tissue from all groups. The 90-REBOA liver sample shows centrilobular necrosis and the kidney sample shows some tubular debris. All remaining samples were unremarkable.

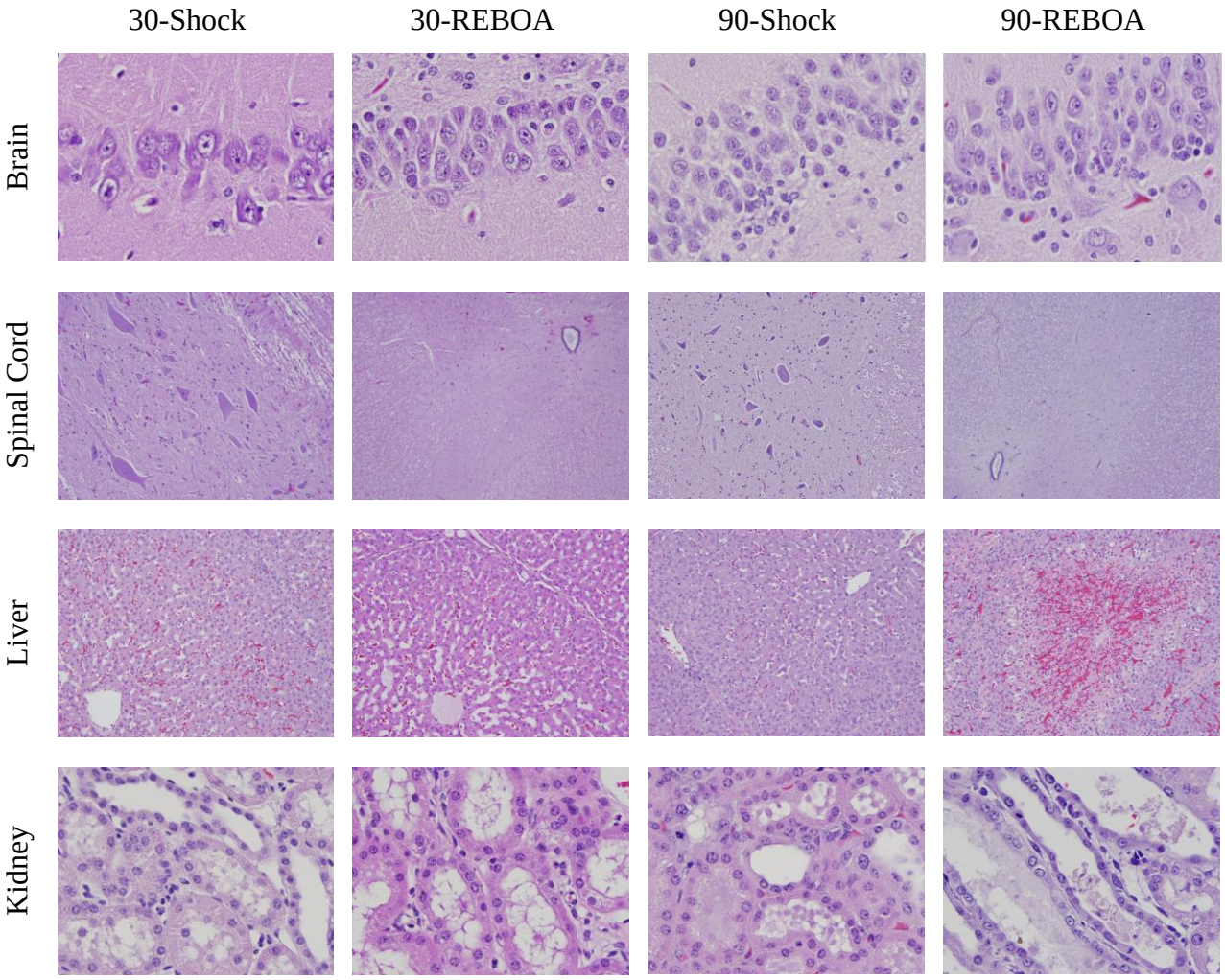


Table 1: Baseline Characteristics

Parameter	30-Shock	30-REBOA	90-Shock	90-REBOA	p
N	6	6	6	6	
Weight/Kg	79.3±4.3	81.3±7.5	87.5±6.7	88.0±11.3	0.171
Female	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	n/a
Hemorrhage, ml/Kg	21.7±4.0	24.6±2.3	23.2±3.1	25.8±0.7	0.104
MCAP, mmHg	73±11	68±11	67±17	72±8	0.752
HR, bpm	83±8	80±4	82±17	76±15	0.775
$PBrO_2$, mmHg	53±37	49±51	43±25	56±24	0.937
Temp, ℃	36.4±1.0	35.3±0.9	36.2±0.9	35.6±0.9	0.230
pH	7.49±0.04	7.47±0.04	7.47±0.04	7.44±0.05	0.387
Lactate, mmol/l	0.9±0.3	1.3±0.4	1.3±0.5	1.2±0.4	0.355
Troponin, ng/ml	0.00±0.00	0.00±0.00	0.22±0.53	0.00±0.00	0.413
AST, U/L	29.5±6.1	36.8±4.9	34.5±5.2	39.0±7.4	0.068
LDH, U/L	437±138	395±117	309±58	339±80	0.170
BUN, mg/dL	11.2±2.0	10.2±2.4	12.3±7.6	11.5±4.6	0.884
Creatinine, mg/dL	1.6±0.3	1.4±0.2	1.7±0.6	1.7±0.4	0.613
K^+, mmol/l	4.4±0.3	4.3±0.2	4.6±0.7	4.6±0.5	0.548
CK, U/L	1176±624	1051±452	1131±396	1121±253	0.971

Table 2: Markers of End-Organ Dysfunction for the 30 minute Groups

	24 Hours			48 Hours		
	30-Shock	30-REBOA	P	30-Shock	30-REBOA	P
Troponin, ng/ml	0.09±0.10	0.28±0.24	0.114	0.04±0.05	0.13±18	0.288
AST, U/L	288±70	560±180	**0.011**	379±224	641±329	0.165
LDH, U/L	1924±391	2625±623	0.058	1462±175	2427±702	**0.016**
BUN, mg/dL	21.2±3.1	18.2±2.6	0.110	22.4±2.9	18.2±1.8	**0.016**
Creatinine, mg/dL	0.9±0.4	1.1±0.4	0.266	0.9±0.4	1.1±0.4	0.363
K+, mmol/l	3.5±0.3	3.6±0.3	0.610	3.8±0.4	3.6±0.2	0.340
CK, U/L	23804±6651	39881±8161	**0.006**	36032±27750	45545±17359	0.504

Table 3: Markers of End-Organ Dysfunction for the 90 minute Groups

	24 Hours			48 Hours		
	90-Shock	90-REBOA	p	90-Shock	90-REBOA	P
Troponin, ng/ml	0.60±1.14	0.38±0.49	0.681	0.16±0.30	0.19±0.27	0.852
AST, U/L	879±131	1292±466	0.089	1006±173	1360±330	0.060
LDH, U/L	8462±5453	9693±4487	0.690	7468±4724	9673±5501	0.499
BUN, mg/dL	24.2±7.3	28.0±2.6	0.263	24.8±7.3	37.3±5.3	**0.009**
Creatinine, mg/dL	1.7±0.3	1.8±1.1	0.847	1.2±0.2	1.5±0.6	0.400
K+, mmol/l	4.1±0.6	4.6±1.1	0.344	4.0±0.5	4.2±0.5	0.559
CK, U/L	85706±33920	76580±41352	0.703	78334±30713	58797±27659	0.296

Table 4: Total Resuscitation Requirements

	30 Minute Groups			90 Minute Groups		
	30-Shock	30-REBOA	p	90-Shock	90-REBOA	p
IV Fluid, ml/24hrs	400±652	833±817	0.336	1000±1225	2667±931	0.034
Norepi Dose, mg/24hrs	0.0±0.0	57.6±91.0	0.176	494.2±1171.7	2381.2±2316.3	0.068