Location is everything: The hemodynamic effects of REBOA in Zone 1 versus Zone 3 of the aorta

Emily M. Tibbits, MD, Guillaume L. Hoareau, DVM, PhD, Meryl A. Simon, MD, Anders J. Davidson, MD, Erik S. DeSoucy, DO, E. Robert Faulconer, MBBS, Joseph J. DuBose, MD, Lucas P. Neff, MD, J. Kevin Grayson, DVM, PhD, Timothy K. Williams, MD, *and* **M. Austin Johnson, MD, PhD**, *Sacramento, California*

OBJECTIVES: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emerging technology to augment proximal blood pressure during the resuscitation of patients with noncompressible torso hemorrhage. Currently, placement choice, supraceliac (Zone 1) versus infrarenal (Zone 3) aorta, depends on injury patterns, but remains a highly debated topic. We sought to compare the proximal hemodynamic support provided by Zone 1 versus Zone 3 REBOA placement and the degree of hemodynamic instability upon reperfusion following intervention.

METHODS: Eighteen anesthetized swine underwent controlled hemorrhage of 25% total blood volume, followed by 45 minutes of Zone 1 REBOA, Zone 3 REBOA, or no intervention (control). They were then resuscitated with shed blood, aortic balloons were deflated, and 5 hours of critical care ensued prior to euthanasia. Physiologic parameters were recorded continuously, and blood was drawn for analysis at specified intervals. Significance was defined as $p < 0.05$.

RESULTS: There were no significant differences between groups at baseline or during the initial 30 minutes of hemorrhage. During the intervention period, average proximal MAP was significantly greater in Zone 1 animals when compared with Zone 3 animals (127.9 ± 1.3 vs. 53.4 ± 1.1 mm Hg) and greater in Zone 3 animals when compared with control animals (42.9 ± 0.9 mm Hg). Lactate concentrations were significantly higher in Zone 1 animals (9.6 ± 0.4 mmol/L) when compared with Zone 3 animals (5.1 ± 0.3 mmol/L) and control animals (4.2 ± 0.8 mmol/L).

CONCLUSIONS: In our swine model of hemorrhagic shock, Zone 3 REBOA provided minimal proximal hemodynamic support when compared with Zone 1 REBOA, albeit with less ischemic burden and instability upon reperfusion. In cases of impending hemodynamic collapse, Zone 1 REBOA placement may be more efficacious regardless of injury pattern, whereas Zone 3 should be reserved only for relatively stable patients with ongoing distal hemorrhage. (*J Trauma Acute Care Surg.* 2018;85: 101–107.

KEY WORDS: Endovascular; intra-aortic balloon; resuscitation; shock.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emerging technique that serves as an alternative to resuscitative thoracotomy for the treatment of noncompressible torso hemorrhage by limiting hemorrhage and augmenting proximal blood pressure.[1–4] By utilizing an endovascular approach, the physiologic impact of a thoracotomy can be avoided, and the threshold for aortic occlusion prior to cardiovascular collapse is lowered.[5–9] Although the international trauma community has reported mixed outcomes with REBOA when compared with resuscitative thoracotomy, observational data from the United States suggest that REBOA has equivalent or even improved outcomes when used prior to cardiac arrest.[10] These favorable reports have led to increased interest in the technique, with more than 200 US trauma centers now utilizing REBOA-specific catheters (personal communication), and the advent of multiple provider training courses for REBOA.

Contemporary descriptions of REBOA technique refer to occlusion of the aorta within one of three discrete zones: Zone 1,

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From the Clinical Investigation Facility, David Grant USAF Medical Center, Travis Air Force Base, California (E.M.T., G.L.H., M.A.S., A.J.D., E.S.D., E.R.F., L.P.N., J.K.G., T.K.W); Department of General Surgery, David Grant USAF Medical Center, Travis Air Force Base, California (E.M.T., A.J.D., E.S.D.); Department of Surgery, University of California Davis Medical Center, Sacramento, California (E.M.T., M.A.S., A.J.D., E.S.D., J.J.D.); Heart, Lung, and Vascular Center, David Grant USAF Medical Center, Travis Air Force Base, California (M.A.S., J.J.D., T.K.W.); Department of Surgery, University of Maryland Medical Center, Baltimore, Maryland (J.J.D.); Department of Surgery, Emory University Hospital, Atlanta, Georgia (L.P.N.); Department of Surgery, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina (T.K.W.); Department of Emergency Medicine, University of California Davis Medical Center, Sacramento, California (M.A.J.).

Address for reprints: Emily M. Tibbits, MD, 2315 Stockton Blvd, OP512, Sacramento, CA 95817; email: emtibbits@ucdavis.edu.

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the descending thoracic aorta between the left subclavian artery and the celiac axis; Zone 2, the paravisceral aorta from the celiac axis to the renal arteries; and Zone 3, the infrarenal aorta.[4] In the setting of impending cardiovascular collapse due to noncompressible torso hemorrhage, current REBOA guidelines suggest that balloon placement be dictated by the injury pattern (e.g., Zone 3 placement for isolated pelvic injuries and Zone 1 placement for solid organ and/or abdominal vascular injuries resulting in a positive focused assessment with sonography for trauma [FAST] examination).[1,11,12] Notably, all of the current REBOA guidelines were developed for patients with impending hemodynamic collapse who were unresponsive to initial fluid or blood challenges, and they were written based on expert consensus with anecdotal evidence and limited clinical data. One notable consensus opinion concerned the positioning of the REBOA catheter for pelvic hemorrhage, as Zone 3 occlusion seems intuitive for pelvic or distal limb hemorrhage. While Zone 3 occlusion may control hemorrhage, there are no clinical or translational data to suggest that Zone 3 REBOA can provide the degree of proximal hemodynamic support to the heart, lungs, and brain that is required to sustain those organs. With many trauma surgeons advocating for REBOA to be used primarily in the setting of pelvic injuries, quantifying the level of proximal hemodynamic support between Zone 1 REBOA and Zone 3 REBOA is necessary.

Given this knowledge gap, we sought to quantify the physiologic differences between Zone 1 REBOA and Zone 3 REBOA. We hypothesized that Zone 1 occlusion would provide greater proximal blood pressure support when compared with Zone 3 REBOA or with a control group with no intervention. Furthermore, we hypothesized that the ischemia-reperfusion injury would be greater at the conclusion of Zone 1 REBOA compared with Zone 3 REBOA.

MATERIALS AND METHODS

Overview

The Institutional Animal Care and Use Committee at David Grant Medical Center, Travis Air Force Base, CA, approved this study. All animal care and use were in strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Healthy adult, castrate male and nonpregnant female Yorkshire-cross swine (*Sus scrofa*; S&S Farms, Ramona, CA) were acclimated for a minimum of 7 days. At the time of experimentation, animals weighed between 65 and 92 kg and were between 4.5 and 6 months of age.

Conduct of the protocol, including animal preparation, injury, intervention, and critical care, is illustrated in Figure 1. Animals were subjected to a 25% total blood volume hemorrhage over 30 minutes. During this time, animals were assigned, using a block randomization strategy, to one of three intervention arms: Zone 1 REBOA (Zone 1 group, n = 6), Zone 3 REBOA (Zone 3 group, n = 6), or no intervention (control group, n = 6). At the end of the 30-minute hemorrhage, the assigned intervention was implemented for the following 45 minutes. All animals then underwent resuscitation with their shed blood and entered a critical care phase. Critical care was continued for a total experimental time of 360 minutes. During that period, vasopressors were titrated, and isotonic fluid boluses were administered via an automated critical care platform based on predefined physiologic parameters that were the same for all groups.

Animal Preparation

Animals were premedicated with 6.6 mg/kg intramuscular tiletamine/zolazepam (TELAZOL; Fort Dodge Animal Health, Fort Dodge, IA). Following isoflurane induction and endotracheal intubation, general anesthesia was maintained with 2% isoflurane in 100% oxygen. To offset the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine (0.01 μg/kg per minute) was titrated to achieve a target mean arterial pressure (MAP) between 65 and 75 mm Hg. Animals were mechanically ventilated with tidal volumes of 7 to 10 mL/kg and a respiratory rate of 10 to 15 breaths per minute, sufficient to maintain end-tidal CO_2 at 40 ± 5 mm Hg. Balanced electrolyte solution (Plasma-Lyte A; Baxter Healthcare Corporation, Deerfield, IL) was administered to overcome insensible losses at 10 mL/kg per hour until the abdomen was closed and then decreased to 5 mL/kg per hour for the remainder of the study. All animals received an initial bolus of 1 L Plasma-Lyte A prior to instrumentation. Intravenous heparin was administered to achieve an activated clotting time of 100 seconds, similar to human baseline values. An underbody warmer was used to maintain core body temperature between 35 and 37°C.

The spleen was removed via laparotomy to minimize hemodynamic variation from autotransfusion.[13] The supraceliac aorta was exposed by dividing the diaphragm and dissected circumferentially for 5 to 10 cm. Two adjacent intercostal arteries were ligated to facilitate placement of a periaortic flow probe (Transonic Systems Inc., Ithaca, NY) and ensure no aberrant flow was detected during aortic occlusion. The right renal artery was then exposed by incising the peritoneum and dissected circumferentially, and a second perivascular flow probe was placed. The abdomen was closed with cable ties.

The right carotid artery was exposed and circumferentially dissected for placement of a third perivascular flow probe. Both external jugular veins were cannulated to facilitate medication and fluid administration, as well as for central venous pressure (CVP) monitoring. The right brachial artery was exposed and cannulated with a 7-Fr sheath for controlled hemorrhage. The left axillary artery was exposed and cannulated with a 9-Fr sheath for proximal blood pressure monitoring. The left femoral artery was exposed and cannulated with a 12-Fr sheath for balloon catheter placement (CODA; Cook Medical, Bloomington, IN) in Zone 1 and distal blood pressure monitoring. The right femoral artery was exposed and cannulated with a 7-Fr sheath for REBOA catheter placement (ER-REBOA; Prytime Medical, Boerne, TX). The left femoral vein was exposed and cannulated with a dual-lumen resuscitation catheter for blood transfusion. Fluoroscopy was used to confirm the position of the CODA balloon in Zone 1, at the level of the periaortic flow probe, and the ER-REBOA balloon in Zone 3.

Intervention and Critical Care

At the conclusion of the 30-minute hemorrhage phase, the intra-aortic occlusion balloons were inflated according to the randomized assignments. In the animals assigned to the control group, the prepositioned balloons were not inflated. Complete aortic occlusion was confirmed in the Zone 1 group by loss of

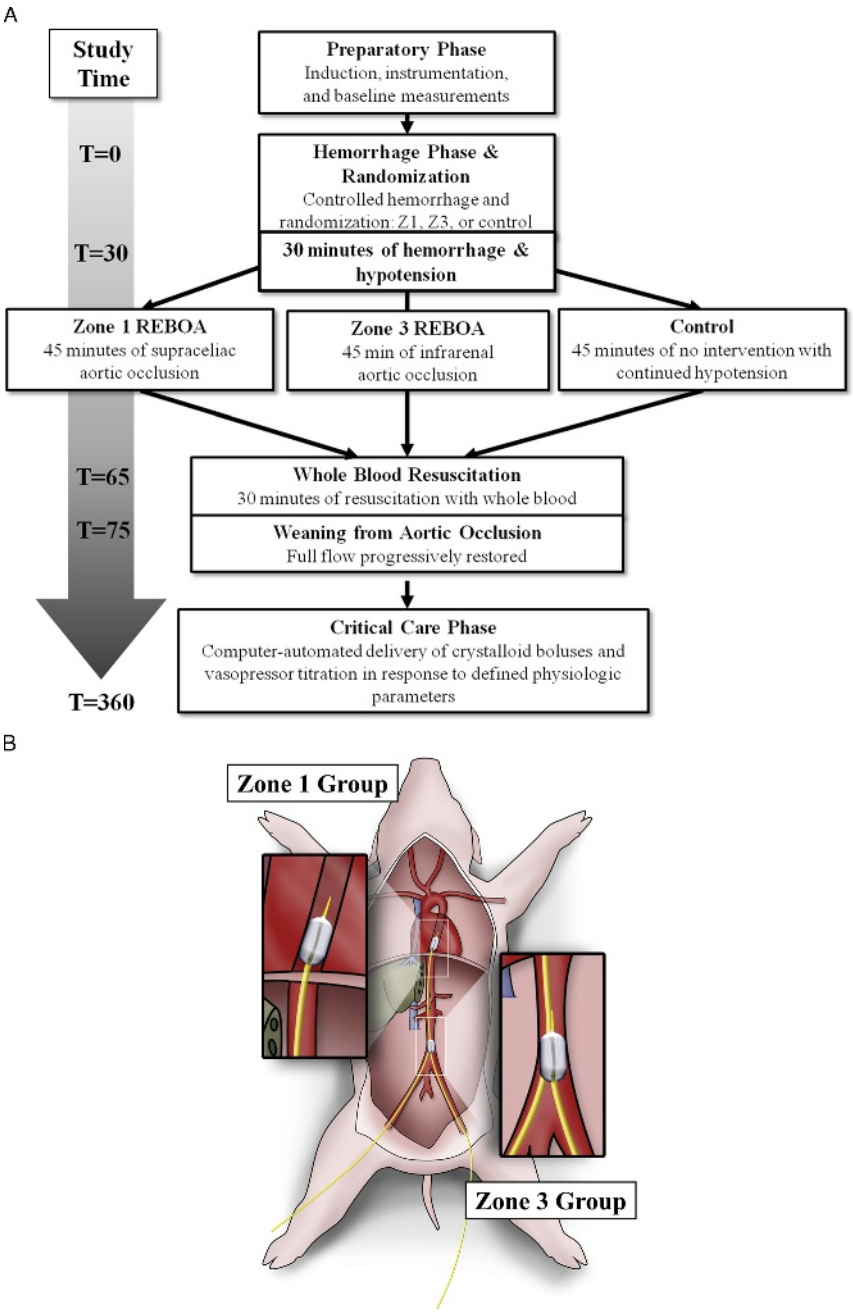

Figure 1. Experimental design.

aortic flow at the level of the Zone 1 balloon, and in the Zone 3 group by loss of the femoral arterial pressure waveform. Occlusion was maintained for 45 minutes. Transfusion of shed blood began 10 minutes prior to deflation of the balloon. The volume of shed blood was transfused over 30 minutes with a Belmont Rapid Infuser (Belmont Instrument Corp., Billerica, MA). The balloon was deflated over 5 minutes, starting at T75.

Critical care with isotonic fluid boluses, vasopressor titration, and electrolyte correction proceeded in all animals from T80 to T360. Boluses of 500 mL Plasma-Lyte A were administered when the proximal MAP (pMAP) was less than 60 mm Hg and the CVP was less than 7 cm H_2O.The norepinephrine infusion rate was increased by 0.02 μg/kg per minute when the pMAP was less than 60 mm Hg and the CVP was greater than or equal to 7 cm H_2O. The norepinephrine infusion rate was decreased by 0.01 mg/kg per minute when the pMAP was greater than 70 mm Hg. All of these interventions were delivered automatically in a closed-loop algorithm by a custom automated syringe pump for norepinephrine and a Masterflex peristaltic pump (Cole-Parmer, Vernon Hills, IL) for fluid boluses. Serum potassium concentrations greater than 6.0 mmol/L were corrected with insulin and dextrose. Serum glucose concentrations less than 60 mg/dL were corrected with dextrose boluses and continuous infusions. Serum calcium concentrations less than 1.00 mmol/L

were corrected with calcium gluconate. Animals were killed at the conclusion of the study.

Data Collection

Physiologic parameters and aortic flow measurements were collected in real time using a multichannel data acquisition system (Biopac MP150; Biopac Systems, Inc., Goleta, CA). Parameters measured included heart rate, blood pressure proximal and distal to the intra aortic balloons, CVP, and core temperature, as well as aortic, renal, and carotid flow. Arterial blood was collected at routine intervals throughout the study for blood gas analysis, chemistries, and complete blood counts. Urine was collected and quantified at similar intervals.

Statistical Analysis

Data were assessed for normality and are presented as mean ± SEM or median (interquartile range) for parametric and nonparametric data, respectively. Data were analyzed using analysis of variance or Kruskal-Wallis analysis of variance, as appropriate. The Bonferroni correction was used to adjust for multiple comparisons. Statistical analysis was performed using a commercial software (STATA version 14.0; Stata Corp., College Station, TX). Statistical significance was set as $p < 0.05$.

RESULTS

There were no differences in physiologic data at baseline or during the initial 30 minutes of hemorrhage (Table 1). All animals survived to the end of the 6-hour study. During the intervention, the mean pMAP was significantly higher in Zone 1 animals when compared with Zone 3 animals (127.9 ± 1.3 vs. 53.4 ± 1.1 mm Hg; $p < 0.01$), and both were higher than control animals (42.9 ± 0.9 mm Hg) (Fig. 2). During the critical care phase following intervention, average pMAP was similar in Zone 3 animals and control animals (65.0 ± 0.2 vs. 66.8 ± 0.2 mm Hg), but was significantly lower in Zone 1 animals (60.8 ± 0.3 mm Hg; $p < 0.01$). Physiologic and biomarker data are shown in Table 2. Peak lactate was higher in Zone 1 animals (9.6 ± 0.4 mmol/L) when compared with Zone 3 animals (5.1 ± 0.3 mmol/L) and control animals (4.2 ± 0.8 mmol/L; $p < 0.01$) (Fig. 3). Zone 1 animals required more crystalloid fluid than Zone 3 or control animals (Zone 1: 11,630 ± 495 mL; Zone 3: 6,402 ± 538 mL; control: 7,120 ± 1,380 mL; $p < 0.01$). Volume of norepinephrine required to maintain the goal pMAP was higher in the Zone 1 animals (50.0 ± 4.3 μg/kg; $p < 0.01$), but there was no difference between Zone 3 animals and control animals (13.0 ± 3.4 and 14.0 ± 8.1 μg/kg, respectively).

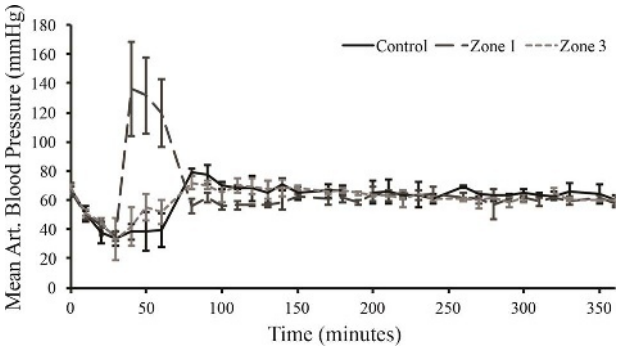

Figure 2. Comparison of mean arterial blood pressure over time among Zone 1 REBOA, Zone 3 REBOA, and control groups. Pressures were significantly different among all groups during the intervention phase (T30–T75).

DISCUSSION

As REBOA utilization increases for trauma victims, it is essential to develop data-driven guidelines for its use and positioning. In this study, we described the direct comparison of proximal hemodynamic support provided by Zone 1 versus Zone 3 REBOA. We demonstrated that there is a modest increase in proximal blood pressure during Zone 3 REBOA

TABLE 1. Baseline Physiologic, Laboratory, and Hemodynamic Characteristics

	Zone 1 (n = 6)	Zone 3 (n = 6)	Control (n = 6)	*p*
Weight, kg	77.5 ± 3.3	78.7 ± 3.6	78.9 ± 1.9	0.94
Sex, male:female	1:5	3:3	2:4	0.47
Temperature, °C	35.7 (35.3–36.0)	35.9 (35.5–36.3)	35.9 (35.6–36.0)	0.89
Laboratory results				
pH	7.46 (7.42–7.48)	7.44 (7.40–7.49)	7.45 (7.44–7.46)	0.83
P:F ratio	383 (335–431)	409 (229–423)	383 (299–477)	0.76
Hemoglobin, g/dL	10.7 (9.6–10.9)	10.7 (10.0–10.8)	10.8 (10.2–11.0)	0.70
White blood cells, $\times 10^9$/L	15.5 (14.2–17.3)	15.0 (14.2–15.4)	12.5 (12.3–14.5)	0.27
Platelets, $\times 10^9$/L	265 (262–269)	200 (181–346)	246 (241–252)	0.29
Potassium, mmol/L	3.8 (3.6–3.8)	3.7 (3.5–3.7)	3.7 (3.4–3.8)	0.75
Creatinine, mg/dL	1.3 (1.2–1.3)	1.5 (1.5–1.6)	1.5 (1.5–1.6)	0.02
Lactate, mmol/L	2.3 (2.2–2.7)	3.1 (2.1–3.3)	2.6 (2.4–2.8)	0.32
Hemodynamics				
pMAP, mm Hg	66.1 (64.6–68.8)	68.0 (64.8–70.9)	67.1 (63.2–71.8)	0.89
dMAP, mm Hg	53.6 (45.0–58.2)	59.1 (54.5–63.9)	61.2 (56.6–67.0)	0.67
Aortic flow, mL/min	3,159 (2,887–3,594)	3,242 (3,129–3,364)	2,748 (2,554–3,234)	0.17

P:f, PaO2:FiO2; dMAP, distal MAP.

TABLE 2. Physiologic, Laboratory, and Hemodynamic Outcomes

	Zone 1 (n = 6)	Zone 3 (n = 6)	Control (n = 6)	*p*
Resuscitation totals				
Crystalloid, mL	11,630 ± 495*	6,402 ± 538	7,120 ± 1,380	<0.01
Norepinephrine, μg/kg	50.0 ± 4.3*	13.0 ± 3.4	14.0 ± 8.1	<0.01
Total urine output, mL/kg	33.7 ± 6.3*	18.5 ± 3.5	16.0 ± 3.1	0.03
Hemodynamics				
pMAP T0–T30, mm Hg	46.4 ± 0.2	49.0 ± 0.4	47.5 ± 0.4	0.68
pMAP T30–T75, mm Hg	127.9 ± 1.3*	53.4 ± 1.1**	42.9 ± 0.9	<0.01
pMAP T75–T360, mm Hg	60.8 ± 0.3*	65.0 ± 0.2	66.8 ± 0.2	<0.01
Laboratory				
Peak lactate, mmol/L	9.6 ± 0.4*	5.1 ± 0.3	4.2 ± 0.8	<0.01
Final hemoglobin, g/dL	9.1 (8.8–9.4)	10.5 (10.0–10.8)	10.2 (9.8–11.0)	0.15
Final creatinine, mg/dL	1.7 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	0.73
Final alanine aminotransferase, U/L	47 (39–60)	38 (36–49)	44 (42–48)	0.36

*Significantly different from Zone 3 and control.
**Significantly different from control.

compared with controls. However, this increase may not be clinically useful and certainly does not approach the robust blood pressure augmentation afforded by Zone 1 REBOA.

The benefit of this dramatic increase in proximal perfusion with Zone 1 occlusion does come at the cost of a greater distal ischemic burden than was seen in animals receiving Zone 3 REBOA. With Zone 1 REBOA, we observed similar degrees of distal tissue ischemia that are increasingly described in the literature. In addition to the ischemia-reperfusion injury suffered by patients upon reperfusion following complete aortic occlusion, current reports suggest a significant physiologic burden inflicted by the extremely high cardiac afterload and proximal blood pressures during Zone 1 occlusion.[14,15] This exaggerated hemodynamic response often results in pulmonary edema, myocardial dysfunction, and intracranial hypertension.[7,14,16,17] In our study, the absence of such a physiologic burden in the Zone 3 REBOA animals when compared with the Zone 1 REBOA animals translated to less hemodynamic instability upon reperfusion. This instability was inferred through several resuscitation metrics, notably the difference in resuscitation requirements between groups.

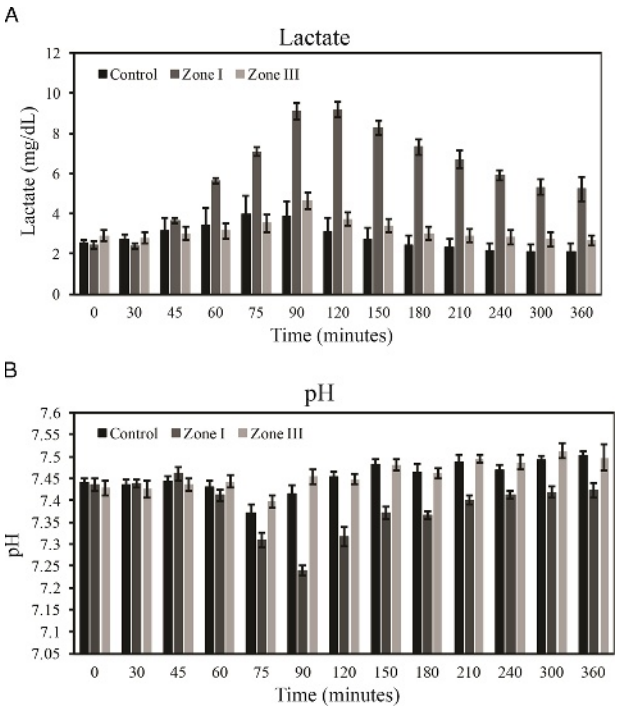

Figure 3. Trend of lactate (*A*) and pH (*B*) over time throughout the experiment. This figure illustrates the difference in ischemic burden based on level of aortic occlusion, as well as the effectiveness of critical care resuscitation at clearing the lactic acidosis.

In the context of current guidelines for REBOA balloon positioning within the aorta, the present study suggests that the recommendation to use Zone 3 REBOA in hypotensive patients should be reconsidered.[1,18] We were only able to demonstrate an average increase in pMAP during Zone 3 REBOA by approximately 10 mm Hg above baseline. It is unclear whether this would translate to a clinical benefit, but it is likely inadequate to rescue a patient on the brink of cardiovascular collapse. In contrast, occlusion in Zone 1 of the aorta resulted in a 80- to 90-mm Hg increase in pMAP, and Zone 1 occlusion has successfully resuscitated patients nearing cardiovascular collapse.[19] This large difference in proximal hemodynamic support can most likely be attributed to the large volume of distribution of the vascular beds of the abdominal viscera, which occupy much of the proximal blood flow during Zone 3 REBOA, but essentially none during Zone 1 REBOA.[20]

This study suggests that Zone 3 REBOA alone may be inadequate to restore normotension prior to resuscitation. In light of these findings, we propose an adjusted algorithm for the hypotensive patient with abdominal or pelvic injury (Fig. 4). In a patient presenting in hemorrhagic shock with an initial systolic blood pressure less than 90 mm Hg, initial REBOA placement, when indicated, should be in Zone 1, even if the injuries are known to be isolated to the pelvis and lower extremities. This will allow for rapid stabilization and the greatest improvement in pressure to the heart, lungs, and brain. After proximal perfusion is

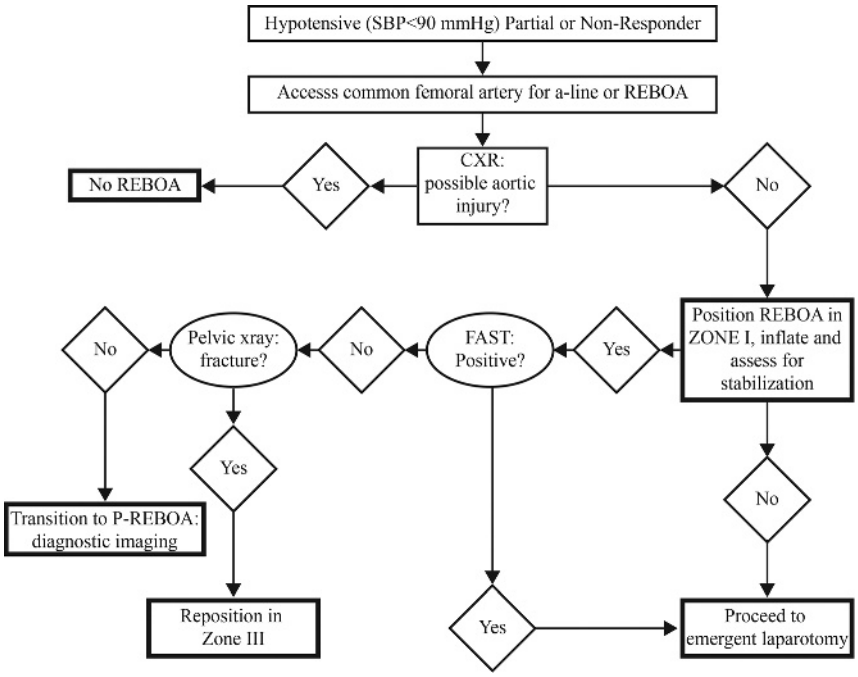

Figure 4. Proposed new REBOA algorithm. P-REBOA indicates partial-REBOA.

restored and resuscitation is underway, the surgeon may use ultrasound and/or a pelvic x-ray to then determine if Zone 1 occlusion should be maintained because of a positive FAST, or if the balloon can be transitioned to Zone 3 occlusion if the FAST is negative but there is clear evidence of a pelvic injury. Finally, if the FAST is negative, there is no evidence of pelvic injury, and the patient has stabilized with Zone 1 occlusion, the provider may elect to transition to partial REBOA or another strategy to minimize the ischemic burden.

The design of this study made blinding of the investigators to the experimental arm impossible. We attempted to minimize the impact of this limitation by fully automating our critical care interventions. All fluid boluses and norepinephrine dose adjustments were delivered automatically under computer control in response to predefined physiologic parameters in a closed-loop feedback system. Resuscitative endovascular balloon occlusion of the aorta balloon inflation and deflation were similarly timed and automated. In addition, this study was not designed to evaluate functional outcomes related to these interventions and therefore cannot provide an advanced level of clinical context. Further investigation is warranted to determine sequelae upon recovery from anesthesia and survival past the acute setting.

In our swine model of hemorrhagic shock, Zone 3 REBOA provided minimal proximal hemodynamic support when compared with Zone 1 REBOA, albeit with less ischemic burden and instability upon reperfusion. The data from this study suggest that, in cases of impending hemodynamic collapse, Zone 1 REBOA is more efficacious regardless of injury pattern, whereas Zone 3 REBOA should be reserved for relatively stable patients with distal hemorrhage.

AUTHORSHIP

E.M.T., G.L.H., A.J.D., J.J.D, J.K.G, T.K.W., and M.A.J. conceived and designed the study. E.M.T., G.L.H., M.A.S., A.J.D., E.S.D., E.R.F., J.K.G, T.K.W., and M.A.J. acquired the data. E.M.T., G.L.H., J.K.G, L.P.N., T.K.W., and M.A.J. analyzed and interpreted the data. E.M.T., G.L.H., L.P.N., T.K.W., and M.A.J. drafted the manuscript. E.M.T., G.L.H., M.A.S., A.J.D., E.S.D., E.R.F., J.J.D, L.P.N., J.K.G, T.K.W., and M.A.J. critically revised the manuscript.

DISCLOSURE

T.K.W., M.A.J., and L.P.N. are founders and stockholders of Certus Critical Care, Inc.

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The animals involved in this study were procured, maintained, and used in accordance with the Laboratory Animal Welfare Act of 1966, as amended, and NIH 80-23, Guide for the Care and Use of Laboratory Animals, National Research Council.

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The authors declare no conflicts of interest.

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