Original Article

Vol. 2, No. 3; 2018; pp 95–102
DOI: 10.26676/jevtm.v2i3.61

Stepwise Reperfusion After Zone 1 REBOA: Is Repositioning to Zone 3 a Useful Maneuver?

Emily M Tibbits MD[1–3], Guillaume L Hoareau DVM PhD[1], Meryl A Simon MD[1,3,4], Anders J Davidson MD[1–3], Erik S DeSoucy DO[1-3], E Robert Faulconer MBBS[1], Lucas P Neff MD[1,5], J Kevin Grayson DVM PhD[1], M Austin Johnson MD PhD[6] and Timothy K Williams MD[1,4,7]

[1]Clinical Investigation Facility, David Grant USAF Medical Center, Travis Air Force Base, CA, USA
[2]Department of General Surgery, David Grant USAF Medical Center, Travis Air Force Base, CA, USA
[3]Department of Surgery, University of California Davis Medical Center, Sacramento, CA, USA
[4]Heart, Lung, and Vascular Center, David Grant USAF Medical Center, Travis Air Force Base, CA, USA
[5]Department of Surgery, Emory University Hospital, Atlanta, GA, USA
[6]Department of Emergency Medicine, University of California Davis Medical Center, Sacramento, CA, USA
[7]Department of Surgery, Wake Forest Baptist Medical Center, Winston-Salem, NC, USA

Background: One limitation of resuscitative endovascular balloon occlusion of the aorta (REBOA) is hemodynamic instability upon balloon deflation due to distal hyperemia and washout of ischemic metabolites. We sought to determine whether stepwise reperfusion after supraceliac (Zone 1) REBOA by transitioning to infrarenal (Zone 3) occlusion would mitigate the physiologic consequences of balloon deflation and decrease hemodynamic instability.
Methods: Twelve anesthetized swine underwent controlled hemorrhage of 25% blood volume, 45 minutes of Zone 1 REBOA, then resuscitation with shed blood. Standardized critical care began with deflation of the Zone 1 balloon in all animals, and continued for six hours. Half of the animals were randomly assigned to Zone 3 REBOA for an additional 55 minutes following Zone 1 balloon deflation.
Results: There were no differences in physiology at baseline, during the initial 30 minutes of hypotension, or during the 45 minutes of Zone 1 occlusion. After Zone 1 balloon deflation, there was no difference in proximal mean arterial pressure (pMAP) with or without Zone 3 occlusion or percentage of critical care time spent within the target pMAP range between 65 and 75 mm Hg. There were also no significant differences in peak lactate concentration or resuscitation requirements.

Corresponding author:

Emily M. Tibbits, 2315 Stockton Blvd, OP512, Sacramento, CA 95817, USA.

Email: emtibbits@ucdavis.edu

Author contributions: EMT, GLH, AJD, JKG, MAJ, and TKW conceived and designed the study. Acquisition of data: EMT, GLH, MAS, AJD, ESD, ERF, JKG, MAJ, and TKW acquired the data. EMT, GLH, LPN, JKG, MAJ and TKW analyzed and interpreted the data. EMT, GLH, LPN, MAJ, and TKW drafted the manuscript. EMT, ERF, LPN, JKG, MAJ, and TKW undertook the critical revision.

Conflicts of interest: EMT, MAJ, and LPN are founders and stockholders of Certus Critical Care, Inc.

Funding: Funding for this study was provided by the Clinical Investigation Facility, David Grant USAF Medical Center, Travis Air Force Base, CA, USA.

Presentation: This research was presented at the 2017 Excelsior Surgical Society Meeting in San Diego, California, USA on 22 October 2017, and at the Northern California Chapter of the American College of Surgeons Annual Meeting in Berkeley, California, USA on 6 April 2018.

Disclosure: 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. The views expressed in this material are those of the authors and do not reflect the official policy of the US Government, the Department of Defense, the Department of the Air Force, or the University of California Davis. The work reported herein was performed under United States Air Force Surgeon General approved Clinical Investigation No. FDG20160026A.

Conclusions: In an animal model of hemorrhagic shock and Zone 1 REBOA, subsequent Zone 3 aortic occlusion did not add a significant ischemic burden, but it also did not provide significant hemodynamic support. The effect of this strategy on functional outcomes warrants further study. Continued investigation is necessary to determine optimal resuscitative support strategies during reperfusion following Zone 1 REBOA.

Keywords: *REBOA; Shock; Ischemia-reperfusion*

Received: 19 June 2018; Accepted: 12 September 2018

INTRODUCTION

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is becoming an acceptable and effective intervention for hemorrhage control and hemodynamic support in the setting of non-compressible torso hemorrhage (NCTH). One limitation of REBOA is the profound hemodynamic lability that occurs upon reinstituting distal aortic flow. The hemodynamic instability following balloon deflation is a product of distal vascular vasodilation from ischemia as well as the ischemia-reperfusion injury that occurs upon reinstitution of blood flow [1–3]. This vasodilation can result in a profound shock state that may require extensive resuscitation efforts regardless of the initial injury. With the ongoing evolution of REBOA, several strategies have been described in an attempt to mitigate the ischemic burden of REBOA and minimize the subsequent ischemia-reperfusion state. Among them, intermittent REBOA (I-REBOA) [4,5], partial REBOA (P-REBOA) [6–8], and endovascular variable aortic control (EVAC) [9] have all demonstrated promise, but the applicability of each is currently limited by technologic challenges [10]. Although REBOA use continues to increase in patients with NCTH, there remains a need for a practical, effective strategy to manage the resultant reperfusion injury.

The 2018 guidelines from the American College of Surgeons Committee on Trauma do not recommend any specific steps for weaning from REBOA, except that the balloon should be deflated as soon as possible, and the patient must be monitored for at least 24 hours thereafter [11]. The Joint Trauma System Clinical Practice Guideline recommends slow deflation in conjunction with ongoing resuscitation and mentions the potential need for intermittent balloon inflation and deflation as hemodynamic stability is restored [12]. Finally, the Basic Endovascular Skills for Trauma (BEST) course recommends stepwise deflation over a 5-minute period to slowly reperfuse distal vasculature [13]. Prior translational work has demonstrated that the timing of aortic flow return upon deflation of a REBOA balloon is inconsistent and unpredictable, with a return to full flow occurring over a very small range of balloon volumes [14,15]. Furthermore, due to the distal vasodilation that occurs during complete aortic occlusion, aortic flow returns at a higher rate than initial baseline flow resulting in rapid washout of ischemic metabolites from distal vascular beds [14]. Based on the current literature, the optimal method of weaning a patient from complete aortic occlusion remains unclear, yet critical for increasing the safety and therapeutic duration of REBOA technologies.

Considering the hemodynamic compromise upon Zone 1 balloon deflation, one potential solution would be simply to reposition the balloon more distally into Zone 3 while resuscitation continues. Even though the degree of hemodynamic support provided by Zone 3 REBOA remains unclear based on the current literature, it is reasonable to infer that Zone 3 REBOA would provide some hemodynamic support, albeit less than that provided by Zone 1 REBOA. We proposed this stepwise reperfusion strategy as an immediately clinically relevant method to address the hemodynamic instability upon REBOA balloon deflation. Our objective for this study was to determine if immediately transitioning from Zone 1 REBOA to Zone 3 REBOA would have physiologic benefits compared to deflation from Zone 1 occlusion alone. We hypothesized a net benefit of hemodynamic support that would outweigh any additional ischemic burden incurred. We used a swine model to investigate this strategy, using proximal MAP following reperfusion as a primary outcome. Secondary outcomes included resuscitation requirements, serum lactate concentration, and markers of renal function.

MATERIALS AND METHODS

Overview

The Institutional Animal Care and Use Committee at David Grant Medical Center, Travis Air Force Base, California 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 non-pregnant female Yorkshire-cross swine (*Sus scrofa*) from various vendors were acclimated for a minimum of seven days. Animals were housed in individual cages with 12-hour day-night cycles. They had free access to food and water until 12 hours prior to experimentation. Every experiment was supervised by an attending veterinarian. At the time of experimentation,

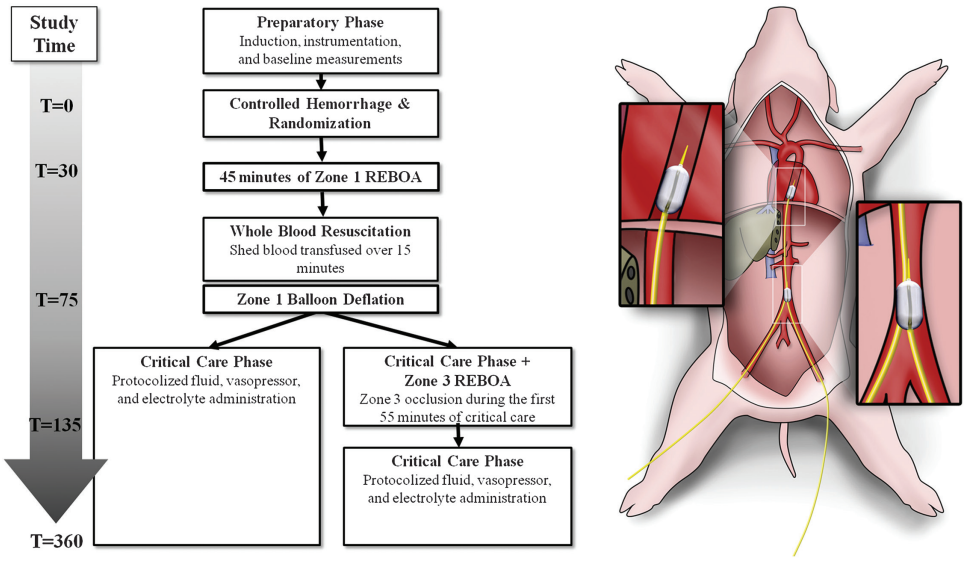

Figure 1 Experimental design.

animals weighed between 70 and 92 kg and were between 4.5 and 5.5 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, followed by 45 minutes of Zone 1 REBOA. During this time, animals were assigned, using a block randomization scheme, to one of two experimental arms: standardized critical care along with an additional 55 minutes of Zone 3 REBOA following deflation of the Zone 1 balloon (Z1Z3 group, $n=6$), or standardized critical care without Zone 3 REBOA (Z1 group, $n=6$). Critical care was continued for a total experimental time of 360 minutes, during which vasopressors were titrated and isotonic fluid boluses were administered based upon predefined physiologic parameters.

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/min) was instituted upon venous access and titrated prior to experimentation to achieve a target mean arterial pressure between 65 and 75 mm Hg. Animals were mechanically ventilated with tidal volumes of 7–10 mL/kg and a respiratory rate of 10–15 breaths per minute, which was sufficient to maintain end-tidal CO_2 at 40 ± 5 mm Hg. Balanced electrolyte solution (Plasma-Lyte A, Baxter Healthcare Corporation, Deerfield, IN) was administered at a rate of 10 mL/kg/h until the abdomen was closed, at which point the rate was decreased to 5 mL/kg/h for the remainder of the study to replace insensible losses. All animals received a bolus of 1 L Plasma-lyte A upon venous access. Intravenous heparin was administered to achieve an activated clotting time (ACT) of 100 seconds, similar to human baseline values. An underbody warmer was used to maintain core body temperature between 35 and 37°C.

Following celiotomy, the spleen was removed to minimize hemodynamic variation from autotransfusion [16]. The supraceliac aorta was exposed by dividing the diaphragm and dissected circumferentially for a length of 5–10 cm. Two adjacent intercostal arteries were ligated to facilitate placement of an 11 mm periaortic flow probe (Transonic Systems Inc, Ithaca, NY). The abdomen was closed with cable ties.

Bilateral external jugular veins were cannulated (7 Fr sheath on the left, 9 Fr dual lumen catheter on the right) to facilitate medication and fluid administration, as well as for central venous pressure 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 mean arterial pressure (pMAP) monitoring. The left femoral artery was exposed and cannulated with a 12 Fr sheath for Coda balloon placement (Coda, Cook Medical, Bloomington, IN) and distal mean arterial pressure (dMAP) monitoring. The right femoral artery was exposed and cannulated with a 7 Fr sheath for ER-REBOA placement (ER-REBOA, Prytime Medical, Boerne, TX). The left femoral vein was exposed and cannulated with a dual lumen resuscitation catheter for blood transfusion. The position of the Coda balloon in Zone 1, just proximal to the diaphragmatic hiatus, and the ER-REBOA balloon in Zone 3, just distal to the most distal renal artery, were guided by palpation during

celiotomy and confirmed by fluoroscopy after abdominal closure but prior to the start of experimentation.

Data Collection

Physiologic parameters and aortic flow measurements were collected in real time using a multichannel data acquisition system (MP150, Biopac Systems Inc., Goleta, CA). Measured parameters included heart rate, blood pressure proximal and distal to the intraaortic balloons, central venous pressure, core temperature, and aortic blood flow. Arterial blood was collected at routine intervals throughout the study for blood gas analysis, basic metabolic profile, and blood counts. Urine was collected and quantified at similar intervals.

Hemorrhage, Intervention, and Critical Care

At the start of the experiment, animals underwent controlled hemorrhage of 25% of their estimated total blood volume. Blood volume was estimated at 60 mL per kilogram of body weight. Blood was withdrawn over 30 minutes into citrated blood collection bags. During this time, animals were randomized.

At the end of 30 minutes, the Zone 1 balloon was inflated in all animals. Complete aortic occlusion was confirmed by loss of aortic flow. Occlusion in Zone 1 was maintained for 45 minutes. Transfusion of shed blood began 10 minutes prior to deflation of the Zone 1 balloon. The volume of shed blood was transfused over 30 minutes with a rapid infuser (Belmont Instrument Corporation, Billerica, MA). The Zone 1 balloon was deflated over 5 minutes, starting at T75. At T80, critical care commenced for all animals. The animals randomized to the Z1Z3 group immediately underwent inflation of the Zone 3 balloon. Complete aortic occlusion was again confirmed by the loss of the distal arterial pressure waveform. This balloon remained inflated in Zone 3 for an additional 55 minutes. It was deflated over a 5-minute interval starting at T135. This duration of Zone 3 occlusion was chosen based upon previous experience in our lab as the amount of time that would provide support during the most tenuous period in resuscitation after Zone 1 reperfusion, but would not produce a burden of ischemia from which the animal could not recover.

For all study animals, critical care with isotonic fluid boluses, vasopressor titration, and electrolyte correction proceeded from T80 to T360. Boluses of 500 mL Plasmalyte A were administered for pMAP less than 60 mm Hg with CVP less than 7 mm Hg. The norepinephrine infusion rate was increased by 0.02 mcg/kg/min for pMAP less than 60 with CVP greater than or equal to 7 mm Hg. The norepinephrine infusion rate was decreased by 0.01 mg/kg/min when the pMAP exceeded 70 mm Hg. These interventions were administered 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 euthanized at T360 without recovering from general anesthesia.

Data Analysis

Experimental data were entered into Excel datasheets (Microsoft Corporation) and transferred to STATA version 14.0 (Stata Corporation, Bryan, TX) for analysis. Continuous variables are presented as means and standard errors of the means (SEMs) if normally distributed, and as medians with interquartile ranges if not normally distributed. Between groups, comparisons were conducted with a *t*-test or Mann–Whitney *U*-test, as appropriate. Statistical significance was set at p less than 0.05. The sample size was determined using an a priori power calculation using G*Power (Heinrich-Heine Universität Düsseldorf, Germany) to detect a difference in MAP of 15 mm Hg with a standard deviation of 9 mm Hg, a power of 80%m and a statistical significance if $p < 0.05$.

RESULTS

There were no differences in baseline hemodynamics or laboratory analysis between groups, except that animals in the Z1Z3 group had a higher starting creatinine (1.7 mg/dL 95% confidence interval (CI) 1.6–1.8 versus 1.3 mg/dl 95% CI 1.2–1.5) (Table 1). After the initial hemorrhage period both groups had a similar minimum pMAP (Z1 32 mm Hg 95% CI 29–36 versus Z1Z3 30 mm Hg 95% CI 23–36) and had similar average pMAP during the initial Zone 1 intervention phase (Z1 129 mm Hg 95% CI 106–152 versus Z1Z3 118 mm Hg 95% CI 103–133) (Figure 2).

During the Zone 3 phase there were no differences in proximal MAP (Z1 57 mm Hg 95% CI 50–64 versus Z1Z3 61 mm Hg 95% CI 56–65), aortic flow (Z1 3,984 mL/min 95% CI 3,247–4,721 versus Z1Z3 3,362 mL/min 95% CI 2,961–3,762), need for IV crystalloids (Z1 1,633 mL 95% CI 1,272–1,995 versus Z1Z3 1,150 mL 95% CI 543–1,757), norepinephrine dose (Z1 7 µg /kg 95% CI 4–10 versus Z1Z3 4 µg/kg 95% CI 1–7), or urine output (Z1 237 mL 95% CI 91–382 versus Z1Z3 265 mL 95% CI 222–307) between groups (Table 2).

By the end of the study there were no differences in final lactate (Z1 5.2 mmol/L 95% CI 3.7–6.8 versus Z1Z3 4.4 mmol/L 95% CI 3.1–5.7), although the creatinine was higher in the Z1Z3 group when compared to the Z1 group (2.3 mg/dl 95% CI 1.9–2.6 versus 1.7 mg/dl 95% CI 1.4-2.0). However, there was no difference in the change in creatinine from baseline to the end of

Table 1 Baseline physiology, labs, and hemodynamic characteristics.

	Z1 (n = 6)	*Z1Z3 (n = 6)*	*p-Value*
Weight kg	78 (69–85)	79 (71–86)	0.76
Sex male:female	1:5	3:3	
Temperature (°C)	35.8 (35.1–36.5)	35.2 (34.7–35.7)	0.11
Labs			
pH	7.43 (7.40–7.47)	7.42 (7.40–7.45)	0.42
P:F ratio	372 (272–473)	381 (299–463)	0.87
Hemoglobin (g/dL)	10.3 (9.5–11.1)	10.7 (9.8–11.6)	0.42
White blood cells ($\times 10^9$/L)	15.2 (12.0–18.4)	15.4 (13.8–17.0)	0.89
Platelets ($\times 10^9$/L)	275 (228–323)	273 (170–375)	0.95
Potassium (mmol/L)	3.7 (3.5–3.9)	3.7 (3.5–3.9)	0.78
Creatinine (mg/dL)	1.3 (1.2–1.5)	1.7 (1.6–1.8)	<0.01
Lactate (mmol/L)	2.4 (2.0–2.9)	2.5 (2.2–2.8)	0.82
Glucose (mg/dL)	93 (84–101)	85 (75–96)	0.18
Hemodynamics			
Proximal MAP (mm Hg)	66 (60–73)	69 (63–74)	0.51
Aortic flow (mL/min)	2,959 (2,492–3,425)	3,027 (2,697–3,359)	0.76

Error presented as standard error of the mean.

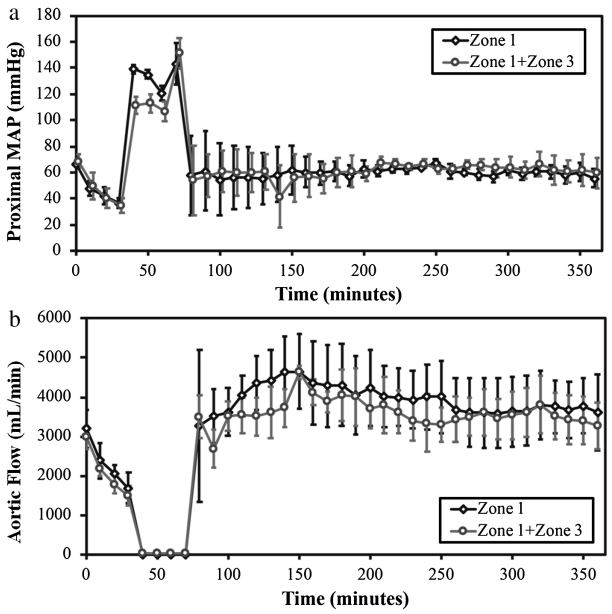

Figure 2 Comparison of mean arterial blood pressure (**a**) and mean aortic flow (**b**) over the time of the entire study between the groups with and without Zone 3 REBOA during the first hour of critical care (T80-T135) following Zone 1 balloon deflation. Neither pressure nor flow was significantly different between the groups at any point during the course of the experiment. Data are presented as the mean and standard error of the mean. $n = 6$ per group.

study between groups (Z1 0.4 mg/dl 95% CI 0.1–0.7 versus Z1Z3 0.6 mg/dl 95% CI 0.3–0.9). There was also no difference in final urine output between the two groups across the timeline of the study (Z1 3,057 mL 95% CI 1,727–4,384 versus Z1Z3 1,872 mL 95% CI 863–2,881, $p = 0.10$).

DISCUSSION

The physiologic consequences of reperfusion after Zone 1 REBOA are a significant barrier to increasing its accepted therapeutic duration and widespread adoption. Balloon deflation results in rapid washout of ischemic metabolites as well as the initiation of reperfusion injury. This combined physiologic insult leads to significant hemodynamic instability. To counter this, we tested an alternate method of REBOA weaning by repositioning the REBOA catheter in the distal aorta after initial Zone 1 occlusion. In this study, our data showed no difference in MAP with or without Zone 3 occlusion, therefore we concluded that this repositioning strategy does not provide any further support to the vital organs when compared to a standardized resuscitation with intravenous crystalloids and vasopressors for this particular pathologic state. We have also demonstrated that Zone 3 occlusion below the level of the renal arteries does not increase the overall ischemic burden, but does result in a trend toward decreased urine output following deflation of a Zone 1 balloon. While the decrease in urine output did not reach statistical significance, it may be clinically significant and is an area of ongoing investigation. Taking these findings into consideration, Zone 3 occlusion does not appear to be a helpful adjunct following prolonged Zone 1 occlusion to counter hemodynamic depression or for the treatment of the ischemia-reperfusion injury.

Current REBOA instructional programs suggest balloon deflation should be performed in a stepwise manner over a 5-minute period to allow for a slow reintroduction of blood flow to distal vascular beds. This time period will allow the vascular beds proximal to the point of occlusion to compensate for the decreased perfusion that can result from the reintroduction of blood flow

Table 2 Physiologic, laboratory, and hemodynamic outcomes.

	Z1 (n = 6)	*Z1Z3 (n = 6)*	*p-Value*
Resuscitation totals			
Crystalloid (mL)	7,400 (6,148–8,652)	5,700 (2,462–8,938)	0.24
Norepinephrine (µg/kg)	50 (38–62)	45 (17–73)	0.67
Urine output (mL/kg)	3,057 (1,727–4,384)	1,872 (863–2,881)	0.10
Resuscitation during T80–T135			
Crystalloid (mL)	1,633 (1,272–1995)	1,150 (543–1,757)	0.11
Norepinephrine (µg/kg)	7 (4–10)	4 (1–7)	0.14
Urine output (mL/kg)	237 (91–382)	265 (222–307)	0.64
Labs			
Peak lactate (mmol/L)	9.6 (8.5–10.7)	10.6 (9.5–11.7)	0.12
Final lactate (mmol/L)	5.24 (3.7–6.8)	4.4 (3.1–5.7)	0.30
Final creatinine (mg/dL)	1.7 (1.4–2.0)	2.3 (1.9–2.6)	<0.01
Delta creatinine (mg/dL)	0.4 (0.1–0.7)	0.6 (–.3–0.9)	0.19
Hemodynamics			
pMAP nadir during hemorrhage (mm Hg)	32 (29–36)	30 (23–36)	0.29
pMAP average during Zone 1 REBOA (mm Hg)	129 (106–152)	118 (104–133)	0.34
pMAP average T80–T135 (mm Hg)	57 (50–64)	61 (56–65)	0.25
pMAP average during critical care (mm Hg)	60 (57–63)	61 (56–66)	0.59
Aortic flow average T80–T135 (mL/min)	3,984 (3,247–4,721)	3,362 (2,961–3,762)	0.09
Aortic flow average during critical care (mL/min)	3,960 (3,176–4,743)	3,604 (3,160–4,048)	0.33

T80–T35 represents the first 55 minutes of the critical care phase, during which the Zone 3 balloon was inflated in the Z1Z3 group. pMAP, proximal mean arterial pressure. Error presented as standard error of the mean.

into a dilated distal vasculature that can occur following even short periods of complete Zone 1 aortic occlusion. Prior work has demonstrated that the reintroduction of distal flow likely occurs in an unpredictable fashion, and that aortic flow after a period of occlusion is hyperemic, with rates over twice the baseline aortic flow rate [14,15]. This can result in profound hemodynamic instability. Recent data from translational animal models have shown that Zone 3 REBOA alone provides a modest degree of proximal hemodynamic support in the setting of hemorrhagic shock, but not enough to rescue a patient on the brink of cardiovascular collapse [17]. In this current study, the Zone 3 occlusion was implemented not as a resuscitative maneuver during hemorrhage, but as a weaning adjunct after resuscitation and deflation of a Zone 1 occlusion balloon. Therefore, this was essentially a Zone 3 occlusive intervention during an ischemia-reperfusion shock state. When comparing the earlier studies with Zone 3 occlusion during hemorrhagic shock, it seems that the lack of significant hemodynamic support by the Zone 3 balloon in this study may be explained by the difference in the pathophysiology of the shock state in these animals [18–21]. Instead of hypovolemia with the possibility of vasoconstriction in vascular beds above the Zone 3 occlusion, these animals had a combination of profound vasodilation from 45 minutes of ischemia combined with the inflammatory mediators released during the reperfusion when the Zone 1 occlusion ended. Prior work has demonstrated that circulating cytokines following reperfusion can lead to systemic vasodilation, inflammatory state, and multi-organ dysfunction [2]. The synergistic hit of maximal vasodilation and release of the ischemic metabolites may be too great for Zone 3 REBOA to be of benefit. Further work is warranted to specifically isolate and study the effects of REBOA and subsequent weaning on cardiac performance.

The most recent Joint Trauma System Clinical Practice Guideline advises no longer than 30–60 minutes of REBOA in Zone 1, but the recommendations for Zone 3 are less specific [12]. In our study, we expected to observe a second hemodynamic insult upon reperfusion after Zone 3 REBOA, but we did not see one that reached statistical significance. The equivalence of final lactate concentrations between the two groups also suggests that any "second hit" was likely to be of no significant consequence to the animal. The animals in our Z1Z3 experimental arm underwent a total of 100 minutes of hindlimb ischemia. The lack of a second hit in terms of physiologic complications suggests that longer occlusion times are possible with Zone 3 REBOA, and further study is warranted to guide maximum duration recommendations for REBOA in Zone 3.

One unexpected finding of this experiment was the trend toward lower urine output in the Z1Z3 group. Our expectation was that diverting blood flow from the hindlimbs to the abdominal viscera with Zone 3 occlusion would improve perfusion of abdominal vascular organs, even in the absence of systemic hemodynamic augmentation. We did find a significant difference in final creatinine, but this was accounted for by a baseline difference in creatinine between the two groups. Specifically, when the change in creatinine over the entire experimental

duration was calculated, there was no difference between groups. There was a trend toward oliguria in the animals randomized to the Z1Z3 group which was surprising and is not yet fully elucidated. However, this trend has been noted in canine studies of Zone 3 occlusion that demonstrated decreased renal blood flow [22,23]. A potential next step will be to determine if the visceral organs did, in fact, receive more flow during the Zone 3 occlusion period. Future analysis will be aimed at understanding the relationship of these trends to renal blood flow.

There are several limitations to this study. First, it was impossible to blind the investigators to the study arm assigned to each animal and there is always the possibility of investigator bias in a non-blinded study. However, with full automation of balloon inflation and deflation, as well as delivery of resuscitative interventions, we attempted to minimize treatment variability among subjects. Another limitation of this study was the small sample size. We did observe some trends in data that did not elaborate into significant differences between the groups, but that may indeed become statistically significant at larger sample sizes. It is unclear based upon this study whether these would amount to clinical significance. Additionally, this study's relatively short time period after initial resuscitation prevented fuller understanding of longer-term benefits or consequences that may have manifested later in a survival study. Also, without the utilization of proteomics or advanced biomarker analysis, it is possible that there were unrecognized physiologic phenomena underlying the trends that we demonstrated. It is unclear from this study if alternative methods of transitioning from Zone 1 to Zone 3 could provide benefit. For this study, we allowed a 5-minute period between Zone 1 deflation and Zone 3 inflation to adhere to the BEST course guidelines. It is possible that the immediate washout of the additional ischemic metabolites in the hindlimbs was enough to cause sufficient instability in the animal such that Zone 3 REBOA was not effective. It is possible that a two-balloon method with slower deflation of Zone 1 while Zone 3 is already inflated would provide a more hemodynamically stable transition, although this maneuver may prove to be too complex with current technology to be clinically applicable. Along the same lines, it is possible that the partial obstruction of the bilateral femoral arteries with the sheaths that we used may have contributed to the ischemic burden in the hindlimbs. We attempted to control for this with uniform sheath placement among all animals regardless of the experimental arm, but different results may have been seen if a different model had been used. Another potential limitation is in the design of our resuscitation paradigm, as it was based upon CVP and MAP. Since there is currently no consensus regarding the best estimator of volume status, we chose CVP due to its ease of measurement and clinical applicability. There is certainly room for future investigation using other resuscitation parameters, which may yield different results. These limitations notwithstanding, this study does provide quantifiable data regarding the relative contribution of an alternate weaning method that is possible with current REBOA technology.

CONCLUSION

In our swine model of ischemia-reperfusion injury induced by hemorrhagic shock with Zone 1 REBOA, the subsequent transition to Zone 3 aortic occlusion as a method of weaning did not provide increased hemodynamic stability but also did not add a significant ischemic burden. Continued investigation is necessary to develop optimal support strategies to wean from Zone 1 REBOA and minimize hemodynamic instability.

REFERENCES

[1] Markov NP, Percival TJ, Morrison JJ, et al. Physiologic tolerance of descending thoracic aortic balloon occlusion in a swine model of hemorrhagic shock. Surgery. 2013;153:848–56.

[2] Morrison JJ, Ross JD, Markov NP, Scott DJ, Spencer JR, Rasmussen TE. The inflammatory sequelae of aortic balloon occlusion in hemorrhagic shock. J Surg Res. 2014; 191:423–31.

[3] Stannard A, Eliason JL, Rasmussen TE. Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock. J Trauma. 2011;71: 1869–72.

[4] Ogura T, Lefor AT, Nakano M, Izawa Y, Morita H. Nonoperative management of hemodynamically unstable abdominal trauma patients with angioembolization and resuscitative endovascular balloon occlusion of the aorta. J Trauma Acute Care Surg. 2015;78:132–5.

[5] Saito N, Matsumoto H, Yagi T, et al. Evaluation of the safety and feasibility of resuscitative endovascular balloon occlusion of the aorta. J Trauma Acute Care Surg. 2015;78:897–903.

[6] Johnson MA, Neff LP, Williams TK, DuBose JJ. Partial Resuscitative Balloon Occlusion of the AORTA (P-REBOA): Clinical Technique and Rationale. J Trauma Acute Care Surg. 2016;81:S133–7.

[7] Russo RM, Neff LP, Lamb CM, et al. Partial Resuscitative Endovascular Balloon Occlusion of the Aorta in Swine Model of Hemorrhagic Shock. J Am Coll Surg. 2016;223(2):359–68.

[8] Russo RM, Williams TK, Grayson JK, et al. Extending the golden hour: Partial resuscitative endovascular balloon occlusion of the aorta in a highly lethal swine liver injury model. J Trauma Acute Care Surg. 2016;80:372–8.

[9] Williams TK, Neff LP, Johnson MA, et al. Extending REBOA: Endovascular variable aortic control (EVAC) in a lethal model of hemorrhagic shock. J Trauma Acute Care Surg. 2016;81:294–301.

[10] Russo R, Neff LP, Johnson MA, Williams TK. Emerging Endovascular Therapies for Non-Compressible Torso Hemorrhage. Shock (Augusta, Ga). 2016;46:12–19.

[11] Brenner M, Bulger EM, Perina DG, et al. Joint statement from the American College of Surgeons Committee on

Trauma (ACS COT) and the American College of Emergency Physicians (ACEP) regarding the clinical use of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). Trauma Surgery; Acute Care Open. 2018;3(1).
[12] Pasley J, Cannon J, Glaser J, et al. Joint Trauma System Clinical Practice Guideline: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for Hemorrhagic Shock. Department of Defense. 2017; http://www.usaisr.amedd.army.mil/cpgs/REBOA_%2006Jul2017 CORRECTED.pdf (accessed Jan 2018).
[13] Brenner M, Hoehn M, Teeter W, Stein D, Scalea T. Trading scalpels for sheaths: Catheter-based treatment of vascular injury can be effectively performed by acute care surgeons trained in endovascular techniques. J Trauma Acute Care Surg. 2016;80:783–6.
[14] Davidson AJ, Russo RM, Ferencz SE, et al. Incremental balloon deflation following complete resuscitative endovascular balloon occlusion of the aorta results in steep inflection of flow and rapid reperfusion in a large animal model of hemorrhagic shock. J Trauma Acute Care Surg. 2017;83:139–43.
[15] Johnson MA, Davidson AJ, Russo RM, et al. Small changes, big effects: The hemodynamics of partial and complete aortic occlusion to inform next generation resuscitation techniques and technologies. J Trauma Acute Care Surg. 2017;82:1106–11.
[16] Brenner M, Hoehn M, Pasley J, Dubose J, Stein D, Scalea T. Basic endovascular skills for trauma course: bridging the gap between endovascular techniques and the acute care surgeon. J Trauma Acute Care Surg. 2014;77:286–91.
[17] Moore LJ, Brenner M, Kozar RA, et al. Implementation of resuscitative endovascular balloon occlusion of the aorta as an alternative to resuscitative thoracotomy for noncompressible truncal hemorrhage. J Trauma Acute Care Surg. 2015;79:523–30.
[18] Sondeen JL, Dubick MA, Holcomb JB, Wade CE. Uncontrolled hemorrhage differs from volume- or pressure-matched controlled hemorrhage in swine. Shock (Augusta, Ga). 2007;28:426–33.
[19] Tibbits EM, Hoareau GL, Simon MA, et al. Location is everything: The hemodynamic effects of REBOA in Zone 1 versus Zone 3 of the aorta. J Trauma Acute Care Surg. 2018; 85:101–7.
[20] Martinelli T, Thony F, Declety P, et al. Intra-aortic balloon occlusion to salvage patients with life-threatening hemorrhage shocks from pelvic fractures. J Trauma. 2010;68:942–8.
[21] Morrison JJ, Percival TJ, Markov NP, et al. Aortic balloon occlusion is effective in controlling pelvic hemorrhage. J Surg Res. 2012;177:341–7.
[22] Abbot WM, Cooper JD, Austen WG. The effect of aortic clamping and declamping on renal blood flow distribution. J Surg Res. 1973;14:385–92.
[23] Abbot WM, Austen WG. The reversal of renal cortical ischemia during aortic occlusion by mannitol. J Surg Res. 1974;16:482–9.