Injury, Int. J. Care Injured 50 (2019) 1908–1914

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Renal effects of three endoaortic occlusion strategies in a swine model of hemorrhagic shock

Guillaume L. Hoareau[a,*], Emily M. Tibbits[a,c,d], Meryl A. Simon[a,c,e], Anders J. Davidson[a,c,d], Erik S. DeSoucy[a,c,d], E. Robert Faulconer[a], J. Kevin Grayson[a], Ian J. Stewart[a,f], Lucas P. Neff[a,g], Timothy K. Williams[a,g], M. Austin Johnson[a,b]

[a] Clinical Investigation Facility, David Grant USAF Medical Center, Travis Air Force Base, CA, United States
[b] Division of Emergency Medicine, University of Utah Health, Salt Lake City, UT, United States
[c] Department of Surgery, University of California Davis Medical Center, Sacramento, CA, United States
[d] Department of General Surgery, David Grant USAF Medical Center, Travis Air Force Base, CA, United States
[e] Heart, Lung, and Vascular Center, David Grant USAF Medical Center, Travis Air Force Base, CA, United States
[f] Uniformed Services University of the Health Sciences, Bethesda, MD, United States
[g] Department of Surgery, Wake Forest Baptist Medical Center, Winston-Salem, NC, United States

ARTICLE INFO

Article history:
Accepted 21 August 2019

Keywords:
Acute kidney injury
Ischemia-reperfusion
REBOA
Resuscitation
Resuscitative endovascular balloon occlusion of the aorta
Trauma

ABSTRACT

Introduction: Trauma patients are predisposed to kidney injury. We hypothesized that in shock, zone 3 REBOA would increase renal blood flow (RBF) compared to control and that a period of zone 3 occlusion following zone 1 occlusion would improve renal function compared to zone 1 occlusion alone.
Materials and methods: Twenty-four anesthetized swine underwent hemorrhagic shock, 45 min of zone 1 REBOA (Z1, supraceliac), zone 3 REBOA (Z3, infrarenal), or no intervention (control) followed by resuscitation with shed blood and 5 h of critical care. In a fourth group (Z1Z3), animals underwent 55 min of zone 3 REBOA following zone 1 occlusion. Physiologic parameters were recorded, blood and urine were collected at specified intervals.
Results: During critical care, there were no differences in RBF between the Z1 and Z3 groups. The average RBF during critical care in Z1Z3 was significantly lower than in Z3 alone (98.2 ± 23.9 and 191.9 ± 23.7 mL/min; p = 0.046) and not different than Z1. There was no difference in urinary neutrophil gelatinase-associated lipocalin-to-urinary creatinine ratio between Z1 and Z1Z3. Animals in the Z1Z3 group had a significant increase in the ratio at the end of the experiment compared to baseline [median (IQR)] [9.2 (8.2–13.2) versus 264.5 (73.6–1174.6)]. Following Z1 balloon deflation, RBF required 45 min to return to baseline.
Conclusion: Neither zone 3 REBOA alone nor zone 3 REBOA following zone 1 REBOA improved renal blood flow or function. Following zone 1 occlusion, RBF is restored to baseline levels after approximately 45 min.

Introduction

Serious injury to abdominal or thoracic viscera may lead to non-compressible torso hemorrhage (NCTH), which has historically been treated with resuscitative thoracotomy (RT) and aortic cross clamping. Trauma patients with NCTH treated with RT have universally poor outcomes with survival rates of 9% for patients with penetrating injuries and 1% for those with blunt trauma [1]. Those limitations and the development of new endovascular catheters have led to development of resuscitative endovascular balloon occlusion of the aorta (REBOA). REBOA is an endovascular intervention that allows for aortic occlusion at various levels of the aorta (or zones) with the use of a balloon-tipped catheter. Zone 1 of the aorta extends from the left subclavian artery to the celiac artery, zone 2, which is rarely used, extends from the celiac to the renal arteries, and zone 3 extends from the renal arteries to the aortic bifurcation. While endovascular balloon occlusion of the aorta interrupts life-threatening hemorrhage and sustains proximal blood pressure until definitive surgical intervention, it also exposes distal tissue beds to significant ischemia-reperfusion injury. One advantage of using endovascular methods for aortic

* Corresponding author at: Travis Air Force Base, Clinical Investigation Facility, 101 Bodin Cir, Fairfield, CA, 94533, United States.
E-mail address: guillaume.hoareau@utah.edu (G.L. Hoareau).

https://doi.org/10.1016/j.injury.2019.08.037
0020-1383/

occlusion, when compared to RT, is the ability to choose the level of occlusion based on the patient's injury pattern. Therefore, isolated injuries in the pelvis and catastrophic lower extremity injuries can be treated with zone 3 (between the most inferior renal artery and the aortic bifurcation) occlusion, which theoretically would result in less of an ischemic insult to the kidneys and other abdominal viscera.

Patients with NCTH following trauma, regardless of the need for aortic occlusion, are predisposed to acute kidney injury (AKI) [2]. This is further potentiated by profound ischemia-reperfusion if the patient is treated with RT or REBOA. When patients are treated with either RT or REBOA, there is a wide range of incidence of AKI reported (4–64%) [3–5].

We sought to understand the effects that different zones of aortic occlusion have on the kidneys. Specifically, we hypothesized that zone 3 (infrarenal) REBOA would augment renal blood flow (RBF) and lead to less renal injury when compared to zone 1 (supraceliac) REBOA. We also hypothesized that zone 3 REBOA following zone 1 REBOA would improve perfusion to the kidneys.

Materials and methods

Overview

Data described in this manuscript is part of a larger experiment sharing common control groups. Some results from the larger experiment have been previously reported [6–8]. This manuscript focuses on the renal effects of endovascular aortic occlusion at various levels. The study was approved by the Institutional Animal Care and Use Committee at David Grant Medical Center, Travis Air Force Base, California. All animal care and use was in strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by AAALAC International. Twenty-four healthy adult, castrate male (N = 9) and non-pregnant female (N = 15) Yorkshire-cross swine (*Sus scrofa*, S&S Farms, Ramona, CA) were acclimated for a minimum of 7 days. Animals were housed in individual cages with 12 -h day-night cycles. They had free access to food and water until 12 h prior to experimentation. Every experiment was supervised by an attending veterinarian. Animals weighed between 65 and 92 kg.

A summary of the experiment is presented in Fig. 1. Animals were subjected to a controlled hemorrhage of 25% of total blood volume over 30 min. During this time, animals were assigned, using a block randomization scheme, to a 45-minute intervention period: zone 1 REBOA (Z1 group, n = 6), zone 3 REBOA (Z3 group, n = 6), zone 1 followed by zone 3 REBOA (Z1Z3 group, n = 6) or no intervention (control group, n = 6). After the intervention period, animals were resuscitated with shed blood, and critical care was continued to a total experimental time of 360 min. During this time, norepinephrine was titrated and isotonic fluid boluses were administered following a predefined, computer-driven algorithm based on physiologic parameters [7]. In the Z1Z3 group, an additional 55 min of zone 3 occlusion was initiated following the zone 1 intervention in addition to the standardized critical care.

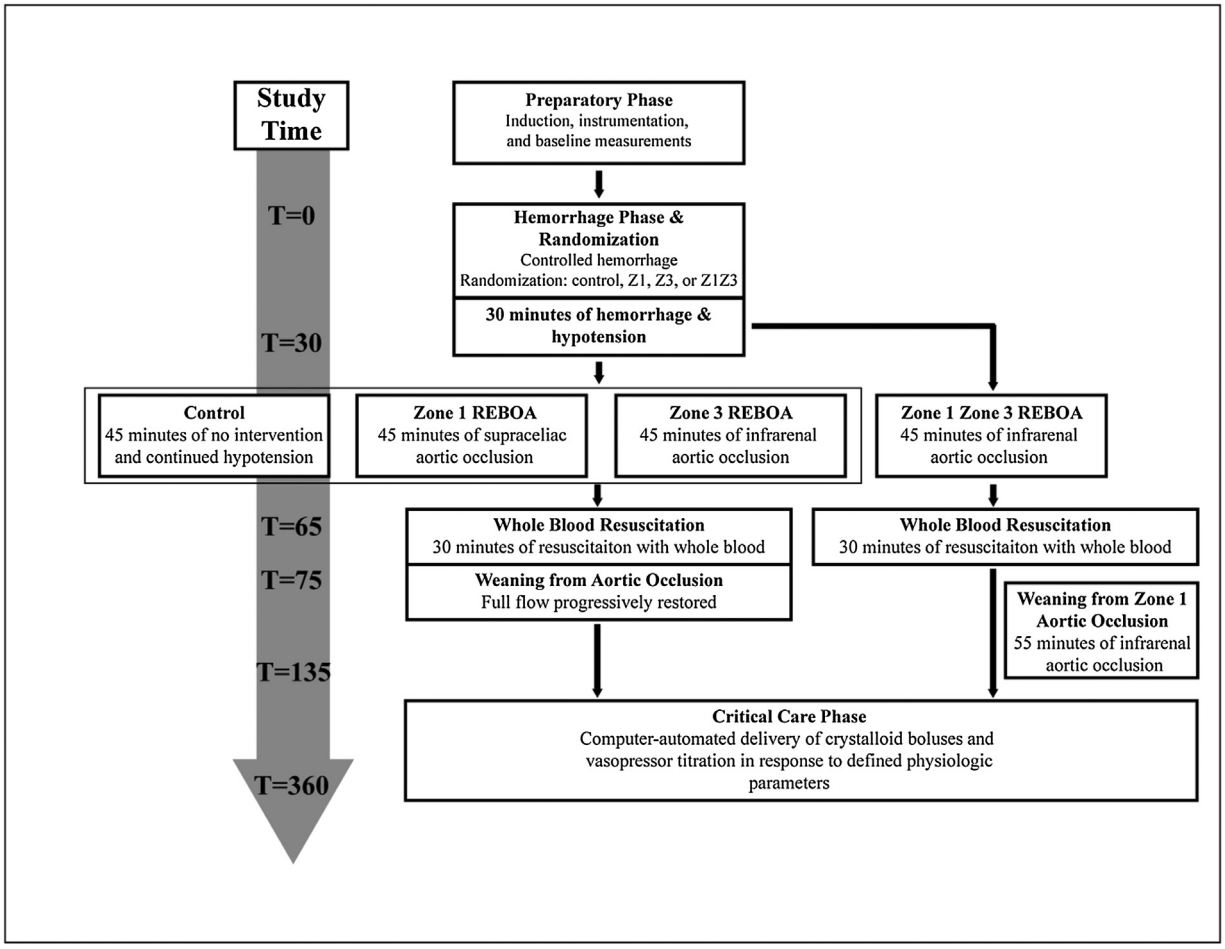

Fig. 1. Experimental overview.

Animal preparation

Animals were premedicated with a 6.6 mg/kg tiletamine/zolazepam (Telazol, Fort Dodge Animal Health, Fort Dodge, IA) intramuscular injection. Following isoflurane (Baxter, Deerfield, IL) induction and endotracheal intubation, general anesthesia was maintained with 2% isoflurane in 100% oxygen. An intravenous infusion of norepinephrine (Teva Pharmaceutical Industries, Petach Tikva, Israel) (0.01 μg/kg/min) was instituted upon venous access and titrated prior to experimentation to offset the vasodilatory effects of general anesthesia and achieve a target mean arterial pressure (MAP) of 65–75 mmHg. Animals were mechanically ventilated with tidal volumes of 7–10 mL/kg and a respiratory rate of 10–15 breaths per minute to maintain end-tidal carbon dioxide at 40 ± 5 mmHg. Plasmalyte 148 (Baxter, Deerfield, IL) was administered at 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 overcome insensible losses. All animals received a bolus of 1 L Plasmalyte 148 upon venous access. Intravenous heparin (APP Pharmaceuticals, Schaumburg, IL) was administered to achieve an activated clotting time of 100 s, similar to human baseline values. An underbody warmer and a warming blanket were used to maintain core body temperature between 35 and 37 °C.

The spleen was removed via a midline laparotomy to minimize hemodynamic variation from autotransfusion [9]. The supraceliac aorta was exposed by dividing the diaphragm, and dissected circumferentially for 5–10 cm. Two adjacent intercostal arteries were ligated to facilitate placement of a periaortic flow probe (Transonic Systems Inc, Ithaca, NY). The caudal peritoneum was incised to expose the right renal artery, which was dissected circumferentially for the placement of a second perivascular flow probe (Transonic Systems Inc., Ithaca, NY). The abdomen was then closed.

Bilateral external jugular veins were cannulated to facilitate medication and fluid administration, as well as 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 MAP (pMAP) monitoring. The left femoral artery was exposed and cannulated with a 12 Fr sheath for Coda balloon catheter placement (Cook Medical, Bloomington, IN) and distal MAP (dMAP) monitoring. The right femoral artery was exposed and cannulated with a 7 Fr sheath for ER-REBOA® (Prytime Medical, Boerne, TX) placement. The left femoral vein was exposed and cannulated with a dual lumen 14 Fr resuscitation catheter for blood transfusion. Proper positioning of the Coda balloon in zone 1 and of the ER-REBOA balloon in zone 3 was confirmed via fluoroscopy.

Hemorrhage, intervention, and critical care

At the start of the experiment, animals underwent controlled hemorrhage of 25% of their estimated total blood volume, which was estimated at 60% of their body weight (kg). The blood was withdrawn over 30 min into citrated blood collection bags under constant agitation. Animals were randomized to experimental groups at the end of the hemorrhage period. Blood was stored in a 37 °C water bath after collection and until transfusion.

At the end of the 30-minute hemorrhage period, the intra-aortic occlusion balloons were inflated according to the randomized assignments. In the animals assigned to the control group, no balloon was inflated. Complete aortic occlusion was confirmed in the Z1 group by loss of aortic flow, and in the Z3 group by loss of the distal arterial pressure waveform. Occlusion was maintained for 45 min.

Transfusion of shed blood began ten minutes prior to the end of the intervention period. The volume of shed blood was transfused over 30 min with a Belmont Rapid Infuser (Belmont Instrument Corporation, Billerica, MA). The balloon was deflated over five minutes, starting at T75. At T80, in the Z1Z3 group, the ER-REBOA balloon in zone 3 was inflated until complete aortic occlusion was confirmed by the loss of the distal arterial pressure waveform. This balloon remained inflated for an additional 55 min and was deflated over 5 min starting at T135. The balloon in zone 1 remained deflated until the end of the experiment.

Critical care with isotonic fluid boluses, norepinephrine titration, and electrolyte correction proceeded in all animals from T80 to T360 as outlined previously [7]. Boluses of 500 mL Plasmalyte 148 were administered for pMAP < 60 mmHg with CVP < 7 mmHg over 10 min. Norepinephrine infusion rate was increased by 0.02 μg/kg/min for pMAP < 60 mmHg with CVP ≥ 7 mmHg. These interventions were administered automatically via computer driven automated critical care system. Animals were euthanized at T360 with an intravenous injection of pentobarbital without recovering from general anesthesia.

Data collection

Aortic and right renal artery flow measurements were collected in real time using perivascular flow probes and a Biopac MP150 multichannel data acquisition system (Biopac Systems, Goleta, CA). Urinary output was quantified throughout the experiment. Renal tissue damage was graded via hematoxylin and eosin histological evaluation by a veterinarian blinded to the intervention. Kidneys were examined for early signs of acute tubular necrosis defined by thinning and dilation of renal tubules, cytoplasmic eosinophilia, blebbing, pyknosis of nuclei and sloughing of cells into tubular lumens. Scores were assigned using the following scale: tubular necrosis was graded as 0 (no evidence), 1 (minimal), 2 (minor), 3 (moderate), 4 (severe), and injury distribution was scored as 0 (none), 1 (focal), 2 (multifocal), 3 (locally extensive), and 4 (diffuse).

Laboratory analysis

Arterial blood was collected at routine intervals throughout the study for creatinine concentration evaluation (Vet Axcel, Alfa Wassermann, West Caldwell, NJ). Plasma and urine concentrations of sodium were quantified at T0 and T360 (Vet Axcel, Alfa Wassermann, West Caldwell, NJ). Fractional excretion of sodium (FeNa) was calculated with the following formula:

$$FeNa = \frac{[\text{Sodium}]_{Urine} \times [\text{Creatinine}]_{Plasma}}{[\text{Sodium}]_{Plasma} \times [\text{Creatinine}]_{Urine}} \times 100$$

Urinary and serum neutrophil gelatinase-associated lipocalin (NGAL) concentration was assessed at T0 and T360 via enzyme-linked immunosorbent assay (BioPorto Diagnostics, Hellerup, Denmark). NGAL is reported as the ratio between urinary NGAL and urinary creatinine concentrations, [$NGAL_{urine}$/$Creatinine_{urine}$] to adjust for changes in renal urine concentrating abilities.

Statistical analysis

Data distributions were assessed for normality and expressed as mean ± standard error of the mean or median (interquartile range), as appropriate. RBF during the critical care phase ($RBF_{Crit\ care}$) was averaged from T75 until the end of the experiment for each animal and compared between groups with ANOVA testing with Bonferroni-corrected pairwise comparisons. Plasma creatinine concentration was analyzed with repeated measure ANOVA and pairwise comparisons adjusted with the Bonferroni correction. [$NGAL_{urine}$/$Creatinine_{urine}$],

FeNa, and urine output were compared at T0 and T360 between groups with ANOVA or Kruskall Wallis ANOVA for parametric and non-parametric data, respectively. Changes within groups between T0 and T360 were analyzed with paired *t*-test or Wilcoxon signed rank test for paired parametric or non-parametric data, respectively. Ordinal data from histological analysis was compared with Kruskall Wallis ANOVA. Statistical significance was set at $p < 0.05$. Statistical analysis was conducted with a commercial software (Stata 14.2, Stata, College Station, TX).

Results

Except for the serum creatinine concentration, there was no significant difference in baseline parameters between groups (Table 1).

Proximal mean arterial pressure

Proximal MAP results are presented in Fig. 2. There was a significant difference between groups in the average pMAP during critical care ($p = 0.009$) (66.9 ± 1.6; 59.5 ± 1.4 ; 64.5 ± 0.8; 61.0 ± 1.9 mmHg in the control, Z1, Z3, Z1Z3 groups, respectively). Pairwise comparison showed a significant difference between the control group and the Z1 ($p = 0.019$).

Renal blood flow

RBF results are presented in Fig. 3. There were no differences during the intervention between the control and Z3 groups. There were no differences in $RBF_{Crit\ care}$ between the control (190.8 ± 24.8 mL/min), Z1 (174.4 ± 15.7 mL/min), and Z3 (191.9 ± 23.7 mL/min) groups, but animals in the Z1Z3 group had statistically lower $RBF_{Crit\ care}$ (98.2 ± 23.9 mL/min) than the control and Z3 group. While there was no statistical difference in $RBF_{Crit\ care}$ between the Z1 and Z3 groups, RBF in the Z1 group returned to levels similar to the control and Z3 groups around after 45 min after balloon deflation (T120). The average RBF between T120 and T360 was significantly higher in the Z1 group when compared to the Z1Z3 group ($p = 0.02$).

Renal function

There was no significant difference in urine production between groups at the end of the experiment ($p = 0.08$) (Table 2). There were differences between groups at T0 ($p = 0.003$) with serum creatinine being significantly lower in the Z1 group when compared to the Z3 and Z1Z3 groups ($p = 0.038$ and 0.002, respectively). The change in serum creatinine compared to baseline (Δ creatinine) was therefore evaluated over time (Fig. 4). There was a significant difference in Δ creatinine between groups ($p = 0.007$) and over time ($p = 0.001$). The interaction between treatment and time was not statistically significant ($p = 0.26$). Adjusted comparisons of Δ creatinine at T 30, 90, 150, and 360 showed no difference between groups ($p = 0.25$, 0.10, 0.23, 0.07, respectively). There was no change over time in Δ creatinine for the Z3 group ($p = 0.29$). For the other groups, Δ creatinine was significantly different over time ($p = 0.02$ for all 3 groups). Δ creatinine was significantly higher than baseline starting at T 30 for the control and Z1 groups ($P < 0.003$ for each group) and starting at T 90 for the Z1Z3 group ($P < 0.003$).

NGAL concentrations ratio and fraction of excretion of sodium

[$NGAL_{urine}$/$Creatinine_{urine}$] results are presented in Table 2. There was a significant difference between groups at T360 ($p = 0.003$). Adjusted pairwise comparison showed a significant difference between the control and Z1 ($p = 0.002$) as well as between control and the Z1Z3 ($p = 0.001$) group. There were no other significant differences between groups. There was a significant increase in [$NGAL_{urine}$/$Creatinine_{urine}$] over time for the control, Z1, and Z1Z3 groups ($p = 0.03$ for each group). There was no difference in FeNa between groups at T0 and T360 ($p = 0.74$ and 0.09, respectively) (Table 2). [$NGAL_{urine}$/$Creatinine_{urine}$] was significantly higher at T360 than at T0 for the Z1 ($p = 0.004$) and Z1Z3 ($p = 0.004$) groups. FeNa was significantly higher at T360 than at baseline in the Z1 group ($p = 0.04$).

Renal histopathology

There was no evidence of renal damage in the control, Z1, and Z3 groups. Histologic evidence of renal injury was graded 1 (IQR: 0–3) in the Z1Z3 group, although there were no statistically significant difference across the groups ($p = 0.34$).

Discussion

There is limited description of the effects of endovascular aortic occlusion on renal function in trauma patients. The present study highlights the complexity of the cascade of events occurring following hemorrhagic shock, aortic occlusion, and resuscitation. First, zone 3 occlusion did not confer significant improvement in renal perfusion or function over controls. Furthermore, zone 3 occlusion after zone 1 occlusion led to a paradoxical reduction in RBF for the remainder of the study. Renal function measured at the end of the study is significantly worse than at baseline but does not manifest as histologic evidence of injury. Finally, we established that after a period of complete aortic occlusion, RBF does not return immediately, but gradually to baseline levels over approximately 45 min.

AKI following endovascular aortic occlusion has been inconsistently reported in trauma patients but appears to be common. Using the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria, one study reported an AKI incidence of 64% (3, 1, and 5 of 14 patients in the R, I, and F categories, respectively) [3]. Analysis of the AAST prospective Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) registry showed no difference in renal

Table 1
Baseline parameters. MAP: mean arterial pressure, Z1: zone 1 REBOA, Z3: zone 3 REBOA, Z1Z3: zone 3 REBOA following zone 1 balloon deflation.

Parameter	Control	Z1	Z3	Z1Z3	p
Sex					0.58
Male (%)	2 (33)	1 (17)	3 (50)	3 (50)	
Female (%)	4 (67)	5 (83)	3 (50)	3 (50)	
Weight (kg)	79.0 ± 1.86	77.5 ± 3.25	78.67 ± 3.64	78.83 ± 2.86	0.98
Proximal MAP (mmHg)	68.3 ± 2.3	66.8 ± 1.1	67.7 ± 2.4	68.9 ± 2.2	0.90
Distal MAP (mmHg)	65.2 ± 2.7	62.4 ± 1.1	63.1 ± 2.1	63.8 ± 2.5	0.83
Aortic blood flow (mL/min)	2835.1 ± 160.1	3196.9 ± 198.4	3318.9 ± 129.5	2982.9 ± 120.5	0.16
Renal blood flow (mL/min)	197.9 ± 20.8	224.4 ± 25.5	223.8 ± 24.9	199.2 ± 29.4	0.8
[Creatinine] (mg/dL)	1.40 ± 0.06	1.31 ± 0.05	1.57 ± 0.09	1.65 ± 0.08	**0.02**

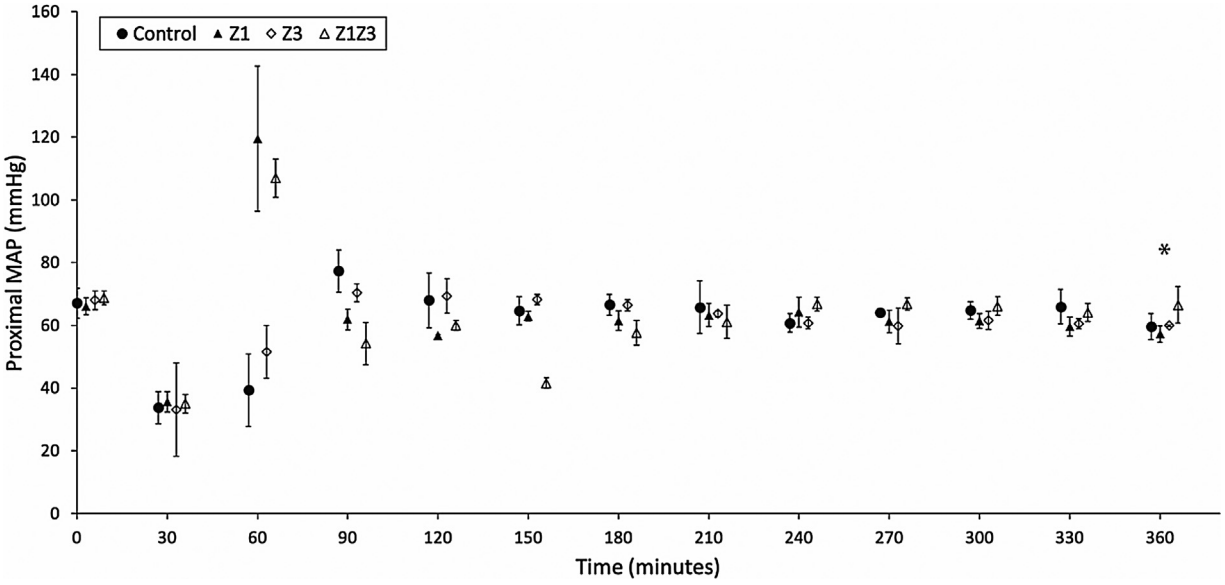

Fig. 2. Mean (± standard error of the mean) proximal mean arterial pressure over time. *: significant difference between the control and Z1 groups (p = 0.019). MAP: mean arterial pressure, Z1: zone 1 REBOA, Z3: zone 3 REBOA, Z1Z3: zone 3 REBOA following zone 1 balloon deflation.

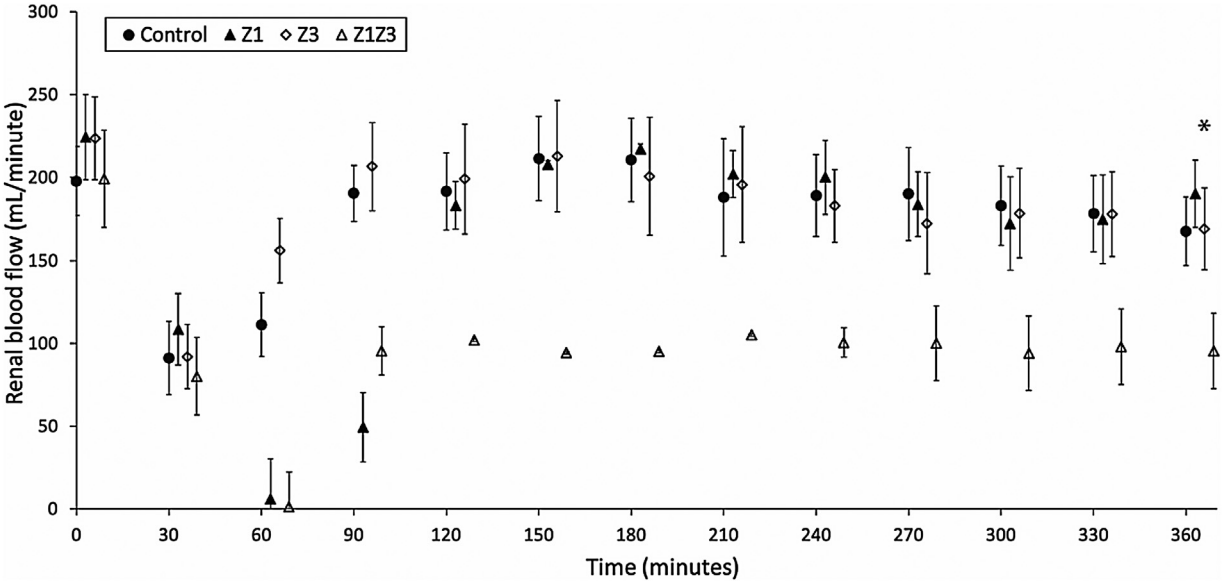

Fig. 3. Mean (± standard error of the mean) renal blood flow over time. *: The Z1Z3 group had significantly lower $RBF_{Crit\ care}$ (98.2 ± 23.9 mL/min) than the control (190.8 ± 24.8 mL/min) and Z3 (191.9 ± 23.7 mL/min) groups (p = 0.049 and 0.046, respectively). $RBF_{Crit\ care}$: renal blood flow during critical care, Z1: zone 1 REBOA, Z3: zone 3 REBOA, Z1Z3: zone 3 REBOA following zone 1 balloon deflation.

replacement therapy requirements between patients treated with endovascular aortic occlusion and those with RT (2/46 and 2/68, respectively) [4]. AKI in this population is likely multifactorial owing to the original trauma, followed by hemorrhagic shock and subsequent ischemia/reperfusion associated with aortic occlusion. These findings underscore the need for intervention to minimize the incidence of AKI following REBOA therapy in trauma patients.

In our study, zone 3 occlusion following hemorrhagic shock did not augment RBF when compared to controls; while there was no change in Δ creatinine over time, the final value was comparable to that of other groups. No change in urinary biomarkers of injury was nonetheless observed overtime for the Z3 group. Overall, the use of zone 3 REBOA in patients without hemorrhage distal to the balloon is unlikely to provide significant renal benefits.

We had also hypothesized that following zone 1 occlusion, balloon inflation in zone 3 would enhance blood flow to organs proximal to the balloon and improve perfusion and function. However, our data demonstrated similar renal function (as evidenced by final Δ creatinine) at the end of the study when compared to the Z1 group. Furthermore, $RBF_{Crit\ care}$ in the Z1Z3 group was even lower than in animals in the Z3 group for the entirety of the critical care phase of the study. During critical care, there was no difference in the average proximal MAP between the Z1Z3 and the Z1 group, and despite a consistent MAP the Z1Z3 group maintained the lowest $RBF_{Crit\ care}$. Differences in RBF without differences in pMAP suggest complex alteration in RBF autoregulation in response to the level of aortic occlusion. From the RBF findings, it therefore is not surprising that there was no

Table 2
Markers of renal function. FeNa: fractional excretion of sodium, NGAL: neutrophil gelatinase-associated lipocalin, UOP: urine output, Z1: zone 1 REBOA, Z3: zone 3 REBOA, Z1Z3: zone 3 REBOA following zone 1 balloon deflation. * Significantly different than baseline. ** Significantly different than control (p = 0.002 and 0.001 for the Z1 and Z1Z3 groups, respectively).

Parameter	Control	Z1	Z3	Z1Z3	p
T0					
[$NGAL_{urine}$/$Creatinine_{urine}$] (%)	9.1 (7.1-10.7)	11.6 (10.2-13.1)	21.9 (10.9-45.3)	9.2 (8.2-13.2)	0.1
FeNa (%)	1.52 ± 0.35	1.64 ± 0.80	1.33 ± 0.39	1.31 ± 0.36	0.74
UOP (mL/kg/hr)	3.83 ± 0.93	1.64 ± 0.79	3.41 ± 0.38	4.72 ± 1.07	0.64
T360					
[$NGAL_{urine}$/$Creatinine_{urine}$] ($x10^{-3}$)	11.3 (10.7-33.5)*	248.8 (110.2-551.9)*,**	24.0 (19.6-70.5)	264.5 (73.6-1174.6)*,**	**0.003**
FeNa (%)	1.46 ± 0.63	4.41 ± 0.97 *	1.95 ± 0.70	2.96 ± 0.95	0.09
Total UOP (mL/kg)	16.02 ± 3.11	33.69 ± 6.33	18.45 ± 3.49	24.03 ± 5.58	0.08
p for the change from T0 to T360					
[$NGAL_{urine}$/$Creatinine_{urine}$]	**0.03**	**0.03**	0.6	**0.03**	
FeNa	0.93	**0.03**	0.33	0.19	

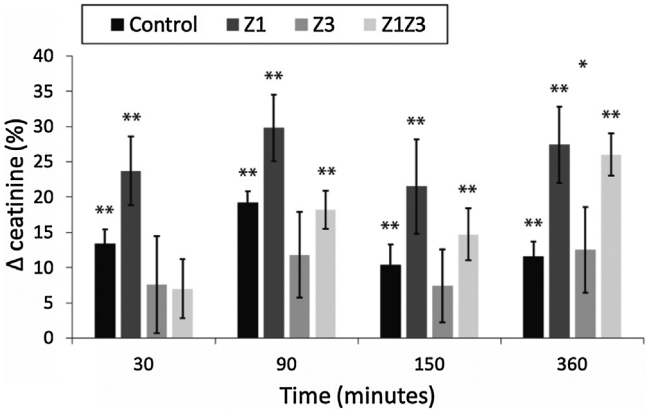

Fig. 4. Mean (± standard error of the mean) Δ creatinine over time. Δ creatinine represents the change in serum creatinine compared to baseline. Z1: zone 1 REBOA, Z3: zone 3 REBOA, Z1Z3: zone 3 REBOA following zone 1 balloon deflation. *: significant difference between groups (p = 0.007) and over time (p = 0.001). Adjusted comparisons at T 30, 90, 150, and 360 showed no difference between groups (p = 0.25, 0.10, 0.23, 0.07, respectively). **: significantly higher than baseline (p < 0.003).

difference in the [$NGAL_{urine}$/$Creatinine_{urine}$] between the Z1 and Z1Z3 groups.

Similarly, occlusion in zone 3 had no beneficial effect on $RBF_{Crit\ care}$, when compared to zone 1. Mechanisms behind the lack of RBF augmentation in the Z3 and Z1Z3 group remain unknown but could be the result of afferent renal artery constriction or decreased vascular resistance in the arterial tree proximal to the zone 3 balloon from the ischemia-reperfusion burden. While there was no difference in [$NGAL_{urine}$/$Creatinine_{urine}$] between the Z3 and Z1 groups, there is little overlap in results between the two groups. The lack of difference may therefore be the result of lack of power, which is potentiated by the more stringent statistical significance associated with adjustment for multiple comparisons. Furthermore, there was no significant increase over time in [$NGAL_{urine}$/$Creatinine_{urine}$] in the Z3 group, which indicates that renal damage was limited compared to the other groups. Future studies should evaluate endocrine responses as well as blood flow distribution in the setting of zone 3 and zone 1 followed by zone 3 occlusion in traumatic exsanguination.

Finally, we demonstrated that following zone 1 balloon deflation, RBF returns to baseline levels over approximately 45 min. This delayed in return to normal flow following reperfusion might be related to alteration in renal vasomotor tone. In a macaque model of hemorrhagic shock and aortic cross clamping for 45 min, RBF remained lower than baseline despite resuscitation with shed blood [10]. Thrombosis, vasomotor dysfunction, or accumulation of white blood cells or other cellular debris aggregates may account for this reversible increased resistance to flow.

This study has several limitations. First, RBF is not a marker of renal function, rather a macroscopic marker of renal perfusion. Renal autoregulation and alteration in renal tissue microcirculation have a direct impact on renal function. Such changes are partially controlled by the renin-angiotensin-aldosterone system, which can be altered by aortic occlusion [12]. We reported both markers of renal function and injury in addition to blood flow. Second, the findings of the present study are limited by the lack of tissue damage that is expected in normal trauma patients with NCTH. This may have limited the extent of the inflammatory response and may have led to smaller differences between groups. Third, we used traditional pathologic and histologic analysis when grading tissue injury. Advanced analysis, such as with electron microscopy or immunohistochemistry, might demonstrate early morphological changes. Second, we only utilized complete occlusion in all groups. A partial REBOA strategy may have provided beneficial effects by maintaining a carefully titrated flow rate across the balloon to minimize ischemic burden [11]. Finally, this study was a non-survival protocol and long-term consequences (such as increases in serum creatinine or histologic damage) may not have had time to manifest during the time period. These limitations notwithstanding, our study outlines the complexity of renal responses to aortic occlusion in various zones of the aorta following hemorrhagic shock using a wide array of markers.

Conclusions

We demonstrated that zone 3 occlusion alone or following zone 1 occlusion in a porcine model of hemorrhagic shock did not improve renal function. Zone 3 occlusion after zone 1 occlusion had a detrimental effect on overall RBF. We have also demonstrated that even after resuscitation and deflation of a REBOA balloon, RBF does not immediately return to normal but takes up to 45 min to return to baseline levels. Future studies are needed to evaluate mechanistic approaches behind those observations.

Sources of support and conflicts of interest

Funding for this study was provided by the Clinical Investigation Facility, David Grant USAF Medical Center, Travis Air Force Base, CA. This research was supported in part by an appointment to the Postgraduate Research Participation Program at the USAF David Grant Medical Center Clinical Investigation Facility administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of

Energy and USAF-DGMC-CIF. Drs. Johnson, Williams, and Neff are co-founders of Certus Critical Care, Inc.

None of those entities had influence in in the study design; collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication.

Acknowledgments

We acknowledge the outstanding technical assistance of SSgt Kelly Caneen, SrA Anna Ferro, Ms. Eileen Foster, Mr. Carl Gibbons, Ms. Diane Gonzalez, Ms. Sally Knode, SrA Athena Lagman, SrA Tyler Lock, Mr. Miguel Rodriguez, Mr. Aric Sawyer, Ms. Amy Taylor, and the entire staff of the 60th Clinical Investigation Facility, Travis AFB, California.

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