Resuscitative endovascular balloon occlusion of the aorta induced myocardial injury is mitigated by endovascular variable aortic control

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BACKGROUND: The cardiac effects of resuscitative endovascular balloon occlusion of the aorta (REBOA) are largely unknown. We hypothesized that increased afterload from REBOA would lead to cardiac injury, and that partial flow using endovascular variable aortic control (EVAC) would mitigate this injury.

METHODS: Eighteen anesthetized swine underwent controlled 25% blood volume hemorrhage. Animals were randomized to either Zone 1 REBOA, Zone 1 EVAC, or no intervention (control) for 45 minutes. Animals were then resuscitated with shed blood, observed during critical care, and euthanized after a 6-hour total experimental time. Left ventricular function was measured with a pressure-volume catheter, and blood samples were drawn at routine intervals.

RESULTS: The average cardiac output during the intervention period was higher in the REBOA group (9.3 [8.6–15.4] L/min) compared with the EVAC group (7.2 [5.8–8.0] L/min, $p = 0.01$) and the control group (6.8 [5.8–7.7] L/min, $p < 0.01$). At the end of the intervention, the preload recruitable stroke work was significantly higher in both the REBOA and EVAC groups compared with the control group (111.2 [102.5–148.6] and 116.7 [116.6–141.4] vs. 67.1 [62.7–87.9], $p = 0.02$ and $p < 0.01$, respectively). The higher preload recruitable stroke work was maintained throughout the experiment in the EVAC group, but not in the REBOA group. Serum troponin concentrations after 6 hours were higher in the REBOA group compared with both the EVAC and control groups (6.26 ± 5.35 ng/mL vs 0.92 ± 0.61 ng/mL and 0.65 ± 0.38 ng/mL, $p = 0.05$ and $p = 0.03$, respectively). Cardiac intramural hemorrhage was higher in the REBOA group compared with the control group (1.67 ± 0.46 vs. 0.17 ± 0.18, $p = 0.03$), but not between the EVAC and control groups.

CONCLUSION: In a swine model of hemorrhagic shock, complete aortic occlusion resulted in cardiac injury, although there was no direct decrease in cardiac function. EVAC mitigated the cardiac injury and improved cardiac performance during resuscitation and critical care. (*J Trauma Acute Care Surg.* 2019;87: 590–598. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Resuscitative endovascular balloon occlusion of the aorta; endovascular variable aortic control; myocardial injury; partial aortic occlusion; hemorrhage control.

The use of resuscitative endovascular balloon occlusion of the aorta (REBOA) for the treatment of hemorrhagic shock is increasing. The appeal of this technique arises from its dual ability to arrest hemorrhage while augmenting perfusion to the heart and brain.[1–4] However, there are significant limitations to aortic occlusion (AO) primarily thought to be due to ischemia in tissue beds distal to the level of occlusion.[5–7] Astute observations from translational and clinical reports have also suggested deleterious effects to organs proximal to level of AO from supraphysiologic arterial blood pressure.[8–10] Attempts to mitigate the harmful effects of REBOA, both proximal and distal to the level of occlusion, have led to the development of alternative methods for partial AO, including endovascular variable aortic control (EVAC).[11–14] Endovascular variable aortic control is a partial AO strategy that uses automation to carefully titrate distal blood flow past the balloon to both off-load supraphysiologic proximal blood pressure and minimize ischemia by facilitating some perfusion of distal tissue beds.[15,16]

Despite the mounting anecdotal clinical evidence of the damaging effects of REBOA, there are still significant knowledge gaps. Optimal selection of the patients who will benefit from AO remains unclear, and the true effects of REBOA and EVAC on the proximal circulation and cardiac function are unknown.[10,17] While parallels may be drawn from classic cardiac physiology studies that demonstrated myocardial dysfunction following open AO in humans and animal models, the specific cardiac effects of REBOA and EVAC in the clinically relevant context of hemorrhage, AO, and massive ischemia-reperfusion have not been reported in detail.[18–20] One recent publication demonstrated biochemical and histologic changes consistent with myocardial injury following prolonged periods of AO, but there is no data yet on the cardiac effects of AO during the shorter

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durations that are recommended clinically.[10] Together, these earlier AO physiology studies may not reflect the current clinical implementation of REBOA for patients in hemorrhagic shock.

The United States trauma population is becoming older and the incidence of comorbid heart disease in trauma patients will increase.[21] This aging trauma population is coupled with an expanding interest in nontraumatic indications for REBOA, such as gastrointestinal bleeding and myocardial infarction.[22–24] Therefore, the need for a more accurate appraisal of REBOA and EVAC's effects on cardiac function is warranted, because some potential recipients of aortic occlusion may have underlying heart disease.[14,17] To date, AO researchers have primarily described cardiac performance via pulmonary artery catheter (PAC) measurements in large animal models.[14,25,26] However, the granularity of the data is insufficient because PAC derived variables are largely based on calculated metrics, like cardiac output (CO), which do not provide a load-independent metric for cardiac function and may be rendered inaccurate by very high aortic afterload.[27] Furthermore, electrocardiographic changes and troponin elevations have been documented as indicators of myocardial strain following REBOA.[10] Yet it is not known if this damage would be attenuated by partial AO strategies like EVAC.

The purpose of this study is to characterize the timing and magnitude of the Zone 1 REBOA and EVAC effects on cardiac function using direct physiologic measurements from the left ventricle. We hypothesized that cardiac damage from Zone 1 REBOA would manifest soon after intervention and lead to decreased cardiac performance and increased myocardial injury when compared to EVAC or no occlusion in a swine model of hemorrhagic shock.

METHODS

Overview

The Institutional Animal Care and Use Committee at David Grant USAF Medical Center, Travis Air Force Base, California approved this study. 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 the AAALAC. 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 prior to use. At the time of experimentation, animals weighed between 70 kg and 92 kg and were between 4 months and 6 months of age.

Figure 1A shows the experimental timeline. Eighteen swine underwent controlled hemorrhage of 25% blood volume (estimated at 60 mL/kg) over 30 minutes. During this period, animals were assigned using a block randomization approach, to either Zone 1 REBOA (complete occlusion, n = 6), Zone 1 EVAC (partial occlusion, n = 6), or no intervention (control, n = 6). At the end of the 30-minute hemorrhage, the assigned intervention commenced for 45 minutes. Balloon volume in the EVAC arm was autonomously titrated to maintain a weight-based aortic flow between 1.5 mL/kg per minute and 4.4 mL/kg per minute (approximately 100–300 mL/min for a 70 kg animal) predicated on proximal pressure as previously described.[16,28] At the end of the intervention, animals were resuscitated with shed blood, intraaortic balloons were gradually deflated over 5 minutes, and the experiment entered the critical care phase. During this phase, an automated critical care platform initiated isotonic fluid boluses and titrated vasopressors based on a predefined algorithm that was the same for all groups. Cardiac function was continuously measured with a pressure-volume (PV) loop catheter in the left ventricle. After a total experimental time of 360 minutes, animals were euthanized and underwent necropsy.

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 1.5% to 2.5% 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 to maintain end tidal CO_2 at 40 ± 5 mm Hg using tidal volumes of 6 to 10 mL/kg and a respiratory rate of 10 to 15 breaths per minute.

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 to prevent intravascular clotting around indwelling devices. An underbody warmer was used to maintain core body temperature between 35°C and 37°C. No negative chronotropic agents were administered during the study.

The spleen was removed via laparotomy to minimize hemodynamic variation from autotransfusion.[29] The supraceliac aorta was exposed by dividing the diaphragm and dissected circumferentially for 5 cm to 10 cm. A perivascular flow probe (Transonic Systems Inc., Ithaca, NY) was placed around the distal descending thoracic aorta proximal to the planned location of the aortic balloon catheter. Two adjacent intercostal arteries were ligated to ensure no flow was detected between the flow probe and balloon during AO. The abdomen was closed with cable ties.

The left external jugular vein was cannulated with a triple lumen catheter for medication and fluid administration, as well as central venous pressure (CVP) monitoring. The right external jugular vein was cannulated with a 14-Fr sheath to accommodate an occlusion balloon catheter (Bridge Balloon; The Spectranetics Corporation, Colorado Springs, CO). This balloon catheter was positioned with fluoroscopy, spanning the junction of the superior and inferior vena cava, to enable intermittent cessation of right atrial filling for the measurement of preload-independent cardiac work (Fig. 1B).[30] The left femoral vein was cannulated with a dual lumen resuscitation catheter for blood transfusion.

The right brachial artery was surgically exposed and cannulated with a 7-Fr sheath to allow for controlled hemorrhage during the initial phase of the experiment. The left axillary artery was surgically exposed and cannulated with a 9-Fr sheath for proximal MAP (pMAP) monitoring, and to accommodate a 5-Fr PV loop catheter (Transonic Systems Inc., Ithaca, NY), which was positioned in the left ventricle under fluoroscopic guidance (Fig. 1B). The catheter was positioned in the long axis of the

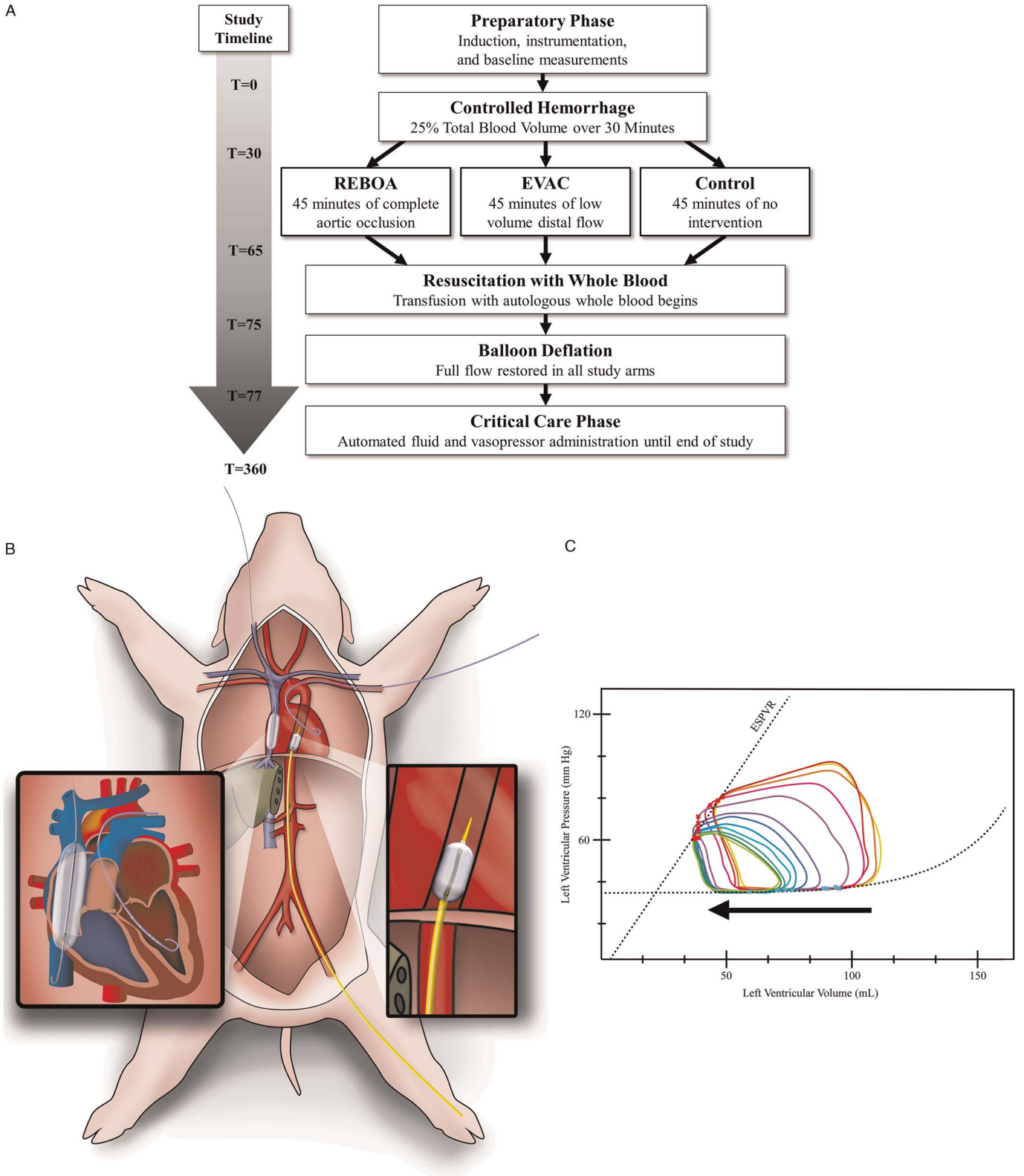

Figure 1. Experimental protocol timeline (*A*). Experimental set-up with enlarged views showing the vena cava occlusion balloon, PV loop catheter, and intraaortic balloon (*B*). Representative image of PV loops captured at one time point (*C*) with decreasing levels of end-diastolic volume (black arrow) and derivation of the ESPVR.

left ventricle with the tip at the apex.[31] The left femoral artery was cannulated with a 12-Fr sheath for distal MAP (dMAP) monitoring and to accommodate a 9-Fr Coda LP balloon catheter (Cook Medical LLC, Bloomington, IN). This balloon catheter was prepositioned in Zone 1 of the aorta, between the takeoff of the left subclavian artery and the celiac trunk, under fluoroscopic guidance to provide the AO intervention.[32]

Intervention

At the end, the 30-minute hemorrhage phase, the intraaortic balloon was inflated according to the group assignment. For animals randomized to the control group, no balloon was inflated, and the balloon catheter was removed. For animals in the REBOA group, complete occlusion was confirmed by flattening of the dMAP waveform. In the EVAC group, balloon volume was titrated by an automated syringe pump in a closed feedback loop to maintain partial aortic flow at the specified rates.[16] The intervention period lasted 45 minutes, and transfusion of shed blood was initiated 10 minutes prior to the balloon deflation. A rapid transfusion system (Belmont Medical Technologies, Billerica, MA) was used to transfuse the total shed blood volume evenly over 30 minutes. Intraaortic balloons were gradually deflated over 5 minutes at the end of the intervention phase according to established clinical guidelines.[33]

All animals then entered the critical care phase which lasted until the animal died or was euthanized 6 hours after the start of the experiment. During this phase, a computerized critical care platform autonomously titrated vasopressor medication and delivered isotonic fluid boluses in response to predefined physiological triggers as previously described.[34] Plasma-Lyte boluses of 500 mL were administered in response to a pMAP less than 60 mm Hg with a CVP less than 7 mm Hg. The norepinephrine infusion rate was increased by 0.02 μg/kg per minute in response to a pMAP less than 60 mm Hg with a CVP greater than or equal to 7 mm Hg. The norepinephrine infusion rate was decreased by 0.01 μg/kg per minute when the pMAP was greater than 70 mm Hg. The maximum norepinephrine infusion rate was 0.2 μg/kg per minute. All 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. Plasma potassium, glucose, and calcium concentrations were monitored and corrected according to our standard protocols.[34]

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). Measured parameters included heart rate, arterial pressures proximal and distal to the intraaortic balloon, CVP, core temperature, and aortic flow.

Cardiac performance was measured using the PV loop catheter. Cardiac output and ejection fraction (EF) were calculated using LabChart (ADInstruments, Colorado Springs, CO) at prespecified intervals. To measure preload-independent metrics of cardiac performance, right-sided cardiac inflow was occluded with the prepositioned vena cava occlusion balloon during a ventilatory pause at predetermined time points. The PV loops from each occlusion period were used to measure the end-systolic PV relationship (ESPVR) and preload recruitable stroke work (PRSW) using LabChart (ADInstruments) (Fig. 1C). The ESPVR and PRSW are measures of cardiac contractility that provide a load-independent measure of intrinsic cardiac function rather than metrics that are not load-independent, such as EF.[35,36] Furthermore, PRSW is accurate for measuring intrinsic cardiac function in the setting of AO because ESPVR can vary with changes in afterload.[27,37]

Myocardial tissue samples were collected from each animal during necropsy and pathological evaluation was performed by a veterinary pathologist blinded to the intervention. The myocardium was evaluated grossly for subendocardial hemorrhage and microscopically in hematoxylin and eosin stained sections. The degree of intramural hemorrhage at the chordae tendineae insertion in the left ventricle was assigned an ordinal grade from 0 to 4, with zero representing no hemorrhage and four representing severe hemorrhage.[38]

Statistical Analysis

Data were assessed for normality and are presented as mean ± standard deviation or median (interquartile range) for parametric and nonparametric data, respectively. Bartlett's test was used to compare variances and data were analyzed using analysis of variance (ANOVA), Kruskal-Wallis ANOVA, or repeated-measures ANOVA as appropriate. The Bonferroni correction was used to adjust for multiple comparisons for normally distributed data and Dunn's test was used for multiple comparisons following nonparametric tests. Statistical analysis was performed using a commercial software package (STATA version 14.1; Stata Corp., College Station, TX). Statistical significance was set as $p \leq 0.05$.

RESULTS

There were no differences in baseline characteristics between the three groups (Table 1). At the end of the hemorrhage phase, all groups demonstrated shock physiology with average MAP less than 40 mm Hg, heart rate greater than 170 bpm, and lactate levels from 3 to 4 mmol/L. One animal in the EVAC group died prior to the end of the study. By the end of the study, animals in the REBOA group received significantly more resuscitation fluid compared to the other groups (REBOA 96.6 ± 21.9 mL/kg vs. EVAC 42.2 ± 26.0 mL/kg, $p = 0.02$; and vs. Control 36.9 ± 36.8 mL/kg, $p < 0.01$). Animals in the REBOA group also required significantly higher doses of norepinephrine compared to the other groups (REBOA 38.8 ± 9.3 μg/kg vs. EVAC

TABLE 1. Baseline Characteristics of Animals in the Zone 1 REBOA, Zone 1 EVAC, and Control Groups

	Control Group (n = 6)	Zone 1 REBOA Group (n = 6)	Zone 1 EVAC Group (n = 6)	*p*
Sex, male/female	2:4	4:2	4:2	1.0
Weight, kg	79 ± 5	78 ± 8	83 ± 4	0.35
Troponin, ng/mL	0.06 ± 0.05	0.04 ± 0.01	0.03 ± 0.02	0.33
pMAP, mm Hg	68 ± 6	66 ± 7	70 ± 8	0.69
CO, L/min	4.4 ± 1.1	4.9 ± 2.2	3.9 ± 1.0	0.98
EF, %	45 ± 8	44 ± 8	46 ± 12	0.61

Continuous data presented as mean ± standard deviation.

17.4 ± 14.9 μg/kg, $p = 0.04$; and vs. Control 10.7 ± 15.2 μg/kg, $p < 0.01$). The average CO during the intervention period was higher in the REBOA group (9.3 [8.6–15.4] L/min) compared to the EVAC group (7.2 [5.8–8.0] L/min, $p = 0.01$) and the control group (6.8 [5.8–7.7] L/min, $p < 0.01$). There were no differences in CO or EF between groups at the end of hemorrhage, at the end of the intervention period, or at the end of the study (Table 2).

Left Ventricular Contractile Strength

The ESPVR and PRSW did not differ between groups at baseline (Table 2). Upon pairwise comparison, there were no differences between groups in ESPVR at the end of the intervention or at the end of the study (Fig. 2A). At the end of the intervention phase, the PRSW was significantly higher in the REBOA group (REBOA, 111.2 [102.5–148.6] vs. control, 67.1 [62.7–87.9], $p = 0.02$) and EVAC group (EVAC, 116.7 [116.6–141.4] vs. control 67.1 [62.7–87.9], $p < 0.01$). The elevated PRSW was maintained through the end of the experiment in the EVAC group (105.3 [84.0–119.5]), compared with both the REBOA group (66.0 [38.8–77.1], $p < 0.01$) and the control group (65.8 [41.9–80.2], $p < 0.01$). There was no difference in PRSW between the REBOA and control groups at the end of the experiment ($p = 0.39$; Fig. 2B).

Biochemical and Pathological Markers of Myocardial Injury

There were significant differences in serum troponin concentration between the groups over time (Fig. 3). While there were no baseline differences in serum troponin concentrations between groups ($p = 0.33$), the serum troponin concentration was higher in the REBOA group compared to the control group 75 minutes after the intervention phase at Time 150 (2.80 ± 2.33 ng/mL vs. 0.33 ± 0.25 ng/mL, $p = 0.03$) and at the end of the experiment (6.26 ± 5.35 ng/mL vs. 0.65 ± 0.38 ng/mL, $p = 0.03$). There were no significant differences between serum troponin concentrations in the EVAC group and control group at any time point. While the mean serum troponin concentration was not different in the REBOA group compared with the EVAC group at Time 150 (2.80 ± 2.33 ng/mL vs. 0.91 ± 1.00 ng/mL, $p = 0.13$), it was significantly higher at the end of the study (6.26 ± 5.35 ng/mL vs. 0.92 ± 0.61 ng/mL, $p = 0.05$).

Subendocardial hemorrhage was noted grossly in animals from all groups (Fig. 4A). On microscopic pathological examination (Fig. 4B), cardiac intramural hemorrhage scores were higher in the REBOA group compared to the control group (1.67 ± 0.46 vs. 0.17 ± 0.18, $p = 0.03$). A similar trend was observed between the EVAC and control groups (1.50 ± 0.47 vs. 0.17 ± 0.18, $p = 0.06$), but the comparison did not reach statistical significance.

DISCUSSION

This study characterizes the effects of REBOA and EVAC on the heart. We have demonstrated that in a swine model of hemorrhagic shock, REBOA results in myocardial injury while CO and EF are preserved. Furthermore, we have established that by permitting carefully titrated flow past the aortic balloon with EVAC, cardiac injury is mitigated while cardiac performance is enhanced.

Resuscitative endovascular balloon occlusion of the aorta can not only arrest hemorrhage, but also augment perfusion of the heart for a hypovolemic trauma patient *in extremis*. While REBOA can salvage moribund patients with immediate hemodynamic support, the unintended sequelae of REBOA can quickly make the therapy as morbid as the inciting injury. Traditionally, the ischemic injury to tissues beds distal to the point of occlusion has been thought to be the most critical side effect. However, recent reports suggest a dose-dependent relationship between AO and cardiac injury. While this study further emphasized the potential for proximal deleterious effects due to REBOA, a lack of a control group made it difficult to determine the contribution that the underlying shock state had on the myocardial injury.[10] We have demonstrated that in a swine model of

TABLE 2. Cardiac Function of Animals in the Zone 1 REBOA, Zone 1 EVAC, and Control Groups

	Control Group (n = 6)	Zone 1 REBOA Group (n = 6)	Zone 1 EVAC Group (n = 6)	*p*
CO				
At end hemorrhage, L/min	4.3 ± 2.4	4.8 ± 2.0	5.0 ± 1.4	0.93
At end intervention, L/min	8.2 ± 2.1	11.3 ± 5.1	6.7 ± 2.8	0.11
End of study, L/min	6.8 ± 6	11.2 ± 6.5	7.1 ± 3	0.37
EF				
At end hemorrhage, %	52 ± 11	49 ± 12	58 ± 8	0.93
At end intervention, %	57 ± 5	49 ± 12	46 ± 9	0.14
End of study, %	45 ± 11	58 ± 15	52 ± 12	0.13
ESPVR				
Baseline	1.03 (0.87–1.11)	0.81 (0.68–1.33)	1.13 (0.90–1.50)	0.50
Time 74 min	1.85 (1.31–2.11)	2.73 (1.79–3.59)	2.45 (2.42–3.41)	0.08
End of study	1.09 (0.74–2.02)	1.39 (0.93–2.29)	2.04 (1.55–4.08)	0.28
PRSW				
Baseline	44.4 (42.0–62.6)	49.1 (42.1–56.4)	51.8 (40.1–63.7)	0.85
Time 74 min	67.1 (62.7–87.9)	111.2 (102.5–148.6)	116.7 (116.6–141.4)	0.04
End of study	65.8 (41.9–80.2)	66.0 (38.8–77.1)	105.3 (84.0–119.5)	0.01

Parametric data presented as mean ± standard deviation and nonparametric data presented as median (interquartile range).

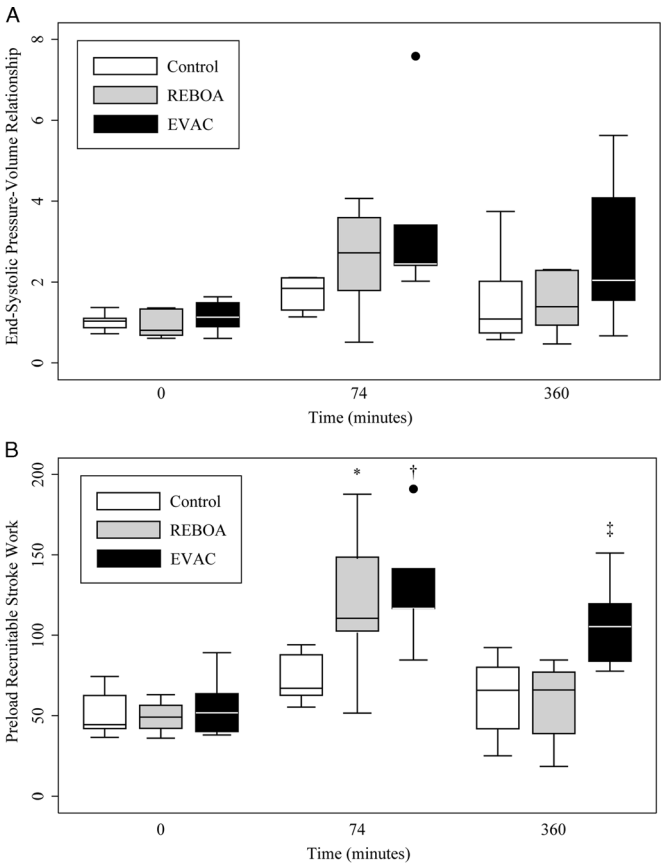

Figure 2. Comparison of the ESPVR (*A*) and PRSW (*B*) over time between Zone 1 REBOA, Zone 1 EVAC, and control groups. The horizontal line within each box defines the median value; upper and lower limits of each box denote the interquartile range. Whiskers delineate the 5% to 95% range. Individual data points outside of this range are plotted as individual circles. * REBOA vs. control, $p = 0.02$; † EVAC vs. control, $p < 0.01$; ‡ EVAC vs. REBOA, $p < 0.01$, and EVAC vs. control, $p < 0.01$.

hypovolemic shock, there is minimal myocardial damage, and that the damage to the heart is primarily due to the effects of REBOA. More importantly, we have demonstrated that this cardiac damage can be mitigated using partial occlusion strategies like EVAC.

The typical surge in both proximal arterial pressure and heart rate from REBOA is well described. However, the effects of REBOA on cardiac physiology are less clear. Swine studies using a PAC during REBOA have reported increased CO during intervention.[14,25] Canine studies have demonstrated a transient increase in CO during AO following hypertonic saline infusion, but not during AO alone.[26] In previous experiments, our lab has observed considerable variability and inconsistency with the CO and EF data derived from PAC measurements during REBOA (unpublished data). Recognition of the limitations of PAC-derived measurements in the setting of AO has led to our use of a PV loop catheter in the present study. Left ventricular preload reduction via vena cava occlusion allows the acquisition of PV measurements at consecutively decreased preload states and end-diastolic pressures.[27,30] This enables the calculation of the ESPVR and PRSW, which are preload-independent indices of cardiac contractility. Notably, PRSW is less influenced by changes in afterload.[27,35] This may explain why the PRSW was elevated during the intervention phases of EVAC and REBOA despite similar ESPVR. While this increase in intrinsic contractility may partly result from a rise in circulating catecholamines during hemorrhage, as evidenced by the small increase in PRSW in the control group over time, the differences are driven primarily by AO. The dramatic increase in afterload during AO is coupled with increased PRSW and a substantial increase in CO, creating a myocardial strain analogous to hypertensive urgency observed clinically. Following balloon deflation, the heart must then compensate for the effects of the ischemia reperfusion injury (vasodilation, loss of systemic vascular resistance, systemic hypotension) by maintaining a high CO at the expense of cardiac efficiency. In contrast, partial occlusion with EVAC appears to place less strain on the heart during intervention. Less strain, coupled with less ischemia reperfusion injury, resulted in improved cardiac efficiency during the critical care phase with higher PRSW at the end of the experiment.

Recent large animal studies have demonstrated the negative consequences of REBOA on the heart with rising troponin concentrations over long occlusion times.[10] The present study builds on this recent report by providing direct measurements of cardiac performance during REBOA and its aftermath as the heart compensates for the profound ischemia reperfusion injury. The present study is also the first to demonstrate the benefit of partial aortic flow strategies like EVAC to improve cardiac function and mitigate the direct cardiac damage. With the increasing use of REBOA for trauma resuscitation and a variety of nontraumatic hemorrhage control indications, the age of AO recipients is likely to increase.[21] The need to balance effective hemorrhage control while mitigating the negative effects of AO will be the key characteristic of any successful next-generation REBOA-like technology. We have demonstrated that EVAC, in which automated balloon deflation allows partial flow, effectively mitigates the negative consequences of REBOA on the heart, but

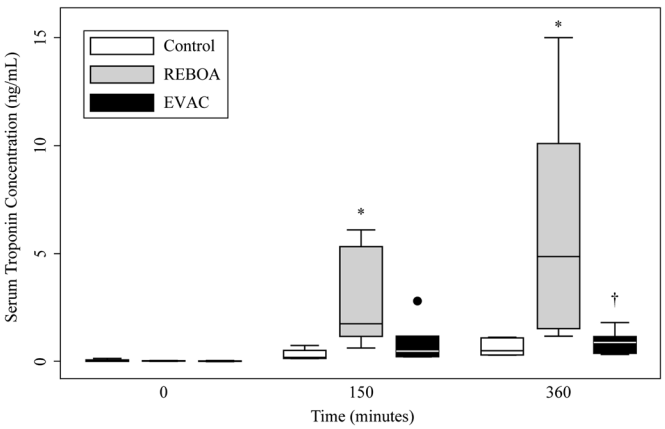

Figure 3. Comparison of serum troponin concentration over time between Zone 1 REBOA, Zone 1 EVAC, and control groups. The horizontal line within each box defines the median value; upper and lower limits of each box denote the interquartile range. Whiskers delineate the 5% to 95% range. Individual data points outside of this range are plotted as individual circles. * REBOA vs. control, $p = 0.03$; † EVAC vs. REBOA, $p = 0.05$.

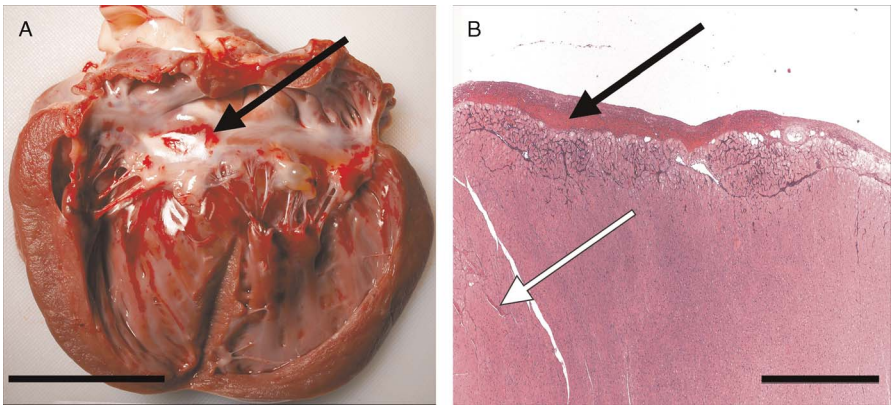

Figure 4. Representative images of heart with subendocardial hemorrhage (black arrows). Gross specimen (*A*), scale bar = 5 cm. Histological section (*B*) also shows intramural hemorrhage (white arrow), hematoxylin & eosin stain, 4×. Scale bar = 1 mm.

alternative techniques as well as pharmacologic adjuncts need to be explored.

Nevertheless, the dynamic and chaotic nature of trauma resuscitation has prevented any detailed description of the cardiac effects of REBOA in clinical situations. As such, it is difficult to make direct comparisons between these experimental observations and human physiology. Broader generalizations are further limited by the fact that clinical use of REBOA is often in the setting of cardiac arrest and active cardiopulmonary resuscitation. In these settings, the potential benefits of improved coronary artery filling and cerebral perfusion take priority over potential future cardiac strain. Still, a recent series of REBOA for nontraumatic hemorrhage reported no post-REBOA myocardial infarction in a cohort of patients with a mean age of 55 who presented in shock or cardiac arrest.[24]

This study is subject to the inherent limitations present in any large animal translational study. As this work was specifically focused on cardiac performance, we did not include an injury with ongoing uncontrolled hemorrhage in this model. By using a controlled hemorrhage model instead of an uncontrolled injury model, the control group could survive without an endovascular intervention for comparison with the REBOA and EVAC groups. However, the physiologic effects of partial occlusion with respect to cardiac function in the setting of ongoing hemorrhage cannot be extrapolated from the present study and warrant further investigation. Additionally, REBOA and EVAC therapies result in different degrees of physiologic derangement to the entire animal, thereby resulting in different vasopressor and fluid requirements, which my impact cardiac performance across groups. Furthermore, due to logistical constraints, there was only limited whole blood available for transfusion prior to the use of crystalloid fluids, which may not reflect current resuscitation strategies. While the vasopressor and fluid amounts were dramatically different and do have implications for cardiac physiology, these resuscitation requirements are reflective of the overall health of the REBOA group during the critical care phase. To not provide systemic cardiovascular support with fluids and vasopressors would have resulted in a negative biasing of the sicker REBOA group and would have been even less reflective of standard clinical practice. Additionally, the anatomic evidence of cardiac injury was only available for comparison at necropsy. Without multiple time points, it is difficult to ascertain whether the cardiac injury was a result of a heart overburdened by compensatory hypotension and ischemia-reperfusion injury during critical care, directly from the high afterload of REBOA, or a combination of the two. Furthermore, the animals used in this study were young healthy animals without preexisting cardiac disease. It is difficult to predict how REBOA may affect cardiac performance in older patients with underlying cardiac disease. Finally, the natural progression of troponin increases following myocardial injury is normally delayed, first becoming detectable hours after injury but not peaking until 24 hours.[39] The large rise in troponin observed 4 hours after REBOA may indicate an even more extensive injury than we were able to document, and the limited duration of the study prohibited further understanding of the true troponin profile and peak.

In a swine model of hemorrhagic shock, we have demonstrated that complete AO results in evidence of cardiac injury without a direct decrease in cardiac performance. EVAC, a method of partial occlusion, mitigated the cardiac injury and improved cardiac contractility following resuscitation. Further work on next-generation REBOA technologies and pharmacologic adjuncts is needed to ameliorate cardiac strain for the increasingly heterogeneous patient population that may benefit from AO techniques.

AUTHORSHIP

C.A.B., G.L.H., E.M.T., J.K.G., T.K.W., and M.A.J. conceived the study. All authors designed the study and acquired the data. C.A.B., G.L.H., E.M.T., J.K.G., and M.A.J. analyzed and interpreted the data. C.A.B., E.M.T., L.P.N., and M.A.J. drafted the article. All authors critically revised the article and approved it for publication.

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DISCLOSURE

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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, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the University of California Davis, or Wake Forest University.

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