Extending the golden hour: Partial resuscitative endovascular balloon occlusion of the aorta in a highly lethal swine liver injury model

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BACKGROUND: Combat-injured patients may require rapid and sustained support during transport; however, the prolonged aortic occlusion produced by conventional resuscitative endovascular balloon occlusion of the aorta (REBOA) may lead to substantial morbidity. Partial REBOA (P-REBOA) may permit longer periods of occlusion by allowing some degree of distal perfusion. However, the ability of this procedure to limit exsanguination is unclear. We evaluated the impact of P-REBOA on immediate survival and ongoing hemorrhage in a highly lethal swine liver injury model.

METHODS: Fifteen Yorkshire-cross swine were anesthetized, instrumented, splenectomized, and subjected to rapid 10% total blood loss followed by 30% liver amputation. Coagulopathy was created through colloid hemodilution. Randomized swine received no intervention (control), P-REBOA, or complete REBOA (C-REBOA). Central mean arterial pressure (cMAP), carotid blood flow, and blood loss were recorded. Balloons remained inflated in the P-REBOA and C-REBOA groups for 90 minutes followed by graded deflation. The study ended at 180 minutes from onset of hemorrhage or death of the animal. Survival analysis was performed, and data were analyzed using repeated-measures analysis of variance with post hoc pairwise comparisons.

RESULTS: Mean survival times in the control, P-REBOA, and C-REBOA groups were, 25 ± 21, 86 ± 40, and 163 ± 20 minutes, respectively ($p < 0.001$). Blood loss was greater in the P-REBOA group than the C-REBOA or control groups, but this difference was not significant (4,722 ± 224, 3,834 ± 319, 3,818 ± 37 mL, respectively, $p = 0.10$). P-REBOA resulted in maintenance of near-baseline carotid blood flow and cMAP, while C-REBOA generated extreme cMAP and prolonged supraphysiologic carotid blood flow. Both experimental groups experienced profound decreases in cMAP following balloon deflation.

CONCLUSION: In the setting of severe ongoing hemorrhage, P-REBOA increased survival time beyond the golden hour while maintaining cMAP and carotid flow at physiologic levels. (*J Trauma Acute Care Surg.* 2016;80: 372–380.

KEY WORDS: Trauma; endovascular; resuscitation; intra-aortic balloon; swine.

Hemorrhage on the battlefield is the leading cause of death among US service members who have potentially survivable injuries.[1–3] In recent conflicts, treatment initiated within 60 minutes has been associated with reduced mortality.[4] Despite this success, the inherent difficulty achieving the "golden hour" benchmark in remote environments has led to a NATO standard transport time of 90 minutes.[5] These prolonged transport times will require initiation of resuscitative strategies earlier after injury and the duration of intervention to be extended beyond the golden hour.[6] Resuscitative endovascular balloon occlusion of the aorta (REBOA) has emerged as a less invasive alternative to thoracotomy with aortic cross-clamping and can be used proactively before hemodynamic collapse, potentially in the prehospital setting.[7–10] Emerging clinical data on the use of REBOA report successful 30-day survival following brief periods of aortic occlusion (20–40 minutes); however, longer periods of aortic occlusion are associated with significantly increased mortality.[8–12]

REBOA confers a short-term survival advantage by preventing exsanguination and augmenting perfusion of the heart, lungs, and brain.[7,9,13] However, experimental observation suggests that REBOA causes supraphysiologic increases in central mean arterial pressure (cMAP).[14,15] The resultant high aortic afterload may cause myocardial dysfunction, adult respiratory distress syndrome, and exacerbation of traumatic brain injury.[16–19] Furthermore, eventual weaning from aortic occlusion via balloon deflation results in the rapid loss of aortic afterload, release of toxic

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

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metabolites from ischemic tissues, and redistribution of circulating blood volume.[7] Taken together, these effects can make weaning from complete occlusion challenging if not impossible.[7] Ischemia-reperfusion injury is also responsible for the high morbidity associated with REBOA therapy, leading to multiple-organ dysfunction and poor outcomes after relatively short periods of occlusion.[8,20] As efforts to use REBOA in early trauma resuscitation progress, finding solutions to overcome the deleterious side effects of extended intervention is paramount.[5]

One potential strategy to minimize the consequences of sustained aortic occlusion is to preserve limited distal aortic flow with an endovascular device. This concept of partial REBOA (P-REBOA) could augment cMAP and cerebral perfusion without inducing significant distal ischemia and this attenuated aortic flow may lessen hypotension during weaning from aortic occlusion.[21–23] In addition, decreased distal pressure and flow may result in diminution or cessation of distal hemorrhage through the promotion of clot formation and stabilization. Despite the potential benefits of P-REBOA, rapid exsanguination may occur with anything less than complete aortic occlusion in the setting of noncompressible truncal hemorrhage. The objective of this study was to examine the feasibility and effectiveness of sustained P-REBOA compared with complete REBOA (C-REBOA) in a porcine model of lethal hemorrhagic shock. In addition, this investigation aimed to characterize the impact of P-REBOA compared with C-REBOA on cMAP, distal hemorrhage, and markers of ischemia-reperfusion injury.

MATERIALS AND 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 Association for the Assessment and Accreditation of Laboratory Animal Care International. Healthy adult, castrate male and nonpregnant female Yorkshire-cross swine (*Sus scrofa*), obtained from the University of California, Davis, were acclimated for a minimum of 7 days. At the time of experimentation, animals weighed between 72 kg and 90 kg, with an age between 5 months and 7 months.

Conduct of the protocol, including animal preparation, injury, intervention, damage-control surgery, and postoperative observation are depicted Figure 1.

Animal Preparation

Animals were premedicated with 6.6-mg/kg tiletamine/zolazepam (TELAZOL, Fort Dodge Animal Health, Fort Dodge, IA) intramuscularly. Following isoflurane induction and endotracheal intubation, maintenance anesthesia consisted of 2% isoflurane in 100% oxygen. To overcome the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine (0.01 μg/kg/h) was initiated. Animals were mechanically ventilated with tidal volumes of 7 mL/kg to 10 mL/kg and a respiratory rate of 10 breaths per minute to 15 breaths per minute sufficient to maintain end-tidal CO_2 at 40 ± 5 mm Hg. The animals were placed on a warming blanket set at 39°C to minimize hypothermia.

Bilateral carotid arteries, bilateral femoral arteries, and the left brachial artery were exposed. Arterial access was obtained for blood collection and hemodynamic monitoring and to facilitate endovascular intervention. Proximal aortic pressure was measured via a 6 Fr 30-cm introducer sheath (Super Sheath, Boston Scientific Corporation, Natick, MA) inserted in the left common carotid artery, with the tip positioned under fluoroscopic guidance at the level of the proximal descending thoracic aorta to measure cMAP. A 4-mm perivascular Doppler flow probe (Transonic Corporation, Ithaca, NY) was secured around the right common carotid artery to monitor cerebral blood flow. Distal aortic pressure was similarly obtained via a 7 Fr 30-cm introducer sheath (Super Sheath) inserted retrograde via the right femoral artery, with the tip residing within the infrarenal abdominal aorta. A 7 Fr 13-cm sheath was inserted retrograde into the left brachial artery (Super Sheath) to enable controlled hemorrhage and arterial access for blood collection. In addition, a 12 Fr 13-cm introducer sheath (Cook Incorporated, Bloomington, IN) was inserted retrograde into the left femoral artery, through which the occlusion balloon catheter was introduced.

Concurrently, a laparotomy was performed through which a splenectomy was completed to minimize hemodynamic variation from autotransfusion. Normal saline was then administered at a rate of 10 mL/kg per hour.

Injury

Procedural blood loss was quantified, and additional blood was removed to standardize preinjury blood loss at 10% of the total circulating blood volume (6.6 mL/kg) over 5 minutes. The liver was marked along the planned transection plane, 2 cm to the left of Cantlie's line, to provide amputation of approximately 80% of the left lateral lobe of the liver and 40% of the left medial lobe of the liver (approximately 30% of the total liver volume) similar to previous descriptions.[11] The swine were then assigned via a block randomization scheme to no intervention (controls), P-REBOA, or C-REBOA. One minute following the completion of controlled blood removal, the liver was sharply transected, and the abdomen was rapidly closed. Intervention in the P-REBOA and C-REBOA groups was achieved 2 minutes following the initiation of injury. Beginning 15 minutes after injury, severe dilutional coagulopathy was created by the rapid infusion of 21-mL/kg hetastarch solution (Hextend, BioTime, Inc., Berkley, CA).

Intervention

Control animals had a femoral sheath in place, but no balloon catheter. To provide adequate aortic flow attenuation, P-REBOA was performed using a noncompliant 14 × 80-mm balloon catheter (Armada, Abbott Laboratories Vascular Enterprises, Beringen, Switzerland). The balloon was advanced over a stiff guide wire into the descending thoracic aorta, and its position was confirmed with fluoroscopy. Proximal to distal mean aortic pressure gradient was calculated in real time, which served as surrogate marker for the degree of aortic occlusion. The balloon was then maximally inflated for 10 minutes with the intent of achieving full aortic occlusion for initial clot formation and stabilization, after which the balloon was gradually deflated using a standard rotational inflation device (Encore Advantage Kit, Boston Scientific Corporation, Natick, MA),

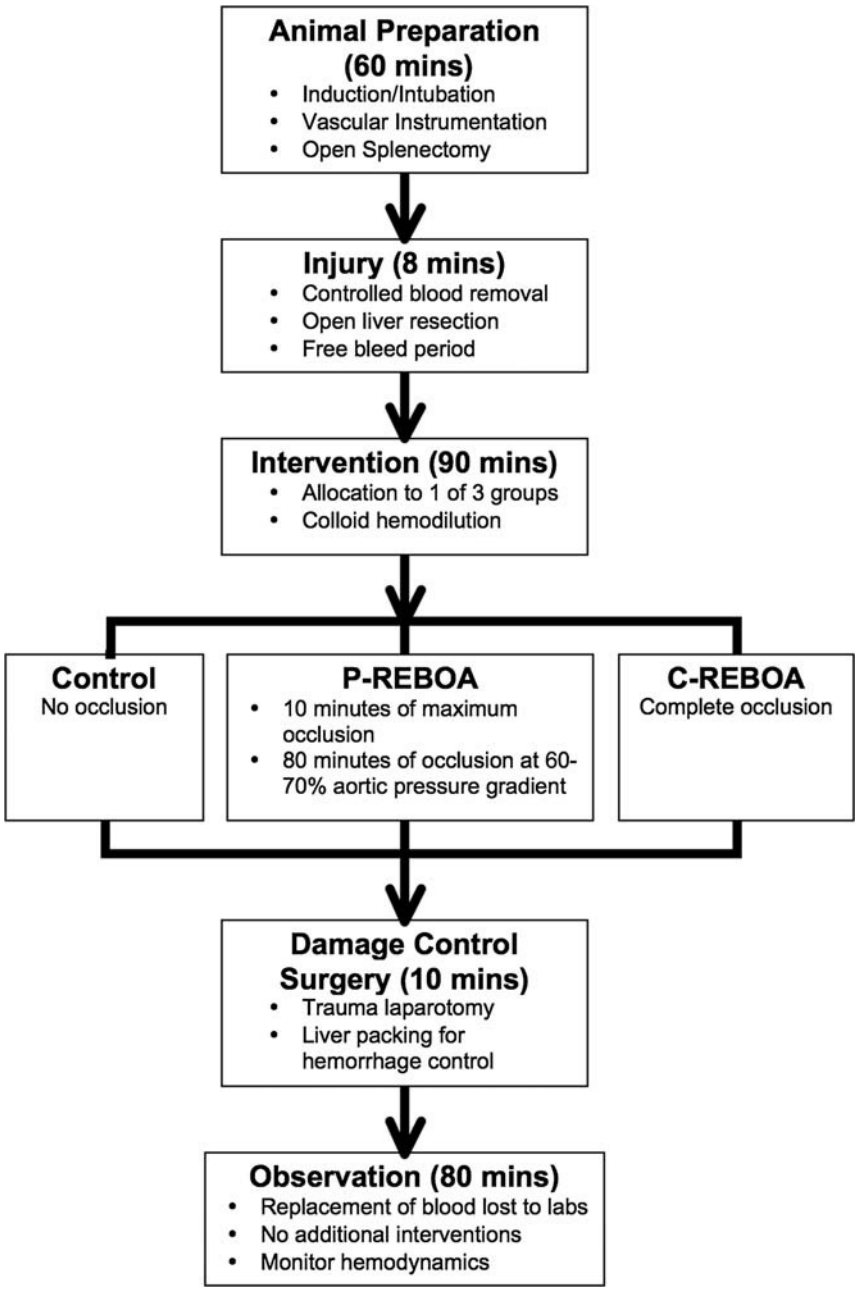

Figure 1. Experimental design.

with the aim to achieve a gradually tapering 60% to 70% pressure gradient over the intervention phase. C-REBOA was achieved via a standard aortic occlusion catheter (CODA, Cook Medical, Bloomington, IN) inflated until the distal aortic wave form was extinguished. Each intervention was sustained for 90 minutes or until the animal expired. At 90 minutes, the abdomen was opened, the liver was packed, and balloons in the P-REBOA and C-REBOA groups were slowly deflated over 2 minutes until distal flow was completely restored and the pressure gradient across the balloons was lost. Autologous arterial blood collected during the controlled hemorrhage portion of the injury phase was used for limited blood transfusion. At the conclusion of the 10-minute damage-control surgery phase, blood was transfused up to a maximum of 3 mL/kg to replace the volume of blood lost to laboratory collection during the first 90 minutes. Animals were then observed for an additional 80 minutes before being euthanized at 180 minutes or until death. The time of death was defined a priori as the moment at which cMAP first fell to less than 20 mm Hg.[12]

Data Collection

Physiologic data, including proximal and distal aortic pressures, heart rate, core body temperature, right carotid artery blood flow, and ECG monitoring, were continuously captured

throughout the experiment using a multichannel data acquisition system (MP150, Biopac Systems Incorporated, Goleta, CA).

Complete blood counts and coagulation studies were performed at baseline and then every 30 minutes until the end of the study. At the conclusion of the study, intra-abdominal blood loss was quantified by weighing intra-abdominal laparotomy pads and blood suctioned from the abdomen in preweighed canisters. All animals underwent necropsy with samples from hind limb adductor muscles, duodenum, ileum, colon, kidneys, myocardium, liver, and lumbar spinal cord. Specimens were preserved in 10% buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for histopathologic evaluation of changes associated with ischemia and inflammation by a pathologist blinded to the interventions.

Data Analysis

Data are presented as means and SEMs, unless otherwise specified, and were analyzed using repeated measures-analysis of variance with post hoc pairwise comparisons, when indicated. Kaplan-Meier survival analysis was performed. All calculations were completed using STATA version 13.0 (Stata Corporation, Bryan, TX). Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics were not significantly different between the groups (Table 1). Without intervention, the liver injuries were rapidly lethal. Mean survival times in the control, P-REBOA, and C-REBOA groups were 25 ± 21, 86 ± 40, and 163 ± 20 minutes, respectively ($p < 0.001$) (Fig. 2). In the face of continued hemorrhage, P-REBOA resulted in maintenance of near-baseline cMAP and carotid blood flow, while C-REBOA generated proximal hypertension and carotid blood flow much higher than baseline through 90 minutes (Figs. 3 and 4, respectively). Blood loss was greater in the P-REBOA group than either in the C-REBOA or in the control groups, but this difference was not significant (4,722 ± 224, 3,834 ± 319, 3,818 ± 37 mL, respectively; $p = 0.10$). Hemoglobin and platelet levels were significantly lower in the P-REBOA group than in the C-REBOA group at the end of the study (Table 2). Because of profound hemodilution, concentrations of laboratory markers of ischemia and inflammation were below the limit of detection. Both experimental groups experienced profound decreases in cMAP following balloon deflation at 90 minutes (Fig. 3).

During the initial 10-minute period of maximal balloon inflation in the P-REBOA group, proximal to distal aortic mean

TABLE 1. Baseline Physiology and Hematology Parameters by Treatment Group

Value	C-REBOA	P-REBOA	Control	*p*
Body weight, kg	78.0 ± 1.0	78.8 ± 3.4	81.8 ± 2.8	0.57
Sex, male-female	3:2	5:0	5:0	0.10
Temperature, °C	37.0 ± 0.2	37.1 ± 0.2	36.7 ± 0.3	0.53
Preoperative blood loss, mL/kg	106 ± 57	23 ± 6	41 ± 10	0.23
Controlled hemorrhage, mL	409 ± 52	497 ± 26	499 ± 22	0.17
Preparation time, min	67.8 ± 4.4	67.2 ± 4.7	62.4 ± 5.5	0.70
Spleen weight, g	692 ± 63	871 ± 111	750 ± 108	0.43
Heart rate, beats/min	67.3 ± 5.6	73.2 ± 4.6	91.5 ± 6.2	0.02
cMAP, mm Hg	71.7 ± 3.2	68.4 ± 5.6	65.8 ± 6.3	0.80
WBC, $\times 10^9$/L	14.3 ± 1.9	17.6 ± 0.2	14.9 ± 2.5	0.45
Hemoglobin, g/dL	10.7 ± 0.5	10.9 ± 0.3	11.6 ± 0.2	0.17
Platelets, $\times 10^9$/L	215 ± 32	240 ± 48	237 ± 13	0.77
Lactate, mmol/L	1.7 ± 0.4	1.2 ± 0.2	1.7 ± 0.2	0.42
pH	7.49 ± 0.02	7.50 ± 0.02	7.46 ± 0.03	0.36
Total protein, g/dL	5.5 ± 0.2	5.5 ± 0.1	5.3 ± 0.2	0.59
Liver injury characteristics				
Resection volume, %	28 ± 2	24 ± 2	31 ± 3	0.14
Cut surface area, cm^2	68.1 ± 4.0	79.2 ± 6.3	74.2 ± 4.9	0.35
Normalized resection weight, % total body weight	0.44 ± 0.04	0.36 ± 0.01	0.46 ± 0.04	0.09
Blood lost by EOS, mL	3,834 ± 319	4,722 ± 224	3,818 ± 37	0.10

All groups n = 5. Values are means ± SEM except for sex, which is presented as a ratio.
EOS, end of study; WBC, white blood cell count.

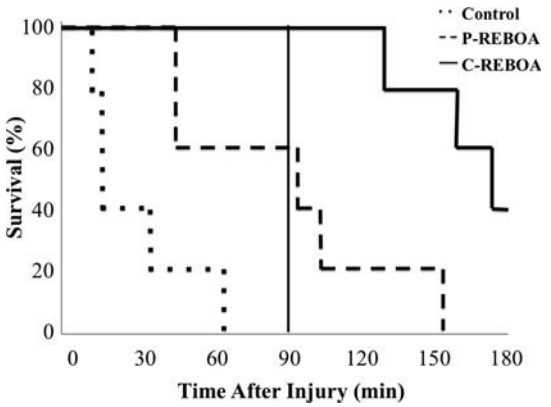

Figure 2. Kaplan-Meier analysis demonstrating time to death for control, P-REBOA, and C-REBOA groups. Time of balloon deflation marked with *vertical line*.

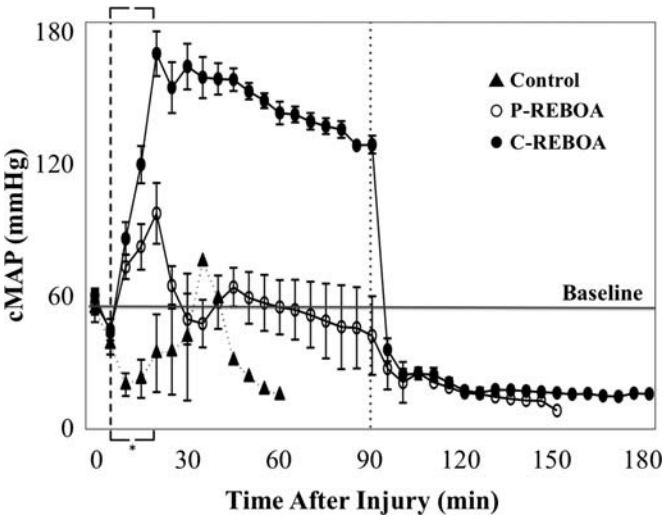

Figure 3. cMAP over time, as measured in the proximal aorta, for control, P-REBOA, and C-REBOA groups. Time of balloon inflation marked with *dashed line*. Time of balloon deflation marked with *dotted line*. *Asterisk* indicates initial period of maximum occlusion for the P-REBOA group.

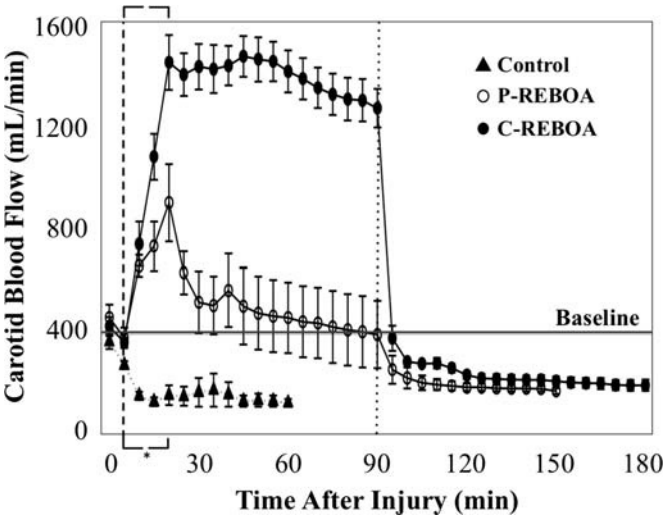

Figure 4. Carotid blood flow over time for control, P-REBOA, and C-REBOA groups. Time of balloon inflation marked with *dashed line*. Time of balloon deflation marked with *dotted line*. *Asterisk* indicates initial period of maximum occlusion for P-REBOA group.

arterial pressure gradients was maintained between 73% and 80% in all animals. Following the initial period of maximum occlusion, the aortic pressure gradient across the P-REBOA balloon steadily declined (77–50%) as cMAP declined during the course of the experiment until the time of balloon deflation at 90 minutes.

Histologic analysis failed to reveal any differences in the amount of ischemia in any of the collected tissues. Duodenal mucosal height loss with areas of necrosis was present in all animals across all groups. Half of the animals in each group demonstrated subendocardial hypereosinophilia, multifocal acute tubular necrosis, and hepatic sinusoidal congestion. One animal from each group demonstrated partially denuded ileum and colon. No animals demonstrated ischemic change in the lower extremity skeletal muscles or in the spinal cord at any level.

DISCUSSION

As clinical experience with REBOA grows, the detrimental consequences of sustained aortic occlusion are increasingly recognized.[8,14,15,20,24] Novel strategies to preserve cMAP while minimizing distal ischemia are necessary to overcome these limitations. This study examined P-REBOA as one such alternative in a trauma model of uncontrolled hemorrhage. P-REBOA was able to extend survival beyond the golden hour in a highly lethal injury while preserving cMAP and carotid flow closer to baseline compared with C-REBOA in a swine model.

While such a lethal liver injury is likely nonsurvivable in an austere prehospital setting, this model highlights the feasibility of P-REBOA under extreme conditions. Even in the setting of severe dilutional coagulopathy, P-REBOA delayed exsanguination in these severely injured animals beyond the golden hour, with the majority surviving past the average military transport time of 90 minutes.[5] While a statistically significant difference in blood loss between the groups was not detected, the trend toward more blood loss in the P-REBOA group was of clinical significance. The P-REBOA group had a larger volume of intra-abdominal hemorrhage than the control group; however, P-REBOA still resulted in improved survival despite the absence of resuscitation with blood products. This increased survival despite increased blood loss may reflect a slower, more physiologically tolerable rate of hemorrhage compared with controls. The C-REBOA group lost nearly a liter less blood than the P-REBOA group, which may contribute to the increased survival of the C-REBOA group at 90 minutes compared with the P-REBOA or control animals. The ability of C-REBOA to stem hemorrhage may confer a short-term survival benefit when compared with P-REBOA applied in the setting of coagulopathy without additional resuscitative measures such as blood transfusion. In a clinical scenario, larger hemorrhage volumes might be expected with P-REBOA compared with C-REBOA and may be an important consideration in austere environments where blood products are limited. However, this theoretical constraint would need to be weighed against the time-limited intervention afforded by C-REBOA.

In this study, cMAP in the C-REBOA group increased to nearly triple baseline. Existing literature suggests central hypertension created by complete aortic occlusion may result in myocardial dysfunction, pulmonary edema, and adult respiratory distress syndrome.[17–19] This acute increase in aortic afterload has been demonstrated to adversely affect myocardial oxygen

TABLE 2. Comparison of Physiologic Parameters and Laboratory Values From Baseline to End of Intervention at 90 Minutes for C-REBOA and P-REBOA Groups

Values	C-REBOA			P-REBOA			90-min Treatment Comparison**
	Baseline	90 min	p*	Baseline	90 min	p*	
Heart rate, beats/min	67.3 ± 5.6	146.1 ± 4.9	<0.01	73.2 ± 4.6	125.6 ± 13.4	<0.01	NV
Temperature, °C	37.0 ± 0.2	37.0 ± 0.4	0.96	37.1 ± 0.2	37.2 ± 0.3	0.83	NV
Hemoglobin, g/dL	10.7 ± 0.5	5.5 ± 0.4	<0.01	10.9 ± 0.3	2.5 ± 0.5	<0.01	0.01
WBC, $\times 10^9$/L	14.3 ± 1.9	7.5 ± 1.2	<0.01	17.6 ± 0.7	6.8 ± 1.1	<0.01	0.45
Platelets, $\times 10^9$/L	216 ± 32	131 ± 12	<0.01	240 ± 28	75 ± 18	<0.01	0.06
aPTT	9.8 ± 0.5	13.3 ± 0.8	0.08	10.9 ± 0.5	9.6 ± 6.4	0.14	0.31
PT	10.2 ± 0.3	13.2 ± 1.3	0.04	10.3 ± 0.1	16.4 ± 3.2	0.05	0.20
Fibrinogen	27.6 ± 2.0	UD	NV	27.8 ± 2.5	UD	NV	NV

*t test test comparing baseline value to value at 90 minutes.
**t test comparing C-REBOA to P-REBOA at 90 minutes.
All groups n = 5, values are means ± SEM.
aPTT, activated partial thromboplastin time; NV, no value; PT, prothrombin time; UD, undetectable; WBC, white blood cells.

supply-demand ratio, resulting in myocardial dysfunction and loss of cardiac contractility.[18] Increased pressure in the pulmonary vasculature, in combination with inflammatory injury from ischemia-reperfusion, results in respiratory failure in up to 26% of patients following thoracoabdominal aneurysm repair.[17,25] This association with increased pulmonary dysfunction is particularly relevant in the military setting, where blast injury is the most common mechanism of noncompressible torso hemorrhage and is frequently associated with concomitant injuries, specifically pulmonary and brain injury.[26,27] The increased cMAP in the C-REBOA group in this study correlates with a dramatic increase in carotid blood flow to nearly three times baseline levels. These findings are consistent with other studies noting that C-REBOA dramatically increases cMAP, carotid flow, and cerebral perfusion. Increased cerebral perfusion pressures could increase intracranial pressure and worsen outcomes in the setting of traumatic brain injury.[28,29] Preserving cMAP closer to baseline levels during intervention may reduce injuries to proximal tissue beds that result from exposure to excessively high pressure and high blood flow and may reduce the inflammatory burden associated with these injuries.

The P-REBOA group demonstrated augmentation of cMAP and carotid flow to near-baseline levels throughout the intervention phase, consistent with findings of other studies examining the effects of partial aortic occlusion on cerebral perfusion.[21] While the P-REBOA group had a decline in cMAP over time because of ongoing blood loss without replacement, carotid blood flow was still preserved at the 90-minute mark. Research in the setting of acute cerebrovascular stroke has demonstrated that a mild increase in cMAP and carotid flow from partial aortic occlusion augments cerebral perfusion in the ischemic penumbra without increasing the risk of expanding intracerebral hemorrhage.[30–32] This effect is noted even in stroke patients treated with thrombolytics.[32] These findings suggest that P-REBOA may confer benefits over C-REBOA in the context of brain-injured patients. While this study was not designed to specifically address the impact of REBOA on proximal organ injury, the implication that P-REBOA may mitigate further injury resulting from excessive cMAP and carotid flow warrants further study.

To determine if P-REBOA can extend survival beyond the golden hour, a severe liver injury model with arterial and venous bleeding, extreme coagulopathy, and negligible resuscitation was chosen. This design allowed for direct comparison of P-REBOA and C-REBOA on the end points of survival and blood loss while minimizing confounders introduced during resuscitation, such as variability in the use of vasopressors, fluid volume, and blood transfusion. However, with inadequate hemostasis, severe coagulopathy, and insufficient resuscitation, cMAP plummeted following balloon deflation in both the P-REBOA and C-REBOA groups, leading to nonsurvivable declines in cMAP and the rapid death of several animals. The short duration of the study limited the evaluation of the impact of ischemia-reperfusion injury after balloon deflation. Furthermore, the aggressive hemodilution protocol inhibited evaluation of laboratory markers of ischemia and inflammation and prevented any meaningful conclusions regarding hemostasis and clot stabilization to be drawn. Because the aim of evaluating markers of ischemia-reperfusion injury was not achieved, the impact of P-REBOA on end-organ ischemia will be addressed in future iterations of this study.

Attempts to generate consistent partial aortic occlusion with standard aortic occlusion balloons such as the CODA balloon catheter proved unsuccessful during model development for this study. The conformation of a compliant balloon upon deflation results in a very short length of apposition to the aortic wall, which inhibits precise control of distal aortic flow. A more favorable geometry is that of a noncompliant balloon catheter as is typically used for angioplasty. The long cylindrical conformation of these balloons can oppose the aortic wall over the entire working length of the balloon. Because resistance to flow is a direct function of length, these balloons afford increased fidelity for achieving a desired pressure gradient. For these reasons, a long noncompliant balloon catheter was used to achieve partial aortic occlusion for this study.

While this strategy has proven effective experimentally to consistently maintain a desired pressure gradient, it requires that the catheter be sized to the native aortic diameter, as noncompliant balloons have a narrow working diameter range. Given the dynamic nature of the aorta, it was difficult to achieve sustained full aortic occlusion with these balloons, as aortic diameter increases in response to increased proximal pressure, allowing blood to flow around the balloon. This early reestablishment of distal aortic flow is evidenced by the disparate proximal aortic pressures in the P-REBOA and C-REBOA groups during the period immediately following liver injury. In addition, early return of pulsatile pressure wave forms was observed in the partial group despite full balloon inflation, which was not seen in the complete arm. This may account for further inhibition of clot stabilization, leading to ongoing hemorrhage throughout the intervention period. Based on these limitations, this experimental model for achieving partial aortic occlusion with noncompliant balloon architecture lacks clinical applicability.

A brief period (approximately 15–20 minutes) of complete aortic occlusion may be necessary to establish clot stabilization before reinstating distal flow; however, the experimental design of the present study did not permit evaluation of this theory. Current device technology is insufficient to achieve precise control across the full range of aortic occlusion to provide gradated flow restoration. This limitation also highlights the problem of controlling distal blood flow when there is no accurate way to measure distal blood flow. The measurement of distal flow will be of importance in future iterations of the partial aortic occlusion concept. The ability to control distal aortic flow to variable degrees will require new study techniques and, ultimately, innovation in catheter design.

In this study of highly lethal uncontrolled hemorrhage in swine, P-REBOA proved effective at maintaining a reliable and reproducible aortic pressure gradient over time, despite ongoing hemorrhage. P-REBOA increased survival time beyond the golden hour while maintaining physiologic cMAP and carotid blood flow. This preservation of baseline proximal pressure and flow may theoretically reduce injury to tissue beds above the point of aortic occlusion. Additional translational research is needed to effectively determine if P-REBOA confers a survival benefit over C-REBOA in a more clinically relevant model of uncontrolled hemorrhage. Despite the limitations of this study, it provides important feasibility experience and data that stand

to underpin future, more comprehensive studies of next-generation REBOA. P-REBOA may offer a promising new approach to reducing the morbidity associated with C-REBOA while increasing survival of combat-injured patients as therapy is pushed further forward into austere environments.

AUTHORSHIP

R.M.R., T.K.W., J.K.G., J.W.C., and L.P.N. designed this study. R.M.R., J.K.G., L.P.N., and T.K.W. conducted the literature search. R.M.R., T.K.W., C.M.L., J.K.G., and L.P.N. contributed to the data collection. R.M.R., J.K.G., T.K.W., and L.P.N. performed the data analysis. R.M.R., T.K.W., C.M.L., N.F.C., J.K.G., and L.P.N. interpreted the data. R.M.R., J.K.G., L.P.N., and T.K.W. wrote the manuscript. All authors contributed to the critical revision.

DISCLOSURE

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DISCUSSION

Dr. Todd Rasmussen (Fort Detrick, Maryland): I'd like to congratulate the authors on what is a smart and very highly-technical, if not very cool, model examining what could aptly be referred to as "next generation" REBOA. This line of effort aims to examine and mitigate what can be expected to be ischemic

complications associated with complete balloon occlusion of the aorta or even supra-normal cerebral blood flow or perfusion in the setting of shock.

Now, I'd like to thank you for providing me a copy of the manuscript well ahead of time. It was a well-written manuscript. And I have just a few questions for you from the podium.

First of all, would you elaborate on the phenomenon of permissive bleeding? You mentioned this but I would ask you to elaborate on the phenomenon or practice of permissive bleeding associated with the use of partial REBOA and how this might be advantageous, not only from the standpoint of reducing distal ischemia but also at reducing supra-normal cerebral perfusion pressures.

Are you advocating for allowing ongoing bleeding in order to offload brain and heart? Can you please elaborate on that? And if so, how might this be better controlled so as not to be harmful, either too much or too little?

Another question is, was it your sense that had you been able to control the balloon inflation and deflation in the partial REBOA group that they would have had an equal survival as the complete REBOA group?

The complete REBOA group had a mean survival of 160 minutes and the partial had a survival of 80 minutes. If you had been able to manipulate the balloon during that time was it your sense that they would have had equal survival?

You seem to imply that there may be a "sweet spot" or a "sweet spot gradient," perhaps augmented by other endpoints, hemodynamic, circulating or other, that could hone or tune partial REBOA such that a specimen could be kept alive almost indefinitely with this, with some form of blood replacement, of course. Is this correct? And could you elaborate on the concept of informed or automated partial REBOA?

And I will stop there. I will congratulate you on such an excellent presentation. I have heard it, this work and this line of effort by you and your senior authors a couple of times.

Congratulations on such an outstanding presentation and forward-leaning translational research project. And I look forward to your answers. Thank you.

Dr. Ernest E. Moore (Denver, Colorado): I would like to emphasize, which is perhaps obvious, that this work has relevance beyond military. As we introduce REBOA into rural America, this may permit prolonged transport of patients from hospitals that don't have operative capabilities to control active bleeding.

I would encourage you to look at spinal ischemia as you proceed on in modeling because even though organs may survive prolonged ischemia, the anterior spinal artery tolerance to warm ischemia in the human is 30 minutes.

Of course, I recognize that it may be better to be a paraplegic than in heaven.

Finally, some of the newer generation REBOAs have multiple channels. Thus, it's conceivable that you could do partial aortic occlusion and then use a channel proximal to the balloon to selectively infuse blood products to enhance hemostasis or antioxidants to prolong ischemia tolerance.

Dr. Matthew Martin (Tacoma, Washington): This is great work. And I think this will help us overcome that time factor where we know there is a finite limitation to the duration of complete aortic occlusion that is survivable. This appears to only be in the 30 to 50 minute range in humans, so extending this time is a major advance.

You talked about this as in prolonged field care so what is the lowest level you see this being pushed out to? Do you ever really see this becoming a medic-level intervention in practice? Does this require a surgeon, especially when you are talking about the prolonged field care aspect for deploying a REBOA?

Thanks.

Dr. Sasha Adams (Houston, Texas): We were listening to some presentations on REBOA yesterday and they talked about the Japanese protocols that have a frequent release of the balloon to decrease, I think, some of the reperfusion injuries. Didn't know if you had considered using that in your model and how you think that would affect your outcomes. Thank you.

Dr. Rachel M. Russo (Sacramento, California): Thank you, Dr. Rasmussen, Dr. Kozar, Dr. Rotondo. Dr. Rasmussen, to your question about future studies and our findings with permissive bleeding and the potential advantages of controlling aortic blood flow, we do believe that partial REBOA would permit modulation of proximal pressures and allow us to provide graded degrees of distal perfusion.

One of the things that we are working on as we move forward is a form of dynamic variable aortic occlusion. We would like to have a catheter that would be able to sense the patient's cardiovascular physiology and then respond appropriately as the situation changes- both as the patient's injury progresses, if there is ongoing bleeding, but also as resuscitation continues.

With respect to your second question "Do [we] think that this would improve survival, if we had that capability?"—absolutely I do. We have been working in the lab on some additional modeling since this study has come out.

We have found that implementing several of the changes that we have alluded to in this paper allowed us to improve upon our initial concepts of partial REBOA. We have been able to achieve much longer survival in these animals than we had seen in the results that I presented today, primarily as a result of improving initial hemostasis by implementing a brief period of complete occlusion prior to restoring distal blood flow.

While we are still in the process of conducting these experiments, survival in the partial REBOA group has been equivalent to complete REBOA in most animals and superior to complete REBOA in others.

You asked if there was a "sweet spot" an automated catheter would be able to find, that is the subject of ongoing research.

I don't think there is a particular gradient that is going to work correctly every time for everyone. But that's all the more reason why we need an automated, dynamic system that can sense the patient's physiology and respond in real time.

Dr. Moore, to your questions and comments about the relevance of this outside of the military, we could not agree more.

We definitely see the potential for this type of technology to be used, not only in the military, but also in rural environments where there may be prolonged duration between injury and time of definitive care. This type of intervention could even be applied not just to hemorrhagic shock, but to any shock state where additional afterload is needed for a period of time.

There are many places throughout the world where there may not be availability of a surgeon to provide hemostasis.

Not only do we think that this technique may be able to buy time while awaiting definitive care, but it may offer an alternative approach to facilitating non-operative management of injuries that would otherwise require surgery.

We are looking at spinal ischemia with future studies. We were unable to see it in this particular group of animals, because their death was so rapid. In the longer-term survival models we are working on now, we are collecting information to examine spinal cord ischemia.

The concept of providing multiple infusion channels in an aortic catheter capable of partial occlusion is a very good idea and something that we will definitely consider as we move forward.

To address Dr. Martin's question about the lowest level that we will be able to deploy this technology, it's definitely an area of concern when we talk about any new technology that we want to move forward into environments where there are no surgeons.

Not only is there going to be the need to have additional training, which may add to the training burden of pre-hospital providers, for example, but also the need to figure out who these patients are who would require REBOA therapy.

One of the main goals of our line of research (and the research that is being conducted by similar labs) is trying to determine how to reduce the training burden for endovascular interventions.

It is also conceivable that automating therapy can minimize the burden of advanced medical decision making and can reduce the risks associated with catheter use.

To avoid harms associated with inappropriate patient selection we imagine a catheter that could be placed in every patient—if it was determined by the catheter that there was no need for aortic occlusion, it would not inflate. If the catheter determined that a patient needed to have complete occlusion, it would do that. And then as the situation changed it would adapt. Lower profile, percutaneous catheter designs can facilitate catheter placement by lower level providers and reduce access site complications.

And then, finally, for Dr. Adams' question regarding the intermittent inflation and deflation of CODA balloons and similar balloons as are used in Japan, we have not specifically looked at that but other groups have.

In 2014, the Institute for Surgical Research at Ft. Sam Houston published an animal study comparing continuous aortic occlusion to intermittent aortic occlusion achieved by periodic inflation and deflation of a CODA balloon (Shock. 2014;41 (2):130–7). They looked specifically at ischemia reperfusion injury and the impact on distal organs. They found no benefit to inflating and deflating the balloon during a 90-minute period.

We believe that the reason why they found no benefit to providing distal perfusion in this way was because of the "all or nothing" phenomenon that is provided by current catheters.

The rebound hypotension that we observe following balloons deflation is starkly in contrast to the profound hypertension that is created whenever the balloon is inflated. The resultant rapid oscillation in physiology undermines any autoregulation occurring within the animal or patient.

We believe a more gradual approach to the restoration of systemic circulation would better accommodate the patient's compensatory physiologic responses.

Thank you.