Endovascular variable aortic control (EVAC) versus resuscitative endovascular balloon occlusion of the aorta (REBOA) in a swine model of hemorrhage and ischemia reperfusion injury

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BACKGROUND: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is effective at limiting hemorrhage from noncompressible sources and restoring but causes progressive distal ischemia, supraphysiologic pressures, and increased cardiac afterload. Endovascular variable aortic control (EVAC) addresses these limitations, while still controlling hemorrhage. Previous work demonstrated improved outcomes following a 90-minute intervention period in an uncontrolled hemorrhage model. The present study compares automated EVAC to REBOA over an occlusion period reflective of contemporary REBOA usage.

METHODS: Following instrumentation, 12 Yorkshire-cross swine underwent controlled 25% hemorrhage, a 45-minute intervention period of EVAC or REBOA, and subsequent resuscitation with whole blood and critical care for the remainder of a 6-hour experiment. Hemodynamics were acquired continuously, and laboratory parameters were assessed at routine intervals. Tissue was collected for histopathologic analysis.

RESULTS: No differences were seen in baseline parameters. During intervention, EVAC resulted in more physiologic proximal pressure augmentation compared with REBOA (101 vs. 129 mm Hg; 95% confidence interval [CI], 105–151 mm Hg; $p = 0.04$). During critical care, EVAC animals required less than half the amount of crystalloid (3,450 mL; 95% CI, 1,215–5,684 mL] vs. 7,400 mL [95% CI, 6,148–8,642 mL]; $p < 0.01$) and vasopressors (21.5 ng/kg [95% CI, 7.5–35.5 ng/kg] vs. 50.5 ng/kg [95% CI, 40.5–60.5 ng/kg]; $p = 0.05$) when compared with REBOA animals. Endovascular variable aortic control resulted in lower peak and final lactate levels. Endovascular variable aortic control animals had less aortic hyperemia from reperfusion with aortic flow rates closer to baseline (36 mL/kg per minute [95% CI, 30–44 mL/kg per minute] vs. 51 mL/kg per minute [95% CI, 41–61 mL/kg per minute]; $p = 0.01$).

CONCLUSIONS: For short durations of therapy, EVAC produces superior hemodynamics and less ischemic insult than REBOA in this porcine-controlled hemorrhage model, with improved outcomes during critical care. This study suggests EVAC is a viable strategy for in-hospital management of patients with hemorrhagic shock from noncompressible sources. Survival studies are needed to determine if these early differences persist over time. (*J Trauma Acute Care Surg.* 2018;85: 519–526.

KEY WORDS: Automated; EVAC; hemorrhage; REBOA; resuscitation.

Hemorrhage is a leading cause of preventable death in civilian and military populations and is particularly challenging to control when arising from a noncompressible vascular injury. Resuscitative endovascular balloon occlusion of the aorta (REBOA) has emerged as a therapy to provide temporary hemodynamic support and hemorrhage control with a balloon catheter prior to definitive surgical hemostasis.[1–4] However, the sustained complete aortic occlusion achieved by REBOA may create several potentially adverse physiologic effects, including progressive ischemia to tissue beds distal to the point of occlusion, as well as proximal hypertension and increased cardiac afterload proximal to the balloon.[5–7] These adverse effects are

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greatest during Zone 1 occlusion, which significantly limits the patient tolerance of REBOA. To overcome these limitations and extend the therapeutic duration of REBOA, methods of regulating partial occlusion with REBOA catheters to provide low-volume distal blood flow have been proposed. Partial REBOA (p-REBOA) with manual balloon inflation control has been used clinically with variable success as a means to address these complications. Yet, early animal experiments demonstrate that an inability to tightly control an occlusion balloon manually results in large fluctuations in downstream aortic flow to injured areas. The result is early death from exsanguination.[8–11]

Our group has recently described the technique of endovascular variable aortic control (EVAC) as an alternative to p-REBOA, in which automated control of aortic occlusion is used to precisely and dynamically regulate distal aortic flow across the full spectrum from complete occlusion to full unimpeded flow.[12] For trauma-specific applications, EVAC can be used to restrict this distal aortic flow to a very low level and precisely regulate the delicate balance between ongoing hemorrhage and progressive distal ischemia. Simultaneously, the proximal cardiovascular effects of EVAC augment blood flow to the heart, lungs, and brain. Therefore, EVAC serves to simultaneously optimize blood flow above and below the level of flow restriction, termed regional perfusion optimization.

We have previously demonstrated that EVAC is able to extend the duration of aortic intervention to 90 minutes in a lethal liver injury swine model, with improved survival, end organ function, and lower resuscitation requirements compared with complete aortic occlusion (ie, REBOA).[13] The prior study supported the potential use of EVAC during prolonged transport scenarios for military trauma care, civilian rural trauma, or interfacility transfers. However, the study did not address whether EVAC would be superior to standard REBOA in the clinical scenarios where shorter occlusion times are encountered, such as in large urban trauma centers where typical REBOA times are less than 60 minutes.[4] Furthermore, the extracorporeal flow circuit used in our previous work to dynamically control distal aortic flow provided proof of concept but did not directly translate into a clinically relevant solution from a device perspective.

Several important issues remain unresolved following our initial EVAC study. First, would the improvements in hemodynamics and metabolic derangements in the EVAC group after 90 minutes of intervention still be demonstrable during a shorter duration of intervention? In addition, would a completely endovascular-based approach to EVAC be feasible from a technical perspective? This study seeks to address these key unanswered questions. We hypothesized that short-duration EVAC would lead to improved physiologic outcomes following reperfusion and resuscitation compared with standard REBOA. We also hypothesized that commercially available balloon catheters are capable of providing the fidelity required for the carefully titrated flow necessary for EVAC.

METHODS

Overview

The Institutional Animal Care and Use Committee at David Grant Medical Center, Travis Air Force Base, CA, approved this study. Animal care and use were in strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by AAALAC International. Healthy adult, castrate male and nonpregnant female Yorkshire-cross swine (*Sus scrofa*) weighing between 60 and 95 kg were acclimated for a minimum of 7 days prior to experimentation.

All animals were subjected to a 25% total blood volume hemorrhage over 30 minutes, followed by block randomization to a 45-minute intervention with either Zone 1 REBOA or EVAC (n = 6 per group). Shed blood was then returned, and all animals received protocolized critical care, during which vasopressor and isotonic fluid administration were automatically provided based on predefined physiologic parameters (Fig. 1*A*).

Animal Preparation

Animals were premedicated with 6.6 mg/kg intramuscular tiletamine/zolazepam (Telazol; Fort Dodge Animal Health, Fort Dodge, IA). Following isoflurane induction and endotracheal intubation, general anesthesia was maintained with 2% isoflurane and 100% oxygen, which was titrated to 40% oxygen to maintain a pulse oximetry between 92% and 98%. To offset the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine (0.01 mg/kg per minute) was instituted upon venous access and titrated prior to the beginning of the experiment 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. All animals received a bolus of 1 L Plasmalyte-A (Baxter, Deerfield, IL) upon initial venous access. Following the bolus, Plasmalyte-A maintenance intravenous fluid was administered at 10 mL/kg per hour until the abdomen was closed, after which it was decreased to 5 mL/kg per hour for the remainder of the study. Intravenous heparin was administered prior to experimentation to achieve an activated clotting time of 100 seconds. An underbody warmer was used to maintain core body temperature between 35 and 37°C. Exclusion criteria were a baseline aortic flow below 75% of anticipated weight-based flow (35 mL/kg per minute) following the initial 1-L crystalloid bolus, a baseline leukocytosis (white blood cell count >25,000 per μL), or a preprocedure blood loss greater than 5% total blood volume (0.05 × weight (kg) × 0.6 L/kg).

A splenectomy was performed to minimize hemodynamic variation from autotransfusion. The supraceliac aorta was exposed by dividing the left diaphragm followed by circumferential dissection of the aorta for a length of 5 to 10 cm. Two adjacent intercostal arteries were ligated, and a perivascular aortic flow probe (Transonic Systems Inc., Ithaca, NY) was placed proximal to the ligated vessels preventing intervening flow between the flow probe and the endovascular occlusion balloon. The abdomen was closed with cable ties. Vascular access was performed as previously described.[14] A 9 Fr Coda LP balloon (Cook Medical Inc., Bloomington, IN) was positioned just distal to the aortic flow probe. The inflation syringe was connected to the custom-developed EVAC automated syringe pump capable of both complete REBOA and EVAC.

Intervention

Following hemorrhage and subsequent randomization, animals in the EVAC arm had tightly controlled aortic flow below the balloon for 45 minutes, ranging from 1.5 to 4.4 mL/kg

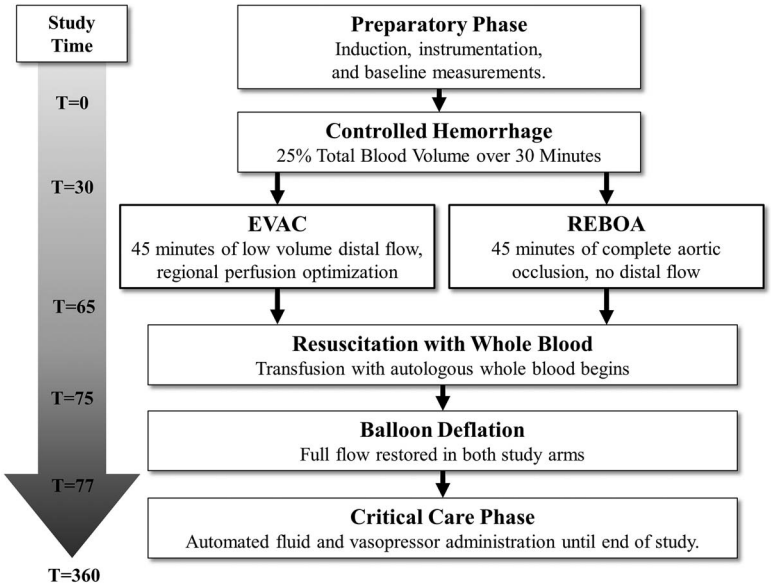

Figure 1. Study flow.

per minute (i.e., 100–300 mL/min for a 70-kg animal), achieved using a wireless automated syringe pump running custom closed-loop feedback algorithms. In the REBOA arm, animals were subjected to 45 minutes of sustained complete aortic occlusion, which was maintained with the same automated syringe pump running an algorithm for complete occlusion. At 75 minutes, balloons sequentially deflated in both arms over a period of 5 minutes.

Resuscitation

Ten minutes prior to balloon weaning (65 minutes), resuscitation with whole blood was initiated, back to 90% of initial blood volume, which occurred over the ensuing 30 minutes. Beginning at 80 minutes and through the end of study, the administration of intravenous crystalloid fluid boluses and the titration of vasopressors were performed in an automated fashion using a custom microcontroller, a custom infusion syringe pump, and a standard peristaltic fluid pump (Masterflex;Cole-Parmer, Vernon Hills, IL). Fluid boluses were triggered based on central venous pressure and MAP values. Vasopressors were titrated up or down in response to hypotension (MAP <60 mm Hg) or hypertension (MAP >70 mm Hg), respectively (see Figure, Supplemental Digital Content 1, http://links.lww.com/TA/B187). Animals were euthanized at T360, followed by prompt necropsy.

Data Collection and Analysis

Physiologic parameters and aortic flow measurements were collected in real time using a multichannel data acquisition system (Biopac MP150; Biopac, Goleta, CA). Parameters measured included heart rate, blood pressure proximal and distal to the intra-aortic balloon catheters, central venous pressure, core temperature, and aortic flow. Arterial blood and urine samples were collected at routine intervals throughout the study for analysis. End-organ histology was analyzed by a veterinary pathologist who was blinded to the treatment groups. Data analysis was performed with STATA version 14.0 (Stata Corporation, Bryan, TX). Continuous variables are presented as means and SEM if normally distributed and as medians with interquartile ranges if not distributed normally and analyzed using the appropriate test. Dichotomous and categorical variables were analyzed by Fisher exact test and presented as percentages. Statistical significance was set at $p < 0.05$.

RESULTS

There were no differences in baseline characteristic between groups, including hemodynamics, laboratory parameters, and baseline vasopressor requirements (Table 1). Resuscitative endovascular balloon occlusion of the aorta and EVAC animals had a similar hypotensive response to hemorrhage (33 mm Hg [95% confidence interval [CI], 29–36 mm Hg] vs. 38 mm Hg [95% CI, 32–44 mm Hg]; $p = 0.08$) (Fig. 2). During intervention, REBOA animals had significantly higher proximal MAP as compared with EVAC (129 mm Hg [95% CI, 105–151 mm Hg] vs. 101 mm Hg; 95% CI, 83–119 mm Hg]; $p = 0.04$); however, there was no difference in peak MAP across the two groups (Table 2). There was no appreciable flow beyond the balloon in the REBOA arm during intervention, whereas EVAC animals had a mean flow of 5.2 mL/kg per minute (95% CI, 4.86–5.62 mL/kg per minute). Following the 5-minute balloon deflation interval, EVAC animals maintained higher proximal MAP compared with REBOA (Fig. 2*A*).

During the critical care phase, animals from the EVAC group were able to maintain an average proximal MAP within the target range (60–70 mm Hg) and had a higher overall MAP than REBOA animals (Table 2). Endovascular variable aortic control animals also demonstrated aortic flow rates closer to baseline values during critical care as compared with REBOA animals (36 mL/kg per minute [95% CI, 30–44 mL/kg per minute] vs.

51 mL/kg per minute [95% CI, 41–61 mL/kg per minute]; $p = 0.01$).

Notable differences were seen in resuscitation requirements during the critical care phase of the experiment. Based on fewer episodes of hypotension and low central venous pressure, EVAC animals required less than half the volume of crystalloid when compared with REBOA animals (3,450 mL; 95% CI, 1,215–5,684 mL] vs. 7,400 mL [95% CI, 6,148–8,642 mL]; $p < 0.01$). Vasopressor requirements for EVAC were also less than half that of REBOA animals (21.5 ng/kg; 95% CI, 7.5–35.5 ng/kg] vs. 50.5 ng/kg [95% CI, 40.5–60.5 ng/kg]; $p = 0.05$) (Fig. 3).

One animal in the EVAC group experienced progressive hemodynamic deterioration during the critical care phase and died 40 minutes prior to the end of study. Overall fluid and vasopressor requirements in this animal were greater than 2 SDs greater than the mean fluid and vasopressor requirements for the entire EVAC cohort and 3 SDs compared with the five surviving EVAC animals. This animal was also the only animal in either group to have a baseline aortic flow below inclusion criteria prior to the initial pre-experiment fluid bolus but did meet inclusion criteria for aortic flow following pre-experimental fluid administration and was therefore included in the study.

Renal function was preserved in both groups following reperfusion, with a trend toward higher total urine output in the REBOA arm (40 mL/kg; 95% CI, 32–48 mL/kg] vs. 23 mL/kg [95% CI, 20–26 mL/kg]; $p = 0.08$). There was no difference in final creatinine levels across groups. Histological analysis of kidney, bowel, skeletal muscle, and liver did not reveal any significant differences between REBOA and EVAC animals. Both peak and final lactate levels were significantly lower in the EVAC group (Table 2). There were no differences in hemoglobin values across groups following resuscitation.

DISCUSSION

In this large animal model of hemorrhage with a period of intervention reflective of current clinical REBOA use, EVAC resulted in less distal ischemia and physiologic derangement when compared with REBOA. This improvement is evidenced by lower levels of serum lactate and decreased resuscitation requirements during the critical care phase. In addition, EVAC augmented proximal pressure in a more physiologic manner during hemorrhagic shock, reducing proximal hypertension to the heart, lungs, and brain compared with REBOA. These beneficial physiologic outcomes were demonstrated over the clinically relevant occlusion period of 45 minutes. Finally, this study demonstrates that carefully titrated distal aortic flow is possible by combining an automated syringe pump with a standard, currently available aortic occlusion catheter.

Resuscitative endovascular balloon occlusion of the aorta is now an established clinical strategy in the management of noncompressible truncal hemorrhage, providing hemodynamic support and minimizing hemorrhage.[3,4,15,16] Its expanding use within the trauma community has been facilitated by the convergence of innovative endovascular technology and techniques with strong support from the thought leaders within the fields of vascular and trauma surgery. Despite the growing enthusiasm and exponential increase in clinical use, it is important to recognize that REBOA itself produces additional physiologic insult in an already physiologically deranged patient.[5] Therefore, is it quite feasible that deleterious consequences of sustained complete aortic occlusion will become more commonplace with increased use of this technology. As such, concerns regarding the progressive ischemic burden and the potential for cardiac dysfunction with complete aortic occlusion may limit broader application of this technology in scenarios where prolonged occlusion is anticipated, effectively constraining the scope of REBOA and marginalizing its utility in geographically isolated prehospital environments and for patient transport (Fig. 4).

The EVAC concept has been developed to address the limitations of REBOA by striking a delicate balance between hemorrhage control and the adverse physiologic consequences of aortic occlusion.[5] By achieving carefully titrated low-volume distal aortic flow, this strategy allows regional perfusion optimization both above and below the level of flow restriction.[13,17] Endovascular variable aortic control was initially devised as an intervention for prolonged military transport applications, to bridge the critical time window between point of injury and arrival at a facility capable of definitive surgical hemostasis. In a previous proof-of-concept experiment, an extracorporeal circuit was utilized to precisely control distal aortic blood flow in a porcine liver injury model, where all control animals died within minutes.[13] An intervention period of 90 minutes was used to simulate the reality of modern tactical evacuation on the battlefield, recognizing that complete REBOA is not survivable in scenarios where prolonged intervention (>60 minutes) is required. The degree of distal ischemia from complete aortic occlusion (REBOA) resulted in dramatic increases in mortality and resuscitation requirements compared with animals provided carefully titrated distal aortic flow. Importantly, this study demonstrated that a mere 10% of baseline aortic flow delivered by the EVAC device was sufficient to reduce distal ischemic burden while promoting proximal aortic pressures closer to baseline values. In addition, this prior study demonstrated that allowing 10% distal aortic flow in the face of a devastating, uncontrolled liver injury did not create clot disruption and fatal ongoing hemorrhage. This was a striking difference from previous attempts to achieve partial aortic flow using manual titration in an analogous liver

TABLE 1. Baseline Characteristics

	REBOA (n = 6)	EVAC (n = 6)	*p*
Sex, %			1.0
Male	4 (66.7)	4 (66.7)	
Female	2 (33.3)	2 (33.3)	
Weight, kg	77.5 (8.0)	82.5 (4.4)	0.21
pH	7.4 (0.0)	7.4 (0.0)	0.59
Hemoglobin, g/dL	10.3 (0.8)	11.0 (0.09)	0.18
White blood cells, $\times 10^9$/L	15.2 (3.0)	15.4 (1.9)	0.91
Platelets, $\times 10^9$/L	275 (45)	183 (35)	0.75
Potassium, mmol/L	3.7 (0.2)	3.7 (0.2)	0.99
Lactate, mg/dL	2.4 (0.5)	2.9 (0.6)	0.20
Creatinine, mg/dL	1.3 (0.13)	1.5 (0.2)	0.08
Glucose, mg/dL	93 (8)	87 (19)	0.47
Proximal MAP, mm Hg	66 (7)	70 (8)	0.44
Aortic flow, mL/kg per minute	38.3 (4.9)	35.7 (3.8)	0.37

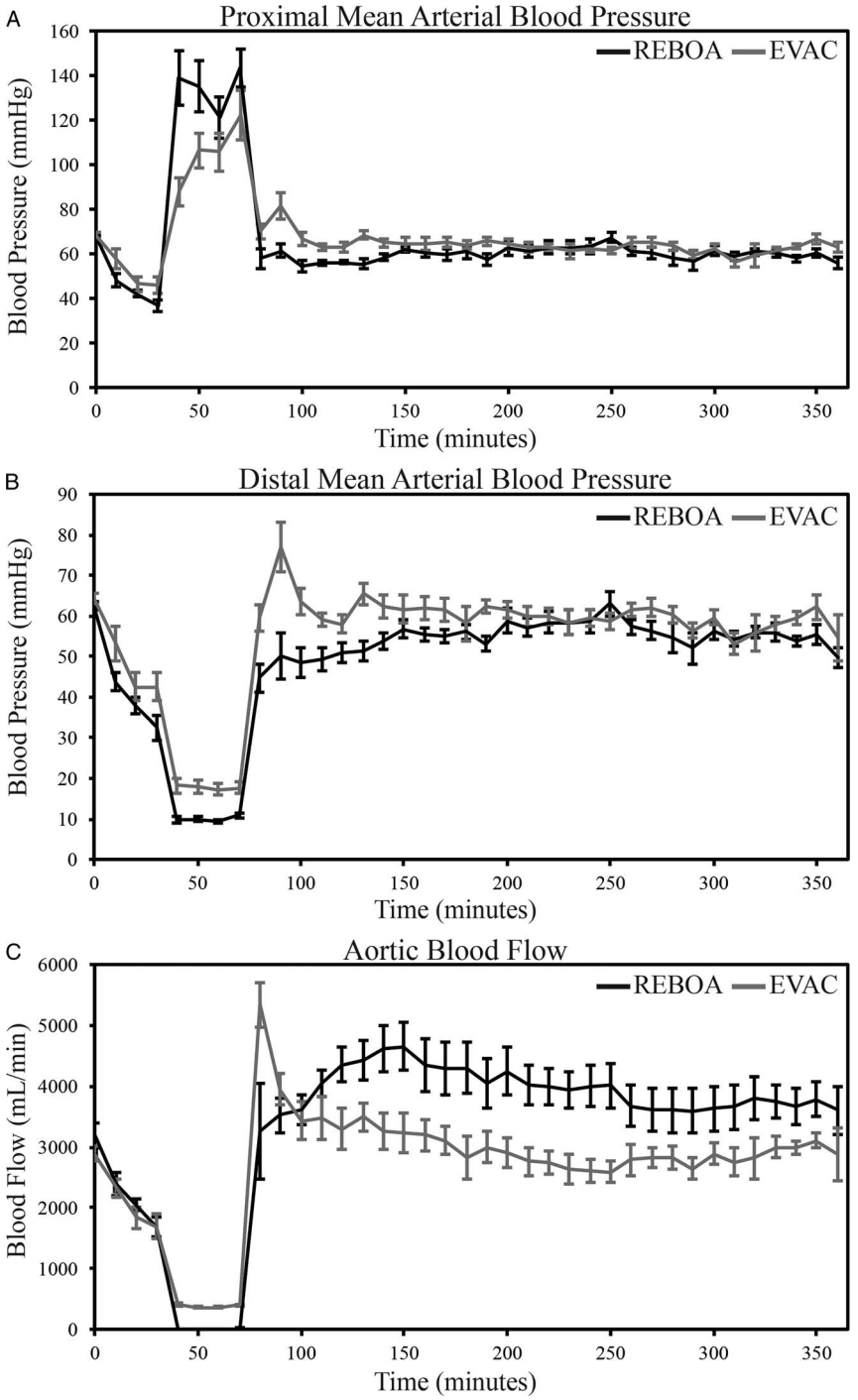

Figure 2. Hemodynamics over time: (*A*) EVAC resulted in more modest proximal pressure augmentation during intervention. During critical care, EVAC maintained proximal pressure within target range more frequently. (*B*) EVAC on average maintained higher distal pressure during both intervention and critical care. (*C*) Aortic flow was maintained at a low level during intervention in EVAC. During critical care, EVAC animals had aortic flow rates closer to baseline values.

injury model, where early demise was encountered because of uncontrolled downstream blood flow and subsequent ongoing hemorrhage.[9]

These initial experiments suggested that titrated aortic flow may be a viable approach to extend the benefits of aortic occlusion for prolonged periods of intervention. However, these preliminary studies did not address the more common scenario of in-hospital application of REBOA, where maximum occlusion time is typically limited to less than 60 minutes. For these shorter occlusion periods, no previous data exist, either clinical or translational, suggesting that a partial flow strategy would provide a physiologic benefit over complete aortic occlusion.

TABLE 2. Hemodynamic, Physiologic, and Metabolic Endpoints

	EVAC (n = 6)	REBOA (n = 6)	*p*
Hemorrhage phase			
Lowest pMAP, mm Hg	38 (32–44)	33 (29–36)	0.06
Intervention phase			
Average pMAP, mm Hg	101 (83–119)	129 (105–151)	**0.04**
Maximum pMAP, mm Hg	144 (125–162)	161(141–182)	0.13
Critical care phase			
Average pMAP, mm Hg	64 (62–67)	60 (57–63)	**0.02**
Average dMAP, mm Hg	61 (57–64)	55 (51–59)	**0.02**
Average aortic flow, mL/min	3,028 (2,458–3,598)	3,960 (3,176–4,743)	**0.03**
Average aortic flow, mL/kg per minute	36 (30–44)	51 (41–61)	**0.01**
Urine output—total, mL/kg	23 (20–26)	40 (32–48)	0.08
Serum creatinine—final, mg/dL	1.66 (1.63–1.69)	1.68 (1.56–1.80)	0.86
Lactate—maximum, mg/dL	7.9 (6.7–9.0)	9.6 (8.5–10.7)	**0.02**
Lactate—final, mg/dL	3.0 (2.4–3.6)	5.2 (3.7–6.8)	**0.01**

Error presented as standard error of the mean.
dMAP indicates distal MAP; pMAP, proximal MAP.

This current study sought to address this key concern regarding the clinical applicability of EVAC for scenarios that more closely approximate the current clinical application of REBOA. Although the goal for clinical use of REBOA is to minimize the duration of complete aortic occlusion periods, recent data from the American Association for the Surgery of Trauma AORTA registry demonstrate median aortic occlusion durations of 60 minutes for patients undergoing REBOA prior to the need for cardiopulmonary resuscitation, the subset of patients in whom REBOA has shown the greatest survival benefit.[15] For intervention periods as short as 45 minutes, EVAC still dramatically reduced the physiologic impact of sustained aortic occlusion, resulting in a more modest physiologic proximal pressure augmentation. Following resuscitation, both fluid and vasopressor requirements were less than half that required following REBOA. Moreover, EVAC resulted in less hyperemic flow throughout the critical care phase, as evidence by lower aortic flow rates during the critical care phase. Taken together, these findings likely reflect the reduced physiologic insult of this intervention. In all, the present study provides

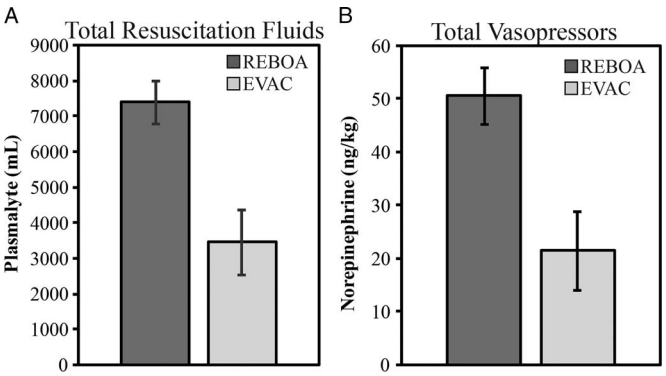

Figure 3. Resuscitation requirements: EVAC resulted in less than half the amount of (*A*) fluids and (*B*) vasopressors during automated critical care as compared with REBOA.

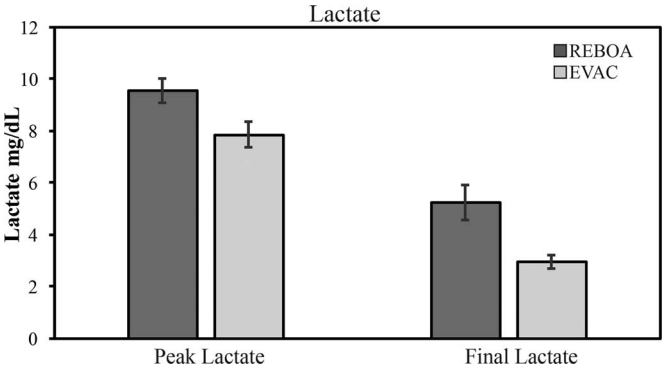

Figure 4. Ischemic burden: EVAC resulted in lower peak and final lactate levels than REBOA.

experimental support for an EVAC partial flow strategy for intervention periods reflective of typical in-hospital use.

One of the greatest clinical concerns for aortic-based resuscitation technologies is the potential for acute kidney injury (AKI). The strong association between AKI and worse outcomes in trauma victims is well known.[18,19] Although AKI has been described as an adverse effect of REBOA in clinical cases, we did not observe renal injury in the REBOA arm of this study following the 45-minute intervention.[4] This may reflect inherent differences between our porcine model and the complex pathophysiology of human trauma. Interestingly, there was a trend toward higher urine output in the REBOA arm, which may reflect the increased fluid requirements of this group during critical care. Nonetheless, our previous work utilizing a 90-minute intervention with uncontrolled hemorrhage demonstrated improved renal function and urine output with variable aortic control (ie, EVAC) compared with complete aortic occlusion (ie, REBOA), likely due in large part to the longer intervention period.[13] Reduction in AKI is one of the potential benefits of EVAC during prolonged interventions.

Mounting clinical evidence suggests that applying REBOA at or after the onset of cardiac arrest results in survival rates equivalent to patients undergoing resuscitative thoracotomy. Conversely, application of REBOA prior to hemodynamic collapse does result in improved survival.[15] Therefore, early intervention at the onset of resuscitative efforts should be a priority in the overall management of the hemorrhaging trauma patient. Based on the improved ischemic profile and physiologic response of EVAC, this strategy could theoretically be applied even earlier in the resuscitation prior to reaching the threshold for REBOA, however low or high that might be. Early EVAC may not only lead to improved survival, but also minimize morbidity by reducing the well-described consequences of large-volume transfusions, vasopressors, and crystalloids that are common in trauma resuscitations.[20–23]

Through continued technological development, our group refined a strategy to achieve controlled, titrated distal aortic flow using conventional compliant balloon catheters inflated with an automated syringe pump. This pump and controller represent a major advancement forward. Given the complex interplay of pressure, cardiac output, vascular tone, and neuroendocrine factors, precision aortic flow regulation with EVAC is possible only with automation using closed-loop feedback. As a result,

the automated EVAC syringe pump utilized in this study can make microliter-sized changes in balloon volume beyond the capacity of manual control and execute those changes without latency. The development of this experimental EVAC syringe pump advances the field closer to a clinically relevant endovascular device for the management of noncompressible truncal hemorrhage. The development of a commercial device is underway and will hopefully bring this therapy to the clinical realm in the future.

Although the only death in this experiment was in the EVAC study arm, it is important to highlight that this animal was an outlier, requiring significantly more fluid and vasopressors by comparison. The present study was a subset of a broader study involving six randomization arms, evaluating several derivative applications of this technology. This was the only-animal out of nearly 60 to not survive the duration of the study. Despite these aberrations, all physiologic and laboratory data from this animal were included in the analysis, which decreases the overall differences between groups. Nonetheless, the present study demonstrated significant differences between the groups across multiple physiologic and biochemical endpoints, only strengthening the perceived benefit of EVAC compared with REBOA.

There are several limitations to the current study. First, this was a nonsurvival study with a total experimental time of only 6 hours. It is likely that critical differences between groups with respect to physiology or histology would manifest with studies of longer duration. Alternatively, it is conceivable that the early differences in hemodynamics and resuscitation requirements noted in this study will not translate to differences in outcomes at longer time points. Therefore, limited survival studies to address these issues are justified.

In addition, our use of aortic flow is meant to serve as a surrogate marker of tissue perfusion. However, this study did not directly measure perfusion of tissues at the organ level in favor of broader metrics of hemodynamic performance, resuscitation requirements, and basic laboratory and histological markers of ischemia and tissue injury. Additional studies are warranted to evaluate the local tissue perfusion effects with EVAC, including additional biomarkers of tissue perfusion and/or injury.

Our study also did not compare EVAC to currently achievable partial flow strategies such as p-REBOA. It is our belief that EVAC, through the use of automation, will result in precision control of partial aortic flow, reduce the need for extensive end-user experience, and cognitively offload the provider, enabling attention to other critical aspects of patient care or to care for multiple patients simultaneously (ie, mass-casualty situation). Nonetheless, it remains unclear how the EVAC approach would perform compared with manually titrated p-REBOA, which is used clinically by select high-end users. Comparative studies evaluating the fidelity of control, the frequency of balloon movements, and other outcomes measures would be incredibly informative. Fully understanding the differences between these similar yet distinct approaches may illuminate how these technologies should be best applied clinically.

This study also did not utilize a control arm with no aortic occlusion following hemorrhage. In this controlled hemorrhage model, it is conceivable that a control arm would have improved outcomes compared with either experimental arm. However, our previous work using variable aortic control in an injury model demonstrated that control animals uniformly exsanguinated within minutes of injury. Given this therapy is intended for using in scenarios of uncontrolled hemorrhage, we did not feel it would add meaningfully to this study.

In addition, this study utilized a controlled hemorrhage model without ongoing blood loss or major hemodynamic shifts during the intervention. Therefore, this study does not fully reflect how REBOA is or EVAC would be applied clinically. Also, the ability of EVAC syringe pump to achieve stable distal flow and limit ongoing hemorrhage in the context of uncontrolled hemorrhage cannot be assessed in this study. Nonetheless, fidelity of the EVAC syringe pump to deliver stable aortic flow, particularly during active resuscitation with whole blood at the end of the intervention period, was on par with our previous extracorporeal flow circuit model.

The current hardware implementation to generate EVAC via endovascular means is experimental, with aortic flow being regulated based on direct aortic flow measurements via a perivascular probe encircling the supraceliac aorta. However, consistent with previous reports from our laboratory, there is a strong correlation between the distal aortic pressure and downstream aortic flow beyond the balloon, specifically at the low flow rates targeted in this study. This suggests that distal pressure may serve as a viable surrogate metric for aortic flow by which to regulate EVAC clinically. These limitations notwithstanding, the results of this study represent a significant advancement in technique and technology to mitigate the deleterious consequences of REBOA while maintaining the lifesaving advantages.

CONCLUSIONS

By utilizing an automated EVAC syringe pump and commercially available balloon occlusion catheters, we demonstrate improved hemodynamics, decreased metabolic derangements, and lower resuscitation requirements with EVAC compared with REBOA over a 45-minute intervention duration. This study represents incremental progress toward a viable method of achieving regional perfusion optimization with EVAC, to extend the duration of aortic occlusion technologies for both in-hospital and pre-hospital use. Further technique refinement and limited survival studies are warranted to enable translation of EVAC into the clinical realm.

AUTHORSHIP

T.K.W., E.M.T., G.L.H., M.A.S., A.J.D., E.S.D., E.R.F., J.K.G., L.P.N., and M.A.J. contributed to the literature search and study design. T.K.W., E.M.T., G.L.H., M.A.S., A.J.D., E.S.D., E.R.F., J.K.G., and M.A.J. collected the data and performed the data analysis and interpretation. T.K.W., E.M.T., G.L.H., M.A.S., A.J.D., E.S.D., E.R.F., J.K.G., L.P.N., and M.A.J. wrote and critically revised the manuscript.

DISCLOSURE

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