A novel fluoroscopy-free, resuscitative endovascular aortic balloon occlusion system in a model of hemorrhagic shock

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BACKGROUND: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a potentially lifesaving maneuver in the setting of hemorrhagic shock. However, emergent use of REBOA is limited by existing technology, which requires large sheath arterial access and fluoroscopy-guided balloon positioning. The objectives of this study were to describe a new, fluoroscopy-free REBOA system and to compare its efficacy to existing technology. An additional objective was to characterize the survivability of 60 minutes of REBOA using these systems in a model of hemorrhagic shock.

METHODS: Swine (70–88 kg) in shock underwent 60 minutes of REBOA using either a self-centering, one component prototype balloon system (PBS, n = 8) inserted (8 Fr) and inflated without fluoroscopy or a two-component, commercially available balloon system (CBS, n = 8) inserted (14 Fr) with fluoroscopic guidance. Following REBOA, resuscitation occurred for 48 hours with blood, crystalloid, and vasopressors. End points included accurate balloon positioning, hemodynamics, markers of ischemia, resuscitation requirements, and mortality.

RESULTS: Posthemorrhage mean arterial pressure (mm Hg) was similar in the CBS and PBS groups (35 [8] vs. 34 [5]; $p = 0.89$). Accurate balloon positioning and inflation occurred in 100% of the CBS and 88% of the PBS group. Following REBOA, mean arterial pressure increased comparably in the CBS and PBS groups (81 [20] vs. 89 [16]; $p = 0.21$). Lactate peaked in the CBS and PBS groups (10.8 [1.4] mmol/L vs. 13.2 [2.1] mmol/L; $p = 0.01$) 45 minutes following balloon deflation but returned to baseline by 24 hours. Mortality was similar between the CBS and PBS groups (12% vs. 25%, $p = 0.50$).

CONCLUSION: This study reports the feasibility and efficacy of a novel, fluoroscopy-free REBOA system in a model of shock. Despite a significant physiologic insult, 60 minutes of REBOA is tolerated and recoverable. Development of lower profile, fluoroscopy-free endovascular balloon occlusion catheters may allow proactive aortic control in patients at risk for hemorrhagic shock and cardiovascular collapse. (*J Trauma Acute Care Surg*. 2013;75: 122–128. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Endovascular occlusion of aorta; hemorrhagic shock; swine.

Hemorrhage is the leading cause of death in civilian and military trauma.[1–6] In the military setting, 70% of deaths are caused by exsanguination from truncal injuries, of which 9 of 10 occur before hospital admission.[4] The civilian experience is similar, with bleeding shown as a major contributor to trauma deaths and the leading cause of potentially preventable death.[5,6] Noncompressible torso hemorrhage has recently been defined as hemorrhage arising from trauma to the torso vessels, pulmonary parenchyma, and solid abdominal organs and disruption of the bony pelvis resulting in hypotension or shock.[7,8]

Hemorrhage leads to cardiovascular collapse and death unless myocardial and cerebral perfusion can be maintained. In the setting of noncompressible torso hemorrhage, resuscitative aortic occlusion mitigates hemorrhage and increases after-load and central aortic pressure until hemostasis can be achieved. For decades however, this maneuver has required thoracotomy and aortic clamping, relegating it as a reactive procedure performed after the loss of pulses.[7] In the endovascular era, there has been a reappraisal of resuscitative endovascular balloon occlusion of the aorta (REBOA) as an alternative to resuscitative thoracotomy.[9] Unlike thoracotomy, REBOA is performed in a series of less invasive steps beginning with transfemoral arterial access and pressure monitoring. As such, REBOA may facilitate a proactive approach to aortic control ready to support the central circulation of patients at imminent risk of cardiovascular collapse.[9,10]

Emerging animal evidence demonstrates the benefits of REBOA in shock, with occlusion time of up to 90 minutes generating a significant but survivable metabolic penalty.[11,12] However, today's technology requires that this adjunct be performed with a large-caliber balloon catheter passed over a wire through a large sheath. In addition, REBOA is currently constrained by the requirement of fluoroscopy to guide the wire and balloon positioning. Characteristics of existing technology

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limit the ability of this maneuver to be performed in the emergent setting.[9] The objective of this study was to report a new, low-profile REBOA system designed to be placed without fluoroscopic guidance. An additional objective was to compare this system to existing endovascular technology in accuracy of placement and effectiveness in supporting central aortic pressures upon balloon inflation. Finally, this study aimed to characterize the physiologic consequence and survivability following 60 minutes of aortic occlusion with these systems in a model of hemorrhagic shock.

MATERIALS AND METHODS

Overview

This study was performed at an accredited facility (Clinical Research Division, Lackland Air Force Base, TX) under supervision of a veterinary staff with Institutional Animal Care and Use Committee approval. Female Yorkshire swine (*Sus scrofa*), (70–90 kg) in shock were randomized in groups of eight to either conventional balloon system (CBS) or prototype balloon system (PBS). The CBS consisted of commercially available devices including a stiff 0.035-inch Amplatz wire with an 8-cm flexible tip (Cook Medical, Bloomington, IN) and a 14 Fr, 120-cm Coda Balloon (Cook Medical).

Fluoroscopy-Free, Endovascular Aortic Balloon Occlusion System

The PBS was a fused wire and balloon catheter scheme (Pryor Medical, Arvada, CO) (Fig. 1). This unibody construct allowed the PBS to be passed through an 8 Fr femoral artery sheath into the abdominal aorta and positioned in the thoracic aorta using a "one-pass," fluoroscopy-free method. The main body was 100 cm, consisting of a semistiff 0.035-inch core wire extending 20 cm beyond the trail end of the device. The lead or insertion end consisted of a curved or floppy tipped wire fused inside a compliant balloon catheter, alleviating traditional "over-the-wire" insertion steps. At the insertion end of the PBS was a collapsible, self-centering, nitenol rail system (Fig. 1). This system was positioned between the wire tip and the compliant balloon for purposes of centering the system in the arterial lumen during advancement (Fig. 1).

Study Design and Baseline Phase

The study had four phases as follows: baseline, hemorrhage, REBOA, and resuscitation (Fig. 2). After induction of anesthesia with ketamine and isoflurane, animals underwent cannulation of the jugular vein through an open incision. The carotid artery was encircled with a transonic probe (Transonic Systems Inc., Ithaca, NY) to monitor flow. Ultrasound-guided access to the brachial artery was achieved using a microcatheter (Cook Medical), which was advanced into the aortic arch for pressure monitoring. The femoral artery opposite the device sheath was cannulated for blood pressure measurement in the distal aorta. Ultrasound-guided access to the femoral artery (device side) was achieved, and a sheath (8 or 14 Fr) was positioned. A cerebral oximetry probe (LICOX, Integra LifeSciences, Plainsboro, NJ) was placed to monitor cerebral oxygenation.

Hemorrhage Phase

Hemorrhagic shock was established during a 30-minute period using a previously described method of rate and volume controlled hemorrhage.[10,11] In brief, 35% of blood volume (total circulatory volume of the pig calculated as 66 mL/kg) was withdrawn through the catheter in the femoral artery, half taken over 7 minutes and the remaining half over 13 minutes. To avoid splenic autotransfusion, animals were subjected to ongoing hemorrhage at a rate of 0.15 mL/kg per minute for an additional 10 minutes to ensure hemorrhagic shock was maintained. Shed blood was banked in citrated bags for transfusion during the resuscitation phase. If mean arterial pressure (MAP) decreased less than 30 mm Hg, hemorrhage

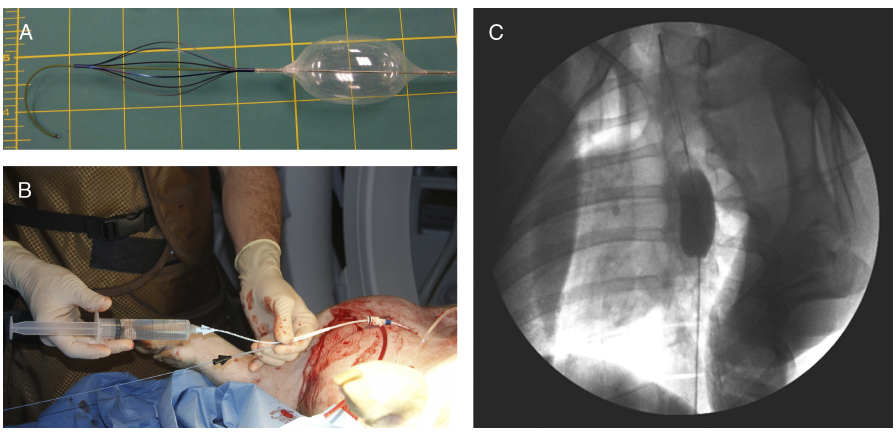

Figure 1. *A,* Single component PBS designed to be positioned and inflated without fluoroscopy. The lead or insertion end is a floppy tipped 0.035-inch wire fused to the compliant balloon catheter. A collapsible nitenol rail system is positioned between the floppy tip of the wire and the compliant balloon for the purpose of centering the system within the axial arterial lumen as the device is inserted and positioned. *B,* Photograph of the PBS having been inserted through an 8 Fr right femoral artery sheath. The syringe is filled with a mixture of contrast agent and saline for balloon inflation. *C,* Fluoroscopic image of the PBS inflated in the thoracic aorta with the floppy wire tip and flexible nitenol rail system proximal to the inflated balloon.

was stopped until the pressure was greater than 30 mm Hg, at which point hemorrhage was resumed.

REBOA Phase

Following hemorrhage, REBOA was performed with either the prototype or the conventional system. In the PBS group, devices were inserted through the femoral sheath (8 Fr) without fluoroscopic guidance (Fig. 1). The depth of insertion was determined using an estimated external measure of torso extent, which spanned a line from the inguinal crease to the midsternum. This distance was used as the estimated transfemoral insertion distance or depth for the PBS device. PBS devices were advanced to this depth or distance without fluoroscopy and inflated with a mixture of saline and contrast agent. Placement was confirmed with fluoroscopy and recorded as accurate if in the thoracic aorta (Fig. 1). If resistance was met during insertion, the PBS was stopped, and the catheter position was checked with fluoroscopy; placement was not adjusted after imaging. Inaccurate positioning was defined as placement of the PBS within a branch vessel of the aorta or in the abdominal aorta. In the CBS group, the Amplatz wire was advanced into the thoracic aorta through the femoral artery sheath (14 Fr) using fluoroscopic guidance. The wire was pinned in place, while the Coda balloon catheter was advanced into position in the thoracic aorta using conventional "over-the-wire" maneuvers. The Coda was inflated under fluoroscopic visualization using a mixture of saline and contrast agent.

Resuscitation Phase

Following 60 minutes of REBOA with CBS or PBS, the balloon was deflated and a 6-hour resuscitative phase initiated. Gradual balloon deflation was performed to avoid sudden cardiovascular collapse. Specifically, attention was given to blood pressure during and after balloon deflation with whole shed blood and vasopressor medications given to maintain a goal MAP of 60 mm Hg or greater. After shed, whole blood was transfused, 1 L boluses of saline were administered to maintain MAP until a threshold of 20 mL/kg of crystalloid was reached. Persistent hypotension was treated with vasopressor norepinephrine starting at 4 μg/h and titrated to MAP of 60 mm Hg; animals which were refractory and nearing cardiovascular collapse received a 10-μg bolus of norepinephrine until an infusion could be established. Following resuscitation, animals were transitioned from isofluorane to ketamine and versed infusion and survived in an intensive care phase for 48 hours.

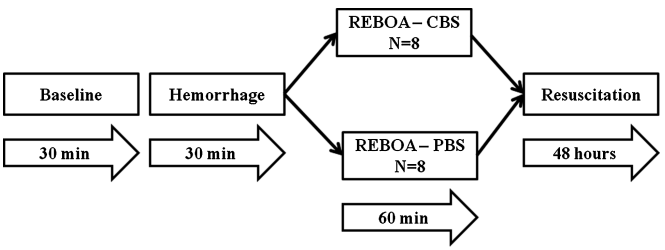

Figure 2. Consort diagram of the study protocol which included baseline, hemorrhage, REBOA, and resuscitation phases.

TABLE 1. Baseline Measurements and Hemorrhage Volumes of the Study Groups (Mean and SD)

Variable	CBS Group	PBS Group	*p*
n	8	8	
Weight, kg	77.5 (5.9)	78.5 (6.6)	0.755
Female	8 (100%)	8 (100%)	n/a
Physiologic			
SBP, mm Hg	94 (37)	81 (10)	0.180
MAP, mm Hg	65.1 (10.4)	64.3 (6.4)	0.895
HR, beats/min	81 (8)	93 (13)	0.270
Temperature, °C	34.9 (1.3)	35.5 (1.2)	0.300
$PBrO_2$, mm Hg	18.7 (14.4)	49.6 (78.4)	0.209
Carotid Flow, mL/min	346.8 (87.4)	375.9 (87.8)	0.548
Laboratory measures			
pH	7.50 (0.03)	7.51 (0.05)	0.853
P_{CO_2}, mm Hg	38 (4)	38 (5)	0.910
P_{O_2}, mm Hg	247 (47)	209 (33)	0.077
K+, mmol/L	3.39 (0.02)	3.36 (0.13)	0.951
Glucose, mg/dL	84 (13.7)	98.8 (27.2)	0.526
Lactate, mmol/L	0.84 (0.15)	1.18 (0.41)	0.710
Base excess, mEq/mL	6.45 (2.12)	6.63 (1.20)	0.917
HCO_3, mmol/L	30.4 (1.9)	30.6 (1.3)	0.929
Hemoglobin, g/dL	9.4 (1.0)	8.2 (1.1)	0.076
Hemorrhage			
Predicted volume, mL	2,072 (174)	2,044 (156)	0.741
Actual volume, mL	1,942 (278)	1,867 (294)	0.609
SBP after hemorrhage, mm Hg	46 (11)	46 (7)	0.940
HR after hemorrhage, mm Hg	167 (15)	148 (46)	0.571

p value less than 0.05 was considered significant.
$PBrO_2$, partial pressure of brain oxygen; n/a, not applicable.

At the conclusion of the resuscitation phase, animals were euthanized and underwent necropsy.

Data Acquisition, Timeline, and Outcome Measures

Systolic blood pressure (SBP), heart rate (HR), core temperature, partial pressure of brain oxygen, and carotid flow were monitored, and circulating markers of perfusion and end-organ injury were measured. After baseline observations, data were recorded at 30, 45, 60, minutes and 3, 6, 24, 48, hours after hemorrhage. The primary outcome measure was accurate placement of either the CBSor PBS in the thoracic aorta. Secondary outcome measures included mortality, carotid flow, partial pressure of brain tissue oxygenation, central arterial pressure or MAP, serum pH, base deficit, lactate, fluid volume and vasopressor requirement, and histologic analysis of the aorta, heart, lung, kidney, brain, and spinal cord.

Statistical Analysis

Data were analyzed with SAS version 9.2 (SAS Institute Inc., Cary, NC). Normally distributed measures were compared with *t* test, while Wilcoxon rank-sum method was used for nonparametric measures. Proportions were compared by either χ^2 or Fisher's exact test as appropriate. For repeated measures, comparisons were conducted using a model with autoregressive first-order covariance structure treating time as a

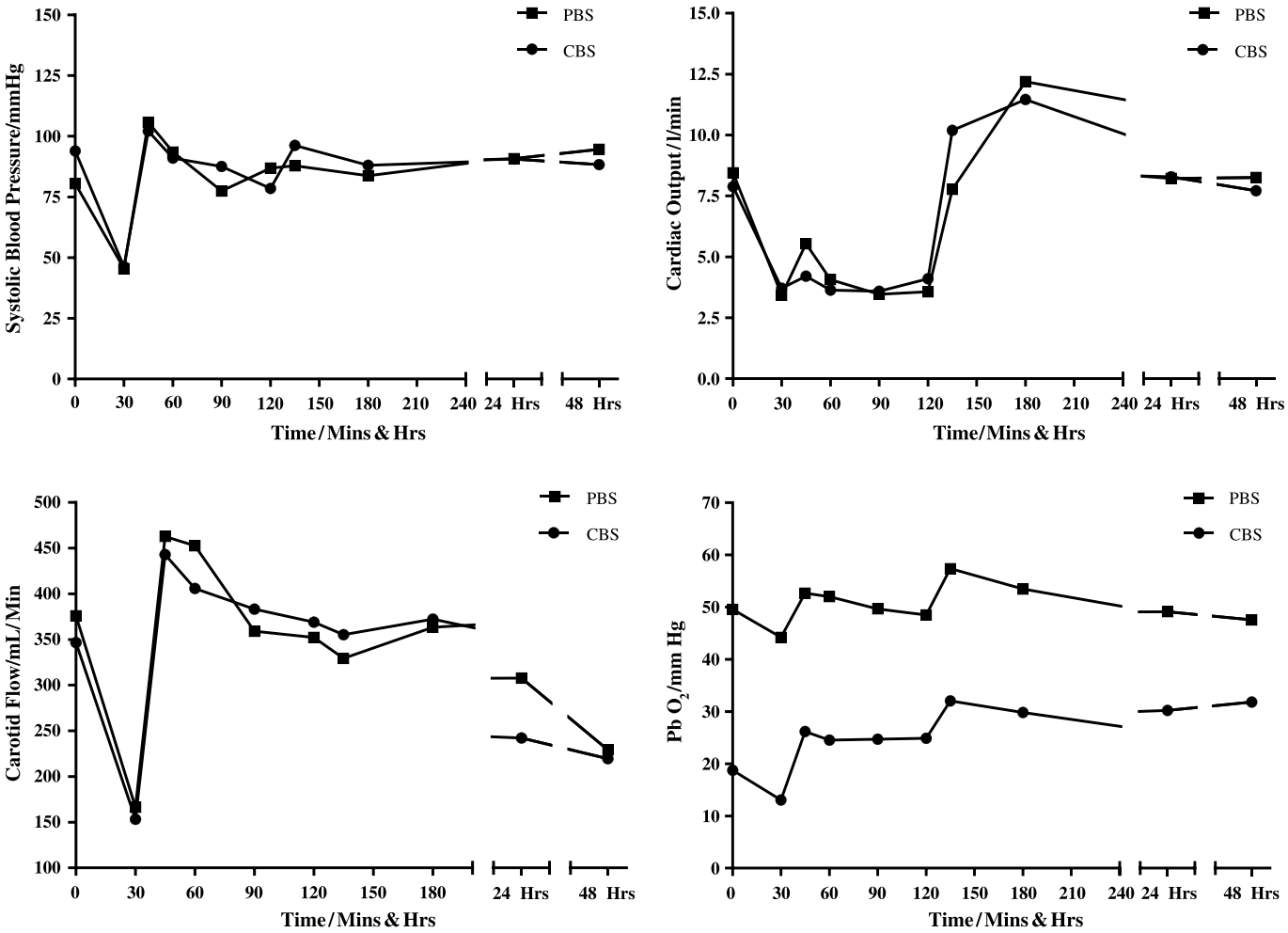

Figure 3. Hemodynamic measurements performed during the course of the study. There was no difference in the hemodynamic response to REBOA between the PBS and the CBS groups.

categorical factor. A p value less than 0.05 was considered significant.

RESULTS

Baseline Characteristics and Hemorrhagic Shock

Sixteen animals were randomized to the PBS or the CBS group (n = 8 per group), and baseline characteristics are shown in Table 1. There were no differences between groups with respect to weight, baseline vital statistics, and laboratory values. The induction of Class IV shock was achieved with a mean (SD) shed blood volume of 1,904 (280) mL (predicted of 2,058 [160.4] mL, p = 0.17). At the end of hemorrhage phase, immediately before balloon inflation (t_{30}), SBP was equally reduced in both groups (PBS vs. CBS, 46 [7] mm Hg vs. 46 [11] mm Hg; p = 0.91), and HR was equally elevated (PBS vs. CBS, 167 mm Hg [15] vs. 148 [46] mm Hg; p = 0.91).

Balloon Deployment, Inflation, and Resuscitation

Accurate balloon positioning and inflation rate was 87.5% in the PBS and 100% in the CBS group. One aberrant placement in the PBS group occurred when the device entered a right renal artery, which had a cephalad angle or takeoff at its origin from the abdominal aorta. REBOA resulted in similar increases in MAP, carotid blood flow, and partial pressure of brain oxygenation in the PBS and CBS groups, while there was no increase in cardiac output following balloon inflation in either group (Fig. 3). Balloon occlusion times were the same in PBS and CBS (77.0 [11.3] minutes vs. 70.3 [12.3] minutes, p = 0.30) as were times to complete balloon deflation (17.6 [11.6] minutes vs. 13.1 [10.2] minutes, p = 0.46). Animals in the PBS and CBS groups required similar volumes of saline during 48 hours (14,301 [6,197] mL vs. 12,014 [6,699] mL, p = 0.46). Norepinephrine was the only vasopressor administered during resuscitation, and there was no difference between PBS and CBS with respect to total requirements (5,733 [8,129] μg vs. 1,157 [2,579] μg, p = 0.21).

Physiologic Derangement, Mortality, and Histologic Examination

During resuscitation, the PBS and CBS groups demonstrated similar trends in serum lactate, which peaked between

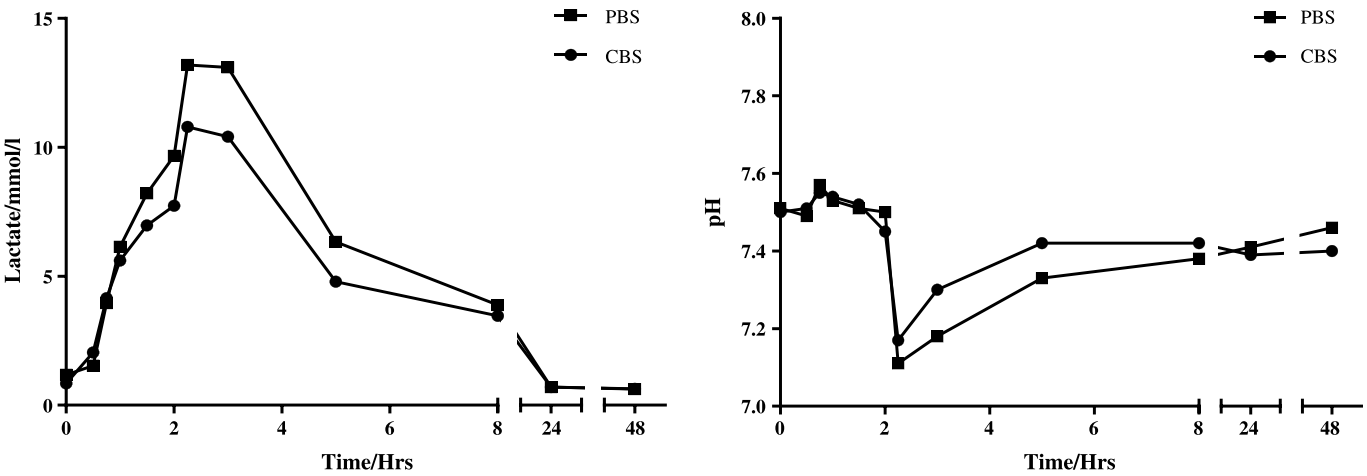

Figure 4. Serum lactate and pH during the course of the study. There was no difference in lactate or pH between the PBS and the CBS groups.

2 hours and 3 hours following balloon deflation and returned to normal by 24 hours and 48 hours (Fig. 4). A similar trend was observed in serum pH between the PBS and CBS groups. Other measures of end-organ dysfunction were elevated 24 hours following balloon deflation (Table 2). The same circulating markers remained elevated at 48 hours just before termination of the study with a higher potassium level in the CBS compared with the PBS group (7.7 [1.5] mmol/L vs. 6.1 [3.3] mmol/L, $p = 0.007$) and a higher creatine kinase level in PBS than in CBS (144,290 [138,363] U/L vs. 68,876 [57,291] U/L, $p = 0.0002$) (Table 2). Mortality was similar between groups (PBS vs. CBS, 25% vs. 12.5%, $p = 0.50$), with each of the deaths occurring during resuscitation owing to cardiac arrest from physiologic disturbances. There were no histologic differences observed among end organs examined (brain, heart, kidney, and spinal cord) in the PBS and CBS groups.

DISCUSSION

This report describes a new resuscitative endovascular balloon occlusion system designed to be placed into the thoracic aorta without the aid of radiographic imaging. Findings demonstrate the feasibility of this unibody system to be positioned and inflated in the thoracic aorta without fluoroscopy. REBOA using the new prototype results in increased central aortic pressure and cerebral perfusion, which are equivalent to those observed with the use of existing endovascular technology. Finally, results from this study demonstrate that 60 minutes of REBOA with either system is associated with a recoverably metabolic acidosis and acceptable short-term survival.

Context of Previous Research

This research confirms and extends a series of studies characterizing temporary resuscitative aortic occlusion as a maneuver used in the setting of end-stage hemorrhagic shock. In an experiment that compared the efficacy of resuscitative thoracotomy with aortic clamping to REBOA, White et al.[10] demonstrated both approaches to be effective at restoring central aortic pressure and myocardial and cerebral perfusion. White et al. also demonstrated a more severe metabolic derangement during the recovery or resuscitation phase in the resuscitative thoracotomy group compared with the endovascular balloon occlusion group.

Markov et al.[11] recently characterized the ischemic threshold of REBOA in the setting of shock comparing 30 minutes to 90 minutes of aortic occlusion in a 48-hour survival model. Using circulating markers, mortality, and histology, Markov et al. demonstrated that 90 minutes of REBOA was survivable, although it was associated with severe physiologic derangement and nonreversible end-organ damage. In that same study,

TABLE 2. Markers of End-Organ Dysfunction (Mean and SD)

	24 h			48 h		
	CBS	PBS	*p*	CBS	PBS	*p*
Lactate, mmol/L	0.70 (0.28)	0.70 (0.07)	0.522	0.63 (0.21)	0.62 (0.08)	0.693
AST, U/L	970 (626)	881 (433)	0.790	1,198 (984)	1,065 (403)	0.628
LDH, U/L	10,527 (12,915)	10,392 (7,995)	0.989	7,259 (7,216)	8,742 (5,423)	0.452
Creatinine, mg/dL	2.3 (1.2)	1.7 (0.4)	0.029	1.7 (0.8)	1.5 (0.2)	0.418
K+, mmol/L	7.49 (1.72)	7.60 (1.28)	0.845	7.66 (1.45)	6.10 (3.27)	0.007
CK, U/L	47,031 (14,109)	70,152 (32,362)	0.228	68,876 (57,291)	144,290 (138,363)	<0.001

AST, aspartate aminotransferase; CK, creatine kinase; K+, potassium; LDH, lactate dehydrogenase.

Markov et al. found that 30 minutes of REBOA was well tolerated, recoverable, and required no additional organ support during the resuscitation phase. Based on these findings, it was proposed that the maximum REBOA is 60 minutes or fewer.[11] Findings from the current study confirm that 60 minutes of REBOA with either the commercially available or the newly designed device is recoverable in this model, with a normalization of acidosis within 24 hours of balloon deflation.

Others have demonstrated the effectiveness of REBOA in the setting of uncontrolled hemorrhage and shock. Avaro et al.[12] subjected pigs to splenic disruption and compared control animals with groups of 40 minutes and 60 minutes of REBOA. Animals were resuscitated with normal saline and not shed whole blood for a 2-hour recovery phase. Avaro et al. demonstrated a mortality benefit in both REBOA groups compared with controls, and all animals in the 40-minute occlusion time group survived. From that study, the authors observed a more severe physiologic derangement in the 60-minute versus the 40-minute occlusion time group and postulated 40 minutes to be the maximum REBOA time. However, in contrast to the current study, the report of Avaro et al. used normal saline as a resuscitation fluid, which may have limited the resiliency of their cohorts to reperfusion injury and introduced conservative bias to their findings.

Endovascular Technology for Proactive Aortic Control

The most significant aspect of the current study is introduction of a new, low-profile REBOA technology able to be positioned and inflated without radiographic imaging. To date, REBOA has been studied using commercially available balloons designed to be used in the setting of complex vascular operations with support of an operating room and fluoroscopy.[13–15] As such, existing balloon technology is typically large diameter (12–14 Fr) and better suited for the management age-related vascular disease. As an example, the compliant Coda (Cook Medical) balloon used in this study has a diameter of 32 mm to 40 mm and requires large sheath (14 Fr) access for placement. Although well suited for dilated or ectatic aortas in elderly patients with aneurysm disease, this device is too large to be routinely used for REBOA in younger trauma patients. Other occlusion balloons have similarly large diameters and require "over-the-wire" fluoroscopic guidance for positioning and inflation.

In this context, the PBS (Pryor Medical, Arvada, CO) represents technology designed with hemorrhage control and resuscitation for trauma as the originating premise. The most important characteristic of this and future technologies for REBOA in trauma is liberation from radiographic imaging. Although a lower insertion profile is imperative, the ability to accurately introduce, position, and inflate REBOA devices without fluoroscopy represents the paradigm shift, which would allow this maneuver to be performed in urgent settings. If REBOA devices also included the ability to monitor central aortic pressure before, during, and following inflation of the balloon, one could envision proactive access and control of the aorta in patients prone to cardiovascular collapse. In this context, resuscitative aortic occlusion could move from a reactive and terminal operation to a proactive, less invasive maneuver. Other favorable characteristics of future REBOA devices may include pressure regulated inflation to guard against aortic wall injury and catheters designed to resist balloon egress or "retreat" with the return of central aortic pulse pressure. Although not all of these characteristics are present in the prototype used in this study, the current technology introduces the concepts and demonstrates feasibility in a live tissue model.

Limitations

This study has limitations worth considering. Foremost, the prototype balloon catheter in this study was designed for this translational model, and these results do not necessarily translate to human aortic anatomy or shock physiology. It should be pointed out that one of the balloon insertions in the PBS group inadvertently entered a renal artery. While the renal arteries in the quadruped are directed cephalad and more easily accessed from a transfemoral approach, this aberrant placement should not be overlooked. Misplacement of the PBS in this one case underscores the preliminary nature of this prototype and suggests that a "self-centering" mechanism requires modification and further study.

The results of this study were in a model with limited survival without assessment of lower-extremity strength. As such, the deleterious effects of 60 minutes of REBOA may not have been fully ascertained. Although spinal cord ischemia was not present on histology, a longer survival would be required to examine the effects of REBOA on cord and extremity function. Another limitation is the controlled nature of hemorrhage and what was ostensibly artificial hemorrhagic shock. In this context, the model did not assess REBOA in the most extreme cases of free hemorrhage but was chosen instead to assess the technical deployment of these devices and basic hemodynamic consequences of balloon inflation. Future studies are underway in models of free hemorrhage and high mortality to assess lifesaving benefits of these devices.

CONCLUSION

In conclusion, this study reports a newly designed resuscitative endovascular balloon occlusion system able to be placed without radiographic imaging. This unibody system is able to be positioned and inflated in the thoracic aorta without fluoroscopy, although additional design and study are required to assure consistent positioning. REBOA with this prototype is an effective adjunct in this model, equivalent to existing endovascular technology. Future development of lower-profile, fluoroscopy-free endovascular balloon catheters may allow for proactive aortic control in patients at risk for hemorrhagic shock and cardiovascular collapse.

AUTHORSHIP

J.L.E., J.R.S., and T.E.R. designed the study. D.J.S. and C.V. searched the literature. D.J.S., C.V., and J.R.S. collected the data, which D.J.S., C.V., J.J.M., R.H., and T.E.R. analyzed and J.L.E. interpreted. D.J.S., J.L.E., C.V., J.J.M., R.H., and T.E.R. wrote the manuscript, which J.L.E., J.J.M., R.H., and T.E.R. critically revised. D.J.S., C.V., and J.R.S. handled the conduct of protocol and T.E.R. handled the funding of the study.

DISCLOSURE

J.L.E. and T.E.R. declare a current patent relationship (item 8 on Copyright Transfer Agreement) related to the content of this manuscript: Application No. PCT/US11/33368, and the US National Phase: US Application No. 13/642,465.

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