Resuscitative endovascular balloon occlusion of the aorta (REBOA): Comparison with immediate transfusion following massive hemorrhage in swine

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BACKGROUND: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is less invasive than emergency department thoracotomy for the treatment of massive hemorrhage. We evaluated the effects of REBOA on carotid blood flow ($Q_{carotid}$) in a porcine model of massive hemorrhage. We hypothesized that REBOA restores $Q_{carotid}$ faster than reinfusion of blood.

METHODS: Spontaneously breathing sedated Sinclair pigs underwent exponential hemorrhage of 65% total blood volume in 1 hour. They were randomized into three groups. Positive control (PC, n = 7) underwent immediate transfusion of shed blood. REBOA (n = 21) received a novel 7 Fr ER-REBOA catheter (Pryor Medical, Arvada, CO) placed into aortic Zone 1 via a femoral artery introducer for 30 minutes or 60 minutes, with transfusion either after deflation or midway through inflation. Negative control (n = 7) received no resuscitation. $Q_{carotid}$ was recorded continuously using an ultrasonic flow probe. Survival and time between $Q_{carotid,\ min}$ and both a stable maximal value ($Q_{carotid,\ max}$) and restoration of baseline flow ($Q_{carotid,\ new\ BL}$) were compared by Kaplan-Meier analysis.

RESULTS: Median time to $Q_{carotid,\ max}$ was 3.0 minutes in the REBOA group versus 9.6 minutes in the control group ($p = 0.006$). Median time to $Q_{carotid,\ new\ BL}$ was 6.0 minutes in the REBOA group versus 20.5 minutes in the PC group ($p = 0.11$). Slope of the linear regression between $Q_{carotid,\ min}$ and $Q_{carotid,\ new\ BL}$ was 16.7 in REBOA and 10.4 in PC ($p = 0.31$). Four-hour survival was 95% (20 of 21) in the REBOA group versus 71% (5 of 7) in the PC group ($p = 0.06$) and 0% in the negative control group.

CONCLUSION: REBOA resulted in the restoration of $Q_{carotid}$ ("cerebrovascular resuscitation") at least as rapidly as retransfusion of shed blood, with equivalent 4-hour survival. Further studies of REBOA, to include mitigation of end-organ effects and longer follow-up, are needed.

KEY WORDS: Swine; shock, hemorrhagic; aorta; endovascular procedures.

Recent conflicts in Afghanistan and Iraq, while demonstrating the efficacy of techniques for control of compressible extremity bleeding such as tourniquets and hemostatic dressings, have only highlighted the difficulty in controlling noncompressible torso hemorrhage (NCTH).[1,2] Thus, study of Eastridge et al.[3] of deaths on the battlefield for 2001 to 2011 showed that of the potentially survivable prehospital deaths, 91% were caused primarily by hemorrhage and that the site of such bleeding was truncal in 67%. Kisat et al.[4] applied the military definition of NCTH to civilians in the US National Trauma Data Bank for 2007 to 2009, finding a mortality rate of 45%; the most lethal injury was a major torso vessel injury. These studies underscore the lethality of NCTH in both civilian and military settings and the need to develop new interventions if survival is to be improved.

When NCTH causes profound hemorrhagic shock or loss of vital signs, a standard surgical intervention is emergency department resuscitative thoracotomy (EDT) with cross-clamping of the aorta. In a large civilian series, EDT was associated with an overall survival rate of 8%. Survival was best for those with penetrating cardiac injuries (31%) and worst for those with blunt injuries (2%).[5] In the military, Edens et al.[6] reported 101 EDTs during 2003 to 2007 from one combat support hospital in Iraq. Most (92%) had cardiopulmonary resuscitation in progress at the time of EDT; 11% of US casualties survived EDT; and all survived neurologically intact. Morrison et al.[7] reviewed 65 EDTs from a British hospital in Afghanistan. There were 14 survivors (22%); 40% of those arresting in the ED survived; survivors had a shorter delay from time of arrest to EDT than did nonsurvivors. These civilian and military studies indicate that traumatic cardiac arrest is a highly, but not universally, lethal event. They also prove that earlier intervention correlates with improved survival.

Could an endovascular approach—by allowing earlier intervention and by reducing the morbidity associated with thoracotomy—further improve the survival of selected patients with massive NCTH? Temporary occlusion of the aorta with an endovascular balloon has emerged as an alternative to EDT. Brenner et al.[8] reported on six patients treated in Baltimore and Houston who underwent resuscitative endovascular balloon

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occlusion of the aorta (REBOA) during 2012 to 2013. These patients underwent insertion of a 12 Fr to 14 Fr introducer into a femoral artery via percutaneous access or cut-down, followed by placement of a Cook Coda balloon catheter. In this case series, there were no hemorrhage-related deaths or REBOA complications. In this article, insertion was performed by acute care surgeons rather than by vascular surgeons, which highlights the decreasing role of specialty consultation for this endovascular procedure. These and similar experiences engendered enthusiasm for REBOA.

Meanwhile, US military researchers conducted a series of studies of REBOA in porcine models of hemorrhagic shock, summarized in Table 1. These studies used anesthetized swine and a 35% blood volume hemorrhage. Recently, Pryor Medical, Inc. (Arvada, CO) developed a fluoroscopy-free REBOA device (ER-REBOA), which is smaller in diameter (7 Fr) and which also enables monitoring of the arterial blood pressure through the catheter. Thus, early "prophylactic" placement of the device is envisioned, with subsequent inflation of the balloon if needed. The purposes of this study were to assess the utility of REBOA for the treatment of otherwise lethal hemorrhagic shock in a more severe (65% blood volume) conscious sedated porcine model and specifically to determine whether REBOA restores cerebral blood flow more quickly than does immediate transfusion of shed blood. We hypothesized that survival in REBOA-treated animals would be superior to that in transfusion-treated animals and that REBOA would restore carotid blood flow more quickly. A secondary aim was to test the new ER-REBOA for ease and efficacy of insertion.

MATERIALS AND METHODS

This study was approved by the US Army Institute of Surgical Research Animal Care and Use Committee (protocol number A-14-002). It was conducted in compliance with the Animal Welfare Act and the implementing Animal Welfare Regulations, and in accordance with the principles of the *Guide for the Care and Use of Laboratory Animals*. It was performed at a facility accredited by AAALAC International.

Sexually mature, noncastrated male Sinclair Miniature Swine (Sinclair Bio-Resources, Columbia, MO), 38 ± 9 kg, were used in this study. Animals were purpose bred, socialized, vaccinated, and free from common domestic swine diseases. Thirty-five animals were studied. They were divided into five subgroups, n = 7 each. All animals underwent 65% total blood volume hemorrhage, with subsequent care as follows:

- Positive control (PC): 65% blood volume hemorrhage and then immediate transfusion of shed blood.
- Negative control (NC): 65% blood volume hemorrhage and then no intervention.
- A30: REBOA × 30 minutes, followed by transfusion of shed blood.
- A60: REBOA × 60 minutes, followed by transfusion of shed blood.
- AR: REBOA × 60 minutes, with transfusion of shed blood (via the right jugular vein catheter) after 30 minutes of REBOA.

The three subgroups (A30, A60, and AR) in which REBOA was performed are subsequently referred to as the REBOA group.

Surgical Procedures

After an overnight fast, with water available ad libitum, animals were transferred to a procedure room where they were anesthetized with an intramuscular injection of buprenorphine HCl (0.05 mg/kg) and Telazol (tiletamine HCl and zolazepam HCl, Zoetis, Florham Park, NJ, 4 mg/kg). Animals were endotracheally intubated, and inhalational anesthesia was maintained using isoflurane (1–5 vol%), delivered in 100% oxygen. A Dräger Fabius GS anesthesia machine (Dräger Medical Inc., Telford, PA) was used. The following procedures were performed. In the left neck, an 8.5 Fr introducer sheath (Teleflex, Inc., Wayne, PA) was inserted into the external jugular vein via a cut-down. An Arrow 7 Fr multilumen central venous catheter (Arrow International Inc., Reading, PA) was inserted via the introducer sheath. A 6 Fr introducer sheath (Teleflex, Inc.) was inserted into the common carotid artery, and a 5 Fr VolumeView catheter (Edwards Lifesciences Corp., Irvine, CA) was then placed. This catheter was connected via a high-pressure monitoring line (Smith Medical ASD Inc., Dublin, OH) to an Infinity HemoMed Pod (Dräger Medical Inc.). In the right neck, an 8.5 Fr introducer sheath (Teleflex, Inc.) was inserted into the external jugular vein via a cut-down, and a high-pressure tubing (ICU Medical, San Clemente, CA) was inserted through the sheath. A 3-mm perivascular flow probe (PS-series, side wire exit, Transonic Systems, Inc., Ithaca, NY) was placed around the common carotid artery. In the right groin, the common femoral artery was accessed via a cut-down and cannulated with a 7 Fr introducer sheath (Teleflex Inc.), for future REBOA insertion (discussed later). In the left groin, the common femoral artery was accessed via a cut-down and cannulated with an 8 Fr introducer sheath (Teleflex Inc.), and a high-pressure tubing (ICU Medical) was advanced through the sheath. A tracheostomy was

TABLE 1. Selected Zone I REBOA Studies in Swine

Reference	First Author	Year	Design (Groups)	Results
12	White	2011	No occlusion; thoracotomy and aortic clamping; REBOA	REBOA causes less physiologic adverse effects than thoracotomy, same effect on BP
9	Scott	2013	ER-REBOA; traditional two-component approach (Cook Medical Amplatz wire and Coda Balloon)	Similar efficacy
13	Markov	2013	30-min shock; 30-min shock with REBOA; 90-min shock; 90-min shock with REBOA	Higher BP in REBOA groups. Lactate cleared. End-organ injury in the 90-min REBOA group.
14	Morrison	2014	30-min REBOA, 60-min REBOA, 90-min REBOA	IL-6 increased in the 60-min and 90-min groups vs. baseline at 8 h.

All studies involved 35% hemorrhage (23 mL/kg) over 20 minutes, plus additional hemorrhage (1.5 mL/kg or 2%) over ensuing 10 minutes to ensure Class IV shock.
BP, systolic arterial blood pressure.

performed, and a 10-mm cuffed endotracheal tube (Lo-Pro, Mallinckrodt Inc., St. Louis, MO) was inserted.

After instrumentation, all incisions were closed with sutures or staples, and the wounds were infiltrated with 0.5% bupivacaine. Electrocardiography leads were attached (Cardiotronic QDOT-ST electrodes, Osypka Medical Inc., La Jolla, CA). Animals were transferred into a custom-built sling, which allows an animal to remain in an anatomic quadruped position. Inhalational anesthesia was discontinued, and buprenorphine continuous intravenous infusion was started at 5 mL/h (1 μg/kg/h). In addition, once the animal recovered sufficiently to breathe spontaneously, a midazolam bolus 2 mg was administered intravenously, and a continuous intravenous infusion 0.1 mg/kg per hour was started. A bispectral index electroencephalographic sensor (BIS, Aspect Medical Systems, Inc., Newton, MA) was placed on the animal's forehead. Subsequently, infusion rates were titrated to BIS 80–90 as well as to lack of a response to painful stimuli such as toe pinch. Infusion rates were decreased by half when mean arterial pressure (MAP) decreased to lower than 80 mm Hg and were held when MAP was lower than 50 mm Hg.

After the animal was transferred into the sling, lines and sensors were connected to the appropriate devices. Electrocardiography leads from the Dräger Infinity Delta XL Patient Monitor (Dräger Medical Inc.) were attached. The EV1000 Clinical Platform was connected to the previously inserted VolumeView Set (Edwards Lifesciences Corp.). The carotid flow probe was connected to a perivascular flow meter (TS420, Transonic Systems, Inc.).

Hemorrhage Pump System

Hemorrhage was performed using a computer-controlled peristaltic pump (Masterflex, Cole-Parmer, Vernon Hills, IL). Blood was removed via Tygon tubing (E-Lab [E3603] L/S 16, Cole-Parmer) into 500-mL Teruflex blood-collection bags containing citrate-phosphate-dextrose (CPD) with OPTISOL red/cell preservative solution (Terumo Corp., Tokyo, Japan). The bags rested on a digital balance (Mettler-Toledo Inc., Columbus, OH), which provided feedback to the blood withdrawal system. Estimated total blood volume (EBV) was calculated using the following formula: EBV = weight in kilogram × 65 mL/kg. After correcting for the blood volume withdrawn for baseline laboratory values (48.5 mL), animals were bled 65% of EBV over 60 minutes in an exponential manner:

- 7.5 minutes—13% EBV hemorrhage.
- 11.5 minutes—13% EBV hemorrhage.
- 12 minutes—13% EBV hemorrhage.
- 13 minutes—13% EBV hemorrhage.
- 16 minutes—13% EBV hemorrhage.

Tubing was primed with CPD buffer. In addition, during hemorrhage, CPD solution was infused continuously using a Hospira Plum A+ infusion pump (Hospira, Lake Forest, IL) through the hemorrhage line at a rate of 30 mL/h via a double-stopcock system to prevent line clotting.

Transfusion System

A second peristaltic pump (Masterflex Easy-Load II, Cole-Parmer) loaded with Tygon tubing (E-Lab [E3603] L/S 16, Cole-Parmer) was used to reinfuse blood in the treatment groups. The pump was connected in line with a Ranger blood warmer (3 M, St. Paul, MN), which in turn was connected via Tygon tubing to the previously inserted resuscitation line positioned in the right external jugular vein. Resuscitation tubing was primed with normal saline. Blood was reinfused at a constant rate of 100 mL/min. Calcium chloride solution (8 mg/mL) in D5W was infused concurrently with the blood transfusion at a rate of 834 mL/h.

ER-REBOA Device and Insertion

The investigational REBOA device used in this study (ER-REBOA, Pryor Medical, Inc.) is shown in Figure 1. In the REBOA groups, this device was inserted at the end of hemorrhage, via the 7 Fr introducer previously placed in the right common femoral artery. This device differs from the standard, two-component endovascular approach as follows: (1) it does not require a separate Amplatz or similar guide wire; it has a smaller diameter; it is purpose designed for this application and thus does not require fluoroscopic placement verification; and it uniquely permits above-the-balloon blood pressure monitoring. The proximal portion incorporates a stiffer component to provide sufficient column strength to withstand aortic occlusion pressures and to support catheter insertion and placement. The stiffness of the catheter shaft transitions to a distal tip, which is flexible and atraumatic in design. There are several design changes relative to the earlier prototype tested by Scott et al.,[9] including elimination of the collapsible nitenol rail system ("cage"), improved flexibility and kink resistance, mechanisms to keep catheter in the central lumen of the aorta, atraumatic tip, dedicated lumen for pressure monitoring, improved balloon design, addition of external length markers, platinum-iridium marker bands, smaller profile, and absence of any guide wire (the previous prototype used an integrated guide wire as part of its design).

Insertion was performed by a postgraduate year 3 general surgery resident (T.S.P.). This operator underwent a brief informal course of instruction on device insertion by the manufacturer but had no further endovascular training. The intended zone of insertion for the balloon was Zone 1, that is, between the left subclavian and the celiac arteries. Insertion depth was guided by the centimeter marks on the catheter. Experience with model development pigs indicated that for this weight range of pig, insertion to a depth of 40 cm would result in correct placement (i.e., 6–8 cm above the diaphragm). On-the-table confirmation of

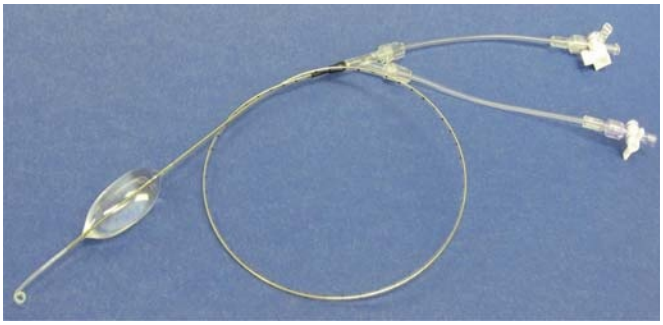

Figure 1. ER-REBOA used in the study (courtesy of David Spencer, Pryor Medical, Inc.).

placement was not performed. Postmortem placement was confirmed by (1) computed tomography (CT) and (2) necropsy. A predetermined volume (8 mL) of normal saline solution was used to inflate the ER-REBOA balloon; successful inflation was inferred by a decrease in arterial blood pressure below the balloon to near zero.

Vital Signs and Laboratory Assays

The following vital signs were recorded: heart rate (HR), carotid arterial pressures, femoral arterial pressures, and carotid blood flow. These data were recorded and stored using proprietary data acquisition software (Integrated Data Exchange and Archival [IDEA] system). Arterial blood gas analysis was performed at the bedside using an iSTAT 300-G blood analyzer (Abbott Point of Care Inc., Princeton, NJ; VetScan CG4+ and CG8+ cartridges, Abaxis Inc., Union City, CA).

Carotid Flow Data

Continuous carotid blood flow ($Q_{carotid}$) was recorded to a computer using IDEA software. A 60-second moving average window was used to derive a stable measurement of flow. Three analyses were performed. First, the data were plotted over time and were manually reviewed to identify flow rate nadirs at the end of hemorrhage ($Q_{carotid,\ min}$) and stable maximum flow rates ($Q_{carotid,\ max}$) after REBOA inflation (in the REBOA group) or after transfusion (in the PC group). Then, the time difference between the $Q_{carotid,\ max}$ and $Q_{carotid,\ min}$ time points was calculated. In the second analysis, the baseline value ($Q_{carotid,\ BL}$) was computed. The time point after the nadir when carotid blood flow again reached the baseline value ($Q_{carotid,\ new\ BL}$) was identified. Then, the time difference between the $Q_{carotid,\ new\ BL}$ and $Q_{carotid,\ min}$ time points was calculated. Third, linear regression of the points between $Q_{carotid,\ min}$ and $Q_{carotid,\ new\ BL}$ was performed, and the slope of this line was calculated. This slope represents how fast carotid blood flow increased from its nadir to regain its baseline value.

Histopathology

Following euthanasia, tissue samples were fixed in neutral-buffered 10% formalin for 24 hours, trimmed, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin. Histologic images were recorded with 10× objective under a slide scanner (Axio Scan. Z1 v1.0, Zeiss, Germany). Histologic grading of injury was performed by a single pathologist blinded to the identity of the animal. For each slide, total injury score was calculated as the sum of the severity and the extent of injury. Unless otherwise indicated, severity was scored on a scale from 0 (absent) to 4 (severe). Extent of injury was scored as follows: 0, absent; 1, more than 25%; 2, 25% to 50%; 3, 50% to 75%; and 4, more than 75%. For most organs, several characteristics were scored, as follows. For the lung, five characteristics were scored (alveolar edema, alveolar hemorrhage, septal thickening, intra-alveolar inflammation, and congestion). For the heart, five characteristics were scored (edema, degeneration, inflammation, congestion, and subendocardial hemorrhage). For the liver, five characteristics were scored (vascular congestion, thrombosis, hepatic apoptosis, cellular degeneration, and inflammation). For the jejunum, each slide was scored according to the following scale: 0, normal villi; 1, villi with tip distortion; 2, villi lacking goblet cells and containing Guggenheim's spaces; 3, villi with patch disruption of the epithelial cells: 4, villi with exposed but intact lamina propria and epithelial cell sloughing; 5, villi in which the lamina propria was exuding; and 6, hemorrhaged or denuded villi. For the kidney, each slide was scored according to this scale: 0, normal histology; 1, slight alteration (loss of brush border, mild hydropic degeneration, mild congestion); 2, mild (intensive hydropic degeneration, mild vacuolization, and interstitial edema); 3, moderate (nuclear condensation, intensive vacuolization, modulate interstitial edema); and 4, severe (necrotic/apoptotic cells, denudation/rupture of basement membrane). For the aorta, four characteristics (hemorrhage, necrosis, thrombosis, and inflammation) were used to assess the injury at the each layer of tunica intima, tunica media, and tunica adventitia in the aorta. Total injury score was calculated as the sum of each layer. For the cerebral cortex, four characteristics were scored (cytotoxic edema, vasogenic edema, inflammation, and congestion). For the brain stem and hypothalamus, five characteristics were scored for each (cytotoxic edema, vasogenic edema, inflammation, hemorrhage, and congestion).

Statistical Analysis

Statistics were performed using JMP version 10.0 (SAS Institute Inc., Cary, NC) and Excel version 14.0 (Microsoft Corporation, Redmond, WA). In these analyses, REBOA and PC groups were compared, without further subgroup analysis unless otherwise stated. Survival (Kaplan-Meier) analysis was used to examine differences in survival time and in times from $Q_{carotid,\ min}$ to either $Q_{carotid,\ max}$ or $Q_{carotid,\ new\ BL}$. Continuous data were subjected to repeated-measures analysis of variance, with post hoc Bonferroni corrections, or to equivalent nonparametric tests. Significance was accepted at $p < 0.05$.

RESULTS

All attempts at introduction of the ER-REBOA device through the 7 Fr introducer sheath and at thoracic aortic occlusion were successful. Time required to advance the device through the introducer up to the desired location was less than 10 seconds in all cases. Once the technique was perfected during model development, the device was correctly placed on the first attempt every time. No REBOA-related complications—such as aortic rupture, intimal tear, or dissection; access site hematoma, dissection, transection, or pseudoaneurysm; and so on—were observed. The animals were not evaluated for possible long-term neurologic complications in this acute experiment. Successful placement in Zone 1 of the aorta was confirmed by postmortem CT scan and by necropsy in all pigs (Figs. 2 and 3). Misplacement into side vessels or distal catheter migration was not observed.

Four-hour survival was 95% (20 of 21) in the REBOA group versus 71% (5 of 7) in the PC group ($p = 0.06$, log-rank test; see Supplemental Digital Content 1, http://links.lww.com/TA/A658).

$Q_{carotid}$ in the REBOA group increased to a median of 26% (interquartile range [IQR], 10–48) of $Q_{carotid,\ min}$ after 1 minute, 78% (IQR, 49–137) after 2 minutes, and 136% (IQR, 86, 197) after 3 minutes. Restoration of $Q_{carotid}$ was compared using two methods (see Supplemental Digital Content 2, http://links.lww.com/TA/A659). In the first method, a stable postbleed maximum ($Q_{carotid,\ max}$) was identified. By this method,

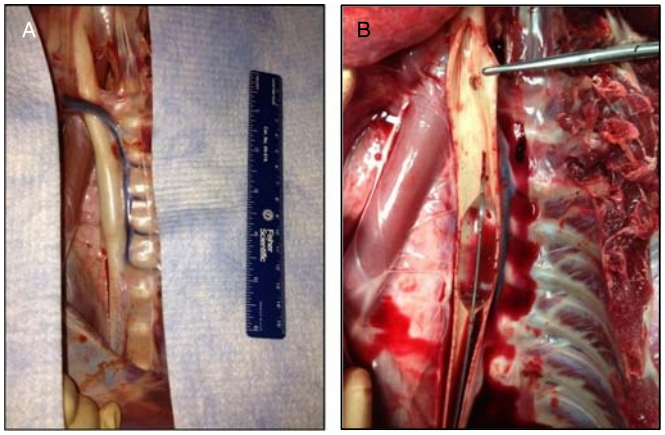

Figure 2. ER-REBOA device on necropsy. *A*, View of the intact aorta. *B*, View of the aorta lumen with the device in place.

REBOA restored $Q_{carotid}$ more rapidly. Median time to $Q_{carotid, max}$ was 3.0 minutes (IQR, 1.8–3.6) in the REBOA group and 9.6 minutes (IQR, 4.8–13.2) in the PC group ($p = 0.006$, log-rank test). In the second method, the time point at which $Q_{carotid}$ was restored to its prebleed baseline ($Q_{carotid, new\ BL}$) was identified. By this method, median time to $Q_{carotid, new\ BL}$ was 6.0 minutes (IQR, 3.5–30.0) in the REBOA group and 20.5 minutes (IQR, 8.8–40.8) in the PC group ($p = 0.114$, log-rank test).

In addition, linear regression of the data between the nadir ($Q_{carotid, min}$) and $Q_{carotid, new\ BL}$ was performed, and the slope (i.e., the rate of change of $Q_{carotid}$) was calculated. Median slope was 16.7 (IQR, 3.7–34.8) in the REBOA group and 10.4 (IQR, 2.4–16.6) in the PC group ($p = 0.307$, Wilcoxon rank-sum test).

Other data are presented in Table 2. These data are significant for the following. By 30 minutes after completion of resuscitation, HR and blood pressure remain persistently different from baseline in the REBOA group, but without a difference compared with the PC group at that time point. Lactate levels are elevated compared with those in the baseline in both groups at the 30-minute time point, with a higher lactate in the REBOA group than in the PC group. At the end of hemorrhage, $Q_{carotid}$ was decreased in both groups compared with baseline. In addition, a difference between groups is also seen at that time point. At its maximal value after resuscitation, $Q_{carotid}$ is not different from baseline in either group. In addition (for REBOA animals only), we compared MAPs above the balloon with those below the balloon; we did this before, during, and after REBOA inflation. The purpose of this analysis was to determine whether balloon inflation was effective in decreasing downstream pressure. As expected (see Supplemental Digital Content 3, http://links.lww.com/TA/A660), we found that pressure below the balloon decreased to near-zero levels with balloon inflation.

Quantitative histopathology scores demonstrated the following. There was a significant difference between REBOA and NC groups on the kidney and liver scores, with REBOA animals higher (more injured) than the NC animals ($p < 0.05$). Specifically, median kidney scores were 2.00 (IQR, 0–5.25) for REBOA and 0 (IQR, 0–0) for NC; median liver scores were 1.20 (IQR, 0–2.85) for REBOA and 0 (IQR, 0–0) for NC. All other differences were nonsignificant.

DISCUSSION

The principal findings of this study were as follows: (1) REBOA was at least as effective as immediate blood transfusion in restoring carotid blood flow following hemorrhage of 65% of the estimated blood volume in swine. (2) REBOA resulted in short-term (4-hour) survival, which was equivalent to immediate reinfusion of shed blood. (3) Hemorrhage and resuscitation resulted in significant lactic acidosis in both groups. Residual lactic acidosis was greater in the REBOA group in the early postresuscitation period. (4) Insertion of the ER-REBOA

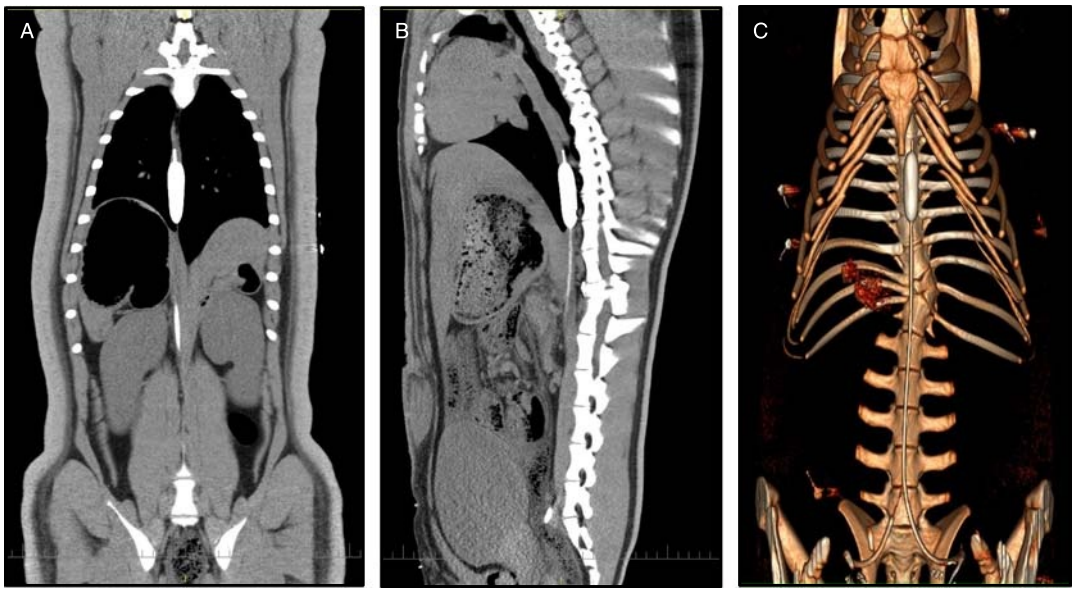

Figure 3. ER-REBOA device on CT scan. *A*, Coronal plane. *B*, Saggittal plane. *C*, Three-dimensional reconstruction.

TABLE 2. Selected Vital Sign and Laboratory Results

	Group	BL	MH	EH	t_{Qmax}	R30
HR, beats/min	REBOA	73 ± 17	129 ± 30*	179 ± 28*		119 ± 28*
	PC	84 ± 17	151 ± 47*	172 ± 40*		111 ± 30
MAP, mm Hg	REBOA	117 ± 13	63 ± 18*	43 ± 11*		92 ± 21*
	PC	123 ± 21	82 ± 33*	31 ± 14*		105 ± 32
LAC, mmol/L	REBOA	0.6 ± 0.2	1.4 ± 0.4	5.2 ± 2.3***		12 ± 1.5***
	PC	0.7 ± 0.2	2.0 ± 1.0	8.2 ± 1.4***		8.8 ± 3.7***
$Q_{carotid}$, mL/min	REBOA	194 ± 78	141 ± 54*	78 ± 36***	218 ± 68	180 ± 59*
	PC	197 ± 56	123 ± 61*	53 ± 29***	236 ± 78	232 ± 62

*$p < 0.05$ compared with baseline.
**$p < 0.05$ between groups.
BL, baseline; EH, at the end of hemorrhage; LAC, arterial blood lactate; MH, midway through hemorrhage, that is, after 31 minutes; $Q_{carotid}$, carotid blood flow; R30, 30 minutes after completion of resuscitation (i.e., after infusion of blood for PC group and after deflation of REBOA and infusion of blood for the REBOA group); t_{Qmax}, time point at which postresuscitation $Q_{carotid}$ is maximal.

was fast, easy, and successfully performed without image guidance, in a scenario in which vascular access (introducer sheath) had already been achieved.

NCTH has been identified as the cause of death in a large percentage of combat casualties judged to have potentially survivable injuries.[3,10] EDT is a standard approach to the patient with penetrating thoracic trauma who presents in extremis, but improved endovascular techniques inspired the application of REBOA to selected patients in trauma centers, with promising results in small series.[8] Morrison et al.[11] performed a retrospective gap analysis of severely injured UK casualties in Iraq and Afghanistan, with mean Injury Severity Score (ISS) of 40. Of these, 244 (18.5%) had an indication for REBOA, defined as a torso or junctional injury. The mortality in this high-risk group was 173 patients (70.9%); 165 (57.6%) of the 244 patients had signs of life en route, of whom 95 (57.6%) died. This group of 165 torso- and junctional-injured patients with a high risk of death but with signs of life in the field is the target of opportunity for REBOA, to include potentially prehospital REBOA.

A US military group (Rasmussen and colleagues),[9,12–14] in a series of studies in swine with hemorrhagic shock, demonstrated the utility of REBOA as an adjunct to resuscitation, with inflation times between 30 minutes and 90 minutes, and postoperative follow-up of up to 48 hours (Table 1). In 2013, Scott et al.[9] described experience with a new, fluoroscopy-free REBOA catheter, an earlier version of the catheter used in the present study. They compared catheter (Pryor Medical) with a traditional over-the-wire approach, using an Amplatz wire and a Cook Coda balloon. Further development has led to the ER-REBOA device tested in the present study; the manufacturer expects FDA 510(k) clearance of the device by first quarter of 2016 (D. Spencer, personal communication, August 28, 2015).

Our goals were to perform an independent evaluation of the next-generation ER-REBOA device and to examine its efficacy in restoring brain perfusion in comparison with immediate reinfusion of shed blood. Our model differed from the model used by the Rasmussen group. in the following respects. We used a more severe model (65% vs. 35% blood volume hemorrhage). We used mature, sexually intact male Sinclair miniature swine, whereas Rasmussen et al. used female Yorkshire-Landrace crossbreeds. We maintained our animals in slings in the ventrally recumbent position, conscious, and spontaneously breathing (but sedated). Rasmussen et al. maintained their animals in the dorsally recumbent position under isoflurane general anesthesia. The differences in animal management help explain why a much greater volume of hemorrhage was achieved in our study. Specifically, anesthesia and dorsal recumbency in the studies by Rasmussen et al. likely decreased the animals' tolerance of hemorrhage.

In this study, we estimated cerebral perfusion by means of carotid blood flow measurements using an ultrasonic flowmeter. We used two methods of assessing the rapidity with which a resuscitative intervention (transfusion or REBOA inflation) restored carotid blood flow. The first method was based on visual inspection of individual blood flow curves and identification of the point at which blood flow reached a stable maximum after the intervention. With the use of this method, flow was restored more quickly by REBOA than by transfusion.

Because this method is subject to observer bias, we used a second method. This was based on determining the time point at which blood flow returned to its baseline value. With the use of this method, flow was restored equally quickly by REBOA and by transfusion. This also enabled us to calculate the rate of change in blood flow after intervention. This indicated, again, no difference between the groups. This approach allowed us to correct, at least in part, for the observation (Table 2) for the fact that $Q_{carotid}$ was lower in the PC group than in the REBOA group at the end of hemorrhage. Taken together, the analyses indicate that REBOA, even in severely volume-depleted animals (65% hemorrhage), restores blood flow to the brain at least as rapidly as transfusion.

This finding is reassuring and points to the utility of REBOA as a method of rapid cerebrovascular resuscitation during profound hemorrhagic shock. Although not addressed in this study, this method should be effective even in the face of ongoing hemorrhage below the level of the balloon. Future work should focus on the following issues: (1) methods to resuscitate animals during the ischemia-reperfusion insult following balloon deflation; (2) methods to perfuse the lower body, even if intermittently, during prolonged balloon inflation; (3) other methods of protecting the vital organs, lower extremities, and spinal cord during prolonged balloon inflation and after deflation.

In the present study, ER-REBOA placement was performed by a novice interventionalist with no formal training yet took less than 10 seconds to perform in all cases. It is important to point out that the introducer was already in place in the right common femoral artery before REBOA insertion, adding to the ease and rapidity of deployment. This speaks to the importance of rapid vascular access techniques in managing actual patients with REBOA; access is likely the rate-limiting step. Despite the ease and rapidity of placement, complications relating to aortic or femoral injury were not observed. This study was not designed to evaluate the pigs for long-term organ damage, to include neurologic damage. The introducer was placed via cut-down, rather than percutaneously. However, this reflects technical differences between pigs and humans, and we anticipate percutaneous introducer placement in human patients. Another limitation is the absence of uncontrolled hemorrhage in this model. We can surmise, but not conclude, that REBOA would be effective in decreasing lower body exsanguination. Future studies should evaluate efficacy in such models.

We conclude that this work, together with previous work by others,[9] signals the advent of technology that will likely save lives in a very high-risk population.

AUTHORSHIP

T.S.P., A.I.B., M.A.D., and L.C.C. designed this study. T.S.P., S.M.B., B.S.J., W.L.B., and C.N.N. collected the data. W.L.B., A.I.B., C.N.N., J.K.A., and L.C.C. contributed to the data analysis. A.I.B., J.K.A., M.A.D., and L.C.C. performed the data interpretation. T.S.P., S.M.B., and L.C.C. wrote the manuscript. A.I.B., B.S.J., W.L.B., J.K.A., M.A.D., and L.C.C. contributed to the critical revision.

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DISCLOSURE

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