Automated variable aortic control versus complete aortic occlusion in a swine model of hemorrhage

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BACKGROUND: Future endovascular hemorrhage control devices will require features that mitigate the adverse effects of vessel occlusion. Permissive regional hypoperfusion (PRH) with variable aortic control (VAC) is a novel strategy to minimize hemorrhage and reduce the ischemic burden of complete aortic occlusion (AO). The objective of this study was to compare PRH with VAC to AO in a lethal model of hemorrhage.

METHODS: Twenty-five swine underwent cannulation of the supraceliac aorta, with diversion of aortic flow through an automated extracorporeal circuit. After creation of uncontrolled liver hemorrhage, animals were randomized to 90 minutes of treatment: Control (full, unregulated flow; n = 5), AO (no flow; n = 10), and PRH with VAC (dynamic distal flow initiated after 20 minutes of AO; n = 10). In the PRH group, distal flow rates were regulated between 100 and 300 mL/min based on a desired, preset range of proximal mean arterial pressure (MAP). At 90 minutes, damage control surgery, resuscitation, and restoration of full flow ensued. Critical care continued for 4.5 hours or until death. Hemodynamic parameters and markers of ischemia were recorded.

RESULTS: Study survival was 0%, 50%, and 90% for control, AO, and VAC, respectively ($p < 0.01$). During intervention, VAC resulted in more physiologic proximal MAP (84 ± 18 mm Hg vs. 105 ± 9 mm Hg, $p < 0.01$) and higher renal blood flow than AO animals ($p = 0.02$). During critical care, VAC resulted in higher proximal MAP (73 ± 8 mm Hg vs. 50 ± 6 mm Hg, $p < 0.01$), carotid and renal blood flow ($p < 0.01$), lactate clearance ($p < 0.01$), and urine output ($p < 0.01$) than AO despite requiring half the volume of crystalloids to maintain proximal MAP ≥50 mm Hg ($p < 0.01$).

CONCLUSION: Permissive regional hypoperfusion with variable aortic control minimizes the adverse effects of distal ischemia, optimizes proximal pressure to the brain and heart, and prevents exsanguination in this model of lethal hemorrhage. These findings provide foundational knowledge for the continued development of this novel paradigm and inform next-generation endovascular designs. (*J Trauma Acute Care Surg.* 2017;82: 694–703.

KEY WORDS: Trauma; endovascular; resuscitation; hemorrhage; swine.

Endovascular therapies for the management of non-compressible hemorrhage have emerged as a viable option to overcome the limitations of resuscitative thoracotomy and are effective at restoring perfusion to proximal vascular beds.[1,2] Resuscitative endovascular balloon occlusion of the aorta (REBOA) is one such strategy that provides a minimally invasive alternative to resuscitative thoracotomy.[2–6] However, current REBOA techniques do not sufficiently address the adverse physiologic consequences of complete aortic occlusion (AO) on vascular beds both proximal and distal to the site of occlusion. In proximal vascular beds, AO can result in supraphysiologic blood pressure and increased cardiac afterload that may be detrimental to the heart, lungs, and brain.[1,7–10] Distal to the site of occlusion, progressive end-organ ischemia develops rapidly and eventually leads to irreversible damage.[11,12] Additionally, balloon deflation and restoration of distal flow often results in severe ischemia reperfusion injury and rebound hypotension.[13] Despite these limitations, catheter-based interventions hold

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

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great potential for improving outcomes in noncompressible torso hemorrhage.

To address the limitations of REBOA, partial flow restoration using a balloon catheter before definitive hemorrhage control has been proposed and described in both isolated clinical reports and in translational research efforts.[14–18] However, the techniques of partial REBOA (P-REBOA) and intermittent REBOA (I-REBOA) using existing technology pose a risk of ongoing hemorrhage.[17,19] Studies with large animal injury models have demonstrated that P-REBOA can lead to increased blood loss when compared to complete REBOA.[17] Furthermore, hemodynamic instability during attempts at partial flow restoration has been observed in early clinical experience.[20] Although this approach to aortic flow reintroduction is rational in resource-rich environments with access to blood products and operating rooms, it will be limited in scenarios in which a prolonged time period exists between injury and hemorrhage control. In an effort to address these limitations, we have proposed an experimental technique to deliver tightly controlled, low-volume aortic blood flow, termed variable aortic control (VAC).[21] In the context of exsanguinating hemorrhage, achieving low-volume distal aortic blood *flow* can pave the way for a novel therapeutic concept called *permissive regional hypoperfusion* (PRH). PRH with VAC is designed to meet the needs of prehospital and resource-poor environments, while simultaneously addressing the challenges that result from REBOA in heavily resourced trauma setting. This method of resuscitation aims to strike a delicate balance between the competing interests of hemorrhage control and the adverse physiologic impact of aortic occlusion on both proximal organ function and distal organ viability.

An initial proof-of-concept case series for PRH with VAC has been previously reported in a large animal model involving a severe mixed arterial and venous liver injury.[21] These previous experiments demonstrated the ability of PRH to extend the presurgical interval to 90 minutes without demise caused by exsanguination or distal ischemia. However, the short-term outcome of PRH compared to complete aortic occlusion has not been investigated. The hypothesis of this study is that permissive regional hypoperfusion with VAC will prevent exsanguination before definitive hemorrhage control and result in less physiologic derangement than complete aortic occlusion after prolonged intervention in a lethal porcine hemorrhagic shock model.

MATERIALS AND METHODS

Overview

The Institutional Animal Care and Use Committee at David Grant Medical Center, Travis Air Force Base, California, approved this study. All animal care and use was in strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. Healthy adult, castrate male and nonpregnant female Yorkshire-cross swine (*Sus scrofa*) were acclimated for a minimum of 7 days and weighed between 57 and 93 kg.

The experimental design is depicted in Figure 1. Animals were subjected to a severe injury, followed by a 1.5-minute free hemorrhage interval. During this phase, animals were assigned to an intervention using a block randomization scheme to one of three arms: complete aortic occlusion (AO group, n = 10) with cessation of distal aortic flow for 90 minutes, permissive regional hypoperfusion with VAC (PRH group, n = 10) through an automated extracorporeal aortic bypass circuit, or no aortic occlusion (control, n = 5). After the 90-minute intervention phase, laparotomy and hemostasis was achieved in the surviving animals. At laparotomy, allogeneic whole blood was transfused matching the volume of intraperitoneal shed blood. Ten minutes after onset of damage control surgery, blood flow was reintroduced via the extracorporeal circuit in the AO and PRH arms.

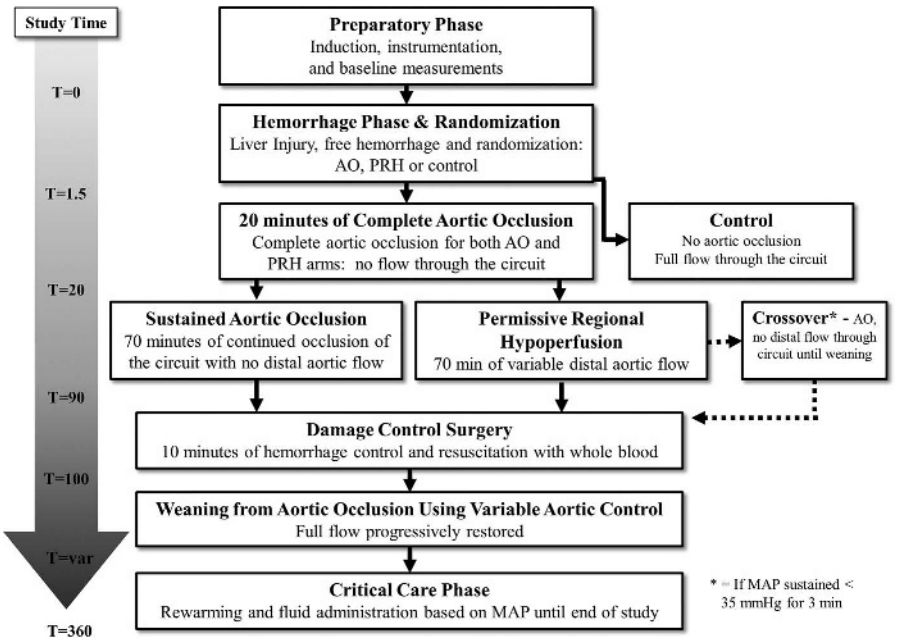

Figure 1. Study flow.

Subsequently, the animals entered an intensive care unit (ICU) phase during which normal saline was administered in boluses based on predefined physiologic parameters until end of study (EOS) or death.

Animal Preparation

Animals were premedicated with 6.6 mg/kg tiletamine/zolazepam (TELAZOL; Fort Dodge Animal Health, Fort Dodge, IA) intramuscularly. After isoflurane induction and endotracheal intubation, maintenance anesthesia consisted of 2% isoflurane in 100% oxygen. An intravenous infusion of norepinephrine (0.01 μg/kg/h) was used to offset the vasodilatory effects of general anesthesia and titrated before experimentation to a mean arterial pressure between 65 and 75 mm Hg. Animals were mechanically ventilated to maintain end-tidal CO_2 at 40 ± 5 mm Hg. Normal saline was administered at a rate of 5 mL/kg/h to overcome insensible losses. Swine were heparinized with intravenous heparin to achieve an activated clotting time of 100 seconds, similar to human baseline values. An underbody warmer was used to maintain core body temperature between 35 and 37 °C.

Vascular access and monitoring for this setup has been previously described.[21] After laparotomy, a splenectomy was performed to minimize hemodynamic variation from autotransfusion.[22] The supraceliac aorta was exposed by longitudinally dividing the diaphragm. The aorta was dissected circumferentially for a distance of 5 to 10 cm. Two to three adjacent intercostal arteries were ligated.[23] The aorta was then clamped proximally and distally, followed by insertion of inflow and outflow aortic cannulas. These were connected to the circuit and distal aortic flow was then reinstituted by unclamping of the circuit (Fig. 2). Circuit flow was regulated in an automated fashion according to predefined hemodynamic parameters. Additional details regarding the flow circuit design and function are available online (see Attachment, Supplemental Digital Content 1, http://links.lww.com/TA/A889).

Injury

The liver was marked along the planned transection plane, 2 cm to the left of Cantlie's line, to provide amputation of approximately 80% and 40% of the left lateral and left medial lobes, respectively. A custom liver tourniquet was used to allow for precise quantification of the resection weight (0.4–0.5% of total body weight). Body weight was used to standardize liver resection, given the inability to quantify total liver weight before necropsy.

Intervention and Critical Care

At the start of the experiment, the liver tourniquet was released and free hemorrhage was initiated. Control animals underwent no intervention, with delivery of unimpeded abdominal aortic flow. Complete aortic occlusion was achieved by automated clamping of the circuit in both the AO and the PRH arms to simulate the physiologic effect of REBOA, which was sustained in the AO arm for the entire 90-minute intervention period. In the PRH group, low-volume flow was reintroduced after 20 minutes of complete occlusion at an initial flow rate of 150 mL/min until T40, followed by dynamic regulation up to a rate of 300 mL/min if the proximal aortic blood pressure exceeded 70 mm Hg. Two colloid 500-mL boluses of hetastarch (HEXTEND; BioTime

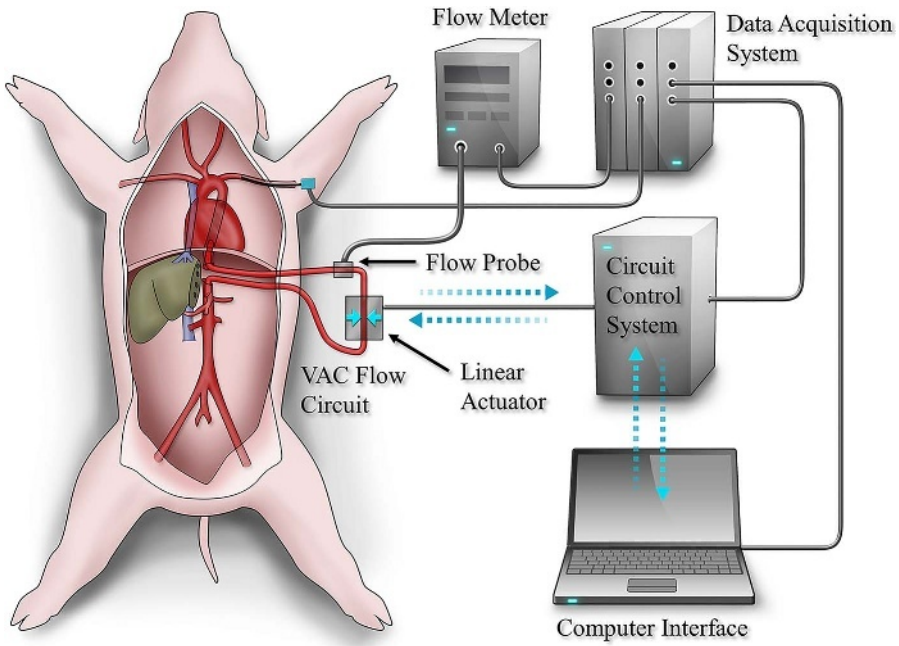

Figure 2. Schematic of experimental setup—right angle aortic cannulas placed proximally and distally in a divided aorta and connected to the clamped circuit. Data from the proximal pressure and inline flow monitors is relayed in real time back to the data acquisition system. The control system regulates flow in the circuit based on a prescribed algorithm by extrinsically compressing the circuit tubing using a linear actuator.

Inc., Alameda, CA) were permitted at T40 and T70, if proximal MAP fell below 70 mm Hg. Crossover from PRH to AO occurred when proximal MAP was below 35 mm Hg for 3 minutes. Death was defined as a sustained proximal MAP less than 35 mm Hg for 5 minutes.

At T90, damage control laparotomy was performed, with immediate hemorrhage control achieved by reapplication of the liver tourniquet and quantification of shed blood. Whole blood resuscitation in the amount of shed blood was instituted between T90 and T100. At T100, blood flow was reinstituted progressively back to full native flow. At T100, computer-controlled hemodynamic analysis was used to guide fluid administration in all groups, with 500-mL boluses of normal saline solution administered after 2 minutes of sustained hypotension (MAP less than 60 mm Hg). Glucose and electrolyte abnormalities were corrected throughout the ICU phase.

Data Collection

Physiologic data, including proximal and distal aortic pressures, heart rate, core body temperature, carotid artery blood flow, and ECG monitoring, were continuously captured (Biopac Systems Inc., Goleta, CA). Blood flow was measured using perivascular and in-line flow probes (Transonic, Ithaca, NY). Arterial blood and urine were collected at routine intervals throughout the study. Tissue samples were collected from animals surviving the EOS, with histologic analysis performed by a veterinarian pathologist blinded to the intervention.

Data Analysis

Data analysis was performed with STATA version 14.0 (Stata Corporation, Bryan, TX). Continuous variables are presented as means and standard errors of the means if normally distributed and as medians with interquartile ranges if not distributed normally. Dichotomous and categorical variables were analyzed by Fisher's exact test and presented as percentages unless otherwise specified. Continuous variables were analyzed with repeated measures analysis of variance with post hoc pairwise comparisons when indicated. Kaplan-Meier survival curves were calculated and the log-rank test used for time-series analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline physiology and laboratory values were similar among the groups (Table 1). There was no difference in liver injury resection weight or amount of intraabdominal hemorrhage encountered at damage control laparotomy. In the absence of intervention, the liver injury was rapidly lethal. None of the control animals, 50% of the AO animals, and 90% of the PRH animals survived to EOS (Fig. 3). Mean survival time (min) was 9.2 ± 6.7 for control, 327.7 ± 102.1 for PRH, and 270.0 ± 105.5 for AO ($p = 0.23$, AO vs. PRH).

During the intervention phase, mean circuit flow was 230 ± 57 mL/min in the PRH group, compared to 0.2 ± 0.8 mL/

TABLE 1. Baseline Physiology, Labs, and Injury Characteristics

	Control (n = 5)			PRH (n = 10)			AO (n = 10)			*p*
Weight, kg	73.8	±	9.1	65.6	±	5.0	71.3	±	12.7	0.24
Core temperature, °C	36.0	±	0.4	35.8	±	0.6	35.9	±	0.8	0.76
Labs										
pH	7.49	±	0.04	7.47	±	0.05	7.47	±	0.04	0.70
P/F ratio	5.14	±	0.57	5.28	±	0.51	5.47	±	0.50	0.49
Hgb, g/dL	12.2	±	0.9	12.3	±	0.7	12.1	±	1.2	0.91
WBC, $\times 10^9$/L	19.3	±	3.5	20.0	±	4.4	21.6	±	4.9	0.58
Potassium, mmol/L	4.6	±	0.2	4.6	±	0.3	4.5	±	1.0	0.90
Creatinine, mmol/L	1.8	±	0.0	1.5	±	0.3	1.7	±	0.3	0.24
Lactate, mmol/L	2.4	±	0.0	2.4	±	0.11	2.7	±	0.16	0.33
Glucose, mmol/L	89.6	±	18.2	107.3	±	19.6	101.5	±	15.6	0.22
ACT	98.5	±	6.9	100.9	±	11.0	101.0	±	10.3	0.89
Hemodynamics										
Proximal MAP	75.8	±	6.1	74.5	±	7.3	77.6	±	8.0	0.65
Heart rate, beats/min	96.6	±	12.4	104.0	±	17.9	98.6	±	15.8	0.76
Carotid flow, mL/min	478.9	±	58.7	494.1	±	157.0	512.7	±	93.9	0.87
Renal flow, mL/min	194.0	±	5.6	157.2	±	85.0	191.6	±	76.2	0.57
Circuit flow, mL/min	1015.7	±	110.9	957.0	±	118.0	1009.7	±	198.6	0.69
Injury										
Liv Inj EBL	1713.6	±	369.9	1640.6	±	592.3	1437.6	±	450.6	0.53
% EBL at DCS	NA		NA	44.4	±	12.6	36.5	±	9.0	0.13
Free bleed MAP	52.08	±	4.95	35.4	±	9.5	37.7	±	11.6	0.89
Spleen, g	630.4	±	116.0	523.0	±	117.1	662.4	±	276.5	0.29
Liver removed*	0.41	±	0.01	0.42	±	0.01	0.42	±	0.01	0.80

% EBL reflects percentage of total circulating blood volume.

*Resection mass/total body mass (kg).

MAP, mean arterial pressure (mm Hg); EBL, estimated blood loss (mL); ACT, activated clotting time (s); DCS, damage control surgery; PRH, permissive regional hypoperfusion; AO, complete aortic occlusion.

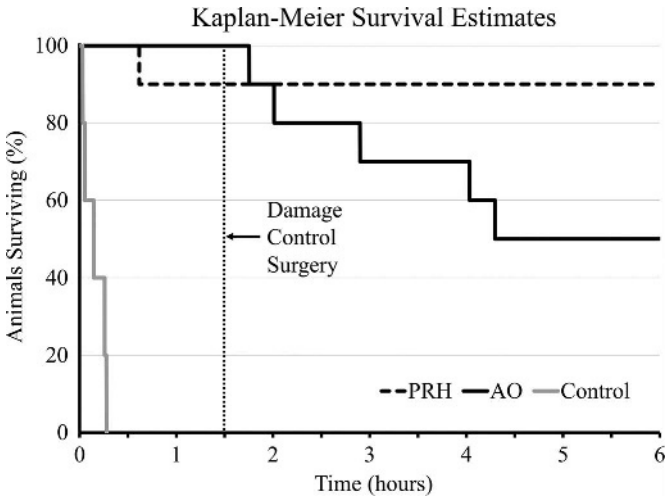

Figure 3. Kaplan-Meier survival estimates—the permissive regional hypoperfusion resulted in a 90% survival at the end of the study period, compared to only 50% of the complete aortic occlusion arm. The time of damage control surgery is denoted by the *dashed vertical line*. The liver injury was uniformly fatal in the absence of intervention, with rapid death of all control animals.

min in the AO group. Distal aortic flow was greater in the PRH group upon entry into the ICU phase, with delayed restoration of flow observed in the AO group (Fig. 4*A*). The average proximal MAP during the intervention phase was higher in the AO group (104.9 ± 8.9 mL/min) compared to PRH (84.9 ± 18.8 mL/min, $p < 0.01$). After restoration of flow at T100 and throughout the ICU phase, proximal MAP was higher in the PRH group (73.7 ± 8.5 mL/min) compared to the AO group (50.5 ± 6.0 mL/min, $p = 0.01$) (Fig. 4*B*).

Lactate levels were higher in the PRH group between T45 and T90. After flow restoration at T105, lactate levels decreased in the PRH animals, whereas levels in the AO group continued to increase until T150, decreasing thereafter (Fig. 4*C*). By EOS, lactate concentrations were similar across groups (PRH 4.8 ± 2.7 mmol/L vs. AO 5.0 ± 1.2 mmol/L, $p = 0.86$). Similarly, pH levels were lower with PRH during intervention but rebounded upon full flow restoration and remained higher than the AO group at all time points until EOS (Fig. 4*D*).

There was no difference in carotid blood flow at baseline or throughout the intervention period (Table 2). However, carotid flow during the ICU phase was lower in the AO group than the PRH group (320 ± 114 mL/min vs. 618 ± 163 mL/min, $p < 0.01$). Renal blood flow was also greater with PRH during intervention and ICU phases (Table 2). Although there was no difference in urine production during the intervention phase, the PRH group had greater urine output during the ICU phase than AO (105 ± 107 mL vs. 4 ± 3 mL, $p < 0.01$).

There were no differences between groups in volume of blood administered during resuscitation (Table 2). Volume of crystalloid administered during the intensive care phase was 10-fold less for the PRH group compared to AO (265 ± 321 mL vs. 2744 ± 1651 mL, $p < 0.01$).

On histologic analysis, animals in both groups demonstrated similar amounts of subendocardial hemorrhage, focal pulmonary congestion, edema, and inflammation, hepatic inflammation and congestion, and the number of necrotic neurons (see Figure, Supplemental Digital Content 2, http://links.lww.com/TA/A890; see Table, Supplemental Digital Content 3, http://links.lww.com/TA/A891). A greater degree of duodenal necrosis occurred with AO compared to PRH ($p = 0.01$) group, and there was an apparent but nonsignificant ($p = 0.06$) increase in extent of colonic necrosis in the AO group compared to PRH.

DISCUSSION

This study compared early outcomes of permissive regional hypoperfusion (PRH) using variable aortic control (VAC) versus complete aortic occlusion (AO) in a large animal model of lethal liver injury. Findings demonstrate that PRH is as effective as AO at preserving life and minimizing hemorrhage and results in more favorable hemodynamic parameters proximal and distal to the aortic occlusion site, with less distal ischemia. Automated PRH also reduces hemodynamic instability upon reintroduction of full aortic flow as compared to AO and results in less physiologic derangement during the immediate postoperative period. These findings support the concept of PRH with VAC as a viable therapy in the management of noncompressible truncal hemorrhage (NCTH) and justify continued development of this potentially transformative technology.

REBOA has emerged as a minimally invasive adjunct in the management of NCTH and improves and/or restores hemodynamics in early clinical experience.[4,6,13,24] The principal objective of REBOA is to arrest life-threatening hemorrhage until definitive hemorrhage control can be achieved. Previous large animal studies have confirmed its efficacy at preventing early death from exsanguination, with 100% survival during the "prehospital" intervention phase.[16,17] However, the duration of REBOA is finite because of the adverse consequences of prolonged complete aortic occlusion on both proximal and distal vascular beds.[1,11] This poses a significant challenge in scenarios where prolonged intervention is required, such as extended transport distances, prolonged care in austere environments, or mass casualty situations. As such, any potential therapeutic benefit of REBOA may be negated by prolonged application beyond a currently unknown critical threshold.

Partial perfusion strategies such as partial REBOA (P-REBOA) and intermittent REBOA (I-REBOA) aim to address these limitations. However, P-REBOA may result in hemodynamic instability and ongoing hemorrhage, which limits its usefulness particularly in resource-constrained environments. Our previous attempts at P-REBOA in a large animal liver injury model using commercially available balloon catheters were promising, yet early survival was inferior to that of complete REBOA, with 40% mortality for P-REBOA animals caused by ongoing hemorrhage.[17] We hypothesized that the early mortality observed with P-REBOA resulted from poorly controlled distal aortic flow, an inherent limitation of current catheter technology to control the extent of aortic occlusion with sufficient fidelity. Inherently, trading late mortality from ischemic and cardiovascular complications for early mortality from hemorrhage is not acceptable, which resulted in a critical re-appraisal of this entire resuscitative paradigm.

An ideal resuscitative endovascular adjunct would minimize the adverse physiologic consequences of complete and

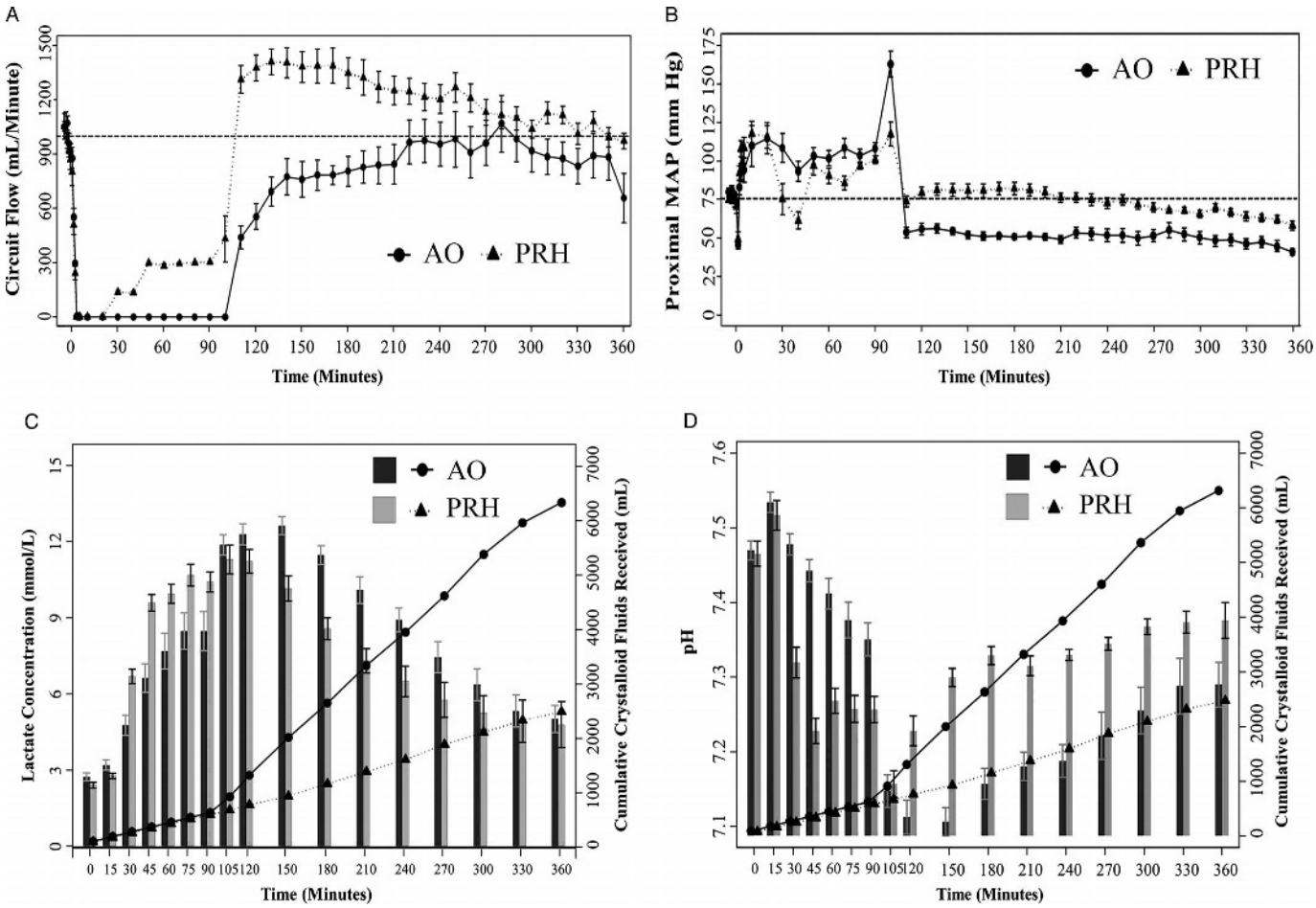

Figure 4. Hemodynamics and markers of ischemia—(*A*) PRH achieved with highly regulated, low-volume aortic blood flow via the circuit before definitive hemorrhage control at 90 minutes compared to no aortic blood flow in the AO group. After 90 minutes, the effects of profound ischemia–reperfusion injury resulted in less mean aortic flow during the remainder of the study. (*B*) Likewise, proximal MAP was higher with AO, but this effect was reversed after hemorrhage control and throughout the intensive care phase. (*C*) Blood lactate concentrations were significantly higher initially in the PRH group during the first 90 minutes and then cleared more rapidly with resuscitation (*primary y-axis*). Concurrently, fluid requirements were higher for the AO group, especially during the intensive care phase after surgical hemorrhage control and resuscitation (*secondary y-axis*). (*D*) In similar fashion, pH worsened during PRH then improved after resuscitation compared to the persistent acidosis seen in the AO group throughout the remainder of the study (*primary y-axis*) along with cumulative fluid requirements (*secondary y-axis*). PRH, permissive regional hypoperfusion; AO, aortic occlusion; MAP, mean arterial pressure.

sustained aortic occlusion, but also prevent ongoing hemorrhage or reduce it to a tolerable degree. Permissive regional hypoperfusion with variable aortic control is a novel strategy designed to meet this need, and its application in this study resulted in 90% survival in an otherwise highly lethal model. The one death in the PRH group in this study occurred despite crossover of the animal to complete aortic occlusion (Fig. 3). Although this death was likely attributable to acute hemorrhage (51% total blood volume), the current PRH paradigm minimizes blood loss to the degree that there was no difference in average shed blood between the two groups (PRH vs. AO).

Although definitive comparisons between P-REBOA and PRH are difficult to draw at this stage, the observed differences in mortality in this study suggest fundamental hemodynamic and physiologic differences between the two approaches. First, the current approach to PRH employs a novel computer-controlled VAC flow circuit that can reliably deliver a precise low-volume distal aortic flow rate. In theory, preventing spikes in flow and ensuring flow remains at a low level may allow clot stabilization and prevent clot disruption. It is likely that the flow rates in our previous P-REBOA studies were variable and in excess of a critical threshold, whereby bleeding persisted and resulted in early death. Additionally, the current PRH protocol included an initial 20-minute period of complete AO, which may prove beneficial in promoting clot stabilization and improved hemodynamics. The ideal duration of AO to establish clot stabilization remains unclear; however, this study demonstrated no significant difference in total hemorrhage volume utilizing 20 minutes of AO in the PRH arm.

The ability to mitigate the physiologic debt incurred by prolonged complete aortic occlusion represents a tension between causing bleeding and providing tissue perfusion. In the

TABLE 2. Hemodynamics, Urine Output, and Resuscitation

	PRH			AO			*p*
T1.5–T21.5							
Prox MAP	113.8	±	7.6	111.3	±	9.5	0.84
Heart rate	153	±	17	143	±	17	0.22
Carotid flow	693.0	±	267.8	697.6	±	277.2	0.97
Circuit flow	23.6	±	9.4	28.6	±	3.4	0.13
Renal flow	1.0	±	0.9	1.4	±	0.8	0.38
T21.5–T90							
Prox MAP	84.9	±	18.8	104.9	±	8.9	**<0.01**
Heart rate	146	±	14	154	±	13	0.19
Carotid flow	577.7	±	281.4	649.6	±	559.6	0.47
Circuit flow	230.2	±	57.0	0.2	±	0.8	**<0.01**
Renal flow	10.6	±	10.7	1.0	±	1.2	**0.02**
Urine volume	9.9	±	8.9	6.2	±	3.0	0.22
T90–T100							
Prox MAP	117.8	±	9.0	156.4	±	24.3	**<0.01**
Heart rate	127	±	12	146	±	20	**0.03**
Carotid flow	973.9	±	228.7	1117.2	±	170.7	0.13
Circuit flow	316.4	±	50.2	0.14	±	0.8	**<0.01**
Renal flow	17.7	±	14.6	1.7	±	0.8	**<0.01**
T100–T360							
Prox MAP	73.7	±	8.5	50.5	±	6.0	**<0.01**
Heart rate	150	±	17	140	±	20	0.26
Carotid flow	617.5	±	162.8	320.3	±	113.7	**<0.01**
Circuit flow	1227.3	±	180.4	682.9	±	207.8	**<0.01**
Renal flow	121.5	±	61.0	50.2	±	21.7	**<0.01**
Urine volume	105.0	±	107.4	4.4	±	2.6	**<0.01**
Whole blood							
Units transfused	5.7	±	2.9	5.7	±	1.8	0.98
Total blood transfused	1706.4	±	884.8	1716.3	±	554.8	0.98
Colloid fluid							
Hextend	650	±	337.5	350	±	336.5	0.06
Crystalloid fluid							
Crystalloid bolus	264.7	±	320.5	2743.9	±	1651.3	**<0.01**
Total IVF	4942.5	±	1712.9	7654.9	±	5097.1	**0.04**

Urine volume = mL; flow = mL/min; heart rate = beats/min.

MAP, mean arterial pressure (mm Hg); AO, complete aortic occlusion; PRH, permissive regional hypoperfusion.

Statistical significance with $p < 0.05$ highlighted in bold.

patient with multiple injuries and with concomitant hemorrhagic shock, the ischemic threshold of the visceral organs is not known. There is clinical evidence in noninjured patients that the liver and kidneys can tolerate up to 60 minutes of warm ischemia without irreversible injury.[25–27] In the trauma population, it has been reported that 20 to 40 minutes of REBOA can result in acceptable survival rates. However, studies evaluating longer interventions have reported higher rates of organ failure and mortality compared to no intervention.[6,11,12] There is a paucity of data evaluating the feasibility of 90 minutes of complete REBOA or its immediate effects on end-organ function, but it is reasonable to surmise from the growing body of literature that this is unlikely to result in a favorable outcome.

This study demonstrates the positive impact of controlled and even very low rates of distal aortic flow on cumulative ischemic burden. Lactic acidosis during the intervention phase was more pronounced in the PRH group compared to AO, presumably caused by continuous washout of lactate into the systemic circulation. However, PRH animals were able to more rapidly normalize lactate levels and pH after restoration of complete aortic flow. These findings may be a result of both a decreased metabolic burden in distal tissues and improved hepatic function from persistent—albeit limited—perfusion.

Although lactate levels at the end of the study were similar in both groups, this comparison is complicated by differences in mortality and resuscitation requirements. The final lactate levels represent only 50% of AO animals, those hardier animals capable of surviving to the end of the study, introducing a potential survivor bias in favor of the AO group. Additionally, there may have been an impact of hemodilution on lactate because of large volume crystalloid resuscitation required in the AO group. This is supported by down-trending hematocrit levels with AO compared to increasing hematocrit levels in the PRH group during the ICU phase, despite a lack of ongoing hemorrhage (data not shown). Clearance of lactate in both groups does suggest early preservation of hepatic function, yet there was liver dysfunction in the AO group as evidenced by higher INR levels beginning at T90 (data not shown).

With respect to renal function, both groups were essentially anuric throughout the intervention period, demonstrating similar histologic findings of tubular necrosis. Nonetheless, PRH resulted in a greater proportion of animals with return of urine output during the ICU phase, whereas most AO animals remained anuric for the study duration. The factors influencing this are complex, likely involving the effects of prolonged initial ischemic insult, the sequelae of cardiac dysfunction, and an inability to normalize perfusion during the ICU phase for the AO group. Irrespective of the mechanism, acute renal failure in the setting of trauma is an independent predictor of mortality, resulting in a greater than threefold higher mortality rate.[28]

There were proximal and distal hemodynamic differences between groups. PRH resulted in less hypertension during the intervention phase and near-baseline MAP after resuscitation through EOS. Carotid blood flow was also maintained close to baseline after the brief period of complete aortic occlusion for PRH animals, which persisted throughout the remainder of the experiment. In contrast, AO animals failed to maintain baseline carotid flow rates after resuscitation. Additionally, PRH animals were able to maintain distal aortic flow at or above baseline values throughout the ICU phase with subsequent higher renal blood flow, whereas the surviving AO animals consistently had aortic flow rates below baseline with decreased renal flow. Taken together, these differences suggest that AO resulted in poor cardiac function either from direct myocardial damage or from a generalized greater burden of injury. This adverse effect on myocardial contractility is described in the context of aneurysm repair, where collateral pathways do not exist to support the increased afterload incurred by complete aortic occlusion.[8,10]

There were large differences in the amount of resuscitation fluid required during the ICU phase. In the current critical care paradigm, hypotension after whole blood resuscitation was treated with crystalloid boluses. Using this standardized approach, animals in the AO group required substantially more fluid, with many remaining refractory (50% mortality during ICU phase). Even the surviving animals in the AO group failed

to normalize blood pressure despite this ongoing fluid resuscitation. Although clear differences in crystalloid requirements existed, there were no differences on pulmonary pathology, with both groups demonstrating at least some level of edema and pulmonary venous congestion, suggesting that ARDS was not the cause of death in the AO animals (data not shown).

The current study has limitations worth highlighting. First, the extracorporeal circuit is an experimental surrogate for future endovascular device designs and is not a clinically viable entity. However, in the absence of an available endovascular technology that provides reliable and automated variable aortic control, this model allows a means by which to study aortic and branch vessel flow in the setting of injury and shock with a high degree of fidelity. Additionally, the circuit itself likely resulted in mild attenuation of native distal aortic flow. Given that this effect was uniform across all experimental arms and still resulted in a uniformly lethal injury in the control group, the impact on outcomes is likely negligible.

The differences seen across experimental arms likely represent the aggregate effects on both proximal and distal organ function, particularly differences in distal ischemia and cardiac performance. It is possible that the detrimental effect of sustained aortic occlusion on cardiac performance accounts for much of the observed differences seen in this study. However, because of limitations of the current design, this was not able to be examined. Efforts are underway to address this clinically relevant issue.

Additionally, the current approach to critical care did not mirror best practices for the management of a critically injured patient. Future development of automated decision support utilizing more complex data analysis will provide a nuanced approach to critical care management while preserving the objectivity captured in the present study. Also, the current nonsurvival study design precludes conclusions regarding the impact of PRH on longer-term outcomes and survival. Finally, the injury pattern utilized in the present study does not replicate or mimic all truncal injury patterns. It is plausible that certain injuries, such as large vessel arterial injuries, will prove refractory to attempted reintroduction of flow before hemorrhage control. With respect to the extended intervention duration of 90 minutes, the authors recognize that this may not represent contemporary application of REBOA in well-resourced facilities. However, this extended intervention period was chosen to accomplish two specific objectives: demonstrate the feasibility of PRH to minimize hemorrhage over extended intervals and demonstrate the impracticality of complete aortic occlusion for this interval. Limitations notwithstanding, the current study demonstrates that PRH holds promise as a next-generation resuscitation paradigm and provides a platform from which next-generation, catheter-based variable aortic control devices can be developed.

CONCLUSION

This is the first description comparing the novel resuscitation concept of permissive regional hypoperfusion to complete aortic occlusion in a translational model. This study demonstrates that in the setting of exsanguination and cardiovascular collapse from liver injury, a period of complete aortic occlusion followed by permissive regional hypoperfusion results in controlled hemorrhage and high rates of survival. Automated permissive regional hypoperfusion minimizes distal ischemic burden compared to sustained complete aortic occlusion and allows for a prolonged period of viability before laparotomy and surgical hemostasis. It also facilitates more physiologic hemodynamics proximal to the level of aortic occlusion and facilitates rapid weaning back to baseline aortic flow.

This study is also the first to characterize the low level of distal aortic flow (5–10% of native) needed to maintain viability of the viscera in the setting of injury with concomitant hemorrhagic shock. Although the principle of permissive regional hypoperfusion results in an ischemic burden with end-organ dysfunction relative to the noninjured, euvolemic state, it sustains viability and allows restoration of organ function compared to sustained complete aortic occlusion. As REBOA evolves, a better understanding of the intricacies of automated variable aortic occlusion and permissive regional hypoperfusion is required.

AUTHORSHIP

All authors contributed to the literature search and study design. T.K.W., L.P.N., M.A.J., R.M.R., S.-A.F., J.K.G., and A.J.D. collected the data. T.K.W., L.P.N., M.A.J., R.M.R., N.F.C., J.K.G., and T.E.R. performed the data analysis and interpretation. T.K.W., L.P.N., M.A.J., N.F.C., J.K.G., and T.E.R. wrote the article, which all authors critically revised.

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DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

Dr. Thomas M. Scalea (Baltimore, Maryland): The authors have introduced a new concept in aortic occlusion—variable aortic control and permissive regional hypoperfusion.

Certainly everyone in this audience has heard of the increasing use of aortic occlusion via the REBOA. This new concept allows for the refinement of this minimally-invasive aortic, control of the aorta.

The scheme they have used is, indeed, elegant. As you saw, catheters are inserted proximally and distally in the aorta, adjacent to the diaphragm. Flows are controlled via a circuit control system, data acquisition system, and computer interface.

There was little description of the actual technique in the manuscript. And while I am perhaps the world's stupidest person about computers and will certainly be confused, perhaps Dr. Williams could explain a little bit more about how this really works.

As all of my partners in Baltimore know, for many years I've stopped cross-clamping the aorta when I do ED thoracotomy following cardiac arrest. I have believed that the huge increase in left ventricular afterload that occurs with aortic occlusion is, in fact, injurious to cardiac performance.

Now I have rationalized the use of REBOA, believing that its minimally-invasive nature or ability to insert it rapidly and, perhaps most importantly, the ability to move the balloon down mitigated some of these physiologic downsides.

The authors' data seems to agree with that. They observed better distal aortic flow and better renal blood flow in the experimental animals. And the animals also required less crystalloid in the ICU phase of care.

This sounds to me like the heart is working better. However, the authors didn't measure cardiac function. Perhaps in future studies they could consider measuring cardiac function with an echocardiogram and/or a pulmonary artery catheter, if you can actually still find one of those around somewhere. I'd appreciate Dr. Williams' thoughts.

Why 90 minutes? It seems like a long time to use complete aortic occlusion. It's a lot longer than we typically leave the REBOA up. And maybe that's simply not a fair way to look at this.

As he detailed in his presentation, the same group recently published a paper on partial aortic occlusion using a balloon catheter. This is obviously much simpler than their current method and certainly worked very well when you compare it to traditional REBOA. So which is it? Is this better? Are you going to compare this now to P-REBOA? How are you going to work that out?

And, finally, assuming that this actually pans out, the EVAR seems like a great idea. It seems like it's going to be unbelievably complicated to design. And I have some concerns that the, our ability to bring that level of technology to an already chaotic trauma bay or operating room may be optimistic.

REBOA has certainly revolutionized the way that many of us—certainly our group in Baltimore—cares for terribly injured patients. But there are some downsides.

Todd Rasmussen and now the group at U.C. Davis continue to push this envelope, seeking to both help us understand the physiology and now design systems to care for the sickest patients.

I look forward to their continued work from their group as well as others. And I would like to thank the Association for the privilege of the floor.

Dr. David P. Blake (Norfolk, Virginia): I enjoyed that presentation. And it certainly is, as Dr. Scalea pointed out, the next

step for pushing the edge of the envelope with regard to this minimally-invasive therapy. The question I have relates more to the downstream effects.

You showed in the short-term that the renal blood flow and the clearance of lactate, et cetera, seemed to be improved with this bypass, if you will, of the aortic injury or the massive injury in the midsection of the vascular tree.

However, you didn't really look at the downstream effects in terms of the second-hit model. What is the potential that there are some metabolic effects that come down the road? Did you consider looking at some tissue samples, say, from the lungs to see if there is any comparable difference in terms of secondary effects from the metabolites of any level of ischemia that goes along with that?

I enjoyed that presentation. I do look forward to additional data on this subject. Thank you.

Dr. Matthew J. Wall, Jr. (Houston, Texas): I'd like to compliment you on a very thought-provoking presentation. As I listened it reminded me of when we wean patients from left atrial-femoral bypass when we do thoracic aneurysm repairs.

We don't talk a lot about how to deflate the fully-inflated REBOA balloon or wean them. Have you considered adopting your algorithm to use it to progressively deflate the REBOA balloon at the end of the repair? Thank you.

Dr. Timothy K. Williams (Travis Air Force Base, California): Thank you, again, to the Association and particularly Dr. Scalea, for reviewing our manuscript and providing these insightful comments.

With regard to how the system works, we constructed it around a closed-loop feedback system, gets inputs from proximal aortic pressure and from aortic flow in the circuit.

Essentially, the way we arrange the algorithms is we have three target flow rates, basically high, medium and low. At the upper end of it if the pressure was above 70 the set point was 300mls a minute.

And what the system does is it, it's reading the real-time flow rate and comparing that to the set point and simply either opening or closing this actuator to compress the tubing. And by achieving that you can very tightly regulate the aortic flow.

But, you know, I just want to take one moment to highlight the degree of precision that that thing is working in. You go from basically no flow to complete flow within the space of 2 millimeters of linear compression of that tubing.

And we're working, actually, in a much smaller space than that, on the order of 10% of that range. So when this thing is moving, it's really imperceptible almost to the naked eye.

With respect to cardiac performance, Dr. Scalea, we, too, are very interested in the adverse effects of aortic occlusion and partial occlusion on cardiac performance.

We did attempt to utilize Swan Ganz catheters but had difficulty achieving reproducible measurements. But beyond that simply measuring cardiac output alone I think doesn't tell the whole story because certainly cardiac output can be influenced directly by systemic vascular resistance, which is what the system creates.

And so one thing we are looking at pressure volume loop analysis which enables us to gain direct measurements of cardiac work independent of after load.

And we're going to – unfortunately in this study due to the limitations of the porcine arch anatomy we were unable to include that but that's something that we are actually looking at currently.

In terms of "why 90 minutes," part of this entire research effort is really meant to target survival in the war fighter.

As an Air Force member we're looking at extending the duration of intervention. So looking at viability of any new therapy for prolonged transport times is something that's keenly relevant to military health and is something that I'm very interested in as well.

Regarding the recent publications in *JACS,* that paper was – actually represented our original work and was done in a controlled model of hemorrhage; but it was tied up in a resident paper competition so it is just now coming out to press.

But subsequent to that work, using that same technique we did this in a liver injury model and had inferior results. That was presented at last year's AAST meeting.

And although that was favorably received, many of those experimental animals died prior to the end of intervention which, in turn, we viewed as essentially a failure of the therapy which forced us to really rethink our strategy of how to deal with this.

So we went basically back to the drawing boards and ripped this down to the studs and completely rethought about it, shifting our focus from a pressure-based system to more of a flow-based system; hence, all of this is driven off of direct flow measurements.

How are we going to implement this therapy? That's a great question. It's not entirely clear; but we do have ideas about how to package this therapy down into a single catheter and achieve this.

But, again, I want to emphasize that what we've tried to achieve here is to emphasize that maintaining a low flow state is really critical to the success of this therapy.

So whatever device is developed to achieve this therapy really has to have essentially a built-in governor that when it's deployed is not going to really exceed some critical threshold beyond which you could start to re-hemorrhage.

Dr. Blake's question, downstream effects and second hit, we did look at tissue histology. We did not see significant differences, although the timeframe of this experiment may not lend itself well to changes that we would see potentially in a survival model. So that's something that we want to look at down the line is the impact of this therapy at 24 and 48 hours in a limited survival model.

And in terms of how to deflate the balloon, we have looked at the physiology surrounding balloon deflation. And it is something that we're interested in evaluating. But I don't think that's something that it can be achieved in the field.

It's certainly something that needs to be accomplished in a very resource-rich environment because, as we have seen in some of our clinical experience at U.C. Davis, it creates a significant amount of hemodynamic instability, even with really minor changes in the balloon volume.

But I think there is potentially a role for automating that process in the future.

Thank you.