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ENDOVASCULAR PERFUSION AUGMENTATION FOR CRITICAL CARE: PARTIAL AORTIC OCCLUSION FOR TREATMENT OF SEVERE ISCHEMIA–REPERFUSION SHOCK

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ABSTRACT—**Background:** The resuscitation of patients in shock is materially intensive and many patients are refractory to maximal therapy. We hypothesized that partial inflation of an intra-aortic balloon, termed Endovascular Perfusion Augmentation for Critical Care (EPACC), would minimize material requirements while improving physiologic metrics. **Methods:** Swine underwent a 25% controlled bleed and 45 min of complete aortic occlusion to create a severe ischemia–reperfusion shock state. Animals received either standardized critical care (SCC) composed of IV fluids and norepinephrine delivered through an algorithmically controlled platform or EPACC in addition to SCC. Physiologic parameters were collected, and blood was sampled for analysis. Primary outcomes were total IV fluids and average MAP during the critical care phase. Differences ($P < 0.05$) were measured with *t* test (continuous data) and Wilcoxon rank-sum test (ordinal data). **Results:** There were no differences in baseline characteristics. There were no differences in the maximum lactate; however, animals in the EPACC group had a higher average MAP (EPACC 65 mmHg, 95% confidence interval [CI], 65–66; SCC 60 mmHg, 95% CI, 57–63; $P < 0.01$) and remained within goal MAP for a greater period of time (EPACC 95.3%, 95% CI, 93.2–97.4; SCC 51.0%, 95% CI, 29.5–72.6; $P < 0.01$). EPACC animals required less IV fluids when compared with the SCC group (EPACC 21 mL/kg, 95% CI, 0–42; SCC 96 mL/kg, 95% CI, 76–117; $P < 0.01$). There were no differences in final lactate. Animals in the EPACC group had a higher final creatinine (EPACC 2.3 mg/dL, 95% CI, 2.1–2.5; SCC 1.7 mg/dL, 95% CI, 1.4–2.0; $P < 0.01$), but there were no differences in renal cellular damage on histology ($P = 0.16$). **Conclusion:** Using a swine model of severe shock, the addition of EPACC to SCC significantly reduced fluid resuscitation requirements and improved blood pressure. This is the first description of a new therapy for patients in refractory shock or in resource-limited settings.

KEYWORDS—Critical care, endovascular, ischemia–reperfusion, REBOA, shock

ABBREVIATIONS—AAALAC—Association for the Assessment and Accreditation of Laboratory Animal Care; ACT—activated clotting time; CPU—central processing unit; dMAP—distal mean arterial blood pressure; EPACC—endovascular perfusion augmentation for critical care; IV—intravenous; MAP—mean arterial blood pressure; N-Gal—neutrophil gelatinase-associated lipocalin; pMAP—proximal mean arterial blood pressure; P-REBOA—partial resuscitative endovascular balloon occlusion of the aorta; REBOA—resuscitative endovascular balloon occlusion of the aorta; SCC—standardized critical care

INTRODUCTION

Restoring homeostasis for a patient in shock is difficult and labor intensive. The dynamic nature of the patient's physiology after a severe initial insult requires both medical expertise and continuous appraisal and modification of the care provided. Yet, for all the sophistication and innovation of modern medicine, the current ''state of the art'' in critical care medicine remains a fairly imprecise ''one size fits all'' resuscitation and critical care strategy. The mainstay of this approach to shock consists of cardiovascular support via titration of vasoactive medications and intravenous (IV) fluids to restore and maintain intravascular volume. For example, the primary focus in hemorrhagic shock is aggressive transfusion of blood products in roughly the same amounts and composition of the blood that was lost (1, 2). Likewise, in sepsis and ischemia–reperfusion injuries, resuscitation is initiated with large IV crystalloid

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boluses irrespective of the underlying pathophysiology (3–5). However, in these instances, and many other critical care scenarios, the doses of fluid and vasopressors are approximations and the endpoints are fairly subjective. In short, modern shock resuscitation is still not precisely tailored to the physiologic demands of the individual patient.

The lack of precision in the initial resuscitation of critically ill patients ultimately arises from the inability to efficiently analyze the efficacy of care in real time and provide rapid adjustments in response to a critically ill patient's physiology (i.e., second-to-second and minute-to-minute). This is compounded by the latency period between an intervention and the recognition of the physiologic effect of the intervention (e.g., increase in blood pressure, urine output, and oxygen saturation) as well as the often transient nature of physiologic effects (6). Boluses of IV fluids require anywhere from several minutes to an hour to be infused, whereas vasopressor medications often take 10 to 15 min to prepare, administer, and achieve an effect large enough to be detected by a healthcare provider at the bedside. As a result, valuable time is lost while attempting to restore cardiovascular homeostasis and meet physiologic goals (e.g., target blood pressure or markers of end organ perfusion). Furthermore, the end goals of resuscitation are frequently not achieved despite maximal intervention with blood products, fluids, and multiple vasoactive agents. As even short periods of tissue ischemia can result in increased morbidity and mortality, innovative approaches are needed to optimize blood flow and pressure more expeditiously and reliably.

The significant advancement of endovascular techniques to treat vascular pathology and injury over the past 25 years has provided a unique set of tools to facilitate a completely different approach to resuscitation in severe shock by directly optimizing coronary, pulmonary, and cerebral perfusion at the level of the aorta. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is an extreme version of afterload augmentation increasingly utilized by trauma providers for uncontrolled torso hemorrhage (7–9). By completely occluding the proximal descending thoracic aorta with a balloon catheter, REBOA instantly isolates the distribution of circulating blood to the upper torso, thereby improving proximal organ perfusion and decreasing bleeding downstream (10). Yet, the hemodynamic augmentation provided by REBOA does have a significant drawback: ischemia to all tissue distal to the point of occlusion. To counter this disadvantage, dynamic partial occlusion of the aorta, termed partial REBOA (P-REBOA), has been proposed as a method of supporting perfusion to vital organs (heart, lungs, and brain) while still allowing for a low rate of distal blood flow (11, 12). However, the clinical utility of P-REBOA is currently limited by imprecise control of the degree of occlusion.

Recent translational experiments in our lab have demonstrated that incorporating automation to control partial aortic occlusion enables precision distal aortic flow regulation in response to dynamic changes in blood pressure (13, 14). Although initially applied to ongoing hemorrhagic shock, we hypothesized that lesser degrees of partial aortic occlusion may optimize hemodynamics in any type of shock by instant and dynamic changes in aortic afterload in a way that IV fluids and medications cannot. This report describes the use of a novel automated endovascular therapy termed Endovascular Perfusion Augmentation for Critical Care (EPACC) to support perfusion to the heart, lungs, and brain in the setting of profound vasodilatory shock. Using automated devices to carefully control an endovascular aortic balloon catheter, EPACC augments blood pressure to vascular beds above the balloon while permitting continued perfusion distal to the catheter balloon. The purpose of this study was to determine if EPACC would be able to restore cardiovascular homeostasis and maintain adequate perfusion to distal organs while using less IV fluids and vasopressors when compared with standardized critical care in a large animal model of ischemia–reperfusion injury.

METHODS

Overview

The Institutional Animal Care and Use Committee at David Grant Medical Center, Travis Air Force Base, Calif 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 AAALAC. Healthy adult, castrate male, and nonpregnant female Yorkshire-cross swine (*Sus scrofa*—S & S Farms, Ramona, Calif) weighing between 60 kg and 95 kg and 4 to 6 months of age were acclimated for a minimum of 10 days before experimentation.

A hemorrhagic shock ischemia–reperfusion injury was created by performing a splenectomy followed by a 30-min controlled hemorrhage of 25% of total blood volume. The ensuing hypotension was treated with 45 min of descending thoracic aortic occlusion to improve proximal hemodynamics and to induce distal ischemia. After the 45-min occlusive phase, all animals were resuscitated with their shed blood before randomization into one of two critical care groups—SCC or EPACC. SCC was provided via an automated critical care platform that delivered crystalloid fluid boluses and titrated vasopressors based on a predefined critical care algorithm (Supplemental Figure 1, http://links.lww.com/SHK/A764). Animals randomized to EPACC were provided with automated partial aortic occlusion of the descending thoracic aorta to maintain mean blood pressure within 60 to 70 mmHg, with a minimum aortic flow threshold of 75% of baseline weight based aortic flow. Once flow reached this threshold due to progressive balloon inflation, no further balloon support was provided. To increase blood pressure toward the goal range in this scenario, the same automated IV fluid and vasopressor administration algorithm as the SCC group was applied. After a total study duration of 6 h, the animals were euthanized and underwent necropsy with histologic analysis of organs. The study flow is outlined in Supplemental Figure 2 (see http://links.lww.com/SHK/A765).

Animal preparation

Animals were fasted for 12 h before experimentation, then premedicated with 6.6 mg/kg intramuscular tiletamine/zolazepam (TELAZOL, Fort Dodge Animal Health, Fort Dodge, Iowa). After isoflurane induction and endotracheal intubation, general anesthesia was maintained with 2% isoflurane in 100% oxygen. All animals received a 1-L bolus of balanced electrolyte solution (PLASMA-LYTE A, Baxter Healthcare Corporation, Deerfield, Ill) to ensure fluid optimization at the onset of the experiment. To offset the vasodilatory effects of isoflurane, an intravenous infusion of norepinephrine (0.01 mg/kg/min) was instituted upon venous access and titrated before experimentation to achieve a target MAP between 65 and 75 mmHg. Animals were mechanically ventilated to maintain end-tidal CO_2 at 40 ± 5 mmHg. During initial surgical preparation maintenance intravenous fluid was administered at a rate of 10 mL/kg/h until the abdomen was closed. After abdominal closure maintenance fluids were continued at 5 mL/kg/hr for the remainder of the study. Intravenous heparin was administered to achieve an activated clotting time (ACT) of 100 s. An underbody warmer was used to maintain core body temperature between 35°C and 37°C and a hot-air body warmer was instituted if core body temperature dropped below 35°C.

After a generous laparotomy and placement of a cystotomy tube, a splenectomy was performed to minimize hemodynamic variation from autotransfusion. The supraceliac aorta was exposed by dividing the left diaphragm and incising the left inferior pulmonary ligament. The aorta was dissected circumferentially for a length of 5–10 cm and two adjacent intercostal arteries were ligated. A

perivascular flow probe (Transonic, Ithaca, NY) was placed proximal to the two ligated intercostal arteries. Additional flow probes were placed on the right carotid artery and the left renal artery. After a left renal biopsy, the abdomen was closed with cable ties. After surgical cut-down, a 7 Fr arterial sheath (Teleflex, Morrisville, NC) was placed in the right common femoral artery, a 12 F arterial sheath (Teleflex) was placed in the left common femoral artery. A dual lumen 10 Fr venous resuscitation line (Cook Medical, Bloomington, Ind) was placed in the left femoral vein for blood transfusion and resuscitation fluids. Both external jugular veins were surgically exposed and cannulated with a 7 Fr triple lumen catheter (left, Teleflex, Morrsville, NC) and a 9 Fr dual lumen catheter (right, Teleflex, Morrsville, NC) to allow for maintenance fluid and vasoactive medication administration. A 9 Fr arterial sheath (Teleflex) was placed in the left axillary artery after surgical exposure for proximal blood pressure measurements. The right brachial artery was exposed and cannulated with a 7 Fr sheath (Teleflex) to facilitate initial hemorrhage. A balloon catheter (CODA-LP catheter, Cook Medical) was introduced through the left femoral 12 Fr arterial sheath and positioned just distal to the aortic flow probe. Catheter placement was confirmed via fluoroscopic visualization.

Data collection

Physiologic measurements of proximal and distal blood pressure, aortic blood flow, heart rate, central venous pressure, and core temperature were collected in real time with a multichannel data acquisition system (MP150, Biopac Systems, Inc., Goleta, Calif). A complete blood count and basic metabolic panel were performed at the start of the experiment and prior to euthanasia. Arterial blood gases, urine, and serum were collected routinely throughout the experiment and urine and serum were frozen at −80°C for later analysis. Serum and urine neutrophil gelatinase-associated lipocalin (N-gal) concentrations were quantified with commercially available ELISA kits (Enzo Life Sciences, Farmingdale, NY) to calculate the urine-to-serum N-gal ratio at baseline and before euthanasia. After euthanasia, a necropsy was performed with notation of any gross anatomic abnormalities. Samples from heart, lungs, brain, kidney, liver, pancreas, aorta, small and large bowel, spinal cord and distal muscle tissue were fixed in 10% formalin were routinely processed and stained with hematoxylin and eosin for analysis. Tissue injury was scored by a blinded veterinarian pathologist as: 0 (no evidence), 1 (minimal), 2 (minor), 3 (moderate), 4 (severe) and injury distribution was scored as 0 (none), 1 (focal), 2 (multifocal), 3 (locally extensive), and 4 (diffuse).

Automated care platform

The automated care platform consisted of four devices capable of wireless communication. A microprocessor within a central processing unit (CPU) received physiologic data from the BioPac data acquisition system. The CPU wirelessly transmitted instructions based on predefined algorithms to three peripheral devices; an automated syringe pump controlling the endovascular balloon, a syringe pump titrating the administration of norepinephrine, and a peristaltic pump providing IV crystalloid boluses.

EPACC and standardized critical care

After whole blood resuscitation, animals were randomized to either automated EPACC or SCC. Animals in the EPACC group received automated endovascular support based on custom closed loop adaptive feedback algorithms to control the balloon volume of the CODA-LP balloon catheter in the supraceliac aorta. Animals in the automated SCC arm were administered crystalloid boluses and had titration of vasopressor medications based on a standard protocol (Supplemental Figure 1, http://links.lww.com/SHK/A764). For animals in the EPACC group, when the proximal mean arterial (pMAP) blood pressure fell below 60 mmHg and aortic flow exceeded 75% of baseline endovascular support was provided via partial balloon inflation. If aortic flow dropped below 75% of baseline, fluid boluses or vasopressors would be provided based upon the SCC algorithm. If aortic flow fell below 60% of native aortic flow despite fluid boluses the degree of aortic occlusion was decreased by reducing balloon volume until aortic flow returned to the target threshold.

We defined 60 to 70 mmHg as a target MAP range for the critical care phase, *a priori.* Animals with a blood pressure greater than 70 mmHg were weaned from vasopressor medications preferentially until preexperimentation vasopressor medication doses were met before having balloon support weaned. Once vasopressor medications reached baseline rates, balloon support was weaned until full restoration of flow.

Data analysis

Data analysis was performed with STATA version 14.0 (Stata Corporation, Bryan, Tex). Continuous variables are presented as means and standard errors of the means if normally distributed and as medians with interquartile ranges if not. *T* tests were used to compare normally distributed continuous data and Wilcoxson–rank-sum tests were used for data that were not normally distributed. Dichotomous and categorical variables were analyzed by chi-square statistics and presented as percentages. Statistical significance was set at $P < 0.05$.

RESULTS

There were no differences in baseline characteristics or initial laboratory parameters between the SCC and EPACC groups (Table 1). After the hemorrhage phase, both groups had similar decreases in blood pressure. Likewise, during aortic occlusion, there were no differences in maximum proximal MAP or average proximal MAP (Table 2, Fig. 1). During the critical care phase, animals in the EPACC group had a higher average proximal MAP, a lower average distal MAP, and a lower aortic flow (Table 2, Figs. 1–2, $P = 0.01$). EPACC animals remained within goal proximal MAP during critical care for a greater period of time when compared with the SCC animals (EPACC 95.3%, 95% CI, 93.2–97.4; SCC 51.0%, 95% CI, 29.5–72.6; $P < 0.01$). EPACC animals received balloon support for 95.5% (95% CI, 92.6–98.4) of the critical care period and none of the animals were completely weaned from EPACC support by the end of the study.

Immediately after balloon deflation there were no differences in the maximum lactate concentrations (SCC 9.6 mg/dL, 95% CI, 8.5–10.7; EPACC 9.8 mg/dL, 95% CI, 9.1–10.6; $P = 0.87$) (Fig. 2). During the critical care portion of the study, EPACC animals required less IV crystalloid (EPACC 1,583 mL, 95% CI, 12–3,154; SCC 7,400 mL, 95% CI, 6,148–8,642; $P < 0.01$; Fig. 2) and required a lower dose of norepinephrine (EPACC 5 mcg/kg/min, 95% CI, 0–16; SCC 51 mcg/kg/min, 95% CI, 37–64; $P < 0.01$) when compared with the SCC group. In addition, the EPACC group had a lower incidence of hypoglycemic episodes during the critical care phase of the study (EPACC 1 of 6 animals, 16.7%; SCC 4 of 6 animals, 66.7%, $P = 0.08$), although this did not meet significance.

By the end of the study, there were no differences in final lactate (EPACC 4.7 mg/dL, 95% CI, 4.1–5.3; SCC 5.2 mg/dL, 95% CI, 3.7–6.8; $P = 52$) or final P:F ratio (EPACC 320, 95%

TABLE 1. **Baseline physiology and laboratory recordings**

	REBOA (n = 6)	EPACC (n = 6)	*P*
Sex			1.0
Male	4 (66.7)	4 (66.7)	
Weight, kg	77.5 (8.0)	77.0 (3.5)	0.89
pH	7.4 (0.0)	7.4 (0.0)	0.94
PaO_2FiO_2	373 (96)	409 (83)	0.50
Hemoglobin, g/dL	10.3 (0.8)	10.0 (0.8)	0.49
WBC, per mcL	15.2 (3.0)	12.9 (1.7)	0.13
Platelets, 10^3/mcL	275 (45)	292 (105)	0.73
Potassium, mEq/L	3.7 (0.2)	3.6 (0.2)	0.51
Lactate, mg/dL	2.4 (0.5)	3.0 (0.7)	0.14
Creatinine, mg/dL	1.3 (0.13)	1.4 (0.2)	0.49
Glucose, mmol/L	93 (8)	87 (7)	0.20
Proximal MAP, mmHg	66 (7)	67 (8)	0.90
Aortic flow, mL/min/kg	38.3 (4.9)	36.7 (9.3)	0.72

FiO_2, fractional inspiratory oxygen concentration; PaO_2, partial pressure arterial oxygen; WBC, white blood cell count.

Table 2. **Compiled hemodynamics during the study period**

	SCC (n = 6)	EPACC (n = 6)	*P*
Minimum pMAP end of bleed, mmHg	33 (29–36)	31 (26–37)	0.63
Average pMAP during intervention, mmHg	129 (105–151)	113 (101–123)	0.20
Maximum pMAP during intervention, mmHg	161 (141–182)	152 (142–160)	0.15
Average pMAP during critical care, mmHg	60 (57–63)	65 (64–66)	<0.01
Average dMAP during critical care, mmHg	55 (51–59)	42 (38–46)	<0.01
Percent of time at goal pMAP	51.0 (29.5–72.6)	95.3 (93.2–97.4)	<0.01
Average Weight Based Aortic Flow During Critical Care, mL/min/kg	51 (41–61)	35 (32–38)	<0.01

dMAP, distal mean arterial blood pressure; pMAP, proximal mean arterial blood pressure.

CI, 234–405; SCC 259, 95% CI, 103–414; $P = 0.63$), but animals in the EPACC group had a higher creatinine (EPACC 2.3 mg/dL, 95% CI, 2.1–2.5; SCC 1.7 mg/dL, 95% CI, 1.4–2.0; $P < 0.01$, Fig. 3). There were no differences in the ratio of urine N-Gal to serum N-Gal between groups (EPACC 76.0%, 95% CI, 0–185.1; SCC 53.7%, 95% CI, 0–132, Fig. 3). Animals in the EPACC group had more edema within the kidneys on histological analysis (EPACC 2, IQR 2–2; SCC 0.5 IQR 0–2, $P = 0.02$), but there were no differences in the amount of cellular damage (EPACC 2, IQR 0–3; SCC 0, IQR 0–2, $P = 0.16$, Fig. 4). There were no differences in the histologic analysis of heart, lung, small bowel, large bowel, pancreas, liver, distal muscle or lumbar spinal cord.

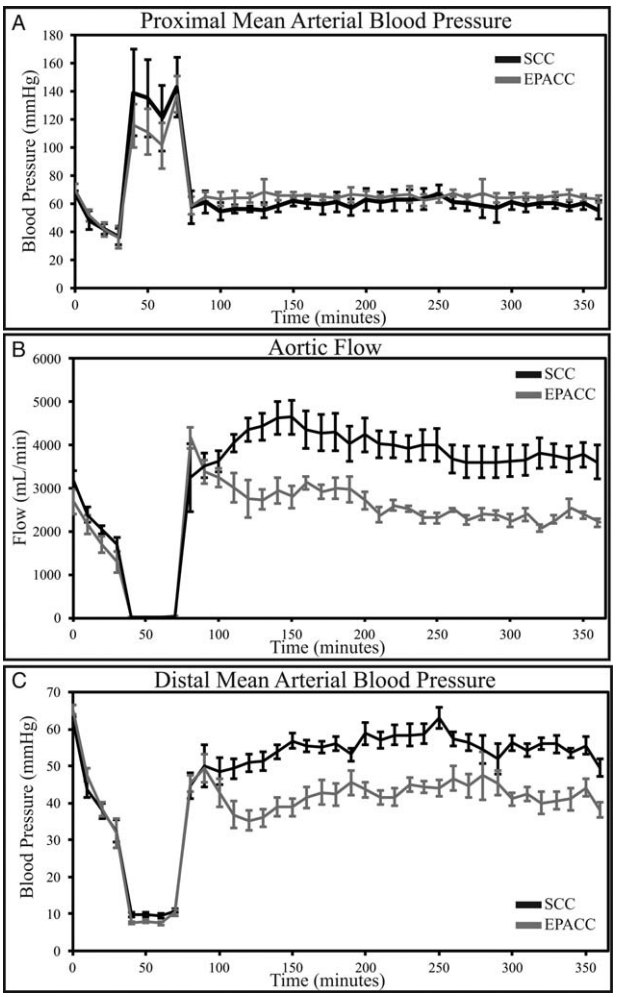

Fig. 1. **(A) Proximal mean arterial blood pressure, (B) distal mean arterial blood pressure, and (C) aortic flow during the study period.**

DISCUSSION

The intent of this study was to determine if partial augmentation of proximal blood pressure using an automated endovascular aortic balloon catheter in a swine model of vasodilatory shock could improve blood flow to the heart, lung, and brain while maintaining adequate distal flow to clear ischemic metabolites and perfuse distal vascular beds. Our automated syringe pump precisely controlled balloon volume in response to proximal blood pressure and aortic flow. This approach significantly reduced fluid and vasopressor requirements without increasing the overall ischemic burden or decreasing the rate of clearance of ischemic metabolites. EPACC improved both the average blood pressure proximal to the balloon as well as the duration of time within the predefined target blood pressure range. Although serum creatinine was increased with EPACC and there was evidence in increased renal edema, there were no differences in the extent of renal injury on histologic analysis.

Vasodilatory shock from ischemia reperfusion injuries is common after procedures requiring complete aortic occlusion (15). Similar to septic shock states, patients are often unresponsive to initial interventions and may require large volumes of crystalloid infusions and high doses of vasopressor medications to optimize perfusion to the heart and brain. During the treatment of shock, these interventions themselves can be harmful, leading to pulmonary edema, heart failure, cerebral edema, and ischemia to distal organs and limbs from excessive vasoconstriction (16–22). In the most extreme cases, a patient's cardiovascular system can be unresponsive to all currently available therapies. This refractory state leads to persistent hypotension, electrolyte and glucose metabolism abnormalities, multi-organ ischemia, and death. Although clinical consensus on the resuscitation algorithms and medications used to treat shock are continually refined, there has been no recent innovation proposed for refractory states. In these scenarios, EPACC may be a viable adjunct.

Endovascular techniques and tools have improved greatly over the past 20 years with a steady advance toward smaller devices and greater functionality. For example, small 7 Fr

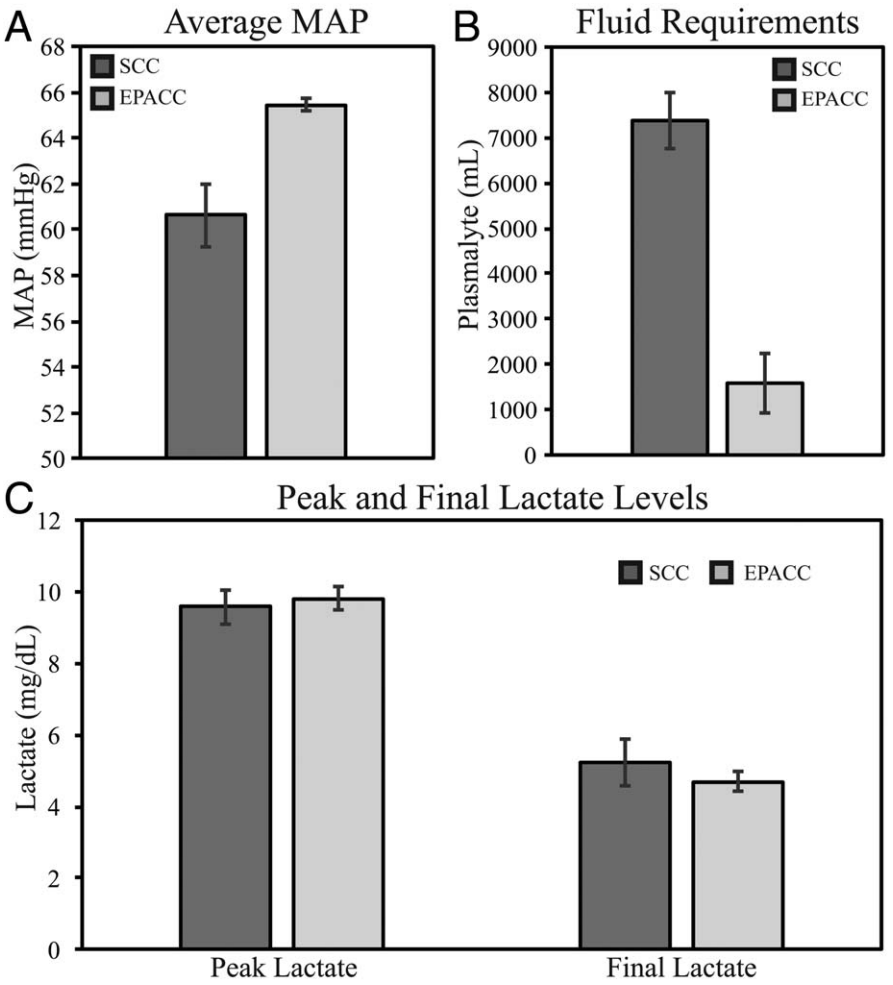

FIG. 2. **(A) Peak and final lactate concentrations, (B) average proximal mean arterial blood pressure during the critical care phase of the study, and (C) total resuscitation fluid requirements during the critical care phase of the study.**

catheters are now being routinely used to arrest hemorrhage in exsanguinating trauma patients with promising results (23). The development of these low-profile catheters has paved the way for endovascular techniques as an adjunct to current critical care resuscitation. Using a vasodilatory hyperdynamic model of shock, we have demonstrated that partial aortic occlusion can augment proximal pressure and decrease resuscitation requirements while maintaining a sufficient level of distal perfusion to clear ischemic metabolites at a rate similar to conventional critical care strategies based on intravenous fluids and vasopressors. With the exception of cardiac and neurogenic shock, most types of shock initially exhibit a hyperdynamic cardiac

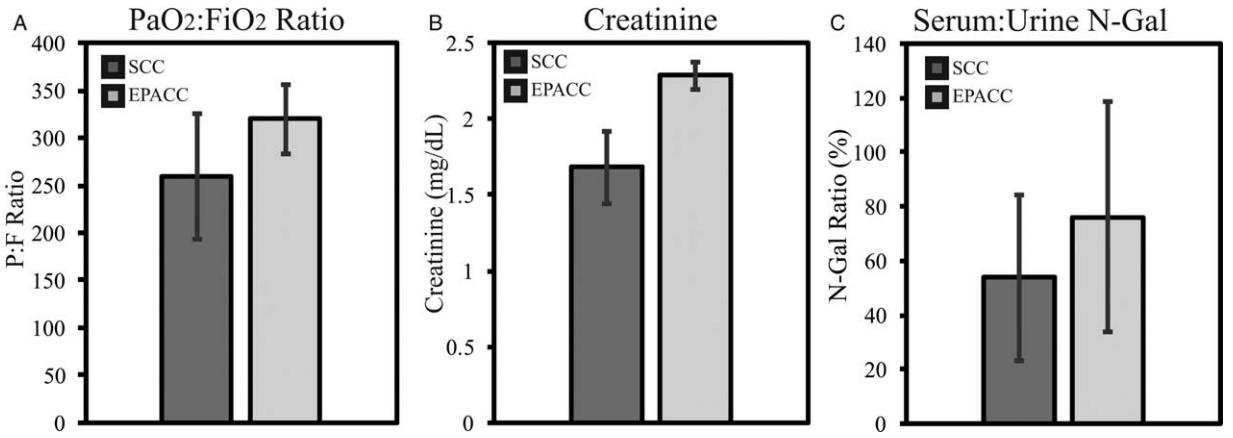

FIG. 3. **(A) PaO_2 to FiO_2 ratio at the end of the study, (B) final serum creatinine concentration at the end of the study, and (C) serum to Urine N-Gal concentration at the end of the study.**

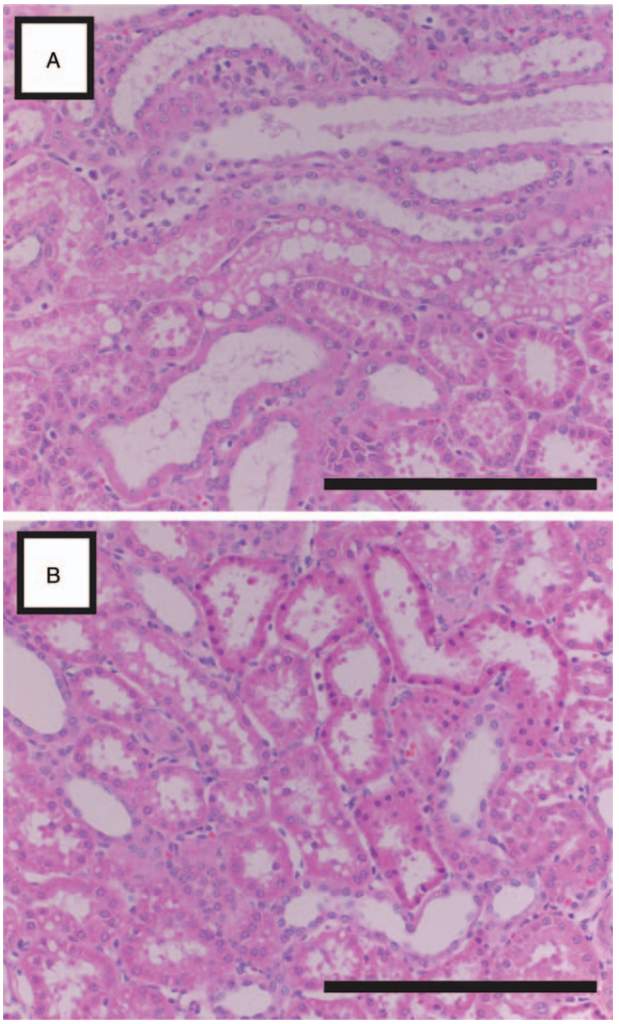

Fig. 4. **Representative image of renal histology from a SCC animal (A) and an EPACC animal (B). (scale bar = 200 microns).**

output state after even minimal interventions (24–26). This increased cardiac output results in increased blood flow to thoracic and abdominal organs, but fails to augment perfusion to the brain (27). Current therapeutic adjuncts for shock states can only address global hemodynamics, and therefore large amounts of IV fluids and high doses of vasopressors may be required before cardiac and cerebral perfusion are optimized. EPACC offers a novel intervention that augments current approaches to critical care management. Although distal aortic flow was attenuated by EPACC, the animals were still able to clear the large lactate burden as well as the SCC group. This result suggests that excessive aortic flow above weight-based norms to distal tissue beds does not necessarily hasten clearance of ischemic by-products. This is a critical finding when understanding the potential safety of this novel therapy, namely that attenuating aortic flow back to a normal preinjury level with EPACC does not result in additional ischemia to injured tissues. In essence, a hyperemic aortic flow state in response to ischemia is not necessarily beneficial and may actually represent a pathologic response to injury. Conversely, attenuating aortic flow with EPACC toward a more physiologic range in the context of a hyperdynamic cardiac state may be of benefit by reducing overall cardiac work without incurring additional distal ischemic debt.

In settings of severe vasodilatory shock, maintaining adequate blood pressure is often difficult despite mobilizing maximal resources and efforts for an individual patient. We have demonstrated that even with similar blood pressure goals, EPACC was able to improve the average mean arterial blood pressure throughout the period of critical care when compared to SCC. These findings may be the result of two separate phenomena noted with EPACC. First, EPACC is capable of near instantaneous adjustments of balloon volume on a second-to-second basis in response to blood pressure fluctuations. Unlike the administration of IV fluids or vasopressor medications that take time to be delivered and take effect, the mechanical augmentation of blood pressure is immediate. Thus, the greater precision of EPACC interventions combined with their rapid effect results in numerous minute adjustments that create hemodynamic consistency. This likely accounts for the greater percentage of time within the target blood pressure range seen with EPACC. The second possible explanation for the improved hemodynamics within the EPACC group is a preferential effect on the coronary artery perfusion that arises from increased afterload near the aortic root that is achieved without increasing arteriolar vasoconstriction with vasopressors. Therefore, EPACC may offer a critical adjunct to IV fluids and vasopressors by optimizing coronary perfusion.

In addition to its general applicability to shock states, EPACC may also have a distinct role in the resuscitation of ischemia–reperfusion injuries after aortic occlusion by controlling the washout of distal ischemic metabolites. Although the multisystem trauma victim with an ischemia–reperfusion injury is a fairly specific patient, the advent of REBOA for trauma is increasing the incidence of ischemia reperfusion injuries from the profound distal ischemia. These ischemic tissues manifest inflammatory cytokines, but can also result in hyperkalemia during reperfusion with resultant cardiac depression (28, 29). Although both groups of animals in the present study had profound ischemic injuries, EPACC controlled distal flow for the majority of the critical care phase as evidenced by lower aortic flow rates. This gradual return to baseline aortic flow rates may have slowed the washout of ischemic metabolites and served to minimize ongoing injury that occurs as a direct result of reperfusion of damaged tissues. Prior work has demonstrated that during ischemia and reperfusion, the injury to the tissue beds are a result not only of the initial ischemia, but also of the reaction of the ischemic tissues to the reintroduction of oxygenated blood. This reintroduction of oxygen into tissues results in the rapid development of reactive oxygen species, mitochondrial dysfunction, an influx of calcium into the cell, endothelial dysfunction, the activation of pro-apoptotic pathways and the generation of a larger inflammatory response (30, 31). It remains unclear at this time whether a slower reintroduction of oxygenated blood to distal tissues will be beneficial, or even when and how that reintroduction should occur. Nevertheless, the present study demonstrates that EPACC has the functionality to tightly control distal reperfusion. This controlled reintroduction of flow may ultimately serve to minimize the reperfusion injury that ensues.

The resuscitation of a critically ill patient represents a significant demand on medical facilities, consuming physical

resources as well as cognitive capacity. Not only is this demand substantial in the moment but is frequently sustained for extended periods. In resource limited environments, a single critically ill patient can overwhelm available resources and preclude high quality care in the context of multiple critically ill patients. Therefore, strategies to minimize utilization of these scarce resources will inherently enable higher quality care for more patients. EPACC addresses several of these key considerations for critical care environments. First, EPACC may limit reliance on large volume crystalloid administration and the need for prolonged infusion of vasoactive agents. This is of particular relevance for care in resource poor scenarios, where the ability to maintain large volumes of crystalloid or vasoactive drugs is not feasible. Second, through the use of automation, EPACC can maintain hemodynamics without reliance on continuous provider involvement, effectively offloading the cognitive requirements needed to care for critically injured patients. This affords the opportunity to provide simultaneous high-level care to multiple patients. Finally, this technology enables transitions of care or transport of patients without the need for extensive resources. This applies to scenarios of prolonged critical care transport from rural medical facilities or austere military environments.

The development of EPACC for critical care has been driven by military requirements for prolonged field care (32, 33). We chose an aggressive amount of mechanical pressure augmentation in an attempt to minimize the material requirements, at the risk of incurring some distal ischemia. This strategy in which fluid administration was not initiated until native aortic flow was less than 75% of weight-based norms resulted in a dramatic reduction in fluid and vasopressor requirements, however was met with an increasing serum creatinine concentration and increased renal edema. Interestingly, the increase in creatinine was not associated with histologic evidence of renal cell damage or necrosis or a difference in the ratio of urine:serum N-gal concentration, a marker of direct renal injury (34, 35). The increase in creatinine may be secondary to the expected decrease in renal blood flow and subsequent decrease in filtration. A small but not significant increase in the N-gal ratio may also be early evidence of renal injury that is either not yet apparent given the short duration of the study or not significant due to the small number of animals in the study. Future long-term survival studies as well as dose response curves to establish the optimal minimum aortic flow threshold beyond which fluid and vasopressor administration must be reinstated are necessary to fully realize the potential and maximize the safety of EPACC.

There are several limitations to the present study. First, this was a nonsurvival study with a total experimental time of only 6 h. It may be that critical differences between groups with respect to physiology or histology would manifest with studies of longer duration. A second limitation is that only a single ''dose'' of EPACC was tested. Like any intervention, EPACC can be adjusted in the amount of balloon support provided before the addition of intravenous fluids or vasopressors. For this study, a ''dose'' of 75% of weight-adjusted baseline aortic flow was chosen for fluid administration and 60% of weight-adjusted baseline aortic flow for decreasing balloon volume. The use of aortic flow to titrate EPACC represents another limitation in this manuscript. Placement of an aortic flow meter requires a surgical intervention which is not feasible in the settings of eventual proposed EPACC use. Although aortic flow allowed for improved control of EPACC in this initial experiment, future studies and any eventual clinical use will use surrogate markers of aortic flow to remove any surgical requirements for deployment of this technology. Finally, only one shock state was tested in this study. It is possible that the shock state from ischemia–reperfusion is distinct from other etiologies of shock. Therefore, future studies are needed to fully understand the potential utility of endovascular support for other types of shock such as septic shock. These limitations notwithstanding, the current manuscript is the first description of a fully automated critical care platform that incorporates endovascular support to minimize material requirements for patients in shock from ischemia reperfusion injury. Furthermore, it represents a novel therapeutic approach to patients in refractory shock and may prove advantageous in lesser degrees of physiologic derangement to minimize the morbidity and mortality associated with conventional treatments.

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