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

Timothy K. Williams, MD^{1,2}, Lucas P. Neff, MD¹, M. Austin Johnson, MD, PhD³, Rachel M. Russo, MD⁴, Sarah-Ashley Ferencz, MD⁵, Anders J. Davidson, MD⁴, Nathan F. Clement, MD¹, J. Kevin Grayson, DVM, PhD¹, and Todd E. Rasmussen, MD⁶

¹Clinical Investigation Facility, David Grant USAF Medical Center, Travis Air Force Base, California

²Heart, Lung and Vascular Center, David Grant USAF Medical Center, Travis Air Force Base, California

³Department of Emergency Medicine, UC Davis Medical Center, Sacramento, California

⁴Department of Surgery, UC Davis Medical Center, Sacramento, California

⁵Department of Surgery, Wright State University, Dayton, Ohio

⁶US Combat Casualty Care Research Program, US Army Medical Research and Materiel Command, Fort Detrick, MD

Abstract

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

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Corresponding author: Timothy K. Williams, MD, Heart, Lung and Vascular Center, David Grant Medical Center, Travis AFB, CA 94535, Phone: 707-423-5208, timothy.williams.72@us.af.mil.

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 manuscript, which all authors critically revised.

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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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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 100–300mL/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 ($p<0.01$) (Figure). During intervention, VAC resulted in more physiologic proximal MAP ($84\text{mmHg}\pm 18$ vs. $105\pm 9\text{mmHg}$, $p<0.01$) and higher renal blood flow than AO animals ($p=0.02$). During critical care, VAC resulted in higher proximal MAP ($73\text{ mmHg}\pm 8$ vs. $50\text{ mmHg}\pm 6$, $p<0.01$), 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 mmHg ($p<0.01$).

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.

Keywords

Trauma; endovascular; resuscitation; hemorrhage; swine

Introduction

Endovascular therapies for the management of non-compressible hemorrhage have emerged as a viable option to overcome the limitations of resuscitative thoracotomy (RT) 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 RT.^{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 supra-physiologic 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 great potential for improving outcomes in non-compressible torso hemorrhage.

To address the limitations of REBOA, partial flow restoration using a balloon catheter prior to 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 While 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 prior experiments demonstrated the ability of PRH to extend the pre-surgical interval to 90 minutes without demise due to 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 prior to definitive hemorrhage control and result in less physiologic derangement than complete aortic occlusion following 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). Following 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 following onset of damage control surgery, blood flow was reintroduced via the extracorporeal circuit in the AO and PRH arms.

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. Following 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 utilized to offset the vasodilatory effects of general anesthesia and titrated prior to experimentation to a mean arterial pressure between 65 and 75 mmHg. Animals were mechanically ventilated to maintain end-tidal CO₂ at 40 ± 5 mm Hg. Normal saline was administered at a rate of 5 mL/kg/hour to overcome insensible losses. Swine were heparinized with intravenous heparin to achieve an activated clotting time (ACT) of 100 seconds, similar to human baseline values. An underbody warmer was utilized to maintain core body temperature between 35–37°C.

Vascular access and monitoring for this setup has been previously described.²¹ Following 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 5–10 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 (Figure 2). Circuit flow was regulated in an automated fashion according to predefined hemodynamic parameters. Additional details are regarding the flow circuit design and function are available online (Supplemental Attachment-1).

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 utilized 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 prior to 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 following 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 mmHg. Two colloid 500ml boluses of hetastarch (HEXTEND, BioTime Inc., Alameda, CA) were permitted at T40 and

T70, if proximal MAP fell below 70 mmHg. Crossover from PRH to AO occurred when proximal MAP was below 35 mmHg for 3 minutes. Death was defined as a sustained proximal MAP less than 35 mmHg 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 500ml boluses of normal saline solution administered after two minutes of sustained hypotension (MAP less than 60 mmHg). 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 (SEMs) if normally distributed and as medians with interquartile ranges if not distributed normally. Dichotomous and categorical variables were analyzed by Fischer'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 (Figure 3). Mean survival time (mins) 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/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 (Figure 4A). 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, $p < 0.01$).

Following 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, $p=0.01$) (Figure 4B).

Lactate levels were higher in the PRH group between T45 and T90. Following flow restoration at T105, lactate levels decreased in the PRH animals, whereas levels in the AO group continued to increase until T150, decreasing thereafter (Figure 4C). By EOS, lactate concentrations were similar across groups (PRH 4.8 ± 2.7 mmol/L versus 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 (Figure 4D).

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/minute vs 618 ± 163 mL/minute, $p<0.01$). Renal blood flow was also greater with PRH during intervention and ICU phases (Table 2). While 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 (Supplemental Figure 1, Supplemental Table 1). A greater degree of duodenal necrosis occurred with AO compared to PRH ($p=0.01$) group and there was an apparent but non-significant ($p=0.06$) 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 post-operative period. These findings support the concept of PRH with VAC as a viable therapy in the management of non-compressible truncal hemorrhage 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 principle 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 “pre-hospital” intervention phase.^{16, 17} However, the duration of REBOA is finite due to 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 due to 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 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 (Figure 3). While 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).

While 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’s 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 multiply injured patient with concomitant hemorrhagic shock the ischemic threshold of the visceral organs is not known. There is clinical evidence in non-injured 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 20–40 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 due to continuous wash-out of lactate into the systemic circulation. However, PRH animals were able to more rapidly normalize lactate levels and pH following restoration of complete aortic flow. These findings may be due to 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 due to 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 3-fold 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 following resuscitation through EOS. Carotid blood flow was also maintained close to baseline following 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 following 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, due to 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 non-survival 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 prior to 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 prior to 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. While the principle of permissive regional hypoperfusion results in an ischemic burden with end-organ dysfunction relative to the non-injured, 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 are required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study Flow

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.

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.

Figure 4.

Hemodynamics & Markers of Ischemia - *A.* PRH achieved with highly regulated, low-volume, aortic blood flow via the circuit prior to definitive hemorrhage control at 90 minutes compared to no aortic blood flow in the AO group. Following 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 following surgical hemorrhage control and resuscitation (*secondary y-axis*). *D.* In similar fashion, pH worsened during PRH then improved following 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

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 Temp °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 ^{\$}	12.2 ± 0.9	12.3 ± 0.7	12.1 ± 1.2	0.91
WBC ^{\$}	19.3 ± 3.5	20.0 ± 4.4	21.6 ± 4.9	0.58
Potassium [#]	4.6 ± 0.2	4.6 ± 0.3	4.5 ± 1.0	0.90
Creatinine [#]	1.8 ± 0.0	1.5 ± 0.3	1.7 ± 0.3	0.24
Lactate [#]	2.4 ±	2.4 ± 0.11	2.7 ± 0.16	0.33
Glucose [#]	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 [@]	96.6 ± 12.4	104.0 ± 17.9	98.6 ± 15.8	0.76
Carotid Flow [*]	478.9 ± 58.7	494.1 ± 157.0	512.7 ± 93.9	0.87
Renal Flow [*]	194.0 ± 5.6	157.2 ± 85.0	191.6 ± 76.2	0.57
Circuit Flow [*]	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	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 [‡]	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

^{\$} g/dL; MAP = mean arterial pressure (mmHg);^{*} mL/min;

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@ beats/min;
# mmol/L
8 x10⁹/L;

g; MAP = mean arterial pressure;
£ resection mass/total body mass (kg)
EBL = estimated blood loss (mL); ACT = activated clotting time (sec)
DCS = damage control surgery, % EBL reflects percentage of total circulating blood volume
PRH = permissive regional hypoperfusion; AO = complete aortic occlusion

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

	PRH	AO	P
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 per minute

MAP = mean arterial pressure (mmHg); AO = complete aortic occlusion

PRH = permissive regional hypoperfusion