Small changes, big effects: The hemodynamics of partial and complete aortic occlusion to inform next generation resuscitation techniques and technologies

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BACKGROUND: The transition from complete aortic occlusion during resuscitative endovascular balloon occlusion of the aorta can be associated with hemodynamic instability. Technique refinements and new technologies have been proposed to minimize this effect. In order to inform new techniques and technology, we examined the relationship between blood pressure and aortic flow during the restoration of systemic circulation following aortic occlusion at progressive levels of hemorrhage.

METHODS: An automated supraceliac aortic clamp, capable of continuously variable degrees of occlusion, was applied in seven swine. The swine underwent stepwise removal of 40% of their total blood volume in four equal aliquots. After each aliquot, progressive luminal narrowing to the point of complete aortic occlusion was achieved over 5 minutes, sustained for 5 minutes, and then released over 5 minutes. Proximal and distal blood pressure and distal aortic flow were continuously recorded throughout the study.

RESULTS: Upon release of the clamp, hyperemic aortic flow was observed following 10% and 20% hemorrhage (1,599 ± 785 mL/min, $p < 0.01$; and 1,070 ± 396 mL/min, $p < 0.01$, respectively). Proximal blood pressure exhibited a nonlinear relationship to aortic flow during clamp removal; however, distal blood pressure increased linearly with distal flow upon clamp opening across all hemorrhage volumes.

CONCLUSIONS: Hyperemic blood flow following return of circulation may contribute to cardiovascular collapse. Reintroduction of systemic blood flow after aortic occlusion should be guided by distal blood pressure rather than proximal pressure. Awareness of hemodynamic physiology during aortic occlusion is of paramount importance to the clinical implementation of next-generation resuscitative endovascular balloon occlusion of the aorta techniques and technologies. (*J Trauma Acute Care Surg.* 2017;82: 1106–1111. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

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Resuscitative endovascular balloon occlusion of the aorta (REBOA) is gaining popularity as a resuscitation technique for patients in hemorrhagic shock from noncompressible torso injuries and is a viable, minimally invasive alternative to traditional emergency thoracotomy with aortic cross clamping.[1–4] However, the use of REBOA is limited by the profound distal ischemia that results from complete aortic occlusion.[5–8] Consequently, REBOA therapy has a maximal duration that cannot be extended beyond that afforded by aortic cross clamping.

Continued technique refinement using intermittent (iREBOA) and partial REBOA (pREBOA) has attempted to minimize distal ischemia to extend the duration of REBOA. Intermittent REBOA, in which the balloon is fully deflated for brief periods of reperfusion, has reportedly increased the tolerable duration of Zone 1 (descending thoracic) aortic occlusion beyond 80 minutes without ischemic complications.[1] However, it is unknown if intermittent reperfusion is beneficial or if complete reperfusion prior to definitive hemorrhage control destabilizes developing clots and subsequently increases blood loss. Partial REBOA, in which the balloon is partially deflated to allow titrated distal aortic flow, has also recently been described in case reports (publication in press). Although used

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successfully, accurate balloon titration is reportedly difficult and may result in hemodynamic instability.[9–11]

We have previously demonstrated in large animal models that very small changes in balloon inflation volume can rapidly create large changes in aortic flow. These abrupt increases in aortic flow may complicate both iREBOA and pREBOA by disrupting clot and promoting ongoing hemorrhage.[10,12] Delivery of tightly regulated low-volume distal aortic flow is a potential strategy to mitigate these limitations. The ability to directly measure and titrate distal flow in an automated fashion has been performed successfully in large animal models, providing proof of concept.[13] Unfortunately, the ability to directly measure aortic flow in a clinical setting is currently not feasible, and a surrogate parameter is needed. Thus, titration of balloon inflation volume to achieve pREBOA must be based on the only hemodynamic parameter that can be simply and reliably measured, namely, arterial blood pressure.

Currently, the relationships between arterial blood pressure, aortic flow, and the degree of pREBOA during hemorrhagic shock are poorly understood. Defining these relationships may not only improve the safety and efficacy of iREBOA and pREBOA but will serve to underpin the development of next-generation endovascular devices for trauma resuscitation. We hypothesized that proximal blood pressure would be an inaccurate predictor of distal aortic flow but that distal mean arterial blood pressure (MAP) would provide a more accurate estimate of aortic flow at various levels of hemorrhage following complete aortic occlusion. The aim of this study was to examine the relationship between blood pressure and aortic flow at varying degrees of occlusion, across iterative levels of hemorrhage.

METHODS

Overview of Experimental Design

This study was approved by the Institutional Animal Care and Use Committee at David Grant USAF Medical Center, Travis Air Force Base, California. All animal care and use were in 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, castrated male and nonpregnant female Yorkshire-cross swine (*Sus scrofa*), obtained from the University of California, Davis, were acclimated for a minimum of 7 days. At the time of experimentation, animals weighed between 55 kg and 65 kg, with an age between 5 months and 7 months.

Animals were anesthetized, instrumented, and splenectomized and had an automated clamp capable of varying degrees of occlusion placed around the supraceliac aorta. The animals then underwent four iterative cycles of hemorrhage. During each cycle, 10% of circulating blood volume was removed over 5 minutes from the femoral artery to simulate progressive levels of hemorrhagic shock. A 5-minute observation period was provided to allow hemodynamic equilibration. A prescribed, computed-controlled aortic occlusion sequence was performed in the euvolemic state and at each level of hemorrhage (Fig. 1). Gradual, progressive aortic occlusion was achieved using an

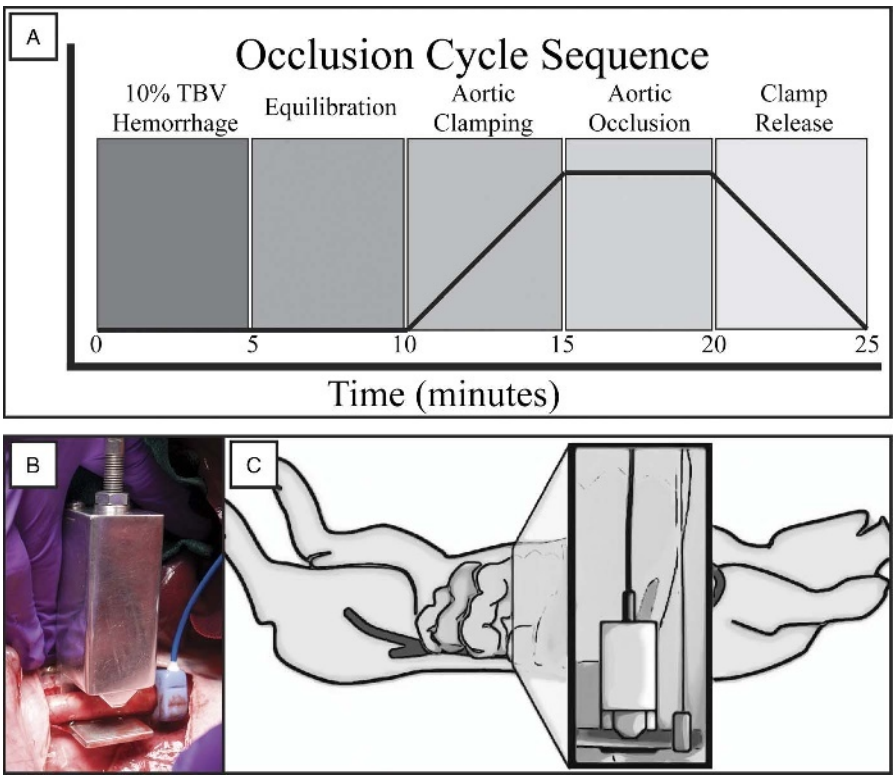

Figure 1. Occlusion cycle sequence (*A*), aortic clamp placed on supraceliac aorta (*B*), representation of aortic clamp in place (*C*).

automated aortic clamp (described below) over a 5-minute period until aortic flow ceased. A 5-minute period of complete occlusion was then followed by a graduated release of the aortic clamp over 5 minutes. All animals had a 5-minute recovery period between cycles. Animals were humanely euthanized following the conclusion of the fourth cycle.

Hyperemia was defined as an increase in aortic flow above baseline upon return of flow following occlusion. Supraphysiologic blood pressure was defined as a MAP greater than 110 mm Hg, in accordance with current definitions of hypertension.

Development of the Variable Aortic Clamp

Current endovascular balloon technology does not provide precise, reproducible degrees of aortic occlusion. Therefore, an alternative approach to modeling the physiologic effects during the transition to and from complete occlusion was necessary. To overcome this limitation, we developed an automated aortic clamp capable of precisely modulating aortic occlusion by mechanical external compression of the vessel. This custom-made, automated, cable-driven aortic clamp is controlled using an Arduino Mega 2560 microcontroller (Arduino, Somerville, MA). The clamp is fully programmable, can be instructed to perform an infinite array of experimental aortic occlusion protocols, and moves with a precision of 0.01 mm per step. Bench-top testing on an aortic flow simulator was carried out prior to use in the animal models to ensure precision and reproducibility of aortic occlusion (unpublished data).

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. To overcome the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine (0.01 μg/kg per minute) was initiated. Animals were mechanically ventilated with tidal volumes of 7 to 10 mL/kg and a respiratory rate of 10 to 15 breaths/min sufficient to maintain end-tidal CO_2 at 40 ± 5 mm Hg. The pigs were placed on a warming blanket set at 39°C to minimize hypothermia.

Bilateral brachial arteries were exposed through axillary incisions, and the right femoral artery was accessed through an oblique groin incision. Proximal blood pressure was measured via a 7 Fr 13-cm introducer sheath (Super Sheath; Boston Scientific Corporation, Natick, MA) inserted in the right brachial artery, and distal blood pressure was measured via a 9 Fr 13-cm introducer sheath (Super Sheath) inserted retrograde into the right femoral artery. A 7 Fr 13-cm introducer sheath was inserted into the left brachial artery to enable controlled hemorrhage and blood collection for laboratory analysis.

A laparotomy and splenectomy were performed to minimize hemodynamic variation from autotransfusion.[14] The left hemidiaphragm was incised longitudinally, and the inferior pulmonary ligament was divided to expose the supraceliac aorta. The aorta was circumferentially exposed, and two adjacent lumbar arteries were ligated to facilitate placement of the aortic clamp and to minimize collateral flow around it. The clamp and 14-mm perivascular flow probe (Transonic Corporation, Ithaca, NY) were positioned on the supraceliac aorta for continuous aortic flow measurement, with the clamp located distal to the flow probe (Fig. 1*B*). The abdomen was loosely closed with the clamp cable emerging from the abdomen anteriorly (Fig. 1*C*). During the entirety of the experiment, normal saline was administered at a maintenance rate of 5 mL/kg per hour.

Data Collection

Physiologic data, including proximal and distal MAP, heart rate, core body temperature, aortic flow proximal to the clamp, and electrocardiogram monitoring, were continuously captured throughout the experiment using a multichannel data acquisition system (Biopac Systems Inc, Goleta, CA). The position of the aortic clamp in reference to complete occlusion (zero flow) was streamed from the Arduino microcontroller over a serial connection and captured in real time. All data were exported to Microsoft Excel (Redmond, WA) for data storage and analysis.

Statistical Analysis

Microsoft Excel and STATA (version 14; College Station, TX) were used for data analysis. Continuous data are presented as means with SEs. Comparisons were made with the Student

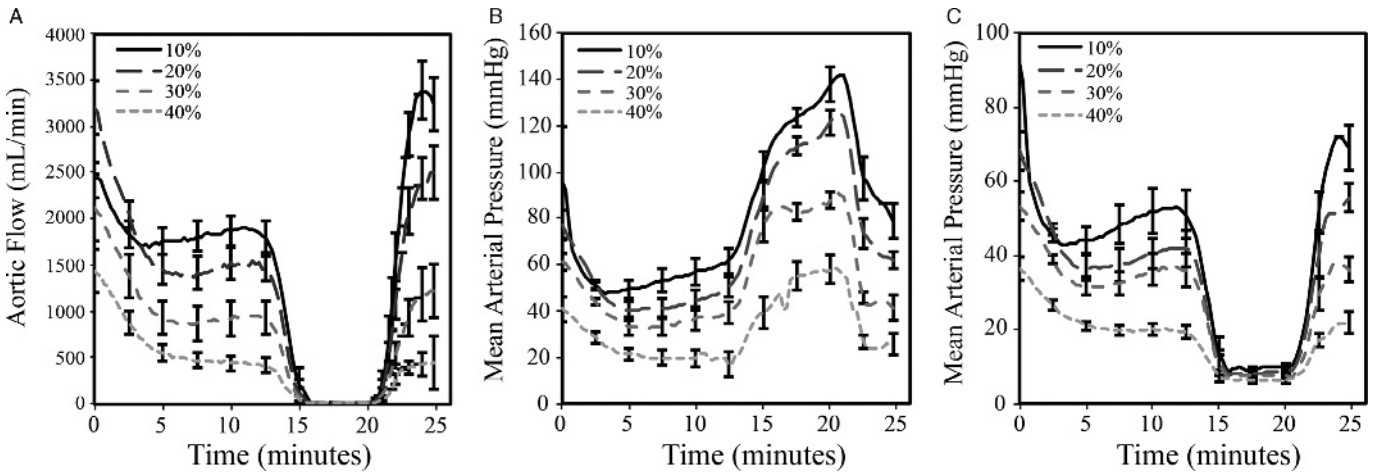

Figure 2. Aortic blood flow (*A*), proximal MAP (*B*), and distal MAP (*C*) during cycles of occlusion at iterative levels of hemorrhage.

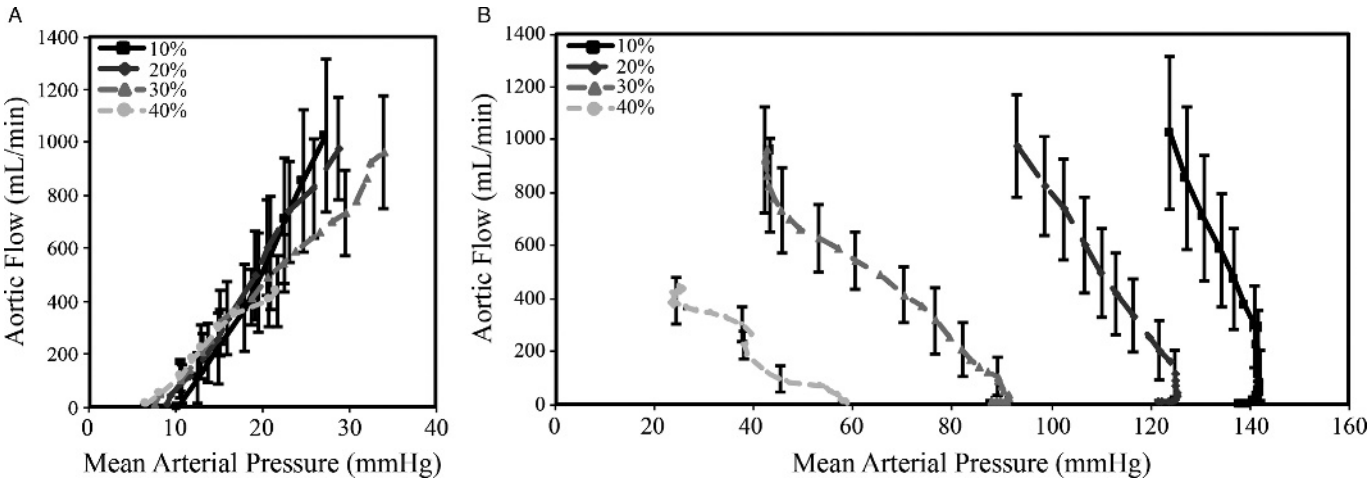

Figure 3. Distal (*A*) and proximal (*B*) MAP versus aortic flow during release from clamp.

t test where appropriate. For statistical significance, p values were set at 0.05.

RESULTS

The seven animals used in this experiment had no significant differences in baseline physiology. Figure 2*A* demonstrates average aortic flow throughout each cycle of the experiment. Following full clamp release at both 10% and 20% hemorrhage, aortic flow was markedly increased relative to baseline flow (10%: 1,599 ± 785 mL/min, $p < 0.01$; 20%: 1,070 ± 396 mL/min, $p < 0.01$), but increased flow was not evident after 30% and 40% hemorrhage (30%: 337 ± 490 mL/min, $p = 0.12$; 40%: −83 ± 256 mL/min, $p = 0.42$) (Fig. 2*A*, Table 1).

During aortic occlusion, proximal MAP increased for all levels of hemorrhage when compared with baseline (Fig. 2*B*, Table 1). During occlusion, a distal MAP was present at all levels of hemorrhage. The average distal MAP during occlusion was smaller after 40% hemorrhage when compared with 10% hemorrhage (6.5 ± 2.6 mmHg vs 10.0 ± 1.7 mmHg, Fig. 3*C*, $p = 0.03$).

During clamp release, aortic flow was linearly related to distal MAP across all levels of hemorrhage (Fig. 3*A*). Aortic flow increased at a rate of 30.7 ± 10.1 mL/min (40% hemorrhage) to 50.5 ± 10.8 mL/min (10% hemorrhage) for every increase of 1 mm Hg in MAP, with no statistical differences between groups ($p > 0.05$, Table 1). Aortic flow was not linearly related to proximal MAP at any level of hemorrhage (Fig. 3*B*).

TABLE 1. Hemodynamics at Iterative Levels of Hemorrhage

	10% Hemorrhage	20% Hemorrhage	30% Hemorrhage	40% Hemorrhage
Aortic hyperemia	1,599 ± 785*	1,070 ± 396*	337 ± 490	−83 ± 256
Max proximal occlusive MAP	137.8 ± 19.2	122.2 ± 13.6	91.9 ± 10.1	58.6 ± 16.2
Increase in proximal MAP	80.2 ± 27.9*	76.9 ± 20.1*	54.7 ± 12.5*	37.8 ± 12.3*
Slope	50.5 ± 10.8	50.2 ± 10.6	48.9 ± 10.8	30.7 ± 10.1
Occlusive distal MAP	10.0 ± 1.7	8.7 ± 1.7	7.7 ± 2.3	6.5 ± 2.6

*$p < 0.01$.

DISCUSSION

The physiologic response to aortic occlusion and reperfusion at varying levels of hemorrhage has important implications for the use of REBOA and its emerging variants during trauma resuscitations. By utilizing a novel automated aortic clamp, we have described critical physiologic responses to aortic occlusion and subsequent reperfusion. We have demonstrated that supraphysiologic proximal blood pressure occurs during occlusion at 10% and 20% hemorrhage of total blood volume. We also demonstrated that reperfusion following complete aortic occlusion results in significant blood flow hyperemia, except at profound levels of hemorrhagic shock. Furthermore, we have demonstrated that a linear relationship between distal MAP and aortic flow exists during early reperfusion when transitioning from complete occlusion. These findings are integral concepts that can inform decisions during the transition from complete REBOA and may guide future innovation in techniques of aortic occlusion for hemorrhage control.

Complete aortic occlusion during trauma resuscitation augments proximal perfusion to the heart, lungs, and brain but has the potential to lead to supraphysiologic changes.[12,15] Animal studies of REBOA, as well as early clinical case reports, have demonstrated proximal MAPs that are supraphysiologic, but it has been unclear if these occur at all levels of hemorrhagic shock. As demonstrated here, complete aortic occlusion is capable of increasing proximal blood pressure at all levels of hemorrhage; however, only animals in Classes I and II shock experienced blood pressures beyond physiologic norms.

Restoration of systemic circulation following complete aortic occlusion often results in hemodynamic instability, requiring repeat occlusion to maintain adequate proximal blood pressure. Although tissue hypoxia, the accumulation of ischemic metabolites from anaerobic metabolism, and loss of distal vascular tone are known consequences of aortic occlusion, the pattern of distal blood flow after REBOA has not previously been described.[16] We have demonstrated that extreme distal hyperemia

occurs during Classes I and II shock, with an increase in distal aortic flow greater than 1 L/min above baseline levels. Clinically, this may lead to disruption of developing hemostasis when restoration of aortic flow is attempted prior to hemorrhage control.

Although the short duration of complete occlusion in this study resulted in transient hyperemia upon restoration of full flow, prolonged periods of aortic occlusion with a more substantial ischemic burden may result in delayed hemodynamic collapse. This can occur because of a washout of ischemic metabolites from distal tissues into systemic circulation, leading to profound metabolic acidosis, hyperkalemia, and cardiac dysfunction, which have been previously described in large animal models of REBOA and following aortic cross clamping.[6,7,16,17]

Partial REBOA has been suggested as a mechanism of overcoming the limitations of iREBOA.[10,17] Continuous, low-volume aortic flow may reduce the production and release of ischemic metabolites into the systemic circulation, while allowing the body to compensate through innate autoregulatory mechanisms. This regionalized hypoperfusion of the viscera and distal organs may also minimize clot destabilization and subsequent hemorrhage.[12] Unfortunately, limited initial clinical experience with pREBOA has demonstrated that hemodynamic stability is difficult to achieve. Initial balloon deflation results in significant lability in proximal blood pressure, resulting in hemodynamic profiles not dissimilar to iREBOA (publication in press). This is in part due to challenges of current balloon technology to precisely regulate aortic blood flow. Small changes in balloon volume can result in substantial fluctuations in aortic blood flow and subsequently blood pressure, and identifying optimal hemodynamic parameters to guide balloon deflation remains a critical question.[10] The present study highlights that proximal blood pressure does not correlate with aortic blood flow across various levels of hemorrhage. Therefore, clinical attempts to reintroduce stable low-volume distal blood flow cannot be reliably guided by proximal blood pressure.

The most clinically relevant finding from the present study is the relationship of distal blood pressure to aortic flow. We have demonstrated that a linear relationship exists between distal blood pressure and aortic flow, which is preserved across various levels of hemorrhage. Moreover, the absolute distal pressure value closely correlates with the absolute aortic flow rate across levels of hemorrhage. This is likely attributable to the profound vasodilation that occurs in response to complete aortic occlusion.[16] Previous studies in animals have demonstrated that even brief durations of aortic occlusion result in maximal hyperemia within minutes; therefore, it is likely that following any clinically meaningful application of REBOA distal systemic vascular resistance will be similar at any level of hemorrhage.[18] As long as proximal pressure and cardiac output is preserved, the reintroduction of low aortic flow will result in a conserved distal pressure. The simplicity of this relationship suggests that distal blood pressure is a more reliable estimate of aortic flow than proximal blood pressure when transitioning to pREBOA.

There are several limitations to this study. First, this study used a controlled hemorrhage model without organ injury. Therefore, the influence of inflammatory mediators of organ injury and the potential for ongoing bleeding following restitution of aortic flow were not modeled. Ongoing hemorrhage has the potential to alter the relationship between aortic flow and distal blood pressure, although our previous animal experiments have demonstrated that low aortic flow rates between 150 mL/min and 300 mL/min do not result in increased bleeding in a uniformly lethal liver injury model (publication in press). This study also models aortic occlusion and reperfusion after only 5 minutes of complete occlusion. It is possible that the physiologic response to reperfusion after prolonged durations of occlusion changes. However, animal evidence suggests that maximal hyperemia is experienced after only 30 seconds of occlusion, suggesting that the alterations in vascular tone that may affect the relationship between pressure and flow may be stable after a short period.[18] This study used an iterative model of increasing hemorrhage with 5-minute periods for equilibration between cycles. It is possible that a cumulative ischemic burden developed with each cycle, resulting in a significant increase in ischemic metabolites throughout the experiment that altered the physiologic response to occlusion and reperfusion. Although our prior experiments have demonstrated no significant increase in lactate or inflammatory cytokines from baseline following a full 15 minutes of complete occlusion, there may be ongoing processes not measured in the current experimental model. This limitation of the study design was intentional to limit the number of animals utilized in this experiment, but may represent an area of future study. Finally, it is important to understand that the automated aortic clamp has much more precision during occlusion and reinstitution of aortic flow when compared with current endovascular technologies used for REBOA. Therefore, practitioners should not expect to be able to obtain precise increases in distal MAP when partially deflating a balloon, but these data do describe general physiologic relationships that may be useful when attempting to transition from complete to pREBOA. These limitations notwithstanding, the physiologic findings described in this article have important implications for the transition from complete aortic occlusion. These findings have the potential to inform future innovations in aortic occlusive technology.

CONCLUSIONS

This study described the relationship between proximal blood pressure, distal blood pressure, and distal aortic blood flow during aortic occlusion and reperfusion at varying shock states. We have demonstrated that supraphysiologic blood pressure occurs during occlusion in Classes I and II shock, which has the potential to exacerbate injuries to the brain and create increased stress on the cardiopulmonary system. Furthermore, we have demonstrated that aortic hyperemia occurs during reperfusion from complete occlusion in Classes I and II shock. Finally, we have demonstrated that aortic blood flow has a linear relationship with distal blood pressure during reperfusion, a critical concept that can be used to help transition from complete to pREBOA. These concepts can be applied to direct patient care immediately, with monitoring of distal pressure from the arterial introducer sheath of currently fielded, low-profile REBOA catheters.

AUTHORSHIP

M.A.J., T.K.W., and L.P.N. conceived of the study, executed the study, and drafted and critically reviewed the manuscript. M.A.J. conducted the data

analysis and statistical analysis. S.-A.E.F., A.J.D., R.M.R., T.E.R., and O.G. assisted in execution of the study and critically reviewed the manuscript.

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DISCLOSURE

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