

A Novel Automated Endovascular Variable Aortic Control Device to Expand Function of Standard REBOA Catheters

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Background: Endovascular methods for hemorrhage control, including resuscitative endovascular balloon occlusion of the aorta (REBOA), are evolving and are increasingly being applied clinically. Partial flow strategies to mitigate the consequences of complete aortic occlusion have been demonstrated in pre-clinical models to enhance REBOA and expand its application to various shock states. Initial studies demonstrated that controlled partial flow requires precision beyond the capabilities of manual balloon volume adjustment, therefore automation is required. Our group previously developed a proof-of-concept computer-controlled extracorporeal flow circuit capable of precision aortic flow regulation, but it was not clinically applicable. To bring this concept closer to clinical applicability, we have developed the first endovascular strategy to achieve precision aortic flow regulation, termed endovascular variable aortic control (EVAC).

Methods: Following instrumentation, five Yorkshire-cross swine were subjected to controlled 25% hemorrhage, followed by precision low volume aortic flow regulation using a commercially available compliant balloon catheter pre-positioned in the descending thoracic aorta, connected to a custom, wireless syringe pump. Closed-loop feedback algorithms based on streaming physiologic data were used to determine balloon volume changes.

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Author contributions: TKW, LPN, EMT, GLH, MAS, AJD, ESD, ERF, and MAJ contributed to the literature search and study design. TKW, LPN, EMT, GLH, MAS, AJD, ESD, ERF, and MAJ collected the data, performed the data analysis and interpretation. TKW, LPN, EMT, GLH, MAS, AJD, ESD, ERF, and MAJ wrote and critically revised the manuscript.

Conflicts of interest: Dr. Williams, Dr. Neff, and Dr. Johnson are named inventors on intellectual property indirectly related to this work, jointly owned by the University of California Davis and the United States Air Force, and are co-founders of Certus Critical Care, Inc, which has licensed this technology from UC Davis.

Funding: Funding for this study was provided by the Clinical Investigation Facility, David Grant Medical Center, Travis Air Force Base, CA.

Presentation: none.

Disclosure: The views expressed in this material are those of the authors and do not reflect the official policy or position of the U.S. Government, the Department of Defense, the Department of the Air Force, or the University of California Davis. The animals involved in this study were procured, maintained, and used in accordance with the Laboratory Animal Welfare Act of 1966, as amended, and the Guide for the Care and Use of Laboratory Animals, National Research Council. The work reported herein was performed under United States Air Force Surgeon General-approved Clinical Investigation No. FDG20170005A.

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Results: The EVAC syringe pump was highly effective at maintaining precise aortic flow throughout the 45-minute intervention period during steady-state conditions as well as during rapid fluid administration. Aortic flow and distal mean arterial pressure remained stable during EVAC, despite changing proximal hemodynamics. Balloon volume was dynamic, averaging over 500 changes during intervention, with a mean volume change of 6.7 μ L and a maximal change of 100 μ L.

Conclusions: The EVAC syringe pump is capable of achieving aortic flow regulation with high precision, beyond what is achievable with manual control. This serves as a model for future device design, enabling as-of-yet unachievable clinical therapies for hemorrhage and shock states. Future technological development is required to fully translate this into clinical use.

Keywords: EVAC; P-REBOA; REBOA; Automation; Hemorrhage

Received: 1 August 2018; Accepted: 18 October 2018

INTRODUCTION

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a viable strategy to salvage trauma victims dying from non-compressible torso hemorrhage (NCTH) [1–4]. However, the distal ischemia that develops in tissues below the level of occlusion limits the duration of REBOA therapy to 30–45 minutes [5]. This limitation has prompted the development of new techniques to extend support beyond the finite period. Partial occlusion with REBOA catheters to allow distal flow past the point of occlusion has emerged as a promising means to mitigate the deleterious consequences of REBOA [6–10]. To date, the clinical efficacy of partial REBOA (P-REBOA) has been elusive because the control of balloon inflation and deflation with existing technology can only be accomplished by low-fidelity manual manipulation with a handheld syringe [9–11].

Manual regulation of P-REBOA represents a challenge for two principle reasons. First, the interplay of aortic physiology, cardiac performance, neuroendocrine responses, volume status and flow dynamics at high levels of aortic occlusion is highly complex and highly dynamic. Because of this, manual titration of partial flow requires very subtle changes in balloon volume to maintain stable flow, which is not possible with current REBOA balloon technology. Even small occlusion balloon volume shifts can result in rapid changes in aortic blood flow and pressure, creating significant challenges for medical providers trying to stabilize a critically ill patient [11,12]. Future balloon technology aimed at decreasing the wide swings in blood flow in response to changes in balloon volume may be able to improve manual control of P-REBOA.

Second and most important, achieving the type of consistent low-volume aortic flow needed for hemostasis requires rapid responsiveness to dynamic factors apart from simply the amount of volume in the balloon. Active intravascular volume resuscitation with and without ongoing blood loss, administration of vasopressors, distal tissue bed ischemia, and vasodilation all introduce additional layers of complexity that influence

aortic flow past a static balloon. Therefore, compensatory changes in balloon volume must be just as dynamic as the changing physiology of an active trauma resuscitation to maintain stable flow past the balloon and ensure hemostasis. This need for a dynamic and “intelligent” balloon has major implications for the conduct of P-REBOA in the pre-hospital or resource-constrained environments, where rapid increases in blood flow from blood or IV fluid administration may destabilize clots and lead to continued life-threatening hemorrhage. Conversely, blood flow past the balloon may cease in response to decreased proximal perfusion pressure leading to a decreased aortic diameter and complete occlusion, resulting in additional downstream ischemia from complete REBOA. Even with manual balloon titration in the most skilled provider’s hands, these physiologic considerations demand constant attention to balloon volume and real-time physiologic metrics including blood pressure above and below the balloon to maintain a consistent amount of distal perfusion. Early clinic experiences with P-REBOA during dynamic trauma resuscitations in level 1 trauma centers have indicated how labile the physiology can be with this process [8,11]. Thus, maintaining consistent patient physiology with P-REBOA is a resource and labor-intensive process that may prevent a key medical provider from focusing on more important aspects of patient care, such as definitive hemorrhage control. In many settings, particularly austere environments with limited medical providers, this may make P-REBOA impractical.

Our group’s prior studies with robotic control systems have demonstrated that the precise regulation of ultra-low downstream aortic flow rates can balance the competing management priorities of hemostasis, blood pressure augmentation, and distal organ perfusion in the face of uncontrolled hemorrhagic shock [13–15]. This novel therapeutic concept, termed regionalized perfusion optimization (REPO), is predicated on a method that can precisely and dynamically control the flow of blood to the abdominal aorta, responding in real time to changing patient physiology. Given the difficulties surrounding manual control, REPO must be accomplished

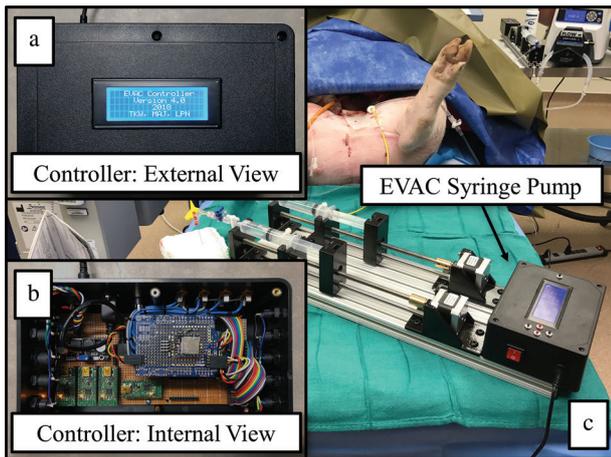


Figure 1 Endovascular variable aortic control (EVAC) hardware platform. (a) External view of the custom wireless EVAC controller. (b) Internal view. (c) Automated EVAC syringe pump in use during a representative experiment.

with endovascular devices that provide automated precision control by sensing the physiology of the patient and responding in real time with appropriate balloon volume changes. As an initial step toward the development of an endovascular variable aortic control (EVAC) device that can autonomously vary the degree of aortic occlusion, we developed a novel extracorporeal flow circuit to achieve precision regulation of aortic blood flow [14]. This and other experimental aortic flow regulation devices have achieved REPO successfully in multiple large animal models of controlled and uncontrolled hemorrhage, improving outcomes compared to REBOA for multiple physiologic endpoints including mortality, hemodynamics, and end-organ function [13,16]. Yet, these initial studies did not employ endovascular devices that could readily translate into a clinically viable technology. Nonetheless, the extracorporeal flow device and the subsequent automated aortic clamp served as a proof-of-concept for the physiologic implications of automated aortic flow regulation and regional perfusion optimization [15,16]. To advance these concepts closer to a clinically relevant therapy, we have developed an automated syringe pump and controller that can regulate the filling volume of a commercially available endovascular balloon catheter based on physiologic data inputs from the patient. The purpose of this communication is to describe the first-in-animal experience with a fully automated, endovascular method to achieve the precise regulation of aortic flow.

METHODS

Overview

The conduct of this experimental study involved *in vivo* animal testing of a custom-built hardware and software

system to control aortic flow. 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 were 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, castrated male and non-pregnant female Yorkshire-cross swine (*Sus scrofa*) were acclimated for a minimum of seven days. At the time of experimentation, animals weighed between 60 and 95 kg.

Hardware Architecture

The novel components of this platform include a precision automated syringe pump coupled with a custom microcontroller that integrates streaming physiologic data from the patient (Figure 1). Development and testing of the hardware and software platform were performed internally at the 60th Clinical Investigation Facility, Travis AFB, CA. The fundamental architecture of the master control system has been previously described, however, this experiment utilized a more compact design [14]. In brief, the hardware architecture utilizes a commercially available microcontroller (Arduino, Somerville, MA) with wireless functionality and a multichannel 16-bit analog-to-digital converter for the acquisition of real-time physiologic data including aortic flow, proximal arterial pressure, and distal arterial pressure (Figure 1a,b). The custom syringe pump utilizes a NEMA 17 stepper motor that drives a standard lead screw, a commercially available stepper motor controller (BigEasyDriver, Sparkfun, Niwot, CO), custom 3D-printed components that hold the syringe and plunger, and a wireless microcontroller that performs bidirectional communication with the master controller unit (Figure 1c).

Custom software algorithms were developed to precisely regulate aortic flow using a closed loop feedback mechanism. A weight-based aortic flow rate of 4.3 mL/kg/min was established, which is approximately 10% of baseline distal aortic flow for a 70 kg animal.

In Vivo Testing

Animals were premedicated with 6.6 mg/kg intramuscular tiletamine/zolazepam (Telazol, Fort Dodge Animal Health, Fort Dodge, IA). Following isoflurane induction and endotracheal intubation, general anesthesia was maintained with 2% isoflurane in 100% oxygen. To offset the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine (0.01 mg/kg/min) was instituted upon venous access and titrated prior to experimentation to achieve a target mean arterial pressure between 65 and 75 mmHg. Animals were mechanically ventilated to maintain end-tidal CO₂ at 40 ± 5 mmHg.

Plasmalyte (Baxter, Deerfield, IL) maintenance intravenous fluid was administered at a rate of 10 mL/kg/h until the abdomen was closed, at which point the rate was decreased to 5 mL/kg/h for the remainder of the study to overcome insensible losses. Intravenous heparin was administered to achieve an activated clotting time (ACT) of 100 seconds, similar to human baseline values. An underbody warmer was used to maintain core body temperature between 35 and 37°C.

Following laparotomy, a splenectomy was performed to minimize hemodynamic variation from autotransfusion. The supraceliac aorta was exposed by dividing the left diaphragm and dissected circumferentially for a length of 5–10 cm. A perivascular aortic flow probe (Transonic Systems Inc, Ithaca, NY) was placed with ligation of two adjacent intercostal arteries distally, thus preventing intervening flow between the flow probe and the endovascular occlusion balloon. The abdomen was closed with cable ties. External jugular veins were cannulated to facilitate medication and fluid administration. The right brachial artery was exposed and cannulated with a 7F sheath (SuperSheath, Boston Scientific, Marlborough, MA) for controlled hemorrhage. The left axillary artery was exposed and cannulated with a 9F sheath (SuperSheath, Boston Scientific) for proximal arterial pressure monitoring. The left femoral artery was exposed and cannulated with a 12F sheath (Cook Medical, Bloomington, IN), through which a 9F Coda LP balloon (Cook Medical, Bloomington, IN) was advanced under fluoroscopic guidance to the level of the supraceliac aorta (zone 1), just distal to the aortic flow probe. Distal pressure was also monitored via this sheath.

Data Collection and Analysis

Physiologic parameters and aortic flow measurements were collected in real time using a Biopac MP150 multichannel data acquisition system and the custom Arduino-based data acquisition system/controller (BioPac, Goleta, CA). Parameters measured included heart rate, blood pressure proximal and distal to the intra-aortic balloons, and aortic flow beyond the Zone I balloon.

Data analysis was performed and graphs constructed using Excel (Microsoft Corporation, Redmond, WA) and STATA version 14.0 (Stata Corporation, Bryan, TX). Continuous variables are graphically presented as means and standard error of the means. Categorical variables are presented as means with standard deviation and standard error of the means.

Experimental Design

At the beginning of experimentation (T0), animals were subjected to a 25% total blood volume hemorrhage over 30 minutes. Following this 30-minute hemorrhage interval, the master controller initiated stepwise balloon inflation over approximately 3 minutes until the

target weight-based flow rate was achieved. The EVAC syringe pump automatically adjusted the balloon volume to actively maintain aortic flow at this level for the duration of the 45-minute EVAC interval. To ascertain the performance of the EVAC syringe pump during active resuscitation, whole blood transfusion was initiated at T65. The EVAC syringe pump then initiated a 5-minute balloon deflation and weaning sequence, beginning at T75.

RESULTS

Five animals underwent instrumentation, hemorrhage and a subsequent 45 minutes of Zone 1 EVAC. All animals survived the experimental phase. Hemorrhage was associated with an anticipated decline in distal aortic flow and in mean arterial pressure as measured in both the proximal descending thoracic aorta and the distal abdominal aorta (Figure 2). Upon initiation of EVAC at T30, there was an abrupt increase in proximal mean arterial pressure and a concurrent decrease in distal mean arterial pressure. The EVAC syringe pump was able to maintain stable aortic flow throughout the 45-minute intervention period with minimal deviation from the aortic flow goal (Figure 2c). Distal aortic pressure also remained stable throughout EVAC, at approximately 16 mmHg.

Upon initiation of blood transfusion at T65, there was a steep rise in proximal mean arterial pressure (Figure 2a). The EVAC syringe pump responded with a compensatory increase in balloon volume to maintain the specified aortic flow rate. Both aortic flow and distal aortic pressure remained stable and unchanged during active volume resuscitation as a result of these compensatory balloon adjustments (Figure 2b,c).

The relationship between balloon volume and the various hemodynamic parameters is represented in Figure 3. The EVAC syringe pump made small, yet discernible changes in balloon volume throughout the EVAC interval, with the largest changes occurring during the 10-minute period of blood transfusion. Mean aortic flow throughout EVAC closely approximated the target aortic flow (4.5 vs 4.4 ml/kg/min) (Figure 3d). The EVAC syringe pump maintained aortic flow within a range of 4.2–4.6 ml/kg/min (12–13% of estimated baseline flow) for 62% of the intervention and 3.9–4.9 ml/kg/min (11–14% of estimated baseline flow) for 98% of the experiment (Figure 2d, Figure 3a).

Stepwise balloon deflation resulted in a rapid, steep increase in aortic flow around the balloon. Return to full baseline flow rates was observed following withdrawal of 2.5 mL from the balloon, with nearly twice the baseline flow observed upon full balloon deflation (34 ml/kg/min and 67 ml/kg/min, respectively, Figure 3a).

Throughout the 45-minute period of EVAC, the syringe pump made an average of 537 balloon adjustments, with a mean balloon volume change of 6.4 μ L per adjustment. The largest average balloon volume

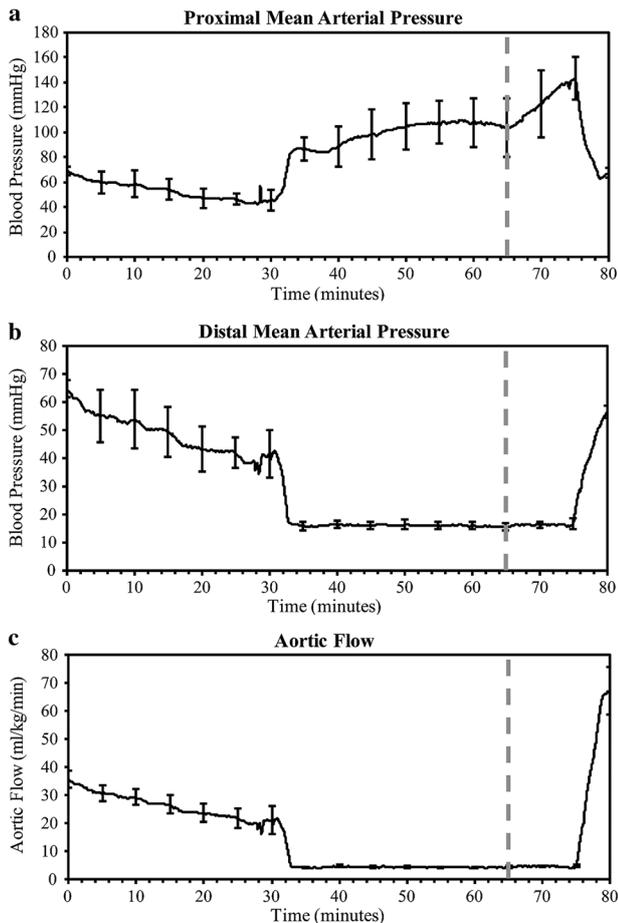


Figure 2 Endovascular variable aortic control (EVAC) hemodynamics during hemorrhage and intervention. The vertical dashed line represents the onset of whole blood resuscitation. (a) Proximal mean arterial pressure rises abruptly in response to EVAC, with a slow progressive rise during intervention. Note the steep inflection in blood pressure with transfusion. (b) Distal mean arterial pressure remains very stable during EVAC. (c) Aortic flow remains very stable during EVAC. Note the hyperemic response to balloon deflation beginning at T75.

change required in order to maintain flow within the specified range was approximately 100 μL (Table 1).

Figure 4 demonstrates the control of balloon volume by the EVAC syringe pump in response to aortic flow and proximal mean arterial pressure for a single representative experiment. Flow remains essentially unchanged over time due to small, dynamic adjustments in balloon volume (Figure 4a). Note that the profile of balloon volume closely mirrors the trend in proximal mean arterial pressure throughout the intervention (Figure 4b).

DISCUSSION

The present communication is the first-in-animal experience with EVAC using commercially available aortic occlusion catheters and an entirely automated flow regulating device. We have demonstrated that precision

aortic flow regulation is feasible and imminently achievable with commercially available aortic occlusion catheters by adjusting occlusion balloon volumes with an algorithm-driven, autonomous syringe pump.

With the increase in REBOA use for hemorrhage control, innovations to address certain key limitations have swiftly ensued. REBOA, while effective at controlling hemorrhage at bleeding points below the level of occlusion, is limited by the adverse effects of proximal aortic hypertension and progressive ischemic burden to distal tissue beds [1,2,5,7,13]. Therefore the technique of partially inflating a balloon catheter was proposed to slow bleeding and improve blood flow to the heart, lungs, and brain, while mitigating the ischemic insult below the balloon. Yet, early clinical experiences have demonstrated that P-REBOA is extremely challenging and results in labile hemodynamics due to the lack of fidelity with manual balloon titration [8,11]. Additionally, large animal models of P-REBOA have demonstrated a tendency toward perpetuating ongoing hemorrhage [6]. Continued bleeding is a serious concern in every clinical environment, but especially in scenarios where blood products are in limited supply or when a significant delay to surgical hemostasis is anticipated.

In response, our group has explored the use of automation to improve upon the P-REBOA concept. Automation addresses several key limitations of the manual approach to aortic flow regulation. First, the EVAC syringe pump is capable of executing very small changes in balloon filling volume. The current hardware design of the syringe pump is capable of delivering or withdrawing aliquots of fluid less than 10 μL . These changes are too precise to be performed manually with any manner of fidelity or consistency, thereby necessitating robotic control. As we have demonstrated in prior experiments and again in the present experiment, very small adjustments in the degree of aortic occlusion translate into large variations in aortic flow rate [12,15]. Hyperemic aortic flow was again observed during the balloon deflation phase of this experiment and likely reflects the hyperdynamic cardiac state induced by aortic occlusion, combined with low systemic vascular resistance from vasodilated distal tissue beds. This hyperemic flow is fairly unpredictable in its onset and occurs at different balloon volumes depending on the individual animal [12]. Therefore, establishing clinical guidelines for manual balloon deflation based on a prescribed volume is not practical. Precise control of balloon filling volume based on real-time physiologic metrics is therefore necessary to prevent avoid rapid changes in aortic flow and distal perfusion pressure, which could lead to hemodynamic collapse or precipitate clot destabilization and hemorrhage. With balloon volume changes of less than 10 μL producing discernible differences in aortic flow rates, it is apparent why previous attempts at manual flow titration have resulted in erratic hemodynamics [6,11].

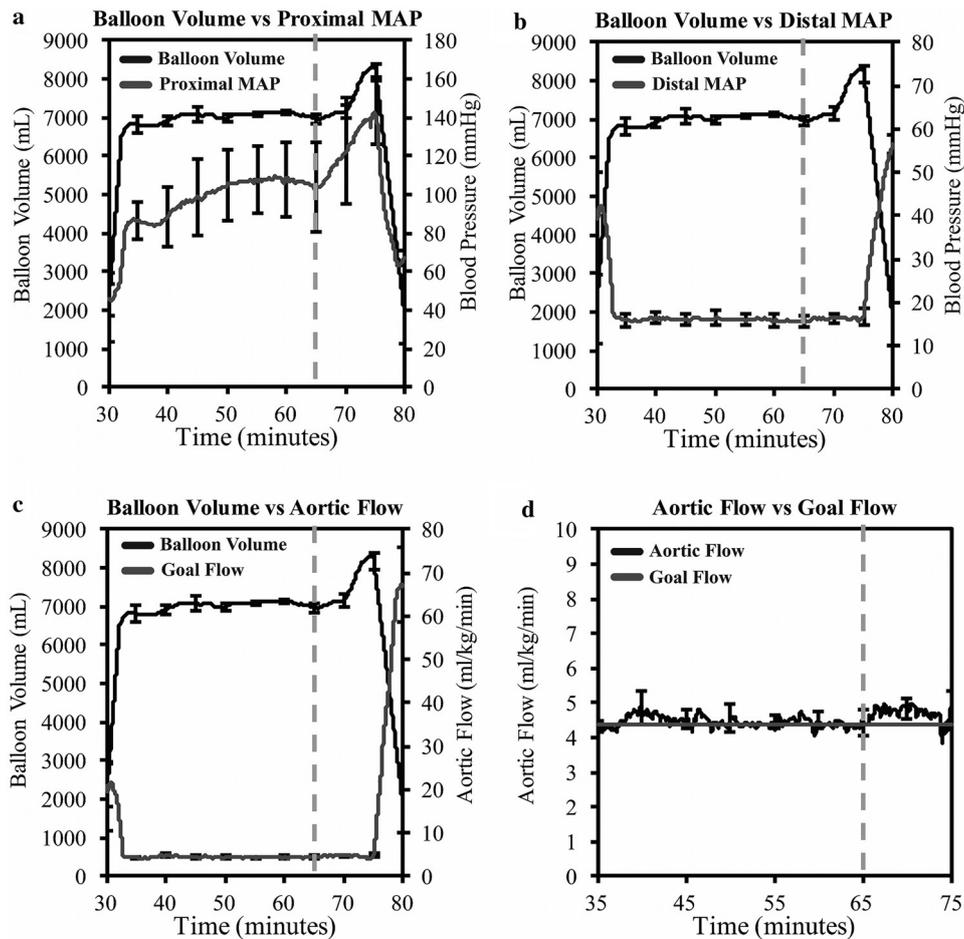


Figure 3 Endovascular variable aortic control (EVAC) hemodynamic and balloon volume during hemorrhage. The vertical dashed line represents the onset of whole blood resuscitation. (a) Balloon volume undergoes subtle changes during EVAC but inflates significantly in response to blood transfusion. (b) Distal mean arterial pressure (MAP) remains stable throughout EVAC. (c) Aortic flow remains stable throughout EVAC. Note the marked hyperemic response to early balloon deflation. (d) Aortic flow closely approximated the target distal flow for the EVAC controller and automated syringe pump.

Table 1 Balloon characteristics during a 45-minute EVAC intervention period

	Average	Standard deviation	SEM
Total volume moved (μL)	3,490.8	1,575.1	643.0
Total No. of movements	537	33	14
Largest volume change (μL)	98.7	101.5	41.4
Average volume change (μL)	6.4	2.5	1.0

Additionally, this syringe pump responds within milliseconds to changing patient physiology. In the present study, there was an average of nearly 600 balloon adjustments made over a 45-minute period to maintain the desired aortic flow rate. This frequency of adjustments would be difficult, if not impossible, to achieve with hand control of the balloon volume. Moreover, humans are highly inefficient at integrating multiple streams of continuous data and responding in a timely fashion with an appropriate, measured response.

Yet, computers and robots excel at these focused computational tasks. Even if balloon technology evolves to where flow can be manually titrated with acceptable precision, this would still require near constant attention of the provider to manage balloon titration. Many environments lack the manpower capabilities needed to execute this type of focused task while simultaneously managing other acutely life-threatening issues, including achieving definitive surgical hemostasis. This potential misallocation of key medical expertise and manpower

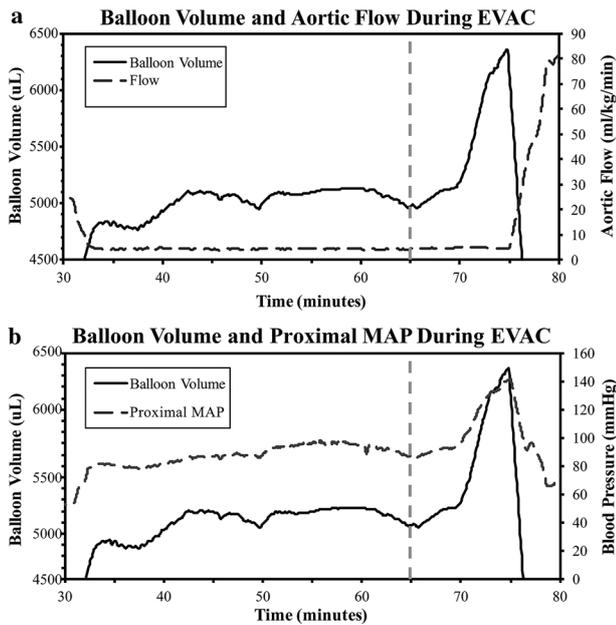


Figure 4 Endovascular variable aortic control (EVAC) hemodynamics in a single representative animal. The vertical dashed line represents the onset of whole blood resuscitation. **(a)** Note the stability of aortic flow during EVAC, whereas balloon volume remains dynamic throughout, particularly in response to resuscitation. **(b)** Note that balloon volume and proximal mean arterial pressure (MAP) closely mirror each other over time, underscoring the need for dynamic balloon regulation in response to changing proximal hemodynamics.

may prevent the adoption of partial aortic occlusion as a viable resuscitation adjunct in austere environments. If this rationale is extended to the care of multiple simultaneous casualties, then the notion of performing partial aortic flow regulation techniques with manual control alone becomes entirely impractical.

In comparison to our previous extracorporeal flow control circuit, the current EVAC syringe pump provides an equivalent, if not superior, degree of aortic flow control. With earlier approaches, we demonstrated that tight regulation of low volume distal aortic flow can effectively mitigate the ischemic burden of sustained aortic occlusion, while simultaneously minimizing hemorrhage. Unfortunately, utilizing aortic flow data as the target physiologic metric upon which balloon titration is based remains an experimental construct. In our experiments, this data is acquired from a surgically implanted perivascular flow probe, which is clinically impractical. Presently, there is no commercially available method of obtaining an accurate measure of aortic flow with a minimally invasive or endovascular means to enable careful titration of a balloon catheter. Despite this fact, this study does demonstrate that distal aortic pressure and aortic flow do correlate in this particular model of hemorrhage and ischemia. Therefore, it is

conceivable that titrating the degree of occlusion to a specific distal aortic pressure would result in a stable downstream aortic flow. However, it is unclear whether other disease states or injury patterns would exhibit this same relationship.

Additionally, the present study did not directly compare the performance of the EVAC syringe pump to manual balloon control or other catheters designed specifically for P-REBOA. Future comparative studies with EVAC and manual P-REBOA may be justified. Yet, manual balloon titration will remain a less favorable option regardless due to its intense demands from a skilled provider. It also remains unclear whether this degree of precision flow regulation achieved by the EVAC syringe pump is required to achieve acceptable clinical outcomes. Further investigation to elucidate these points is essential prior to full clinical translation.

CONCLUSION

The development of a completely automated endovascular solution provides an important next step toward the clinical translation of EVAC as a novel resuscitation paradigm for non-compressible torso hemorrhage. The EVAC syringe pump is capable of continuous, dynamic control of a commercially available aortic occlusion catheter. Further work to refine balloon control algorithms based on readily available pressure-based metrics is warranted. Additionally, comparison of the EVAC syringe pump to manual P-REBOA is indicated to justify the in-human use of automated control in this context.

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