Incremental balloon deflation following complete resuscitative endovascular balloon occlusion of the aorta results in steep inflection of flow and rapid reperfusion in a large animal model of hemorrhagic shock

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INTRODUCTION: To avoid potential cardiovascular collapse after resuscitative endovascular balloon occlusion of the aorta (REBOA), current guidelines recommend methodically deflating the balloon for 5 minutes to gradually reperfuse distal tissue beds. However, anecdotal evidence suggests that this approach may still result in unpredictable aortic flow rates and hemodynamic instability. We sought to characterize aortic flow dynamics following REBOA as the balloon is deflated in accordance with current practice guidelines.

METHODS: Eight Yorkshire-cross swine were splenectomized, instrumented, and subjected to rapid 25% total blood volume hemorrhage. After 30 minutes of shock, animals received 60 minutes of Zone 1 REBOA with a low-profile REBOA catheter. During subsequent resuscitation with shed blood, the aortic occlusion balloon was gradually deflated in stepwise fashion at the rate of 0.5 mL every 30 seconds until completely deflated. Aortic flow rate and proximal mean arterial pressure (MAP) were measured continuously over the period of balloon deflation.

RESULTS: Graded balloon deflation resulted in variable initial return of aortic flow (median, 78 seconds; interquartile range [IQR], 68–105 seconds). A rapid increase in aortic flow during a single-balloon deflation step was observed in all animals (median, 819 mL/min; IQR, 664–1241 mL/min) and corresponded with an immediate decrease in proximal MAP (median, 30 mm Hg; IQR, 14.5–37 mm Hg). Total balloon volume and time to return of flow demonstrated no correlation ($r^2 = 0.016$).

CONCLUSION: This study is the first to characterize aortic flow during balloon deflation following REBOA. A steep inflection point occurs during balloon deflation that results in an abrupt increase in aortic flow and a concomitant decrease in MAP. Furthermore, the onset of distal aortic flow was inconsistent across study animals and did not correlate with initial balloon volume or relative deflation volume. Future studies to define the factors that affect aortic flow during balloon deflation are needed to facilitate controlled reperfusion following REBOA. (*J Trauma Acute Care Surg.* 2017;83: 139–143.

KEY WORDS: REBOA; balloon occlusion; balloon; deflation; trauma.

Resuscitative endovascular balloon occlusion of the Aorta (REBOA) is an emerging therapeutic adjunct for noncompressible torso hemorrhage.[1,2] Despite increasing clinical use, REBOA remains limited by the profound distal ischemia created by complete aortic occlusion.[3] The degree of ischemia corresponds with the duration of balloon occlusion and has led to the recommendation that the balloon be deflated as soon as possible.[4] Despite this recommendation, the physiologic consequences of

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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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balloon deflation after REBOA have not been adequately described. As in open aortic cross-clamping, REBOA balloon deflation results in a dramatic decrease in aortic afterload, a rapid washout of ischemic metabolites, and the rapid influx of arterial blood into maximally vasodilated distal vasculature.[5] The aggregate effect of these physiologic derangements has the potential to cause hemodynamic collapse upon balloon deflation.

Initial clinical experiences describe deflating the REBOA balloon in a simple yet controlled manner.[6] However, this simple method was subsequently questioned after it reportedly led to several instances of hemodynamic collapse that were refractory to balloon reinflation.[7] In an attempt to mitigate the physiologic impact of balloon deflation following REBOA, current practice recommendations advocate slow and methodical balloon deflation to gradually reintroduce distal aortic flow.[8,9] In theory, graded balloon deflation reduces physiologic derangement by creating a protracted washout of distal ischemic metabolites, while simultaneously providing partial proximal hemodynamic support. Yet, anecdotal evidence suggests that even graded balloon deflation may result in hemodynamic instability.[10] Given the lack of clarity from both a translational and clinical perspective, we sought to characterize the hemodynamic effect of incremental balloon deflation following sustained REBOA, particularly with respect to mean arterial pressure (MAP) and aortic flow.

MATERIALS AND METHODS

Animal Preparation

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, castrate male, and nonpregnant female Yorkshire-cross swine (*Sus scrofa*), were acclimated for a minimum of 7 days. At the time of experimentation, animals weighed between 57 and 75 kg. 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 offset the vasodilatory effects of general anesthesia, an intravenous infusion of norepinephrine (0.01 μg/kg per hour) was instituted upon venous access and titrated to achieve a target MAP between 65 and 75 mm Hg. The infusion rate was then held constant for the remainder of the experiment. Animals were mechanically ventilated with tidal volumes of 7 to 10 mL/kg and a respiratory rate of 10 to 15 breaths per minute sufficient to maintain end-tidal CO_2 at 40 ± 5 mm Hg. Isotonic sodium chloride solution was administered at a rate of 5 mL/kg per hour to overcome insensible losses. An underbody warmer set at 39°C was used to maintain body temperature.

Venous access was obtained through a central line in the right internal jugular vein. Proximal and distal arterial access was obtained through a 7 Fr 13-cm introducer sheath (Boston Scientific, Marlborough, MA) placed in the right femoral artery and right and left brachial arteries via surgical cutdowns. The animals then underwent midline laparotomy, and a splenectomy was performed to minimize hemodynamic variation from autotransfusion.[11] The supraceliac aorta was then exposed by longitudinally dividing the diaphragm to facilitate placement of a periaortic flow probe (Transonic Systems Inc, Ithaca, NY). A 32-mm aortic occlusion balloon (ER-REBOA, Prytime Medical, Boerne, TX) was positioned in the descending thoracic aorta and confirmed to be in Zone 1 by manual palpation during test inflation. The abdomen was closed with cable ties.

Intervention

Hemorrhagic shock was simulated by withdrawing 25% of estimated blood volume (body weight (kg) × 66 mL/kg × 0.25) through an arterial sheath into citrated blood collection bags.[12] The animals underwent a 30-minute equilibration period to simulate the prehospital environment. Complete aortic occlusion was initiated by inflating the ER-REBOA balloon catheter until there was loss of a distal arterial waveform and occlusion was sustained for 60 minutes. After 55 minutes of occlusion, shed blood volume was returned through the central venous line via rapid infusion (Belmont Instruments, Billerica, MD) at the rate of 150 cc/min. This was then followed by incremental balloon deflation at a rate of 0.5 cc every 30 seconds until the balloon was completely deflated (Fig. 1). Physiologic parameters and aortic flow measurements were collected in real time using a Biopac MP150 multichannel data acquisition system (Biopac

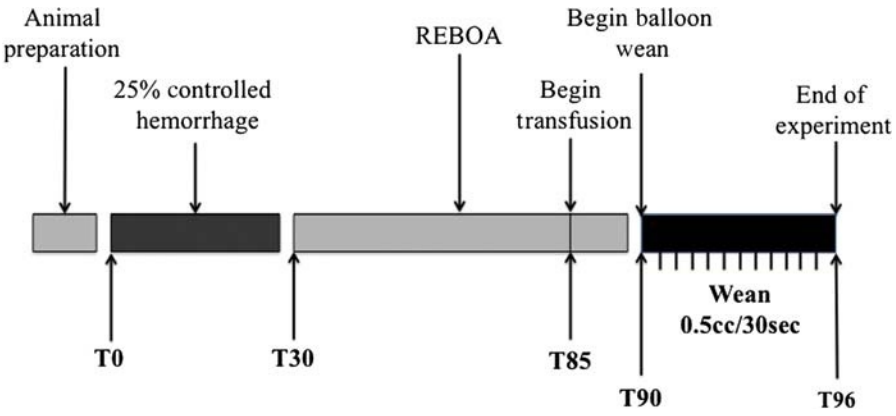

Figure 1. Study protocol.

TABLE 1. Hemodynamics of Study Animals Before Balloon Deflation

	Proximal MAP (mm Hg)	Aortic Flow (mL/min)
Baseline	71.1 ± 1.0	2350 ± 119
End of hemorrhage (T30)	35.8 ± 5.2	1192 ± 117
Before balloon wean (T90)	76.3 ± 6.1	0

Data are presented as mean ± standard error of the mean.

Systems Incorporated, Goleta, California). Parameters measured included heart rate, blood pressure proximal to the ER-REBOA catheter, and aortic flow. Onset of aortic flow during balloon deflation was defined as the time point when flow reached 50 mL/min (approximately 2% of baseline full flow) to account for the fidelity of the aortic flow probe at very low flow rates. At the end of the experiment, the animals were humanely euthanized.

Statistical analysis was conducted with Stata 14 (StataCorp, College Station, TX). Data are presented as medians with interquartile ranges (IQRs). Correlation was determined using the Pearson correlation coefficient.

RESULTS

Hemodynamic parameters were similar between animals at baseline (T0), at the conclusion of hemorrhage (T30), and just before balloon deflation (T90) (Table 1). The total balloon volume required to eliminate aortic flow varied (median, 6.5 mL; range, 3–9 mL). After 60 minutes of occlusion, graded balloon deflation resulted in variable onset of initial aortic flow (median, 78 seconds; IQR, 70–100 seconds), corresponding to a median deflation volume of 1.5 mL and a median of three deflation steps (Table 2). There was no correlation between balloon volume and the timing of onset of aortic flow ($r^2 = 0.016$; Fig. 2).

A rapid increase in aortic flow during a single-balloon deflation step was observed in all animals (median, 820 mL/min; IQR, 683–1242 mL/min), corresponding to approximately one third of native aortic flow (median, 37%; IQR, 25–54%). Furthermore, this rapid increase in flow corresponded with a decrease in proximal MAP in all animals (median, 28.7 mm Hg; IQR, 15.1–37.3 mm Hg). The timing of the inflection point was variable across animals (Table 2). Figure 3 is a representative image of the hemodynamics in a study animal.

DISCUSSION

This goal of this study was to characterize the hemodynamic consequences of incremental balloon deflation following sustained REBOA. The intent of gradual balloon deflation is to provide predictable and graded restoration of aortic flow. Despite replicating the current best practices of REBOA balloon deflation consistently, there was wide variation in the hemodynamic response to deflation during this critical period. There were several key observations in this study: (1) a large proportion of aortic flow returned during a discrete time point (i.e., deflation step); (2) the precise onset of this rapid return of flow was variable and unpredictable across animals; (3) this rapid reintroduction of aortic flow corresponded with a significant drop in MAP despite ongoing aggressive blood resuscitation. Providers should rely on other metrics such as return of a distal arterial waveform and an increase in distal MAP (as measured from the flush port of the arterial introducer sheath) to indicate return of aortic flow rather than a prespecified number of balloon deflation steps.[13]

Inherently, there are numerous factors influencing the point at which downstream flow is restored during active deflation of a balloon catheter including: the initial balloon filling volume, proximal aortic pressure, cardiac output, ongoing resuscitation, vascular tone, and aortic diameter. Most of these factors, with the exception of balloon volume, remain unmeasurable, unpredictable, and dynamic in nature. Balloon filling volume is certainly a variable within the control of the provider. However, overinflation likely does occur during clinical application of REBOA, further complicating the later process of balloon deflation. To minimize the impact of balloon volume on our results, inflation of the balloon in this study was ceased once the distal arterial waveform was lost. Theoretically, this method should mitigate the influence of balloon volume on our results, as well as to minimize the potential for aortic injury or balloon rupture.[14,15] However, despite this technique, the onset of flow past the balloon proved to be highly variable with respect to

TABLE 2. Data from Study Animals

Animal	Time to Flow Restoration (Seconds)	No. of Steps Until Return of Flow	No. of Steps Until Maximum Increase in Flow	Max Increase in Flow in 1 Step (mL/min)	Max Increase in Flow as Percent of Baseline Aortic Flow	Maximum Decrease in MAP During 1 Deflation Step (mm Hg)*	Total Balloon Volume (mL)
1	70	3	4	683	35%	15.1	5
2	62	3	4	1,212	67%	6.5	8
3	76	3	3	448	19%	27.8	3
4	185	7	9	607	25%	36.3	6.5
5	100	4	6	720	25%	12.7	7
6	78	3	7	1,627	65%	40.2	5.5
7	39	2	6	919	39%	32.3	9
8	119	5	8	1,330	51%	57.5	6.5
Median	77.5	3	6	819	37%	30	6.5
IQR	68–105			664–1,241	25%–54%	14.5–37	5.25–7.25

* MAP decrease corresponds to shown increase in aortic flow.

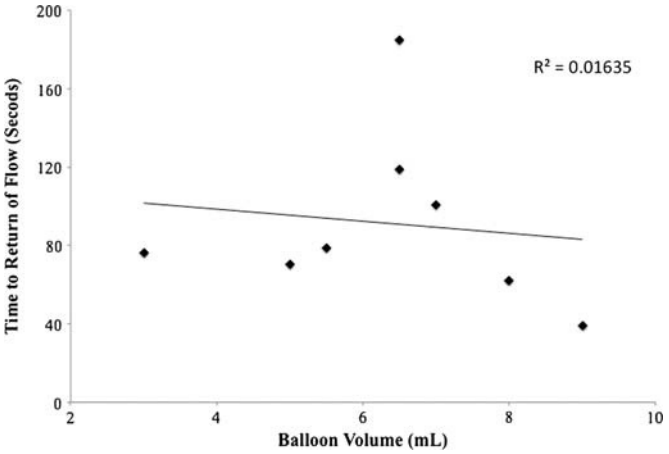

Figure 2. *Scatter plot* of balloon volume versus time to return of flow. Note poor correlation between balloon volume and time to return of flow.

time, absolute balloon volume remaining, and percentage of volume remaining (Fig. 2). Ultimately, balloon volume and time to return of flow were not correlated, indicating that the onset of aortic flow is likely controlled by factors not captured in the current study design and not routinely monitored in the clinical setting (Fig. 4).

All animals in this study were actively undergoing resuscitation and had MAPs similar to baseline at the time of balloon deflation (Table 1), indicating that the cause of unpredictable return of aortic flow was not fully explained by differences in proximal MAP or due to differences in resuscitation. Similar hemodynamic instability has been reported in studies of intermittent REBOA. This technique is intended to reduce ischemia from prolonged aortic occlusion by intermittently deflating the balloon by a set volume (usually 1 cc) for a short period of time. Hemodynamic instability from unpredictable return of aortic blood flow has been implicated in the death of at least one patient and is a reason cited for unfavorable outcomes associated

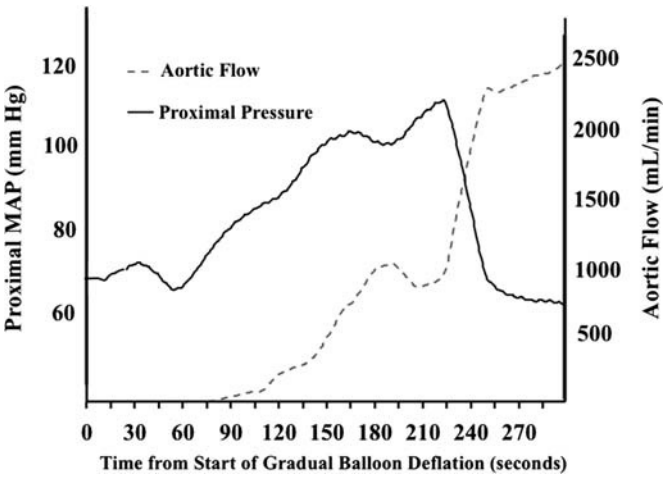

Figure 3. Hemodynamics of a representative study animal. Note the *steep inflection point* with dramatic increase in flow with concurrent decrease in proximal MAP.

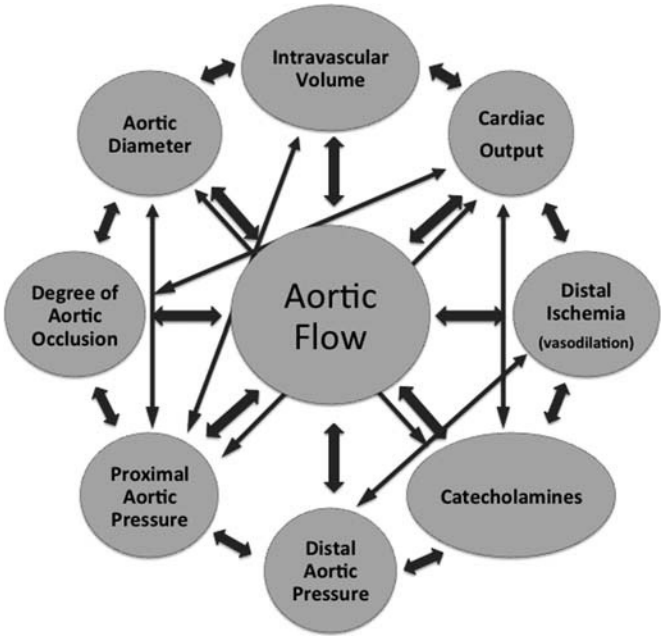

Figure 4. Determinants of aortic flow conceptual diagram: *conceptual diagram* outlining many of the hypothesized factors that may influence aortic flow during balloon deflation after REBOA.

with intermittent REBOA in animal studies.[16,17] Our results suggest that relying on balloon volume alone is an inaccurate surrogate marker for return of initial aortic blood flow. The most reliable indicator for the onset of aortic flow is the appearance of a distal arterial waveform and the increase in distal MAP. It was shortly after this time point that a steep inflection in return of flow was observed. Providers should note the reappearance of a distal arterial waveform and exercise caution by making small nuanced balloon manipulations or prolonging this period to prevent dramatic changes in blood flow. It is worth highlighting that monitoring equipment should be optimized and scaled to detect subtle waveform and pressure changes that occur during restoration of distal flow, given that an increase of the distal MAP by a mere 10 mm Hg can result in significant downstream flow.[13]

The primary intent of graded balloon deflation following REBOA is to produce gradual reintroduction of distal flow, thereby minimizing the potential for hemodynamic collapse or clot destabilization. However, we observed a large volume increase in aortic flow during a variable, unpredictable and discrete balloon deflation step (Table 2, Fig. 3). This dramatic increase was observed in all study animals equating to a median of approximately one third of baseline flow (Table 2). This massive influx of pressurized arterial blood into maximally vasodilated ischemic distal tissue beds results in a rapid redistribution of circulating blood volume and washout of ischemic metabolites, which may contribute to the hemodynamic collapse sometimes observed following REBOA.[7,8] Providers should be aware of this phenomenon and prepared to treat the effects of this rapid ischemia-reperfusion injury.

Lastly, gradual balloon deflation after REBOA is thought to reduce rebound hypotension by augmenting proximal MAP

during this period. Nevertheless, all animals experienced significant drops in MAP at the time aortic flow rapidly increased, despite receiving aggressive resuscitation with shed blood (Table 2). This relative hypotension and abrupt loss of afterload may worsen perfusion to vital organs at a time when they are concurrently exposed to the systemic effects of ischemia-reperfusion injury. Clinical reports of volatile proximal hemodynamics during stepwise or partial balloon deflation support our finding that graded balloon deflation in this fashion may be insufficient to support proximal MAP during this critical period.[10,18] Thus, partial reinflation of the balloon may be required to maintain or restore adequate proximal perfusion pressure to the heart and brain during this process.

This study was focused on a very specific moment during REBOA. As such, it lacks more extensive physiologic outcomes after intervention. Additionally, the absence of comparison group(s) limits any evaluation of alternative balloon deflation techniques. Instead, this small study was designed to provide a descriptive analysis of proximal hemodynamics during balloon deflation and their relationship to aortic blood flow. Moreover, the present study is the first of its kind to take an in-depth look at the critical period of balloon deflation using a technique currently taught as best practice in REBOA training courses.[9,19] Our findings highlight that the period of balloon deflation after REBOA is dynamic and difficult to predict. Weaning from REBOA may be an overlooked yet critical area for future study given the risk of cardiovascular collapse and hypotension reported in the literature. Many complex factors appear to influence the variability in hemodynamics during this period (Fig. 4). This study would suggest that weaning from REBOA should be guided by multimodal physiologic and hemodynamic inputs and not based simply on balloon volume manipulation. Providers should be aware of potential hemodynamic instability during balloon deflation and should remain vigilant with adjunctive resuscitative measures at the ready.

Further studies are needed to better define the hemodynamic intricacies of blood flow around aortic occlusion balloons and optimize future transformations of the technique of REBOA. Future studies should promote perfusion optimization by facilitating controlled restoration of distal flow after REBOA.

AUTHORSHIP

A.J.D., R.M.R., S.-A.E.F., and T.K.W. searched the literature. A.J.D., J.W.C., T.E.R., L.P.N., M.A.J., and T.K.W. designed the study. A.J.D. and S.-A.E.F. collected the data. A.J.D., R.M.R., J.W.C., L.P.N., M.A.J., and T.K.W. analyzed the data. A.J.D., R.M.R., and T.K.W. prepared the manuscript. All authors revised the manuscript.

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DISCLOSURE

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