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## Experimental paper

# Automated aortic endovascular balloon volume titration prevents re-arrest immediately after return of spontaneous circulation in a swine model of nontraumatic cardiac arrest



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### Abstract

**Objectives:** Endovascular aortic occlusion as an adjunct to cardiopulmonary resuscitation (CPR) for non-traumatic cardiac arrest is gaining interest. In a recent clinical trial, return of spontaneous circulation (ROSC) was achieved despite prolonged no-flow times. However, 66% of patients re-arrested upon balloon deflation. We aimed to determine if automated titration of endovascular balloon volume following ROSC can augment diastolic blood pressure (DBP) to prevent re-arrest.

**Methods:** Twenty swine were anesthetized and placed into ventricular fibrillation (VF). Following 7 minutes of no-flow VF and 5 minutes of mechanical CPR, animals were subjected to complete aortic occlusion to adjunct CPR. Upon ROSC, the balloon was either deflated steadily over 5 minutes (control) or underwent automated, dynamic adjustments to maintain a DBP of 60 mmHg (Endovascular Variable Aortic Control, EVAC).

**Results:** ROSC was obtained in ten animals (5 EVAC, 5 REBOA). Sixty percent (3/5) of control animals re-arrested while none of the EVAC animals re-arrested ( $p = 0.038$ ). Animals in the EVAC group spent a significantly higher proportion of the post-ROSC period with a DBP > 60 mmHg [median (IQR)] [control 79.7 (72.5–86.0)%; EVAC 97.7 (90.8–99.7)%],  $p = 0.047$ . The EVAC group had a statistically significant reduction in arterial lactate concentration [7.98 (7.4–8.16) mmol/L] compared to control [9.93 (8.86–10.45) mmol/L],  $p = 0.047$ . There were no statistical differences between the two groups in the amount of adrenaline (epinephrine) required.

**Conclusion:** In our swine model of cardiac arrest, automated aortic endovascular balloon titration improved DBP and prevented re-arrest in the first 20 minutes after ROSC.

**Keywords:** Arrhythmias, Cardiopulmonary resuscitation, Endovascular procedures, Intra-aortic balloon, Resuscitation, Resuscitative endovascular balloon occlusion of the aorta

## Introduction

Each year over half a million people suffer a nontraumatic cardiac arrest in the United States.<sup>1</sup> Cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS) prioritize maintaining coronary and cerebral perfusion to obtain return of spontaneous circulation (ROSC) with good neurological function.<sup>2</sup> Despite intense research, out-of-hospital cardiac arrest mortality still exceeds 90%.<sup>3</sup> There is increasing interest in using endovascular aortic occlu-

sion to augment CPR in nontraumatic cardiac arrest.<sup>4</sup> Translational studies<sup>5–9</sup> and recent clinical case series<sup>10–13</sup> demonstrated that aortic occlusion increases coronary artery perfusion pressure (CPP) and rates of ROSC when used as an adjunct to standard-of-care therapies. Aortic occlusion is achieved with an endovascular balloon device, which is inserted into the femoral artery and advanced into the aorta during CPR.<sup>4</sup> Inflation of the balloon in the descending thoracic aorta restricts the limited blood flow generated by CPR to the thoracic vasculature, maximizing perfusion of the heart and brain. This raises aortic pressure, CPP, and cerebral perfusion, which

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increases the likelihood for ROSC and neurologically intact survival.<sup>4,14</sup>

Recent reports of out-of-hospital use of aortic occlusion in non-traumatic cardiac arrest found high rates of ROSC despite time from dispatch to balloon occlusion of 45–50 minutes.<sup>10,13</sup> However, the positive results were tempered by the high rate of re-arrest after ROSC and balloon deflation. Re-arrest is common in the post-ROSC period without aortic occlusion.<sup>15–17</sup> In one study, 50% of the patients that obtained ROSC re-arrested within 20 minutes of balloon deflation.<sup>10</sup> These clinical data suggest aortic occlusion is a promising resuscitation technique for nontraumatic cardiac arrest but new techniques must be developed to prevent re-arrest after ROSC.

The Endovascular Variable Aortic Control (EVAC) system was designed to maximize the benefits of resuscitative endovascular balloon occlusion of the aorta (REBOA) while limiting complications.<sup>18–20</sup> The EVAC system consists of a REBOA catheter connected to an automated syringe controller to make second-to-second changes in balloon volume in response to the diastolic blood pressure (DBP) measured above the balloon (Fig. 1). Balloon inflation impedes flow within the aorta thereby augmenting blood pressure at the aortic root. Mechanical blood pressure augmentation is nearly instantaneous, unlike pharmacologic adjuncts with variable latency, duration, and magnitude of haemodynamic effects. EVAC was originally tested to balance the benefits of aortic occlusion and haemodynamic support with ischemic risk in an animal model of truncal hemorrhage.<sup>18,21</sup> EVAC may confer benefits after nontraumatic cardiac arrest by targeting a set DBP and maintaining CPP during the deflation phase. We sought to study the impact of EVAC on haemodynamics in the first 20 minutes after ROSC in a model of nontraumatic cardiac arrest. We hypothesized that EVAC would result in a lower re-arrest rate after ROSC by providing haemodynamic support through variable intra-aortic balloon inflation compared to pharmacologic support alone.

## Methods

### Overview

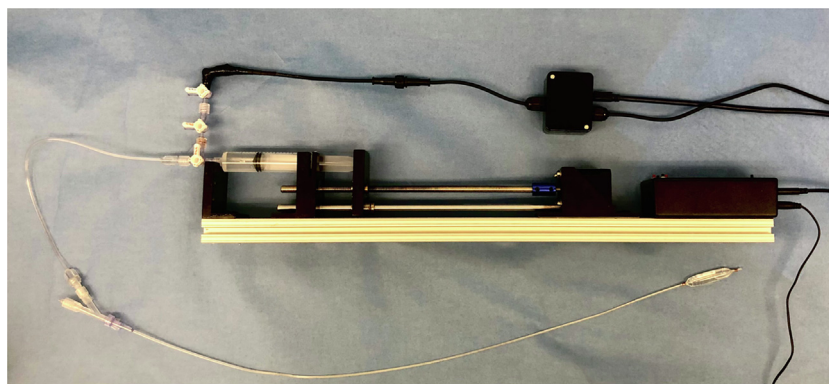
The Institutional Animal Care and Use Committee at the University of Utah approved this study (Protocol 19-07012). Animal care was in

strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by AAALAC, International. Twenty healthy adult, castrated male, and nonpregnant female Yorkshire-cross swine (*Sus scrofa*; Premier BioSource, Ramona, CA) were acclimated for a minimum of 7 days in temperature- and light-controlled pens with access to environmental enrichment. Animals weighed between 65 and 73 kg, were between 4.5 and 6 month old, and were fasted the night before the experiment. The conduct of the protocol is illustrated in Fig. 2.

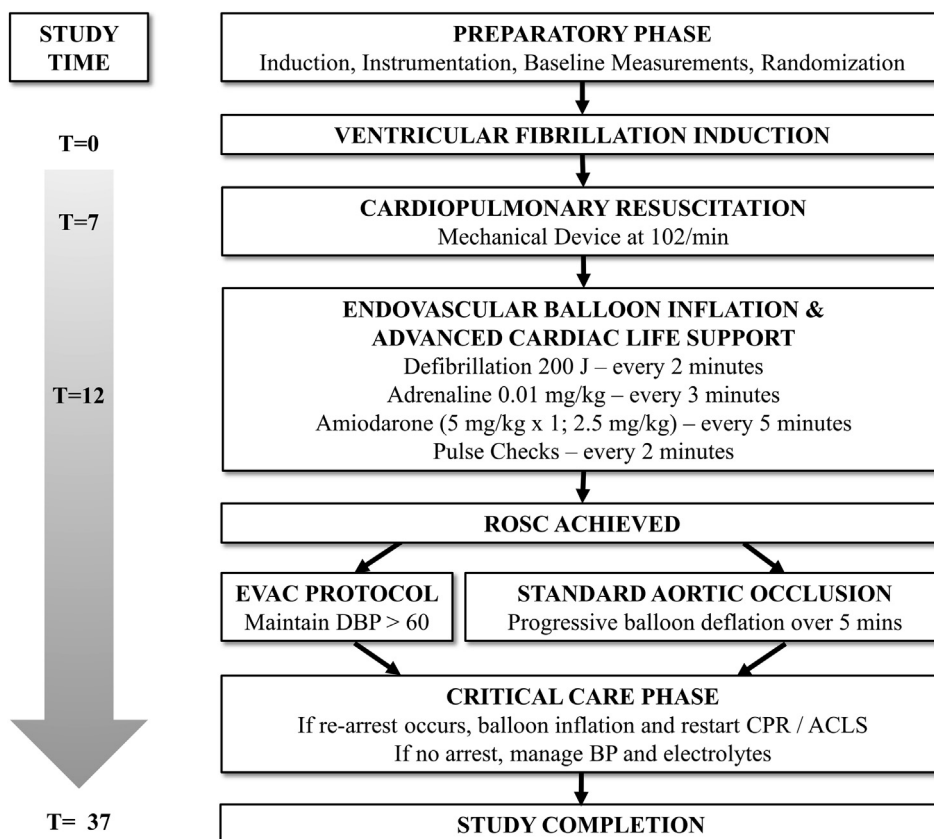
### Animal preparation

Twenty pigs were included in the study. Animals were premedicated with 6.6 mg/kg intramuscular tiletamine/zolazepam (Telazol; Zoetis US, Parsippany, NJ). Following endotracheal intubation, general anesthesia was maintained with 1.5–2.5% isoflurane in 30–100% oxygen. Pigs received 5 mL/kg of balanced isotonic crystalloids intravenously. Animals were mechanically ventilated with tidal volumes of 8–10 mL/kg, a positive end-expiratory pressure of 4 cmH<sub>2</sub>O, and a respiratory rate of 10–15 breaths per minute, titrated to maintain end-tidal CO<sub>2</sub> at 40 ± 5 mmHg.

All vascular access was obtained via Seldinger technique under ultrasound guidance. Both external jugular veins were cannulated to facilitate medication and fluid administration. A transvenous pacer (TVP) wire was placed through the right external jugular via a 9-Fr resuscitation catheter (Arrowg + ard Blue® MAC; Teleflex, Wayne, PA) to induce ventricular fibrillation (VF). The left femoral and carotid arteries were cannulated with a 7-Fr sheath to monitor proximal and distal blood pressure, respectively. The right femoral artery was cannulated with a 9-Fr sheath for REBOA catheter placement (laboratory-grade, custom-built catheter). Fluoroscopy confirmed the position of the uninflated aortic balloon in Zone 1 and the TVP within the right ventricle. The animals were connected to an electrocardiogram monitor and defibrillator (R Series, ZOLL, Chelmsford, Massachusetts) with pre-positioned defibrillator pads (Stat-padz, ZOLL, Chelmsford, Massachusetts). A mechanical CPR device (LUCAS 2 Chest Compression System; Stryker Corp, Kalamazoo, MI) was placed around the chest with the suction cup positioned against the sternum. Padding was placed around the animal's chest to prevent body shifting. Baseline laboratory and arterial blood gas samples were obtained after instrumentation.



**Fig. 1 – The Endovascular Variable Aortic Control (EVAC) device. The illustration showed the endovascular catheter placed into Zone 1 of the aorta with the external syringe controller attached to the patient's leg. The syringe controller will change the endovascular balloon volume as needed to maintain diastolic blood pressure > 60 mmHg.<sup>1</sup>**



**Fig. 2 – Experimental design.**

### Intervention

The animals were placed into VF by connecting a 9-V battery to the TVP. Mechanical ventilation and isoflurane were discontinued ( $T = 0$  min). After 7 minutes of no-flow VF ( $T = 7$  mins), mechanical CPR was initiated and the ventilator was set at 10 breaths/min with 100% oxygen. After 5 minutes of continuous CPR in a low-flow VF state ( $T = 12$  mins), the pre-positioned aortic occlusion balloon was inflated and ACLS algorithms were initiated. Complete aortic occlusion was confirmed by the loss of distal femoral arterial pressure waveforms during CPR. Defibrillation was performed at two-minute intervals (200 joules, biphasic) if VF was observed upon electrocardiogram evaluation. Intravenous 0.01 mg/kg adrenaline (epinephrine) was administered in three-minute intervals while the animal remained in cardiac arrest. Amiodarone was administered every 5 minutes after 5 min of ACLS (5 mg/kg IV for the first dose and 2.5 mg/kg thereafter), if required. Animals were assessed for ROSC at two-minute intervals with brief CPR pauses. If ROSC was not obtained after 25 minutes of resuscitation, efforts were ceased, and the animal was excluded.

Following ROSC, animals were randomized to receive EVAC or standard REBOA deflation according to a random number sequence. Upon ROSC, ACLS drugs and CPR were discontinued. Mechanical ventilation and isoflurane administration were resumed per the above protocol. The aortic occlusion balloon was deflated according to group assignment. In the control group, the aortic occlusion balloon was deflated manually over 5 minutes (removal of 1/10th of the volume used to inflate every 30 seconds). In the EVAC group, the balloon was progressively deflated by 100  $\mu$ L increment every 6

seconds by the EVAC Controller. The automated algorithm allowed the balloon to deflate only if the DBP remained above 60 mmHg. If DBP fell below 60 mmHg, the balloon was immediately re-inflated to achieve the 60 mmHg target. After initial ROSC, any subsequent loss of pulses in either group initiated full balloon inflation, and resumption of CPR/ACLS algorithms. ACLS with a re-inflated balloon was continued until study completion ( $T = 37$  mins) or until ROSC was achieved, whichever occurred sooner. If ROSC was achieved again, the balloon was deflated by the same protocols according to the randomization assignment.

Blood pressure was managed according to group assignment. In control animals, blood pressure after ROSC was controlled with pharmacologic management alone. Adrenaline titration followed American Heart Association guidelines for MAP > 65 mmHg.<sup>22</sup> Following 60 seconds of hypotension (MAP < 65 mmHg), a continuous intravenous infusion of adrenaline was started at 0.1 mcg/kg/min and was increased by 0.1 mcg/kg/min every 2 minutes to a maximum of 1.0 mcg/kg/min. Once the MAP goal was reached, the infusion was adjusted by 0.1 mcg/kg/min to maintain the MAP between 65–75 mmHg. In the EVAC group, blood pressure was controlled by a combination of adrenaline and EVAC balloon support. The EVAC system automatically varied balloon volume based on real-time blood pressure feedback to achieve a DBP > 60 mmHg. EVAC was programmed to maintain the aortic DBP goal while maintaining a <20 mmHg gradient across the balloon (proximal minus distal DBP), when able, to preserve distal aortic blood flow. This gradient was set to avoid balloon over inflation at the expense of downstream perfusion to tissue beds.

Plasma potassium, glucose, and calcium concentrations were corrected according to pre-established protocols.<sup>23</sup> All animals were euthanized after thirty-seven minutes.

### Data acquisition and analysis

Physiologic parameters (heart rate, blood pressure proximal to the intra-aortic balloon, etc.) were collected in real-time using a multi-channel data acquisition system (PowerLab; ADInstruments, Colorado Springs, CO). The primary outcome was the rate of re-arrest after ROSC. The secondary outcome was the cumulative time an animal's blood pressure was outside of guideline goals after initial ROSC. Arterial blood gases were obtained at baseline, the initiation of ventricular fibrillation, and at completion of the study. Blood gases were obtained from the proximal port of the endovascular catheter in the proximal aorta.

An a priori power analysis showed that 6 animals in each group would be required to detect a significant difference in re-arrest between the two groups, assuming rates of re-arrest of 90% and 10% in the control and EVAC groups, respectively (power of 80% and an alpha error of 0.05 with a one-tailed Fisher's exact test, G\* Power). Enrollment was discontinued due to COVID19-imposed laboratory closure. An interim analysis then showed that significance was reached after 5 animals per group were used. Data were assessed for normality and are presented as mean  $\pm$  standard error of the mean or median (interquartile range) for parametric and non-parametric data, respectively. Groups were compared with a t-test or Mann-Whitney U-test for normal and non-parametric data, respectively. Categorical data were compared with the chi square test. Statistical analysis was performed using commercial software (STATA version 14.0; Stata Corp., College Station, TX). Statistical significance was set as  $p < 0.05$ .

## Results

ROSC was obtained in 10 animals (5 EVAC, 5 controls). The other ten animals that did not achieve ROSC were excluded. There were no significant baseline differences in animals that underwent randomization (Table 1). After VF initiation, animals had similar median DBP during both the no-flow VF and low-flow VF periods prior to randomization.

Data regarding the timing of ROSC, post-ROSC haemodynamics, and re-arrest for each group are shown in Table 2. In the 20 minutes after ROSC, EVAC support provided a statistically significant reduction in the incidence of re-arrest (0/5), compared to 60% (3/5) of control animals ( $p = 0.038$ ). The control animal re-arrests events occurred 13–17 minutes after initial ROSC. These arrests occurred after a progressive decline in blood pressure despite increasing vasopressor support. VF was seen in two re-arrest events, while pulseless electrical activity was noted in the third animal. Subsequent ROSC was obtained in 2 of the 3 animals near the experiment's conclusion. One animal that remained in VF at the end of study while the other 9 animals were in sinus rhythm. At the conclusion of the study, one control animal that remained in VF had a fully inflated balloon while the other four control animals had fully deflated endovascular balloons. By comparison, two EVAC animals had partially inflated balloons and three had fully deflated balloons.

There was no difference in the median DBP between groups after ROSC. Comparison of DBP after ROSC was calculated both including and excluding the periods in which the control animals had re-

arrested. After excluding the periods in which control animals had re-arrested and were receiving CPR, the median mean DBP after ROSC was 105.4 (88.5–117.0) mmHg for control and 108.8 (108.0–122.7) mmHg for the EVAC group ( $p = 0.17$ ). If re-arrest periods of the control animals are included, the relative DBP of control animals [97.2 (92.0–105.4) mmHg] was even lower than that of the EVAC animals ( $p = 0.06$ ).

However, both including and excluding the re-arrest periods, the animals in the EVAC group spent a significantly higher proportion of the post-ROSC period with a DBP  $> 60$  mmHg. There were statistically significant differences in the percentage of the post-ROSC period with a DBP  $> 60$  both including [control 79.7 (71.7–88.8)%, EVAC 97.7 (90.8–99.7)%,  $p = 0.03$ ] and excluding the re-arrest periods [control 79.7 (72.5–86.0)%; EVAC 97.7 (90.8–99.7)%,  $p = 0.047$ ]. In the three control animals that re-arrested, the mean DBP in the 30 seconds before re-arrest was  $35.1 \pm 5.2$ ,  $60.2 \pm 2.0$ ,  $36.3 \pm 1.5$  mmHg. By contrast, in the 30 seconds before initial EVAC balloon activation, the 5-animal median mean DBP was 63.5 (63.0–63.6) mmHg.

There was no statistically significant difference in adrenaline dose between the two groups throughout the experiment (during CPR and after ROSC) [control: 31.92 (20.96–51.88) mcg/kg; EVAC: 20.95 (20.56–31.04) mcg/kg,  $p = 0.11$ ].

Data from final arterial blood samples are shown in Table 3. The EVAC group [7.98 (7.4–8.16) mmol/L] had a statistically significant reduction in arterial lactate concentration compared to control [9.93 (8.86–10.45) mmol/L,  $p = 0.047$ ].

Fig. 3 displays the impact of EVAC on a representative animal's DBP profile compared to a control animal that re-arrested and required reinflation of the aortic occlusion balloon. The graphs for all ten animals, including DBP and periods of balloon inflation, are included in Supplemental Materials.

## Discussion

Endovascular aortic occlusion is a promising adjunct to CPR in non-traumatic cardiac arrest and is currently undergoing human trials in both the United States and Europe.<sup>24–27</sup> However, the abrupt changes in aortic afterload and blood pressure that occur even with methodical balloon deflation can cause haemodynamic compromise and re-arrest. In this study, we demonstrated that by providing non-pharmacologic haemodynamic support with an automated endovascular balloon catheter to maintain DBP  $> 60$  mmHg, re-arrest rates in the immediate post ROSC period were significantly reduced. This was associated with a reduction in plasma lactate concentration at the end of the experiment.

Translational research has demonstrated the physiologic benefits of full aortic occlusion during CPR.<sup>14,28</sup> Early clinical data reinforce these benefits, but the high rates of re-arrest after ROSC have obscured any ability to see improvements in survival.<sup>10,12–13</sup> Standard REBOA provides a binary state of occlusion (balloon fully inflated or deflated) and balloon volume is controlled manually. There is no clinical or translational data to guide providers in the best methods to deflate the balloon once ROSC is achieved, much less titrate to a consistent post-ROSC DBP. Moreover, standard aortic occlusion deflation strategies may result in abrupt drops in blood pressure at unpredictable moments during manual deflation of the balloon.<sup>29–31</sup> This was evident in the rapid decline of DBP in the control group during and after manual balloon deflation making manual titration of

**Table 1 – Demographic-physiologic-and laboratory parameters of the control (n = 5) and EVAC (n = 5) groups. “Pre-CPR” diastolic blood pressure and heart rate were defined as 60-seconds of data collected prior to initiation of ventricular fibrillation. No-flow Diastolic Blood Pressure is defined as 60-seconds of data collected during ventricular fibrillation-without CPR. Low-Flow Diastolic Blood Pressure is defined as 60-seconds of data collected during CPR-representing the period immediately before randomization and ROSC. Data is presented as median (interquartile range).**

Parameter	Control	EVAC	p
Weight (kg)	72 (68–73)	71 (69–72)	0.46
Sex (m:f)	2:3	3:2	0.53
White Blood Cells (10 <sup>9</sup> cells/L)	15.2 (13.1–17.5)	18.0 (18.0–18.1)	0.18
Hemoglobin (g/dL)	10.9 (10.4–11.3)	11.7 (10.6–11.9)	0.30
Sodium (mEq/L)	138 (137–139)	139 (139–139)	0.39
Potassium (mEq/L)	4.4 (4–4.4)	4.0 (3.9–4.0)	0.39
Chloride (mEq/L)	101 (99–101)	98 (97–99)	0.25
Calcium ion (ng/dL * 0.25)	1.41 (1.37–1.42)	1.35 (1.33–1.4)	0.25
Creatinine (mg/dL)	2.3 (2.2–2.5)	2.0 (1.7–2.6)	0.46
Glucose (mg/dL)	121 (108–125)	106 (95–107)	0.08
pH	7.45 (7.43–7.46)	7.44 (7.40–7.44)	0.75
pCO <sub>2</sub> (mmHg)	44.7 (42.4–46.2)	46.4 (46.2–47.5)	0.14
PO <sub>2</sub> (mmHg)	52 (52–59)	51 (48–56)	0.40
HCO <sub>3</sub> (mEq/L)	30.3 (29.9–31.8)	32.3 (31.0–33.1)	0.21
Base Excess (mEq/L)	6 (6–7)	8 (7–9)	0.20
Arterial Oxygen Saturation (%)	88 (87–91)	86 (84–88)	0.40
Lactate (mmol/L)	1.48 (1.41–2.21)	1.09 (0.96–1.33)	0.08
Pre-CPR Diastolic Blood Pressure (mmHg)	81.5 (75.5–82.4)	73.2 (73.0–77.8)	0.46
Pre-CPR Heart Rate (beats/min)	75 (62–80)	81 (75–82)	0.22
No-Flow Diastolic Blood Pressure (mmHg)	26.56 (22.7–30.48)	26.42 (24.9–27.4)	0.92
Low-Flow Diastolic Blood Pressure (mmHg)	48.97 (39.7–60.0)	46.4 (43.1–68.6)	0.35

**Table 2 – Timing of ROSC, post-ROSC hemodynamics, and re-arrest data of the control (n = 5) and EVAC (n = 5) groups. Post-ROSC hemodynamic data is represented in two ways: including and excluding the DBP during periods where the control animal re-arrested. DBP Post-ROSC “In Aggregate” is defined as all DBP values after initial ROSC, regardless of re-arrest. This includes periods where the control animals had rearrested, CPR was re-started, and the endovascular balloon was re-inflated. DBP post-ROSC with Re-arrest Excluded represents the post-ROSC period without periods where the control animals re-arrested. As the EVAC animals had no periods of re-arrest, there are no differences between the EVAC animals “in aggregate” or “with re-arrest excluded.” Data is presented as median (interquartile range). DBP: diastolic blood pressure; ROSC: return of spontaneous circulation.**

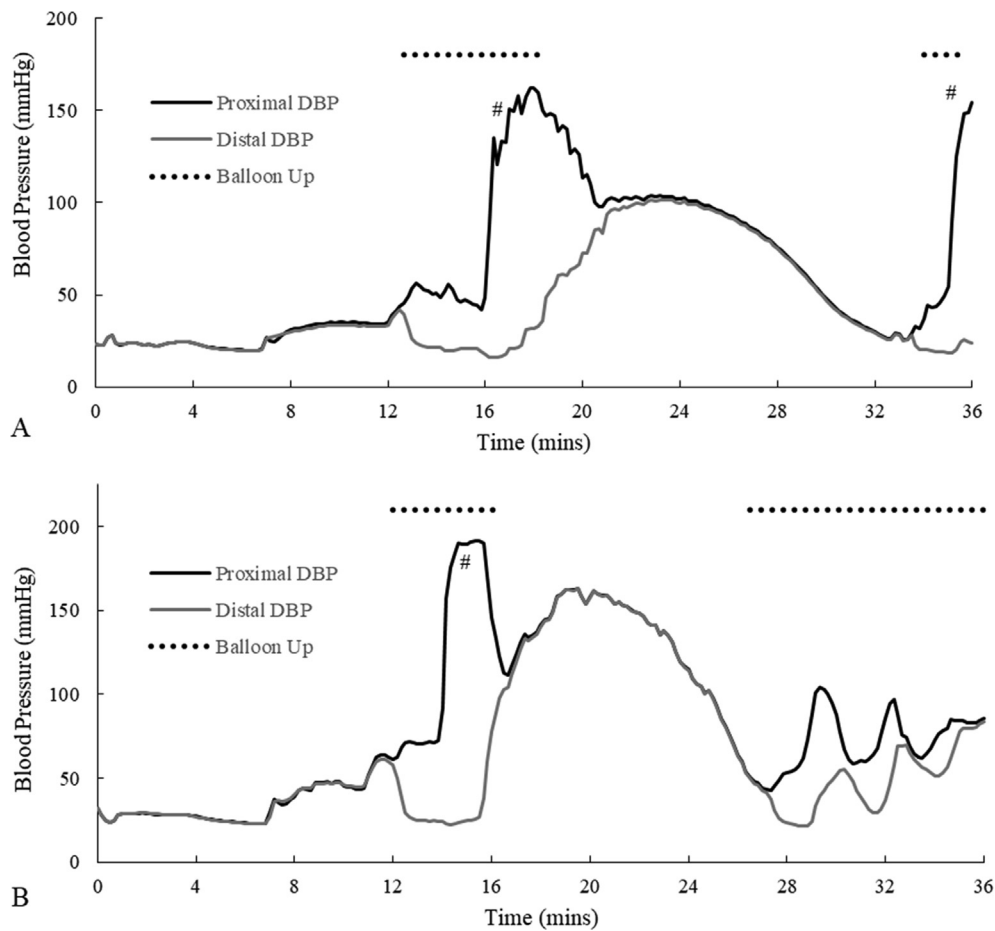
Parameter	Control	EVAC	p
Initial ROSC Time (min)	14.2 (14.1–16.5)	14.2 (14.0–14.2)	0.45
Rearrest (#)	3	0	0.04
DBP Post-ROSC “In Aggregate”			
DBP After ROSC (mmHg)	97.2 (92.0–105.4)	108.8 (108.0–122.7)	0.06
DBP After ROSC > 60 mmHg (%)	79.7 (71.7–88.8)	97.7 (90.8–99.7)	0.03
DBP Post-ROSC with Re-Arrest Excluded			
DBP After ROSC (mmHg)	105.4 (88.5–117.0)	108.8 (108.0–122.7)	0.17
DBP After ROSC > 60 mmHg (%)	79.7 (72.5–86.0)	97.7 (90.8–99.7)	0.05
Total Adrenaline Dose (mcg/kg)	31.92 (20.96–51.88)	20.95 (20.56–31.04)	0.11

an intra-aortic balloon difficult. The risk of cardiovascular collapse is magnified by haemodynamic instability common in the post-arrest phase due to global ischemia–reperfusion injury, myocardial stunning, and inflammatory responses.<sup>32</sup> New strategies are required to manage haemodynamics during this perilous post-ROSC period. Automated critical care solutions, such as EVAC, may provide improved hemodynamic management while simultaneously freeing providers to perform other tasks during resuscitation.

Hypotension occurs in greater than 45–65% of patients after non-traumatic cardiac arrest and is associated with re-arrest and increased mortality.<sup>33,34</sup> Current evidence supports maintaining a CPP of 55 mmHg to prevent re-arrest.<sup>35</sup> Therefore, assuming a central venous pressure (CVP) around 5 mmHg, the EVAC control algorithm ensured that the animal’s DBP would remain above 60 mmHg. DBP was chosen as the experimental variable for this translational pilot study as it can be directly measured from an intra-aortic device,

**Table 3 – Arterial blood gas samples at the conclusion of the study of the control (n = 5) and EVAC (n = 5) groups. Data is presented as median (interquartile range).**

Parameter	Control	EVAC	<i>p</i>
pH	7.23 (7.21–7.25)	7.31 (7.27–7.35)	0.08
pCO <sub>2</sub> (mmHg)	50.4 (45.0–53.6)	46.0 (42.6–47.5)	0.46
PO <sub>2</sub> (mmHg)	121 (117–133)	184 (89–212)	0.60
HCO <sub>3</sub> (mEq/L)	19.1 (18–23.3)	23.3 (21.5–24.1)	0.14
Base Excess (mEq/L)	–9 (–9 to –4)	–3 (–6 to –2)	0.08
Arterial Oxygen Saturation (%)	98 (98–98)	99 (96–100)	0.91
Lactate (mmol/L)	9.93 (8.86–10.45)	7.98 (7.4–8.16)	0.05



**Fig. 3 – The proximal and distal aortic diastolic blood pressures of a representative (A) control and (B) EVAC animal throughout the entire experiment. Mechanical CPR was started at 7 minutes in each animal. ACLS and aortic occlusion were initiated at 12 minutes. Both animals obtained ROSC at approximately 16 mins (denoted by the #). The dotted line marks periods of full or, in the case of EVAC, partial endovascular balloon inflation. Of note, each animal was hypertensive after ROSC, with a progressive decline in blood pressure. The control animal re-arrested at 34 minutes, and the endovascular balloon was fully re-inflated before obtaining ROSC at 36 minutes. The EVAC animal had a “sine wave” of blood pressures, as the adaptive algorithms changed the balloon volume to ensure diastolic blood pressure remained > 60 mmHg.**

allowing practitioners to rapidly deploy adaptive balloon management without placement of a second invasive device to measure CVP. If DBP dropped below this threshold, the EVAC balloon is programmed to inflate, acting as a “resistor” within the aorta. EVAC may also limit unnecessary afterload increases arising from

overzealous balloon inflation, the negative impacts of which were established in prior models.<sup>18,36</sup> In several EVAC animals, the amplitude of blood pressure fluctuations steadily decreased, indicating decreasing amounts of EVAC balloon support as the study progressed. This activity is a result of the adaptive algorithms tailoring

magnitude of balloon volume changes based on the haemodynamic effects from prior balloon movements. EVAC successfully maintained DBP above this DBP threshold for 97% of the post-ROSC period. Sustaining DBP above this threshold, re-arrest was prevented in the EVAC animals.

Both the EVAC and control animals had high DBP immediately after ROSC (Fig. 3). This was likely due to residual adrenaline used during ACLS in conjunction with a surge of endogenous catecholamines associated with ROSC.<sup>37</sup> During this period, the balloon in the control group was deflated manually and the EVAC balloon fully deflated, as haemodynamic allowed. However, over approximately 15 minutes, all animals saw a progressive decline in DBP. Because of EVAC's just-in-time DBP support, the EVAC animals did not have periods of more profound hypotension, whereas such periods led to re-arrest in the control group. The relative haemodynamic stability and prevention of re-arrest in the EVAC group resulted in improved perfusion, as evidenced by the statistically significant reduction in lactate levels by the end of the experiment. Thus, despite the balloon remaining partially inflated in three of the EVAC animals at the end of experiment, EVAC reduced global ischemia in the post-arrest period simply by reducing re-arrest rates and the attendant ischemia that comes with no- or low-flow VF periods.

There is increasing evidence that current cardiac arrest therapies either provide no substantial benefit or may worsen patient-centered outcomes in exchange for marginal improvements in ROSC rates. For example, the effectiveness of adrenaline, the mainstay pharmacologic intervention in cardiac arrest, has been questioned. Animal studies have demonstrated that high-dose adrenaline leads to vasoconstriction in the cerebral microcirculation, causing cerebral ischemia in models of cardiac arrest.<sup>38–40</sup> Recently, the largest clinical trial of adrenaline during out of hospital ACLS demonstrated a 0.8% survival benefit. There was however no evidence that it significantly improved neurological outcomes.<sup>41</sup> Our study suggests that EVAC could lower re-arrest rates without additional vasopressor usage. Such next generation variable aortic occlusion devices may decrease adrenaline requirements and improve functional survival. A larger study is needed to delineate the impacts of EVAC on adrenaline use as a primary outcome.

These conclusions must be considered in the context of this study's limitations. First, the study was terminated early, future studies should enroll more animals and follow them longer. Second, investigators were not blinded to the randomization of each animal. However, animals underwent randomization immediately before ROSC, which limits potential bias. Third, despite similarities between species, there are anatomic and physiologic differences between humans and swine. Furthermore, while the study animals developed cardiac injury during the no-flow and low-flow VF periods, the animals do not have the typical underlying cardiac diseases of patients suffering nontraumatic cardiac arrest. However, this model is commonly used in nontraumatic cardiac arrest translational studies.<sup>8,28,38</sup> Additionally, due to the experimental nature of animal models, there was variability in ROSC and re-arrest times between groups. This makes direct temporal comparisons in the post-ROSC period challenging, as animals are in different hemodynamic states at the same experimental time. Finally, we sought to determine the effectiveness of EVAC within the first 20 minutes after ROSC in light of clinical data suggesting high rates of re-arrest during this immediate post-ROSC timeframe. Future research is required to determine EVAC's ability to sustain ROSC during longer periods. These limitations notwithstanding, this is the first study demonstrating the potential impact of

adaptive and automated balloon control to decrease rates of re-arrest after ROSC in a swine model of nontraumatic cardiac arrest.

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## Conclusions

In this study, adaptive, automated aortic occlusion prevented re-arrest for 20 minutes by maintaining a DBP above 60 mmHg after ROSC in a swine model of nontraumatic cardiac arrest. EVAC improved haemodynamic support without additional pharmacologic intervention compared to standard aortic occlusion which resulted in a significant reduction in re-arrest rates and lower final lactate concentrations.

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## Animal use statement

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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## Conflicts of interest

Drs. M. Austin Johnson, Timothy Williams and Lucas Neff are founders and stockholders of Certus Critical Care, Inc, which developed the Endovascular Variable Aortic Control device. Craig D. Nowadly has worked as an independent contractor for Certus Critical Care. Guillaume L. Hoareau is a stockholder of Certus Critical Care, Inc.

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## CRediT authorship contribution statement

**Craig D. Nowadly:** Formal analysis, Writing – original draft, Visualization. **M. Austin Johnson:** Investigation, Writing – review & editing. **Scott T. Youngquist:** Investigation, Writing – review & editing. **Timothy K. Williams:** Software, Writing – review & editing. **Lucas P. Neff:** Software, Writing – review & editing. **Guillaume L. Hoareau:** Conceptualization, Funding acquisition, Methodology, Investigation, Resources, Formal analysis, Writing – original draft.

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## Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Brooke Army Medical Center, the University of Utah, the Salt Lake City Fire Department, Atrium Health Wake Forest Baptist, US Army Medical Department,

Department of the Army, Department of the Air Force, Department of Defense, or the US Government.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2022.100239>.

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