RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA IN EXPERIMENTAL CARDIOPULMONARY RESUSCITATION: AORTIC OCCLUSION LEVEL MATTERS

Emanuel M. Dogan,* Linus Beskow,* Fredrik Calais,† Tal M. Hörer,* Birger Axelsson,* and Kristofer F. Nilsson*

*Department of Cardiothoracic and Vascular Surgery, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; and †Department of Cardiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

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ABSTRACT—Introduction: Aortic occlusion during cardiopulmonary resuscitation (CPR) increases systemic arterial pressures. Correct thoracic placement during the resuscitative endovascular balloon occlusion of the aorta (REBOA) may be important for achieving effective CPR. Hypothesis: The positioning of the REBOA in the thoracic aorta during CPR will affect systemic arterial pressures. Methods: Cardiac arrest was induced in 27 anesthetized pigs. After 7 min of CPR with a mechanical compression device, REBOA in the thoracic descending aorta at heart level (zone Ib, REBOA-Ib, n = 9), at diaphragmatic level (zone Ic, REBOA-Ic, n = 9) or no occlusion (control, n = 9) was initiated. The primary outcome was systemic arterial pressures during CPR. Results: During CPR, REBOA-Ic increased systolic blood pressure from 86 mmHg (confidence interval [CI] 71–101) to 128 mmHg (CI 107–150, P < 0.001). Simultaneously, mean and diastolic blood pressures increased significantly in REBOA-Ic (P < 0.001 and P = 0.006, respectively), and were higher than in REBOA-Ib (P = 0.04 and P = 0.02, respectively) and control (P = 0.005 and P = 0.003, respectively). REBOA-Ib did not significantly affect systemic blood pressures. Arterial pH decreased more in control than in REBOA-Ib and REBOA-Ic after occlusion (P = 0.004 and P = 0.005, respectively). Arterial lactate concentrations were lower in REBOA-Ic compared with control and REBOA-Ib (P = 0.04 and P < 0.001, respectively). Conclusions: Thoracic aortic occlusion in zone Ic during CPR may be more effective in increasing systemic arterial pressures than occlusion in zone Ib. REBOA during CPR was found to be associated with a more favorable acid–base status of circulating blood. If REBOA is used as an adjunct in CPR, it may be of importance to carefully determine the aortic occlusion level. The study was performed following approval of the Regional Animal Ethics Committee in Linköping, Sweden (application ID 418).

KEYWORDS—Cardiac arrest, cardiopulmonary resuscitation, hemodynamics, metabolism, resuscitative endovascular balloon occlusion of the aorta, return of spontaneous circulation

INTRODUCTION

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emerging method to stop ongoing bleeding (1). It temporarily stabilizes the circulation in trauma patients in life-threatening hemorrhagic shock until definitive surgical repair can be accomplished (2–4). The REBOA causes a mechanical shift in the circulating blood volume from the lower part of the body to the heart and brain (5). In nontraumatic and nonhemorrhagic cardiac arrests, the coronary and cerebral perfusion pressures during CPR are the main determinants of outcome (6–8). The conventional method for increasing the coronary perfusion pressure in CPR is to administer adrenaline (epinephrine), although adrenaline might not increase the long-term survival rate (9). Previous experimental studies in animal models of cardiac arrest have shown that aortic occlusion increases systemic arterial pressures, increases cerebral and cardiac blood pressure and flow, and improves the rate of return of spontaneous circulation (ROSC) (10–19). Human studies, with the exception of some case reports, are lacking, but may be initiated in the near future because of the recent advancement of endovascular methods, in particular endovascular resuscitation, in emergency patients (20–23). In a patient with a ruptured thoracic aortic aneurysm in cardiac arrest, endovascular aortic occlusion was successfully initiated during cardiopulmonary resuscitation (CPR) (24). There is an urgent need of novel treatment modalities for nontraumatic and nonhemorrhagic out-of-hospital cardiac arrest because of a low rate of survival to hospital discharge (25, 26). In addition to increasing ROSC frequency, REBOA may be used to optimize cerebral and coronary blood flows during conventional CPR as a bridge to extracorporeal membrane oxygenation (27). However, before the initiation of clinical trials of REBOA in cardiac arrest, knowledge of optimal use and the positioning of REBOA during CPR must be gathered. The descending aorta is divided into 3 main REBOA zones. Zone I is in the thoracic descending aorta, and zones II and III are in the abdominal aorta (5). However, because of the proximity of the descending thoracic aorta to the heart, the exact position of REBOA in zone I could be of importance in CPR with chest compressions. Therefore, in this study, based on fluoroscopic appearance, the thoracic descending aorta was divided into 3 subzones: Ia, above the
upper heart margin; Ib, behind the heart contour; and Ic, below the lower heart margin. We hypothesized that the exact position of REBOA in the thoracic descending aorta during CPR is of importance for generating increased systemic arterial pressures. In a porcine model of cardiac arrest and CPR, the effect on systemic arterial pressures of REBOA in zone Ib is compared with REBOA in zone Ic. The effects of REBOA on arterial metabolic status during CPR are also investigated.

**MATERIALS AND METHODS**

**Animals**

The Regional Animal Ethics Committee in Linköping approved the study (ID: 418) prior to experimentation. The animals were handled in accordance with the European Convention for Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (28). Twenty-eight male and female pigs of Swedish country breed (Hampshire and Yorkshire, 3–4 months old, mean weight of 28 kg [range 25–34 kg]) were included. The animals were bred and housed at a local farm in a 16 h/d night cycle with free access to fodder and water until the morning of experimentation. The research was performed by an experienced research team, and was supervised by a licensed veterinarian. Two simultaneous experiments were performed each day, between October 2016 and April 2017, in a laboratory equipped for animal experimentation at the Örebro University Hospital, Örebro, Sweden.

**Preparation, anesthesia, ventilation, and fluid treatment**

At the farm, the pigs received 200–250 mg azaperone (i.m., 40 mg ml⁻¹; Stresnil, Elanco, Herlev, Denmark) for sedation and were thereafter transported for 30 min by road to the laboratory. On arrival, anesthesia was induced by an i.m. injection of tiletamine and zolazepam (6 mg kg⁻¹ of each; Zoletil Forte, Virbac, Kolding, Denmark), azaperone (4 mg kg⁻¹) and atropine (to reduce salivation; 1.5 mg; Mylan, Stockholm, Sweden). Two peripheral venous catheters (1.1 mm, Venflon Pro Safety, BD, Helsingborg, Sweden) were inserted into the pigs’ ear veins, and they received Cefuroxim (750 mg, i.v.; GSK, Solna, Sweden). If needed, Propofol (1–2 mg i.v.; Fresenius Kabi, Uppsala, Sweden) was continuously infused i.v. by motorized syringe pumps (Alaris CC, Cardinal Health, Rolle, Switzerland). The rates of infusion were adjusted to maintain a heart rate greater than 100 beats min⁻¹ and for a bipolar pacemaker electrode, if needed (see below). A midline incision was performed and a 14 Fr urinary catheter (Penky, Unomedical, Flintshire, UK) was inserted into the urinary bladder. An ultrasound flow probe (4–6 mm, PV probe, Medistim, Oslo, Norway) was fixed around the superior mesenteric artery (SMA) to measure blood flow. A 6 Fr catheter (Tumisale 2, Vygon, Ecouen, France) was inserted into the superior mesenteric vein for measurement of blood pressure. Thereafter, the animals received heparin (10,000 IU i.v.) was given. Thereafter, the LAD was catheterized using a 0.035” guide wire (Abbott Vascular, Santa Clara), a 5 Fr guide catheter (Launher Medtronic, Minneapolis, MN), a 0.014” wire to reach the LAD, and a balloon catheter (Powerline balloon diameter 2.5 mm, balloon length 15 mm; Biosensors International, Morges, Switzerland). Subsequently, the LAD was occluded, either distally or proximally, for 6 to 30 min by inflation of the balloon (10 psi, 2.5 mm balloon diameter, Fig. 1). Coronary angiograms were obtained by contrast injection in the guide catheter to confirm correct placement and inflation of the balloon. If ventricular fibrillation (VF) did not occur (Fig. 1), it was induced by applying a voltage of 9 V at the bipolar pacemaker electrode inserted in the right ventricle. Similar model for myocardial infarction have been described (29). When VF was confirmed by ECG readings, the ventilator and infusion pumps were disabled until the start of CPR. The duration of circulatory arrest was between 2 and 8 min (Fig. 1). At the start of CPR, mechanical chest compressions by a device (Lusca, Jolife AB, Lund, Sweden) were commenced with a 50% compression phase and 50% decompression phase lasting about 0.3 s each and a compression rate of 100 min⁻¹. Ventilation was restarted at 8 to 12 breaths min⁻¹, with 5 L min⁻¹ of oxygen flow into the ventilator. The CPR followed an algorithm with ECG analysis and defibrillation of 200 J (if VF or ventricular tachycardia without spontaneous circulation) every second minute and adrenaline administration i.v. (0.02–0.03 mg kg⁻¹) every four minute starting after 6 min of CPR (Fig. 1). In animals allocated to aortic occlusion, the occlusion balloon was inflated after 7 min of CPR (Fig. 1). The CPR was continued for at least 30 min. During CPR, hemodynamic and respiratory data were collected, and arterial blood was analyzed intermittently (Fig. 1). If sinus rhythm was identified on the ECG and pulse waves were produced on the systemic arterial pressure recording, CPR was discontinued. If circulatory arrest reappeared, the CPR protocol was resumed. ROSC was defined in our protocol as a spontaneous mean arterial pressure (MAP) greater than 40 mmHg for at least 5 min.

**Statistical method**

The data were tested to meet the assumptions of a normal distribution, no significant outliers and homogeneity within the different groups using SPSS (SPSS version 23, IBM Corp, Armonk, NY). If the data did not strongly violate these assumptions, they were analyzed using a linear mixed model (repeated factor time, the other factor group; SPSS). If the linear mixed model identified a significant effect of interaction between group and time, multiple comparisons were performed using a Bonferroni adjusted post-hoc test (SPSS). P < 0.05 was considered significant. Data are presented as means with 95% confidence intervals.

**RESULTS**

**Hemodynamic measurements**

Before cardiac arrest, no statistical differences were detected between the groups, except that diastolic blood pressure (DBP) was slightly higher in REBOA-Ib than in REBOA-Ic (P = 0.01, Fig. 2B). During CPR but before intervention, systolic blood pressure (SBP) increased to circa 90 mmHg to 100 mmHg in all groups, indicating adequate compressions at 100 beats min⁻¹ (Fig. 2B). In REBOA-Ic, SBP increased by approximately 42 mmHg after aortic occlusion (P < 0.001 compared with before intervention), in comparison with 17 mmHg in
REBOA-Ib and 7 mmHg in the control group (Fig. 2A). In parallel, MAP and DBP were significantly higher in REBOA-Ic compared with before intervention ($P < 0.001$ and $P = 0.006$, respectively), to REBOA-Ib ($P = 0.04$ and $P = 0.02$, respectively) and to the control group ($P = 0.005$ and $P = 0.003$, respectively, Fig. 2B and C). In REBOA-Ib and the control group, there were no significant changes in systemic arterial blood pressures when comparing within the groups before and after the time of intervention (Fig. 2A–C). During CPR, but before intervention, blood flow in the SMA was present in all groups although it was substantially lower than at baseline (approximately 15–25% of baseline flow at 1 min of CPR, $P < 0.001$ in all groups compared with baseline, Fig. 2D). At aortic occlusion, the blood flow in the SMA decreased to almost zero in REBOA-Ib and REBOA-Ic ($P = 0.001$ and $P = 0.001$, respectively, compared with the control group; Fig. 2D). In the control group, the blood flow in the SMA decreased with the duration of CPR (Fig. 2D). There were no significant changes between the groups regarding heart rate, mean central venous pressure, mean mesenteric pressure, or body temperature throughout the experiment.

Respiratory variables and blood analysis

Baseline values of the respiratory variables and arterial blood gases, including lactate, did not significantly differ between the groups (Table 1, Fig. 3). Arterial lactate concentrations were slightly higher in REBOA-Ib compared with REBOA-Ic at the time point before intervention (6 min of CPR, $P = 0.004$; Fig. 3C). Arterial PO2 was maintained during CPR and did not significantly differ between the groups (Table 1). Arterial acidosis was more pronounced in the control group with lower arterial pH compared with both REBOA-Ib and REBOA-Ic ($P = 0.004$ and $P = 0.005$, respectively after 21 min of CPR; Fig. 3A). There was a tendency toward decreased arterial PCO2 levels after aortic occlusion in both REBOA-Ib and REBOA-Ic compared with the control group (Fig. 3B). After intervention, arterial lactate levels were significantly lower in REBOA-Ic compared with both the control group and REBOA-Ib ($P = 0.04$ and $P < 0.001$, respectively, after 27 min of CPR, Fig. 3C).

Return of spontaneous circulation

Two animals in REBOA-Ic and 1 in REBOA-Ib achieved ROSC, whereas none of the animals in the control group achieved ROSC (Fig. 2).

**DISCUSSION**

The results of this study suggest that the location of the REBOA affects the hemodynamic response during CPR, and
FIG. 2. SBP (panel A), DBP (panel B), MAP (panel C), and blood flow in the SMA (panel D), during CPR in anesthetized pigs. Aortic occlusion (REBOA, intervention) at heart level (REBOA-Ib, n = 9) or diaphragmatic level (REBOA-Ic, n = 9) and control (no aortic occlusion, n = 9). Values are displayed as means with 95% CI. P < 0.05 was considered as statistically significant. * indicates a significant difference between control and REBOA-Ib. # indicates a significant difference between control and REBOA-Ic. § indicates a significant difference between REBOA-Ib and REBOA-Ic. ¶ indicates a significant difference between the measurement before intervention (6 min) and the time points thereafter within each group. ▲ indicates ROSC in an animal with REBOA-Ic and ● indicates ROSC in an animal with REBOA-Ib. CI, confidence interval; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; MAP, mean arterial pressure; REBOA, resuscitative endovascular balloon occlusion of the aorta; ROSC, return of spontaneous circulation; SBP, systolic blood pressure; SMA, superior mesenteric artery.
TABLE 1. Respiratory values and blood samples during CPR in anesthetized pigs

| Variables                        | Groups          | Baseline | 1       | 6       | 8       | 12      | 21      | 27      | 36      | 45      | 60      | 72      |
|----------------------------------|-----------------|----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Fraction of inspired O₂ (%)      | Control         | 25 (22–29) | 80 (64–97) | 77 (68–89) | 75 (70–82) | 75 (70–82) | 68 (62–74) | 73 (66–77) | 71 (65–77) | 67 (61–73) | 69 (63–77) | 72 (67–79) |
|                                  | REBOA-Ib        | 25 (22–29) | 25 (22–29) | 17 (14–21) | 21 (17–27) | 21 (17–27) | 21 (17–27) | 14 (10–18) | 13 (10–16) | 10 (7–14) | 8 (6–12)  | 10 (7–14) |
|                                  | REBOA-Ic        | 25 (22–29) | 24 (20–27) | 17 (14–21) | 21 (17–27) | 21 (17–27) | 21 (17–27) | 14 (10–18) | 13 (10–16) | 10 (7–14) | 8 (6–12)  | 10 (7–14) |
| Arterial PO₂ (kPa)               | Control         | 15.3 (12.5–18.2) | 21.7 (7.8–35.6) | 26.2 (14.5–37.9) | 24.4 (15.9–32.9) | 22.0 (14.6–29.7) | 19.9 (13.1–26.7) | 17.1 (15.2–18.9) | 14.7 (12.7–18.8) | 11.9 (9.6–14.3) | 11.9 (9.9–13.9) | 11.9 (9.9–13.9) |
|                                  | REBOA-Ib        | 16.2 (13.3–19.0) | 16.8 (3.1–30.5) | 27.3 (15.6–39.0) | 28.8 (20.1–37.5) | 24.2 (15.9–32.5) | 24.3 (15.6–33.1) | 17.1 (15.2–18.9) | 14.7 (12.7–18.8) | 11.9 (9.6–14.3) | 11.9 (9.9–13.9) | 11.9 (9.9–13.9) |
|                                  | REBOA-Ic        | 14.4 (11.5–17.2) | 20.1 (6.4–33.8) | 29.1 (17.4–40.8) | 25.6 (16.6–34.5) | 30.4 (22.3–38.6) | 22.2 (14.8–29.7) | 17.1 (15.2–18.9) | 14.7 (12.7–18.8) | 11.9 (9.6–14.3) | 11.9 (9.9–13.9) | 11.9 (9.9–13.9) |
| Arterial bicarbonate (mmol·L⁻¹)  | Control         | 30.8 (29.0–32.6) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) | 23.5 (21.7–25.7) |
|                                  | REBOA-Ib        | 28.7 (27.9–31.5) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) |
|                                  | REBOA-Ic        | 28.7 (27.9–31.5) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) | 20.6 (18.8–22.4) |

Values are displayed as means with a 95% CI. REBOA, resuscitative endovascular balloon occlusion of the aorta; CPR, cardiopulmonary resuscitation; CI, confidence interval.
metabolites will reach the circulating blood volume first at reperfusion. In contrast, in the control group, an existing but inadequate perfusion caused partial hypoxic tissues leading to a constant production of acidotic substances to the circulating volume. A short aortic occlusion period during CPR compared with no aortic occlusion might be more favorable in maintaining arterial pH, lactate, and electrolytes closer to the normal range, which would enhance the probability to achieve ROSC. However, following the release of the occlusion, the ischemic substances that have gathered in the occluded tissues are released to the body through the replenished blood flow (35).

This study has some obvious limitations. It was part of a model-development process, which means that some experimental factors (dose of adrenaline, location and duration of LAD occlusion, and duration of circulatory arrest) were varied slightly between the experiments to find the optimal model. Nevertheless, we believe that these variations do not interfere with our major conclusions. The most important factors for hemodynamic and metabolic impact during CPR (e.g., duration of circulatory arrest) were similar in all the groups. In fact, the mean duration of circulatory arrest was almost identical across groups (6.8, 6.9, and 6.7 min in the control group, REBOA-Ib and REBOA-Ic, respectively). The relatively small number of

Fig. 3. Arterial pH (panel A), PCO₂ (panel B), and lactate (panel C) during CPR in anesthetized pigs. Values are displayed as means with 95% CI. Aortic occlusion (REBOA, intervention) at heart level (REBOA-Ib, n = 9) or diaphragmatic level (REBOA-Ic, n = 9) and control (no aortic occlusion, n = 9). P < 0.05 was considered as statistically significant. * indicates a significant difference between control and REBOA-Ib. † indicates a significant difference between control and REBOA-Ic. ‡ indicates a significant difference between REBOA-Ib and REBOA-Ic. § indicates significant differences between the measurement before intervention (6 min) and the time points thereafter within each group. ▲ indicates ROSC in an animal with REBOA-Ic and ■ indicates ROSC in an animal with REBOA-Ib. CI, confidence interval; CPR, cardiopulmonary resuscitation; PCO₂, partial pressure of carbon dioxide; REBOA, resuscitative endovascular balloon occlusion of the aorta.
animals in each group is a limiting factor, but the study emphasizes that greater knowledge of optimal use of REBOA in cardiac arrest and CPR is needed before initiating clinical trials. Another limitation of the study is that research on healthy animals is not directly transferable to diseased humans. However, pigs are the ideal animals for modeling cardiac arrest because of their similarities to humans in the anatomy of their heart and abdominal organs (36). Also, the anesthetic drugs could depress the hemodynamic results, however, all animals were anesthetized with the same protocol which enables comparison between the groups.

Previous studies have concluded that REBOA increase ROSC frequency during nontraumatic cardiac arrest (10, 13, 15). This study was not designed, nor had the power to compare the rates of ROSC between the groups.

CONCLUSION

Aortic occlusion in the thoracic descending aorta during CPR in zone 1c might generate higher systemic arterial pressures compared with aortic occlusion in zone 1b and no occlusion. REBOA during CPR was found to be associated with a more favorable acid–base status of circulating blood. If REBOA is used as an adjunct in traumatic or nontraumatic CPR, it might be of importance to carefully determine the aortic occlusion level prior to inflation of the balloon. REBOA in cardiac arrest seems to be a promising therapeutic intervention to be investigated in humans, as a primary intervention to achieve ROSC or as a bridge to more definitive care like percutaneous coronary intervention or/and extracorporeal membrane oxygenation. However, the optimal use of REBOA must be further explored in randomized studies.

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