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A randomized porcine study of the hemodynamic and metabolic effects of combined endovascular occlusion of the vena cava and the aorta in normovolemia and in hemorrhagic shock

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BACKGROUND: Mortality from traumatic retrohepatic venous injuries is high and methods for temporary circulatory stabilization are needed. We investigated survival and hemodynamic and metabolic effects of resuscitative endovascular balloon occlusion of the aorta (REBOA) and vena cava inferior (REBOVC) in anesthetized pigs.

METHODS: Twenty-five anesthetized pigs in normovolemia or severe hemorrhagic shock (controlled arterial bleeding in blood bags targeting systolic arterial pressure of 50 mm Hg, corresponding to 40–50% of the blood volume) were randomized to REBOA zone 1 or REBOA+REBOVC zone 1 (n = 6–7/group) for 45 minutes occlusion, followed by 3-hour resuscitation and reperfusion. Hemodynamic and metabolic variables and markers of end-organ damage were measured regularly.

RESULTS: During occlusion, both the REBOA groups had higher systemic mean arterial pressure (MAP) and cardiac output ($p < 0.05$) compared with the two REBOA+REBOVC groups. After 60 minutes reperfusion, there were no statistically significant differences between the two REBOA groups and the two REBOA+REBOVC groups in MAP and cardiac output. The two REBOA+REBOVC groups had higher arterial lactate and potassium concentrations during reperfusion, compared with the two REBOA groups ($p < 0.05$). There was no major difference in end-organ damage markers between REBOA and REBOA+REBOVC. Survival after 1-hour reperfusion was 86% and 100%, respectively, in the normovolemic REBOA and REBOA+REBOVC groups, and 67% and 83%, respectively, in the corresponding hemorrhagic shock REBOA and REBOA+REBOVC groups.

CONCLUSION: Acceptable hemodynamic stability during occlusion and short-term survival can be achieved by REBOA+REBOVC with adequate resuscitation; however, the more severe hemodynamic and metabolic impacts of REBOA+REBOVC compared with REBOA must be considered. (*J Trauma Acute Care Surg.* 2021;90: 817–826. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Prospective, randomized, experimental animal study. Basic science study, therapeutic.

KEY WORDS: Abdominal injuries; shock; traumatic; hepatic veins.

Injuries to the retrohepatic inferior vena cava (IVC) and the hepatic veins are rare, also at Level 1 trauma centers, and gaining proper practical surgical experience may be difficult, even for senior trauma surgeons.[1–4] However, once appearing, the mortality rates are high (30–80%).[5–11] Three major hepatic veins drain into the IVC in the retrohepatic area, where the IVC is partly adherent to the liver and the area is hostile for exploration. Once the liver is mobilized, the contained venous injuries often start bleeding profusely, which may cause life-threatening hemorrhagic shock.[2,9–15] The thin-walled nature of the veins, with a nonpulsatile, low-pressure, high volume flow, also contributes to the lethality of these injuries.[9] Gaining proximal and distal control of the retrohepatic vena cava is a surgical challenge. Total hepatic vascular isolation traditionally involves occlusion of the hepatic artery and portal vein (Pringle maneuver) combined with inflow and outflow occlusion of the infrahepatic and suprahepatic vena cava.[4,16–18] However, two thirds of the cardiac output (CO) is supplied by the IVC and the sudden reduction of venous return caused by proximal occlusion of the IVC may cause circulatory collapse.[4,5,17–19] Thoracoabdominal aortic cross-clamping has been necessary to compensate for the reduced preload caused by proximal vena cava occlusion.[4,16] If the suprahepatic IVC is too short to be clamped in the abdomen, the intrapericardial portion of the IVC can be reached by a transdiaphragmatic incision from the abdomen, as suggested by Heaney (Heaney maneuver).[4,11,16] Other pathways described to reach the suprahepatic or intrapericardial IVC is by median sternotomy or by right anterolateral thoracotomy, although the disadvantage of opening another body cavity than the abdomen must be considered.[3,4,12,20,21] Endovascular techniques enable occlusion of major vessels from more distal/peripheral sites. In retrohepatic venous injuries, where the exposure procedure often enhances bleeding, endovascular bleeding control is

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especially attractive.[11,12] Usage of endovascular balloons in veins is a relatively unexplored area of experience and research. In recent years, a few case reports have presented various combinations of endovascular techniques for occlusion of the vena cava (REBOVC) to control bleeding from the retrohepatic area.[22,23] According to the World Society of Emergency Surgery new guidelines on retrohepatic injuries, resuscitative endovascular balloon occlusion of the aorta (REBOA) "should be considered if, despite all damage control procedures, there is still active surgical bleeding" and a REBOVC positioned simultaneously in "the level of retrohepatic vena cava."[24] Only a few studies, so far, have extensively investigated the effects of REBOA+REBOVC, with or without the Pringle maneuver.[17,23,25,26] In a recent study, we found that a concomitant REBOA in zone 1 can compensate for the negative hemodynamic effects of a proximal vena caval occlusion and allow a suprahepatic REBOVC in normovolemic animals for 5 minutes occlusion.[26] In the present study, we aimed to examine survival and the hemodynamic and metabolic effects of 45 minutes occlusion using REBOVC+REBOA in zone 1 compared with REBOA in two study conditions: in normovolemia and in hemorrhagic shock. The purpose of the hemorrhagic shock groups was to perform measurements during fast-developing hemorrhagic shock, not to measure amounts or rates of bleeding, nor to address the retrohepatic injuries *per se*. We, therefore, opted to use controlled bleeding from the femoral artery into designated blood bags to achieve hemorrhagic shock and enable autotransfusion. The choice to compare REBOA with the REBOA+REBOVC was based on data from our recent study, showing that REBOVC is only hemodynamically tolerable in combination with REBOA.[26] Thus, a comparison of REBOA with REBOVC for 45 minutes of occlusion was not possible; the comparison of REBOA and REBOA+REBOVC was, therefore, relevant to explore the additional effects of REBOVC in a clinical scenario. To our knowledge, this has not been previously explored and represents a crucial step toward the clinical use of REBOA+REBOVC. We hypothesized that using REBOA+REBOVC for 45 minutes might be hemodynamically possible, but the metabolic insult would be more severe compared to REBOA alone.

METHODS

Animals

A randomized experimental animal study was performed during October 2018 to April 2019 at a research laboratory at the Örebro University Hospital, Örebro, Sweden. Twenty-five Swedish cross-breed, Hampshire and England Yorkshire pigs (3 months old; mean weight, 26 kg; weight range, 20–33 kg; gender ratio of approximately 1:1) were used. The animals had free access to food and water at a local farm before the experimental start.

Ethical approval was obtained from the regional ethical committee prior to study start (registration number 1660, Linköping, Sweden). The study was led by a researcher trained in animal experimentation, supervised by a veterinarian and adheres to the ARRIVE guidelines for reporting animal studies and to a directive of the European Union for the protection of animals used for scientific purposes.[27]

Anesthesia

The anesthetic management, including medications, ventilation, and euthanasia, have been previously reported.[26] The use of continuous anesthetic infusions differed between the two study conditions because of a nationwide shortage of fentanyl. Fentanyl at 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (Meda AB, Solna, Sweden) was used in the normovolemic animals and remifentanil at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was used in the hemorrhagic shock animals, infused using syringe pumps (Alaris CC; Cardinal Health Rulle, Switzerland). The use of different opiates was not considered to have any major impact on the results and was approved by the supervising veterinarian.

The animals were injected intramuscularly (i.m.) with azaperone before transportation to the laboratory. On arrival, a mixture of tiletamine, zolazepam, and azaperone was given i.m. to induce anesthesia, followed by continuous intravenous (i.v.) infusions of propofol and fentanyl or remifentanil to maintain general anesthesia. Atropine i.m. and cefuroxime i.v. were given before endotracheal intubation. After intubation, constant ventilation at tidal volume 10 mL/kg was preset and the respiratory frequency was adjusted for normoventilation. Continuous i.v. infusions of Ringer's acetate (10 $mL \cdot kg^{-1} \cdot h^{-1}$) and 5% glucose solutions (1 $mL \cdot kg^{-1} \cdot h^{-1}$) were given throughout the experiment to compensate for basal fluid loss. Body temperature was kept at 37.5°C to 39.5°C using thermal blankets. After the experiments, the animals were euthanized while under general anesthesia by administering an overdose of potassium chloride to quickly induce cardiac arrest.

Surgical Preparation

The basic surgical preparations have been recently reported in detail.[26] Briefly, a Swan-Ganz arterial pulmonary catheter was inserted via the right external jugular vein to sample mixed venous blood and monitor CO, central venous pressure (CVP) and pulmonary capillary wedge pressure. In the right common carotid artery, a sheath was placed by open surgical exposure to measure systemic blood pressure (SBP) and heart rate, and for sampling arterial blood. A sheath in the left external jugular vein was used for sampling venous bloods, autotransfusion of blood, and administration of fluids and drugs. The left femoral artery was cannulated to induce hemorrhagic shock by controlled bleeding. The right femoral artery was used for aortic balloon insertion and the femoral vein for insertion of the vena cava balloon. A catheter was placed in the urinary bladder to measure urine output and take samples of urine. The superior mesenteric vein was catheterized from a distal mesenteric vein, for pressure monitoring and venous blood sampling. At the end of the surgical preparations, 5000 E Heparin was administered i.v.

Study Protocol

Guided by fluoroscopy (Philips BV 300, Stockholm, Sweden), the aortic zone 1 balloon occlusion (the REBOA) was at the level of diaphragm, and the occlusive balloon in the IVC (the REBOVC) was placed above the hepatic veins, below the right atrium. The REBOA (Rescue Balloon; Tokai Ltd, Japan) was inflated first, followed by the REBOVC (Equalizer; Boston Scientific, Ireland). At deflation, the REBOVC was first released, followed by the REBOA. In both study conditions, total balloon occlusion was performed for 45 minutes in all

animals, followed by 180 minutes of reperfusion. No vasopressor drugs, or additional fluid resuscitation than the fixed infusion of Ringer's acetate and glucose stated above, were administered in any study group. The same measurements were performed in both study conditions; hemodynamic, respiratory and metabolic variables were recorded at regular intervals before, during, and after the intervention (Fig. 1). An intestinal specimen was taken from the jejunum and placed in formalin solution for histological examination. The primary outcomes were hemodynamic variables, such as CO, SBP, MAP, CVP, and mesenteric vein pressure (MVP) (Fig. 2). Secondary outcomes were indirect signs of end-organ damage to the heart, kidneys, liver, bowel and anaerobe metabolism using markers such as pH, lactate, potassium, alanine aminotransferase (P-ALT), aspartate aminotransferase (P-AST), P-creatinine, troponin I and histological grading of specimens from the small bowel mucosa[28] (Table 2).

Normovolemia

Seven animals were randomized to REBOA and six animals to REBOA+REBOVC using blind draws from a ballot. After 45-minute occlusion, the balloons were deflated. During the 180-minute reperfusion, measurements were performed according to the study protocol at regular intervals, 15, 60, 120 and 180 minutes after balloon deflation.

Hemorrhagic Shock

Six animals were randomized to REBOA and six animals to REBOA+REBOVC. First, hemorrhagic shock was induced by bleeding at a rate of 60 mL/min from the femoral artery into anticoagulant citrated blood donor bags to a target systolic blood pressure of 50 mm Hg, corresponding to 40% to 50% of the blood volume (66 mL/kg, weight range of the pigs 20–33 kg). The collected blood bags were stored for later resuscitation. After 30-minute hemorrhage, the balloons were inflated. Occlusion for 45 minutes, followed by balloon deflation. Immediately thereafter, autotransfusion of the collected blood started. The first transfusion bag of 450 mL was administered during the first 15 minutes, thereafter blood was given at a slower rate but within 1 hour. Calcium was measured 15 minutes after REBOA deflation and, if the arterial ionized calcium concentration was less than 1 mM, 5 mL of calcium-gluconate i.v. (0.025 mM) was given. Reperfusion followed for 180 minutes, with the same measurements as described above for the normovolemic study groups (Fig. 1*A*).

Statistics

A power calculation was not performed because of the lack of preliminary data from pilot experiments or published data in a similar model with these interventions. Furthermore, this was an exploratory study which did not include only one primary outcome variable to use in an *a priori* power calculation. Approximate normal distribution was analyzed using the Shapiro-Wilk test and nonnormal distributed data were transformed by the logarithm (aspartate aminotransferase, troponin I and diuresis) and then reanalyzed in the Shapiro-Wilk test. Data were analyzed with a linear mixed model using three

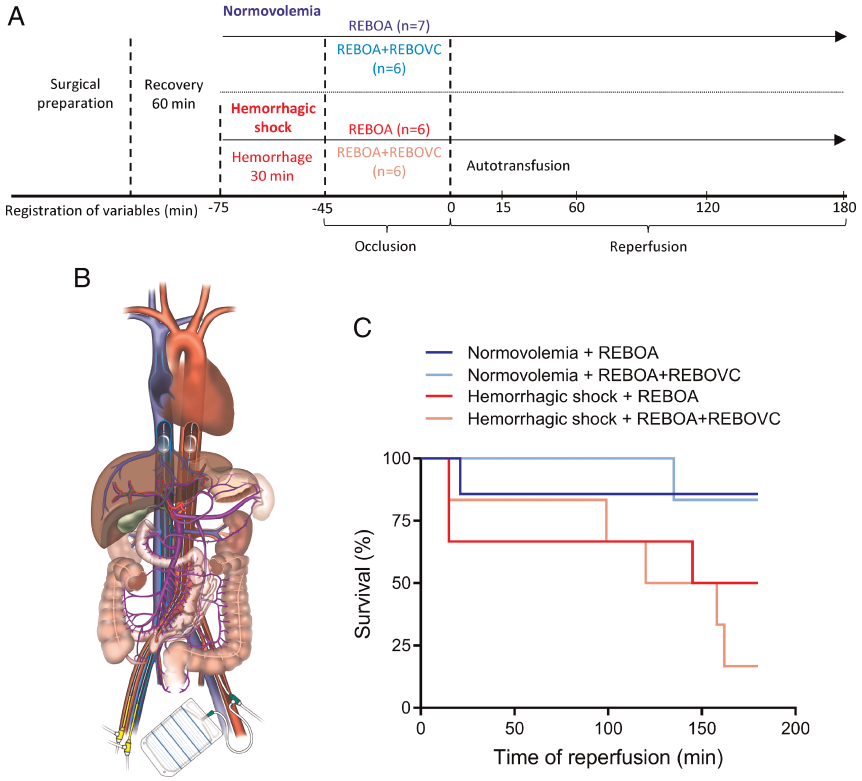

Figure 1. The experimental flow chart of the study (panel A) showing the two interventions investigated, the combination of REBOA and REBOVC or REBOA in the two study conditions (normovolemia and hemorrhagic shock). The anatomical placement of REBOA and REBOVC via catheterization in the right femoral artery and vein, respectively, and the withdrawal of blood into a citrate-containing bag via an introducer in the left femoral vein (panel B). The survival of the animals randomized to each group (panel C).

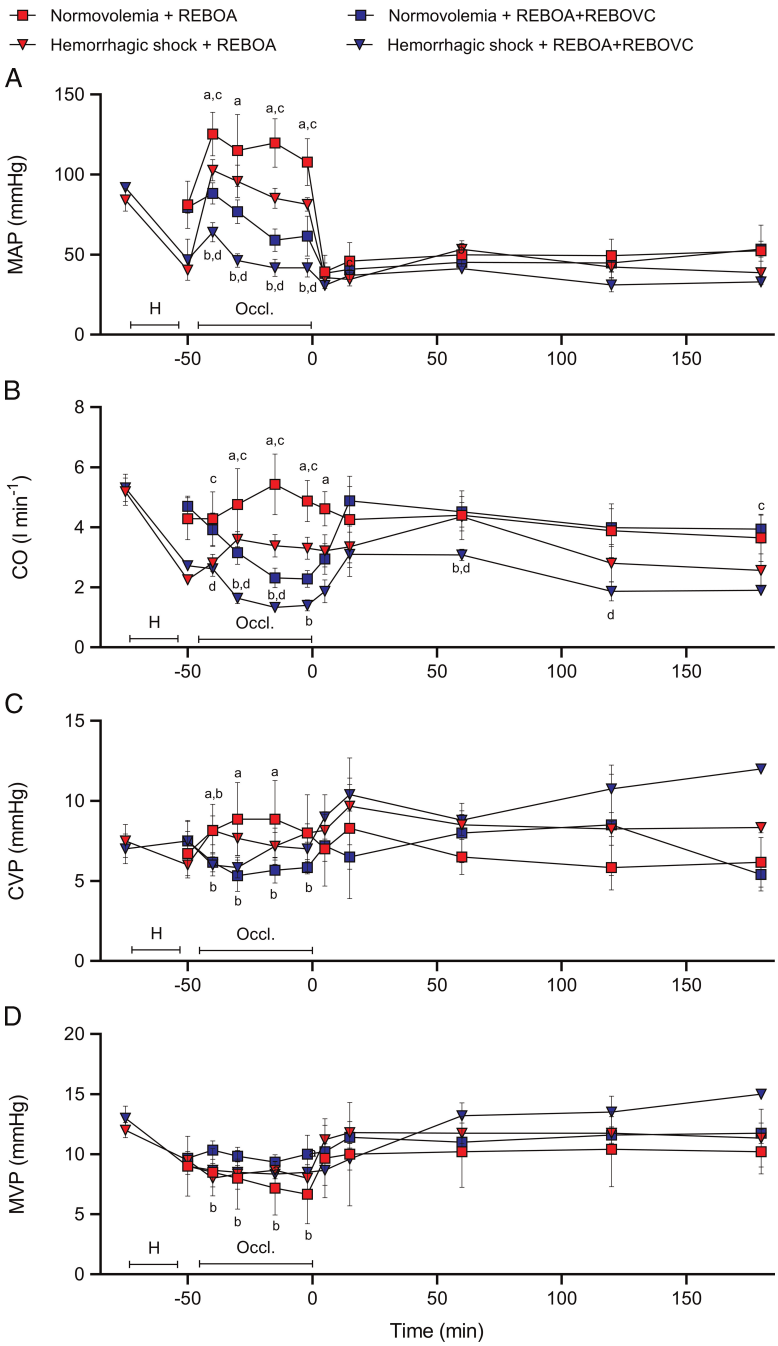

Figure 2. Systemic mean arterial blood pressure (MAP, panel A), CO (panel B), CVP (panel C) and mean MVP (panel D) in anesthetized pigs subjected to either REBOA or a combination of REBOA and REBOVC for 45 minutes in normovolemia and hemorrhagic shock (H) followed by 3 hours of reperfusion and resuscitation. Number of animals in each group at start of reperfusion: Normovolemia + REBOA (n = 7), Normovolemia + REBOA+REBOVC (n = 6), Hemorrhagic shock + REBOA (n = 6) and Hemorrhagic shock + REBOA+REBOVC (n = 6). (*A*), Statistically significant difference during normovolemia between REBOA and REBOA+REBOVC, (*B*) Statistically significant difference during hemorrhagic shock between REBOA and REBOA+REBOVC, (*C*) Statistically significant difference between normovolemia and hemorrhagic shock with REBOA, (*D*) Statistically significant difference between normovolemia and hemorrhagic shock with REBOA +REBOVC. (*B*) and (*D*), significances are not analyzed at the last time point due to low number of surviving animals in hemorrhagic REBOA+REBOVC. Data are means and 95% confidence intervals.

factors and their interaction (time [repeated], normovolemia or hemorrhagic shock, and REBOA or REBOA+REBOVC). If a significant interaction was found, post hoc multiple comparison was performed using Bonferroni correction. Survival at 60 and 180 min of reperfusion between the groups were analyzed with Fischer's exact test. A p value less than 0.05 was considered

statistically significant. Data are presented as means with 95% confidence intervals. The hemodynamic and laboratory data from the animals that expired prior to the endpoint were included in the statistical analysis until they expired.

RESULTS

Survival

There were no statistical differences in survival between the groups, but there were apparent numerical differences, indicating that lower survival was associated with hemorrhagic shock and the combination of REBOA+REBOVC and hemorrhagic shock (Fig. 1*C*).

Hemodynamic Variables and Arterial Blood Analysis

Except for MVP and arterial Hb, there were no statistically significant differences between the groups at baseline (Fig. 2, Table 1).

TABLE 1. Arterial Blood Gas Variables in Anesthetized Pigs Subjected to Either REBOA or a Combination of REBOA and REBOVC in Normovolemia and in Hemorrhagic Shock

Variable	Baseline	Hemorrhage	45 Min Occl.	15 Min Reperf.	1 h Reperf.	2 h Reperf.	3 h Reperf.
Arterial pO_2 (kPa)							
Normovolemia + REBOA	13.2 (11.5–14.9)	na	15.9 (14.6–17.3)	13.1 (11.3–14.9)	12.0 (10.2–13.8)	11.7 (10.1–13.3)	11.5 (10.7–12.4)
Normovolemia + REBOA +REBOVC	12.4 (9.0–15.8)	na	16.4 (15.1–17.6)	11.4 (9.1–13.8)	11.8 (10.0–13.6)	11.3 (8.4–14.2)	10.5 (6.3–14.7)
Hemorrhagic shock + REBOA	11.1 (9.7–13.0)	12.6 (11.9–13.4)	14.8 (13.6–15.9)	13.5 (11.9–15.2)	11.8 (9.9–13.8)	11.0 (9.5–12.5)	11.6 (11.4–11.7)
Hemorrhagic shock + REBOA+REBOVC	11.1 (9.8–12.5)	12.7 (11.6–13.8)	16.0 (14.6–17.5)	10.5 (7.5–13.5)	12.2 (10.0–14.3)	11.9 (10.3–13.5)	11.3§
Arterial pCO_2 (kPa)							
Normovolemia + REBOA	5.2 (4.9–5.4)	na	3.2 (2.9–3.5)	5.0 (4.2–6.0)	5.1 (4.5–5.6)	5.4 (4.7–6.0)	5.4 (5.0–5.8)
Normovolemia + REBOA +REBOVC	5.7 (4.4–7.0)	na	3.3 (1.8–4.8)‡	6.3 (4.7–7.9)‡	5.2 (4.3–6.0)‡	5.1 (3.9–6.3)‡	5.7 (4.9–6.5)
Hemorrhagic shock + REBOA	5.2 (4.8–5.6)	4.7 (4.5–5.0)	2.8 (2.5–3.0)	4.0 (3.0–5.1)	4.4 (3.6–5.1)	4.9 (3.8–5.9)	4.3 (1.8–6.8)
Hemorrhagic shock + REBOA+REBOVC	5.3 (5.0–5.5)	4.3 (3.4–5.2)	2.2 81.9–2.6)‡	5.2 (4.0–6.4)‡	4.0 (3.3–4.9) [d]	3.8 (2.6–5.0)‡	4.3§
End-tidal CO_2 **(%)**							
Normovolemia + REBOA	4.9 (4.5–5.2)	na	2.7 (2.5–2.9)	4.6 (3.8–5.4)	4.7 (4.3–5.0)	4.9 (4.4–5.4)	4.9 (4.4–5.3)
Normovolemia + REBOA +REBOVC	5.2 (4.4–5.9)	na	2.1 (1.1–3.0)	5.5 (4.5–6.5)‡	4.8 (4.1–5.4)‡	4.6 (3.4–5.7)	4.9 (4.3–5.6)
Hemorrhagic shock + REBOA	4.6 (4.1–5.2)	4.4 (4.0–4.9)	2.4 (2.1–2.7)**	4.2 (3.1–5.4)	4.4 (3.9–4.8)	4.5 (3.4–5.5)	4.2 (1.2–7.1)
Hemorrhagic shock + REBOA+REBOVC	5.0 (4.7–5.2)	4.0 (2.8–5.1)	1.6 (1.2–2.1)**	3.8 (2.4–5.1)‡	3.5 (2.4–4.6)‡	3.4 (1.1–5.8)	4.8§
Arterial Hb (g/L)							
Normovolemia + REBOA	69 (57–81)	na	66 (55–76)	66 (56–75)†	74 (62–86)	75 (62–88)†	79 (64–94)
Normovolemia + REBOA +REBOVC	70 (64–76)	na	59 (49–68)	69 (60–78)	80 (65–95)	85 (71–100)	94 (71–117)
Hemorrhagic shock + REBOA	83 (76–90)	74 (62–85)	71 (61–81)	71 (80–61)†	93 (71–115)	98 (78–121)†	97 (62–132)
Hemorrhagic shock + REBOA+REBOVC	78 (70–88)	67 (60–74)	59 (52–65)	63 (56–70)	83 (69–97	83 (68–98)	82§
Arterial calcium (mM)							
Normovolemia + REBOA	1.4 (1.4–1.5)	na	1.3 (1.2–1.4)	1.3 (1.2–1.4)†	1.3 (1.2–1.4)†	1.4 (1.2–1.5)†	1,3 (1.2–1.5)
Normovolemia + REBOA +REBOVC	1.4 (1.4–1.5)	na	1.3 (1.2–1.3)	1.4 (1.3–1.4)‡	1.3 (1.2–1.3)‡	1.3 (1.2–1.3)‡	1.3 (1.2–1.3)
Hemorrhagic shock + REBOA	1.4 (1.3–1.4)	1.4 (1.3–1.5)	1.3 (1.2–1.3)	1.0 (0.8–1.1)†	1.1 (1.0–1.2)†	1.3 (1.2–1.4)†	1.3 (1.3–1.4)
Hemorrhagic shock + REBOA+REBOVC	1.4 (1.3–1.4)	1.3 (1.3–1.4)	1.2 (1.2–1.3)	1.0 (0.7–1.3)‡	1.0 (0.9–1.2)‡	1.2 (1.1–1.3)‡	1.2§

Number of animals in each group at start of reperfusion: Normovolemia + REBOA (n = 7), Normovolemia + REBOA+REBOVC (n = 6), Hemorrhagic shock + REBOA (n = 6) and Hemorrhagic shock + REBOA+REBOVC (n = 6).

*Statistically significant difference during normovolemia between REBOA and REBOA+REBOVC.

**Statistically significant difference during hemorrhagic shock between REBOA and REBOA+REBOVC.

†Statistically significant difference between normovolemia and hemorrhagic shock with REBOA.

‡Statistically significant difference between normovolemia and hemorrhagic shock with REBOA+REBOVC.

§No confidence interval since only one surviving animal and statistical significances were not analyzed.

TABLE 2. Variables of End-Organ Injury in Anesthetized Pigs Subjected to Either REBOA or a Combination of REBOA and REBOVC in Normovolemia and in Hemorrhagic Shock

Variable	Baseline	1 h Reperf.	3 h Reperf.
P-Alanine aminotransferase (μkat/L)			
Normovolemia + REBOA	1.2 (1.0–1.5)	1.2 (1.0–1.5)†	1.5 (1.2–1.8)*,†
Normovolemia + REBOA+REBOVC	1.4 (1.1–1.8)‡	1.4 (1.2–1.7)‡	1.9 (1.5–2.2)*
Hemorrhagic shock + REBOA	0.9 (0.7–1.2)	1.0 (0.5–1.4)†	1.3 (0.8–1.7)†
Hemorrhagic shock + REBOA+REBOVC	1.1 (0.9–1.3)‡	1.0 (0.8–1.2)‡	0.9§
P-Aspartate aminotransferase (μkat/L)			
Normovolemia + REBOA	1.0 (0.7–1.3)	1.7 (1.3–2.4)	3.0 (2.5–3.6)†
Normovolemia + REBOA+REBOVC	1.1 (0.8–1.5)	1.6 (1.1–2.2)	2.8 (2.4–3.3)
Hemorrhagic shock + REBOA	1.1 (0.7–1.6)	1.9 (1.0–3.3)	6.3 (1.7–23.0)†
Hemorrhagic shock + REBOA+REBOVC	0.9 (0.7–1-2)	1.8 (1.2–2.6)	4.0§
P-creatinine (μmol/L)			
Normovolemia + REBOA	57 (54–60)	82 (77–88)†	101 (84–118)†
Normovolemia + REBOA+REBOVC	54 (49–59)	78 (71–86)‡	96 (83–109)
Hemorrhagic shock + REBOA	56 (46–66)	98 (77–120)†	138 (112–165)†
Hemorrhagic shock + REBOA+REBOVC	56 (45–68)	91 (79–103)‡	115§
Diuresis (mL/h)			
Normovolemia + REBOA	23 (8–70)	16 (4–66)*,†	17 (2–129)†
Normovolemia + REBOA+REBOVC	14 (1–185)	1 (0–21)*	8 (0–314)
Hemorrhagic shock + REBOA	31 (12–78)	1 (0–10)†	0 (0–0)†
Hemorrhagic shock + REBOA+REBOVC	51 (33–80)	2 (1–3)	1§
P-Tropinine I (μg/L)			
Normovolemia + REBOA	0.6 (0.2–1.6)†	4.3 (2.3–8.1)†	10.4 (6.6–16.5)†
Normovolemia + REBOA+REBOVC	1.1 (0.5–2.5)	4.8 (3.0–7.9)	12.4 (8.2–18.8)
Hemorrhagic shock + REBOA	1.8 (1.2–4.6)**,†	10.1 (6.6–15.4)**,†	26.9 (12.9–56.1)†
Hemorrhagic shock + REBOA+REBOVC	0.6 (0.2–1.5)**	4.6 (1.6–13.1)**	28.6§
Histological mucosal damage score			
Normovolemia + REBOA	na	na	5 (4–6)
Normovolemia + REBOA+REBOVC	na	na	5 (2–5)

Number of animals in each group at start of reperfusion: Normovolemia + REBOA (n = 7), Normovolemia + REBOA+REBOVC (n = 6), Hemorrhagic shock + REBOA (n = 6) and Hemorrhagic shock + REBOA+REBOVC (n = 6).

*Statistically significant difference during normovolemia between REBOA and REBOA+REBOVC.

**Statistically significant difference during hemorrhagic shock between REBOA and REBOA+REBOVC.

†Statistically significant difference between normovolemia and hemorrhagic shock with REBOA.

‡Statistically significant difference between normovolemia and hemorrhagic shock with REBOA +REBOVC.

§No confidence interval since only one surviving animal and statistical significances were not analyzed.

Hemorrhage

Hemorrhage caused circulatory shock with low MAP and CO (Fig. 2), and metabolic lactic acidosis with a small increase in plasma potassium concentration (Figs. 3*A*, *C*).

Occlusion

During occlusion, MAP and CO were higher in the REBOA groups compared to the REBOA+REBOVC groups in both normovolemia and hemorrhagic shock ($p < 0.05$, Fig. 2*A–B*). Central venous pressure was higher in the REBOA groups compared with the REBOA+REBOVC groups in both normovolemia and hemorrhagic shock ($p < 0.05$, Fig. 2*C*). Mesenteric vein pressure was higher in the REBOA+REBOVC group than in the REBOA group during hemorrhagic shock ($p < 0.05$, Fig. 2*D*).

In all groups, the arterial lactate concentration increased, with the arterial lactate concentration being lower in the REBOA+REBOVC group compared with the REBOA group in normovolemia ($p < 0.05$, Fig. 3*B*).

Reperfusion

When deflating the REBOVC, MAP immediately increased (data not shown). On deflation of the REBOA, MAP decreased, CVP and MVP increased in all groups, and CO increased in the REBOA+REBOVC groups (Fig. 2). During reperfusion, there were no statistically significant differences in MAP, CVP, and MVP between the groups. After 60 minutes of reperfusion, there were no statistically significant differences in CO between the REBOA and the REBOA+REBOVC groups (Fig. 2*B*).

Hemorrhagic shock and REBOA+REBOVC were associated with higher arterial lactate and potassium concentrations at the end of reperfusion ($p < 0.05$, Fig. 3). Additionally, in normovolemia, the arterial pH was lower in the REBOA

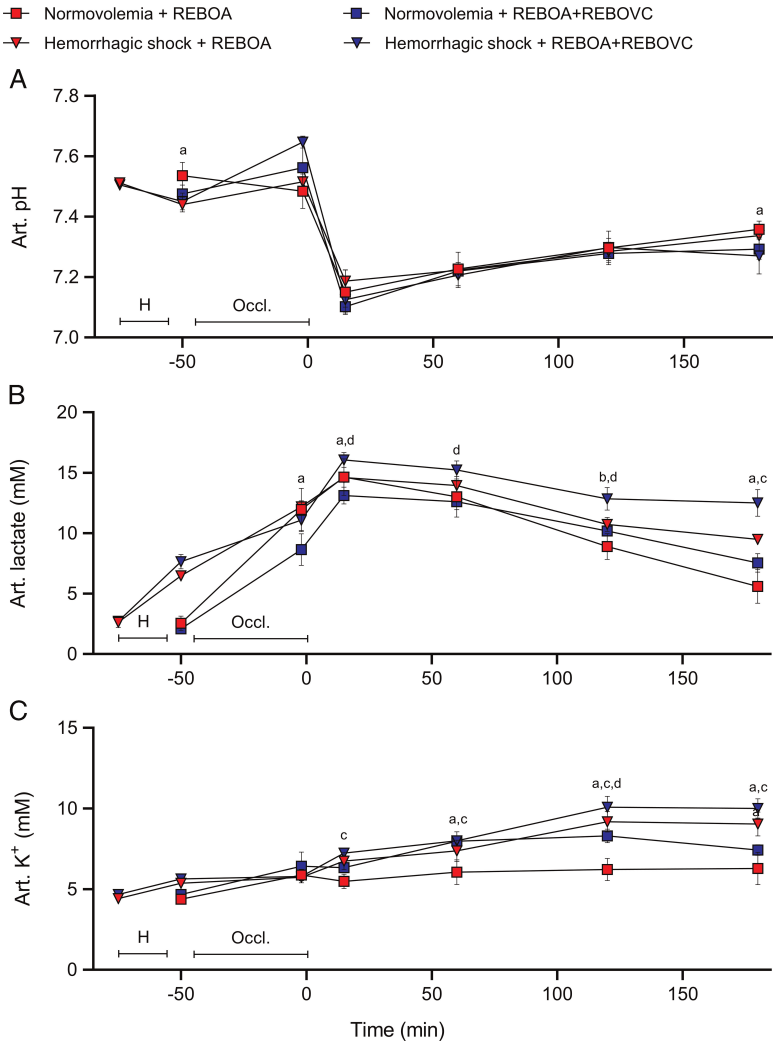

Figure 3. Systemic arterial pH (*A*) lactate concentration (*B*) and potassium concentration (K+, *C*) in anesthetized pigs subjected to either REBOA or a combination of REBOA and REBOVC for 45 minutes in normovolemia and hemorrhagic shock (H) followed by 3 hours of reperfusion and resuscitation. Number of animals in each group at start of reperfusion: Normovolemia + REBOA (n = 7), Normovolemia + REBOA+REBOVC (n = 6), Hemorrhagic shock + REBOA (n = 6) and Hemorrhagic shock + REBOA+REBOVC (n = 6). (*A*), Statistically significant difference during normovolemia between REBOA and REBOA+REBOVC, (*B*) Statistically significant difference during hemorrhagic shock between REBOA and REBOA+REBOVC, (*C*) Statistically significant difference between normovolemia and hemorrhagic shock with REBOA, (*D*) Statistically significant difference between normovolemia and hemorrhagic shock with REBOA +REBOVC. (*B*) and (*D*), significances are not analyzed at the last time point due to low number of surviving animals in hemorrhagic REBOA+REBOVC. Data are means and 95% confidence intervals.

+REBOVC group compared with the REBOA group ($p < 0.05$, Fig. 3*A*).

End Organ Damage

At baseline, there were some statistically significant differences between the groups (Table 2). During reperfusion, the plasma concentration of AST increased in all groups and was higher in the hemorrhagic shock REBOA group compared with the normovolemic REBOA group ($p < 0.05$, Table 2). Plasma concentration of creatinine increased steadily during reperfusion in all groups and was higher in the hemorrhagic shock groups compared with their normovolemic equivalents ($p < 0.05$, Table 2). In the normovolemic REBOA and REBOA+REBOVC groups, all small bowel specimens showed significant signs of microscopic ischemic intestinal mucosal damage, but there were no statistically significant differences between the groups (Table 2; the hemorrhagic shock groups were not analyzed because of the low number of survivors at the end of reperfusion).

DISCUSSION

In a previous study, we found that REBOA in zone 1 can make it hemodynamically possible to use a suprahepatic REBOVC during normovolemia for a short occlusion time of 5 minutes.[26] In the present study, we have shown that acceptable hemodynamic stability and survival can be attained during 45 minutes occlusion of REBOA+REBOVC, although the long duration of occlusion caused compromised hemodynamics and

metabolism in the REBOA+REBOVC groups compared with the REBOA groups. Controlled femoral artery bleed without tissue injury is different from a clinical scenario with retrohepatic injury, but the aim was to simulate a clinical scenario of severe hemorrhagic shock with an intact, immobilized liver, during which the effects of REBOA +/− REBOVC were investigated.

REBOA in zone 1 alone may temporarily decrease bleeding from abdominal veins through a significant influence on truncal perfusion pressure.[22] Using phase contrast magnetic resonance imaging, Izawa et al.[29] recently showed significantly decreased blood flow in the portal vein, IVC and hepatic veins, and a supranormal increase of the superior vena cava blood flow, due to collaterals from the lower body, during aortic occlusion. Berkenstadt et al.[17] reported that aortic occlusion results in "splanchnic venous vasculature collapse" causing a retrograde venous flow from the abdomen to the body region above the aortic occlusion, resulting in a twice as high blood flow in the upper body region. Venous clamping without concomitant arterial clamping may cause irreversible negative effects on the intestinal mucosa, but arterial inflow occlusion is known to provide relative protection against the hydrostatically-induced aggravation of inflammation caused by mesenteric venous outflow occlusion.[30] In the present study, REBOA counteracted the venous pooling in the splanchnic circulation since MVP was unchanged during occlusion in the REBOA+REBOVC groups. The impact of potential collateral arterial blood flow bypassing the REBOA, such as through the internal thoracic artery, the artery of Adamkiewicz and other medullar and lumbar arteries, is still not completely understood, but the potential contribution to venous pooling must be considered.[31] Interestingly, recent findings by Hoehn et al.[32] questioned the significance of both antegrade and retrograde arterial collateral blood flow during REBOA.

Suprahepatic outflow occlusion above the hepatic veins, the REBOVC in this study, is part of total hepatic vascular isolation, to prevent venous backflow from the right atrium, bleeding from the hepatic veins or the collateral inferior phrenic veins.[20,33] Considering the purpose of this study and to simplify the model, we did not include an infrahepatic occlusion even though it should be part of total hepatic vascular isolation. We believe using infrahepatic REBOVC in combination with suprahepatic REBOVC would not change the hemodynamics and metabolic insult significantly. However, using only infrahepatic REBOVCs, for example, in infrahepatic IVC injuries, thus allowing a continuous splanchnic venous return would be circulatory and metabolic beneficial compared with suprahepatic REBOVC. Pigs do not have portosystemic venous collateral channels to the same extent as humans, nor do they have an azygous vein.[19] This difference makes pigs more vulnerable to hepatic vascular exclusion than humans and is important to remember when interpreting results from porcine experimental studies. We opted not to include the Pringle maneuver in this study, to avoid interactions on hemodynamics from the Pringle maneuver, since the main aim was to investigate the effects of REBOVC in resuscitated and noncompensated hemorrhagic shock. A bleeding retrohepatic vascular injury model, properly randomized, with REBOA + suprahepatic and infrahepatic REBOVC + open Pringle maneuver would be an interesting follow up study. During the Pringle maneuver, a 10% residual blood inflow remains in the liver, by backflow perfusion from suprahepatic vena cava via the hepatic veins.[34,35] However, if the hepatic veins are simultaneously occluded by a REBOVC, this residual perfusion is blocked and the ischemic impact on the liver will probably be more severe. Open hepatic veins may thereby have a cytoprotective effect on liver cells during inflow occlusion. On the other hand, open hepatic veins may increase the risk of retrohepatic bleeding and air embolization.[34–36]

The known physiological effects of REBOA, for example, increased SBP and centralization of blood volume, are modified with concomitant REBOVC. Several mechanisms may explain the difference in the hemodynamic and metabolic responses between REBOA and REBOA+REBOVC shown in the study. First, the REBOVC obstructs the emptying of the venous reservoir created by the REBOA. Instead, venous blood is trapped distal to the REBOVC, thus preventing centralization of blood volume. It is, therefore, important to inflate the REBOVC after the REBOA.[17] Second, ischemic tissue distal to the REBOA produces vasoactive substances, such as angiotensin and catecholamines.[37,38] Deflation of the REBOVC before the REBOA increased the SBP (data not shown), probably due to release of the stagnated blood volume and trapped vasoactive substances. Consequently, deflation of the REBOVC before the REBOA may provide endogenous circulatory support to the reperfusion shock initiated when the REBOA is deflated.[39] Third, accumulative venous pooling via collaterals to the lower body cannot be excluded. Furthermore, we experienced that exact positioning of the REBOVC above the most cranial hepatic vein and sufficient balloon inflation were necessary for complete suprahepatic IVC control. In contrast to the stiff aortic wall, the venous walls are more resilient, especially at the level of the confluence. Moreover, the distance between the right atrium and the confluence is short. Therefore, a short and very compliant balloon was used for complete venous occlusion.

We found a slow cardiovascular deterioration in both the REBOA+REBOVC groups during the 45-minute occlusion, most pronounced in the hemorrhagic shock REBOA+REBOVC group. On the other hand, in the REBOA groups, SBP and CO increased during the occlusion period. This difference may reflect the modification of the REBOA response by REBOVC. Importantly, the circulatory and metabolic deterioration during occlusion and reperfusion in the REBOA+REBOVC was clearly aggravated by hemorrhagic shock. Obviously, there were differences in survival (although not statistically significant) between the groups at 3 hours of reperfusion. From the survival curve, it seems that the major difference lies between the normovolemic and hemorrhagic shock group and the combination of hemorrhagic shock and REBOA+REBOVC. Strikingly, the survival was similar at 3 hours of reperfusion in the normovolemic groups, that is, the addition of REBOVC to REBOA in normovolemia was not detrimental. By design, the present experimental protocol did not include resuscitation with volume or vasopressors during the occlusion period. Still, most of the animals survived more than 120 minutes reperfusion, even after severe hemorrhagic shock. The present study suggests that, regardless of whether REBOA or REBOA+REBOVC is used, sufficient resuscitation during occlusion is needed for optimal outcome during the postocclusion period. Indeed, we interpret these findings as if REBOA+REBOVC is applied and the

hemorrhagic shock is early (during occlusion) and adequately resuscitated (i.e., the normovolemic groups), the survival probably would have been much better in the hemorrhagic groups. Considering the high early mortality rates of retrohepatic vascular injuries, there may be a potential clinical use of REBOA +REBOVC to temporarily and initially stabilize patients until definitive surgical treatment can be performed.

The REBOVC deflation caused a temporary increase in SBP, followed by a dramatic decrease after REBOA deflation in parallel with lactic acidosis and hyperkalemia. In the hemorrhagic shock groups, three pigs (two in the REBOA group, one in the REBOA+REBOVC group) had potassium concentrations above 10 mM at the end of reperfusion not explainable by a decline in pH since the pH was constantly improving during the reperfusion. A plausible explanation could be the ischemic insult caused by a combination of hemorrhagic shock and hypoperfusion due to REBOA. During reperfusion, potassium and ischemic metabolites from necrotic cells and the gastrointestinal tract were reintroduced into circulating blood.[39] The reperfusion, rather than the ischemia itself, may cause a more pronounced microscopic mucosal gut injury, known to increase bacterial translocation and release of endotoxins.[30] Return of cardiotoxic metabolites to the heart can potentially cause ventricular fibrillation and cardiac arrest.[30,40]

End-organ damage markers, such as troponin I, transaminases and P-creatinine, were all increased at the end of reperfusion, especially in the hemorrhagic shock groups. Since the normovolemic REBOA+REBOVC group did not show the same high levels, the primary cause of end-organ damage was probably not the REBOVC itself, but rather hemorrhagic shock induced cardiac, liver, and kidney ischemia. However, this interpretation cannot be confirmed because of the loss of animals in the later part of the reperfusion. Importantly, the main differences seem to be between the normovolemic and the hemorrhagic shock groups, rather than between the REBOA and REBOA+REBOVC. This indicates that the harmful effects may be due to the REBOVC to a lesser extent than the hemorrhagic condition and lack of resuscitation in our study.

The potential clinical use of REBOVC may be in selected trauma patients where major retrohepatic vessel injury is suspected. Achieving proximal and distal control before entering the site of injury is a well-known rule in vascular surgery. Ideally, the endovascular balloons are positioned before the laparotomy, guided by fluoroscopy in the operating room, before the incision. We believe such a hybrid solution possibly facilitate the surgical management of the injury by operating in a field of less bleeding and decrease the need for blood transfusions.

The study had some limitations. First, the 45-minute occlusion time is longer than recommended for REBOA in clinical praxis and may have provoked more serious injury than in a normal clinical scenario. Second, in both hemorrhagic groups, there was a significant, nonrandom loss of animals. This has implications for the statistical analysis and interpretation of the results, especially in the later parts of the reperfusion. Third, 180 minutes monitoring period may seem a short time. However, most animals either clearly stabilized and survived or deteriorated and died within the time limit. Moreover, considering the high early mortality rate for retrohepatic injuries, 3-hour survival may still be considered acceptable in an experimental animal study.[5] Fourth, no statistically significant differences were found in survival between the groups. This is probably because of the lack of power for such an analysis, which must be considered when interpreting the results.

In conclusion, acceptable hemodynamic stability can be achieved by REBOA+REBOVC with adequate resuscitation for a clinically relevant duration of occlusion. However, the greater hemodynamic and metabolic impacts in the REBOA +REBOVC groups compared with the REBOA groups must be considered. No major difference in end-organ damage was observed between the two REBOA groups compared with the two REBOA+REBOVC groups. Although not statistically significant, the indicated difference in survival observed in the late reperfusion phase, in the hemorrhagic shock groups and most dramatically in the REBOA+REBOVC group, demands further studies on the topic before clinical use.

AUTHORSHIP

M.B.W., M.S., T.M.H., K.F.N. designed and planned the study. M.B.W., M.S., A.S.H., and K.F.N. performed the experiments, analyzed, and interpreted the data. C.K. analyzed and interpreted the histological specimens. M.W., M.S. and K.F.N. wrote the draft manuscript. All authors critically revised the manuscript and approved the final version.

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DISCLOSURE

The authors declare no conflicts of interest.

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