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Blood pressure–targeted stepwise resuscitation of hemorrhagic shock in a swine model

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ABSTRACT

Background: Prolonged hemorrhagic shock and subsequent resuscitation frequently results in hemodynamic compromise. This study was designed to investigate the hemodynamic effect of the stepwise increase of blood pressure during initial resuscitation.

Materials and methods: Fifteen anesthetized male pigs (35 ± 5 kg) were used. Hemorrhagic shock was induced by losing 40% of estimated blood volume over 40 min and 10% of estimated blood volume over 20 min through the femoral artery and was maintained at a mean arterial pressure (MAP) of 30 ± 3 mm Hg for 2.5 h. The resuscitation of the rapid resuscitation (RR) group was targeted to reach MAP of 70 ± 5 mm Hg immediately by transfusion of shed blood via the femoral artery. The resuscitation of the pressure-targeted stepwise resuscitation (PSR) group was targeted to increase MAP by 10 mm Hg every 10 min up to 70 mm Hg, and then, the MAP was maintained at 70 ± 5 mm Hg until transfusion of the entire shed blood.

Results: During the initial resuscitation period of 30 min, the heart rate was significantly lower in the RR group than in the PSR group ($P < 0.05$), and mixed venous oxygen saturation was significantly higher in the RR group than in the PSR group during the 30 min of initial resuscitation ($P < 0.05$). After 2 h of resuscitation, cardiac output and stroke volume were significantly higher in the PSR group than in the RR group ($P < 0.05$), and the systemic vascular resistance was significantly lower in the PSR group than in the RR group ($P < 0.05$).

Conclusions: A stepwise increase of blood pressure compared with rapid normalization improves hemodynamic parameters in the swine hemorrhagic shock model.

Introduction

Severe prolonged hemorrhagic shock results in myocardial ischemia and resuscitation with fluid and blood products increases ischemia–reperfusion injury to the myocardium leading to cardiac dysfunction and failure. This contributes to hemodynamic compromise and subsequent multiple organ dysfunction and mortality.[1-4]

This study was presented at 38th annual conference on shock in June 2015.

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In trauma patients with uncontrolled bleeding, delayed fluid resuscitation or hypotensive resuscitation has been suggested to decrease blood loss before definite bleeding control.[5,6] Although delayed or hypotensive resuscitation can reduce the loss of blood and prevent clot dislodging, prolonged hypotensive resuscitation leads to tissue hypoxia,[7,8] and it can contribute myocardial dysfunction.[7] Thus, an optimal strategy for reducing cardiac dysfunction in patients with prolonged hemorrhagic shock may be needed.

During ischemic period, cells undergo anaerobic metabolism, and adenosine triphosphate is depleted. As a consequence, lactic acidosis is developed, and intracellular sodium and calcium ions are accumulated. During reperfusion period, sudden restoration of blood flow can result in washout of extracellular protons and accelerate intracellular calcium accumulation. It has been reported that intracellular acidosis during ischemic period is somewhat protective for cellular ischemic injury. Thus, slow reperfusion may be more protective than rapid reperfusion in ischemic cells or tissues. Previously, it was reported that staged reperfusion by increasing the coronary perfusion pressure in a stepwise fashion after coronary ischemia decreased myocardial dysfunction and the effect of staged reperfusion was abolished by sodium bicarbonate.[9] Thus, delayed recovery of acidosis by staged reperfusion was proposed as a protective mechanism. In addition, our group reported that stepwise resuscitation in a hemorrhagic shock model of rats increased survival time and decreased organ injury.[10] Thus, it can be applied to reduce postresuscitation myocardial dysfunction in prolonged severe hemorrhagic shock.

This study was designed to test whether stepwise resuscitation could decrease myocardial dysfunction in a prolonged hemorrhagic shock model of pigs.

Materials and methods

Animal preparation

This study was approved by the Animal Care and Use Committee of our hospital (IACUC No. BA1308-135/078-01) and was conducted in accordance with the guide for the care and use of laboratory animals of the National Institute of Health.[11]

Male, crossbreed, Yorkshire-X domestic pigs (Sus scrofa; age 3-4 months old; average weight of 36.5 kg, range 34.0-38.7 kg) were used for the experiments. The pigs were housed for at least 1 week before the experiment in a controlled environment, which includes 12/12-h light/dark cycle, temperature of 18°C-22°C, humidity of 30%-50% and free access to water and food. Before the experiment, the animals were fasted overnight but were allowed water *ad libitum*.

Anesthesia and instrumentation

Anesthesia was induced with intramuscular injection of atropine (0.05 mg/kg), followed by zoletil (5 mg/kg, Virbac, France) and xylazine (4 mg/kg, Bayer, Korea). After induction of anesthesia, pigs were intubated with a 7.5 endotracheal tube and were mechanically ventilated. The mechanical ventilator (Dräger Fabius GS, Lübeck, Germany) was set to maintain normocapnia. The detailed setting was as follows: FiO_2, 0.21; positive end-expiratory pressure, 10-cm H_2O; tidal volume, 8 mL/kg; respiratory rate, 10-12 breaths/min; inspiratory:expiratory ratio = 1:1.5; peak airway pressure < 40-cm H_2O. The minute ventilation was adjusted to maintain arterial PCO_2 = 35-40 mm Hg after blood gas analysis. Anesthesia was maintained using 1%-2% sevoflurane (Baxter Inc, IL) in combination with medical air, and the dose of anesthetics was not changed throughout the experiment because it can compromise the hemodynamic variables. A 21-gauge intravenous catheter was inserted into an ear vein, and 0.9% saline was administered at a rate of 10 mL/h as a maintenance fluid. Electrocardiogram, capnography, and pulse oximetry (Philips Patient Monitor MP20, Netherlands) were continuously monitored. A Rectal temperature probe was inserted, and body temperature was maintained at 36.5°C-37.5°C using thermal pads.

Under ultrasound-guidance, 6-French introducer catheters (Merit medical, UT) were inserted into right femoral artery for blood pressure monitoring and into left femoral artery for blood withdrawal and infusion. A balloon-tipped thermodilution catheter (Model 131HF, 7Fr. Edwards Lifesciences, CA) was inserted into the right femoral vein and connected to patient monitor (Philips Patient Monitor MP20, Netherlands) to measure central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary artery occlusive pressure, and cardiac output (CO). The mixed venous oxygen saturation ($SmvO_2$) was measured using blood gas analyzer (Critical Care Xpress, Nova Biomedical, MA).

Experimental protocol

Figure 1 shows the experimental protocol. Baseline data were collected before hemorrhage. Modified pressure-controlled hemorrhagic shock was performed. Briefly, hemorrhagic shock was induced by losing 40% of the estimated total blood volume (total blood volume was estimated by body weight, i.e., 70 mL/kg) over 40 min and then losing 10% over 20 min through the left femoral artery using a MasterFlex pump, Model L/S Easy-Load II Pump head, Model 77201-60 (Cole—Parmer Instruments, Vernon Hills, IL). Shock was maintained at 30 ± 3 mm Hg for 2.5 h by additionally removing or retransfusing 50 mL blood every 15 min. Blood was collected in standard citrate-phosphate-dextrose blood bags (BSDC-NP-SB3 S320, Greencross MS, Korea) and was stored at room temperature. During hemorrhagic shock, maintenance fluid was stopped.

After 3.5 h of hemorrhagic shock, pigs were allocated to one of two groups (rapid resuscitation [RR] group [$n = 8$] *versus* pressure-targeted stepwise resuscitation (PSR) group [$n = 7$]). In the RR group, pigs were resuscitated with a rapid infusion of shed blood via the left femoral artery to reach a mean arterial pressure (MAP) of 70 ± 5 mm Hg immediately using the MasterFlex pump. The PSR group was resuscitated by increasing the MAP by 10 mm Hg every 10 min up to 70 mm Hg, and then maintaining at 70 ± 5 mm Hg until the remaining shed blood was transfused. The target MAP in each step in the PSR group was tried to maintain by transfusion and withdrawal of blood during 10-min interval. No additional fluid was administered to reach the target MAP value even if the target MAP was not achieved by transfusion of shed blood. Pigs were observed and