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Ideal target arterial pressure after control of bleeding in a rabbit model of severe traumatic hemorrhagic shock: results from volume loading-based fluid resuscitation

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ABSTRACT

Background: Previously reported ideal target mean arterial pressure (MAP) after control of bleeding in traumatic hemorrhagic shock (THS) requires further verification in more clinically related models. The authors explored this issue via gradient volume loading without vasopressor therapy. As certain volume loading can induce secretion of atrial natriuretic peptide (ANP), which has been shown to be protective, the authors also observed its potential role.

Materials and methods: Fifty male New Zealand rabbits were submitted to 1.5 h of uncontrolled THS (with another eight rabbits assigned to the sham group). After bleeding control, treated rabbits were randomly (n = 10, respectively) resuscitated with blood and Ringer lactate (1:2) to achieve target MAP of 50, 60, 70, 80, and 90 mm Hg within 1 h. During the following 2 h, they were resuscitated toward baseline MAP. Rabbits were observed until 7 h.

Results: After resuscitation, infused fluid was lower and oxidative stress injury was milder in the 70 mm Hg group. Fluid volume loaded during the initial hour after hemostasis was negatively correlated with pH, oxygen saturation, and base excess at the end of resuscitation. It also correlated positively with proinflammatory responses in bronchoalveolar lavage fluid at 7 h and 7-h mortality. Moreover, after volume loading, the 80 mm Hg group showed significantly increased serum ANP level, which correlated with the expression of Akt protein in the jejunum at 7 h.

Conclusions: In rabbits the ideal target MAP during the initial resuscitation of severe THS after hemostasis was 70 mm Hg. ANP may have a critical role in gut protection.

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1. Introduction

Despite the significant advances in trauma resuscitation, hemorrhage continues to be the leading cause of preventable death, with peak mortality occurring within 6 h of admission [1,2]. The ideal approach to the comprehensive management of traumatic hemorrhagic shock (THS) immediately after control of bleeding is still based on experience or low quality of evidence.

Fortunately, the ideal target mean arterial pressure (MAP) in the early goal-directed resuscitation of THS after control of bleeding was recently investigated by Li *et al.* [3]. In their rat model, resuscitating to MAP of 70 mm Hg after bleeding control improved hemodynamics, oxygen delivery, and organ function, with increased 12-h survival when compared with MAP of 50 and 90 mm Hg. To some extent, their results mirror the guideline recommendations for early goal-directed resuscitation in septic shock in which a MAP of 65–70 mm Hg should be goaled [4]. However, the results from Li *et al.* should be further supported in more clinically related models. More importantly, whether target MAP of 60 or 80 mm Hg would result in a better outcome remains unknown because they did not design such comparative groups.

Vasopressors have not been giving higher recommendations for use in resuscitation of THS because of low evidence [5]. However, without vasopressors, patients with severe trauma would receive massive infusion for maintaining tissue perfusion. This has led us to concern the influence of an old hormone serum atrial natriuretic peptide (ANP) because its secretion is consistently linked to the extent of volume stimulus within the heart [6]. ANP is composed of 28 amino acid residues and secreted mainly from atrial myocytes. Apart from its blood pressure lowering, natriuretic, and diuretic properties, ANP has been shown to be protective. Exogenous ANP treatment has proven effective to inhibit inflammation and protect the lung and kidney in animal models of sepsis, acute lung injury, and renal ischemia–reperfusion injury [7–10]. In addition, ANP has been shown to mediate antiapoptosis in rat cardiomyocyte through cyclic guanosine monophosphate-dependent nuclear accumulation of serine/threonine kinase Akt [11]. Gut function may also be protected because the intestinal tract is a target organ for ANP [12]. Unfortunately, in THS, data regarding the effect of volume loading on ANP secretion and its role has not been explored. Whether ANP secretion in THS is associated with cytoprotection remains unknown. Thus, we reassessed the ideal target MAP by large amounts of fluid loaded in a rabbit model without vasopressor therapy. Our results support 70 mm Hg as the ideal target MAP. Additionally, we found that ANP correlated well with gut Akt expression. We suggest that serum ANP may play a role in gut protection.

2. Materials and methods

2.1. Animals

All procedures were in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. Special care was taken to minimize suffering of animals. Male New Zealand rabbits weighting about 2 kg were obtained from the Animal Center of Zhejiang Academy of Medical Sciences, Hangzhou, China. They were fasted overnight but had free access to water before the experiment.

2.2. Surgical preparations

Animals were anesthetized with urethane (1 g/kg, intravenous). Additional doses (0.2 g/kg, intravenous) were given as necessary to avoid distress. Because urethane has minimal influence on the respiratory system [13], mechanical ventilation was not considered but a tracheal tube was inserted to allow unhindered respiration. Rectal temperature (RT) was monitored continuously and maintained at 38.0 ± 0.5°C during preparation. A double-lumen catheter was inserted into the bladder to monitor urine output. A 20-gauge Angiocath (Becton-Dickinson, Sandy, UT) was inserted via the right carotid artery for bloodletting, blood sampling, and pressure monitoring. Blood pressure was monitored on a polygraph (PM-9000; Shenzhen Mindray Bio-Medical Electronics Co, Ltd, Shenzhen, China). The right jugular vein vas cannulated for fluid resuscitation. A 6-cm midline laparotomy was performed and one branch of the ileocecal artery was isolated. Afterward, a 2-0 nylon suture was placed running through the edges of the laparotomy. Animals were stabilized until 2 h after anesthesia.

2.3. Experimental procedure

The study was based on our previous animal model (Fig. 1) [14]. The animal study was divided into three phases as follows: phase 1, uncontrolled THS (0–1.5 h); phase 2, resuscitation (1.5–4.5 h); and phase 3, observation (4.5–7 h). Fifty male New Zealand rabbits were submitted to 1.5 h of uncontrolled THS, with another eight rabbits assigned to the sham group. Animals in the sham group were not hemorrhaged or resuscitated.

During phase 1, unilateral closed tibia fractures were created through quantitative attack. Then hemorrhage was induced at 0 h by bloodletting (usually took 20 min) from the carotid artery until MAP decreased to 20 mm Hg, which was maintained until 0.5 h. Shed blood was stored in anticoagulant citrate dextrose solution, which would be fully retransfused during resuscitation. Uncontrolled hemorrhage was initiated at 0.5 h by penetrating to the prepared artery branch with a 25-gauge syringe needle (outer diameter: 0.51 mm). During 0.5–1.5 h, rabbits received hypotensive resuscitation with lactate Ringer solution (LR) at 1.7 $mL \cdot kg^{-1}$ min^{-1} until MAP rose to 40 mm Hg. Meanwhile, alcohol was sprayed onto the abdominal skin to reduce RT. This was to mimic hypothermia that usually happens during anesthesia, transfusion, and surgery in the operating room. However, RT during hypothermia was controlled stable.

At 1.5 h, the bleeding vessel was ligated and intra-abdominal blood loss was collected. Treated animals were