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The effects of hemorrhagic shock secondary to hepatectomy in a swine model

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ABSTRACT

Background: Ischemia–reperfusion injury caused by severe hemorrhagic shock and subsequent resuscitation leads to deterioration of hepatic homeostasis and possibly to liver failure. The present study focuses on determining whether there is a different biological response to hemorrhagic shock by different sources of hemorrhage, hepatic hemorrhage (HH) *versus* peripheral hemorrhage.

Methods: Twenty-one male swine (Sus scrofa domesticus) were randomly allocated in three groups as follows: sham group (S, $n = 5$), central venous hemorrhage group, (CVH) ($n = 8$), and HH group ($n = 8$). Hepatectomy of the left liver lobe was carried out in groups CVH and HH, and the animals were subjected to controlled bleeding from the internal jugular vein and the traumatic liver surface, respectively. After 10 min of hemorrhage, shock was maintained for 30 min at mean arterial pressure levels of 30 mm Hg–40 mm Hg and resuscitation was initiated with crystalloids and colloids. Hemodynamic parameters and fluid balance were monitored throughout the 6 h of total duration of the experiment. Blood samples were collected at 0-, 40-, and 360-min time points for transaminases, albumin, and interleukin-6 measurement. Hepatic tissue was harvested at the end of the experiment for oxidative marker and proliferation analysis.

Results: Although blood loss was comparable between the two groups, the amount of fluids needed for resuscitation was higher for the HH group. Inflammatory response, measured by interleukin-6, was found higher in HH group. Oxidative stress markers did not reveal statistically significant difference between the two groups. Liver hemorrhage decreased hepatocellular proliferation measured by proliferating cell nuclear antigen.

The authors A.I.M. and N.F.O. declare equal contribution to the writing of this article.

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Conclusions: Our study provides evidence that HH entails worse consequences for the hepatocytes than systemic hemorrhage. Higher needs for resuscitation fluids, decreased proliferation, and augmented inflammatory response when HH takes place are findings with possible clinical importance in liver surgery and trauma.

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1. Introduction

Hemorrhagic shock (HS) affects the liver [1] in a bimodal way through ischemia and reperfusion [2] causing injury that eventually leads to organ failure [3]. Research has been made to elucidate the different effects of cold ischemia (transplantation), warm low flow ischemia (HS), and warm no-flow ischemia (hepatic vascular occlusion) [4]. However, no data have been published to verify whether there is any difference in how the liver responds to hemorrhage caused by the organ itself, as opposed to hemorrhage by a remote site. The purpose of the present experimental study was to investigate whether HS caused by visceral hemorrhage, during liver trauma or liver surgery, has different biological consequences than HS caused by an extra-abdominal source.

2. Materials and methods

2.1. Animals and preparation

The study protocol has been approved by the Ethical Committee of Aretaieion Hospital, University of Athens (Σ-27, 17/02/09) and by the Hellenic Veterinary Services (license No 1376/24-6-2009). The animals were transported 1 wk before experimentation to the research facility (Experimental Research Center ELPEN, European Ref Number EL 09 BIO 03). Twenty-one male pigs weighing approximately 30 kg were purchased from the same breeder (Validakis, Koropi, Greece) and were fed the same food. The animals were fasted the day before the experimentation, but they had free access to water.

2.2. Anesthesia and study design

The swine were premedicated with intramuscular midazolam (Dormicum, Roche, Hellas) 0.5 mg/kg, ketamine (Ketamin-Actavis, IFET, Palini, Attiki, Hellas) 15 mg/kg, and atropine (Atropine sulfate, Demo, Hellas) 0.045 mg/kg. Anesthesia was induced via an auricular vein with propofol (Propofol; Fresenius Kabi, Graz-Puntigam, Austria) 3 mg/kg and fentanyl (Fentanyl, Janssen-Cillag, Belgium) 0.012 mg/kg and the trachea was intubated with an oral tracheal tube. After intubation, cisatracurium (Nimbex; GlaxoSmithKline, Parma, Italy) was administered at a dose of 0.5 mg/kg and the animals were placed on volume-controlled mechanical ventilation (Taema Clarys 2000, Antony, Cedex, France). Tidal volume ranged from 8–12 mL/kg and respiratory rate from 12–15 per min, both adjusted to maintain end-tidal CO_2 of 35 ± 5 mm Hg. Positive end-expiratory pressure was set to zero, inspiration to expiration duration was ½, and FIO_2 was 40%. Anesthesia was maintained with propofol 6–8 mg/kg/h, fentanyl, and cisatracurium at standard infusion rates adjusted to body weight. Temperature was monitored through a rectal probe and maintained at 38.0 ± 1.5°C using a heating pad.

The left femoral artery was cannulated with a 20G arterial catheter, and the left internal jugular vein was dissected and catheterized with a three-lumen catheter (Set Arrow International, Reading, PA). Both catheters were connected to pressure transducers (Transducer ICU Medical, San Clemente, CA) for continuous monitoring. A midline incision was carried out, and a Foley catheter was placed to the urinary bladder through cystostomy.

The animals were randomly allocated in three groups as follows: sham—group S ($n = 5$), central (internal jugular) venous hemorrhage—group (CVH) ($n = 8$), and hepatic hemorrhage—group (HH) ($n = 8$). For the group S animals, the abdominal wall was closed with a full thickness running silk No. 2 suture about 20 min after the cystostomy. After recording the baseline hemodynamic parameters, swine of groups CVH and HH were subjected to left hepatic lobe resection. The resection was technically identical in terms of resected liver mass, duration, parenchymal transection technique, and hemostasis. We transected the liver sharply using scalpel avoiding further parenchymal damage. During the left hepatic lobe excision, the animals were subjected to controlled bleeding either from the internal jugular vein (group CVH) or from the incisions of the left hepatic lobe itself (group HH), by applying manual pressure on the liver stump with the help of atraumatic intestinal clamps. Our technique ensured that liver bleeding in HH group animals was achieved without further parenchymal damage and was done with a steady rate, adjusted by mechanical pressure of the traumatic surface. Both groups were bled for 10 min until a mean arterial pressure of 35 ± 5 mm Hg was reached. At that time, hemostatic clamps were used to temporarily control the bleeding. The state of HS was maintained for 30 min. Additional bleeding was allowed when the mean arterial pressure exceeded the level of 40 mm Hg during the 30-min shock period. In both groups, shed blood was collected in volumetric containers after the suction from the operative field or the central venous catheter. No laparotomy pads were used but the operative field was isolated with a nonabsorbent drape, where all the shed blood was collected and carefully suctioned.

At the 40 min time point, the abdomen was reopened and bleeding from the traumatic surface of the liver was definitively controlled with polypropylene No 3-0 sutures. A cellulose gauze and electrocautery were used when capillary bleeding persisted. Any blood clots in the abdomen were added to the total suctioned blood volume. Simultaneously, fluid resuscitation was initiated in all animals for a duration of 60 min. During this period, swine received normal saline 0.9% (Demo S.A., Krioneri, Hellas) up to 35 mL/kg plus hydroxyethylstarch (HES) (Voluven 6%) up to 18 mL/kg (normal saline to HES ratio 2:1) until restoration of mean arterial pressure

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