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Microcirculatory alterations during haemorrhagic shock and after resuscitation in a paediatric animal model

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ABSTRACT

Background: Haemorrhagic shock is frequent in paediatric trauma patients and after cardiac surgery, especially after cardiopulmonary bypass. It has demonstrated to be related to bad outcome.
Objectives: To evaluate changes on microcirculatory parameters during haemorrhagic shock and resuscitation in a paediatric animal model. To determine correlation between microcirculatory parameters and other variables routinely used in the monitoring of haemorrhagic shock.
Methods: Experimental study on 17 Maryland pigs. Thirty minutes after haemorrhagic shock induction by controlled bleed animals were randomly assigned to three treatment groups receiving 0.9% normal saline, 5% albumin with 3% hypertonic saline, or 5% albumin with 3% hypertonic saline plus a bolus of terlipressin. Changes on microcirculation (perfused vessel density (PVD), microvascular blood flow (MFI) and heterogeneity index (HI)) were evaluated and compared with changes on macrocirculation and tisular perfusion parameters.
Results: Shock altered microcirculation: PVD decreased from 13.5 to 12.3 mm mm^{-2} ($p = 0.05$), MFI decreased from 2.7 to 1.9 ($p < 0.001$) and HI increased from 0.2 to 0.5 ($p < 0.001$). After treatment, microcirculatory parameters returned to baseline (PVD 13.6 mm mm^{-2} ($p < 0.05$), MFI 2.6 ($p < 0.001$) and HI 0.3 ($p < 0.05$)). Microcirculatory parameters showed moderate correlation with other parameters of tissue perfusion. There were no differences between treatments.
Conclusions: Haemorrhagic shock causes important microcirculatory alterations, which are reversed after treatment. Microcirculation should be assessed during haemorrhagic shock providing additional information to guide resuscitation.

Introduction

Haemorrhagic shock is an important cause of disease in children. It is frequent in trauma patients and after cardiac surgery, especially when cardiopulmonary bypass is used. Acute bleeding itself, but also fluid resuscitation and bleeding control strategies have been independently related to increased mortality and morbidity [1].

A decrease in the blood flow in the microcirculatory compartment has been described in hypovolemic shock and especially in haemorrhagic shock [2–7]. Excessive blood loss results in redistribution of blood volume to vital organs such as brain and heart from other organs. Decreased perfusion of splanchnic, renal, musculocutaneous or other microcirculatory regions may cause tissue hypoxia and activation of inflammatory response leading to multiorgan failure [3].

The effect of haemorrhagic shock on microcirculation has been previously studied showing that alterations are not only secondary to macrohemodynamic disturbances [5], but they also involve other factors including changes in endothelial cells, dysregulation of polymorphonuclear neutrophils activity [4] and alterations in structure and function of red blood cells [8].

Management of haemorrhagic shock is primarily focused on haemorrhage control through optimization of coagulation mechanisms and mechanical and surgical strategies. Secondly, treatment of haemorrhagic shock is directed to restore systemic perfusion.

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The most frequently used therapeutic goals in the clinical setting such as blood pressure, heart rate or cardiac output might only focus on macrocirculation, which is only a part of the whole problem. Microcirculatory status might sometimes be dissociated from macrohemodynamics, and thus, restoration of macrohemodynamics is not always followed by improvement in microcirculation [3,8–10].

Several studies have demonstrated that persistent microcirculatory alterations despite normalization of macrohemodynamic parameters are associated with worse outcome in adults in different clinical conditions [3,11,12]. Similarly, other studies have shown that microcirculation evaluation in patients with sepsis and septic shock is capable of detecting occult alterations of tissue perfusion, which might have prognostic value [9,13–17]. Therefore, restoration of microcirculation and tissue perfusion should be considered as a primary goal in the management of haemorrhagic shock.

There are only a few studies focusing on describing microcirculatory alterations in haemorrhagic shock and with the use of different therapeutic approaches in the paediatric patient [2,4,5,18].

It would be useful to determine what kind and what degree of microcirculatory changes are expectable during bleeding and after different therapeutic approaches. Coupling microcirculatory changes evaluated using a direct visualization technique as sidestream dark field imaging (SDF) to other parameters routinely used to evaluate macro- and microcirculation in the paediatric critical patient might help to guide treatment.

The main objective of the present study was to analyze microcirculatory effects of haemorrhagic shock and subsequent resuscitation using fluids and vasoactive drugs. The secondary objective was to determine correlation between microcirculatory and macrocirculatory parameters during haemorrhagic shock and volume resuscitation. The study protocol was approved by the Institutional Review Board for Animal Research.

Materials and methods

The experiments were performed in the Department of Experimental Medicine and Surgery of the Gregorio Marañón General University Hospital. Animal care was performed by qualified technicians supervised by veterinarians according to the Spanish laws on animal research. International guidelines for ethical conduct in the care and use of experimental animals were applied throughout the study.

Animal preparation

Seventeen healthy 2-to-3-month-old Maryland pigs (weight, 8.6 ± 1.2 kg) were used. After premedication with intramuscular ketamine (15 mg kg^{-1}) and atropine (0.02 mg kg^{-1}) and monitoring, anaesthesia was induced by intravenous boluses of propofol (5 mg kg^{-1}), fentanyl (5 mcg kg^{-1}) and atracurium (0.5 mg kg^{-1}). Ventilation was then maintained using a mechanical ventilator (Servo 900, Dräger, Lubeck, Germany) with a respiratory rate of 20 breaths min^{-1}, tidal volume of 10 mL kg^{-1}, FiO_2 of 40%, and positive end-expiratory pressure of 3 cm H_2O. Ventilation was adjusted to achieve a $PaCO_2$ between 35 and 45 mmHg (4.7 and 6 kPa). Sedation and muscle relaxation (propofol 10 mg kg^{-1} h^{-1}, fentanyl 10 mcg kg^{-1} h^{-1}, and atracurium 2 mg kg^{-1} h^{-1}, by continuous infusion) were maintained throughout the procedure.

Monitoring included ECG, peripheral oxygen saturation (Visconnet monitor, RGB, Madrid, Spain), respiratory volumes and pressures, and FiO_2 and $EtCO_2$ measured by means of a spirometer connected to the endotracheal tube and an S5 monitor (Datex Ohmeda, Madison, WI). Brain and liver tissue oxygenation index (TOI) were monitored by Near Infrared Spectrometry (NIRS) (INVOS Cerebral Oximeter monitor, Somanetics, Troy, MI) with sensors positioned on the skin of forehead and in the area of the liver. To measure skin blood flow a laser Doppler perfusion flow probe (BLF21 type R, Transonic Systems Inc., Ithaca, NY) was sutured on the abdominal wall skin. To avoid pressure and light artefacts laser Doppler perfusion probe was then covered with a bandage. A 4F catheter was inserted into the femoral artery to measure the blood pressure and cardiac output using a femoral arterial thermodilution system (PiCCO, Pulsion Medical Systems, Munich, Germany) and 5F catheters were inserted into the external jugular vein and femoral vein to measure the central venous pressure (CVP) and to perform blood withdrawal and volume expansion. A 1.5 mm blood flow probe (HQD1.5FSB, Transonic Systems Inc., Ithaca, NY) was placed around internal carotid artery to measure carotid blood flow. A 7F tonometric catheter (TRIP, Tonometrics Division Instrumentarium Corp., Helsinki, Finland) connected to an S5 Monitor (Datex-Ohmeda, Madison, WI) was passed into the stomach to measure gastric intramucosal pH (pHi). No histamine type 2 (H_2) receptor antagonists were administered. The tonometer balloon was filled with air, and automatic sampling was performed every 10 min. Blood gases were analyzed using the GEM Premier 3000 blood gas analyzer (Instrumentation Laboratory, Lexington, KY).

Evaluation of microcirculation parameters was performed according to international recommendations previously published [19]. Video imaging of the sublingual microcirculation was recorded using the Microscan device (Microvision Medical, Amsterdam, The Netherlands). Five 20 s sequences were recorded in each animal at each of three different time points: baseline, after exsanguination, and 60 min after treatment. All the video sequences were then analyzed by a single investigator using a computer programme for semi-automated vascular analysis (AVA 3.0 Microscan Analysis Software, Microvision Medical, Amsterdam, The Netherlands). To avoid possible bias, the analysis of the videos of the microcirculation was blinded, so that the investigator was unaware of the stage of the experiment in which the video had been recorded or the treatment group of the animal.

Experimental procedures

Following surgical preparation, the animals were allowed to stabilize for 30 min. Once a steady state was achieved and baseline data had been gathered, hypovolemic shock was induced by the withdrawal of 30 mL kg^{-1} of blood over 30 min. Studies on haemorrhagic shock using swine models have used controlled bleed volumes from 28 to 35 mL kg^{-1}. Our group has previously published several studies using controlled bleed volume of 30 mL kg^{-1} to imitate repercussion of haemorrhagic shock [20].

After a 30-min stabilization period, animals were randomized to receive an intravenous bolus of 30 mL kg^{-1} of normal saline (NS) (six animals), 15 mL kg^{-1} of albumin plus hypertonic saline (AHS) (six animals), or 15 mL kg^{-1} of AHS plus terlipressin 20 mcg kg^{-1} (five animals) administered over 30 min. HS was prepared by the addition of 12.5 mL of 20% NaCl to each 100 mL of NS. AHS was prepared by the addition of 22 mL of 20% NaCl plus 50 mL of 20% albumin to each 128 mL of NS. Post-resuscitation parameters were recorded 60 min later.

In order to determine microcirculatory effect of different therapeutic approaches to haemorrhagic shock, three different treatment groups were chosen. Hypertonic solutions compared to normal saline produce mobilization of intracellular water to the intravascular space and reduce microvascular collapse [4]. Terlipressin is an analogue of vasopressin, which, due to its potent vasopressor effect, has been proposed as an alternative treatment to fluid administration on haemorrhagic shock [21].