Resuscitation (2008) **77**, 379—386

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/resuscitation

EXPERIMENTAL PAPER

Increased plasma viscosity prolongs microhemodynamic conditions during small volume resuscitation from hemorrhagic shock☆

Pedro Cabrales[a,*], **Amy G. Tsai**[a,b], **Marcos Intaglietta**[b]

[a] *La Jolla Bioengineering Institute, La Jolla, CA 92037, USA*
[b] *Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA*

Received 3 December 2007; accepted 2 January 2008

KEYWORDS
Microcirculation;
Hemorrhage;
Hemodilution;
Plasma expander;
Intravascular oxygen;
Plasma viscosity;
Hypertonic saline;
Functional capillary density

Summary Systemic and microvascular hemodynamic responses to hemorrhagic shock resuscitation with hypertonic saline (HTS, 7.5% NaCl) followed with a small volume of plasma expander were studied in the hamster window chamber model to determine the role of plasma expander viscosity in the acute resuscitation outcome. Moderate hemorrhagic shock was induced by arterial controlled bleeding of 50% of blood volume (BV) and the hypovolemic state was maintained for 1 h. Volume restitution was performed by infusion of HTS, 3.5% of BV followed by 10% of BV plasma expanders. Resuscitation was followed for 90 min. The experimental groups were named based on the plasma expanders infused after the HTS, namely: [*Hextend*], Hextend® (6% Hetastarch 670 kDa in lactated electrolyte solution, 4 cp), [*Hextend+V*], Hextend® with viscosity enhanced by the addition of 0.4% alginate, 8 cp, and [*NVR*] no volume resuscitation as control group. Measurement of systemic parameters, microvascular hemodynamics and capillary perfusion were performed during hemorrhage, shock and resuscitation. Restitution with *Hextend* yielded the higher mean arterial pressure (MAP), followed by *Hextend+V* and *NVR*. Increasing plasma viscosity did not increase peripheral vascular resistance. Functional capillary density (FCD) was higher for *Hextend+V* than *Hextend* and *NVR*. The level of restoration of acid—base balance correlated with microvascular perfusion and was significantly improved with *Hextend+V* when compared to *Hextend* and *NVR*. These results suggest the importance of restoration of blood rheological properties through enhancing plasma viscosity, influencing the re-establishment of microvascular perfusion during small volume resuscitation from hemorrhagic shock.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2008.01.008.

* Corresponding author at: La Jolla Bioengineering Institute, 505 Coast Boulevard South, Suite #405, La Jolla, CA 92037, USA. Tel.: +1 858 534 2315.
E-mail address: pcabrales@ucsd.edu (P. Cabrales).

0300-9572/$ — see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2008.01.008

Introduction

Hemorrhage after penetrating trauma is a major combat hazard managed, when possible, according to the *Advanced Trauma Life Support* guidelines, which rely on aggressive fluid resuscitation until definitive control of the hemorrhage has been achieved.[1,2] Initial resuscitation strategies are based on recovering intravascular volume to restore blood pressure and metabolic imbalance under the assumption that early and rapid fluid resuscitation will prolong survival. In this context, fluid bolus administration is assumed to rapidly expand plasma volume, resulting in the restoration of circulation and facilitating the correction of metabolic acidosis associated with hypoperfusion and shock.[3,4] This strategy can resolve the hypovolemic syndrome but may lead to fluid overloading disorders that may influence length of recovery, days required for mechanical ventilation and mortality. Current studies suggest that overload morbidity can be significant and are exploring alternative fluid resuscitation methods based on permissive hypotensive resuscitation using relatively small volumes of hypertonic fluids.[5–7]

Current experimental studies focused on the microvascular component of shock resuscitation define restoration of perfusion to be more effective than the recovery of oxygen carrying capacity in determining tissue metabolic conditions, leading to better short and long term outcome.[8] This outcome, however, is critically dependant on the biophysical properties of the resuscitation fluid (plasma expander). To control damage and prevent further injury during resuscitation, the fluid needs to insure recovery of microvascular perfusion, i.e., functional capillary density (FCD), allowing the remaining red blood cells (RBCs) to sustain tissue oxygen delivery. Microvascular strategy does not rely on the restoration of systemic blood pressure as an end point; it emphasizes the restoration of capillary perfusion using low volume resuscitation and limited reoxygenation as a way to prevent and control multiorgan failure from becoming established.[8–10]

To attain the goal of hypotensive recovery of microvascular functional during resuscitation from hemorrhagic shock, the plasma expander is require to restore and sustain FCD and to produce the required volume expansion to sustain cardiac function and a moderate level of central blood pressure. An appropriate plasma expander would also be required to not cause RBCs aggregation, as well as being effective at low concentration.[5,11] How to achieve these properties has been a subject of controversy, particularly regarding the viscosity, colloid osmotic pressure (COP) and the type of colloid which ensure adequate organ perfusion.[12–14]

The objective of the study was to determine whether a currently available and relatively high viscosity plasma expander could reinstate systemic/microvascular conditions from a severe experimental hemorrhagic shock model when used in conjunction with HTS in a moderate volume resuscitation strategy. To achieve this objective, our experimental hamster model was subjected to a hemorrhage of 50% of blood volume (BV) followed by 1 h hypovolemic shock. The resuscitation was implemented in two steps: the initial phase was hypertonic saline (HTS, 7.5% NaCl) 3.5% of BV, and 5 min after HTS, 10% of BV of volume resuscitation was provided. The solutions used for were Hextend® (Hospira; Lake Forest, IL, 6% Hetastarch 670 kDa in Lactated Electrolyte Injection) or Hextend® with enhanced viscosity. The viscosity of Hextend® was increased by the addition of 0.4 g/dl of alginates (FMC Biopolymer, Brakrøya, Norway). Findings were also compared to resuscitation with only HTS. Alginates are produced by brown seaweed (Phaeophyceae, mainly Laminaria) resulting in a viscogenic additive. At a comparatively low concentration (0.7 g/dl), alginate diluted in normal saline has a viscosity of 7.6 cp and low COP. It can be mix or diluted in conventional plasma expander, allowing the design of a plasma expander.

Methods

Animal preparation

Investigations were performed in 55—65 g male Golden Syrian Hamsters (Charles River Laboratories, Boston, MA) fitted with a dorsal window chamber. Animal handling and care followed the NIH Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by the local animal care committee. The hamster window chamber model is widely used for microvascular studies in the unanesthetized state, and the complete surgical technique is described in detail elsewhere.[15,16] Catheters were tunneled under the skin, exteriorized at the dorsal side of the neck, and securely attached to the window frame.

Inclusion criteria

Animals were suitable for the experiments if: (1) systemic parameters were within normal range, namely, heart rate (HR) > 340 beat/min, mean arterial blood pressure (MAP) > 80 mmHg, systemic Hct > 45%, and arterial oxygen partial pressure (PaO_2) > 50 mmHg and (2) microscopic examination of the tissue in the chamber observed under a 650× magnification did not reveal signs of edema or bleeding.

Systemic parameters

MAP and heart rate (HR) were recorded continuously (MP 150, Biopac System; Santa Barbara, CA). Hct was measured from centrifuged arterial blood samples taken in heparinized capillary tubes. Hb content was determined spectrophotometrically (B-Hemoglobin, Hemocue, Stockholm, Sweden).

Blood chemistry and biophysical properties

Arterial blood was collected in heparinized glass capillaries (0.05 ml) and immediately analyzed for PaO_2, $PaCO_2$, base excess (BE) and pH (Blood Chemistry Analyzer 248, Bayer, Norwood, MA). Viscosity was measured at a shear rate of 160 s^{-1} (Brookfield Engineering Laboratories, Middleboro, MA). Colloid osmotic pressure was measured using a 4420 Colloid Osmometer (Wescor, Logan, UT).

Acute hemorrhage and volume replacement protocol

Acute hemorrhage was induced by withdrawing 50% of estimated BV via the carotid artery catheter within 5 min. Total