# MRI Assessment of the Effect of Different Resuscitation Fluids on Cerebral Blood Flow and Edema Following Experimental Traumatic Brain Injury and Hemorrhagic Shock in Mice

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## INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of traumatic death in the US. Morbidity and mortality resulting from TBI are greatly increased by secondary insults such as hemorrhagic shock (HS). The combination of TBI+HS has taken on great importance related to military and civilian casualties from blast injury in combat and terrorist attacks. Brain edema is a common consequence of TBI and is associated with poor outcome [1]. Aggressive fluid resuscitation is recommended to maintain mean arterial blood pressure (MABP), but in patients with TBI, fluid resuscitation raises concerns over exacerbation brain edema and ICP. Currently, there is controversy over how to best treat patients with TBI+HS. We assessed brain and pulmonary edema and cerebral blood flow (CBF) after resuscitation, from TBI+HS using two conventional solutions, namely the crystalloid Lactated Ringers (LR), the colloid hextend (Hex), and an octomeric recombinant hemoglobin (rHb).

## MATERIALS AND METHODS

Male C57Black/6J mice were anesthetized with isoflurane in $N_2O$:$O_2$ (1:1), intubated and mechanically ventilated; then femoral arterial and venous catheters were surgically placed. The mouse controlled cortical impact (CCI) model of TBI was used as described [2] with minor modifications [3]. Mice were placed in a stereotaxic holder and a temperature probe was inserted via a burr hole into the left frontal cortex. The parietal bone was removed for CCI. Once brain temperature reached 37˚C and was maintained at this temperature for 5 min, a vertically directed CCI was delivered at 5.0 m/sec with a depth of 1.0 mm. The bone flap was replaced, sealed and the incision closed. CCI was followed by 90 min of volume controlled HS (2 mL/100 g). After HS, to mimic the clinical situation, mice were aggressively resuscitated with LR, Hextend, or rHB 20 cc/kg (initial bolus) with 10 cc/kg boluses every 5 min for 30 min targeting MABP ≥70 mm Hg. Preparation and purification of the octomeric rHb were as described previously [4].

MR studies were performed on a 4.7-Tesla, 40 cm bore Bruker AVANCE AV1 system, equipped with a 12 cm diameter shielded gradient insert and a home-built RF coil. $T_1$ maps were generated using a spin-echo sequence (TE = 8 ms, 13 TR values ranging from 50-10000 ms, FOV = 2.5 cm, 128 x 66 matrix and 2 averages). During each study, $PaCO_2$, $PaO_2$, MABP, HR and rectal temperature was recorded. At the completion of the experiment animals were euthanized and the brains rapidly removed. Tissue was weighed and dried for 2 days at 110˚C. The percent water content (WW) was calculated using the equation: W = 100 x (wet weight – dry weight)/wet weight [5].

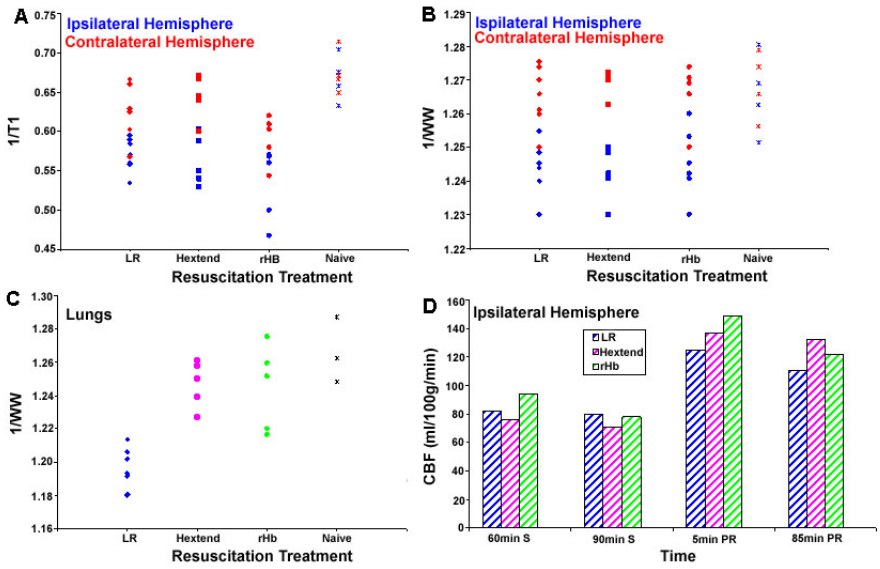


**Figure 1.** Relationship between MRI parameters and water content after experimental CCI+HS in mice. (A) 1/$T_1$ and (B) 1/wet weight for ipsilateral and contralateral hemispheres. (C) 1/wet weight for the lungs, and (D) CBF during the shock period (S) and following post resuscitation (PR).

Figures 1A and 1B show the 1/$T_1$ and 1/WW values for the ipsilateral and contralateral hemispheres respectively. There was a trend in 1/$T_1$ values between the resuscitation treatments with all fluids showing a tendency for more water in both hemispheres, especially the rHb group, when compared to naïve. This trend is not apparent with the wet weight/dry weight values. Although the 1/WW values did not show any obvious difference between treatments acutely in brain, there were marked differences in lung water between groups. Specifically, the LR group displayed greater water content in the lungs vs all other groups (Figure 1C). The LR group also received the most volume of resuscitation fluid (2.44 ml), vs Hextend (2.24 ml), and rHb (0.54 ml). CBF trends were consistent regardless of hemisphere or brain region. CBF was low during HS and tended to decrease further by the end of 90 min (Figure 1D). CBF was increased by all fluids after resuscitation. rHb achieved the largest initial increase which decreased over time. The increase in CBF seen with Hextend was maintained throughout the experiment while the initial increase seen with LR did not last. Our data are surprising in that conventional resuscitation with LR resulted in an early increase in lung (but not brain) water that was prevented by resuscitation with Hextend, or rHb. A rapid increase in MABP produced by rHb was associated with an immediate increase in CBF, but also a trend toward exacerbation of brain edema as quantified by MRI. One possibility is that rapid restoration of CBF in the damaged brain with rHB results in perfusion of severely damage tissue and edema.

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