ASL-MRI Assessment of the Effect of Hemorrhagic Shock on Cerebral Blood Flow After Experimental Traumatic Brain Injury 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 and HS has taken on great importance related to military and civilian casualties from blast injury in combat and terrorist attacks. Hypotension worsens the outcome for patients with TBI, which is thought to be due to secondary ischemia caused by cerebral hypoperfusion. Aggressive fluid resuscitation is recommended to maintain mean arterial blood pressure (MABP), but in patients with uncontrolled hemorrhage increasing MABP can increase blood loss and reduce survival [1]. Currently, there is controversy over how to best treat patients with TBI and uncontrolled hemorrhage. TBI produces CBF reductions that are generally localized to the injury site. The aim of this study was to examine the effect of HS on regional CBF after controlled cortical impact (CCI) in mice.

MATERIALS AND METHODS

Male C57Black/6J mice (11-15 wks of age) were divided into one of four groups for MRI assessment, naïve, CCI, HS and CCI + HS. 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 CCI model is used as previously described [2] with minor modifications [3]. Animals were placed in a stereotaxic holder and a temperature probe was inserted through a burr hole into the left frontal cortex. The parietal bone was removed for trauma. Once brain temperature reached 37˚C and was maintained at this temperature for 5 minutes, a vertically directed CCI was delivered at 5.0m/sec with a depth of 1.0mm. The bone flap was replaced, sealed with dental cement and the incision closed. CCI was followed by 60 min of volume controlled HS (2 mL/100 g) (CCI + HS), or continued anesthesia (CCI), or just 60 min of volume controlled HS (HS). In CCI + HS and HS only groups, mice were resuscitated with Hextend until MABP was >50 mm Hg (pre-hospital) followed 30 min later by the return of shed blood (definitive care). Perfusion images were obtained during the shock, pre-hospital and definitive care periods.

MR studies were performed on a 4.7-Tesla, 40 cm bore Bruker AVANCE system, equipped with a 15 cm diameter shielded gradient insert and a home-built saddle-type RF coil. For all imaging experiments, FOV = 4 cm and slice thickness = 2 mm. Maps of T_{1obs} [4] were generated from a three-parameter exponential fit to a series of spin-echo images with variable *TR* (*TR* = 8000, 4300, 2300, 1200, 650, 350, 185, 100 msec, 2 averages, 128 x 70 matrix). Perfusion spin-echo images were acquired in duplicate using the arterial spin-labeling technique [5] (*TR/TE* = 2000/10, 20, 30, summation of 3 echoes, 2 averages, 128 x 70 matrix) with labeling applied ± 2 cm from the imaging plane. The spin labeling efficieny (α) [6] was determined in each study with gradient echo images with spin-labeling applied at ± 6 mm (*TR/TE* = 100/9.6 msec, 45˚ flip angle, 8 averages, 256 x 256 matrix). Body temperature was maintained at 37 ± 0.5 ˚C using warm air, regulated with a rectal temperature probe. Prior to, and after each MRI study, $PaCO_2$, PaO_2, MABP, HR and rectal temperature was recorded.

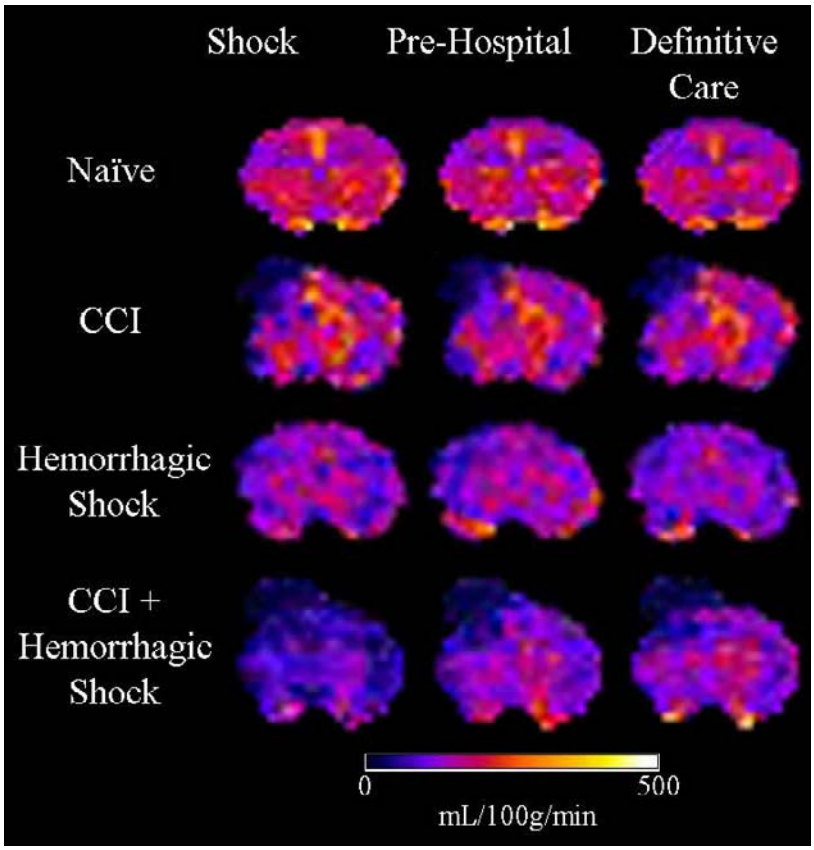

Figure 1: Representative CBF maps of mice brains with and without trauma (CCI) and with and without hemorrhagic shock, during the shock period (2 mL/100 g volume controlled blood withdrawal), pre-hospital period (resuscitation with Hextend), and definitive care period (return of shed blood).

RESULTS AND DISCUSSION

Figure 1 shows representative CBF maps for all groups. After CCI, CBF was significantly lower in the ipsilateral hemisphere, cortex and hippocampus during all phases. For HS alone mice CBF was generally lower than naïve mice but this was not significant. During the shock phase the CCI + HS mice displayed a dramatic global CBF reduction. After resuscitation, CBF the contralateral hemisphere partially recovered, but not to naïve levels, during the prehospital and definitive care phases. CBF in the ipsilateral hemisphere remained significantly decreased vs naïve mice throughout the entire experiment and, resuscitation did not restore contusional CBF. . Our data support the occurrence of a diffuse autoregulatory impairment during HS after TBI. Impaired oxygen delivery by HS superimposed upon increased metabolic demands and disturbed microcirculation after TBI, may magnify the damage, producing poor outcomes. This model using MRI provides a powerful tool to study novel approaches to optimize CBF resuscitation after TBI.

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