Timecourse of early CBF changes after controlled cortical impact in mice.

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Introduction

The influence of impaired cerebral hemodynamics, such as hypoperfusion and autoregulation loss on brain function is mostly unknown. Questions of whether low cerebral blood flow (CBF) reflects the severity of injury, or whether ischemia contributes to the injury are still not clear. In the clinical setting there are perfusion pressure targets for adequate flow in the brain in an attempt to secondary injury damage and ischemia [1]. Mouse models provide an important insight into secondary damage and repair, especially with the increasing use and number of transgenic models. The rat model of traumatic brain injury (TBI) and cerebral blood flow has been well characterized, in contrast the mouse model of controlled cortical impact (CCI) has not been well studied. Using the non-invasive technique of arterial spin-labeled MRI, we were able to observe CBF early after injury in a mouse model of TBI.

Materials and Methods

Male C57Black/6J mice aged between 11-15 weeks were used throughout these studies. Animals were divided into one of three groups for MRI assessment, naïve, trauma and craniotomy only. 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 and 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 4.0m/sec with a depth of 1.0mm. The bone flap was replaced, sealed with dental cement and the incision closed.

MR studies were performed on a 4.7-Tesla, 40 cm bore Bruker AVANCE-DBX 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. CBF maps were generated from: $CBF = \lambda \cdot (T_{1obs} \cdot 2\alpha)^{-1} \cdot (M_C - M_L) \cdot (M_C)^{-1}$, where M_C and M_L are the magnetization intensities from the control and labeled images, respectively. A spatially constant value of 0.9 mL · g^{-1} was assumed for the blood brain partition coefficient for water (λ). 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. Saline was infused via the femoral venous line for fluid replacement during imaging. CBF was quantified for 6 anatomical regions within each hemisphere.

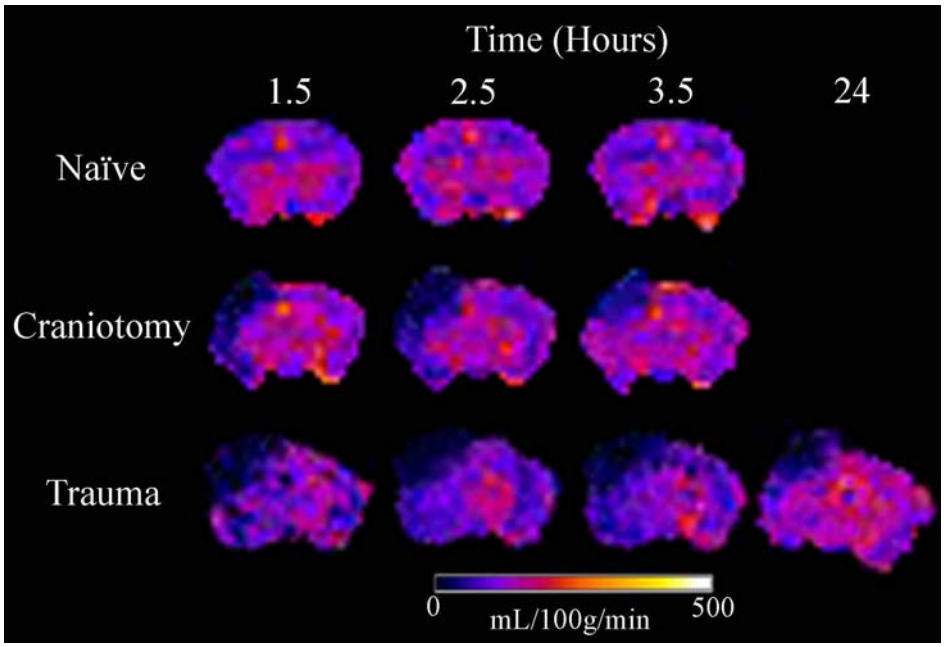

Figure 1: Representative CBF maps of mouse brains.

Results and Discussion

Figure 1 shows regional CBF patterns during the 24 hour time course. Due to technical considerations in the set-up, the first CBF could not be obtained until 1.5 hours after craniotomy or TBI. The naïve animals demonstrate relatively stable blood flow throughout the course of the experiment. The mice that underwent the craniotomy only had a lowered CBF over the entire ipsilateral hemisphere at the beginning of the assessment. After 3.5 hours CBF returned to values similar to those in the contralateral hemisphere for the thalamus, amygdala and hippocampus, the only area with lowered flow was in the cortex. After CCI, CBF in the ipsilateral hemisphere is lower and remains at this level throughout the timecourse. At 24 hours, CBF in the ipsilateral hemisphere has recovered to a certain degree, but still not up to values found in the contralateral hemisphere. Lower CBF over the whole hemisphere after trauma has significant impact on the efficacy of treatment. Arterial spin-labeled MRI is a totally non-invasive method to map blood flow, which is important because it allows serial measurements in one animal, allowing characterization of CBF changes in a mouse model following CCI injury.

References

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