Detection of Vascular Endothelial Leakage in the Brain Stem Following Cardiac Arrest

J. W. Bulte[1,2], J. Kofler[3,4], J. Zhang[1], S. Mori[1], R. J. Traystman[3,4]

[1]Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, [2]Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, [3]Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, [4]Anesthesiology and Perioperative Medicine, Oregon Health and Science University, Portland, Oregon, United States

Introduction

Cardiac arrest affects 500,000 Americans on a yearly basis and, of the survivors, 95% exhibit neurologic and neuropsychologic deficiencies. It has been reported that cardiac arrest followed by restoration of normal blood flow can lead to an increase in the blood-brain barrier permeability (1). As for MR imaging, iron oxide nanoparticles have been used for a sensitive detection of blood-brain barrier (BBB) disruption. Specifically, using a cortical freezing injury model, it was shown that the particles can accumulate in damaged endothelial cells following i.v. injection, allowing mapping of the disrupted BBB-area (2). In addition, dextran-coated USPIO particles have been succesfully used to delineate the affected brain area following an osmotic BBB-disruption (3,4). Using a newly developed mouse model, we investigated whether USPIO particles could be used to detect endothelial permeability changes in the brain following cardiac arrest.

Materials and Methods

Cardiac arrest was induced in male C57/BL6 mice by i.v. injection of 70 µl cold 0.5 M KCl, with body cooling to 27 °C and heating of the brain at 39 °C. After 10 min of cardiac standstill, cardiopulmonary resuscitation (CPR) was initiated by administration of 8 µg epinephrine, ventilation with 100% oxygen, and chest compressions (300/min). The USPIO MION-46L (prepared by the Center for Molecular Imaging Research, MGH, Cambridge, MA) was given i.v. at a dose of 1 mmole Fe/kg immediately following CPR (n=3). As controls, two sham-operated and one normal animal received the same dose of MION-46L, and one cardiac arrest/CPR animal received no contrast agent. After 24 hrs following injection, the mice were fixation-perfused and euthanized, and the brains were removed for high-resolution *ex vivo* MR imaging. Imaging was performed on a 400 MHz (9.4 Tesla) spectrometer. A home-made solenoid RF coil was used as both receiver and transmitter. T2*-weighted gradient echo MR images were obtained with a resolution of 70x66x63 µm after zeropadding, a TR of 120 msec, and four echoes of 5, 10, 15, and 20 msec. For comparison of sensitivity, a T2-weighted spin echo (TR=1200 msec, TE=30 msec) was also included. After completion of the imaging, the brains were cryoprotected and frozen, and 40 µm sections were stained for iron using (DAB)-enhanced Prussian Blue staining.

Results

For the injured animals receiving MION-46L, multiple hypointense lesions were visible throughout the brain stem (see Figure 1). Lesions appeared to be confined to the brain stem and could not be found in other parts of the cerebrum or cerebellum. No such lesions were observed in the controls of uninjured animals that received MION-46L or in the injured animal that did not receive MION-46L. Histology of the injured animals receiving MION-46L showed many dilated vessels in the brain stem (Figure 1C), containing endothelial cells that were uniformly filled with iron-positive magnetic nanoparticles.

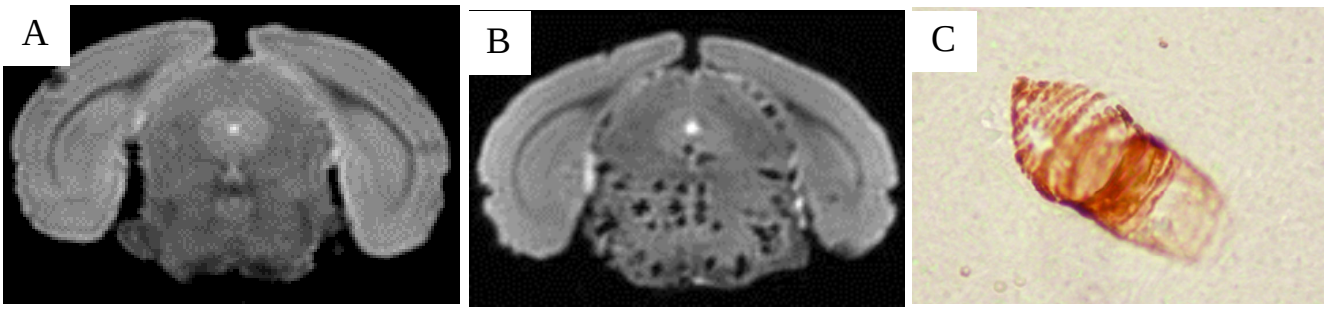

Figure 1: T2*-w gradient echo images of sham-operated (A) and cardiac arrest (B) animals 24 hours post i.v. injection of MION-46L. Note the numerous hypointense lesions in the brain stem in (B). Corresponding DAB-enhanced Prussian Blue staining (C) of animal in B demonstrates endothelial leakage and uptake of contrast agent.

Discussion

The no-flow period during cardiac arrest induces a low intravascular pressure. During resuscitation, epinephrine accelerates the return of spontaneous circulation, and may induce a vascular high-pressure gradient. We hypothesize that this transient high blood pressure induces a loss of the membrane integrity of the endothelial cells, resulting in leakage and uptake of the iron oxide nanoparticles. It is not known why this transient high blood pressure-induced endothelial leakage is restricted to the brain stem, but it may be related to the formation of edema in the brain stem that can occur in patients with arterial hypertension (5).

References

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