Determination of Pulse Sequence and Timing of Contrast-enhanced MRI for Assessing Blood-brain Barrier Disruption Following Transcranial Focused Ultrasound

J-C. Weng[1], S-K. Wu[2], F-Y. Yang[2,3], W-L. Lin[2,4], and W-Y. I. Tseng[1,5]

[1]Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei, Taiwan, [2]Institute of Biomedical Engineering, College of Medicine and College of Engineering, National Taiwan University, Taipei, Taiwan, [3]Department of Biomedical Imaging and Radiological Science, National Yang-Ming University, Taipei, Taiwan, [4]Medical Engineering Research Division, National Health Research Institutes, Miaoli, Taiwan, [5]Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan

Introduction

The delivery of chemotherapeutic, genetic or potentially effective diagnostic drugs to the central nervous system (CNS) requires temporary suspension of the physiological role of the blood-brain barrier (BBB), which blocks larger molecules from entering the CNS [1]. Focused ultrasound (FUS) along with ultrasound contrast agent (UCA) has the potential to locally and reversibly increase the permeability of blood-brain barrier, and the change in BBB permeability can be appropriately indicated by contrast-enhanced MRI [2-4]. There is, however, no reports investigating the optimum imaging sequence and the timing of contrast-enhanced MRI that best indicate the BBB disruption. Therefore, the purpose of this study was to find the optimum scanning parameters of contrast-enhanced MRI in the presence of hemorrhage. Our results suggest that contrast-enhanced T1W spin echo sequence acquired in the early phase post contrast enhancement can reliably indicate the degree and location of the BBB disruption. It might have potential to facilitate local delivery of nanopharmaceutical or upcoming molecular-targeted agents through BBB using MRI-guided transcranial sonication.

Materials and Methods

Sonication (A392S, Panametrics, Waltham, MA) with a center frequency of 1 MHz was applied to twelve rat brains with four different doses of UCA (0, 150, 300, and 450μl/kg, three rats for each dose) causing variable degrees of hemorrhage. The focal pressure in water was estimated to be 1.2 MPa at peak negative pressure for the experiments. Pulsed sonication was applied with a burst length of 50 ms, a duty cycle of 5%, and a repetition frequency of 1 Hz, the duration of a sonication session was 60 s. The experiment was performed on a 3T MRI system (TRIO, Siemens MAGNETOM, Germany). A surface coil was used for RF reception. Two imaging sequences were performed to acquire T1-weighted (T1W) images at two time points, 10 min and 45 min, after the administration of T1-shortening contrast agent (Gd-DTPA). A multi-slice spin echo sequence (SE) was performed to obtain T1W images, TR/TE = 435/12 ms; in-plane resolution = 195μm x 390μm; slice thickness = 1.5 mm. Multi-slice spoiled gradient echo sequences (GE) were performed to obtain T1W images, TR/TE = 203/5 ms; flip angle = 70°, and T2*W images, TR/TE = 400/10 ms; flip angle = 25°, with the in-plane resolution = 260μm x 260μm and slice thickness = 1.5 mm. The contrast enhancement at the sonicated regions was quantified and correlated against Evans blue (EB) staining. Comparison was performed among T1W spin echo and gradient echo sequences at early phase and late phase post contrast enhancement.

Results and Discussions

On the SE T1W images, the normalized signal intensity within the volume of interest (VOI) of significant contrast enhancement increased in proportion to the UCA dose (Fig.1a). As shown in Fig. 2a, the MR signal at 10 min after contrast injection was correlated with the UCA dose ($r=0.976$, $p<0.05$). No correlation with UCA dose was found when this analysis was performed on the GE T1W images at 10 min (Fig.1b). Using the FUS parameters along with the UCA dosage in the current study, there were various degrees of hemorrhage at and around the sonicated sites (Fig.1c). On the SE T1W images, the enhanced signal in the VOI increased with different rates and magnitudes which were proportional to the dose of UCA used. The signal change in time presented a sigmoid curve, rising rapidly in the early phase and gradually reaching the plateau in the late phase (Fig.2b). Again, the proportional signal change with respect to the UCA dose was less obvious on the GE T1W images. The contrast enhancement at the sonicated regions was then quantified and correlated against EB staining (Fig.1d). Figure 2c showed that the EB extravasation was correlated with the UCA dose ($r=0.988$, $p<0.05$). The SE T1W images at 10 min post contrast enhancement showed best correlation with EB staining in both quantity of EB extravasation ($r=0.812$; $p<0.01$) (Fig.3a) and spatial distribution ($r=0.527$, $p< 0.01$) (Fig.1e and 3b). This capability was more robust than the GE sequence in the presence of hemorrhage.

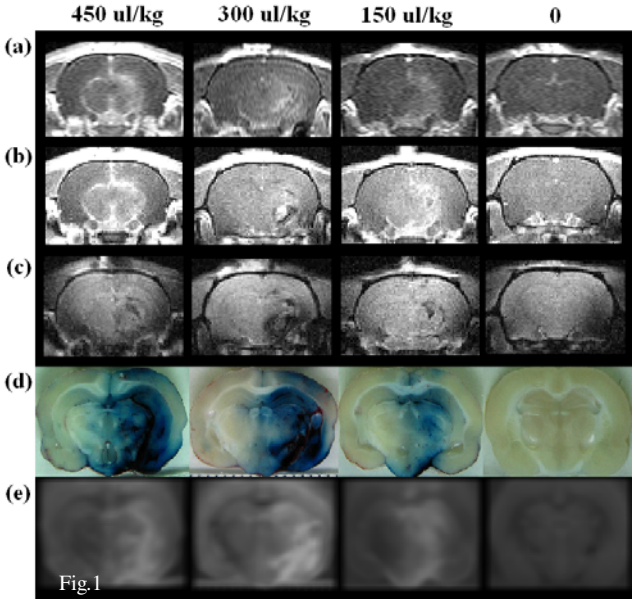

Fig.1

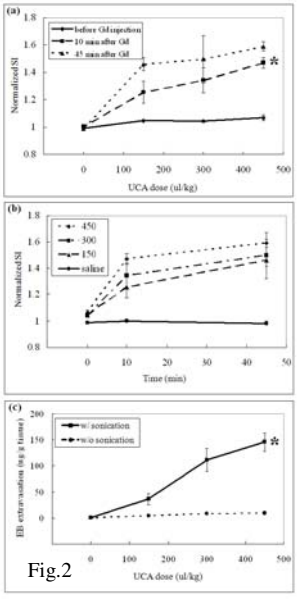

Fig.2

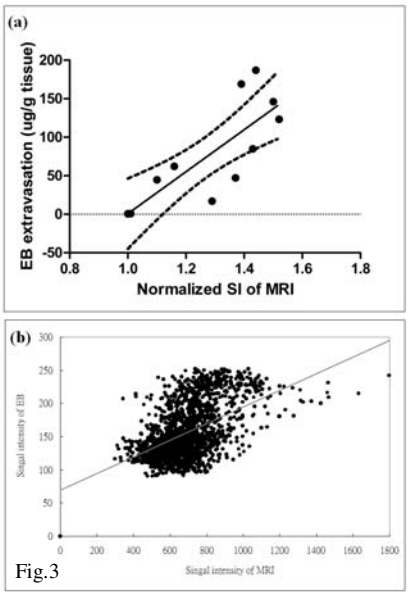

Fig.3

Fig. 1. (a) Contrast-enhanced SE T1W images, (b) contrast-enhanced GE T1W images, (c) T2*W images, (d) extravasation of EB, and (e) spatial cross correlation between SE T1W images and EB staining at the focal planes of sonication with UCA at four different doses, i.e. 450, 300, 150, and 0 μl/kg.

Fig. 2. (a) Normalized signal intensity of contrast- enhanced SE T1W images vs. the UCA at four doses before, 10 min and 45 min post contrast enhancement. (b) Normalized signal intensity of contrast-enhanced SE T1W images vs. time after MR contrast injection at four different UCA doses. (c) Relationship between EB extravasation and the injected dose of UCA in each brain hemisphere with and without sonication.

Fig. 3. (a) EB extravasation as a function of signal enhancement in contrast-enhanced T1W images acquired at 10 min after MR contrast injection. 95% confidence interval was also illustrated. (b) Scatter plot between signal intensity of contrast enhancement on T1W images and EB stains under sonications with UCA at 150μl/kg.

Conclusions

In this study we found that the enhanced signal on the SE T1W images acquired in the early phase post contrast enhancement can reliably indicate the degree of BBB disruption even in the presence of hemorrhage.

References [1] Pardridge, WM, Neuron 2002; 36: 555-558. [2] Hynynen, K, et al., Radiology 2001; 220: 640-646. [3] Hynynen, K, et al., Neuroimage 2005; 24: 12-20. [4] McDannold, N, et al., Ultrasound Med Biol 2008; 34: 930-937.