Detecting Blood-brain Barrier Disruption under Biosafety Regime using Optimum Transcranial Focused Ultrasound and Improved Contrast-enhanced MRI

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Introduction

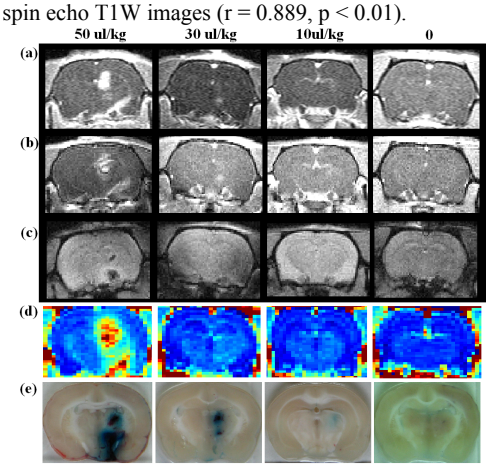
Focused ultrasound (FUS) along with an ultrasound contrast agent (UCA) can induce transient and local increase in the permeability of blood vessel wall or cell membrane, and the change in blood-brain barrier (BBB) permeability can be appropriately indicated by contrast-enhanced MRI [1-3]. Recently, most studies have used optimum FUS parameters with intravascular injection of pre-formed micro-bubbles to produce BBB disruption with minimum damage to the neurons. However, there are no studies reporting that under biosafety regime BBB disruption could still be predicted by MR contrast enhancement. The purpose of this study was to see if the traditional T1-weighted (T1W) imaging sequences, spin echo (SE) and gradient echo (GE), can discern the difference in the BBB disruption in lower dose regime or not. A high sensitivity R1 mapping was used as a gold standard and absolutely quantification. The quantitative analysis indexing the degree of BBB disruption and the correlation against Evans blue (EB) staining were also demonstrated. Our results suggest that, in the absence of hemorrhage, contrast-enhanced T1W gradient echo and spin echo sequence were equally reliable in quantifying the BBB disruption.

Materials and Methods

Sonication (A392S, Panametrics, Waltham, MA) with a center frequency of 0.518 MHz was applied to twelve rat brains with four different doses of UCA (0, 10, 30, and 50μl/kg, three rats for each dose). The focal pressure in water was estimated to be 0.56 MPa at peak negative pressure for the experiments. Pulsed sonication was applied with a burst length of 50 ms, a duty cycle of 1%, and a repetition frequency of 1 Hz, the duration of a sonication session was 20 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 T1W images immediately after the administration of T1-shortening contrast agent (gadodiamide). A multi-slice spin echo sequence was performed to obtain T1W images, TR/TE = 418/12 ms; in-plane resolution = 156μm x 312μm; slice thickness = 1.5 mm. Multi-slice spoiled gradient echo sequences 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 = 20°, with the in-plane resolution = 260μm x 260μm and slice thickness = 1.5 mm. To improve detection sensitivity over the full extent of gadodiamide concentrations, image data for R1 mapping were acquired. To obtain R1 mapping, multi-slice spin echo sequence with half spatial resolution was performed to acquire 6 sets of images corresponding to 6 different TRs, ranging from 418 to 5000 ms, to sample along the recovery of longitudinal magnetization. The contrast enhancement at the sonicated regions was quantified and correlated against EB staining. Comparison was performed among R1 mapping, T1W spin echo and gradient echo sequences post contrast enhancement.

Results and Discussions

On the spin echo T1W images, the normalized signal intensity of significant contrast enhancement increased in proportion to the UCA dose (Fig. 1a). Higher correlation with UCA dose was found when the analysis was performed on the gradient echo T1W images (Fig. 1b) and R1 mapping (Fig. 1d). Using the FUS parameters along with higher UCA dosage (50μl/kg) in the current study, there was hemorrhage at and around the sonicated sites detected by T2*W image and EB staining (Fig. 1c, e). No significant hemorrhage was detected when lower UCA dosage (30 and 10μl/kg) or no UCA was used. The BBB was safely disrupted by FUS in this study when lower UCA dosage (30 and 10μl/kg) was used. Figure 2 showed the correlation between enhanced voxel number of the spin echo/gradient echo T1W images/R1 mapping and UCA dose. T-test was used to provide the statistical significance. The highest correlation with UCA dose was found on the gradient echo T1W image ($r = 0.901$, $p < 0.01$), followed by R1 mapping ($r = 0.894$, $p < 0.01$) and spin echo T1W images ($r = 0.697$, $p < 0.05$). Figure 3 showed the correlation between EB staining and enhanced voxel number of the spin echo/gradient echo T1W images/R1 mapping post contrast enhancement. The EB extravasation was plotted as a function of the indices calculated from MR images. T-test was used to provide the statistical significance. The highest correlation coefficient was found on R1 mapping ($r = 0.947$, $p < 0.01$), followed by gradient echo images ($r = 0.901$, $p < 0.01$) and spin echo T1W images ($r = 0.889$, $p < 0.01$).



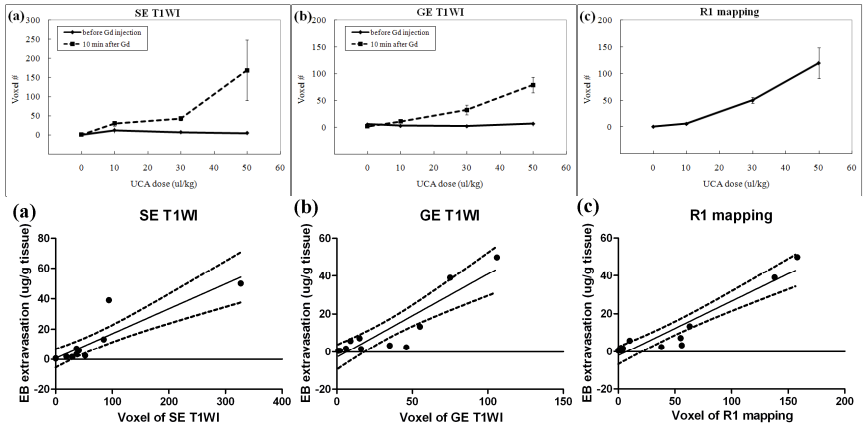


Fig. 1. (a) Contrast-enhanced spin echo T1W images, (b) gradient echo T1W images, (c) T2*W images, (d) R1 mapping, and (e) EB staining at the focal planes of sonication with UCA at four different doses, i.e. 50, 30, 10, and 0 μl/kg.

Fig. 2. Enhanced voxel number of (a) spin echo T1W images, (b) gradient echo T1W images vs. the UCA at four doses before, immediately post contrast enhancement. (c) Enhanced voxel number of R1 mapping vs. the UCA at four doses immediately post contrast enhancement.

Fig. 3. EB extravasation as a function of enhanced voxel number in (a) contrast-enhanced spin echo T1W images, (b) gradient echo T1W images, and (c) R1 mapping acquired after MR contrast injection. 95% confidence interval was also illustrated.

Conclusions

In this study we have demonstrated that traditional MR sequences and R1 mapping can discern the difference in the BBB disruption induced by transcranial FUS under biosafety regime. In the absence of hemorrhage, the gradient echo and spin echo T1W imaging sequences were equally reliable in quantifying the BBB disruption, and almost as good as R1 mapping. The capability of gradient echo was more robust in the absence of hemorrhage than in the presence of hemorrhage.

References

[1] Hynynen, K, et al., Radiology 2001; 220: 640-646. [2] Hynynen, K, et al., Neuroimage 2005; 24: 12-20. [3] McDannold, N, et al., Ultrasound Med Biol 2008; 34: 930-937.