MR-Acoustic Radiation Force Mapping can Quantitatively Predict Drug Delivery following Ultrasound-Induced Blood Brain Barrier Disruption in Rodents

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Background

In the last decade, many studies have shown the capability to disrupt locally and transiently the blood brain barrier (BBB) with low power ultrasound sonication of intravascular microbubbles [1]. However, this promising technique requires an accurate control of the acoustic pressure *in situ* to avoid hemorrhages. In our work, the BBB opening procedure is done in rodents under MR guidance. The acoustic radiation force is mapped *in vivo* before the injection of microbubbles in order to calibrate the acoustic pressure to a desired value between the disruption and the hemorrhage thresholds [2]. Correlations of contrast agent concentration maps with MR-Acoustic Radiation Force Imaging (MR-ARFI) signals show that it is possible to rely on ARFI to predict the amount of drug delivery.

Materials & Methods

A 1.5MHz MR-compatible focused ultrasound transducer (F/D=0.8, F=20mm) was used inside a small bore 7T preclinical scanner (Pharmascan, Bruker, France) with 300mT/m gradient strength. Sprague Dawley rats (125-200g) were maintained in stereotactic position under isoflurane anesthesia with their heads shaved. A multislice spin-echo sequence (TE/TR=40/1700ms, T_{acq}=4min, R=0.5x0.5x1mm^3) was modified with additional motion sensitizing gradients and synchronized to ultrasonic bursts so that the phase signal got proportional to local acoustic intensity [2]. This MR-ARFI sequence was used to localize the ultrasound focus and to estimate the acoustic pressure. An IR-TurboFLASH sequence (TE/TR=2.5/5ms, 60 inversion times from 45 to 4765ms spaced by 80ms, T_{acq}=13minutes) was used to generate T_1 maps following the approach by Deichmann et al. [3]. Then, rats were injected with Sonovue® microbubbles (Bracco, Italy) in the caudal vein (200µL, IV) and sonicated for 60s (3ms bursts every 100ms) with peak negative pressure between 0 and 0.55MPa. Those low pressure levels ensured safe and reversible BBB opening conditions. Dotarem® (gadolinium chelate contrast agent) was then injected (300µL, IV). T_1 maps were acquired before and after Dotarem injection. Gadolinium concentration maps were calculated as $C=1/r_1.(1/T_1-1/T_{10})$ where T_{10} stands for reference T_1 values before injection and r_1 the measured longitudinal relaxivity of Dotarem.

Results

Global and focal BBB disruptions were obtained *in vivo* in rats through intact skulls. The MR-ARFI signal was correlated to Dotarem concentration maps (Figure 1). A pixel to pixel analysis of coregistered maps for the two imaging modalities was performed (Figure 2). The increased penetration of Dotarem in cerebral tissues was quantified and showed a clear threshold on acoustic pressure (around 0.25MPa). Significant Dotarem penetration was observed above 0.3MPa. For a given molecular size, those data show that it is possible to predict spatial distribution of drug delivery on the basis of ARFI signal.

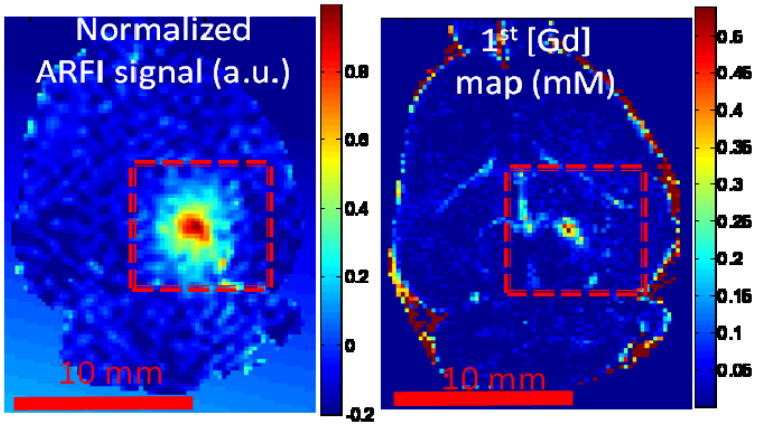

Figure 1. Acoustic radiation force MR measurement in a coronal slice (left); Dotarem® (Gadolinium chelate) concentration in the same slice immediately after BBB local disruption (right).

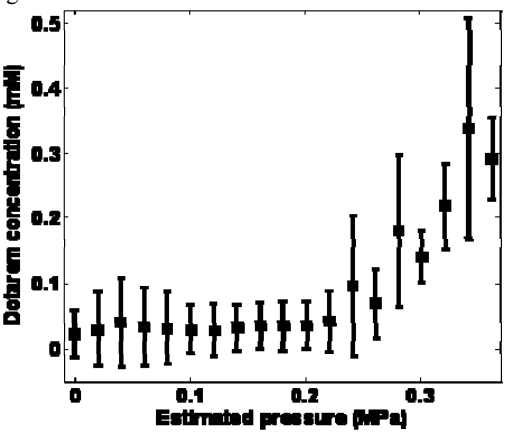

Figure 2. Voxel to voxel analysis of the early stage agent concentration in brain tissue as a function of the estimated acoustic pressure derived from ARFI signal.

Conclusion

The ability to quantify contrast agent distribution *in vivo* within reasonable acquisition time with high sensitivity (~5µM) and high spatial resolution together with the ability to reliably map the acoustic intensity thanks to a high sensitivity to motion (~1µm) enable to calibrate both spatial extent and intensity of BBB opening. Once this calibration is known for a given molecular size, it is feasible to rely on ARFI signal to adjust the quantity of delivered drugs. Being able to work at higher magnetic field (17T) and gradient strength (1T/m) in the future will increase agent quantification capabilities and enable to go further into this study.

References

[1] Hynynen et al. Radiology (2001).
[2] Larrat et al, Phys. Med. Biol. (2010).
[3] Deichman et al, Magn. Res. Med. (1999)