Investigation of the threshold for tissue damage in the rabbit brain using MRI-derived temperature information

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Abstract:
MRI-derived temperature information acquired during focused ultrasound sonications was compared to the presence of histologically confirmed tissue damage in the rabbit brain. In addition, the ability of MRI to detect near-threshold tissue damage was tested. The thermal dose and peak temperature threshold for tissue damage was in the range of 12-40 equivalent min at 43°C and 48.0-50.8°C respectively.

Introduction:
In order to protect normal tissue during thermal therapy and to be able to use sub-threshold heating for targeting therapy devices, it is essential to know what constitutes a safe thermal exposure. While such data exists from hyperthermia studies, it is not clear whether it can be applied to the shorter exposure times used in higher-temperature thermal therapy. The purpose of this study was to: (1) test whether MRI-derived temperature imaging could resolve the threshold for tissue damage in the brain after focused ultrasound, (2) estimate a conservative value for a safe thermal exposure for heating in the brain, and (3) test whether standard MR images can detect threshold-level histologically confirmed brain tissue damage.

Methods:
MRI-derived temperature images¹ were acquired during focused ultrasound exposures in rabbit brains in vivo. Multiple 30s exposures at different power levels were delivered to 2-4 locations 1 cm deep in each brain through a craniotomy. A phased array ultrasound transducer (frequency=1.63MHz, diameter/R.O.C.=10/8cm, sector vortex², ‘mode 2′) was used to generate a spatially flat temperature profile. Based on the temperature measurements, the sonications were repeated up to 14 times (and the power adjusted if necessary) until the accumulated thermal dose³ was near the threshold for tissue damage. A total of 281 sonications at 63 locations in 24 rabbits were performed. The animals were sacrificed ~4h-5d after the sonications. At time points up to immediately before sacrifice, T2W and contrast-enhanced (0.3 mmol/kg, Magnevist) T1W FSE imaging was performed. The brains were removed, sectioned, and stained with H&E to detect tissue damage, TUNEL to detect apoptosis, and Vanadium acid fuchsin to detect ischemic neurons. The accumulated thermal dose and peak temperature rise in a 3×3 voxel ROI at each focal location was compared to the histological findings. A regression of the onset for damage using probit analysis allowed for the calculation of the 50% effective thermal dose and peak temperature rise.

Results:
In general, tissue effects were observed in MRI initially as contrast enhancement in T1W imaging followed by changes observed in T2W imaging. Figure 1 shows the results of the dose-effect and temperature-effect analysis. The thermal dose and peak temperature threshold for tissue damage was in the range of 12-40 equivalent min at 43°C and 48.0-50.8°C respectively. The regression yielded a 50% effective dose and temperature of 18 min and 48.4°C respectively. Histologically, threshold damage appeared as small areas of coagulation necrosis. In 35/36 cases the damage was observed both histologically and in MRI. One lesion (<0.5mm) was not observed in MRI. In 2 cases, damage not observed in MRI ~4h after sonication was detected in images 2-5d later.

Discussion:
These results indicate that a conservative safe thermal dose value would be approximately 1 min. The threshold thermal dose value found here close to what has been found in vivo in hyperthermia studies in the brain (~3 min)⁴. Values suggested for guiding thermal therapies (e.g. 240 min⁵) are appropriately above the threshold for damage. These results also agree well with a similar MR experiment in muscle⁶.

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References