Contrast Enhanced MRI Signal Dynamics of FUS-induced BBB Opening in Mouse Brain

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Introduction
For many therapeutic drugs the blood-brain barrier (BBB) in the brain, a dense monolayer of endothelial cells covering the luminal surface of the blood vessels, is impenetrable. Focused ultrasound (FUS) in combination with gaseous ultrasound (US) contrast agents (gas-filled micro bubbles, 0.1-4 µm) can cause a localized, non-invasive, and reversible opening of the BBB [1] with no apparent acute or chronic damage to neuronal tissue [2]. For FUS-BBB studies, MRI guidance has been demonstrated as a precise tool for detection and monitoring of the signal changes after local BBB disruption. In order to establish FUS-induced BBB disruption as an accurate and effective approach to allow penetration of therapeutic agents into the brain, and hence to predict the efficiency of such a therapy, a full understanding of the dynamic processes of BBB opening is necessary. In this ongoing project, we compared the short-term and long-term signal dynamics of an intratumoral and an intravascular MR contrast agent in mouse brain.

Materials and Methods
A FUS therapy setup was built to treat mouse brain under MRI guidance (Fig. 1a). A 1.7 MHz fix focus US transducer (focal length 68 mm; NA = 0.44; elliptical focus: 8.1 mm length; O.11 mm) was integrated into an acrylic glass housing filled with degassed water. To assure optimal US coupling, a thin flexible latex membrane was used as acoustic window on which the head of the mouse was fixed in supine position for precise targeting. A loop RF coil encompassed the coupling window to improve MR sensitivity. The temperature (1°C) close to the eye) in the mouse brain. For FUS-BBB experiments were carried out in two mice on a 1.5 T whole body MRI system (Magnetom Symphony, Siemens Medical Solutions, Erlangen, Germany). For optimal US coupling, the hair at the head of the mice was removed. During each sonication 50 µl of US contrast agent (SonoVue®, Bracco Altana Pharma, Konstanz, Germany) were injected in the tail vein [3].

Short-term and long-term signal dynamics of two different MR contrast agents were investigated after BBB disruption: Gd-DTPA (Magnevist®) and the intravascular agent gadofosveset (Vasovist®; both: Bayer Schering Pharma, Berlin, Germany). The following contrast agent injection protocols were used: In one animal 10 µl Magnevist (+ 20 µl NaCl) were injected followed by a time delay of 1 min, and in the other 4 µl Vasovist (+ 16 µl NaCl) were applied followed by a waiting time of 10 min. Then, a 3D-FLASH reference data set (TR/TE = 15.6/5.5 ms, FOV: 80x50 mm², matrix: 512x320, th: 0.8 mm, α = 25°, no. slices: 22, tot. acq. time: 1:30 min) was acquired prior to sonication. Fast T1-weighted inversion recovery turbo FLASH images (TR/TE = 10.0/4.04 ms, TI = 50 ms, FOV: 60x45 mm², matrix: 128x128, th: 2 mm, α = 12°, total acq. time: 1 s) were repeatedly acquired for 3 min. FUS exposure (40 s) and SonoVue injection were synchronously started 30 s after starting the T1-imaging series. Next, 3D-FLASH data sets were acquired for 65 min to assess the long-term signal dynamics. To quantify the MRI contrast enhancement after BBB disruption, several ROIs (Fig. 1b) were placed at different positions (1: FUS focus, 2: untreated region in the brain, 3: blood vessel, 4: highly perfused region close to the eye) in the mouse brain.

Results
A local BBB opening was detected after FUS treatment as a clearly circumscribed region of contrast enhancement in all MR images. Fig. 2a shows short-time signal courses for the two different types of MR contrast agent assessed with a fast T1-weighted imaging series. A mono-exponential signal increase was visible with the interstitial contrast agent (time constant 67.4±10.6 s), whereas no signal change could be observed in the FUS focus for the intravascular contrast agent.

Long-term signal courses from the 3D-FLASH acquisitions are given in Fig. 2b,c. In case of the interstitial contrast agent a strong signal decrease was measured after BBB opening quantified by a mono-exponential decay with a time constant of 19.6±2.3/13.5±1.7 s for ROI1/ROI3/ROI4 respectively. For the intravascular contrast agent, a moderate signal increase could be seen in the FUS focus prior to a slow signal decrease. This particular time-course could be described by using the gamma variate function [4] leading to a time constant of 47.6±4.5 min. Corresponding fitting of the long-term signal time-course recorded for blood vessel and a region close to the eye could not be performed. Both signal-time courses delineate a slow, on the time scale of our experiment a nearly linear signal decrease after BBB. During all experiments no significant signal changes could be detected for the untreated region in the brain.

Discussion
In this study, contrast enhanced MRI signal changes after FUS-induced BBB disruption were quantified for two different types of MR contrast agents. The short-term signal changes in the FUS focus observed for the interstitial contrast agent demonstrate an instantaneous BBB disruption by the FUS sonication in combination with an US contrast agent. The time constant of about one minute (67.4 s) may serve as a time scale for the BBB opening process for the specified US parameter set. The intravascular contrast agent has a prolonged half-life in the blood (time constant 47.6 min, see long-term signal decay for blood vessel and FUS region in Fig. 2c) due to its reversible binding to serum albumin, which leads to a significantly larger molecular size of the contrast agent-albumin complex (60 kDa). Thus, we attribute the differences in the short-term signal dynamics to the different mobility of the contrast agent molecules.

During the long-term imaging studies the BBB remains open, which is seen from the wash-out of the contrast agents that is driven by a concentration gradient between interstitial and intravascular compartments. Closure of the BBB happens on a larger time scale (> 65 min) [1,3]. The mean time constant of about 15 min for the Magnevist wash-out seems reasonable when compared to the half-life distribution in blood (for humans) of 20 min given by the manufacturer.

Even though nearly no signal increase is seen with the intravascular contrast agent sonication, for therapy control this agent might be favorable for several reasons: the injection procedure during FUS-BBB therapy would be simplified, and a much longer time window would be available for high-resolution imaging after therapy. This prolonged time window in combination with the expected reduced concentration gradient due to the high intravascular contrast agent concentrations might lead to a more reproducible and quantitative assessment of BBB therapies with MRI.

References