ENHANCEMENT OF GAS-FILLED MICROBUBBLE MAGNETIC SUSCEPTIBILITY BY IRON OXIDE NANOPARTICLES

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INTRODUCTION
Gas-filled microbubbles were originally developed as an intravascular contrast agent to enhance backscattering in ultrasound imaging. Microbubbles possess the ability to be an MR susceptibility contrast agent due to the induction of local magnetic susceptibility differences by the gas-liquid interface. Feasibility of microbubbles as an MR pressure sensor, based on the susceptibility change caused by pressure-induced microbubble size change, has been explored through theoretical and phantom studies. Gas-filled microbubbles have also been shown as an MR susceptibility contrast agent in vivo. However, microbubble susceptibility effect is relatively weak when compared with other intravascular MR susceptibility contrast agents. By optimizing the microbubble size distribution and choice of shell coating material and core gas, it is possible to substantially enhance the microbubble susceptibility effects and reduce the dosage requirement for MR applications. In this study, we aim to demonstrate that microbubble susceptibility effects can be improved by embedding and entrapping iron oxide nanoparticles.

METHODS

Synthesis of iron oxide nanoparticles embedded albumin-coated microbubbles: Iron oxide nanoparticles embedded albumin-coated microbubbles (AMB) were produced by an adapted sonication method. Briefly, 18 mg of monocrystalline iron oxide nanoparticles (MION; MGH) was added into a 5% solution of bovine serum albumin (10857, USB Corporation). The mixture was preheated to about 70°C and sonicated under aseptic conditions using an ultrasonic frequency of 20 kHz.

Synthesis of iron oxide nanoparticles entrapped polymeric microbubbles: Iron oxide nanoparticles entrapped polymeric microbubbles (polymeric MB) were produced by an adapted double emulsion method. Briefly, 0.5 g poly(D,L-lactide-co-glycolic acid 50:50, PLGA; Sigma) was dissolved in 10 mL of ethyl acetate (Sigma). 1 mL of MION solution (1.164 mg/mL) was added to the polymer solution and sonicated for 30 s. The W/O emulsion was then poured into a 5% poly(vinyl alcohol) (PVA; Sigma) solution and homogenized for 5 min. The double (W/O)/W emulsion was then poured into a 2% isopropyl alcohol (Sigma) and stirred at room temperature for 1 h. The capsules were then collected by centrifugation, washed once with distilled water, centrifuged at 15°C for 5 min, at 3000g, and the supernatant discarded. The capsules were then washed three times with hexane (Sigma). The capsules were frozen in a -80°C freezer and lyophilized.

RESULTS AND DISCUSSIONS
Values of $R_1$ were plotted against time in Figure 1 for different microbubbles. As GE signals were acquired, microbubbles started to migrate upward; therefore, in the final state the microbubbles aggregated in the upper part of the tube. Microbubble induced $\Delta R_1$ was then calculated as the difference between $R_1$ in the initial state and that in the final state. To demonstrate that MION were embedded and entrapped, $R_1$ was measured before and after cavitation, which was performed by applying ultrasound frequency of 40 kHz. $R_1$ maps of the suspending solutions were acquired before and after cavitation with multiple gradient echo sequences. In vivo Demonstration: Normal SD rats (~200-250 g) were injected intravenously with 0.2 mL of microbubble suspension (~4% volume fraction; AMB with MION and N = 1 for polymeric MB with MION) at a rate of 1.2 mL/min to avoid possible microbubble destruction due to high pressure and shear stress during femoral vein catheterization.

REFERENCES