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<td><strong>Author(s)</strong></td>
<td>Chow, AMK; Cheung, JSC; Wu, EX</td>
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ENHANCEMENT OF GAS-FILLED MICROBUBBLE MAGNETIC SUSCEPTIBILITY BY IRON OXIDE NANOFACTICLES

A. M. Chow1,2, J. S. Cheung1,2, and E. X. Wu1,2
1Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Hong Kong SAR, China, People's Republic of, 2Department of Electrical and Electronic Engineering, The University of Hong Kong, Hong Kong SAR, China, People's Republic of

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 large 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 changes, has been explored through theoretical1 and phantom2 studies. Gas-filled microbubbles have also been shown as an MR susceptibility contrast agent in vivo3. 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 effects1 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 ultrasound 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-glycolide acid 50:50, PLGA; Sigma) was dissolved in 10 mL of ethyl acetate (Sigma). 1 mL of MION solution (1.164mg/mL) was added to the polymer solution and probe 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) solution and homogenized for 5 min. The microbubbles were then placed in separate 2-mL cylindrical phantom tubes. Each phantom tube was slowly warmed to room temperature and gently mixed for 2 min outside the magnet prior to MR measurements. To ensure uniform suspension of microbubbles, the phantom was then continuously stirred by rotation inside the magnet. It was then arrested in horizontal position immediately before the start of MR acquisition sequence. Apparent transverse relaxation rate enhancement ($\Delta R_2$) was measured by acquiring multi-echo gradient echo (GE) images of the phantom which was placed in a horizontal position. The measurement was repeated six times for each microbubble phantom. The parameters were TR = 1000 ms, TE = 3.5, 7, 10.5, 14, 17.5, 21, 24.5, 28 ms, flip angle = 30º and NEX = 1. Phantom $R_2^*$ values were computed by monoexponential fitting of the peak magnitudes of the multi-echo GE signals using a software toolkit developed in MATLAB (MathWorks). Initially, there was a uniform suspension of microbubbles. As GE signals were acquired, microbubbles started to migrate upward; therefore, in the final state the micr

RESULTS AND DISCUSSIONS
Values of $R_2^*$ 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 values of $R_2^*$ were due to the suspending solution. The different amounts of free MION in the suspended solution accounted for the difference in the $R_2^*$ of the suspending solution. Microbubble induced $\Delta R_2^*$ of different microbubbles were depicted in Figure 2. The MION embedded and entrapped would enhance the susceptibility effect and increase the values of $\Delta R_2^*$ as MION would float along with the microbubbles, resulting in a larger $\Delta R_2^*$ values. Suspending solution $R_2^*$ for AMB without and with MION after cavitation were found to be increased by 1.41 s¹ and 23.91 s¹ respectively. Similarly, suspending solution $R_2^*$ for polymeric MB without and with MION after cavitation were found to be increased by 1.52 s¹ and 75.84 s¹ respectively. These substantial differences for microbubbles with MION demonstrate that there were more MION in the suspending solution after cavitation; suggesting that embedded and entrapped MION were released into suspending solution after the microbubble cavitation. Transmission electron microscopy was done on AMB with MION and depicted in Figure 3. MION as dark dots (red arrows) were observed on the shells of AMB, validating MION was embedded and entrapped in AMB. Nevertheless, small amount of free MION was also observed in suspending solution (green arrow). Figure 4(a) shows one of the preinjection GE-EPI $T_2^*$-weighted images, while (b) shows the postinjection GE-EPI $T_2^*$-weighted image with the maximum susceptibility contrast for polymeric MB with MION injection. Figure 5 depicts the $T_2^*$-weighted signal time course during polymer MB with MION injection with ROI selected from homogeneous liver region (indicated in Figure 4(a)). Similar signal time course was also observed during AMB with MION injection. The $T_2^*$-weighted signals after microbubble injection did not return to the preinjection baseline, this may be caused by accumulation of released MION in Kupffer cells after in vivo microbubble clearance.

CONCLUSIONS
In this study, we demonstrated, for the first time, that embedding iron oxide nanoparticles onto shells of albumin-coated microbubbles could enhance the iron oxide microbubble susceptibility. This is currently underway to characterize the in vivo susceptibility effects of these microbubbles. With such approach, microbubble susceptibility can be significantly enhanced, so that microbubbles can be monitored with high sensitivity and low concentrations under MRI.

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Figure 1 Values of $R_2^*$ were plotted against time for different microbubbles.

Figure 2 Microbubble induced $\Delta R_2^*$ of different microbubbles. The error bars represent one standard deviation.

Figure 3 Transmission electron micrograph shows MION was embedded onto shells of MB.

Figure 4 GE-EPI $T_2^*$-weighted image for polymeric MB w/ MION (a) preinjection image and (b) postinjection with the maximum susceptibility contrast.

Figure 5 $T_2^*$-weighted signal time course in a homogeneous liver region during polymeric MB w/ MION injection.