Preliminary In Vivo Studies of Microbubbles as MRI Susceptibility Contrast Agent

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ABSTRACT Microbubble has been used as ultrasound contrast agent to enhance backscattering for years. Its application in MRI as a unique susceptibility contrast agent is not fully explored. In this preliminary study, the use of microbubble contrast agent, Optison, as a MR susceptibility contrast agent is demonstrated in vivo for the first time with rat liver imaging at horizontal 9.4T and mouse liver imaging at vertical 9.4T. In vitro measurements of $\Delta R2$ and $\Delta R2^*$ of Optison solution are also presented.

INTRODUCTION Optison is a second-generation ultrasound contrast agent made with human albu min microbubbles. It is transpulmonary and has a relatively long life (4 min) in vivo. Its size is about the same as red blood cell. It flows approximately at the same velocity as red blood cells and does not alter hemodynamics (1). Such micro gas bubbles can potentially be used as MR susceptibility contrast agent in vivo since the gas-liquid interface induces magnetic susceptibility and causes transverse relaxation rate increase that is proportional to $B_2^*$. Previously experimental attempt by Moseley et al. (2) with Albunex illustrated the potential of microbubbles as a MR susceptibility contrast agent. Other theoretical attempts and phantom study focused on the potential application of microbubbles as a pressure sensing contrast agent in MRI based on the change in susceptibility due to microbubble size change with pressure (3-4). However, no in vivo results have been reported. Microbubbles may serve as a unique susceptibility contrast agent in MRI applications. For example, they can be destroyed instantaneously and locally in vivo via cavitations by focused ultrasonic irradiation. This may permit the study of refilling kinetics, which can lead to unique applications interventional MR imaging. Other potential applications include perfusion measurement, where a very sharp blood label can be created and followed. In this case, the blood label signal depends only on half-life of the susceptibility contrast agent. Microbubble may also be used for drug delivery imaging.

MATERIALS AND METHODS Optison (Amersham Health, Princeton, NJ) was used in this study (1% w/v albumin content; 2.0-4.5 µm microbubble to detect refilling kinetics in interventional MR procedure and perfusion measurement were proposed. It is possible that their MRI susceptibility effect can be significantly enhanced through optimization of bubble size distribution, indicating Optison may have useable sensitivity as a susceptibility MRI contrast agent. Several issues remain to be investigated. For example, microbubbles have weak susceptibility effects. It is possible that their MRI susceptibility effect can be significantly enhanced through optimization of bubble size distribution, property of the coating shell, and property of the core gas. Microbubbles have the potential to serve as a unique MRI contrast agent. Specific applications of microbubble to detect refilling kinetics in interventional MR procedure and perfusion measurement were proposed.

RESULTS For the in vitro phantom experiment, assuming mono-exponential decay, $\Delta R2$ and $\Delta R2^*$ can be estimated by $1/TE \cdot \ln(S2/S1)$. $S1$ corresponds to the signal when microbubbles are in well-mixed suspension, $S2$ corresponds to the signal when microbubbles are absent in the measurement volume as they all rise to the top of syringe. $\Delta R2$ was calculated to be 50±5 s⁻¹ while $\Delta R2^*$ was calculated to be 490±50 s⁻¹. The typical signal recovery curve measured is shown in Fig. 1. The top and bottom curves correspond to spin echo measurement (TE=7ms) and gradient echo measurement (TE=1.7ms), respectively. In vivo sensitivity of Optison as a MR susceptibility contrast agent was demonstrated by Optison IV bolus injection and dynamic T2* weighted imaging. For the rat study, axial liver images were acquired for 25 minutes during which contrast agent was injected at 8th minute. One slice of liver image is shown in Fig. 2. A ROI is drawn in the liver region, with the corresponding signal time course plotted in Fig. 3. The FWHM of the response function was about 2.4 minutes and the contrast effect completely disappeared after 5.5 minutes. The strongest signal drop was about 35%. Similar results were found in mouse liver study on the vertical 9.4T system. Fig. 4 shows T1-weighted anatomical image (left) and the calculated $\Delta R2^*$ map (right). The maximum signal drop was about 50%. The FWHM of the response is about 2.4 minutes.

CONCLUSION The potential of microbubbles as MR susceptibility contrast agent was demonstrated here in vivo for the first time in rat and mouse liver though they can be applicable to other organs. In vitro measurements of $\Delta R2$ and $\Delta R2^*$ of Optison solution were reported. Significant signal change was observed in the liver, indicating Optison may have useable sensitivity as a susceptibility MRI contrast agent. Several issues remain to be investigated. For example, microbubbles have weak susceptibility effects. It is possible that their MRI susceptibility effect can be significantly enhanced through optimization of bubble size distribution, property of the coating shell, and property of the core gas. Microbubbles have the potential to serve as a unique MRI contrast agent. Specific applications of microbubble to detect refilling kinetics in interventional MR procedure and perfusion measurement were proposed.