Prelimiary 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 ΔR2 and ΔR2* of Optison solution are also presented.

INTRODUCTION Optison is a second-generation ultrasound contrast agent made with human albumin 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_o^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 an 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 mean particle size; 5.0-8.0x10^8/mL microsphere concentration; Octafluoropropane core gas). In vitro studies of Optison phantom were performed at the horizontal Bruker 9.4T system using a RF volume coil. The phantom was composed of 0.3mL well-suspended Optison solution in a 1mL syringe. Fresh Optison vial was used to make the solution phantoms. Each phantom was first warmed to room temperature with gentle mixing for 2 minutes. The phantom was placed vertically and well mixed through continuous rotations right before measurement started. T2 relaxation time of the 0.05mL measurement volume located at the center of syringe was measured by multi-echo spin echo sequence (TR=3000ms, TE=7ms, 14ms, 21ms and 36ms) and T2* relaxation time was measured by multi-echo gradient echo sequence (TR=3000ms, TE=1.7ms, 3.4ms, 5.1ms and 6.8ms). Note that all microbubbles will slowly surface to top of syringe due to buoyancy. This procedure and measurement was repeated.

In vivo liver imaging was performed in (1) normal rats on a horizontal Bruker 9.4T system using a surface RF coil, and (2) normal mice on a vertical Bruker 9.4T microimaging system using a RF birdcage coil. During the imaging, the rats (350g) were anesthetized with halothane-nitrous oxide (1.5 vol. % at 1 L/min air flow for both gases) via a nose cone. Dynamic susceptibility imaging was performed with gradient echo sequence with TR/TE=130ms/5.4ms, FOV 8cm, and 128x128 matrix, and temporal resolution = 17 s. Optison was injected steadily via femoral vein catheterization (1.2 mL/min, 2.6mL/kg) to avoid bubble destruction due to high pressure and shear stress. Similarly, normal wild-type mice (6-mon, 30g, C57BL6/J) were anesthetized with isofluorane gas (1.5 vol. % at 1 L/min air flow) via a nose cone during imaging on the vertical 9.4T system. Single slice gradient echo sequence was used with TR/TE=20ms/3ms, flip angle=3 degree, 64x64, NEX=1, temporal resolution=1.2 seconds. Contrast agent was injected steadily (1.2mL/min, 6.7mL/kg) via femoral vein catheterization.

RESULTS For the in vitro phantom experiment, assuming mono-exponential decay, ΔR2 and ΔR2* can be estimated by $1/TE \cdot \ln(S_2/S_1)$. S_1 corresponds to the signal when microbubbles are in well-mixed suspension. S_2 corresponds to the signal when microbubbles are absent in the measurement volume as they all rise to the top of syringe. ΔR2 was calculated to be 50±5 s^{-1} while ΔR2* 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 ΔR2* map (right). The maximum signal drop was about 50%. The FWHM of the response is about 2.4 minutes.

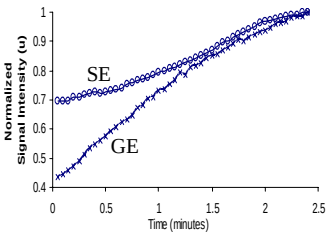

Fig.1

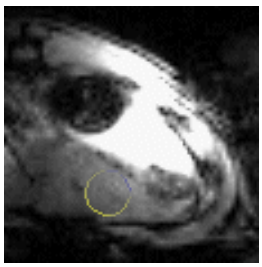

Fig. 2

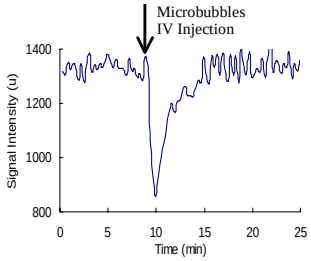

Fig. 3

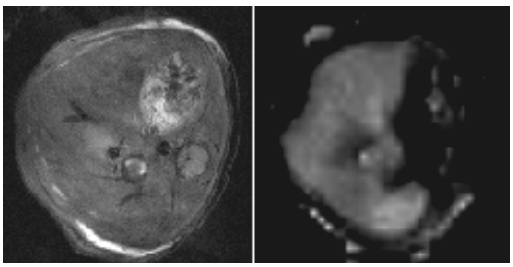

Fig. 4

CONCLUDISON 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 ΔR2 and ΔR2* 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 relatively 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.

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