3D ΔR2 Microscopy MRA with a New Blood Pool Contrast Agent: A Comparison with Resovist®

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Synopsis
We have recently developed a new blood pool contrast agent (Fe_3O_4@SiO_2/PEG) which possesses higher transverse relaxivity and long intravascular half-life. This study was aimed to assess the ability of Fe_3O_4@SiO_2/PEG to improve high-resolution magnetic resonance angiography in visualizing cerebral microvasculature.

Introduction
A novel MR angiographic methodology, 3DΔR2-mMRA (three dimensional and ΔR2 based microscopy magnetic resonance angiography), for depicting cerebral small vessels has been recently developed [1]. This technique employing high-resolution ΔR2 map which based on the measurement of the spin-echo transverse relaxation rate before and after the injection of an iron-oxide contrast agent can be used to both visualize the neuromicrovascular architecture and provide information on the physiological status of the microvascular cerebral blood volume (CBV). However, the visibility of microvasculature and the precision of CBV calculation greatly rely on the transverse relaxivity and intravascular half-life of contrast agent, respectively. We recently developed a blood pool contrast agent named Fe_3O_4@SiO_2/PEG where Fe_3O_4 nanoparticles were encapsulated in a thin silica shell to enhance the T2-relaxivity (R2 =342.8 mM^{-1} s^{-1}) and employed poly(ethylene glycol) (PEG) modification on the outer surface of silica spheres to reduce nonspecific interactions with proteins through its hydrophilicity and steric repulsion effects [2], thus reducing opsonization and prolonging circulation time of nanoparticles. The aim of this study was to report the use of developed Fe_3O_4@SiO_2/PEG with long half-life and high transverse-relaxivity for high-resolution MR imaging of the rat cerebral microvasculature and compare it with commercial contrast agent, Resovist®.

Material and Methods
***Synthesis of Fe_3O_4@SiO_2 /PEG nanoparticles*:** Typically, 20 mg of Fe_3O_4 powder was dissolved in 77 mL of cyclohexane at room temperature. Then, 20 g of Triton X-100, 16 mL of hexanol, and 3.4 mL of H_2O were added with stirring to generate a microemulsion system [3] and 400 μL of tetraethyl orthosilicate (TEOS) was added to the mixture. Six hours later, 1 mL of aqueous ammonia (28~30 wt %) was introduced to initiate the TEOS hydrolysis. After 24 h, ethanol was added to destabilize the microemulsion system. The magnetic Fe_3O_4@SiO_2 nanoparticles were isolated via centrifugation and washed in sequence with ethanol and deionized water to remove surfactant and unreacted chemicals. Fifty milliliters ethanolic Fe_3O_4@SiO_2 suspension, corresponding to 125 mg particle in dry weight, and 729 μL of PEG-silane were stirred under reflux for 7 h. Products were collected by centrifugation, washed with ethanol and deionized water. A schematic graph of Fe_3O_4@SiO_2/PEG was shown in Fig. 1.
***MRI scanning parameters*:** All images were performed on a 4.7-T Biospec 47/40 MR scanner. The rat was initially anesthetized with 5% isoflurane at 1L/min air flow. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. Isoflurane was then maintained with 1~1.2% at 1L/min air flow throughout the experiments. Images were acquired using a 72-mm birdcage transmitter coil and a separate quadrature surface coil for signal detection. To determine ΔR_2, T2-weighted images (T2WI) were performed before and after an injection of iron oxide (Resovist, Schering AG, Berlin, Germany and Fe_3O_4@SiO_2, Taiwan) at a dose of 30 mg Fe/kg. T2WI were acquired using 3D RARE sequence with a TR of 1500 ms, TEeff of 82 ms, ETL of 32, 4 averages, FOV = 2.8 cm × 2.8 cm × 1.4 cm, acquisition matrix = 256×256×96 (zero-padded to 512×512×192). The in-plane resolution and slice thickness were 54.68 and 72.91 μm, respectively. ΔR_2 map was calculated pixel-by-pixel using an in-house software written by Matlab (MathWorks, Natick, MA, USA). 3D view of microvasculature was constructed with 3D ΔR2 map using a volume-rendering utility [1].

Results and Discussion
Figure 2A shows the T2WI of a rat brain before and after injection of Resovist and Fe_3O_4@SiO_2/PEG. The hypointensity signal in post-injection image was due to the presence of contrast agent within the blood vessels. The level of signal interfering by Fe_3O_4@SiO_2/PEG appears to be higher and longer than Resovist. The temporal signal change in T2WI within brain cortex region was shown in Fig. 2B. The image intensity falls off rapidly to 50% and then gradually increases to 70% within 3hrs after the injection of Resovist, while the intensity change due to the presence of Fe_3O_4@SiO_2/PEG drops to 33% and then becomes stable with small increase during the first 8 hours (from 33% to 43%). This result suggests that Fe_3O_4@SiO_2/PEG possess higher T2 relaxivity and exhibits longer intravascular circulation. These newly developed particles may therefore be suitable for high-resolution vascular image. Figure 3 shows the 3DΔR2-mMRA using Resovist and Fe_3O_4@SiO_2/PEG, respectively. More and smaller cerebral vessel can be visualized in Fe_3O_4@SiO_2/PEG particle than Resovist with the same dosage (30 mg/Kg).

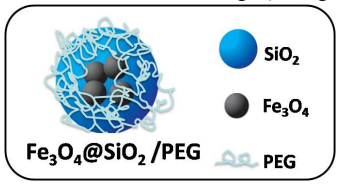

Fig.1 Schematic depiction of Fe_3O_4@SiO_2/PEG

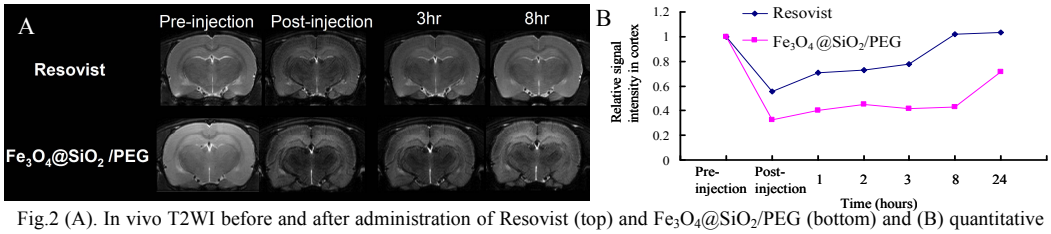

Fig.2 (A). In vivo T2WI before and after administration of Resovist (top) and Fe_3O_4@SiO_2/PEG (bottom) and (B) quantitative curves

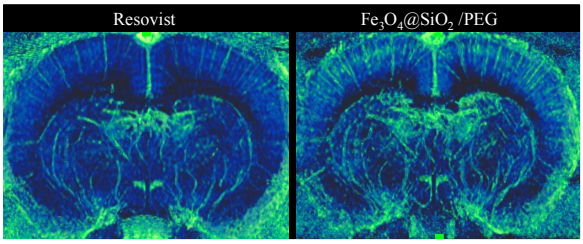

Fig.3 Volume rendering 3DΔR2-mMRA of a same normal rat between the images with the injection of Resoivst and Fe_3O_4@SiO_2/PEG

Conclusion
Newly developed Fe_3O_4@SiO_2/PEG enabled acquisition of high-resolution MRA with higher microvessel conspicuity than Resovist due to the long intravascular half-life and high transverse-relaxivity.

Reference
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