TECHNICAL NOTE

Gd-DTPA-based MR-visible Polymer for Direct Visualization of Interventional Devices

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We developed a Gd-DTPA (gadolinium(III)-diethylenetriaminepentaacetic acid)-based coating copolymer of hydrophilic and hydrophobic subunits to obtain visibility, hydrophilicity, and durability for passive visualization of catheters used in MR-guided interventions. We then examined a metal-free catheter coated with the polymer in a phantom and in porcine brain tissue *ex vivo*. Successful visualization of the coated device demonstrated the applicability of the new coating technique for visualizing catheters used in MR-guided interventions.

Keywords: *coating, device visualization, Gd-DTPA, MR intervention, polymer*

Introduction

In magnetic resonance (MR)-guided intervention, precise and minimally invasive therapeutic procedures require visualization and monitoring of devices such as catheters and guidewires. A variety of techniques have been developed to do this^{1,2} that are typically classified based on whether visualization is “passive,” that is, based on intrinsic properties of materials, or “active,” based on signals from embedded receiver coils or electronics. If visibility is sufficient, the simplicity and safety of a passive technique would make its application preferable to use of active techniques that involve additional electrical signal transmission and reception circuits entering a patient’s body. A passive technique that has been attracting attention is based on MR-visible surface coating polymers that contain T₁ contrast agents like gadolinium(III)-diethylenetriaminepentaacetic acid (Gd-DTPA).³ The primary advantages of this type of passive technique are their positive and defined contrast rather than nega-

tive and broad contrast often caused by susceptibility effect and their capacity to depict the entire length of the devices with no susceptibility. However, an active technique would be better for real-time tracking and guidance of a device because contrast is simply yielded by a relaxation effect.

Basic requirements for coating techniques are their provision of consistent and sufficient visibility of devices so that they can be distinguished from background tissue, and their hydrophilicity to reduce tissue damage.^{4,5} To fulfill these requirements, we developed a Gd-DTPA-based MR-visible block copolymer of hydrophilic and hydrophobic subunits to provide hydrophilicity and durability as a coating material for devices such as catheters used in MR-guided interventions.⁶ Herein, we describe our basic examinations to evaluate the visibility of the polymer-coated catheters in phantoms and porcine brain tissue *ex vivo*.

Material and Methods

We synthesized MR-visible coating material composed of hydrophilic and hydrophobic block copolymer linked with a Gd-DTPA complex. We

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prepared a monomer containing a DTPA unit from *N*-(3-aminopropyl)methacrylamide hydrochloride and diethylenetriaminepentaacetic dianhydride⁷ and dissolved the product and *N,N*-dimethylacrylamide in dimethyl sulfoxide (DMSO) at 80°C. We then followed a previously reported procedure^{8,9} to prepare a solution of poly(glycidyl methacrylate) that contained polymeric peroxide as a radical initiator, quickly added the solution to the reaction mixture, and stirred it for 17 hours. We then added a DMSO solution of gadolinium acetate to the reaction mixture and continued stirring for one hour to form the Gd complex. The MR-visible polymer was precipitated in diethyl ether, filtered, and dried under reduced pressure.

We prepared an MR-visible polymer-coated catheter by dipping a catheter (urethane tube) into a 5 to 7.5-wt% chloroform-methanol mixed solution of MR-visible polymer, drawing it up, and drying it at 80°C for 3 hours, then washing the catheter in a stream of water for 24 hours, soaking it further in saline for 24 hours to remove free Gd ions, and drying the coated catheter at 50°C for 3 hours. We measured the thickness of the coating layer in the swollen state by digital microscope and estimated the content of Gd in the MR-visible polymer by inductively coupled plasma (ICP) emission spectroscopy (ICPS-8000, Shimadzu Corporation, Kyoto, Japan).

We performed a phantom study with catheters (Samples 1–3; outer diameter, 1.55 mm, inner diameter, 1.10 mm) submerged in saline in a plastic container (Fig. 1a). The length of the coated region was 40 mm along the axis of the catheters. We injected saline into each catheter to remove air after submersion. We used a tissue sample from a nor-

mal porcine brain *in vitro*. Based on the regulations of our institutional review board and animal experiment committee, the tissue was dissected from an animal sacrificed for another experiment. Immediately after excision, the brain was immersed in a tray filled with saline. We inserted the polymer-coated catheter (Samples 4 and 5; outer diameter 1.20 mm, inner diameter, 0.80 mm) filled with saline directly into the porcine tissue. The length of the coated region was 100 mm along the axis of the catheter. The catheter was pulled back by 10-mm steps, and the positions were imaged.

All scans were performed on a 1.5-tesla MR system (Signa EXCITE TwinSpeed Ver.11.1, GE Healthcare, Milwaukee, WI, USA) with a birdcage head coil. Inversion recovery-fast spoiled gradient recalled acquisition in the steady state (IR-FSPGR) sequence was used to obtain T_1 enhancement effect suppressing the saline signal in this particular phantom study. The imaging parameters were: repetition time (TR)/echo time (TE)/flip angle (FA), 7.2 ms/3.3 ms/30 degrees; inversion time, 1330 ms (optimized for saline suppression); slice thickness, 5 mm; field of view (FOV), 250 × 250 mm²; acquisition matrix, 256 × 154 (phase FOV, 0.6); reconstruction matrix, 512 × 512; receiver bandwidth (RBW), 31.2 kHz; and number of excitations (NEX), 8. Total acquisition time was 27 s. For *ex vivo* studies, we used fast spin echo (FSE-XL) and FSPGR sequences, with typical parameters for FSE-XL: TR/TE, 300 ms/12.2 ms; slice thickness, 3 mm; FOV, 200 × 200 mm²; acquisition matrix, 256 × 154 (phase FOV, 0.6); RBW, 15.6 kHz; echo train length (ETL), 8; and NEX, 4. Total acquisition time was 26 s. To compare visibility, we also acquired images with slice thickness of 5 mm and

Fig. 1. Outside view of a phantom with 3 catheter samples (a) and a view of the phantom imaged by inversion recovery-fast spoiled gradient recalled acquisition in the steady state (IR-FSPGR) (b). Sample 1 was coated with the magnetic resonance (MR)-visible polymer and Sample 2, with an analogue polymer containing no gadolinium(III)-diethylenetriaminepentaacetic acid (Gd-DTPA); Sample 3 was a control sample with no coating.

NEX of 8. For FSPGR, the parameters were: TR/TE/FA, 5.5 ms/1.2 ms/30 degrees; slice thickness, 5 mm; FOV, $200 \times 200 \text{ mm}^2$; acquisition matrix, 128×77 (phase FOV, 0.6); reconstruction matrix, 512×512 ; RBW, 31.2 kHz; and NEX, 128. Total acquisition time was 55 s. To evaluate the feasibility of passive catheter tracking, we performed imaging with a thick slice by FSE-XL using identical parameters except: TR/TE, 300 ms/12.6 ms; slice thickness, 8 mm; and NEX, 8. Total acquisition time was 50 s.

Results

Figure 1b shows an image of the catheters acquired by IR-FSPGR. Sample 1 with the Gd-DTPA-based polymer was visible with positive signal enhancement. The Gd content of the polymer was 4.9 mg/g, and coating thickness was 150 to 250 μm . The contrast-to-noise ratio (CNR) between the catheter and background saline was 16.1. No signal was observed with the samples coated with an analogue polymer containing no Gd-DTPA (Sample 2) and with no coating (Sample 3). The observed signal enhancement was produced by the T_1 shortening effect of Gd-DTPA confined in the polymer and noted a few minutes after swelling of the coating layer of the catheters in saline.

Figure 2 shows an image of the catheter coated with the polymer in porcine brain tissue obtained by FSE-XL and Fig. 3, by FSPGR. Sample 4 for FSE-XL had 0.79-mg/g Gd content and 100- to 165- μm coating thickness, and Sample 5 for FSPGR had 5.5 mg/g and 100- to 150- μm coating thickness. Signal enhancement was sufficient to distinguish the catheter from the background tissue. The CNR between the catheter and tissue was 7.3 in an FSE-XL image (Fig. 2a) and 3.3 in an FSPGR image (Fig. 3a). Figure 2c–e shows a set of FSE-XL

images taken when the catheter was pulled back inside the tissue in a thick slice (8 mm). The entire coated catheter was visible in the slice. The CNR between the catheter and tissue was 10.4 (Fig. 2c). Signal enhancement of the catheter was stable during the 6-hour procedure, and we observed no detachment of the coating layer upon eye inspection after the experiment. When an image without the catheter was subtracted, highlighting of the coated catheter with signal-to-noise ratios (SNR) of 14.8 (Fig. 2f) and 8.6 (Fig. 3b) demonstrated the feasibility of using the present coating technique for passive catheter tracking.

Fig. 3. (a) Catheter with magnetic resonance (MR)-visible coating (Sample 5) imaged by fast spoiled gradient recalled acquisition in the steady state (FSPGR) in porcine brain tissue. (b) Background-subtracted image.

Fig. 2. Catheter with magnetic resonance (MR)-visible coating (Sample 4) imaged by fast spin echo (FSE-XL) in porcine brain tissue. Slice thickness is 3 mm (a) and 5 mm (b). (c)–(e) Passive tracking of a catheter with 8-mm slice thickness. The catheter was pulled back by 10-mm steps. An example of the background-subtracted images with 8-mm slice thickness (f) depicts the entire view of the coated catheter.

Discussion

We conducted this study to demonstrate the applicability of the novel coating material and technique to passive visualization and tracking of a device such as a catheter. The coating polymer was designed to have sufficient visibility, surface hydrophilicity, and durability. The developed copolymer may form a network of polymer chains by cross-linking reaction of epoxy groups after coating. The low frictional surface of such coating layer, which absorbs water because of its hydrophilicity, enables smooth catheter insertion into tissue. The copolymer is also soluble in organic solvents, so a simple dipping process can be used to coat the catheter surface without any pretreatment. These properties are suitable for flexible catheters with minimum influence to the mechanical properties of the device.

In both phantom and *ex vivo* experiments, the polymer-coated catheters were visible with positive signal enhancement. The presence of Gd-DTPA confined in the polymer shortened the relaxation process of water protons in the vicinity of the hydrophilic polymer to produce sufficient signal enhancement to depict the catheter in the tissue. The CNR of the polymer-coated catheter may be improved by optimizing the polymer's composition, including its Gd-DTPA content, for a specific target tissue or blood in which an interventional procedure is planned. The catheter's clear appearance in the subtraction image suggests a possibility of improving visibility with image processing.

A primary drawback of using the proposed polymers is the relatively longer acquisition time required to achieve a sufficient contrast-to-noise ratio. Because we employed a normal birdcage coil with no parallel imaging capability and a 1.5T static magnetic field in this particular study, acquisition time was 26 to 55 s. These times would be reduced 75% using a parallel imaging technique like SENSE (sensitivity encoding) with a parallel factor of 4 and a higher magnetic field, such as 3T. Moreover, scan time would be less significant if the main purpose of using the polymer coating were visualization of a device with its shape or length in MR imaging rather than real-time tracking, which can be achieved by either conventional X-ray fluoroscopy or, if necessary, an active visualization mechanism under MR guidance. Thus, the present results demonstrated that the proposed polymer technique would be useful for visualizing nonmetal devices, such as meshless catheters, brain drainage catheters,¹⁰ or optical fibers.¹¹ Although intravascular experimentation *in vivo* is obviously needed to demonstrate the clinical applicability of the technique, our

results also demonstrate the viability of such coatings as an important step towards simple MR-guided endovascular interventions.

In conclusion, the newly developed Gd-DTPA-based polymer exhibited visibility with positive signal enhancement in both phantom and *ex vivo* tissue with sufficient hydrophilicity and durability.

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