

Atherosclerotic MR Molecular Imaging Strategy with Superparamagnetic Iron Oxide on a Human Clinical Scanner – Rabbit Model

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Introduction

Atherosclerotic plaques are formed through the accumulation of macrophages, lipids, and fibrous connective tissue underneath the endothelium lining in arterial walls. CD44 is a cell surface receptor at macrophages which tend to accumulate at atherosclerotic plaques. Nanoparticles with high affinity to specific components or molecules of the plaque can be synthesized for the purpose of imaging and drug delivery. One common type of the nanoparticle is superparamagnetic iron oxide (SPIO) which enhances the decay of the T_2^* signal (1,2,3). Hyaluronic acid (HA) is a ligand targeting CD44. In this work, HA molecules were bonded to dextran coated SPIO nanoparticles (DESPIONS) and thus HA-DESPIONS were synthesized. These HA-DESPIONS are expected to specifically target CD44 and in turn highlight the macrophages at the plaque through MRI. Rabbit is a common model for atherosclerotic imaging research (2,3). With HA-DESPION as an example, here we summarize our molecular imaging strategy of a rabbit model on a human clinical scanner.

Methods

All data were collected on a GE 3T HDx MRI scanner (GE Healthcare, Waukesha). To maximize the signal-to-noise ratio, an Invivo 8-channel transmit-receiver human knee array coil (Pewaukee, WI) was selected to match the size of the rabbit. A simple plastic tray was built to hold the rabbit in place. The aorta from the heart to the lumbar region of an adult rabbit has a diameter of 4-5 mm and a length longer than 14 cm. The sizes and length are comparable to human arteries such as carotid arteries, and the rabbit aorta anatomy can be easily resolved on a human clinical scanner as well. The size and length are also appropriate for selectively introducing injury for comparison studies. To plan for one hour of scan time, a rabbit (3.2 kg average weight) was usually anesthetized by the injection of 25mg Katamine/kg (Bioniche Pharma, Lake Forest) at the left lumbar muscles.

Rabbit positioning: To minimize breathing motion artifacts, a rabbit is best placed at a supine position. The aorta is right next to the anterior region of the spine. With the aorta close to the coil, this position helps to maximize the signal-to-noise ratio (SNR) of the aorta images also. The rabbit can be positioned to be feet-first to further simplify the administration of nanoparticles through a vein in the ear. The veins in the ear can be easily identified and thus are ideal for venous injection.

Rabbit aorta visualization and localization: The rabbit aorta is needed for further localization and visualization beyond the typical 3-plan localizer. This can be accomplished through 2D time-of-flight (2D TOF) images. The projection images can serve as the localizer for the high-resolution 3D imaging to monitor the effect of the SPIO nanoparticles. The renal arteries and celiac trunk identified in 2D TOF can serve as the anatomic landmarks for *in vivo* - *in vitro* comparison as well as histology analysis. In 2D TOF, signal suppression has to be applied in a way such that the blood signal enhancement is maximized. 2D TOF is commonly applied to visualize the blood flow from the carotid arteries to the brain. The 2D TOF head protocol can be simply applied assuming that the rabbit is at a head-first position. To minimize breathing motion artifacts, it is necessary to apply frequency-encoding direction in the anterior/posterior (A/P) direction for all imaging protocols. 2D TOF protocol: TE = 4.4 ms, TR = 23 ms, flip angle = 60°, receiver bandwidth (rBW) = ± 15.63 kHz, field of view (FOV) = 14 cm, slice thickness = 2 mm, matrix size = 256×128 , number of excitation (NEX) = 1, Freq direction = A/P, 79 slices, 19 projection images, spatial saturation thickness = 40 mm.

Monitoring the effect of SPIO nanoparticles *in vivo*: The main effect of the SPIO nanoparticles is the reduction of the T_2^* , which is best detected by gradient recalled echo based sequences. To visualize the rabbit aorta with a high resolution and good SNR, 3D gradient recalled echo sequence should be the better choice over its 2D counter-part. The time of echo (TE) should be chosen so that the images are sensitive to the T_2^* effect even at a relatively low concentration of nanoparticles. The proper TE can be identified with a multi-echo gradient echo sequence. The following protocol has been applied in our pre-and-post nanoparticle injection: 3D Fast spoiled gradient recalled (FSPGR) sequence, TE = 13.9 ms (or 9.3 ms), TR = 28 ms, flip angle = 15°, rBW = ± 5 kHz (or 7.81 kHz), FOV = 12 cm, slice thickness = 1 mm, number of slice locations = 90, matrix size = 256×256 , NEX = 2, Freq Dir = A/P. To demonstrate the effect of the SPIO nanoparticles, the following imaging results are expected: (1) Bright blood signal at the lumen and relative iso-intense signal between vessel wall and surrounding muscle are expected before the injection of nanoparticles. (2) Right after the injection of the nanoparticles, the lumen and the wall should be darkened due to T_2^* decay. (3) After a few hours, the nanoparticles at the lumen are expected to be cleared through circulation and image signal at the lumen should return to near its pre-injection level. But if there is a high affinity between the nanoparticles and specific plaque components, dark spots should remain at these plaque components.

Results and Discussion

The descending aorta can be easily visualized by 2D TOF maximum-intensity-projection images with the renal arteries and celiac trunk shown (Fig. 1). Fig. 2 shows the effect of the SPIO nanoparticles *in vivo* by comparing the images before injection, images at 10 minutes after injection and at 3-hour after injection in one of our studies. The effect of the SPIO nanoparticles is shown clearly through different stages. The widening of the dark band at the vessel wall at 3 hours after injection (Fig. 2c) indicates the specific affinity of the SPIO nanoparticles and penetration of these particles into the vessel wall. Our MRI imaging strategy works well with SPIO nanoparticles. If T_1 -sensitive nanoparticles are used, the 2D TOF image protocol is still applicable, but the above gradient-echo sequence is no longer appropriate.

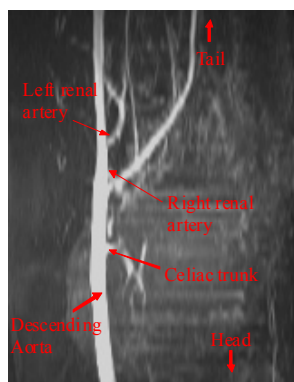


Fig. 1. Anatomical landmarks shown by 2D TOF for visualization and for *in vivo* - *in vitro* comparison.

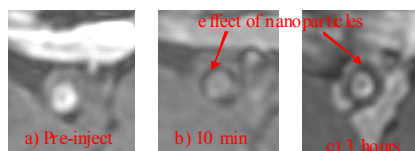


Fig. 2. Monitor the effect of SPIO nanoparticles with 3DFSPGR.

Reference

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