Fluorine MR Angiography with Intravenously Delivered Nanoparticle Emulsions at 1.5 T

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ABSTRACT

Fluorine magnetic resonance imaging, with its lack of competing background signal, has been used for a variety of applications including mapping oxygen tension, studying tumor metabolism, and imaging of vasculature and organ perfusion (1,2,3). In this work, we sought to characterize the use of a systemically-injected perfluoro-15-crown-5-ether fluorinated nanoparticle contrast agent for MR angiography at the clinical field strength 1.5 T.

INTRODUCTION

Fluorine nuclei provide an attractive opportunity for magnetic resonance imaging in that living tissue contains virtually no endogenous fluorine. Flourinated contrast agents that are able to safely accumulate in a high enough concentration in tissues can therefore allow visualization of the desired structures without the competing background signal observed with typical proton imaging. However, the lower concentration of fluorine requires longer scan times, lower resolution, and/or higher field strengths to obtain sufficient signal to noise. For this study, we sought to determine the clinical utility of using a fluorinated contrast agent for angiography with a clinical 1.5T imaging system. The first step in this analysis is to determine the lower limits of detection with our imaging system. We accomplished this by co-labeling perfluoro-15-crown-5-ether nanoparticles with Gd-DTPA-BOA before injection so that upon injection into rabbits and subsequent imaging, we could define the concentration of Gd-DTPA-BOA (and therefore, fluorine) in the blood.

MATERIALS and METHODS

Methods developed in our laboratories were used to prepare perfluorocarbon (perfluoro-15-crown-5 ether, CE) emulsions encapsulated by a lipid-surfactant monolayer (4). ^{19}F imaging was performed on a clinical 1.5 T MR scanner that was modified to include a specialized channel tuned for fluorine nuclei (Philips Intera CV, Philips Medical Systems; Best, Netherlands). A New Zealand white rabbit was anesthetized using a ketamine/xylazine bolus and continuous drip. ^{1}H phase contrast MR angiography (PCA) scans were acquired using the quadrature body coil for excitation and a 4 cm diameter surface coil placed over the rabbit neck for receive, to allow localization of the carotid arteries and other vasculature in the neck (PCA parameters: velocity encoding in foot-head direction of 3 cm/s, 50 slices, TR 20ms, TE 8.8 ms, flip angle 50°, 1.0x0.5x0.5 mm reconstructed resolution). A 7-cm surface coil tuned to 60.1 MHz was then placed over the neck for transmission and receipt of the ^{19}F MR signal, prior to injection of the contrast agent. Over a period of two hours, five bolus injections of 0.5 mL/kg of nanoparticles were delivered intravenously approximately every half hour (total dose per injection was 1.9 mL). Ten minutes after each injection, a projection bFFE ^{19}F image of the vasculature was acquired (TR 4ms, TE 1.4ms, flip angle 60°, NSA 512, 2.03x1.42x20mm reconstructed resolution, 2 min 11s scan time), followed by removal of 1 mL of blood. The blood samples were then analyzed using a 0.47 T Minispec machine (Bruker Optics; Billerica, MA) for determination of gadolinium content.

RESULTS and DISCUSSION

The nanoparticles used in the study were formulated to contain particles of 184 nm nominal diameter and 12.1 M ^{19}F (or, 0.61 M liquid perfluoro-15-crown-5-ether), resulting in a 0.67 g dose of PFC for each injection. The outer lipid layer of the particles also contained gadolinium, in the form of Gd-DTPA-BOA (approx 48,000 gadolinium molecules per particle), which was utilized for analyzing the blood samples. The ^{19}F images that resulted from these injections as well as the ^{1}H angiography scans are shown in Figure 1. The first hint of fluorine signal appeared after the third dose of particles, while the best image was generated after the fifth injection. The blood sample analysis showed a linear dose dependence of the concentration of fluorine in the blood with amount of particles administered. The third dose resulted in a concentration of 0.24 M fluorine in the blood, while the fifth dose increased this value to 0.36 M.

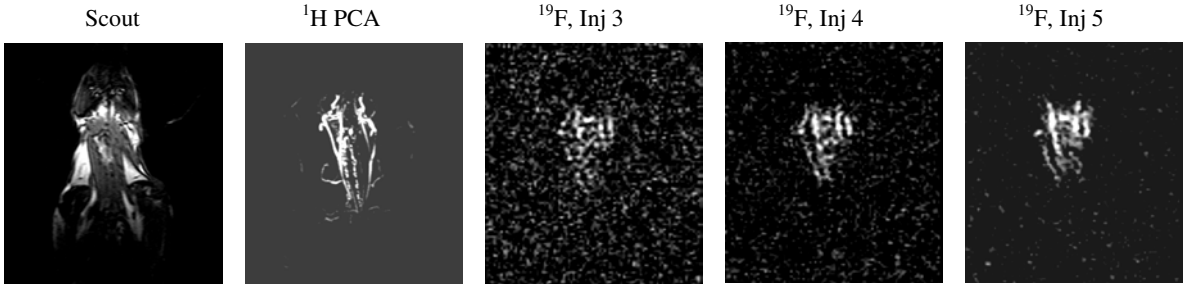

Figure 1: Images showing the ^{1}H image of the rabbit neck (far left), ^{1}H PCA of neck vasculature (mid left), and the ^{19}F projection images acquired after each of the last three injections (middle and right).

CONCLUSIONS

We have demonstrated that fluorine MR angiography of the carotid vessels in a rabbit is possible at 1.5 T with this nanoparticle system. Furthermore, we have established the dose requirements on nanoparticle administration that are required for generating images of arteries with this system. Further improvements in coil and sequence design may allow a reduction in minimum dose and/or faster and higher signal to noise ratio scans. Systemic injection of a contrast agent for which there is no competing background signal may allow more accurate and diagnostically meaningful angiography exams with MR. The rabbit carotid arteries imaged in this scan are similar in size to human coronary arteries, thereby suggesting a clinically relevant analogue to human MR angiography.

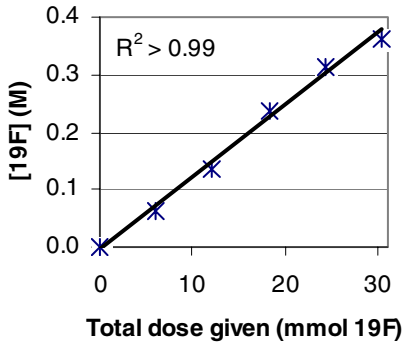

Figure 2: Relationship between the measured concentration of fluorine in the blood and the total dose of fluorinated particles given to the rabbit.

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