Fluorine Spectroscopy and Imaging of Unstable Atherosclerotic Plaque with Fibrin-Targeted Nanoparticles using Fast Balanced Techniques at 1.5T

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Introduction: Ruptured atherosclerotic plaque and associated thrombus is the proximate cause of strokes and heart attacks. Quantification of intimal thrombotic burden with molecular imaging agents will likely be required to support clinical decisions for acute invasive intervention over conservative medical therapy. We have reported that fibrin-targeted paramagnetic nanoparticles can detect microthrombotic deposits as hotspots within ruptured plaques in human carotid endarterectomy specimens using T1-weighted MRI at 1.5T [1]. These proton images of targeted nanoparticles illustrate the presence of unstable plaque, but further quantification may be limited. We suggest that estimates of thrombotic burden may be required for rational clinical risk/benefit decisions of acute invasive intervention versus conventional medical therapy. We have previously shown that the liquid perfluorocarbon (PFC) core of nanoparticles can be varied (*e.g.*, perfluorooctylbromide (PFOB) or 15-crown-5 ether (CE)) and spectrally resolved and quantified with high field strength MR (4.7T) [2]. These early results have suggested an opportunity to quantify one or more targeted nanoparticle agents simultaneously, which would allow noninvasive phenotypic characterization with multiple biosignatures and or quantification of targeted therapeutic agent delivery. The objective of the present research was to determine if the potential of fluorine spectroscopy and imaging demonstrated with high-field, small animal magnets can be translated to clinically relevant 1.5T MR imaging systems

Methods: A clinical 1.5T MR system (NT Intera CV, Philips Medical Systems) was fitted with a second spectrometer channel tuned to the resonance frequency of ^{19}F. A 7cm surface coil, resonating at 60.12 MHz, was used for both transmit and receive. MR spectroscopy without volume selection was performed on PFC phantoms containing both CE and PFOB. Spectra (see Figure 1) were acquired using 90-degree adiabatic RF excitation pulses (0.5ms duration) with a 4 sec TR and 16 samples averaged. In addition, human carotid endarterectomy samples were targeted *in vitro* with fibrin-targeted nanoparticles containing a crown-ether core using classic biotin-avidin interactions as previously reported [3]. The targeted arteries contained within plastic test tubes were extensively washed and imaged with both proton MRI and fluorine spectroscopy and imaging. Spectra were acquired as above using both non-volume selective and volume selective (ISIS) spectroscopy (with 1 sec TR and 192 averages). ^{19}F imaging was performed using a steady-state gradient echo technique (bFFE) offset from ^{19}F resonance frequency by 8250 Hz (the offset of crown ether at 1.5T) with the following parameters: TE/TR = 2.25/4.5ms, FoV = 196mm, Matrix = 77x128, 128 NSA. This sequence could be acquired as a thick 2D "projection" image or as a multi-slice (*i.e.*, 5 slices) acquisition requiring only 35sec per imaging slice.

Results: At 1.5T using ^{19}F MR spectroscopy, the individual peaks of CE and PFOB phantoms were detected and could easily be resolved into the six expected peaks (see Figure 1). Note that the PFOB peaks span a range of approximately 4 kHz at 1.5T, which illustrates the potential for spectrally isolating individual fluorocarbon signatures from judiciously selected PFC combinations. The fluorine signal from minute concentrations of CE nanoparticles targeted to microthrombi along human endarterectomy samples were readily detected and localized using spectroscopy (see Figure 2). ^{19}F bFFE imaging sequences provided three-dimensional information that facilitated the overlay of fluorine images onto higher resolution proton images of the carotid arteries confirming the presence of targeted nanoparticle (see Figure 3).

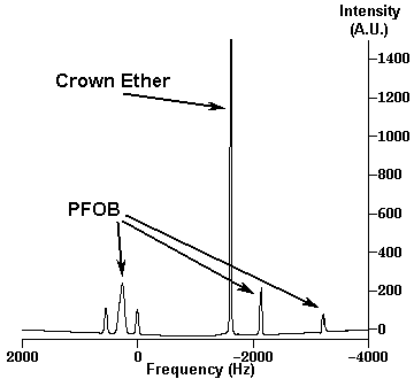

Figure 1. *Fluorine spectrum of two perfluorocarbons, crown ether (one peak) and perfluorooctyl bromide (PFOB, five peaks). For the* in vitro *study in the other figures, crown ether nanoparticles were used.*

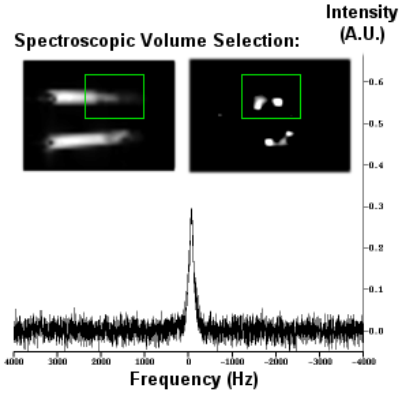

Figure 2. *Fluorine spectrum of crown ether nanoparticles bound to the fibrin in human carotid samples (in test tubes). Spectroscopic volume is localized as shown on a single sample using the proton image (upper left) and a fluorine image (upper right).*

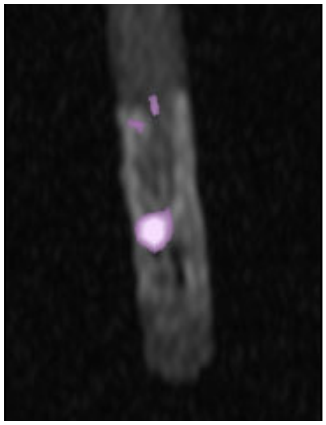

Figure 3. *Proton MR image of a carotid artery specimen in a test tube of saline. Overlaid in violet is the signal from the corresponding slice of the bFFE fluorine image.*

Conclusion: The present study demonstrates that ^{19}F spectroscopy and imaging can be translated from high-field small animal systems to clinically available MR imaging systems at 1.5T using realistic scanning times. These early images provide sufficient quality and signal-to-noise to sensitively resolve independent spectral peaks from different perfluorocarbons and to acquire spatially-encoded ^{19}F images. Moreover, concomitant ^{19}F spectroscopy may permit quantification of biosignatures, such as fibrin deposition, to support rational risk/benefit assessments of therapeutic alternatives.

References:

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