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Quantitative molecular imaging of atherosclerotic endothelial dysfunction with perfluorocarbon (^{19}F) nanoparticle magnetic resonance imaging and spectroscopy

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Introduction

Disturbed endothelial barrier function in atherosclerosis has been detected by MRI by imaging gadolinium leakage into the vascular interstitium but not yet quantified.

Purpose

We propose that the unique, no background ^{19}F signal from crown ether perfluorocarbon-core nanoparticles (NP: ~250 nm) might both visualize *and* quantify endothelial disruption in advanced atherosclerosis.

Methods

Five NZW rabbits were fed a high fat diet for 9-12 months (cholesterol: 1200-1700 mg/dL). Fluorescently-labeled, nontargeted NP were injected (2 ml/kg) intravenously into rabbit ear vein. After circulation *in vivo* for 1, 6 or 24 hours, aortas were excised for ^{19}F MRI and spectroscopy (Varian 11.7 T scanner); and whole mount fluorescence imaging (Xenogen IVIS system). Two human carotid endarterectomy tissues were collected from operation room. After pretreatment with plasmin to digest fibrin on the endothelial surface and incubation with nontargeted NP for 6 hours, tissues were rinsed and formalin fixed for ^{19}F MRI and spectroscopy. A perfluorooctyl bromide standard enabled MRS-based quantification of NP concentration in each imaged voxel.

Results

In rabbit aortas, MRI (^{19}F/^{1}H overlay) revealed abundant ^{19}F signal from intact NP that were localized heterogeneously in the plaque interstitium (Fig. 1A) but not in unaffected areas. The average tissue concentration of NP calculated from MR spectroscopy (Fig. 1B) was 2.36 ± 0.42 × 10^{9} /g aorta. The accumulation of NP is distinct from macrophage uptake, as demonstrated by high resolution fluorescence microscopy (Fig. 1C). Fluorescence imaging (Fig. 1D) also confirmed the presence of NP. In human carotid arterectomy tissues, the detected ^{19}F signals were primary located on the endothelial/luminal side (Fig. 2). Quantitative analysis showed that average NP concentration in carotid arterectomy tissue was 47.1 ± 18.3 × 10^{9} /g tissue.

Conclusion

For both advanced experimental animal atherosclerosis and native human atherosclerosis tissues, nontargeted NP rapidly penetrate the leaky endothelial barrier, which can be visualized and quantified *ex vivo* with the use of "no background" ^{19}F MRI and MRS. This experimental strategy offers a potential new approach for quantification of endothelial dysfunction employing both *in vivo* and *ex vivo* incubation with nanoparticle tracers.

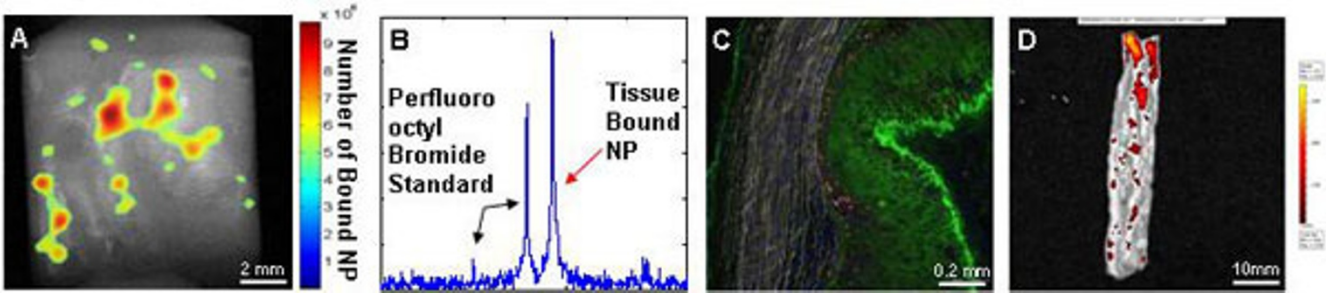

Figure 1
Rabbit Atherosclerotic ^{19}F MRI, MRS, Fluoresceince Microscopy and MS Imagages.

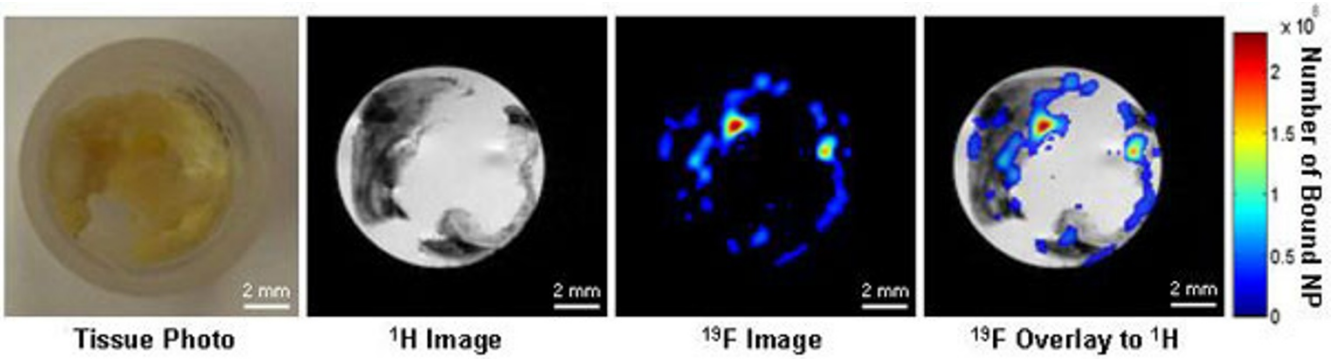

Figure 2
Human Endarterectomy Tissue Photo, ^{1}H and ^{19}F MR Images.