Visualizing Atherosclerotic Plaques with Micelles: Does Size Matter?

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Mixed micelles are nanoparticle (e.g., diameter 5-150 nm) MRI contrast agents that contain a phospholipid, a biocompatible non-ionic surfactant and a lipophilic gadolinium (Gd^{3+}) complex.[1] In vivo atherosclerotic plaque detection and characterization could be potentially improved using MRI lipophilic contrast agents.[2] The purpose of this study was to evaluate several mixed micelles incorporating different lipophilic Gd^{3+} complexes for atherosclerotic plaque imaging and to determine if the size and Gd^{3+} ions/particles of the micelles improves in vivo plaque detection.

Methods. Several formulations employing different phospholipids, Gd^{3+}-chelates, and surfactants were synthesized to obtain the micelles. The micelles were prepared by sonication of the dried lipids and Gd^{3+}-chelates at 65° C in water. After sonication, addition of the surfactant was followed by another 15 minutes sonication. The micelles' diameter were determined with a laser light-scattering submicron particle sizer.[3] All micelles were monodisperse. Relaxivity (R1) was determined by calculating T1 values of various concentrations using an Inversion Recovery Spin Echo sequence at 1.5T. The number of Gd^{3+} complexes per nanoparticle was obtained from the ratio of the concentration of Gd^{3+} and nanoparticles in the emulsion.[4] Thirteen-month-old atherosclerotic Apolipoprotein E knockout (KO) mice (n=4) on a high cholesterol diet and Wild Type (WT) (n=4) group underwent in vivo MR microscopy (MRM) of the abdominal aorta using a 9.4T MR system. Pre- and post- contrast enhanced (1 hour and 24 hours post) MRM was performed using a T1-weighted black blood sequence. Sixteen contiguous 500 μm thick slices with an in-plane resolution of 93 μm were acquired in 30 minutes. Micelles were injected via the tail vein. MRM images of the matched (pre and post) slices were used for analysis.

Table 1

	% Phospholipid	% Contrast Agent	% Surfactant	Diameter (nm)	R1 ($mM^{-1}s^{-1}$)	Gd^{3+} ions/particle
1	79[1]	7[2]	14[3]	123.0	29.2	12,000
2	79[4]	7[2]	14[3]	20.6	26.8	60
3	59.4[5]	37.7[6]	2.8[7]	100.9	22.9	46,000

[1]POPC (palmitoyloleoyl phosphatidylcholine), [2]$GdDOTAC_{14}$ (Ref. 5), [3]Tween 80, [4]DPPC (dipalmitoyl phosphatidylcholine), [5]DPPANa (dipalmitoyl phosphatidic acid, sodium salt), [6]$GdDOTASA(C_{18})_2$ (Ref. 5), [7]Synperonic F108.

Results. The micelles characteristics are presented in Table 1. Micelles **1** and **2** showed an enhancement of the plaque after 24 hours post-injection (p.i.). No measurable enhancement was observed at 1 hour p.i. Micelle **3** showed an enhancement 1 hour and 24 hours p.i. The ratio of the post to pre signal intensity, at 24 hours, of wall normalized with respect to muscle was 1.75 (enhancement by 75%) and 1.28 (enhancement by 28%) by **1** and **2** in KO mice, respectively. There were no enhancements in the WT group for all the micelles. Additionally. there was no enhancement of the plaque using conventional Gd^{3+}-chelate (i.e., Gd-DTPA; 100μmol/kg) in either the KO or WT groups.

Conclusion. We demonstrated in this in vivo study that mixed micelles MR contrast agents localize and substantially enhance atherosclerotic plaques. Both large and small size diameter micelles with different paramagnetic payload (Gd^{3+}/particle) appear to be effective. The specific localization of these contrast agents in the plaques needs to be evaluated. Additionally, these contrast agents could potentially be used to target specific atherogenic markers and could provide a targeted approach for molecular in vivo atherosclerotic plaque MRI.

References:

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