Comparison of Four Clinically Approved Gadolinium-based Contrast Agents for Imaging of Experimental Atherosclerosis in a Rabbit Model

M. de Smet[1,2], J. Ronald[1,3], K. Rogers[3], R. Hegele[1], K. Nicolay[2], and B. Rutt[1,3]

[1]Robarts Research Institute, London, Ontario, Canada, [2]Eindhoven University of Technology, Eindhoven, Netherlands, [3]University of Western Ontario, London, Ontario, Canada

Introduction: It is well established that the composition of atherosclerotic plaque is an important determinant of the risk of plaque rupture. High resolution plaque imaging using contrast-enhanced MRI with gadolinium (Gd)-based contrast agents (CA) has shown potential for improved identification and characterization of plaque components[1,2]. In particular, early studies have yielded improvements in determinations of fibrous cap thickness and the amount of neovascularization present[3]. It has also been shown that parameters extracted from CA kinetic curves can help to identify specific plaque components[4]. Since these early studies, several new clinically approved CAs have become available, each with its own molecular weight, structure, charge, protein binding affinity and associated relaxivity. As a result of these differences, one would expect different capabilities of each agent for plaque visualization and compositional assessment. To permit rational comparison between multiple Gd-based agents, we performed contrast-enhanced imaging of atherosclerotic plaques in a cholesterol-fed rabbit model, with images of the abdominal aorta acquired pre- and up to 2 hours post contrast following administration of four distinctly different CAs to individual animals. To our knowledge, this is the first comprehensive comparison of multiple clinically approved Gd-based agents for this purpose.

Methods: To evaluate these CAs for plaque imaging, we used a NZW rabbit model of atherosclerosis fed a 0.25%-cholesterol diet for 18 months. This model is known to produce atherosclerotic plaque throughout the aorta with human-like compositional elements, including fibrous cap and moderate size lipid-rich necrotic core[5]. Each rabbit (N=5) had four imaging sessions using a 0.2 mmol/kg dose of each of the following CAs: Magnevist™ (Gadopentetate dimeglumine), Omniscan™ (Gadodiamide), Multihance™ (Gadobenate dimeglumine), and Gadovist™ (Gadobutrol). These agents were selected to represent a range of commonly used clinically approved Gd-chelates, including two ionic and two non-ionic agents. Images were acquired using a quadruple inversion recovery fast-spin-echo (QIR-FSE) sequence[6] on a 3T GE Excite scanner (TE/TR/TI= 21.8/800/520, ETL=6, BW=+/-11.9kHz, resolution=320x320, NEX=10, scan time=21:42) pre- and up to 2 hours post-contrast CA administration. Average abdominal aortic wall signal intensities were determined by manually tracing both inner and outer vessel wall boundaries. Plaque enhancement was defined as percent increase in average vessel wall signal intensity relative to pre-contrast baseline.

Results: Image quality was consistently excellent, considering the very high in-plane resolution (150 microns), allowing the discrimination of internal plaque structure in this rabbit model of atherosclerosis. The four CAs that we tested showed very similar ability to enhance the vessel wall in our model. Qualitatively, there were no striking differences in the pattern of enhancement within the vessel wall between all four CAs for the majority of plaques, however slight differences were noticeable (Figure 1). Peak enhancement values (relative to baseline) reached 100-120% for all four CAs, and occurred at approximately 15-20 minutes following CA administration. The four agents displayed very similar wash-out kinetics, with enhancement values falling to approximately 50% of peak enhancement at approximately 2 hours post injection (Figure 2).

Discussion and Conclusion: We have compared four commercially available Gd-based CAs for imaging of atherosclerotic plaque in a relevant model of moderately complex atherosclerosis. The four CAs showed markedly similar plaque enhancement patterns and kinetics. Future work will focus on the characterization of enhancement kinetics in various regions of the vessel wall / plaque, with the aim of relating kinetic parameters to structural differences within individual plaques. This work will help to identify those CAs that are more advantageous for improving definition of plaque boundaries and/or plaque components, and will allow optimization and standardization of CA choice for clinical studies where this type of intensive multi-agent comparison would not be possible.

Acknowledgements: We thank Berlex Canada for providing Magnevist™ and Gadovist™, Bracco Diagnostics Canada for providing Multihance™ and GE Healthcare Canada for providing Omniscan™ for this study.

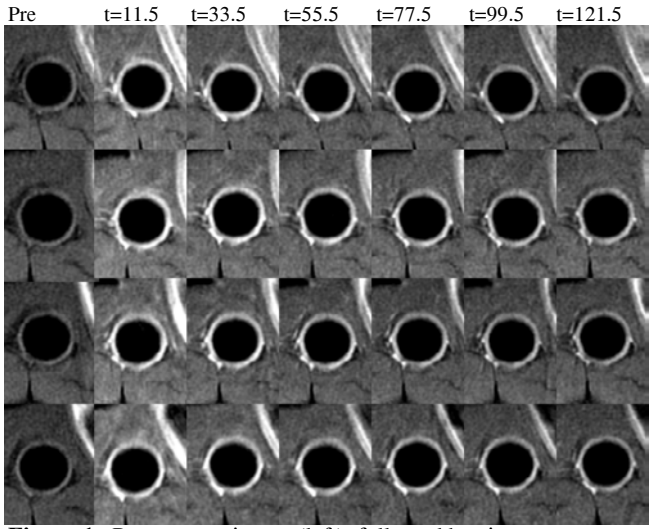

Figure 1. Pre contrast image (left), followed by six post- contrast images. From top to bottom: Magnevist™, Omniscan™, Multihance™ and Gadovist™.

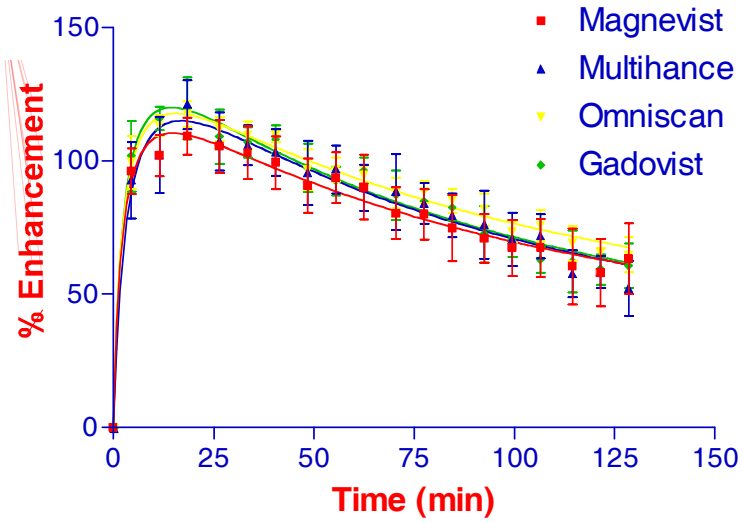

Figure 2. Average % enhancement curves of the four different CAs.

References: (1)Yuan et al. J Magn. Reson. Imaging, 2002, (2)Wasserman et al. RSNA, 2002, (3)Cai et al. Circulation. 2005, (4)Kerwin et al. Circulation, 2003, (5)Daley et al. Atherioscler Thromb 1994, (6)Yarnykh et al. Magn Reson Med 2002