Dynamic MR imaging of injured rabbit aortic wall with a blood pool (MS-325) and conventional ECF agent: Similarities and differences

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Introduction

There is considerable interest in using contrast agents to characterize atherosclerotic plaques. One technique is based on dynamic contrast enhanced MRI to provide information regarding plaque inflammation through lesion neovascularity and abnormal endothelial permeability [1,2]. Evidence suggests that the blood pool contrast agent MS-325 (Vasovist, Epix Pharmaceuticals, Cambridge MA) also enters plaque and may improve *in vivo* depiction of plaque neovascularity and permeability via its higher relaxivity. In comparison to conventional ECF contrast agents, MS-325 binds to albumin in serum and has an approximately five-fold higher T1 relaxivity R_1 (at 1.5T) when bound. The higher relaxivity will increase the contrast-to-noise ratio of plaque enhancement, but only if a significant fraction remains bound within the plaque. To test the hypothesis that MS-325 improves depiction of plaque inflammation, we performed static and dynamic MRI of balloon-injured New Zealand White (NZW) rabbit aortas with both MS-325 and a conventional ECF agent.

Methods

Five NZW rabbits underwent pullback balloon injury of the lower abdominal aorta followed by a 0.2% cholesterol and 5% peanut oil diet to induce complicated aortic plaque. [3] Approximately 18 mo later MRI was performed on a 1.5T system using a prototype 4 channel phased array small animal coil. Time of Flight, proton density (PD), pre- and post-contrast quadruple IR T1 (QIR-T1, designed to null lumen over a wide range of T1 values [4]), and dynamic QIR-T1 was performed twice on each rabbit - once after the administration of 0.1 mmol/kg Magnevist (Schering AG, Berlin, Germany) and once after 0.05 mmol/kg MS-325. Scans were performed at least 2 weeks apart. The dynamic QIR-T1 study was a single slice (chosen at the level of maximal disease) with a true resolution of 0.35 x 0.35 x 2 mm. Seven dynamic time-frames were obtained with a temporal resolution of 47 sec (Figure 1), FOV=90 mm, TR/TE = 800/8, 3 averages. The aortic wall was traced on the dynamic images and percent enhancement as well as integrated-area-under-the-curve (IAUC) was calculated for each rabbit and contrast type (normalized against muscle IAUC). A linear regression of the IAUC was performed. Following imaging, all rabbits were sacrificed and histology was obtained.

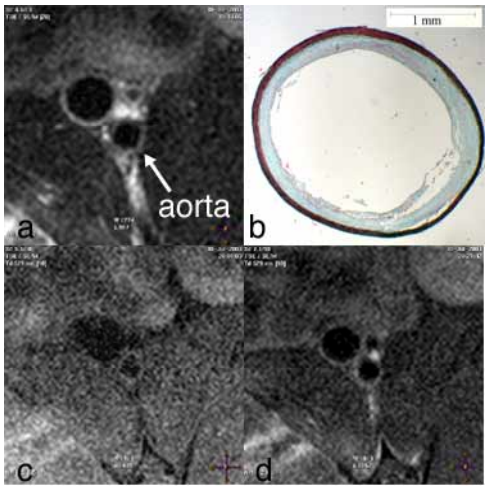

Figure 1. PD MRI (a), histology (Movat stain) (b), and pre- (c) and post- (d) QIR-T1 MS-325 images of the injured aorta.

Findings

The balloon-induced lesions were quite complex, averaging 0.2 mm in thickness (Figure 1). Pre and post contrast QIR-T1 images demonstrated good lumen suppression, although the MS-325 images showed more lumen signal intensity (SI), likely due to the persistence of intra-luminal T1 shortening characteristic of a blood pool agent. Abnormal wall thickening was seen on PD and QIR-T1 images in all animals. Average percent enhancement of the aortic wall plotted against time for both agents at the index level (Figure 2) reveals greater wall enhancement with MS-325 at all time points. Calculation of the enhancement ratio between MS-325 and Magnevist at each time point (Figure 3) demonstrates an early peak in the MS-325 aortic enhancement between 30 – 60 seconds. Normalized (Figure 4) IAUC demonstrates a good correlation between the aortic enhancement obtained with MS-325 and Magnevist. Histologic analysis is currently underway.

Discussion

These preliminary results show that 0.05 mmol/kg MS-325 produces greater enhancement of diseased aortic wall than does a higher dose of 0.1 mmol/kg Magnevist at all time-points (Figure 2). This observation leads to the conclusion that a significant portion of the MS-325 remains bound within the atherosclerotic plaque and thus yields the five-fold increase in relaxivity. In addition, the dynamic distribution of MS-325 differs from that of a conventional ECF agent. It is believed that the large size of the highly bound (85%) MS-325-albumin complex reduces the rate and amount of contrast passage through the endothelium into the diseased arterial wall (although the 15% unbound fraction should extravasate at the same rate as ECF agents). Early in the dynamic sequence (Figure 3, 1st time-point), the ratio of MS-325 enhancement to the ECF agent enhancement is highest, likely reflecting a large contribution of signal from the intravascular space of the plaque (i.e. first pass through the vasa-vasorum). At later time points where extravascular accumulation of the agent dominates, this ratio declines, suggesting that MS-325 extravasates into the aortic wall more slowly than an ECF agent, presumably due to its binding to serum albumin. The observation that the greater enhancement with MS-325 remains for all time points suggests that once extravascular, MS-325 retains a high degree of binding to albumin (or other extracellular proteins), for if this were not the case, its lower concentration and similar unbound R_1 would give it less signal. The IAUC measurement (considered a marker of distribution volume - Figure 4) shows good agreement between agents, which suggests that the analysis of MS-325 dynamics yields similar results to ECF agents. The generally lower values of IAUC for MS-325 (slope of approximately 0.7) may reflect some combination of slower extravasation and a modest fraction in the arterial wall remaining unbound to albumin.

In summary, the dynamic enhancement characteristics of the diseased vessel wall measured after administration of MS-325 differs from that obtained with an ECF agent. The early peak in relative enhancement and greater degree of vessel wall signal seen at all time points may be related to the high protein binding of this blood pool agent. If the protein binding and/or sequestration of MS-325 in the extracellular matrix can be supported by histology, future studies may show that this type of agent can be used with dynamic contrast enhanced MRI to assess the degree of neovascularity, permeability, and protein binding of atherosclerotic plaque.

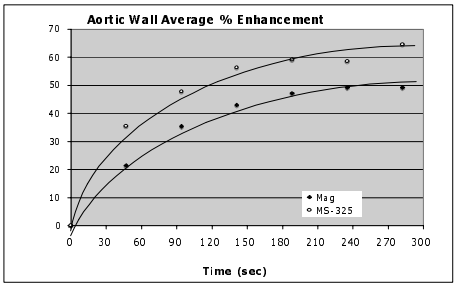

Figure 2. Percent wall enhancement for MS-325 and Magnevist.

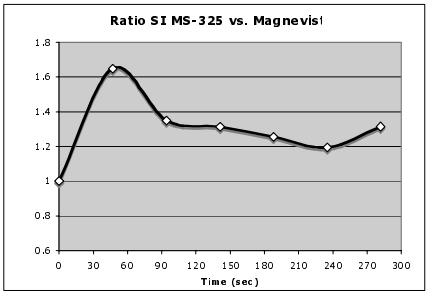

Figure 3. Ratio enhancement MS-325/Magnevist.

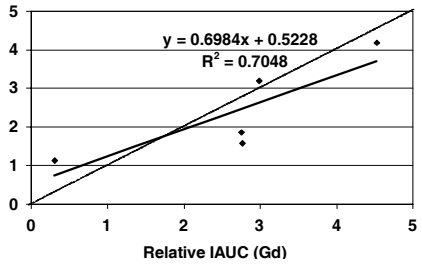

Figure 4. Relative IAUC for MS-325 and Magnevist calculated from dynamic QIR-T1.

Bibliography

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