Dynamic Contrast-Enhanced MRI Detects Progression of Inflammation in a Rabbit Model of Atherosclerosis

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Introduction:
Dynamic contrast-enhanced (DCE) MRI provides the ability to characterize tissue vascularity and permeability by measuring kinetic parameters such as the fractional plasma volume \( v_p \), the transfer constant \( K_{trans} \), or the area under the enhancement versus time curve (AUC). In atherosclerotic plaque, these parameters were found to be strongly influenced by inflammatory activity characterized by macrophages and associated neovessels [1-3]. Thus, DCE-MRI can be used to assess plaque inflammation, an important factor in determining which plaques will progress or lead to clinical complications. An unresolved question is whether DCE-MRI also responds to changes in plaque inflammation. Therefore, the purpose of this investigation was to determine whether the progressive increase in macrophage content within a rabbit model of atherosclerosis from 13 to 26 weeks on atherogenic diet is associated with a corresponding increase in DCE-MRI parameters.

Methods and Materials
Study Design: Twelve New Zealand White rabbits were placed on an atherogenic diet (0.2% cholesterol) and underwent balloon injury of the entire descending aorta by twice pulling back an inflated size 4-F Fogarty embolectomy catheter. The diet was then continued for 13 weeks to establish “baseline” atherosclerotic lesions. At this point, all animals underwent a DCE-MRI examination, after which 6 were chosen at random for euthanization and histological analysis. The other 6 remained on the diet for a total of 26 weeks, at which point they were imaged again, euthanized and histologically analyzed.

MRI Protocol: The DCE-MRI protocol used a black-blood small field-of-view quadruple inversion recovery (sfQIR) sequence [4] for rapid black-blood imaging with a human knee coil on a 3T scanner (Philips Achieva). Images were obtained at 4 locations with sequence parameters \( TR=750\text{ms}, TE=12\text{ms}, T11=325\text{ms}, T12=125\text{ms}, \) field-of-view=10cm x 4cm, matrix=256x48, echo train length=8, slice thickness=3mm, and an imaging time of 4.5 seconds per slice. A total of 15 time points were obtained with 0.05 mmol/kg gadobenate dimeglumine (Bracco) injected after the second time point. The acquired data were analyzed using Matlab (The MathWorks) to identify the vessel boundaries and measure the total integrated AUC in atherosclerotic lesions.

Histological Protocol: Cross sections corresponding to the image locations were obtained and stained via RAM-11 immunocytochemistry to highlight macrophages. These sections were then photographed at high-resolution and analyzed with Image-Pro 4.1 software (Media Cybernetics) to determine the percentage area staining positive for macrophages and the average wall thickness of each location. (see Figure 1 for overall methodology)

Results:
At baseline, the two groups exhibited similar relative AUC measurements (4.50 vs. 4.16; \( p=0.6 \)), whereas at 26 weeks, the relative AUC measurements underwent a significant increase to 7.14 (\( p<0.002 \) compared to baseline by paired t-test). Histologically, this increase coincided with an increase in the percentage macrophage area (6.99 vs. 3.42%; \( p<0.05 \)), but no apparent change in wall thickness (0.48 vs. 0.45 mm; \( p=0.4 \)). Comparing AUC measurements to histology showed no association with wall thickness, but a significant correlation between AUC and percentage macrophage area (\( R=0.50; p<0.001 \)). A linear regression model including percentage macrophage area, duration of follow-up, and wall thickness showed that the macrophage content retained a significant association with AUC (\( p<0.01 \)) even when controlling for these other factors (Table 1).

Conclusion:
Within this rabbit model of atherosclerotic lesion progression, DCE-MRI showed an association with macrophage content similar to that previously reported in human carotid lesions [2]. A key finding of this study was that the DCE-MRI parameter studied, relative AUC, progressed in association with increased macrophage accumulation from 13 to 26 weeks after balloon injury. Moreover, this increase in macrophage content was not associated with an increase in plaque size. Thus, DCE-MRI may be a more sensitive short-term indicator of inflammatory plaque progression or regression than simple measurements of plaque size.

Table 1. Regression Analysis for relative AUC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>( p )</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>0.98</td>
<td>0.5</td>
</tr>
<tr>
<td>% macrophage area</td>
<td>0.18</td>
<td>0.008</td>
</tr>
<tr>
<td>Duration of follow-up (per week)</td>
<td>0.18</td>
<td>0.003</td>
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<tr>
<td>Wall thickness</td>
<td>0.001</td>
<td>0.8</td>
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References