Dynamic Contrast-Enhanced MRI Markers of Inflammation in Carotid Atherosclerosis

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Introduction

Inflammation has long been known to play a role in the initiation of atherosclerosis, but more recently inflammation has emerged as a facilitator of fibrous cap rupture in advanced atherosclerotic plaques [1]. The inflammatory response is characterized by infiltration of macrophages, which express matrix metaloproteinases and pro-inflammatory cytokines that degrade the fibrous matrix, as well as vascular endothelial growth factor (VEGF) that stimulates neovascularization and vessel permeability [1,2]. Because dynamic contrast-enhanced (DCE) MRI is sensitive to vascularity and permeability, kinetic modeling of DCE-MRI should enable the non-invasive detection of inflammatory cell activity. Here, this hypothesis is tested in advanced plaques of the carotid artery by comparing parameters derived from DCE-MRI to histological measurements of inflammation made after carotid endarterectomy surgery. The goal of this study is to establish single, plaque-wide indices of inflammatory activity that can be rapidly measured and used as endpoints in clinical trials or for clinical evaluations of patient risk.

Methods

Eighteen carotid endarterectomy patients participated in an MRI examination within 1 week prior to surgery after obtaining informed consent. The carotid imaging protocol included a 2D time-of-flight dynamic sequence (spoiled gradient echo; TR/TE=100/3.5ms; matrix=256x144; FOV=16x12cm; 5 slices; 10 time frames), wherein a dose of 0.1 mmol/kg of a gadolinium contrast agent (Omniscan, Amersham Health, Oslo) was injected coincident with the second image in the sequence. Within each MRI slice, the inner and outer boundaries of the plaque were drawn and kinetic modeling of the plaque response to the contrast agent was performed to measure the partial volume of plasma (v_p) and the transfer constant (K^{trans}) of the plaque as a whole. Kinetic modeling was based on a two compartment model with reflux neglected and used change in signal intensity of the plaque and lumen as surrogates for concentration [see 3]. After endarterectomy each specimen was histologically analyzed at two cross-sections of the plaque (4mm minimum separation) by staining with HAM56 (for macrophages) and comnputing the average macrophage density. By averaging two histological slices per plaque, the goal was to obtain representative values of the plaques as a whole. The Pearson's correlation coefficient (r) and its significance (p) of the relationship between the MRI variables and histological measurements were then computed. The methods for generating both the MRI and histological parameter are summarized in Figure 1.

Results

The histological measurements of macrophage density were positively and significantly ($p<0.05$) correlated with the DCE-MRI variables as summarized in Table 1. Specifically, macrophages density had correlation coefficients of 0.48 when compared to v_p and 0.58 when compared to K^{trans}. To judge the effect of the histological protocol, which was limited to just two slices per plaque, the DCE-MRI variables were recalculated using just the two slices that best matched the histological samples. Interestingly, both correlation coefficients rose substantially to as much as r=0.74 for K^{trans}, which suggests the tie between inflammation and the DCE-MRI variables is even stronger than the initial results suggested.

Table 1		Macrophage Density	
		r	p
v_p	whole plaque	0.48	.04
	2 slices only	0.51	.03
K^{trans}	whole plaque	0.58	.01
	2 slices only	0.74	<.001

Conclusions

This study shows that meaningful indices of overall plaque characteristics can be extracted from DCE-MRI. Furthermore, the presence of inflammatory cells (macrophages and lymphocytes) in advanced carotid plaque has a marked effect on DCE-MRI. By quantifying this effect with a kinetic model of enhancement, the degree of inflammation or changes in inflammation over time can be inferred. One exciting benefit of this technique is the comparative ease with which the measurements can be made. The only inputs required are the plaque boundaries, leading to a comprehensive evaluation of inflammation in minutes per artery. Near-term applications of this technique include prospectively studying the effect of inflammation in moderate to severe carotid atherosclerosis and observing the anti-inflammatory effect of pharmaceutical agents. If such studies establish a link between enhancement patterns and outcomes, contrast-enhanced techniques could one day be used for clinical decision making such as selecting patients for endarterectomy.

References

1. Libby, *Nature*. 420:868-74, 2002.
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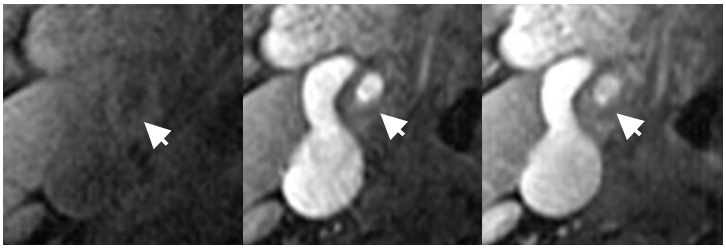
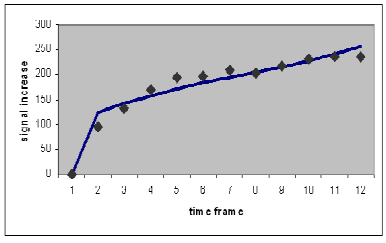
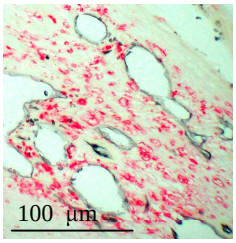
3. Kerwin et al. *Circulation*. 107:851-6, 2003.



(a)



(b)



(c)

Figure 1. Examples of a) DCE-MRI of carotid atherosclerosis (3 time points) with carotid plaque indicated by arrow, b) kinetic modeling of enhancement showing a curve fit to sampled intensity data from the plaque in (a), and c) histological specimen stained (red) for macrophages.