Response of the carotid vessel wall to lipid-lowering therapy: Time course of T1 and T2-weighted signal variation

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Introduction

Vessel wall MRI has emerged as a powerful tool for assessing therapeutic response in atherosclerotic disease. Human studies involving the carotid artery have shown that lipid lowering therapy leads to regression of overall carotid plaque burden [1], and reduction of necrotic core components within the plaque [2-3]. These approaches, however, have some drawbacks. Assessment of plaque burden may only show halted progression and generally requires multi-year studies with large numbers of subjects. Assessment of necrotic core size, on the other hand, only applies to advanced disease, limiting the subject population. We hypothesize that even in subjects without a necrotic core, lipid lowering therapy leads to biological changes in the wall (e.g. reversal of lipid transport and increasing density of fibrous tissue) that manifest themselves as altered contrast on T1-weighted and/or T2-weighted images. In this study, we sought to evaluate subtle contrast changes in the vessel wall of subjects undergoing aggressive lipid lowering therapy.

Methods and Materials

Population This study utilized data collected as part of the Carotid Plaque Composition (CPC) study [4]. With institutional review board approval and informed consent, 112 subjects with established coronary artery disease or carotid stenosis > = 15% by ultrasound and with levels of apolipoprotein B > = 120 mg/dL were enrolled. All received atorvastatin to achieve targeted LDL-C levels < = 80 mg/dL and underwent annual carotid plaque MRI examinations at baseline and for 3 years thereafter. Previously, this group was found to have a significant reduction in vessel wall volume by 2 years and a subset (N=33) of subjects with necrotic cores was found to undergo significant regression of the core by 1 year [3, 5].

MRI The MRI protocol included black-blood T1-weighted and T2-weighted scans on a 1.5T MRI scanner (Signa GE, Waukesha, WI). Sequence parameters were: T1-weighted fast-spin-echo (TR/TE = 800/10ms, ETL = 10, FOV = 160 x 160, matrix = 256 x 256, 2mm slice thickness, 12 slices). T2-weighted fast-spin-echo (TR/TE = 3000/68ms, ETL = 12, FOV = 160 x 160, matrix = 256 x 256, 2mm slice thickness, 12 slices).

Image analysis All images were processed by a custom program CASCADE [6] in which inner and outer wall boundaries and internal plaque components were delineated by a radiologist with expertise in carotid plaque MRI. In addition, CASCADE includes an automated segmentation algorithm (MEPPS [7]) for characterizing plaque components that was run independently from the expert review. Notably, MEPPS has the capability of distinguishing loose fibrous matrix from dense matrix, based primarily on elevated T2-weighted signal.

Data analysis The processed images were analyzed to determine temporal trends in intensity. To control for possible changes due, for example, to equipment variation, the average vessel wall signal intensity was measured within the T2-weighted and T1-weighted images and their ratio (T2/T1) was recorded. In addition, the total volume (in mm^3) of regions identified as loose matrix (LM) by MEPPS was recorded. The presence of significant ($P<0.05$) differences amongst all time points was assessed by GLM repeated measures analysis.

Results

Of 112 subjects in the study, 72 had completed scans with acceptable image quality for review over all 4 time points. Of these 42 had no necrotic core (NC) and 30 exhibited a NC present, the average T2/T1 ratios, volumes of loose matrix, and wall thickness are summarized in Table 1 for those without and with NC. The difference in T2/T1 ratio was found to arise from a reduction of signal in T2-weighted images (Fig 1), with little effect on T1-weighted images.

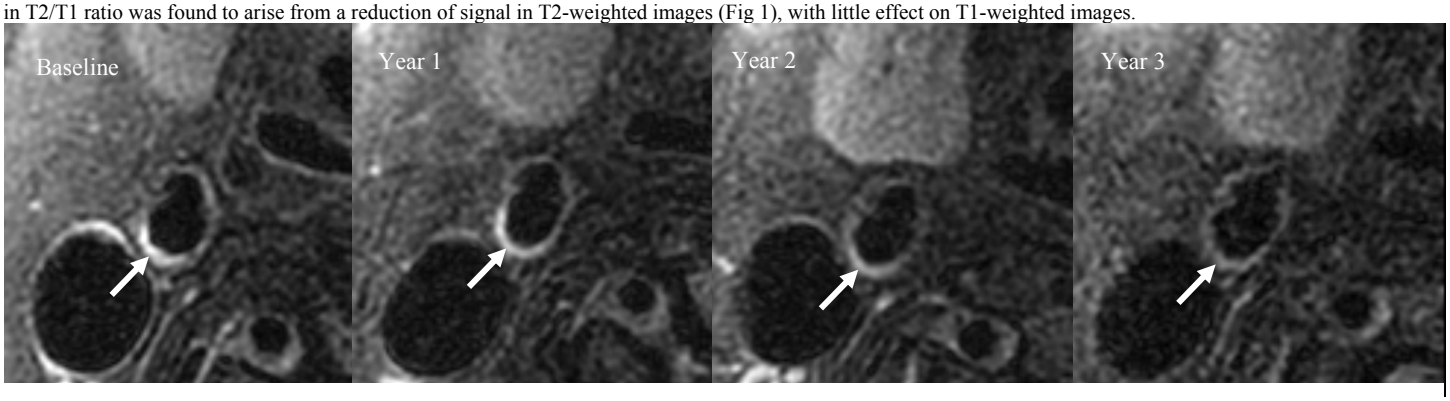

Fig 1. Example of T2-weighted images showing subtle reduction of vessel wall contrast over time during the aggressive lipid lowing therapy.

Discussion

These data indicate a subtle, but highly significant effect of lipid lowering therapy on general vessel contrast. Specifically, the ratio of T2/T1 signal intensity dropped for regions composed predominantly of fibrous tissue. Although the trend was not observed in plaques with necrotic core, this can be explained by the fact that the cores were regressing, which results in an increasing T2 signal for the core region that counteracted the decreasing T2 signal in fibrous tissue. Notably, the MEPPS results showed a consistent and significant downward trend of high T2 signal regions (loose matrix) regardless of the presence/absence of necrotic core. In contrast, wall thickness was not able to detect the change in subjects without necrotic core; thus, for this sub-group, the optimal imaging target may be wall signal properties. The mechanism for the change in T2 contrast is not known, but we speculate that it is due to a change in intimal structure from loose, proteoglycan-rich matrix with interspersed lipid to a dense collagen matrix with smooth muscle cells. In summary, this study indicates that signal changes in the vessel wall could be used as a marker of response to lipid lowering therapy, with highly significant changes observed in minimally diseased vessels without necrotic cores.

Table 1

	BL	Y1	Y2	Y3	P
T2/T1 ratio					
W/O NC	0.847	0.801	0.775	0.767	*0.004*
W/ NC	0.786	0.782	0.787	0.702	0.64
LM volume					
W/O NC	20.53	18.85	12.47	10.21	*<0.001*
W/ NC	34.84	31.02	21.04	14.21	*0.026*
Wall thickness					
W/O NC	1.18	1.17	1.15	1.14	0.38
W/ NC	1.97	1.91	1.74	1.75	*<0.001*

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