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MRI of Carotid Atherosclerosis

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Abstract

OBJECTIVE—Although MRI is widely used to observe atherosclerosis impacts on the vessel lumen, MRI also depicts the size of the plaque itself, its composition, and plaque inflammation, providing information beyond simple stenosis. This article summarizes the state of evidence for a clinical role for MRI of carotid atherosclerosis.

CONCLUSION—MRI of carotid atherosclerosis has a proven role in pharmaceutical trials and may improve patient management once large-scale clinical trials have been completed.

Keywords

atherosclerosis; carotid artery; inflammation; MRI; neovasculature; plaque burden; plaque components

Atherosclerotic disease is the leading cause of death and disability in the United States and Europe [1, 2]. Histologic studies suggest that plaque morphology and composition are important determinants of plaque stability [3–10]. To use information on plaque morphology for diagnostic and other purposes, an imaging method is needed that can provide accurate assessment of plaque tissue components and activity in vivo.

For atherosclerotic plaques in the carotid arteries, the relatively large size of the vessel and superficial location have enabled the development of high-resolution MRI techniques in recent years for direct assessment of plaque tissue composition. Using histologic confirmation, numerous studies have shown that MRI exhibits high contrast for internal plaque features and that combined information from multiple contrast weightings is critical for distinguishing all plaque components [11–16]. The purpose of this article is to summarize the current state of MRI of carotid atherosclerosis and to discuss the potential utility of MRI in clinical practice and research.

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Pathogenesis of Atherosclerotic Plaques

Carotid atherosclerosis is often a relatively benign disease that progresses with aging, but it can be accompanied by acute thrombosis, embolization, and subsequent stroke.

Histopathologic studies comparing coronary and carotid artery disease suggest similar pathways leading to thrombotic events, most commonly caused by ulceration or rupture of the fibrous cap overlying a thrombogenic lipid-rich necrotic core [3] (Fig. 1). In a study of more than 500 carotid endarterectomy (CEA) specimens in patients with prior cerebral ischemic symptoms, 58% exhibited rupture of the fibrous cap [4]. A combined analysis of several smaller studies comparing specimens from symptomatic versus asymptomatic patients showed those with symptoms had significantly higher prevalence of ruptured caps (48% vs 31%, $p < 0.001$) [5].

The risk of fibrous cap rupture appears to be influenced by several factors. In symptomatic patients, a minimum cap thickness under 200 μm was associated with an odds ratio of 5.0 for the presence of fibrous cap rupture [6]. Larger necrotic core size, presence of intraplaque hemorrhage (IPH), and inflammatory cell infiltration of the cap were also found to be predictive of cap rupture [4]. With the exception of cap inflammation, however, these other plaque features have shown mixed results for differentiating symptomatic and asymptomatic patients [5, 7]. Little difference in size of the necrotic core has been observed between symptomatic and asymptomatic patients, but the necrotic core appears significantly closer to the lumen in those with symptoms [8]. Finally, plaque neovascularization, which is often associated with inflammation, has been shown to distinguish symptomatic and asymptomatic plaques [9, 10]. Immature neovessels are also thought to be a source of IPH [17].

In addition to cap rupture, a handful of other mechanisms for thrombosis have been reported. Endothelial erosions, a common source of thrombus in the coronary circulation, are reported to be rare in the carotid arteries [3]. Calcified nodules leading to luminal thrombus were found to be more frequently associated with carotid artery disease than coronary events, although still accounting for a small fraction of total events [3]. Calcified nodules that protrude into the lumen are distinguished from most plaque calcifications, which are separated from the lumen by fibrous tissue and may be indicative of stable lesions [18]. These differences between carotid and coronary lesions suggest differences in pathogenesis that merit further study.

Carotid atherosclerosis has also been described using a modified version of the American Heart Association (AHA) lesion types for coronary plaques [19, 20]. Among advanced lesions, types IV and V are at-risk lesions with a lipid-rich necrotic core. Type VI lesions are the most clinically relevant complex plaques with fibrous cap rupture, ulceration, or IPH. Types VII and VIII are predominantly calcific and fibrous, respectively, and are considered less prone to clinical sequelae.

MRI Techniques

Clinical MR angiography (MRA) is widely available, with time-of-flight (TOF) and contrast-enhanced MRA providing bright lumen signals suitable for measuring stenosis. MRA techniques can also be helpful for identification of ulcerations in the lumen surface [21]. However, MRA is unable to depict plaque burden, particularly in light of positive remodeling, nor is it able to detect high-risk components of the atherosclerotic plaque, with the potential exception of IPH [22]. For these purposes, multiple-contrast black-blood imaging techniques (Fig. 2) have been used for cross-sectional imaging of the artery wall [23].

In one study, in vivo vessel wall measurements from 33 carotid arteries obtained with a combination of T1-weighted, T2-weighted, and proton density-weighted MRI were compared with corresponding ex vivo measurements after CEA [24]. Vessel wall volumes and maximal areas were highly correlated (co-efficients in excess of 0.9) and differed by an amount consistent with the thin rim of the artery left in vivo after surgery. Using the same protocol, Saam et al. [15] provided guidelines for identifying calcification, lipid-rich necrotic core, and loose fibrous matrix based on relative signal intensities in each of the contrast weightings. In 214 matched cross-sectional locations, the measured areas of these components correlated with corresponding histologic measurements with coefficients in excess of 0.7. Improved signal-to-noise ratios at 3-T compared with 1.5-T field strength may further improve performance, although some subtle signal changes have been reported at higher field strengths [25].

The availability of gadolinium-based contrast agents has also been beneficial for MRI of atherosclerosis. Gadolinium agents have been found to preferentially enhance fibrous regions [26, 27]. This phenomenon allows MRI to make measurements of the fibrous cap that correlate with histology in patients with CEA and can be used to identify the lipid-rich necrotic core as a nonenhancing region [14]. Adding contrast-enhanced T1-weighted images to the protocol was found to reduce the interrater coefficient of variation for measuring lipid-rich necrotic core size from 33.5% to 17.6% [28].

Recently, technical developments have focused on the development of 3D sequences for MRI of atherosclerosis. The use of 3D sequences leads to improved signal-to-noise ratios; increased longitudinal coverage; improved resolution, especially in the through-plane direction; and greater acquisition efficiency. A key to developing 3D sequences has been the emergence of blood-suppression techniques that do not depend on through-plane flow to produce black-blood images. For example, Balu et al. [29] used motion-sensitized driven-equilibrium flow suppression with a FLASH readout to obtain 3D carotid artery images with 0.7-mm isotropic resolution. A similar black-blood preparation has also been combined with a steady-state free precession (SSFP) readout [30]. The sampling perfection with application optimized contrast using different flip angle evolution (SPACE) technique permits 3D spin-echo imaging with native blood suppression [31].

Specialized sequences targeting specific components of the atherosclerotic plaque have also been under development. The most notable target has been IPH, to which MRI is uniquely

sensitive. Methemoglobin in IPH serves as an endogenous contrast agent leading to a shortened longitudinal relaxation constant T1 and hyperintensity on T1-weighted images. This hyperintense property of IPH has been noted on general-purpose T1-weighted images, including spin-echo and TOF acquisitions [16, 32]. The mask image from contrast-enhanced MRA acquisitions can also be used to detect IPH and has led to greater detection accuracy than TOF [22]. A heavily T1-weighted sequence using inversion recovery magnetization-prepared rapid gradient-echo (MP-RAGE) has also been proposed [33]. In a comparison of MP-RAGE with general-purpose T1-weighted sequences, Ota et al. [34] found that MP-RAGE had the best overall diagnostic accuracy compared with histology, achieving sensitivity of 80% and specificity of 97%. Further improvements have been proposed using phase-sensitive reconstruction to achieve higher IPH contrast and improved lumen differentiation [35]. This method was subsequently modified to provide simultaneous noncontrast angiography and IPH (fast gradient-echo [SNAP]) imaging, which has the potential to provide stenosis and IPH detection in a single imaging sequence [36].

Another specific imaging target in atherosclerosis has been inflammation, characterized by macrophage accumulation and related neovascularization. Ultrasmall superparamagnetic particles of iron oxide (USPIO) accumulate in macrophages over a period of 24–36 hours, yielding loss of signal intensity on subsequent images [37, 38]. In another example, dynamic contrast-enhanced MR imaging (DCE-MRI) after administration of gadolinium agents can be used to assess plaque perfusion arising from the adventitial vasa vasorum (Fig. 3). In a study of 16 subjects undergoing CEA, a correlation of 0.8 between estimates of fractional blood volume (v_p) estimated by kinetic modeling of DCE-MRI and histologic measurements of neovessel area was found [39]. In a follow-up study, both v_p and the transfer constant (K^{trans}), which is sensitive to vessel permeability, were found to correlate with plaque macrophage content [40].

MRI also offers a number of novel contrast mechanisms other than relaxation that have also been explored for atherosclerosis imaging. Diffusion-weighted imaging of atherosclerosis yields quantitative estimates of the apparent diffusion coefficients, which have been found to be substantially lower in lipid rich cores compared with normal vessel wall or IPH [41]. Susceptibility-weighted imaging has been applied to peripheral arteries and found to have high accuracy for the detection of calcifications [42]. Finally, magnetization transfer imaging may be sensitive to the density of proteins [43].

Prevalence of High-Risk Plaque Features

Using MRI, high-risk plaque features, such as IPH and rupture, have commonly been identified in carotid arteries with minimal to moderate stenosis [44, 45]. By MRI criteria, up to a third of patients with asymptomatic 50–79% stenosis and approximately 10% with 16–49% stenosis have type VI lesions with evidence of cap rupture or IPH [46]. Even arteries with 0% stenosis can exhibit complex plaque, as indicated by a recent study that imaged carotid arteries contralateral to those with stenosis in excess of 50% [47]. Among the contralateral arteries exhibiting 0% stenosis by contrast-enhanced MRA, lipid-rich necrotic core was still present in 67.4% (31 of 46) of arteries, IPH was present in 8.7% (four of 46), and fibrous cap rupture was present in 4.3% (two of 46). These findings confirm that

angiography underestimates carotid plaque burden [47, 48] (Fig. 4) and is ineffective in detecting the presence of complex plaque.

Numerous studies have also compared the prevalence of high-risk features in plaques implicated in cerebrovascular symptoms versus asymptomatic plaques. Reports have indicated that symptomatic plaques are more likely to exhibit MRI evidence of thin or ruptured fibrous caps, IPH, ulceration, or gadolinium enhancement of the adventitia [21, 22, 49, 50]. Saam et al. [51] compared symptomatic carotid plaques to contralateral asymptomatic plaques in the same individuals and found higher incidence of fibrous cap rupture (78% vs 30%) and complex lesions with IPH (63% vs 41%) on the symptomatic side. Murphy et al. [52] reported similar findings in a study of IPH alone (60% on the symptomatic side vs 36% on the asymptomatic side). In a group of 32 patients with stroke of unknown origin, AHA type VI carotid lesions were found on the symptomatic side in 37.5%, but none were found on the asymptomatic side [53]. In another investigation of type VI lesions in patients evaluated for acute cerebrovascular ischemic events, an odds ratio of 11.66 was reported for the finding of transient ischemic attack (TIA) or stroke on the side of the type VI lesion [54].

Plaque Characteristics and Clinical Outcome

The most significant development in MRI of atherosclerosis in recent years has been the completion of numerous studies relating baseline MRI characteristics of carotid atherosclerosis with clinically relevant outcomes. In the largest and most comprehensive study to date, Takaya et al. [55] tested the hypothesis that specific carotid plaque features are associated with a higher risk of subsequent TIA or stroke. This prospective observational study followed 154 subjects with 50–79% carotid stenosis who were asymptomatic at the time of enrollment for a mean follow-up period of 38.2 months. A total of 12 subjects developed cerebrovascular events (four strokes and eight TIAs) that were judged to be carotid related. Cox regression analysis showed significant associations between ischemic events and presence of a thin or ruptured fibrous cap (hazard ratio, 17.0; $p < 0.001$), IPH (hazard ratio, 5.2; $p = 0.005$), larger mean necrotic core area (hazard ratio for 10-mm² increase, 1.6; $p = 0.01$), and maximal wall thickness (hazard ratio of 1-mm increase, 1.6; $p = 0.008$) (Fig. 5). The small size of this study, however, precluded multivariate analysis.

The importance of IPH in particular in predicting cerebrovascular complications has been further shown in similar studies involving both symptomatic and asymptomatic cohorts. Among 91 initially asymptomatic men with 50–70% stenosis followed for a mean period of 25 months, all of the six cerebrovascular events occurred in arteries with IPH present at baseline (hazard ratio, 3.6; $p < 0.001$) [56]. Among 66 symptomatic patients with high-grade stenosis awaiting CEA, a hazard ratio of 4.8 ($p < 0.05$) for IPH predicting the 17 recurrent events was reported [57]. In another study, 64 symptomatic patients with 30–69% stenosis were followed for a mean period of 28 months [58]. At baseline, 39 (61%) showed IPH on MRI and of these, 13 developed ipsilateral ischemic events (eight TIAs and five strokes). Among those with no baseline IPH, only one TIA was reported (hazard ratio, 9.8; $p = 0.03$).

The importance of IPH identified by MRI also appears to be valuable for choosing among treatment options. In one study, the existence of hyperintense signal on T1-weighted images of carotid lesions was investigated in 56 patients undergoing carotid artery stenting versus 25 patients undergoing CEA [59]. Among patients positive for T1-weighted hyperintensity, those undergoing carotid artery stenting were significantly more likely to develop silent ischemic brain lesions than those receiving CEA (61% vs 13%, $p = 0.006$). Among 112 patients undergoing carotid artery stenting, the presence of hyperintense signals consistent with IPH on TOF images was found to yield significantly higher likelihood of periprocedural symptoms (18.4% vs 1.4%, $p = 0.003$) [60]. Thus, IPH identified by MRI may be helpful for determining the appropriateness of carotid artery stenting.

Serial carotid MRI has also been used to investigate the baseline plaque characteristics associated with important pathologic changes in the carotid plaque at follow-up. In a prospective, serial MRI study of 85 subjects with 50–79% stenosis and no luminal surface disruption at baseline, clinical and baseline carotid MRI plaque features were examined for associations with new fibrous cap disruption on follow-up MRI [61]. The size of the lipid-rich necrotic core at baseline was the strongest predictor for development of a new surface disruption at the 36-month follow-up (area under the curve [AUC] = 0.95). Presence of IPH was also a statistically significant, but weaker, classifier of new surface disruption (AUC = 0.73).

Prospective MRI investigations have also studied the role of plaque components in rate of progression of the atherosclerotic lesion. In particular, IPH may represent a potent atherogenic stimulus by contributing to the deposition of free cholesterol, macrophage infiltration, and enlargement of the necrotic core [17]. A case-control study of 29 subjects participating in a longitudinal serial MRI progression study tested the hypothesis that IPH, detected by high-resolution MRI, is associated with greater progression in both necrotic core and plaque volume [62]. The volume of wall, lumen, necrotic core, and IPH were measured at baseline and follow-up. Carotid arteries with IPH on baseline examination showed markedly accelerated rates of progression in wall volume (6.8% with IPH vs -0.15% without IPH, $p = 0.009$) and lipid-rich necrotic core volume (28.4% with IPH vs -5.2% without IPH, $p = 0.001$) over the course of 18 months (Fig. 6). Furthermore, those with IPH at baseline were much more likely to have new plaque hemorrhages at 18 months compared with control subjects (43% vs 0%, $p = 0.006$). A similar pattern was found in 67 asymptomatic subjects with 16–49% stenosis [63]. IPH was associated with accelerated progression in carotid wall volume compared with lesions without IPH (44.1 ± 36.1 vs 0.8 ± 34.5 mm³ per year, $p < 0.001$). Findings from these studies strongly suggest that IPH accelerates plaque progression within a relatively short period of 18 months.

MRI of Atherosclerosis in Pharmaceutical Trials

An additional use of MRI of atherosclerosis with potential clinical ramifications is in clinical trials of lipid lowering and other atherosclerosis-related treatments. The most widely accepted explanation for the clinical event reduction with statin therapy is that lipid-lowering targets the plaque rupture risk features, such as large lipid-rich necrotic core, thin fibrous cap, and high level of inflammatory infiltrates and activity. Therefore, the plaque stability is

improved and cardiovascular events are reduced. Atherosclerotic plaque lipid depletion has been shown in animal studies and human histologic observations [64].

In vivo verification of the lipid depletion hypothesis and establishment of the time course of plaque regression has only recently been enabled by MRI of atherosclerosis. In one early study, the carotid arteries of eight subjects with coronary artery disease undergoing long-term (10 years) lipid-lowering therapy were compared with those of eight matched control subjects who had never been treated with lipid-lowering therapy [65]. Although the treated subjects exhibited plaques that were only marginally smaller in area (58 vs 64 mm², respectively; p = not significant), their lesions had significantly smaller lipid-rich necrotic core areas (0.7 vs 10.2 mm², respectively; p = 0.01).

Of course, the major benefit of MRI for investigating therapeutic response of plaques is the ability to perform noninvasive serial studies to observe temporal changes in plaque. A study following aortic and carotid plaques in hypercholesterolemic patients under simvastatin therapy for 2 years with MRI at 6-month intervals reported vessel wall area was reduced by 11% after only 1 year (p < 0.01), with more moderate increases in lumen area reaching significance by 18 months [66, 67]. In a recent study of dalcetrapib (a cholesterol ester transfer protein inhibitor) in 130 subjects with or at high risk of coronary heart disease, total vessel area was reduced in patients treated with dalcetrapib at 600 mg/d compared with those taking a placebo after 24 months. The absolute change from baseline relative to placebo was -4.01 mm² (p = 0.04) [68].

Other studies have targeted changes in plaque components, most notably the size of the lipid-rich necrotic core. The Carotid Plaque Composition (CPC) study using MRI during lipid therapy [69] was designed as a randomized, double-blind, partial placebo-controlled study [70] in which patients with known coronary or carotid disease were randomized to one of three intensive lipid regimens, all of which included atorvastatin. Annual serial MRI data from 33 pooled patients with a lipid-rich necrotic core on baseline MRI showed a 3-year reduction in average percentage lipid-rich necrotic core from 14.2% to 7.4% (p < 0.001), with a significant 1-year reduction over each of the first and second years but a small non-significant decrease in year 3. An example of plaque lipid depletion is shown in Figure 7. The CPC study also revealed a reduction in vessel wall volume that became significant at 2 years (Table 1). Notably, the CPC study revealed that the regression observed in plaque burden was primarily induced by lipid depletion because substantial and statistically significant carotid wall burden reduction only occurred in the slices containing a lipid-rich necrotic core (Table 1) and the time course of wall burden reduction seemed to follow plaque lipid depletion, with the largest changes occurring during the second year. In another study to investigate the effect of rosuvastatin on lipid-rich necrotic core size in 33 subjects, a 41.4% reduction was reported in the proportion of the vessel wall consisting of lipid-rich necrotic core after 2 years (p = 0.005) [71]. No significant change in plaque volume was observed.

Pharmaceutical studies have also been undertaken using contrast agents to assess the response of inflammatory factors in atherosclerotic plaque. In the ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) study, a significant (p

= 0.0003) reduction in USPIO uptake was reported after only 6 weeks on 80 mg of atorvastatin [72]. No change was observed in a 10-mg group. In the CPC study described previously, DCE-MRI was used to investigate changes in the vasa vasorum under lipid therapy, and a drop in K^{trans} was reported from 0.085 to 0.067 min⁻¹ ($p = 0.02$) [73].

Future Perspectives and Conclusions

In this review of MRI of carotid atherosclerosis, a picture emerges of a technology that is on the cusp of providing clinically relevant information for management of carotid disease. The imaging techniques have been extensively validated. The technologies described can be translated into clinical use. Preliminary evidence indicates that unique features identified by MRI, such as IPH and fibrous cap rupture, are associated with higher risk of clinical and subclinical events. What is lacking, however, is proof that these factors provide marginal utility beyond existing risk variables. Furthermore, these techniques must yield cost-effective guidance to alter current clinical guidance and yield better long-term outcomes. For both of these challenges, large-scale clinical trials of this technology are warranted.

In addition to the clinical potential of MRI of atherosclerosis, it can be the choice of imaging modality to investigate therapeutic mechanisms. In this role, MRI of atherosclerosis is able to depict changes in the plaque in trials that are much smaller than would be required to observe changes in survival. Studies to date indicate that changes in lumen size are slow to develop, whereas changes in wall area appear to be detectable earlier. Changes in lipid-rich necrotic core appear to be observable still earlier and may provide a vascular biologic explanation for the onset and persistence of clinical benefit seen in the placebo-controlled lipid lowering trials [74]. The cardiovascular event reduction in these trials began at 1–2 years after initiation of lipid-lowering therapy, which corresponds with the timing of significant plaque lipid depletion. Markers of inflammation may be the soonest to respond to therapy. Knowledge of such time-dependent responses of different markers can be valuable for designing clinical trials on the basis of the expected mechanism of treatment.

Although the overwhelming majority of imaging development has been based on carotid MRI, similar techniques have been applied to the aorta, coronary arteries, intracranial arteries, and peripheral vasculature of the legs. Each of these targets introduces unique challenges, including small vessel size (intracranial and coronary arteries), deep location and motion (coronary arteries and aorta), highly distributed lesions (peripheral arteries), and tortuosity (intracranial arteries and aortic arch). To address these challenges, emerging 3D and rapid imaging protocols are especially promising.

Finally, the focus of this article has been techniques that are currently viable in the clinic and have shown evidence of utility. Numerous promising technologies are in the development stage. Most notably, molecular imaging holds particular promise with targeted probes under test for detecting neoangiogenesis and macrophages, among other targets [75]. As these and other technologies mature, they will add to the arsenal of MRI for imaging of atherosclerosis.

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Fig. 1. Histologic features of advanced carotid atherosclerotic plaque

A and B, Photomicrographs show thin fibrous cap (**A**) and thick fibrous cap (**B**). NC = necrotic core. (Reprinted with permission from [3])

Fig. 2.

Cross-sectional appearance of carotid atherosclerotic plaque by common imaging techniques: 3D time-of-flight (TOF) MR angiography; T1-weighted (T1W) turbo spin-echo (TSE); contrast-enhanced T1-weighted (CE T1W) TSE; proton density-weighted (PDW) TSE; T2-weighted (T2W) TSE; and inversion recovery magnetization-prepared turbo field echo (IR TFE) (also called magnetization-prepared rapid gradient-echo [MP-RAGE]). MRI results suggest pathology consisting mainly of intraplaque hemorrhage appearing bright on T1-weighted and inversion recovery TFE images, with calcified plaque appearing dark on all images. (Reprinted with permission from [23])

Fig. 3.

Kinetic analysis of dynamic contrast-enhanced (DCE) MRI of carotid atherosclerosis in 46-year-old man yields parametric image (*top*) displaying value of fractional blood volume (v_p) in red and transfer constant (K^{trans}) in green (adventitia indicated by *arrows*). Image is derived from kinetic modeling of changing intensity in serial images (*bottom*) coinciding with contrast agent injection. N denotes number from series. (Reprinted with permission from [73])

Fig. 4.

A and B, Carotid artery MR angiograms (*left*) show no stenosis in 67-year-old woman with contralateral stenosis (**A**), nor in 62-year-old man with contralateral stenosis (**B**). Cross-sectional time-of-flight (TOF) unenhanced T1-weighted (Pre-T1), and contrast-enhanced T1-weighted (Post-T1) MR images show that only **B** exhibits large plaque with lipid-rich necrotic core (*arrows*) and calcification (*arrowheads*). Asterisks indicate carotid artery lumen. (Reprinted with permission from [46])”

Fig. 5. Kaplan-Meier survival estimates for patients remaining free from cerebrovascular symptoms

A and B, Graphs show Kaplan-Meier survival estimates for patients remaining free from cerebrovascular symptoms with and without presence in carotid arteries of intraplaque hemorrhage (IPH) (**A**) and thin or ruptured fibrous cap (**B**) identified by MRI. (Reprinted with permission from [55])

Fig. 6. Carotid plaque with intraplaque hemorrhage (IPH)

A and **B**, IPH is identified as bright signal intensity on baseline T1-weighted (T1W) MRI (**A**) and exhibits substantial increase in plaque size and luminal narrowing after 18 months (**B**). CCA = common carotid artery, Bif = bifurcation, ICA = internal carotid artery, ECA = external carotid artery. (Reprinted with permission from [62])

Fig. 7.

Response of carotid atherosclerotic lesion to 3 years of lipid therapy shows substantial reduction in plaque size (*arrows*). CE TW1 = contrast-enhanced T1-weighted image. (Reprinted with permission from [69])

TABLE 1
Carotid Wall Measurement Change Over 3 Years and Differential Changes Between Slices With Without Lipid-Rich Necrotic Core [69]

Parameter	Baseline vs 3 Years				Annual Changes ^a				Change Over 3 Years in Slices With and Without Lipid-Rich Necrotic Core ^b			
	No.	Baseline	3 Years	p ^c	No.	First Year	Second Year	Third Year	No.	With	Without	p ^c
Wall volume (mm ³)	33	641 ± 200	597 ± 198	< 0.001	30	-16 ± 62	-42 ± 57 ^{d,e}	3 ± 34	31	-45 ± 55 ^f	-11 ± 32	0.004
Percent wall volume (%)	33	46.5 ± 7.1	44.3 ± 7.2	0.006	30	-0.6 ± 2.9	-2.1 ± 3.2 ^{d,e}	-0.2 ± 2.5	31	-4.7 ± 7.1 ^f	-1.4 ± 3.2	0.02
Lumen volume (mm ³)	33	750 ± 249	764 ± 258	0.11	30	2 ± 50	18 ± 52	5 ± 42	31	12 ± 41	7 ± 40	0.3

Note—Values are mean ± SD for the comparison of baseline vs 3 years and mean ± SE for each annual change during the 3 years.

^aChanges between the scans were annualized because of different times between the visits for different subjects. The calculation of changes was limited to patients with all four annual visits. Thus, the sample size is smaller than for the comparison of baseline vs 3 years.

^bThe smaller sample size ($n = 31$) was the result of two patients not having both presence and absence of lipid-rich necrotic core slices.

^cPaired Student *t* test.

^d $p < 0.001$ when compared with null hypothesis of zero change.

^e $p = 0.01$ when compared with year 1.

^f $p < 0.001$ when compared with zero change.