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Magnetic Resonance of Atherosclerotic Plaques

Tissue Characterization of Atherosclerotic Plaque Vulnerability by Nuclear Magnetic Resonance

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ABSTRACT

Developing imaging technologies capable of identifying unstable atheromatous plaques in vivo is a major issue of clinical cardiovascular research. These techniques would permit an earlier surgical or medical therapy and would anticipate acute ischemic syndromes. Plaque vulnerability depends on the relative amount and thickness of its lipid core and fibrous cap. Several means of assessing atherosclerotic plaque composition have been used with nuclear magnetic resonance (NMR): carbon-13 and proton spectroscopy, proton imaging, chemical shift imaging, water diffusion imaging, and magnetization transfer. Recent data have shown that MR allows for accurate in vivo diagnosis and may support large scale prevention studies.

KEY WORDS: *Atherosclerosis; Human; MRI; MR spectroscopy; Plaque rupture.*

INTRODUCTION

The need to detect and characterize all stages of atheroma progression has become more important since it has been shown that unstable coronary syndromes or strokes may result from arterial lesions, which have not yet become severely stenotic (1). The rupture of atheromatous plaques is a major contributor to the development of myocardial infarction; plaque vulnerability, a condition preceding rupture, depends on the chemical characteristics of the lipid pool. However, routine clinical assessment of human atherosclerosis do not rely on biochemical analysis of the diseased organ (the arterial wall) but essentially on stenosis evaluation assessed by conventional angiography. Despite the critical anatomic information it provides, this method has severe limitations. Previous studies have in fact demonstrated that luminal morphometry was unable to predict plaque evolution (2).

Besides angiography, several invasive (intravascular ultrasound, angioscopy) and noninvasive (surface B-mode ultrasound, ultrafast computed tomography) imaging techniques can assess atherosclerotic vessels. Most identify morphology, such as luminal diameter and stenonosis, wall thickness, or in some cases calcifications

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(intravascular ultrasound and ultrafast computed tomography), and some provide an assessment of the relative risk associated with atherosclerosis such as ultrafast computed tomography. However, none of these imaging technologies can characterize the complete composition of an atherosclerotic plaque. They are therefore incapable of identifying vulnerable plaques. As opposed to these techniques, several methods have been developed to assess arterial wall composition with nuclear magnetic resonance (NMR) using ^{13}C-NMR spectroscopy (3–5), T2 contrast (6–8), chemical shift imaging (9), diffusion imaging (10,11), magnetization transfer (12,13), and applied to discriminate in vivo wall components in normal and atheromatous arteries.

CARBON-13 SPECTROSCOPY OF THE MOBILE LIPID COMPONENTS

Natural abundance carbon-13 NMR spectroscopy nondestructively characterizes lipid chemical composition. Because of its broad chemical shift bandwidth, ^{13}C-NMR provides more information regarding chemical constituents than ^{1}H-NMR and has been used for structural and dynamic studies of cholesteryl esters, triglycerides, and phospholipids (3,4). Cholesteryl ester phase transitions determine the lipid state (liquid, smectic, or solid) and its spectral characteristics. It can be demonstrated in vitro that uncomplicated nonulcerated lesions have more polyunsaturated fatty acids (Fig. 1), whereas complex and highly stenotic lesions have more unsaturated fatty acids and less cholesteryl esters (5). The ^{13}C peaks are predominantly derived from the mobile atheromatous lipids (the "soft" lipids) (3,4), which have a large role in plaque vulnerability and rupture (14). Alterations in fatty acid saturation and cholesteryl esters in atheroma have been attributed to lipoprotein oxidation. Oxidation of the cholesterol moiety and the fatty acyl chain double bonds demonstrates a 55% loss of polyunsaturated fatty acid chains (15), with the production of reactive aldehydes and an increase in the content of thiobarbituric acids.

Another factor explaining the decrease of resonances from cholesteryl esters in the most stenotic lesions could be the inhibition of the reesterification cycle by the cytotoxic effect of oxidized lipoproteins as described by Brown and Goldstein (16). This inhibition leads to the accumulation of free cholesterol that precipitates as monohydrate crystals, the hallmark of advanced lesions with a very short T2 relaxation times resulting from the solid phase, making them NMR invisible.

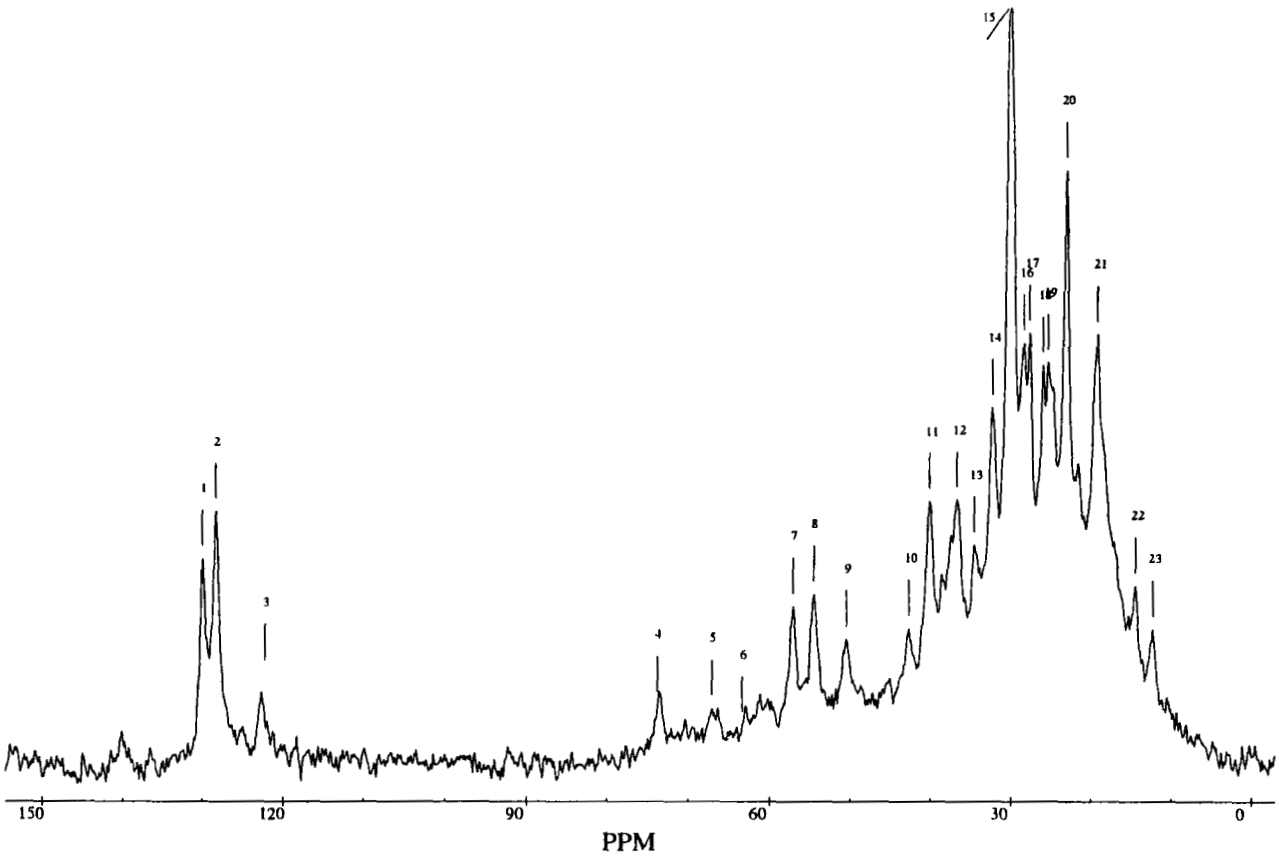
PROTON SPECTROSCOPY

With a narrower bandwidth than ^{13}C-MR spectroscopy, proton spectroscopy essentially characterizes midchain (CH2n) and terminal protons (CH3) of long-chain fatty acids. Again, phase transitions (lipid composition and temperature) determine the lipid state of cholesteryl esters, phospholipids, or triglycerides and the mobility of their proton atoms, which alters MR visibility. The spectral characteristics of fibrous plaques with a water-to-lipid ratio of 9:1 can be distinguished from those of adipose tissue with a water-to-lipid ratio of 1:9 (8,9). The narrow peak of acyl chain resonances in adventitial triglycerides can also be discriminated from the broad peaks of semisolid cholesteryl esters due to dipolar coupling (17). Finally, the temperature dependence of atheromatous lipids can be demonstrated with this technique depending on the triglycerides-cholesteryl esters ratio and ester composition (10,18,19).

ARTERIAL LESIONS CHARACTERIZED BY MR IMAGING

Discriminating plaque components on the basis of chemical composition may be important in determining the factors, which contribute to plaque rupture, such as the distribution of circumferential stress (20), plaque susceptibility and cap thinning by metalloproteases (14,21), or its ability to thrombose (22).

Heretofore, the characterization of atheroma by ^{1}H-NMR imaging has predominantly focused on the acquisition of the lipid signal, acquired with a T1-weighted sequence using either a nonselective sequence, a lipid selective pulse, a modified Dixon pulse (9), chemical shift imaging sequences with long T2 suppression (23), or a pattern recognition technique using multiple sequences (6,7,17,24,25). These studies were conceived to image plaque lipids with long T2 and short T1 relaxation times, similar to adipocyte triglycerides in fat, but atheromatous core is mostly composed of cholesterol and cholesteryl esters in solid (crystal) or smectic (liquid-crystalline) state and associated with a short T2 (Fig. 2) (8,18). Consequently, in arterial walls, bright areas on T2-weighted images do not correspond to lipid-rich regions but to regions predominantly composed of fibers (collagen, elastin, and proteoglycan) either in media or in collagenous



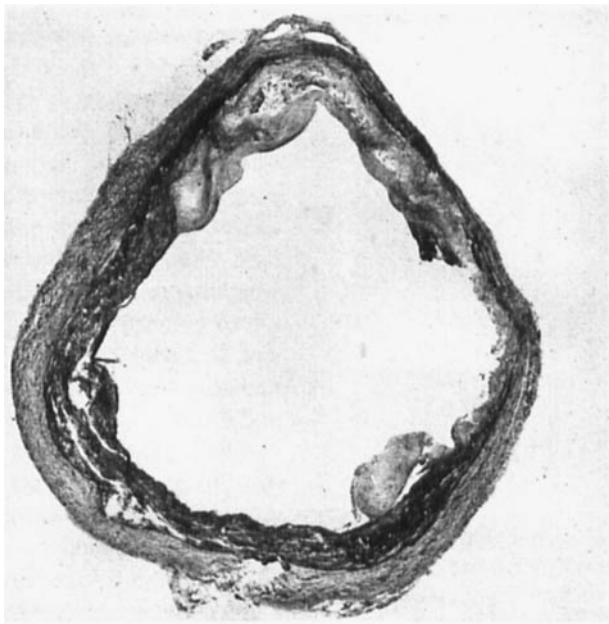
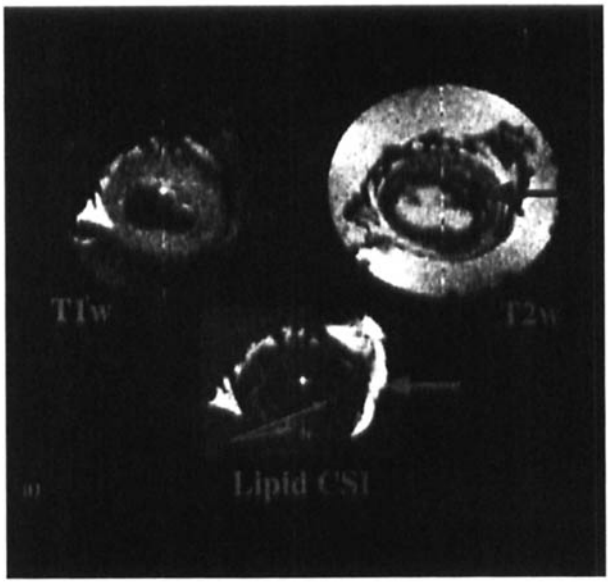
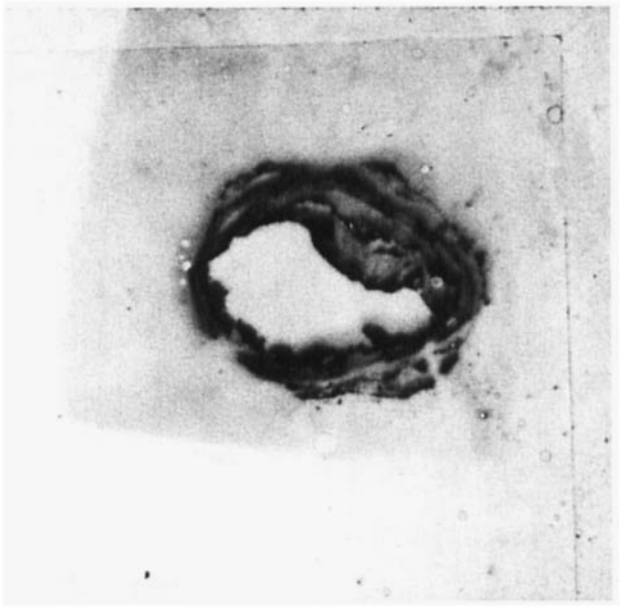


Figure 1. ^{13}C spectrum of a 35% stenotic fibrolipidic plaque. Peak 1 corresponds to the monounsaturated carbons in fatty acid chains (MUFA) and peak 2, polyunsaturated carbons, with a higher amplitude than MUFA. Also note the complex description of the carbon peaks in the aliphatic region (peaks 10–23) corresponding to the different carbon atoms on the cholesterol rings.



(A)



(B)

Figure 2. (A) Fatty carotid lesion. On the chemical shift selective sequence image at the bottom, atheroma signal intensity (thin white arrow) is eight times lower than in perivascular fat (large white arrow). T2 contrast provides a complete description of this plaque with a necrotic core (black arrow), fibrous layers, media, and adventitia. (B) Trichrome staining. From lumen to the outer wall: large necrotic core with cholesterol crystals, collagen fibers, media, adventitia.

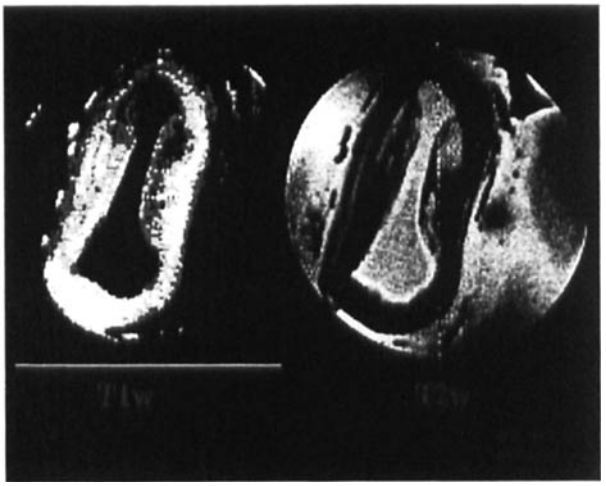


Figure 3. Aortic lesions. Stable plaque on the right side with a complete and thick collagenous cap covering a dense necrotic core. On the left side, the large core was almost in contact with blood components on the lower part of the vessel, providing the conditions for an acute event.

caps (Fig. 3). Different reasons may explain the shorter T2 of the lipid core: the micellar structure of lipoproteins, their denaturation by oxidation, or the exchange between cholesteryl esters and water molecules (both from the fatty acid chain or from the cholesterol ring), with a further interchange between bound water layers and free water.

Several authors developed methods to improve in vitro imaging of the short T2 lipid component in atheromatous plaque. Trouard et al. (10) examined aortic plaques using a stimulated echo diffusion weighted sequence and were able to improve water suppression and lipid visualization illustrating the interest of diffusion weighting in lipid imaging. Gold et al. (23) implemented a back-projection technique with long T2 lipid suppression to image the short T2 lipid component. This sequence could detect species with a T2 between 150 μsec and 9 msec.

Mohiaddin et al. (24) published the first application of a Dixon chemical shift selective sequence for the imaging of atherosclerotic lipids and showed that histologic grade of lipid content correlated with plaque signal intensity. Finally, calcifications, which can be identified by T1 contrast or proton density images (these regions appear as low intensity zones in all sequences due to very low water content [6]) play an important role in plaque aging and arterial dysfunction, and their identification may add to our understanding of hemodynamics, regulation of

stress distribution, and plaque aging associated with low vasoreactivity.

OTHER CONTRAST SOURCES: DIFFUSION AND MAGNETIZATION TRANSFER

Recent experiments have shown that diffusion may be used as well to characterize atherosclerotic tissue (11): In a diffusion experiment, water molecules are labeled by the Larmor precession frequencies of the proton spins at the hydrogen sites. These frequencies are made spatially dependent by the application of a magnetic field varying with position. Measuring displacements of water molecules by calculating the apparent diffusion coefficient D can probe the microstructure of the plaque components. Using this method in vitro, one can demonstrate that water diffusion is limited and behaves isotropically in the lipid core of atheromatous plaques (11): D values are much lower in that region than in the other components of the arterial wall. The mechanisms for altered diffusion in such atheromatous structures are not known, but it may also result from the presence of oxidized lipoproteins or from lipids in smectic phase. D is similar in collagenous cap and media. This result, along with their similar T2, provides another argument for biophysical similarity in tissue structure between these two arterial components. The entangled network of protein matrix produced by smooth muscle cells may explain this similarity.

The short T2 species of atheromatous lipids and the stiffness of the fibrous component allow for magnetization transfer. Numerous sites of exchange are present in proteinic regions (collagen and elastin) and in denatured lipoproteins. Using optimized binomial pulses, a transfer rate of 20% can be shown in vitro in the atheromatous core and of 35% in the fibrous cap and media, both with a high amount of macromolecules (12). Using this technique for MR imaging, it can be seen that plaque magnetization transfer images provide a contrast similar to the T2-weighted images (13). This contrast can be optimized for magnetization transfer weighted ultrafast imaging in vivo, which could be useful when T2 contrast is not easily implementable.

ANTICIPATING VULNERABILITY

Intravascular procedures can be imaged both in vitro and in vivo by combining morphometry and tissue characterization (26–28). Collagenous cap resistance to compression can be investigated in vitro after balloon angioplasty and atherectomy. Angioplasty does not alter plaque or cap in fibrous lesion but enlarges luminal areas by a stretching effect of the disease-free segment. A significant plaque reduction in fatty lesions without cap is obtained due to the reduction of lipid core partly extruded into the lumen and partly redistributed into the wall. Angioplasty of calcified lesions shows dissection at the shoulder of the plaque, where a maximal stiffness gradient is usually found, whereas atherectomy largely reduces collagenous cap and plaque volume (28).

MR IMAGING STUDIES IN EXPERIMENTAL ATHEROSCLEROSIS

Several studies have now confirmed the usefulness of MR imaging to describe progression of atherosclerosis in animal models and its ability to image in vivo plaque components and rupture (29,30) or the effect of a low cholesterol diet on plaque volume (31). Many pharmacologic studies need the repeated sacrifice of successive animal cohorts to determine the histologic evolution with and without therapeutics. These studies will benefit from noninvasive imaging techniques that can diminish total costs by reducing the number of sacrificed animals. Transgenic apolipoprotein-E knockout mice, which develop aortic and coronary lesions very similar to humans, have also been studied at high field (9.4 T), showing the rapid progression of atheroma and plaque rupture (32).

HUMAN STUDIES

In vitro analysis of all arterial trees, including femoral (8), aortic (33,34), carotid (35,36), and coronary (37,38) lesions, has now been imaged in vivo with MR. All have confirmed that MR could detect plaque fine structure in situ using clinical scanners (Fig. 4) (35). The principal challenges associated with MR imaging of thoracic aorta are obtaining sufficient sensitivity for sub-millimetric imaging and exclusion of artifacts due to respiratory motion and blood flow. Comparison of matched MR and transesophageal echocardiography images showed a strong correlation for plaque composition and plaque thickness. These data also demonstrated that the quantification of plaque size could be ideally combined with tissue characterization in large-scale prevention or follow-up studies (33). Carotid imaging may also benefit from recent progress in surface coil design specially with phased-array types, which can increase signal-to-noise ratio by a factor of 1.4 (39).

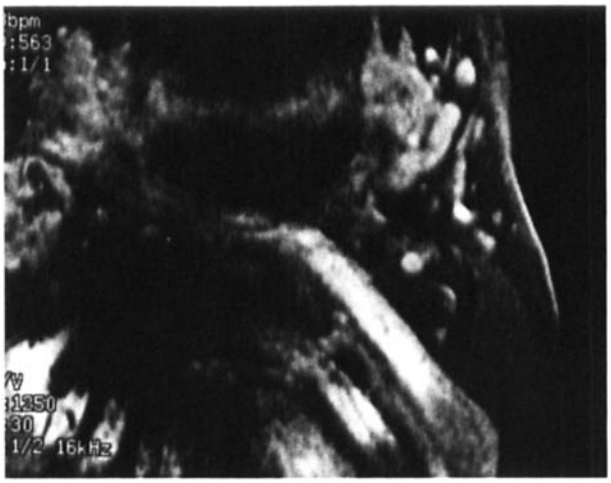


Figure 4. Carotid vessel in vivo at 1.5 T. Left internal carotid with 75% stenosis. T2 contrast reveals a short T2 lipid core between collagenous cap and media. It allows the quantification of plaque, its degree of obstruction, relative to the external elastic lamina, and thus arterial remodeling.

The ultimate goal is in vivo imaging of plaque in coronary arteries. MR has the same potential for coronary characterization as it has shown in the other arterial trees (38): 90% of the ex vivo coronary lesions can be correctly identified based on a 40-msec T2 classification. Preliminary in vivo animal studies showed that the difficulties of coronary wall imaging are similar to the problems encountered in MR coronarography: These are due to cardiac and respiratory motion artifacts, to the nonlinear course and the relatively small size of the coronary arteries (30). For that purpose, a double inversion recovery fast spin echo has been developed for high-resolution imaging (0.46 mm) of normal and atherosclerotic human coronary artery lumen and wall (37). Normal coronary wall shows a uniform hyperintense thin ring, with a circular hypointense lumen. MR images of coronary arteries in patients with 40% stenosis by x-ray angiography showed atherosclerotic plaques 4.1- to 5.7-mm thick with a highly significant difference as compared with normal subjects. This type of sequence may allow the identification of the vulnerable plaques before they rupture.

CONCLUSION

Discriminating atheromatous components with MR imaging allows large-scale clinical studies of plaque progression, regression, and stabilization. It will improve our understanding of the slow evolution of human atherosclerosis in the early decades of life (Fig. 5) and test the concepts of deep injury, plaque growth (edge vs. shoulder), arterial remodeling, and compensatory enlargement. The combination of MR angiography, velocity mapping, or time-of-flight echo planar for determination of flow reserve, perfusion measurements, and tissue characterization may provide a complete description of the atherosclerotic process and its dynamic consequences, from fatty streak to myocardial infarction. The design of optimized surface or intravascular coils and dedicated gradients systems will further improve image quality and provide newer methods for prediction of these life-threatening events.

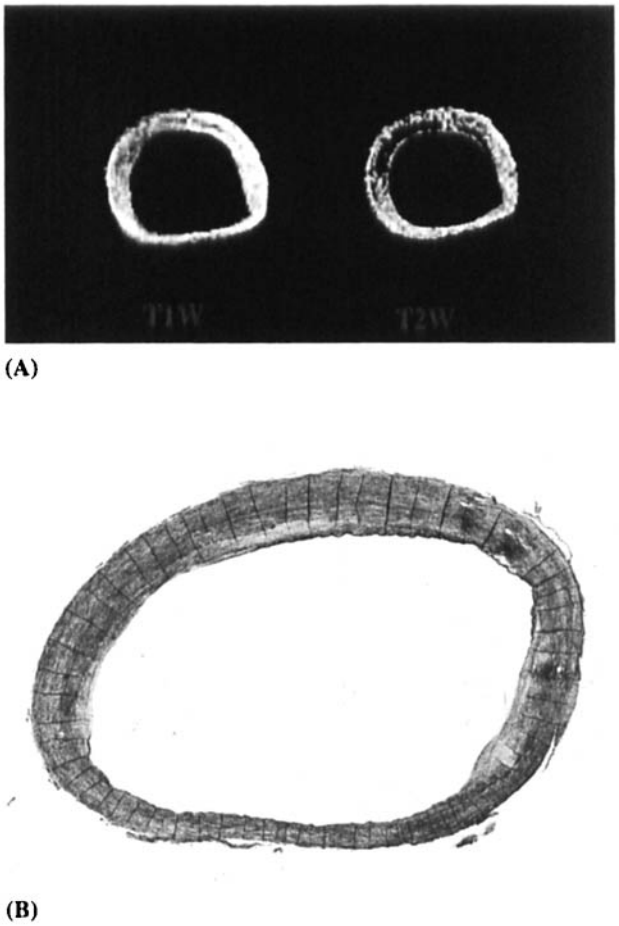


Figure 5. (A) Carotid artery of a 23-year-old patient. The T2 contrast reveals a very mild lipid infiltration (black). (B) Corresponding Masson trichrome showing the intimal thickening of a lipid streak with extracellular lipids (arrowhead) among rare collagen fibers.

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