MR Spectroscopy of Cholesteryl Ester in Human Atherosclerosis *

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The ability to quantify cholesterol and/or cholesteryl ester deposits in vivo noninvasively, a goal not yet achieved, could greatly facilitate new discoveries in atherosclerosis progression and regression. In this issue of JACC, Duivenvoorden et al. (1) report progress in a 1H-magnetic resonance (MR) spectroscopic technique that samples an approximate 5-mm cubic voxel in the region of the carotid artery in humans. Using cholesteryl linoleate and triolein as representative standards for cholesteryl ester and triglyceride, respectively, they suggest that the ratio of cholesteryl ester to triglyceride can be quantified and correlated with plaque tissue volume versus perivascular tissue volume in the voxel of interest. However, only one-half of the MR spectra obtained were of adequate quality for analysis.

Both cholesterol and cholesteryl ester accumulate pathologically in the arterial intima early in lesion development (2,3). Cholesterol is the biologically active molecule. Because cholesterol is rotationally constrained in lipid membranes and sometimes in crystals, however, it is nearly undetectable by MR (4). Cholesteryl ester associates minimally with membranes and instead forms oil phase lipid droplets that provide MR spectra but are largely inert chemically, participating in few reactions other than hydrolysis of the ester bond to produce cholesterol. Metabolically, cholesteryl ester represents a storage or transport form of cholesterol. Cells with increasing cholesterol content will activate acylcoenzyme Acholesterol acyltransferase (ACAT), which sequesters cholesterol in esterified form in lipid droplets and removes the threat of membrane dysfunction posed by excess cholesterol (5). Scull and Tabas (6) have suggested that cell death in atherosclerosis may result in part from overtaxed and eventually failing cholesterol esterification, leading to apoptosis via cholesterol-driven endoplasmic reticulum stress responses.

Therefore, cholesterol participates in atherogenesis by mechanisms that are increasingly well defined. Cholesteryl ester, although not directly harmful, can be a marker for pathological cholesterol excess and ACAT activation. Chemically quantified cholesteryl ester concentrations in atherosclerotic lesions can increase to >100-fold higher than in normal arterial intima (7).

That is not the whole story, however. Cholesteryl ester in atherosclerotic fibrous plaques may also accumulate directly from plasma lipoproteins without the intervening steps of cellular uptake, lysosomal hydrolysis, and ACAT-mediated re-esterification. In plasma lipoproteins, linoleate comprises ~45% of cholesteryl ester fatty acids and oleate 25%, with the remainder mostly saturated fatty acids. In lesions rich in foam cells with large lipid droplets, the oleate fraction increases to 50% and linoleate decreases to 15%, apparently due to preferential use of oleyl coenzyme A by ACAT. However, in the fibrous plaque core region, the bulk of cholesteryl ester retains a fatty acyl composition similar to plasma lipoproteins and resides in small extracellular droplets (7,8). This suggests that most of the cholesteryl ester accumulating in mature atherosclerotic lesions is not re-esterified by ACAT in foam cells, but is derived from an alternative process of lipoprotein aggregation and fusion in the extracellular space (9,10).

Duivenvoorden et al. (1) determined the relative proportion of methylene protons and allylic methylene
protons in the sampled voxel intersecting the carotid artery wall. Cholesteryl linolate has 3.6 methylene protons for each allylic methylene proton, whereas triolein has a corresponding ratio of 6 to 1. The detection of atherosclerotic cholesteryl ester is aided by the fact that it is enriched in linolate compared with the intracellular triglyceride in perivascular tissue, which contains about one-half oleate among its fatty acids.

MR imaging of lipid deposits in atherosclerotic lesions in vivo has been performed previously in a semiquantitative manner, validated by correlations with histology of excised plaques (11). However, application to clinical atherosclerosis remains limited. An impressive initial result was a comparison between 8 control lipid clinic patients and 8 patients who had been treated for 10 years with a combined regimen of lovastatin, niacin, and colesteol. In carotid plaques of control patients, 17% of plaque area was ascribed to lipid core, whereas in the treated patients, only 1% of plaque area appeared to represent lipid core (12). In a subsequent prospective evaluation of 33 subjects with measurable lipid-rich necrotic cores at baseline, core volumes decreased by 38% over 3 years. The 33 subjects are part of a larger ongoing study of 123 subjects with coronary artery disease randomized to 3 different lipid treatment regimens (13).

Niacin, in particular, via activation of the G protein–coupled receptor GPR109A, has been shown to augment cholesterol efflux in macrophages (14,15). In mice, niacin inhibited atherogenesis in a GPR109A-dependent manner (15). Could this translate into cholesterol removal from human atherosclerotic lesions? A more direct approach to cholesterol removal from lesions involves intravenous infusion of reconstituted high-density lipoproteins. When this approach was attempted in a randomized, controlled trial, the limitations of intravascular ultrasound in defining lesion components were sorely apparent (16). Further development of the MR spectroscopic procedures described by Duivenvoorden et al. (1) may eventually allow these kinds of clinical questions to be addressed with a new level of precision and specificity.

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REFERENCES