Effects of Lipid-Lowering by Simvastatin on Human Atherosclerotic Lesions: A Longitudinal Study by High-Resolution, Noninvasive Magnetic Resonance Imaging

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Background—This study was designed to investigate the effects of lipid-lowering by simvastatin on human atherosclerotic lesions.

Methods and Results—Eighteen asymptomatic hypercholesterolemic patients with documented aortic and/or carotid atherosclerotic plaques were selected for the study. A total of 35 aortic and 25 carotid artery plaques were detected. Serial black-blood MRI of the aorta and carotid artery of the patients was performed at baseline and 6 and 12 months after lipid-lowering therapy with simvastatin. The effects of the treatment on atherosclerotic lesions were measured as changes in lumen area, vessel wall thickness, and vessel wall area, a surrogate of atherosclerotic burden. Simvastatin induced a significant (P<0.01) reduction in total and LDL cholesterol levels at 6 weeks that was maintained thereafter. At 6 months, no changes in lumen area, vessel wall thickness, or vessel wall area were observed. However, at 12 months, significant reductions in vessel wall thickness and vessel wall area, without changes in lumen area, were observed in both aortic and carotid arteries (P<0.001).

Conclusions—This in vivo human study demonstrates that effective and maintained lipid-lowering therapy by simvastatin is associated with a significant regression of atherosclerotic lesions. Our observation suggests that statins induce vascular remodeling, as manifested by reduced atherosclerotic burden without changes in the lumen. (Circulation. 2001;104:249-252.)

Key Words: lipids ♦ atherosclerosis ♦ plaque ♦ magnetic resonance imaging

The benefits of statins on cardiovascular diseases have been clearly established in several clinical trials for primary and secondary prevention. Statin administration reduced LDL cholesterol by 30% to 40% and mortality decreased by 25% to 30%. The mechanisms of action responsible for these clinical benefits are not clearly understood.

Postmortem evidence indicated that plaque composition, rather than the degree of stenosis, is a key factor for plaque vulnerability.1,2 Disruption or erosion of atherosclerotic plaques has been associated with the acute onset of cardiovascular events.3-5 These studies characterized the lesions more prone to disruption (vulnerable) as lipid-rich and moderately stenotic. These lipid-rich plaques are highly thrombogenic on disruption.6 Angiographic trials designed to investigate the effect of lipid-lowering on atherosclerosis demonstrated an association between slowed progression of coronary narrowing and cardiovascular event reduction, suggesting that statin therapy may cause regression and/or stabilization of lipid-rich lesions.7

High-resolution MRI is a novel, noninvasive, and safe technique that allows serial visualization of atherosclerotic plaques. Its usefulness for in vivo assessment and characterization of atherosclerotic lesions was previously validated using animal models of atherosclerosis8-10 and in humans.11 Furthermore, MRI permits highly accurate in vivo measurement of artery wall dimensions in human atherosclerotic carotid,12 aortic,13 and coronary14 lesions.

The purpose of the present study was to delineate the effect of lipid-lowering by simvastatin on human atherosclerotic lesions.

Methods

Experimental Design

The study involved asymptomatic, untreated, hypercholesterolemic patients (LDL cholesterol ≥130 mg/dL and triglycerides ≤445 mg/dL). Inclusion criteria were based on the preexistence of atherosclerotic plaques (thoracic aortic ≥4.0 mm and/or carotid ≥2.0 mm thick) detected by B-mode ultrasound transesophageal echocardiog-
raphy or MRI. Serial MRI studies of the thoracic aorta and carotid arteries were performed at baseline and 6 and 12 months after therapy. Exclusion criteria included a clinically significant medical or surgical event within 3 months before study entry, heart failure, renal or hepatic disease, or significant carotid disease. Of 55 screened patients, 18 patients fulfilled the inclusion criteria and were enrolled in the study after providing written consent. The patient characteristics were as follows: 10 were men and 8 were women; mean age was 63.5±9 years; total cholesterol measured 240±37 mg/dL; LDL cholesterol was 159±32 mg/dL; HDL cholesterol was 52±16 mg/dL; and triglycerides measured 164±106 mg/dL. The local institutional review board approved the protocol.

At clinical follow-up (at 6, 12, 24, and 48 weeks), samples were drawn to determine lipid levels and safety parameters (creatinine kinase, aspartate aminotransferase, alanine aminotransferase, and creatinine).

MRI Protocol

MRI was performed on a 1.5-T whole-body MRI system (Signa CV/i; GEMS; 40 mT/m; SR150). A 4-element (2 elements on the right side of the neck and 2 elements on the left side), phased-array coil was used for carotid imaging. A 4-element coil (2 anterior and 2 posterior elements) was used for aortic imaging. After localization with a fast-gradient-echo sequence, all images were obtained with a double-inversion recovery (ie, black-blood), fast spin-echo sequence with ECG-gating during free breathing. A total of 25 to 30 transverse images centered at the carotid bifurcation were taken. Imaging parameters were as follows: repetition time, 2 RR intervals; echo time, 12/45 ms (proton density–weighted/T2-weighted); field of view, 12 cm; slice thickness, 3 mm; no interslice gap; acquisition matrix, 256×256; no phase wrap; number of signals averaged, 1/2 (proton density–weighted/T2-weighted); echo train-length, 32; receiver bandwidth, ±64 kHz; 512 zero filling. A chemical shift suppression pulse was used to suppress the signal from perivascular fat. For the aorta, 25 to 30 transverse images from the origin of the left subclavian artery to the level of the diaphragm were obtained. For the aortic arch, 10 to 12 cross-sectional oblique images (perpendicular to the vessel wall) were acquired. The imaging parameters were similar for carotid imaging except field of view was 20 cm and slice thickness was 5 mm. The total examination lasted 60 to 90 minutes.

Morphometric Analysis

The MR images were transferred to a Macintosh computer for analysis. Special attention was given to match MR images of the same patient at different follow-up time points (Figure 1), using several anatomical landmarks (ie, carotid bifurcation, origin of the coronaries, pulmonary artery bifurcation, and pulmonary veins). To minimize submillimeter errors in the matching of the images at different time points, at least 5 contiguous MR images per plaque were analyzed, and their average was considered for statistical analysis. Computer-assisted morphometric analysis of cross-sectional MR images was used to measure vessel wall dimensions by semiautomatic tracing (Image Pro-Plus, Media Cybernetics). The tracing tool works by following an edge (ie, boundary) of significant contrast. Lumen area; total vascular area; minimal, maximal, and mean vessel wall thickness; and vessel wall area (vessel wall area = total vascular area minus lumen area) were calculated. The measurements were performed by an investigator who was blinded to the patient’s identity and order of images.

The reproducibility of the vessel wall area measurement was tested in 6 patients (5 aortic and 4 carotid plaques) after repeated imaging. The image-specific error (SD between matched image) was 6 mm² for aortic and 2 mm² for carotid images. If the vessel wall area measurement values averaged over 5 contiguous images were considered, the error was reduced to 4.5 mm² for aortic and 1.5 mm² for carotid images. This corresponds to an error of 2.6% for aortic and 3.5% for carotid plaques. On the basis of this reproducibility, we calculated that changes in plaque size >5.2% for aortic lesions and >7% for carotid lesions are likely to be accurately measured by MRI.

The effects of simvastatin on atherosclerotic lesions were assessed as changes in vessel dimensions versus baseline. To rule out any

Figure 1. Serial T2-weighted images of the same patient. Note the adequate matching of the images with a similar pattern of the coronary vessels (top). In detail of the descending aorta (bottom), arrows indicate maximal atherosclerotic plaque size.
Serum Lipid Profiles
Simvastatin induced a significant ($P<0.01$) reduction in total and LDL cholesterol and an increase in HDL cholesterol ($P<0.01$). At 6 weeks, total and LDL cholesterol decreased by 23.1% and 38.0%, respectively, whereas HDL cholesterol increased by 9.1%. These changes were maintained during follow-up.

Changes in Vessel Wall Dimensions
The effects of lipid-lowering on the vascular wall are presented in Figure 2. A total of 35 aortic and 25 carotid plaques were detected and selected for follow-up. No changes in lumen area were observed. A significant reduction in vessel wall area was observed at 12 months in both carotid and aortic lesions (Figure 2), whereas no changes were seen at 6 months. Indeed, the vessel wall area of the aorta decreased from $257\pm59 \text{mm}^2$ at baseline to $237\pm61 \text{mm}^2$ at 12 months ($P<0.001$), corresponding to an 8% decrease. Interestingly, similar changes in vessel wall area were seen at 12 months in the carotid artery plaques. The carotid vessel wall area decreased by 15% ($49\pm11 \text{mm}^2$ at baseline; $42\pm11 \text{mm}^2$ at 12 months; $P<0.001$). Corresponding changes were seen in vessel wall thickness. Indeed, maximal thickness decreased at 12 months (Figure 2), but minimal thickness remained unchanged, confirming the shrinkage of the atherosclerotic plaque but not of the normal vessel wall. The maximal vessel wall thickness of the aortic plaques decreased from $4.6\pm0.6 \text{mm}$ at baseline to $4.2\pm0.6 \text{mm}$ at 12 months ($P<0.001$), and the same was seen for carotid plaques (from $2.7\pm0.5 \text{mm}$ to $2.4\pm0.5 \text{mm}$, respectively; $P=0.005$). The decrease of vessel wall area is a surrogate of regression in plaque size and, considering the unchanged lumen area, an expression of inward remodeling, as evidenced by the significant reduction in the outer vessel area.

A direct effect of simvastatin on normal vessel wall could be ruled out because the vessel wall areas and lumen areas of 28 nonatherosclerotic arterial segments did not change after 12 months of treatment. The difference in vessel wall area was 2.4% ($P=0.8$) for aortic and 3.9% ($P=0.3$) for carotid segments. No cardiovascular events were registered during the 12 months of follow-up.

Discussion
This in vivo MRI study documents a reduction in atherosclerotic lesion size induced by statins in humans. An important observation was that a minimum of 12 months of treatment was required to observe plaque changes. In fact, no changes were detected at 6 months, despite the expected hypolipidemic effect of simvastatin. Our data demonstrate a significant reduction in plaque size without lumen size changes (Figure 2), which is in agreement with Glagov et al.'s observation. Previous angiographic trials detected only minimal changes in the lumen (1% to 2%) in stenotic lesions, despite significant clinical benefits. These results could be explained by the inability of angiography to detect changes in vessel wall and nonstenotic plaques. In fact, clinical events most commonly originate from mild or moderate stenotic lesions that abruptly undergo a disruptive transformation to a culprit lesion.

Even if the changes in vessel wall area seem relatively modest (~10% reduction at 12 months), they most likely indicate a substantial transformation in plaque composition and are in agreement with the hypothesis that lipid-lowering by statins stabilizes the plaque. Experimental studies with aggressive lipid reduction showed that lipid core depletion has important pathophysiological consequences. Recently, Crisby et al. demonstrated a reduction in lipid content, oxidized LDL, apoptosis, macrophages, and matrix metalloproteinase-2 and an increase in collagen content in human carotid plaques after lipid-lowering therapy. These observations could explain the changes in plaque composition affecting lesion size and stability. However, the association between plaque regression and reduced risk for future events must be prospectively studied.
In summary, we present evidence on the beneficial effect of maintained lipid-lowering therapy by simvastatin on atherosclerotic vascular wall. The significant reduction in lesion size without affecting the lumen (inward remodeling) seems to be mediated by reducing lipid content and, thus, is indicative of structural changes favoring plaque stabilization. However, the nature of these changes warrants further investigation.

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