Short-Term Effect of Atorvastatin on Carotid Artery Elasticity
A Pilot Study

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Background and Purpose—Few studies have examined the early effects of statins on carotid artery elasticity, a potential surrogate marker of cardiovascular risk. This study examined the short-term effects of atorvastatin 80 mg daily on carotid elasticity measured by high-resolution B-mode ultrasound.

Methods—The study included 40 stroke-free and statin-naive subjects older than age 45 (mean age, 70±7 years; 55% men; 64% Caribbean-Hispanic). Outcome measures included carotid stiffness indices at 14 and 30 days after initiation of treatment. The systolic and diastolic diameters of the right common carotid artery were averaged from multiple B-mode imaging frames. Absolute and relative changes of strain [(systolic diameter/diastolic diameter)/diastolic diameter], stiffness (\(\beta\) [ln (systolic/diastolic blood pressure)/strain], and distensibility (1/\(\beta\) adjusted for wall thickness) from baseline were compared by the repeated measures t test and were considered significant at \(P<0.05\).

Results—Baseline mean stiffness was 0.08 (95% confidence interval [CI], 0.06–0.10). It significantly decreased at day 30 to 0.05 (CI, 0.04–0.06; \(P<0.01\)). Mean baseline distensibility was 15.25 (CI, 13.18–17.32), increasing significantly at day 30 to 17.23 (CI, 14.01–20.45; \(P<0.05\)). An improvement in distensibility of \(\geq10\%\) from baseline was observed in 29 (73%) subjects. Changes in stiffness and distensibility were maximal among subjects with baseline low-density lipoprotein levels <130 mg/dL.

Conclusions—Short-term treatment with high-dose atorvastatin was associated with improvement in the carotid elasticity metrics. Carotid artery elasticity measured by B-mode ultrasound is a simple noninvasive measure of arterial wall function and may be a useful surrogate end point in clinical trials targeting individuals at increased risk for atherosclerosis. (Stroke. 2011;42:3460-3464.)

Key Words: carotid arteries ▪ carotid ultrasound ▪ elasticity ▪ statins

Endothelial dysfunction is among the earliest events in the cascade of atherogenesis. Much effort has focused on identifying noninvasive measures of endothelial function, as well as on modifying endothelial dysfunction via pharmacological or other means.\(^1\)\(^,\)\(^2\) Identification of a simple noninvasive method by which the immediate effects of therapy could be observed would be ideal, with potential application in both the research and clinical settings.

Carotid artery elasticity may serve as a surrogate marker for cardiovascular risk. Previous population-based studies, including the Rotterdam study,\(^3\) the SMART study,\(^4\) and ARIC,\(^5\) have shown stiffness of the common carotid artery (CCA) to be strongly associated with atherosclerosis and cardiovascular risk factors. In subjects with type 2 diabetes, carotid artery elasticity was related to cardiovascular risk factors and carotid intima-media thickness (IMT).\(^6\) Recently, CCA stiffness was shown to be an independent risk factor for ischemic stroke.\(^7\)

Arterial elasticity represents the ability of the arterial wall to contract and expand with the cardiac cycle. Increased stiffness and decreased distensibility represent impairments of the artery wall function, which may be an early step in development of atherosclerosis. Previous work from our group has demonstrated good reproducibility and reliability of B-mode ultrasound measurements of CCA diameters during the cardiac cycle and derived metrics of carotid elasticity.\(^8\)

Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are well-known to have beneficial effects on...
arterial wall properties, including improvement of an ultrasound measure of flow-mediated dilatation and endothelium-dependent vasodilatation of the brachial artery.10 One group found that 1 year of statin treatment improved carotid artery stiffness,11 but the early impact of statins on carotid artery wall function has not been investigated.

This study aimed to examine the effects of atorvastatin on metrics of carotid artery wall elasticity, including stiffness and distensibility at 14 and 30 days after initiation of atorvastatin using high-resolution B-mode carotid ultrasound imaging. We hypothesized that carotid artery stiffness would decrease with a concomitant increase in carotid artery distensibility within 30 days of initiation of atorvastatin, and that this effect would be independent of the degree of lipid-lowering effect.

Materials and Methods

Subjects
This study included 40 stroke-free and statin-naive subjects older than age 45 years who were eligible for treatment according to the National Cholesterol Education Program: Adult Treatment Panel III.12 To be eligible, participants were required to have: (1) coronary heart disease (CHD) or CHD-equivalent (peripheral artery disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes, or multiple risk factors conferring a 10-year risk for CHD >20%); (2) ≥2 risk factors for CHD and low-density lipoprotein (LDL) ≥130 mg/dL; or (3) <2 risk factors and LDL ≥160 mg/dL. NCEP ATP III risk factors for CHD include: (1) age: men 45 years or older, women 55 years or older; (2) hypertension; blood pressure ≥140/90 mm Hg or need for antihypertensive medication; (3) high-density lipoprotein <40 mg/dL; (4) cigarette smoking; and (5) family history of premature CHD, ie, CHD in a male first-degree relative younger than 55 years or in a female first-degree relative younger than 65 years.

Exclusion criteria were any use of fibrates or other lipid-lowering medication; hospitalization for acute coronary syndrome within the past 6 months; hepatic or renal dysfunction; connective tissue or chronic inflammatory disease; history of malignancy; any acute illness; leukocytosis (white blood cell count >10x10^3/L); thrombocytosis (platelet count >450x10^3/L); anemia (hematocrit <40%); corticosteroid use; pregnancy; and breastfeeding.

The study was performed in the Department of Neurology at Columbia University, New York. It was approved by the Western Institutional Review Board. Written informed consent was obtained from all participants.

All subjects received atorvastatin 80 mg daily for 30 days. Study assessments at each of 3 visits (baseline before atorvastatin, day 14, and day 30) consisted of a carotid scan, blood pressure measurements, and fasting laboratory assays for lipids and liver enzymes. Subjects were also questioned regarding adverse effects, including muscle pain, weakness, and gastrointestinal symptoms.

Measurement of Blood Pressure
After resting for 10 minutes in the supine position, subjects’ blood pressures were obtained using a semiautomated oscillometric blood pressure recorder (Dinamap Pro100; Critikon) on the right brachial artery. Blood pressures were measured before and after the carotid ultrasound examination and were then averaged.

Measurement of Carotid Artery Elasticity
Subjects underwent carotid artery scanning at baseline before initiation of atorvastatin, on day 14, and on day 30 using high-resolution B-mode ultrasound on a GE LOGIQ 700 system (GE Healthcare). The right CCA was scanned using an 11-MHz linear-array transducer according to a standard protocol as previously reported.6 In brief, the systolic diameter and diastolic diameter of the right CCA were obtained by measuring 10 mm of the right CCA below the origin of the carotid bulb. Offline measurement was performed using Image Pro image analysis software (Microscopy Corporation). Carotid IMT was measured in the same 10-mm segment using Image Pro according to the previously reported protocol.8,13 Both near and far wall interfaces defining the blood-intima boundaries were maximized and clearly depicted on B-mode images. M-mode images were obtained perpendicular to the arterial walls and were adjusted for the clearest representation of the CCA walls throughout the cardiac cycle. Two wall interfaces were tracked in up to 10 consecutive cardiac cycles. Systolic diameter and diastolic diameter were measured from the 3 B-mode/M-mode registrations and averaged. Interobserver reproducibility and intraobserver reproducibility were high in our previous reports.8,13

Carotid artery elasticity metrics were calculated as follows:

1. Strain (%)=(systolic diameter−diastolic diameter)/diastolic diameter; where systolic diameter was the systolic CCA diameter and diastolic diameter was the diastolic CCA diameter. Strain was expressed as a percent change representing the amount of wall deformation compared to the unstressed state.

2. Stiffness (β)=ln (systolic blood pressure/diastolic blood pressure)/strain; where systolic blood pressure and diastolic blood pressure were mean systolic and diastolic brachial blood pressures. Strain represents a stress-to-strain ratio.

3. Distensibility=(1/β) adjusted for IMT.

Statistical Analysis
Carotid artery elasticity parameters and blood test results are expressed as means (±SD) and interquartile ranges. ANOVA was used to compare elasticity parameters at baseline, day 14, and day 30. Absolute changes in stiffness and distensibility were compared between day 14 (or day 30) and baseline using the paired repeated-measures t test. Relative changes in these parameters were also calculated by dividing percent differences from baseline by baseline values, multiplied by 100. An improvement of relative change in these parameters was defined as a decrease of ≥10% in carotid stiffness and an increase of ≥10% in carotid distensibility. Improvement in stiffness and distensibility (versus nonimprovement) was compared between day 14 (or day 30) and baseline. Stratified analyses by the LDL levels at baseline (≤130 versus ≥130 mg/dL) were performed. Differences were 1-tailed and considered statistically significant at a=0.05.

Results
The mean subject age was 70±7 years, and 55% were men; 64% were Caribbean-Hispanic, 24% were black, and 12% were white.

There was a significant treatment effect of atorvastatin on reduction of both total and LDL cholesterol levels compared to baseline (P<0.01). LDL decreased from a mean baseline level of 143.98±38.44 mg/dL to 70.08±25.40 mg/dL at day 30. Total carotid IMT did not change from baseline (baseline IMT 0.81±0.09 mm; 30-day IMT 0.79±0.08 mm; P=0.275).

Atorvastatin significantly affected metrics of carotid artery elasticity. Compared to baseline (0.08; 95% confidence interval [CI], 0.06–0.10), carotid artery stiffness decreased at day 14 (0.07; CI, 0.05–0.08) and significantly decreased at day 30 (0.05; CI, 0.04–0.06; P<0.01), as shown in Figure 1. Carotid artery distensibility increased with atorvastatin treatment, as illustrated in Figure 2. Compared to baseline (15.25; CI, 13.18–17.32), distensibility was increased at day 14 (16.09; CI, 13.70–18.48) and was significantly increased at day 30 (17.23; CI, 14.01–20.45; P<0.05).

The overall 30-day decline in LDL cholesterol from baseline was not significantly correlated with the change in
The present study extends these observations to the improvement of arterial function in the carotid artery, another vascular bed commonly affected by early atherosclerosis, and demonstrates that changes may occur as early as 30 days after treatment initiation.

Several possible mechanisms may explain the observed results, further highlighting the pleiotropic effects of statins. First, atorvastatin is known to influence the bioavailability of nitric oxide via effects on endothelial nitric oxide synthase. Simvastatin and lovastatin have been shown to induce transcriptional activation of the nitric oxide synthase gene in human endothelial cells in vitro. Atorvastatin may also improve endothelial function by this mechanism. Second, atorvastatin reduces oxidized LDL, which thus decreases degradation of nitric oxide produced by the endothelium and increases vasodilatation reserve, by which it may improve carotid distensibility. Statins reduce the copper-catalyzed LDL oxidation by increasing the proportion of protein within the LDL particle and decreasing superoxide anion formation.

These findings are consistent with previous clinical studies demonstrating the beneficial effects of statins on endothelial function using brachial artery flow-mediated dilatation. The anti-inflammatory properties of atorvastatin may also contribute to the observed effects on carotid artery elasticity.

Figure 1. Mean carotid artery stiffness and 95% confidence intervals at baseline, day 14, and day 30 of atorvastatin treatment (baseline versus day 30, Student t test, P<0.01).

Figure 2. Mean carotid artery distensibility and 95% confidence intervals at baseline, day 14, and day 30 of atorvastatin treatment (baseline versus day 30, Student t test, P<0.05).

Figure 3. Changes in carotid stiffness (improvement of 10% or more from baseline) by the low-density lipoprotein (LDL) levels.

Figure 4. Changes in carotid distensibility (improvement of ≥10% from baseline) by the low-density lipoprotein levels.
The beneficial effects on endothelial function appear unique to statins and are not seen, for example, with other cholesterol-lowering agents such as ezetimibe. Endothelial function was studied by measuring forearm blood flow responses to acetylcholine and sodium nitroprusside using venous occlusion plethysmography in patients with stable coronary artery disease.27 Both atorvastatin in dose escalation from 10 mg to 40 mg and atorvastatin initiation with 40 mg improved endothelial function after treatment for 4 weeks, but ezetimibe had no effect despite a comparable reduction in LDL levels.

Several explanations may exist for the pronounced effect of atorvastatin on carotid elasticity among subjects with lower baseline LDL levels observed in our study. The short-term duration of treatment could produce improvement of arterial wall function among those with lower LDL levels, but not among those with greater LDL because they may have had a lower degree of proinflammatory state because elevated LDL levels are well-known to decrease the bioavailability of endothelium-derived nitric oxide and to downregulate endothelial nitric oxide synthase.28 Also, the absolute LDL cholesterol levels measured after treatment were lower among those who started with lower LDL levels, although a similar relative LDL reduction was achieved for all. Second, those with higher pretreatment LDL levels might have already had more structural atherosclerotic wall changes; therefore, the effect of atorvastatin on the arterial wall function was less effective. In our measure of carotid distensibility, however, we have accounted for the carotid artery wall thickness (IMT), a measure of the structural atherosclerotic changes. Regardless, the same observation remained, indicating that the alterations in the arterial wall architecture (eg, changes in elastin:collagen ratio) may be more important for arterial wall function than arterial wall thickness per se.29 Finally, this observation may have been found by chance because elevated cholesterol levels measured after treatment were lower among those with greater LDL because they may have had a lower degree of proinflammatory state because elevated LDL levels are well-known to decrease the bioavailability of endothelium-derived nitric oxide and to downregulate endothelial nitric oxide synthase.28 Also, the absolute LDL cholesterol levels measured after treatment were lower among those who started with lower LDL levels, although a similar relative LDL reduction was achieved for all. Second, those with higher pretreatment LDL levels might have already had more structural atherosclerotic wall changes; therefore, the effect of atorvastatin on the arterial wall function was less effective. In our measure of carotid distensibility, however, we have accounted for the carotid artery wall thickness (IMT), a measure of the structural atherosclerotic changes. Regardless, the same observation remained, indicating that the alterations in the arterial wall architecture (eg, changes in elastin:collagen ratio) may be more important for arterial wall function than arterial wall thickness per se.29 Finally, this observation may have been found by chance because of a small number of patients in the stratified analyses.

Future studies are needed to establish the dose-response effect of atorvastatin on arterial elasticity. A previous study found that 10 mg and 20 mg of atorvastatin had similar effects on endothelium-dependent vasodilatation and carotid artery distensibility in patients with ischemic heart disease and hyperlipidemia.30 However, in a study of patients heterozygous for familial hypercholesterolemia,31 80 mg of atorvastatin led to a significant improvement in endothelial function as measured by flow-mediated dilatation, whereas 20 mg had no significant effect. Meanwhile, the flow-mediated dilatation results were independent of the reduction in LDL. Although previous data would suggest a class effect rather than a drug effect, future studies are needed to determine if our observations are specific to atorvastatin.

Limitations of the present study include the small sample size and the population demographics, which included predominantly elderly Caribbean-Hispanics. No control group was available for comparison. Results were not adjusted for changes in blood pressure or for antihypertensive medication use, which could also influence carotid artery elasticity and/or carotid IMT. Withdrawal of atorvastatin with additional measurements to test the reversibility of the effect would also be informative. Although previous work has shown B-mode ultrasound measures of carotid elasticity to be reliable,8 small errors in measurement of the artery diameter can lead to variations in the derived metrics. However, this would bias the observed associations toward null.

Future research should focus on standardizing protocols and techniques for measuring carotid artery elasticity. Currently, there is no recommended gold standard measure of arterial elasticity for clinical research. More knowledge is needed in the area of reliability and predictive validity before widespread use of this technique in clinical practice. Clearly, advantages of measuring carotid artery elasticity by ultrasound lie in its simplicity, user-friendliness, accessibility, and its ability to readily detect changes within weeks. Traditionally, months to years have been required to see the pharmacological effects on structural atherosclerotic lesions, such as carotid plaque or IMT imaged by 2-dimensional ultrasound. In addition to carotid artery elasticity, however, novel ultrasound techniques such as 3-dimensional measurement of plaque volume may also provide a useful tool for assessing the short-term effects of new therapies on atherosclerosis.32

Conclusions

In conclusion, the current study clearly demonstrated an improvement in carotid artery wall elasticity with short-term administration of high-dose atorvastatin. Whether improvement in arterial elasticity translates into better cardiovascular outcomes is yet to be proven. Measurement of carotid elasticity holds promise as another potential surrogate endpoint in clinical trials targeting individuals at increased risk for atherosclerosis.

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Disclosures

None.

References

detection of early stage atherosclerosis in subjects with type 2 diabetes. 


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