Cholesterol Lowering With Pravastatin Improves Resistance Artery Endothelial Function*

Report of Six Subjects With Normal Coronary Arteriograms

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Study objectives: Improvement in coronary artery endothelial function has been demonstrated after cholesterol lowering in hypercholesterolemic patients with significant atherosclerosis. However, to our knowledge, no previous study has shown improvement in resistance artery function in subjects with normal coronary arteries after cholesterol lowering. The purpose of our study was to investigate the effect of cholesterol lowering with pravastatin on coronary resistance artery endothelial function in the setting of angiographically normal coronary arteries.

Methods: Invasive testing of coronary endothelial and vasomotor function was performed at baseline and after 6 months of pravastatin treatment in six patients with normal coronary arteriograms.

Results: After 6 months of pravastatin treatment, low-density lipoprotein cholesterol level dropped from 157 ± 11 to 117 ± 8 mg/dL (p = 0.02) and percent increase in coronary blood flow after acetylcholine improved from 97 ± 13% to 160 ± 16% (p = 0.01). There was a trend (p = 0.17) toward enhanced epicardial dilation in response to acetylcholine after pravastatin treatment when compared with the baseline study.

Conclusions: Our study demonstrates significant improvement in coronary resistance artery endothelial function after 6 months of cholesterol lowering with pravastatin in six subjects presenting with chest pain who were found to have normal coronary arteriograms. A trend toward improved epicardial vasomotion was also observed. (CHEST 2000; 118:756–760)

Key words: coronary microcirculation; endothelial dysfunction; 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor

Abbreviation: LDL = low-density lipoprotein

Improvement in epicardial and resistance coronary artery endothelial function has been demonstrated after cholesterol lowering in hypercholesterolemic patients with significant atherosclerosis.1–4 However, to our knowledge, no study has heretofore demonstrated improvement in resistance artery endothelial function in hypercholesterolemic patients with angiographically normal coronary arteries after cholesterol lowering. The purpose of our study was to investigate the effect of cholesterol lowering with pravastatin over 6 months on coronary resistance artery endothelial function in six hypercholesterolemic patients with normal coronary arteries.

Materials and Methods

Subjects were recruited for the approved investigational study (Albany Medical College and Mary Imogene Bassett Hospital Institutional Review Boards) because of a history of chest pain and hypercholesterolemia of at least a mild degree. Informed consent was obtained that documented the participants’ understanding of the investigational and invasive nature of the protocol. Subjects were recruited through clinical referral and through newspaper advertisements soliciting patients with chest pain.
After obtaining fasting lipoprotein measurements, subjects underwent baseline cardiac catheterization and endothelial function testing. Following this, they were placed on a regimen of pravastatin, 20 mg, for 6 months. Patients found to have low-density lipoprotein (LDL) cholesterol levels >130 mg/dL during follow-up visits (6, 12, and 18 weeks) were instructed to increase the study drug to two tablets (40 mg) at bedtime. After 6 months of pravastatin treatment, fasting lipoprotein measurements were obtained and subjects underwent repeat cardiac catheterization and identical endothelial function testing as before. Subjects completing the entire protocol received honoraria of $1,000.

After diagnostic cardiac catheterization, a 0.018-inch Cardiovascular Flow-Wire Doppler tipped guidewire (Cardiometrics; Mountainview, CA) was advanced through a 7F or 8F coronary artery guiding catheter into the proximal to mid-portion of the left anterior descending or circumflex artery. The Doppler wire was placed in the identical location during baseline and follow-up studies in each patient. The placement of this device was optimized on the basis of Doppler signal quality. At least 15 min elapsed between the diagnostic study and baseline coronary velocity measurements. Coronary flow velocity signals were sampled at a preselected fixed distance of 5.2 mm from the device tip to minimize turbulence caused by the presence of the measuring device. After obtaining stable measurements of baseline coronary flow velocity, agonist drugs were infused into the left main artery to test the capacity for vasorelaxation through endothelium-dependent and endothelium-independent mechanisms. Coronary flow velocity was continuously recorded on super VHS-format videotapes so that peak drug effect could be identified during data processing performed at a time removed from the procedure. Coronary arteriograms were obtained under baseline conditions and at the end of each graded infusion of acetylcholine.

In order to test endothelium-independent coronary vasodilation, adenosine, 8, 16, and 20 μg, was administered sequentially through the guiding catheter into the left main artery. Typically, 60 s elapsed between each bolus infusion of adenosine. Endothelium-dependent coronary vasodilation was tested through graded infusions of acetylcholine ($10^{-8}$, $10^{-7}$, $10^{-6}$, $2 \times 10^{-6}$ mol/L) into the left main artery (assumed blood flow equal to 150 mL/min). Coronary arteriography was performed after each infusion of acetylcholine in an optimal right anterior oblique or anteroposterior projection, so that overlapping of branches and foreshortening of the region of interest were minimized. Optimal end-diastolic cineangiographic frames were selected and coronary artery diameters measured at the site of Doppler velocity measurements using electronic digital calipers (Sandhill Scientific; Colorado Springs, CO). Area was calculated assuming a circular cross-sectional profile. Percent change in coronary vessel diameter above baseline was calculated in response to each infusion of acetylcholine, and was considered a surrogate of epicardial artery vasomotor function. The contrast agent iohexol was used for all studies.

Coronary artery blood flow was calculated as the product of mean coronary blood flow velocity and coronary artery cross-sectional area at the site of Doppler wire velocity measurements. Baseline values were calculated before infusion of the predominantly endothelium-independent agonist adenosine and before the endothelium-dependent agonist acetylcholine. Percent change in coronary blood flow above baseline was calculated in response to each infusion of adenosine and acetylcholine and was considered a surrogate of resistance artery vasomotor function. Coronary vascular resistance was calculated as the quotient of coronary perfusion pressure (mean aortic pressure) and mean coronary blood flow. Minimum endothelium-dependent coronary vascular resistance index was calculated as the coronary vascular resistance at peak effect of acetylcholine divided by that at baseline and expressed as a percentage.

Summary clinical data and outcomes of the research studies (percent change in coronary blood flow and coronary diameter measurements in response to endothelium-dependent and endothelium-independent agonists) are expressed as mean ± SE. Paired Student’s t test (for continuous variables), χ2 test or Fisher’s Exact Test (for categorical variables), and one-way analysis of variance with Bonferroni correction were used for assessment of the statistical significance of differences, where a value of p < 0.05 was considered significant.

**RESULTS**

Six patients with normal coronary arteriograms underwent the entire protocol. Characteristics of these six study subjects are summarized in Table 1. No patient had any history of major medical illness or significant cardiovascular diagnosis.

Total cholesterol level decreased from 230 ± 14 to 184 ± 10 mg/dL, p = 0.03; LDL cholesterol level dropped from 157 ± 11 to 117 ± 8 mg/dL, p = 0.02; and apoprotein B-100 level dropped from 160 ± 16 to 124 ± 8 mg/dL, p = 0.07. There were no significant changes in high-density lipoprotein cholesterol, triglycerides, lipoprotein(a), and apoprotein A-1 levels.

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**Table 1—Clinical and Test Characteristics of Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr/Gender</th>
<th>Study Artery</th>
<th>Baseline CBF Increase After Acetylcholine, %</th>
<th>Follow-up CBF Increase After Acetylcholine, %</th>
<th>HTN</th>
<th>DM</th>
<th>Tobacco</th>
<th>LDL Cholesterol Baseline/Follow-up, mg/dL</th>
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<tr>
<td>1</td>
<td>43/M</td>
<td>LAD</td>
<td>105</td>
<td>183</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>132/95</td>
</tr>
<tr>
<td>2</td>
<td>67/M</td>
<td>LAD</td>
<td>106</td>
<td>183</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>169/129</td>
</tr>
<tr>
<td>3</td>
<td>50/M</td>
<td>LAD</td>
<td>132</td>
<td>106</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>124/167</td>
</tr>
<tr>
<td>4</td>
<td>43/F</td>
<td>LAD</td>
<td>105</td>
<td>92</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>183/153</td>
</tr>
<tr>
<td>5</td>
<td>59/M</td>
<td>CX</td>
<td>114</td>
<td>88</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>144/99</td>
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<tr>
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<td>LAD</td>
<td>86</td>
<td>130</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>178/130</td>
</tr>
</tbody>
</table>

*CBF = coronary blood flow; HTN = hypertension; DM = diabetes mellitus; M = male; F = female; LAD = left anterior descending; CX = circumflex.
Baseline values were 45 ± 3, 145 ± 33, 26 ± 7, and 139 ± 10 mg/dL, respectively.

**Endothelium-Independent and Endothelium-Dependent Resistance Artery Responses**

There were no significant differences in adenosine-mediated increase in coronary blood flow (endothelium-independent vasodilation) at baseline, compared to 6 months later after pravastatin treatment (176 ± 12% vs 220 ± 29%, p = 0.19).

Figure 1 shows percent increase in coronary blood flow during graded infusion of intracoronary acetylcholine (endothelium-dependent vasodilation) at baseline and after 6 months of pravastatin treatment. A highly significant difference during peak effect of acetylcholine was found (97 ± 13% vs 160 ± 16%, p = 0.01). Table 1 details each subject’s responses. Patient 3 alone did not show improvement in coronary blood flow after pravastatin treatment, probably related to the minimal improvement in LDL cholesterol (17 mg/dL). Linear regression analysis relating change in peak coronary blood flow after acetylcholine to improvement in LDL cholesterol level after 6 months of pravastatin treatment revealed a significant correlation (r = 0.87, p = 0.02).

**Minimum Endothelium-Dependent Coronary Vascular Resistance Index**

Mean arterial pressures were 90 ± 2 mm Hg and 90 ± 5 mm Hg during the two procedures separated by 6 months. Baseline values of coronary vascular resistance were 1.32 ± 0.4 mm Hg/min/mL and 1.29 ± 0.2 mm Hg/min/mL during initial and follow-up testing. Minimum endothelium-dependent coronary vascular resistance index was reduced to 39 ± 3% after 6 months of pravastatin treatment, compared with 53 ± 5% during the initial testing (p = 0.03), an improvement of 26%.

**Endothelium-Dependent Epicardial Artery Responses**

Figure 2 shows percent change in epicardial diameter during graded infusion of intracoronary acetylcholine at baseline and after 6 months of pravastatin treatment in the six subjects. Although coronary epicardial diameter responses to acetylcholine were not significantly changed after 6 months of drug therapy (p = 0.17), Figure 2 demonstrates that the epicardial arteries constricted during baseline studies and dilated during follow-up studies, suggesting a trend toward enhanced epicardial dilation after pravastatin treatment.

**DISCUSSION**

Our study shows that endothelial function of coronary resistance arteries can be significantly improved after 6 months of lipid-lowering therapy with pravastatin. This is the first study (to our knowledge) to demonstrate such benefit in patients with normal epicardial coronary arteries and chest pain. Such a group can be conjectured to represent an early stage in the natural history of coronary atherosclerotic disease and/or cardiomyopathy.

**Prevalence of Endothelial Dysfunction in Hyperlipidemia**

A number of conditions are associated with endothelial dysfunction. In addition to hyperlipidemia,
these include increased age, systemic hypertension, left ventricular hypertrophy, cardiomyopathy, atherosclerosis, estrogen deficiency, diabetes mellitus, and long-term tobacco use.5–11 The prevalence of coronary endothelial dysfunction secondary to hyperlipidemia is difficult to ascertain in patients because the diagnosis requires invasive testing. Furthermore, most patients undergoing coronary angiography have multiple cardiac risk factors that contribute in varying degree to abnormalities of endothelial function.

**Treatment of Endothelial Dysfunction With Lipid-Lowering Agents**

Endothelial injury and dysfunction appear to be early events in the development of atherosclerosis and contribute to plaque instability.12,13 Thus, improvement of endothelial dysfunction may delay or avert progression of atherosclerosis, shift vascular tone away from constriction and toward dilation, and contribute to plaque stabilization. Abnormal levels of circulating lipids are associated with endothelial dysfunction and contribute to the development and progression of coronary artery atherosclerosis.14,15 Among patients with advanced coronary artery disease, cholesterol lowering with simvastatin is associated with reduced rates of death and myocardial infarction.16 Even among patients with only moderately abnormal cholesterol levels and coronary artery disease, the use of pravastatin was associated with improved clinical outcomes.17 Reduction in transient ischemia was found among patients with coronary disease and angina pectoris after randomization to pravastatin in addition to conventional care.18 Finally, pravastatin was associated with reduced cardiovascular mortality rates among patients without clinically overt preexisting coronary heart disease.19

Cholesterol lowering with lovastatin was previously shown to improve endothelium-mediated responses at 5.5 months in epicardial coronary arteries in a cohort of patients with atherosclerosis who were referred for angioplasty.1 Similar findings were demonstrated in coronary patients treated with a combination of lovastatin and cholestyramine, or lovastatin and probucol (an antioxidant) at 12 months.2 Both epicardial and resistance artery vasomotor function were previously shown to be improved at 6 months among patients undergoing angioplasty who were treated with pravastatin.4 Finally, among 25 men with angiographically normal coronary arteries, epicardial artery endothelium-dependent responses were improved after 6 months of a cholesterol-lowering diet and cholestyramine.3

**Clinical Implications**

We have shown that significant improvement in coronary resistance artery endothelial function can be achieved after lipid-lowering therapy with pravastatin in subjects with angiographically normal coronary arteries. Since endothelial dysfunction appears to be an early stage in developing atherosclerosis, correction of this condition may prevent or retard the clinical presentation of coronary artery disease. Furthermore, improvement in resistance artery vasomotor function may prove to be efficacious in other disorders such as cardiomyopathy. Future studies investigating the natural history of treated and untreated endothelial dysfunction in the setting of angiographically normal coronary arteries are necessary to determine indications for such treatment.

**Study Limitations**

Because of the invasive nature of our study requiring two intravascular procedures, we enrolled only a small number of subjects. Though the number was sufficient to show statistical benefit of lipid lowering on coronary resistance artery endothelial function, follow-up confirmatory studies are needed.

**References**

9 Herrington DM, Braden GA, Williams JK, et al. Endothelial-
dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy. Am J Cardiol 1994; 73:951–952


