Effects of Short-Term Treatment of Hyperlipidemia on Coronary Vasodilator Function and Myocardial Perfusion in Regions Having Substantial Impairment of Baseline Dilator Reverse

Gordon S. Huggins, MD; Richard C. Pasternak, MD; Nathaniel M. Alpert, PhD; Alan J. Fischman, PhD, MD; Henry Gewirtz, MD

Background—We tested the hypothesis that correction of hyperlipidemia improves coronary vasodilator response and maximal perfusion in myocardial regions having substantial impairment of pretreatment vasodilator capacity.

Methods and Results—Measurements of myocardial blood flow were made with PET [13 N]ammonia in 12 patients with ischemic heart disease (11 men; age, 65±8 years [mean±SD]) at rest and during adenosine at 70 and then 140 μg · kg⁻¹ · min⁻¹ for 5 minutes each before and ∼4 months after simvastatin treatment (40 mg daily). Simvastatin reduced LDL (171±13 before versus 99±18 mg/dL after simvastatin, P<0.001) and increased HDL (39±8 versus 45±9 mg/dL, P<0.05). Myocardial segments were classified on the basis of pretreatment blood flow response to 140 μg · kg⁻¹ · min⁻¹ adenosine as normal (flow ≥2 mL · min⁻¹ · g⁻¹) or abnormal (flow <2 mL · min⁻¹ · g⁻¹). In normal segments, baseline myocardial blood flow (0.95±0.32) increased (P<0.001) at both low- (1.62±0.81) and high- (2.63±0.41) dose adenosine and was unchanged both at rest and with adenosine after simvastatin. In abnormal segments, myocardial blood flow at rest (0.73±0.19) increased at low- (1.06±0.59, P<0.02) and high- (1.29±0.33, P<0.01) dose adenosine. After simvastatin, myocardial blood flow increased more compared with pretreatment at both low- (1.37±0.66, P<0.05 versus pretreatment) and high- (1.89±0.79, P<0.01 versus pretreatment) dose adenosine.

Conclusions—Short-term lipid-lowering therapy increases stenotic segment maximal myocardial blood flow by ∼45%. The mechanism involves enhanced, flow-mediated dilation of stenotic epicardial conduit vessels and may account at least in part for the efficacy of lipid lowering in secondary prevention trials and in reducing ischemic episodes in ambulatory patients.

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Key Words: blood flow ■ ischemia ■ heart diseases ■ simvastatin

Recent studies of patients at risk for ischemic heart disease have shown that hyperlipidemia impairs maximal vasodilator response to dipyridamole in myocardial segments with presumed normal epicardial vessels1-4 and is thought to reflect a microvascular abnormality present at an early stage of atherosclerosis. The effects of hyperlipidemia and its correction on coronary vasodilator function in patients with overt ischemic heart disease and substantial impairment of baseline coronary dilator capacity are less well studied. Reduced perfusion defect size5,6 and improved reactivity of epicardial conduit vessels7-9 have been found after successful lipid-lowering therapy, although data on absolute myocardial blood flow have not been reported. Enhanced flow-mediated dilation of stenotic epicardial coronary vessels, presumably related to improved endothelial function after treatment of hyperlipidemia, could result in augmented myocardial blood flow.5,10 However, the magnitude of the effect is not known, and enhancement of coronary microvascular dilator capacity also could play a role.

See p 1257

It is possible to separate the contributions of conduit artery and microvascular dilation by comparing flow responses of segments with distinctly abnormal baseline dilator capacity, indicative of hemodynamically significant coronary artery stenosis, to those of functionally normal segments of the same patients in which conduit vessel dilation contributes little to the myocardial blood flow response to adenosine. Accordingly, this study tests the hypothesis in humans with ischemic heart disease that correction of hyperlipidemia improves coronary vasodilator function and myocardial perfusion in segments with substantial impairment of baseline dilator reserve by a mechanism involving primarily flow-mediated dilation of conduit vessels.

Methods

Patient Population

Patients with overt ischemic heart disease were recruited for this study after approval was obtained from both the Radiation Safety and
the Human Studies committees of the Massachusetts General Hospital. Twelve subjects (11 men; age, 65±8 years) were enrolled after written informed consent was obtained. Subjects were selected on the basis of a history of positive exercise stress test, triglycerides level <400 mg/dL, and an LDL level >160 mg/dL who were not on lipid-lowering therapy. Subjects were excluded if there was history of active tobacco abuse or diabetes mellitus.

### Study Protocol

Subjects were treated with simvastatin 40 mg daily for 4.8±1.0 months. Cholesterol, triglycerides, and HDL levels were measured in the Clinical Chemistry Laboratory of the Massachusetts General Hospital before, during, and after lipid-lowering therapy. LDL levels were calculated according to the method of Friedwald et al.11 Exercise tolerance was measured with a standard Bruce treadmill protocol before the start of the study. Antianginal medications were continued before the stress test.

### Positron Emission Tomography

PET imaging was performed on a whole-body tomograph (Scanditronix PC4096, GE Medical Systems) in patients after an overnight fast.12,13 Cardiac medications were continued as prescribed. Briefly, images were acquired simultaneously in 15 contiguous sections, with a center-to-center separation of 6.5 mm. After the patients were positioned in the scanner, a 10-minute transmission scan was performed to correct the emission data for attenuation. Patients underwent PET imaging with $[^{13}N]$ammonia at rest and during a 5-minute intravenous infusion of adenosine at 70 and then 140 μg·kg$^{-1}$·min$^{-1}$. Dynamic data acquisition was begun 2 minutes after initiation of intravenous adenosine infusion and just before intravenous injection of ~25 mCi $[^{13}N]$ammonia over ~30 seconds. Data were collected for the first 3 minutes at 6 frames per minute and then at 2 frames per minute for 6 minutes. Radioactivity was allowed to decay for ~30 minutes before the next scan.

Attenuation-corrected $[^{13}N]$ammonia images were reconstructed with a conventional filtered back-projection algorithm as 128×128 pixel images in the transverse plane. Parametric (K1) images for rest and stress conditions were generated from the dynamic images by use of a previously described computer program.11 The K1 images were then used for analysis of myocardial blood flow by placing circular regions of interest (n=8) over standard areas of short-axis rings corresponding to the proximal, middle, and distal thirds of the left ventricle.11 A patient-based analysis of myocardial blood flow at rest and in response to adenosine before and after simvastatin treatment was performed. This was accomplished by taking all normal segments, defined as having myocardial blood flow ≥2 mL·min$^{-1}$·g$^{-1}$ with high-dose adenosine,12,13 and averaging them together to obtain a single value of blood flow for each patient at each stage of the protocol before and after simvastatin. Abnormal segments for each patient, defined as having myocardial blood flow <2 mL·min$^{-1}$·g$^{-1}$ with high-dose adenosine,12,13 were combined in the same fashion.

Myocardial conductance (G) was computed as follows:

\[
G = \frac{MBF}{MAP \times 1000},
\]

where MBF is myocardial blood flow (mL·min$^{-1}$·g$^{-1}$) and MAP is mean arterial pressure (mm Hg). MAP in turn was computed as follows:

\[
MAP = DAP + (0.5 \times PP),
\]

where DAP is diastolic arterial pressure and PP is pulse pressure.

### Statistical Analysis

Data are expressed as mean±SD. The significance of changes in group mean values was assessed with ANOVA and appropriate multiple contrasts test (Statview and SuperAnova, Abacus Concepts). Paired t tests were used to evaluate the significance of changes in hemodynamics, myocardial blood flow data, and serum lipid levels after simvastatin treatment. Linear regression analysis was used to assess the relationship between group mean values of myocardial conductance and adenosine dose before and after simvastatin. Values of P<0.05 were considered significant.

### Results

#### Patient Characteristics

There were 11 men and 1 woman (age, 65±8 years [range, 52 to 74 years]). The 1 woman did not take hormonal replacement therapy. Two patients had histories of prior myocardial infarction. No patient had prior coronary revascularization. Medications (Table 1) were not changed during the trial. Cardiac catheterization data were available for 7 of 12 patients, of whom 5 had single-vessel coronary artery disease (70% lumen diameter reduction) and 2 had double-vessel disease.

#### Serum Lipids and Stress Test Results

Total cholesterol declined from 235±17 to 162±19 mg/dL (P<0.001), while triglycerides were unchanged (125±72 to 97±45 mg/dL). There was a 42±9% reduction in LDL (171±13 before versus 99±18 mg/dL after simvastatin, P<0.001) and a 17±23% increase in HDL (39±8 versus 45±9 mg/dL, P<0.05).

Patients exercised for 6.9±2.8 minutes. Peak heart rate was 132±26 bpm and was 85±19% of age-predicted maximum. The peak double product was 22 213±6758 mm Hg/min. End point for exercise stress was fatigue in all but 2 patients (1 stopped for chest pain and the other because of ventricular tachycardia, which reverted to sinus rhythm without treatment). It should be noted that 7 of 12 patients experienced typical angina during the test (including the 1 who stopped because of it), and 10 of 12 exhibited ≥1-mm horizontal ST-segment depression.

#### Regional Myocardial Blood Flow

### Hemodynamics

Hemodynamic parameters remained unchanged compared with control values at low-dose adenosine both before and after simvastatin (Table 2). However, in response to high-dose adenosine, heart rate increased significantly and arterial
pressure declined (both \( P < 0.01 \)) compared with control both before and after lipid-lowering therapy. Absolute values of all hemodynamic parameters were comparable before and after simvastatin.

**Myocardial Blood Flow and Conductance: Normal Segments**

Myocardial blood flow at rest was 0.95±0.32 and increased (\( P < 0.001 \)) at both low- (1.62±0.81) and high- (2.63±0.41) dose adenosine. After treatment, myocardial blood flow at rest was 0.83±0.16 (\( P = \text{NS} \) versus before simvastatin) and increased (\( P < 0.001 \)) with both low- (1.60±0.70) and high- (2.35±0.64) dose adenosine. Blood flow responses to adenosine did not differ significantly before and after simvastatin.

Myocardial conductance increased significantly versus control values (\( P < 0.001 \)) in response to low- and high-dose adenosine both before and after lipid-lowering therapy. The magnitude of the responses to each dose of adenosine was comparable before and after treatment and was consistent from patient to patient (Figure 1). The ratio of posttreatment to pretreatment conductance was 0.99±0.28 at rest, 1.17±0.40 at low-dose adenosine (\( P = \text{NS} \)), and 1.04±0.42 at high-dose adenosine (\( P = \text{NS} \)) (see Tables 3 and 4 and Figure 1).

**Myocardial Blood Flow and Conductance: Abnormal Segments**

Myocardial blood flow at rest was 0.73±0.19 and increased at both low- (1.06±0.59, \( P < 0.02 \)) and high- (1.29±0.33, \( P < 0.01 \)) dose adenosine. After treatment with simvastatin, myocardial blood flow at rest was 0.74±0.18 (\( P = \text{NS} \) versus before simvastatin) and again increased in response to both low- (1.37±0.66, \( P < 0.01 \)) and high- (1.89±0.79, \( P < 0.001 \)) dose adenosine. The magnitude of blood flow increase to adenosine after simvastatin treatment was greater compared with pretreatment both at low (\( P = 0.05 \)) and high (\( P < 0.02 \)) doses of simvastatin.

Myocardial conductance increased significantly compared with control values (\( P < 0.001 \)) in response to both low- and high-dose adenosine both before and after simvastatin therapy. The magnitude of the responses to each dose of adenosine, however, was greater compared with pretreatment both at low- (\( P < 0.05 \)) and high- (\( P < 0.01 \)) dose adenosine (Figure 2). The response was consistent from patient to patient as demonstrated by Figure 3, which illustrates the ratio of posttreatment to pretreatment conductance for each. The ratio increased from 1.04±0.32 at rest to 1.32±0.41 at low-dose adenosine (\( P < 0.05 \)) and to 1.47±0.40 at high-dose adenosine (\( P < 0.005 \)) (see Tables 3 and 4 and Figures 2 and 3).

**Discussion**

**Principal Findings**

This study tested the hypothesis that short-term lipid-lowering therapy would enhance coronary vasodilator capacity in myocardial segments having substantial impairment of pretreatment vasodilator function. The data obtained clearly support this hypothesis (Figure 2). A left shift in the adenosine dose-response curve in abnormal zones after lipid-lowering therapy occurred and may be explained by improved vasodilator capacity in conduit arteries, microvessels, or both. Although at first glance enhanced microvascular dilation is an attractive mechanism, it appears unlikely because improvement was confined to abnormal zones. Neither maximal myocardial blood flow nor conductance of normal zones improved after simvastatin. Had microvascular

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**TABLE 2. Hemodynamics (Mean±SD)**

<table>
<thead>
<tr>
<th>HR, bpm</th>
<th>SAP, mm Hg</th>
<th>RPP, mm Hg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Simvastatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>58±13</td>
<td>151±26</td>
</tr>
<tr>
<td>Ado 70</td>
<td>61±12</td>
<td>144±21*</td>
</tr>
<tr>
<td>Ado 140</td>
<td>65±17*</td>
<td>143±19*</td>
</tr>
<tr>
<td><strong>After Simvastatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>57±8</td>
<td>147±22</td>
</tr>
<tr>
<td>Ado 70</td>
<td>56±9</td>
<td>142±28</td>
</tr>
<tr>
<td>Ado 140</td>
<td>65±13†</td>
<td>138±30*</td>
</tr>
</tbody>
</table>

HR indicates heart rate; SAP, systolic arterial pressure; RPP, rate-pressure product; Ado 70, adenosine 70μg·kg⁻¹·min⁻¹; and Ado 140, adenosine 140 μg·kg⁻¹·min⁻¹.

*\( P < 0.05 \) vs control; †\( P < 0.01 \) vs control.

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**TABLE 3. Myocardial Blood Flow (mL·min⁻¹·g⁻¹; Mean±SD)**

<table>
<thead>
<tr>
<th>Before Simvastatin</th>
<th>After Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Abnormal</td>
<td>Normal Abnormal</td>
</tr>
<tr>
<td>Control</td>
<td>Ado 70</td>
</tr>
<tr>
<td>0.95±0.32</td>
<td>0.73±0.19†</td>
</tr>
<tr>
<td>0.83±0.16</td>
<td>0.74±0.18</td>
</tr>
<tr>
<td>Ado 70</td>
<td>1.62±0.81†</td>
</tr>
<tr>
<td>1.60±0.70†</td>
<td>1.37±0.66‡</td>
</tr>
<tr>
<td>Ado 140</td>
<td>2.63±0.41†</td>
</tr>
<tr>
<td>2.35±0.64†</td>
<td>1.89±0.79†‡</td>
</tr>
<tr>
<td>Ado 70/control</td>
<td>1.7±0.6</td>
</tr>
<tr>
<td>1.9±0.7</td>
<td>1.8±0.7†</td>
</tr>
<tr>
<td>Ado 140/control</td>
<td>3.0±0.8</td>
</tr>
<tr>
<td>2.9±1.0</td>
<td>2.5±1.0†</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2. Normal and abnormal refer to segment types.

*\( P < 0.05 \) vs control; †\( P < 0.01 \) vs control; ‡\( P = 0.05 \) vs before simvastatin; ††\( P < 0.01 \) vs before simvastatin.
TABLE 4. Myocardial Conductance (mL · min⁻¹ · g⁻¹) mm Hg × 1000; Mean±SD)  

<table>
<thead>
<tr>
<th></th>
<th>Before Simvastatin</th>
<th>After Simvastatin</th>
<th>Before Simvastatin</th>
<th>After Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8.39±1.34</td>
<td>6.92±1.23</td>
<td>8.00±1.26</td>
<td>6.84±1.28</td>
</tr>
<tr>
<td>Ado 70</td>
<td>13.62±1.84†</td>
<td>9.44±1.61*</td>
<td>14.79±1.60†</td>
<td>11.97±1.55‡</td>
</tr>
<tr>
<td>Ado 140</td>
<td>23.63±1.18†</td>
<td>12.05±1.32†</td>
<td>21.37±1.42‡</td>
<td>16.98±1.60§</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2. Normal and abnormal refer to segment types.  
*P<0.05 vs control; †P<0.01 vs control; ‡P<0.05 vs before simvastatin; §P<0.01 vs before simvastatin.

dilator function been enhanced by lipid lowering, then one would have expected normal zones, which were not at maximal potential at baseline, also to show improvement. Improved vasodilator capacity caused by substantial regression of epicardial stenosis in conduit vessels after only 4 months of lipid-lowering therapy is most unlikely.15–17 Thus, enhanced flow-mediated dilation after lipid-lowering therapy, particularly at the site of hemodynamically significant coronary stenosis, appears to be the most likely mechanism responsible. This is especially true given the steep nature of the stenosis pressure-flow relationships for lesions capable of causing a substantial reduction in maximal myocardial flow with adenosine.20–23

Although normal segments had flow response to maximal adenosine ≥2 mL · min⁻¹ · g⁻¹, the absolute value on average (2.63±0.41) was less (P<0.05) than that of normal volunteers studied in our laboratory (3.24±0.87).13 This is consistent with prior reports that vasodilator myocardial segments with anatomically mild or even no coronary stenosis may be reduced in patients with ischemic heart disease.13,24 Failure of microvascular dilator function to improve with lipid-lowering therapy in these patients could reflect any of several factors, including (1) longer duration and more extensive disease in patients with manifest ischemic heart disease, (2) inadequate duration of simvastatin therapy, or (3) a combination of both factors. In any event, it is important to stress that normal segments in fact had room to improve and thus that the absence of change cannot be attributed to the possibility that they were at maximal dilator potential to begin with.

The fact that conduit artery dilator function improved and microvascular function did not may be related to a variety of factors. Flow-mediated vasorelaxation is induced by sheer stress on the vessel wall, which in turn causes release of nitric oxide and other vasodilating compounds by the endothelium.18–19,25–27 Pulse pressure in particular is greater in conduit vessels and could contribute to apparent earlier improvement in endothelial function via a vis the microcirculation. Furthermore, although lipid-lowering therapy improves endothelial function,7–9 it is possible that other endothelium-derived dilators (eg, prostacyclin and endothelium-derived hyperpolarizine factor) recover at different rates or play more- or less-important roles, depending on the level of the coronary circulation studied. Such factors could account for the variation in degree of recovery of endothelial function at different levels of the coronary circulation.

Although adenosine is predominantly an endothelium-independent vasodilator,22,29 Smits et al30 found a clear in vivo contribution of endothelium-derived nitric oxide to adenosine-mediated vasodilation. Accordingly, improved responsiveness of conduit vessels to adenosine after simvastatin may be related to recovery of endothelial nitric oxide release, which has been shown to play an important role in epicardial dilation related to changes in pulse pressure.25–27 Flow-mediated dilation also has been associated with other favorable alterations of stenosis geometry beyond limited increases in minimum lumen diameter.10,11 These changes also could have played a role in enhancing maximal myocardial blood flow with adenosine10,31 and may further explain why improvement was confined to abnormal segments. Indeed, both the baseline level of flow reserve ratio of abnormal segments (1.8; Table 3) and the level of improvement (2.5) in the present study corresponded closely to quantitative coronary angiographic measurements of stenosis geometry and flow reserve of
severe stenoses before (1.9) and after (2.8) aggressive risk factor modification, including 20% total cholesterol reduction, in the Lifestyle Heart Trial.

**Literature Review**

Several prior studies in this area have focused on vasodilator function in normal myocardial segments of hypercholesterolemic patients without manifest ischemic heart disease. Reduced maximal vasodilator response to dipyridamole was documented in each and was thought to reflect impaired endothelial and/or vascular smooth muscle function presumably at the microvascular level. Studies of patients with manifest ischemic heart disease have assessed the effects of lipid-lowering therapy on reactivity of epicardial coronary vessels and myocardial perfusion defect size but have not reported on myocardial blood flow per se. Lipid lowering plus antioxidant therapy in patients with ischemic heart disease has been shown to either blunt or reverse constriction of epicardial coronary vessels to acetylcholine. In 2 other studies, myocardial perfusion defect size declined after lipid-lowering therapy. The mechanism of reduction in defect size was hypothesized to involve a combination of improved flow-dependent, endothelium-mediated, epicardial dilation and enhanced microvascular dilation. Proof of improved function at the microvascular level, however, was unavailable because absolute measurements of myocardial blood flow in normal and abnormal areas were not obtained. The present study demonstrates for the first time that maximal myocardial blood flow of segments with marked impairment of flow reserve is augmented by lipid-lowering therapy and that enhanced conduit artery dilation alone is sufficient to account for the effect.

**Study Limitations**

The absence of coronary arteriography in all patients should not be construed as a limitation in this investigation, which evaluated physiological responses of the coronary circulation to lipid-lowering therapy. Hyperemic blood flow has an inverse, geometric relationship to anatomic coronary stenosis severity. Myocardial segments supplied by coronary vessels with little or no stenosis (<50% area reduction) have blood flow with dipyridamole >2 mL/min·g⁻¹, whereas these with severe stenosis (>90% area reduction) have myocardial blood flow ≈1 mL/min·g⁻¹. Similar data were obtained in the present study with adenosine, a more potent coronary dilator than dipyridamole. We have also shown that maximal myocardial blood flow >1.65 mL/min·g⁻¹ with adenosine has very high negative predictive accuracy (91%) for exclusion of moderate to severe coronary artery stenosis (ie, minimum lumen diameter <1.26 mm in 3-mm diameter artery) and that 30 of 31 (97%) moderate to severe stenoses had maximal myocardial blood flow with adenosine <1.65 mL/min·g⁻¹. Thus, although the focus of the present study was physiological, previous angiographic and physiological investigations in humans with ischemic heart disease support the approach adopted in the present investigation.

The intensive nature of the present study and the need for radiation exposure before and after therapy made it impractical to have a placebo-control group or to use a crossover study design. Instead, each patient served as his or her own control. Moreover, an internal control was present in the form of the normal zones that were unchanged in terms of blood flow responses over the course of the study. Thus, the constancy of hemodynamic and normal zone blood flow measurements documents the reproducibility of experimental methods and argues strongly against a nonspecific or placebo effect accounting for improved abnormal segment flow. The stability of PET measurements of myocardial blood flow in our patients also was demonstrated by the fact that the posttreatment-to-pretreatment conductance ratio for both normal and abnormal segments did not differ from unity at rest. Spontaneous improvement confined to abnormal zones only is also most unlikely because a prior report demonstrated deterioration of abnormal zone perfusion with return to pretreatment status on withdrawal of short-term (3 months) lipid-lowering therapy in patients with ischemic heart disease. Accordingly, in the short term, the natural tendency of abnormal zone vasodilator capacity is to remain abnormal.

**Conclusions**

In the present study of patients with manifest ischemic heart disease, coronary vasodilator function improved substantially in myocardial segments with distinctly abnormal dilator capacity before treatment. Segments with dilator capacity in the normal range, however, failed to improve. Taken together, these data indicate that short-term lipid-lowering therapy improved endothelium-dependent, flow-mediated dilation of stenotic conduit arteries but not microvessels. The magnitude of the effect was substantial, with an increase in maximal myocardial blood flow of ≈45% (Figure 2). Clinically, the data demonstrate a potential mechanism through which lipid-lowering therapy improves prognosis in second-prevention trials and reduces the frequency of ischemic episodes in ambulatory patients in the face of only minimal improvement in anatomic coronary stenosis severity.

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1296 Simvastatin and MBF in Humans With IHD


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