Delayed Response of Myocardial Flow Reserve to Lipid-Lowering Therapy With Fluvastatin

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Background—Lipid-lowering therapy can improve endothelial function in patients with coronary artery disease (CAD) and hypercholesterolemia. Little is known about induced changes in myocardial microcirculation. This study prospectively investigated the temporal effects of lipid-lowering therapy with fluvastatin on coronary flow and flow reserve (CFR) in patients with CAD assessed by PET.

Methods and Results—In an open clinical trial, CFR was studied in 15 patients with angiographically documented multivessel CAD and hypercholesterolemia (LDL >160 mg/dL). Dynamic 13 N-labeled ammonia PET imaging in conjunction with adenosine was used to assess regional and global CFR at baseline as well as at 2 and 6 months during treatment with fluvastatin (60 to 80 mg/d). Despite a rapid decrease in total cholesterol (29±6%) and LDL (37±9%), myocardial blood flow at rest and during stress was unchanged after 2 months of treatment (2.7±0.9 versus 2.5±0.6 mL·g⁻¹·min⁻¹). At 6 months, stress blood flow as well as CFR increased significantly (3.4±1.0 mL·g⁻¹·min⁻¹). No change in hemodynamic parameters was noted during the entire study. Nine of 15 patients increased CFR by >20%. All responders demonstrated improvement in anginal symptoms, whereas nonresponders stated no change (n=4) or worsening of symptoms (n=2). The improvement in CFR was not related to the amount of lipid lowering and was independent of the severity of stenoses.

Conclusions—Improvement in stress blood flow and CFR is delayed compared with the lipid-lowering effect of fluvastatin, suggesting a slow recovery of the vasodilatory response to adenosine. (Circulation. 1999;99:475-481.)

Key Words: lipids ■ fluvastatin ■ blood flow ■ PET ■ adenosine

Large epidemiological studies have shown that lipid-lowering therapy with HMG-CoA reductase inhibitors leads to a significant reduction in cardiac mortality and morbidity.¹–³ Angiographic studies demonstrated a disparity between the decrease in cardiac events and the extent of regression of coronary artery lesions.⁴ These observations suggest that mechanisms other than regression of atherosclerosis are operational in the reduction of coronary events with lipid-lowering therapy. It has been postulated that the clinical benefit is mediated by the stabilization of rupture-prone plaques and the enhancement of endothelial function.⁵,⁶ Other possible mechanisms include reduced thrombotic potential, cytotoxicity, and inflammatory response.⁷

Recent studies have shown beneficial effects of lipid-lowering therapy on the response of epicardial coronary arteries to acetylcholine within 6 to 12 months after initiation of therapy.⁵,⁶ Gould et al⁸ evaluated relative perfusion in patients with coronary artery disease (CAD) using semiquantitative analysis of ¹³N-labeled ammonia PET images and found a significant improvement in stress-induced defect size and perfusion abnormalities after 3 months of lipid-lowering therapy.

Tracer kinetic modeling allows quantitative analysis of regional blood flow and calculation of coronary flow reserve (CFR) with ¹³N-labeled ammonia PET in conjunction with adenosine, which has been demonstrated to be an accurate and reproducible technique.⁹–¹³ Additionally, impaired CFR is one of the earliest abnormalities associated with CAD and thus can be used as a sensitive parameter to monitor the effects of risk factor manipulation.¹⁰

The purpose of this study was to assess the temporal changes of myocardial flow and flow reserve as a marker of microcirculation in response to long-term pharmacological therapy with fluvastatin in patients with modest CAD and hypercholesterolemia.

Methods

Study Population

Patients undergoing elective coronary arteriography for evaluation of chest pain were considered eligible if angiography documented multivessel CAD with atherosclerotic stenoses exceeding 30% of lumen diameter in >1 vascular territory and if LDL cholesterol level exceeded 160 mg/dL. Exclusion criteria included need for revascularization procedure, proximal stenosis of >75%, coronary angio-
plasty or myocardial infarction within the past 6 months, history of coronary bypass surgery, left ventricular ejection fraction <40%, severe arterial hypertension (systolic and diastolic blood pressures >160 mm Hg and >90 mm Hg, respectively), insulin-dependent diabetes mellitus, treatment with ACE inhibitors, prior lipid-lowering therapy, and severe concomitant illness.

Study Protocol
Myocardial perfusion was measured with dynamic $^{13}$N-labeled ammonia PET under rest and stress conditions at baseline and at 2 and 6 months after the initiation of therapy. A symptom-limited bicycle test was performed at the time of study entry and at 6 months (study protocol is outlined in Figure 1). Anginal symptoms were reported with the use of a questionnaire at baseline and at 6 months and classified according to the Canadian Cardiovascular Society (CCS) classification system.14

Patients continued taking their concomitant medications during the entire study interval except on the day of PET studies. After baseline PET investigation, 40 mg of fluvastatin (Cranoc, Astra GmbH) was administered once daily. Patients were scheduled to visit the clinic every 4 weeks, and lipid serum concentrations were evaluated with the patient fasting for 12 hours overnight. Because a reduction of LDL cholesterol of >30% was the goal, the fluvastatin dose was increased to 60 or 80 mg/d after 1 month of medication if LDL cholesterol was not reduced by >30%.

The study protocol was approved by the Ethics Committee of the Technische Universität München. Informed consent was obtained before each patient was enrolled into the study.

Laboratory Methods
Total cholesterol and triglycerides were measured by enzymatic methods (Boehringer Mannheim). Serum HDL cholesterol concentration was measured enzymatically from the serum supernatant after precipitation with polyvinyl sulfate. LDL cholesterol was calculated from precipitation of chylomicrons, VLDLs, and LDLs with phosphotungstic acid and magnesium ions. LDL cholesterol was calculated from the difference between the serum total cholesterol and the cholesterol in the supernatant after precipitation with polyvinyl sulfate.

PET Imaging Protocol
All patients fasted for ≥12 hours. Vasoactive medications were discontinued for ≥24 hours before the PET study. The ECG was continuously monitored. Systolic and diastolic arm blood pressures were obtained at 1-minute intervals. Rate-pressure product (RPP) was calculated as heart rate times systolic blood pressure divided by 100.

Dynamic PET measurements were performed with a whole-body scanner (CTI/ECAT 951R/31; Siemens/CTI). After a transmission scan for attenuation correction, $20 \text{ mCi}$ of $^{13}$N-labeled ammonia was administered as a bolus over 30 seconds by an infusion pump. The dynamic PET data acquisition consisted of varying frame durations (12×10 seconds, 6×30 seconds, and 3×300 seconds). For the stress study, adenosine was infused at a dose of 0.14 mg ⋅ kg$^{-1}$ ⋅ min$^{-1}$ over 5 minutes. $^{13}$N-labeled ammonia was administered in a fashion similar as in the baseline study during the third minute of the adenosine infusion.

After the data were reconstructed with a Hanning filter, each data set was reoriented to 12 short-axis views of the heart by use of a SUN workstation (SUN Microsystems, Inc). Further analysis comprised automated region definition, motion correction, and calculation of regional myocardial blood flow in 3 regions of interest representing the vascular territories of epicardial arteries.11,12

We calculated coronary resistance at rest by dividing the mean blood pressure [(systolic blood pressure + diastolic blood pressure × 2)/3] by the flow at rest, and we calculated resistance at maximal vasodilation by dividing mean blood pressure by flow during hyperemia.

CFR was defined as a ratio of myocardial blood flow during adenosine to flow at rest.

Responders were defined as those with an increase in CFR during follow-up of ≥20% (cutoff threshold of 1 SD above mean of average CFR).

Quantitative Coronary Angiography
Coronary angiograms were analyzed by 3 cardiologists blinded to PET data.

Stenoses were quantified (percent luminal area stenosis) by use of an automated edge-contour detection system (Philips Integris H 3000, Automated Coronary Analysis version 1993[3]). The degree of stenosis in each vessel territory was grouped as <25%, 25% to 50%, 51% to 75%, or 76% to 100% area stenosis of the vessel diameter. Only the most severe stenosis was used to represent each territory for statistical analysis.

Bicycle Exercise Testing
Patients exercising using a bicycle ergometer. The initial workload was 25 W and was increased in 25-W increments every 2 minutes. Exercise was discontinued when the subject developed dyspnea, anginal symptoms, leg fatigue, generalized fatigue, or occurrence of ST-segment depression >0.2 mV. The ECG was considered positive if horizontal or downsloping ST-segment depression >0.1 mV 0.08 seconds after the J point occurred.

Statistical Analysis
All values are expressed as mean±SD.

Friedman test was used to compare the 3 time points, followed by Wilcoxon test in case of significance. Otherwise, the Mann-Whitney U test was used to compare 2 groups of continuous variables. All tests were 2-tailed. Spearman’s correlation coefficients were calculated to study the associations between different variables. A value of $P<0.05$ was considered statistically significant.

Results
Patients
Of the 22 patients enrolled, 7 did not complete the study protocol. Four patients discontinued use of fluvastatin due to adverse effects (nightmare, skin rash, and gastrointestinal symptoms13), and 3 declined follow-up. Fifteen patients (10 men, 5 women) successfully completed the protocol. Baseline characteristics and medication of individual patients are listed in Table 1. All female patients were postmenopausal and did not receive hormonal substitution. During the follow-up period, patients did not change their use of concomitant medication. Neither of the 2 current smokers quit smoking.

Serum Lipid Profiles
Serum lipid profiles at baseline and during pharmacological intervention are summarized in Table 2.

After 2 months, there was a significant decrease ($P<0.05$) in total cholesterol (29±6%), LDL (37±9%), and triglycerides (15±28%), with no further change at 6-month follow-up. Likewise, there was a significant reduction of the total cholesterol to HDL cholesterol ratio (29±14%) and the LDL to HDL cholesterol ratio (37±15%) after 2 months ($P<0.05$), with no further change after 6 months of therapy, whereas...
there were no significant changes of HDL cholesterol during the intervention period.

No significant differences in percent changes of the different cholesterol levels were found between patients receiving 60 (n=5) or 80 (n=10) mg of fluvastatin.

**Hemodynamic Responses to Adenosine Infusion**
Overall, there was no significant decrease in systolic or diastolic pressure, but heart rate and RPP increased significantly during infusion of adenosine (see Table 3). No significant changes in systolic or diastolic blood pressure were seen at rest or during adenosine infusion at baseline or after 2 or 6 months of follow-up. There were no significant differences in heart rate or RPP between baseline and follow-up studies. The increase in RPP was similar at baseline (36 ± 33%), at 2 months (30 ± 25%), and at 6 months (30 ± 31%) (P=NS).

**Myocardial Blood Flow**
Resting blood flow at baseline averaged 0.7 ± 0.2 mL g⁻¹ min⁻¹ and remained unchanged at 2-month follow-up (0.6 ± 0.1 mL g⁻¹ min⁻¹; P=NS). No statistically significant difference was seen at 6-month follow-up, with resting blood flow averaging 0.7 ± 0.2 mL g⁻¹ min⁻¹. Adenosine-induced hyperemic blood flow at baseline was 1.7 ± 0.5 mL g⁻¹ min⁻¹ and remained unchanged at 2-month follow-up, averaging 1.7 ± 0.5 mL g⁻¹ min⁻¹. A significant increase in hyperemic blood flow was obtained at 6-month follow-up, averaging 2.3 ± 0.9 mL g⁻¹ min⁻¹ (P<0.05 versus baseline). Global CFR was similar at baseline (averaging 2.5 ± 0.6) and at 2-month follow-up (averaging 2.7 ± 0.9). At 6-month follow-up, CFR increased significantly by 38 ± 41% to 3.4 ± 1.0 (P<0.05 versus baseline) (Figure 2).

**TABLE 3. Lipid Profiles During Therapy**

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age, y/Gender</th>
<th>BMI, kg/m²</th>
<th>History</th>
<th>Medication</th>
<th>LVEF, %</th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
<th>Most Severe Stenosis (% Luminal Area Stenosis)</th>
<th>CFR</th>
<th>Whole Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/F</td>
<td>28.1</td>
<td>H, FH</td>
<td>A, B, N</td>
<td>75</td>
<td>44</td>
<td>22</td>
<td>72</td>
<td>2.2</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>59/M</td>
<td>23.0</td>
<td>S, MI</td>
<td>A, B, N</td>
<td>73</td>
<td>32</td>
<td>42</td>
<td>48</td>
<td>2.5</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>59/M</td>
<td>25.7</td>
<td>CS</td>
<td>A</td>
<td>62</td>
<td>31</td>
<td>58</td>
<td>47</td>
<td>3.4</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>53/M</td>
<td>22.6</td>
<td>CS</td>
<td>A, B, N</td>
<td>70</td>
<td>63</td>
<td>31</td>
<td>23</td>
<td>3.5</td>
<td>3.7</td>
<td>3.4</td>
</tr>
<tr>
<td>5</td>
<td>55/F</td>
<td>23.1</td>
<td>H, FH</td>
<td>A, B</td>
<td>75</td>
<td>31</td>
<td>24</td>
<td>47</td>
<td>3.3</td>
<td>3.4</td>
<td>2.7</td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>29.4</td>
<td>H, A, B, N</td>
<td>74</td>
<td>88*</td>
<td>48</td>
<td>31</td>
<td>47</td>
<td>2.6</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>7</td>
<td>59/M</td>
<td>23.9</td>
<td>H</td>
<td>A, B, N, C</td>
<td>70</td>
<td>89†</td>
<td>100*</td>
<td>50</td>
<td>2.3</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>8</td>
<td>52/M</td>
<td>24.4</td>
<td>H, S, MI</td>
<td>A, B, N, C</td>
<td>70</td>
<td>14</td>
<td>32</td>
<td>42</td>
<td>2.7</td>
<td>3.3</td>
<td>1.3</td>
</tr>
<tr>
<td>9</td>
<td>70/M</td>
<td>22.8</td>
<td>H, S, FH</td>
<td>A, B</td>
<td>79</td>
<td>58</td>
<td>50</td>
<td>71</td>
<td>2.1</td>
<td>1.8</td>
<td>1.6</td>
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<tr>
<td>10</td>
<td>61/M</td>
<td>24.2</td>
<td>MI</td>
<td>A, B</td>
<td>70</td>
<td>100†</td>
<td>46</td>
<td>44</td>
<td>1.5</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>11</td>
<td>68/M</td>
<td>31.9</td>
<td>H, DM</td>
<td>A, B, N, D</td>
<td>80</td>
<td>50</td>
<td>73</td>
<td>62</td>
<td>2.4</td>
<td>2.0</td>
<td>2.5</td>
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<tr>
<td>12</td>
<td>47/F</td>
<td>24.8</td>
<td>FH</td>
<td>A, B, N</td>
<td>70</td>
<td>61</td>
<td>61</td>
<td>31</td>
<td>3.6</td>
<td>3.4</td>
<td>3.6</td>
</tr>
<tr>
<td>13</td>
<td>75/F</td>
<td>22.6</td>
<td>H, MI</td>
<td>A, B, N, D</td>
<td>42</td>
<td>42</td>
<td>58</td>
<td>69</td>
<td>2.0</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>14</td>
<td>73/M</td>
<td>24.8</td>
<td>S, FH</td>
<td>A, C</td>
<td>68</td>
<td>73</td>
<td>59</td>
<td>78*</td>
<td>1.8</td>
<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>15</td>
<td>72/F</td>
<td>25.3</td>
<td>H, DM</td>
<td>A, B, D</td>
<td>51</td>
<td>47</td>
<td>57</td>
<td>38</td>
<td>2.2</td>
<td>2.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; LVEF, left ventricular ejection fraction; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; H, hypertension; FH, family history; S, history of smoking; MI, myocardial infarction; CS, current smoker; DM, diabetes mellitus; A, aspirin; B, β-blockers; N, nitrates; C, calcium channel blockers; and D, diuretics.

Vessel localization: *middle segment, †distal segment.
Coronary resistance at rest was similar at baseline study (143±29 mm Hg×mL⁻¹·g⁻¹·min⁻¹) and at follow-up (153±29 and 149±27 mm Hg×mL⁻¹·g⁻¹·min⁻¹ at 2 and 6 months, respectively). In contrast, coronary resistance during adenosine infusion decreased by 58±11% to 58±14 mm Hg×mL⁻¹·g⁻¹·min⁻¹ at baseline, to 60±24 mm Hg×mL⁻¹·g⁻¹·min⁻¹ (60±17%; P=NS versus baseline) at 2-month follow-up, and to 45±15 mm Hg×mL⁻¹·g⁻¹·min⁻¹ (70±9%; P<0.05 versus baseline) at 6-month follow-up.

When regional analysis of CFR at baseline was compared with the degree of the maximum stenosis of the territory, a significant negative correlation between percent stenosis and regional stress flow (r=−0.39, P=0.05) and regional CFR (r=−0.42, P<0.05) was found. No significant differences, however, were found between the 4 subgroups of segments in regional CFR or in the percent increase in coronary blood flow during the 6-month follow-up period (Table 4). Moreover, percent changes in blood flow, resistance at rest and during adenosine infusion, and global CFR were not related to age, sex, hemodynamic parameters, or fluvastatin dose.

Nine patients fulfilled the criterion for responders (>20% increase in CFR). There was no statistical difference in age, sex, lipid levels at baseline, amount of lipid lowering during follow-up, other risk factors, or hemodynamic parameters between the 2 groups.

All responders quoted an improvement in anginal symptoms, whereas nonresponders stated no change (n=4) or worsening of anginal symptoms (n=2). However, no differences in exercise capacity or ST-segment depression were observed between the 2 groups.

### Relationship Between CFR and Plasma Lipid Fractions

There was no significant relationship of CFR at baseline to total cholesterol, LDL, HDL, triglycerides, total cholesterol/HDL ratio, or LDL/HDL ratio. No correlation existed between changes in lipid levels and changes in CFR in follow-up studies.

### Relationship Between CFR and Age

There was a significant negative correlation between CFR and age (r=−0.7, P<0.05). This was due to lower maximum flows in the older subjects (r=−0.7, P<0.05), whereas no difference was observed for resting blood flow (r=−0.1, P=0.74). There was a significant correlation between age and resistance at maximum flow (r=0.89, P<0.05) and between age and percent change in resistance (r=0.78, P<0.05). No correlation was found between the adenosine-induced increase in the RPP and age.

### Anginal Symptoms: Exercise Testing

At baseline, 2 patients had CCS III anginal symptoms, 8 were CCS II, and 5 were CCS I. During the follow-up period, anginal symptoms improved in 9 patients, 4 stated no improvement in symptoms, and 2 patients’ symptoms were aggravated. At 6-month follow-up, 1 patient was in CCS III, I was in CCS II, and 13 were in CCS I.

All but 1 patient underwent a symptom-limited bicycle test. At baseline, 4 patients had a positive exercise test. Three of those developed significant ST depression. The average peak exercise workload achieved at baseline was 130±38 W, with an average duration of exercise of 10.0±3.0 minutes. The

### TABLE 4. Regional Coronary Flow and CFR in Relation to Degree of Maximum Stenosis of Corresponding Vessel

<table>
<thead>
<tr>
<th>Maximum Stenosis of Territory (%)</th>
<th>Whole Myocardium</th>
<th>&lt;25</th>
<th>26–50</th>
<th>51–75</th>
<th>76–100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vascular territories</td>
<td>45</td>
<td>4</td>
<td>22</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Baseline rest flow, mL·g⁻¹·min⁻¹</td>
<td>0.7±0.2</td>
<td>0.8±0.3</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.6±0.1</td>
</tr>
<tr>
<td>Baseline stress flow, mL·g⁻¹·min⁻¹</td>
<td>1.7±0.5</td>
<td>2.1±0.3</td>
<td>1.7±0.5</td>
<td>1.6±0.6</td>
<td>1.4±0.5</td>
</tr>
<tr>
<td>Baseline CFR</td>
<td>2.5±0.6</td>
<td>2.9±0.6</td>
<td>2.6±0.6</td>
<td>2.4±0.8</td>
<td>2.1±0.4</td>
</tr>
<tr>
<td>Rest flow at 2 mos, mL·g⁻¹·min⁻¹</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
<td>0.7±0.2</td>
<td>0.5±0.1</td>
</tr>
<tr>
<td>Stress flow at 2 mos, mL·g⁻¹·min⁻¹</td>
<td>1.7±0.5</td>
<td>2.3±0.4</td>
<td>1.8±0.5</td>
<td>1.5±0.6</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>CFR at 2 mos</td>
<td>2.7±0.9</td>
<td>4.2±1.6</td>
<td>2.8±0.8</td>
<td>2.3±0.9</td>
<td>2.6±0.4</td>
</tr>
<tr>
<td>Rest flow at 6 mos, mL·g⁻¹·min⁻¹</td>
<td>0.7±0.2</td>
<td>0.8±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.6±0.1</td>
</tr>
<tr>
<td>Stress flow at 6 mos, mL·g⁻¹·min⁻¹</td>
<td>2.3±0.9*</td>
<td>3.2±1.0</td>
<td>2.2±0.8</td>
<td>2.2±0.8</td>
<td>1.8±0.9</td>
</tr>
<tr>
<td>CFR at 6 mos</td>
<td>3.4±1.0*</td>
<td>4.4±1.4</td>
<td>3.3±0.9</td>
<td>3.3±1.1</td>
<td>2.9±0.9</td>
</tr>
</tbody>
</table>

*P<0.05 vs baseline.
average RPP at rest increased with exercise from 7458 to 25778 bpm per mm Hg. At 6-month follow-up, 2 patients developed significant ST-segment depression. The average peak exercise workload was slightly increased to 139±27 W, with an almost identical average duration of exercise of 10.7±2.4 minutes (P=NS versus baseline). The average RPP at 6 months increased with exercise from 8276 to 25535 bpm per mm Hg (P=NS versus baseline).

**Influence of Gender**

When men (n=10) and women (n=5) were compared, significant differences at baseline were found in total cholesterol levels (250±20 versus 276±24 mg/dL, respectively; P<0.05), HDL levels (48±11 versus 62±12 mg/dL, respectively; P<0.05) and triglycerides (175±62 versus 104±19 mg/dL, respectively; P<0.05). There was no difference in global CFR at baseline or at follow-up studies between men and women. Further analysis revealed no differences between these groups concerning percent changes in CFR, resistance at rest or stress, hemodynamic parameters, or percent changes of lipid levels, but there were differences in changes in triglyceride values (−25±22% for men versus 10±38% for women; P<0.05).

**Discussion**

These data demonstrate that lipid-lowering therapy with fluvastatin increases CFR in patients with hypercholesterolemia and CAD. Although there was a rapid decrease in LDL by >30% after 2 months of treatment, no significant change in CFR was observed at that time. Despite the absence of a further reduction in serum cholesterol levels, there was significant improvement in CFR after 6 months. The improvement in CFR resulted primarily from a decrease in vascular resistance during adenosine infusion, suggesting a beneficial effect of long-term lipid lowering on stress-induced flow capacity. Moreover, the improvement in CFR was associated with an improvement in anginal symptoms.

**Baseline Study**

At baseline, global CFR values of the studied patients with modest atherosclerotic lesions were lower than data reported for normal volunteers, whose coronary blood flow increases 3.5- to 5-fold during adenosine infusion,9,11 and lower than reported for asymptomatic men with high risk for CAD (2.9±0.9).10 Our finding of an inverse relation between the severity of coronary artery stenosis and CFR is consistent with previous studies13,16–19 that have demonstrated that basal flow is not impaired while maximum blood flow begins to decrease at 30% to 40% diameter stenoses. As in previous studies, there was substantial variability among patients with comparable severity of stenoses. This variability may be due to geometric complexity of stenoses, variations in extent and length of vessel involvement, variable collateralization, and endothelial dysfunction.13,16,19

Previous studies in normal volunteers described an age-related increase in resting blood flow, which was correlated with RPP, and a tendency toward lower hyperemic blood flows in older subjects.20,21 In contrast to these findings in normal subjects with low risk for CAD, the decrease in CFR in the present study was primarily determined by decreasing hyperemic blood flow. In this context, it is noteworthy that all studied patients had CAD and ≥1 risk factor, and all but 1 were older than 50 years.

**Time-Course Effects of Lipid-Lowering Therapy**

The onset and mechanisms of the therapeutic benefits of lipid-lowering therapy are not yet clearly understood. Because most clinical studies use only 1 time point to evaluate therapeutic effects, the aim of the present study was to define the time course of changes in the myocardial microcirculation in response to lipid-lowering therapy.

Previous data showed improvement in endothelium-mediated vasodilator responses to acetylcholine in CAD patients by treatment with HMG-CoA reductase inhibitors with or without antioxidants after a period of 6 to 12 months.5,6 In atherosclerotic monkeys, dietary fat restriction has been shown to improve endothelial function within 4 to 18 months.22,23 In contrast to these animal studies, there are findings of fast improvement in endothelium-dependent vasomotor function in the human forearm within 2 to 12 weeks of lipid-lowering therapy24,25 or even after a single session of apheresis.26 Semiquantitative PET studies have shown that lipid-lowering therapy improved stress-induced defect size and perfusion abnormalities in patients with stenoses >50% diameter as early as 3 months after onset of therapy.8 However, the studied patient population included patients with advanced CAD resulting in extensive stress-induced perfusion abnormalities.

The present data document, for the first time, that functional improvement in myocardial perfusion as a marker for the microcirculatory reserve seems to be a slow process, which agrees with the observed time course of beneficial clinical results. The observed reduction in anginal symptoms underlines the clinical relevance of lipid-lowering therapy in our patient population, as has been shown in prior studies.4 At baseline, patients’ exercise capacities were not greatly affected by CAD. This is in contrast to the previous study by Czernin et al,27 whose patients did not undergo cardiovascular conditioning as part of risk factor modification, which may explain the nonsignificant change in exercise capacity in their selected patients with only mild to moderate CAD.

In contrast to previous clinical trials suggesting an increasing benefit associated with longer treatment duration and larger reduction of LDL cholesterol,1,2 improvement in flow reserve in the present study was not related to the amount of lipid lowering, nor were coronary flow or flow reserve at baseline significantly related to serum cholesterol concentrations. This discrepancy can be explained by the highly selected patient group with a narrow range of cholesterol levels and the definition of therapy response we used (>30% reduction of LDL cholesterol).

Improvement in flow reserve was not related to the degree of stenoses, although baseline measurements were significantly correlated with the severity of stenoses. Quantitative flow measurements as used in the present study demonstrated a general improvement in CFR, even in territories with milder stenoses. This underlines the strength and sensitivity of
quantitative flow measurements, because each vascular territory can be evaluated independently of control segments and directly compared with baseline results.

CFR did not normalize during the follow-up period, which is in concordance with previous investigations that indicated that lipid-lowering therapy did not completely restore endothelial function.5,6

Possible mechanisms underlying the improvement in hyperemic blood flow in the present study may include partial anatomic regression of atherosclerotic lesions and a beneficial effect on endothelium-dependent and -independent vasodilation.8,28 CFR as an integrating measure reflects vasomotor dysfunction. Because the pathophysiology is complex, it is difficult with existing in vivo methods to identify specific pathways by which improvement in vasomotor reactivity is achieved.

During therapy, patients could be separated into groups of responders and nonresponders. The decrease in anginal symptoms in responders was highly correlated with improvement in CFR. However, no differences in exercise capacity or ST depression were observed between the 2 groups. Furthermore, no significant differences between the tested variables could be found between the groups. Despite the small number of subjects studied, however, there was a trend to higher cholesterol levels, higher HDL-dependent ratios at baseline, and greater extent of cholesterol lowering during therapy in responders. This suggests a possible relationship between improvement in CFR and these factors that may become significant in larger patient groups to be studied in the future.

When patients were followed up by questionnaire 1 year after termination of the present study, 1 of 6 nonresponders complained of further worsening of symptoms, 2 had been treated by CABG and 1 by PTCA in the interim because of angiographically documented disease progression, and an additional 1 patient’s symptoms worsened again, whereas 4 responders had stable improvement and 3 showed additional improvement in symptoms.

On the basis of these observations, one may speculate that PET flow measurements may be clinically useful in identifying nonresponders to lipid-lowering therapy and predicting adverse clinical outcome.

Limitations of the Study

The main emphasis of this study was to define the time course of changes in myocardial flow by a longitudinal study protocol. Because PET flow studies have been shown to be accurate and reproducible,9–13 the method appears appropriate for studying the effects of lipid-lowering therapy using patients as their own control subjects.

Patients continued taking their antianginal and antihyperensive medications, which were unchanged during the follow-up period. Nitrates, β-1 blockade, and calcium channel blockers have not been shown to significantly alter CFR.29 ACE inhibitors were not used in our study population. Therefore, it is unlikely that the beneficial effects of lipid-lowering therapy on CFR were due to other drug effects.

Clinical Implications

13N-labeled ammonia PET studies have been shown to predict the functional significance of angiographically defined stenoses even in mild disease. Quantification of regional blood flow enables noninvasive monitoring of disease progression or regression with interventions such as lipid-lowering therapy. Additional studies in larger patient populations are needed to demonstrate the prognostic value of improved or unimproved CFR measures early after onset of therapy. According to our findings, this method may be useful in identifying nonresponders to HMG-CoA reductase inhibitor therapy, ie, patients with a rapidly progressive form of CAD, who may require close monitoring and aggressive therapy. The present data also indicate the importance of the time point in evaluating the effects of lipid-lowering therapy on myocardial blood flow, which needs to be considered in future protocol design.

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