Influence of Serum Cholesterol and Other Coronary Risk Factors on Vasomotion of Angiographically Normal Coronary Arteries

Christian Seiler, MD; Otto Martin Hess, MD; Martin Buechi, MD; Thomas Martin Suter, MD; Hans Peter Krayenbuehl, MD

**Background.** It has been shown that there is impairment of the vasodilatory response to acetylcholine in patients with hypercholesterolemia and angiographically normal coronary arteries. Moreover, in patients with angiographically smooth coronary arteries, the number of coronary risk factors is associated with a loss of endothelium-dependent vasodilation. The purpose of the present analysis was to evaluate in patients with and without coronary artery disease coronary vasomotor response to dynamic exercise in angiographically normal and stenosed coronary arteries and to relate the response to serum cholesterol levels as well as to other coronary risk factors.

**Methods and Results.** Luminal area change during exercise (delta-ex, percent change compared with rest=100%) was determined by biplane quantitative coronary arteriography in three groups: Group 1 consisted of 14 patients with normal total serum cholesterol of <200 mg/100 mL; mean, 173 mg/100 mL (mean age, 51 years). Group 2 comprised 23 patients with a slightly elevated cholesterol of 200 to 250 mg/100 mL; mean, 223 mg/100 mL (mean age, 53 years). Group 3 had 24 patients with markedly elevated cholesterol of >250 mg/100 mL; mean, 288 mg/100 mL (mean age, 54 years). Serum cholesterol levels and categorical risk factors such as positive family history, history of hypertension, smoking, obesity, and diabetes were related to exercise-induced vasomotor response. The three groups did not differ with regard to clinical characteristics, exercise work load, and hemodynamic data measured during exercise. However, delta-ex in normal vessels was significantly different between all three groups (ANOVA, *P* < .01): +31% (group 1), +18% (group 2), and +4% (group 3). Delta-ex in stenotic vessels did not differ between the groups: −5% (group 1), −13% (group 2), and −12% (group 3). Delta-ex of the nonstenosed vessel correlated significantly and inversely with total cholesterol, with low-density lipoprotein cholesterol, with the ratio of total to high-density lipoprotein cholesterol, and with the number of coronary risk factors present in a patient. High total cholesterol and a history of hypertension were independent risk factors for impaired coronary vasomotion.

**Conclusions.** In patients with and without coronary artery disease, hypercholesterolemia and a history of hypertension independently impair exercise-induced coronary vasodilation in angiographically normal coronary arteries. In the stenotic vessel, vasomotion during exercise does not appear to be influenced by the actual serum cholesterol. The precise mechanism by which the impaired vasomotion of the angiographically normal coronary arteries is mediated is unknown, but a direct negative effect of hypercholesterolemia on endothelial function or early undetected atherosclerosis appears to be the most likely explanation. (Circulation. 1993;88[part 1]:2139-2148.)

**Key Words** • coronary artery disease • angiography • cholesterol

Coronary artery disease is anatomically defined by luminal irregularities or segmental stenoses and is functionally characterized by a loss of the vasodilatory response to increased blood flow (induced by exercise or papaverine), acetylcholine, or other vasoactive substances (eg, serotonin, norepinephrine, adenosine, vasopressin). In angiographically normal coronary arteries of patients with coronary artery disease, the vasomotor response to flow increase and to acetylcholine is heterogeneous; both dilation and constriction have been demonstrated. In patients without angiographic evidence of coronary artery disease, Vita and coworkers have found that the number of coronary risk factors is associated with a loss of endothelium-dependent vasodilation. Similarly, Zeiher et al have shown that there is impairment of the vasodilatory response to acetylcholine, papaverin, and cold pressor testing in patients with hypercholesterolemia and angiographically normal coronary arteries.

The purpose of the present analysis was to evaluate retrospectively coronary vasomotor response to dynamic exercise in angiographically normal and stenosed coronary arteries and to relate the response to serum cholesterol levels as well as to other coronary risk factors.
Methods

Study Population
Sixty-one patients (59 men, 2 women; age, 52.6±1.3 years) were included in the present, retrospective analysis. The study population comprises patients previously described elsewhere.7,11,14 In those studies, exercise-induced coronary vasomotion has been investigated regardless of the presence or absence of coronary risk factors: Gage et al17 have shown in 15 patients with coronary artery disease that dynamic exercise induces vasoconstriction of the stenosed vessel segment; Bortone et al14 have reported on 13 patients with angiographically normal coronary arteries who revealed exercise-induced vasodilation in relation to their coronary flow reserve determined by thermodilution technique; recently, Suter and coworkers11 have demonstrated in 31 patients undergoing percutaneous transluminal coronary angioplasty that 4 and 30 months after this procedure, there is reestablishment of normal exercise-induced coronary vasomotion of the previously stenosed vessel segment in two thirds of these patients.

The 61 patients of this study were divided into three groups according to their total serum cholesterol level at the time of coronary arteriography. Group 1 consisted of 14 men with a total serum cholesterol of <200 mg/100 mL (normal cholesterol). Mean cholesterol level amounted to 173±26 mg/100 mL. Group 2 consisted of 22 men and 1 woman with a cholesterol level between 200 and 250 mg/100 mL (slightly elevated cholesterol). Mean cholesterol was 223±13 mg/100 mL. Group 3 consisted of 23 men and 1 woman with a cholesterol level of >250 mg/100 mL (markedly elevated cholesterol). Mean cholesterol was 288±43 mg/100 mL in this group.

Thirteen of 61 patients had normal coronary arteriograms without presence of segmental stenoses or luminal irregularities. Forty-eight patients of the entire study population showed segmental coronary artery disease; on the average, 1.5±0.9 vessels per patient were involved (maximum two-vessel disease). Patients with coronary artery disease had a history of exercise-induced angina pectoris; 19 of them had previous myocardial infarction. The 13 patients with normal coronary arteriograms underwent coronary arteriography for exclusion of coronary artery disease in the presence of atypical chest pain. In all 61 patients upright bicycle exercise testing was performed the day before coronary arteriography. ST segment depression of ≥0.1 mV was found in 51 of 61 patients (mean, 0.13±0.11 mV).

Inclusion Criteria
Patients were selected from a group of 70 patients undergoing bicycle exercise coronary arteriography on the basis of the following criteria: (1) presence of at least one angiographically normal coronary artery (n=61), (2) segmental stenotic lesion (n=48) clearly visible for quantitative evaluation, (3) exercise coronary arteriography (n=61), (4) total serum cholesterol (n=61), and possibly high-density lipoprotein (HDL) cholesterol (n=21).

Determination of Serum Cholesterol
The total serum cholesterol level was determined in the Department of Clinical Chemistry at our hospital using an enzymatic dye method (Chol-Pap method, Boehringer, Mannheim, Germany) on a blood sample obtained the day before cardiac catheterization. HDL cholesterol levels were measured in 21 of 61 patients by an enzymatic dye method after ultracentrifugation of the serum specimen (Chol-Pap method). Normal values were 40 to 50 mg/100 mL.15,16 Low-density lipoprotein (LDL) cholesterol values (normal value <130 mg/100 mL; slightly elevated values, between 130 and 159 mg/100 mL; markedly elevated values >159 mg/100 mL)15,16 were calculated according to the Friedewald formula (LDL cholesterol equals total cholesterol minus HDL cholesterol minus [triglycerides/2.2]).17

Definition of Coronary Risk Factors
The following risk factors for coronary artery disease were assessed by history or chart review.

Hypercholesterolemia. No patient had a history of familial hyperlipidemia. Total cholesterol levels <200 mg/100 mL were defined as normal; cholesterol levels between 200 and 250 mg/100 mL were considered to be slightly elevated and levels >250 mg/100 mL markedly elevated.15,16 A ratio of total cholesterol to HDL cholesterol <5 was taken as normal.18

Hypertension. Patients were considered to have a history of arterial hypertension if they had been treated with antihypertensive medication by the referring physician. The control blood pressure in a drug-free period (drugs discontinued 24 hours before cardiac catheterization) at the time of cardiac catheterization was recorded in all patients. At this time patients with and without hypertension had a mean arterial blood pressure at rest of 104±14 and 91±13 mm Hg, respectively (P=.001).

Cigarette smoking. Patients were classified as non-smokers if they had never smoked or if they had stopped smoking at least 1 year before study. All other patients were classified as smokers.

Family history. A positive family history was considered to be present if at least one of the patient's parents or a sibling under the age of 60 years19,20 had documented coronary artery disease such as a history of myocardial infarction, coronary artery bypass surgery, angioplasty, positive exercise test, sudden cardiac death, or angiographically documented coronary artery disease.

Obesity. Patients were classified as obese if their body mass index (BMI) was ≥28 kg/m² (see Reference 21) at the time of cardiac catheterization.

Diabetes mellitus. Four patients had a history of insulin-dependent diabetes mellitus. There were no patients with non–insulin-dependent diabetes.

Cardiac Catheterization
Patients underwent right and left heart catheterization for diagnostic purposes. Informed consent was obtained from all patients. Medication was stopped at least 24 hours before cardiac catheterization. Premedication consisted of 10 mg chloral hydrate administered orally 1 hour before the procedure. Aortic pressure was measured with an 8F Judkins catheter, and pulmonary artery pressure was determined with a 6F pacing catheter with a side hole for pressure measurements. Biplane left ventricular angiography was performed in all patients following diagnostic coronary arteriography.
Study Protocol

An interval of at least 10 minutes was allowed for dissipation of the effect of the nonionic contrast medium (Iopamiro 370R: iopamidol 755.2 mg/mL, trometamol 1 mg/mL) on coronary vasomotion. Simultaneous biplane coronary arteriography was carried out in two orthogonal projections to guarantee optimal visualization of the stenotic lesions. First, a control arteriogram was performed with the patient's feet attached to the bicycle ergometer (model 380 B, Siemens-Albis AG, Zurich). Exercise was begun at 50 to 75 W and was increased every 2 minutes in increments of 25 to 50 W. Coronary arteriography was carried out at the end of each exercise level with the patient holding his breath during injection of the contrast medium. Arteriograms at maximum exercise level were used for analysis of coronary vasomotion. The exercise test was terminated because of angina pectoris, fatigue, or ST segment depression >0.2 mV. The average work load was similar in all three study groups: 103 W, 107 W, and 106 W (all NS). At the end of the exercise test, 1.6 mg nitroglycerin was administered sublingually. Biplane coronary arteriography was repeated 5 minutes thereafter. There were no complications related to the study protocol.

Quantitative Coronary Arteriography

Quantitative evaluation of biplane coronary arteriograms was performed with a semiautomatic computer system based on a film projector (Tagarno A/S film-projector, Horsens, Denmark), a high-resolution CCD camera (slow-scan couple device camera, Institute for Biomedical Engineering, Zurich), and a computer workstation (Apollo DN3000 computer workstation, Apollo Computer AG, Wangen, Switzerland). The system and the methodology for computerized analysis of coronary arteriograms have been described previously.22-24 The reproducibility of luminal area measurements in coronary arteriograms has been reported to have an interobserver variability of 4.1% (standard error of estimate in percent of the mean vessel cross-sectional area) and an intraobserver variability of 2.1%. The standard error of estimate for repeated measurements by one observer was 0.072 mm² in luminal area, and the standard error of estimate for interobserver variability was 0.137 mm².22

Quantitative analysis was performed in a normal vessel segment of a coronary artery unaffected by luminal irregularities or stenoses. In the 48 patients with coronary artery disease, a stenotic vessel segment was evaluated as well. Measurement sites were selected on the basis of the following criteria: (1) sufficient filling of the vessel with radiographic contrast medium, (2) high-quality end-diastolic film frame without movement artifacts, (3) straightness of vessel segment to be analyzed, and (4) biplane x-ray views fulfilling criteria (1) to (3). Angiograms were measured blinded with regard to the variables of interest in this study as well as to the actual study sequence (rest or exercise or nitroglycerin). Data during maximal exercise were used for statistical analyses and are included in tables and figures.

Statistical Analysis

Between-group comparisons of clinical, hemodynamic, and angiographic data were performed by a one-way ANOVA for continuous variables followed by Scheffé's test if ANOVA was significant (P<.05) and by a χ² test for categorical variables (3×2 table).

Univariate analysis of the effects of the cholesterol level on exercise-induced vasomotion was carried out with linear regression for continuous variables (total cholesterol, HDL and LDL cholesterol level, total cholesterol to HDL cholesterol ratio, LDL cholesterol to HDL cholesterol ratio, triglycerides, age, baseline cross-sectional luminal area, pack-years of cigarettes smoked, and BMI) and with one-way ANOVA for categorical variables (history of hypertension, smoking, family history, obesity, and diabetes mellitus). The effect of the number of coronary risk factors (other than hypercholesterolemia) on coronary vasomotion was tested by a one-way ANOVA followed by Scheffé's test if ANOVA was significant (P<.05) (number of coronary risk factors being the variable) followed by a linear regression analysis for the number of risk factors versus mean exercise-induced coronary vasomotor response.

A multivariate analysis (multiple stepwise regression analysis) was used to determine independent risk factors for the degree of impaired coronary vasomotor response to exercise. All values are expressed as mean±SD.

Results

Patient Characteristics

Gender distribution, age, functional classification according to the New York Heart Association (NYHA), and BMI were comparable in the three groups. With regard to patient's history, the frequency of angina pectoris, myocardial infarction, and the number of coronary arteries diseased, there was no difference among the study groups. Risk factors for coronary artery disease and the use of anti-ischemic drug therapy were evenly distributed among the three groups. The distribution of the 13 patients without segmental stenoses on coronary arteriograms among the three groups was as follows: 5 of 14 patients (36%) were in group 1, 6 of 23 (26%) in group 2, and 2 of 24 (8%) in group 3 (NS). See Table 1.

Serum Lipids

Total serum cholesterol level was, due to the selection criteria used in this study, significantly different among the study groups. Mean HDL cholesterol was normal in all three groups and did not differ significantly between them. LDL cholesterol, the ratio of total cholesterol to HDL cholesterol, and the ratio of LDL to HDL cholesterol as well as the serum triglyceride level were significantly elevated in group 3 when compared with either group 1 or 2. See Table 2.

Exercise Data

Exercise work load (absolute values and percentage of the age-, sex-, and height-corrected normal values) in the upright position was normal in all three groups. The frequency of angina pectoris developing during exercise did not differ among the three groups. In the supine position, exercise work load was lower but similar in the three study groups. Changes in heart rate, mean pulmonary artery pressure, and mean aortic pressure during exercise and after sublingual nitroglycerin administra-
tion were comparable in the three groups. Heart rate and mean pulmonary artery pressure increased significantly during bicycle exercise, whereas mean aortic pressure increased only slightly. These variables returned to control levels after administration of sublingual nitroglycerin. Mean arterial pressure among patients with and without hypertension increased during exercise from 104±14 to 117±16 mm Hg and from 91±13 to 107±19 mm Hg, respectively (P<.05 between the groups for both activity levels).

### Angiographic Data
Normal vessels were similar in size, but the response to exercise was different in the three groups: In group 1, there was a +31% increase in coronary artery luminal area during exercise compared with rest, whereas in group 2 an increase of +18% and in group 3 of only +4% was observed (Fig 1A). These differences were significant among all study groups. Figure 1B shows absolute values of cross-sectional areas in all patients of the different study groups measured at rest.

### TABLE 1. Cholesterol and Exercise-Induced Coronary Vasomotor Response: Patient Characteristics

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 mg/100 mL</td>
<td>&gt;200-250 mg/100 mL</td>
<td>&gt;250 mg/100 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>14/14 (100%)</td>
<td>22/23 (96%)</td>
<td>23/24 (96%)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; Age, y &gt;</td>
<td>51.1±8.0</td>
<td>53.1±7.2</td>
<td>53.5±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.0±0.6</td>
<td>1.6±0.6</td>
<td>1.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.2±2.1</td>
<td>25.4±2.1</td>
<td>26.0±2.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Patient history | Angina pectoris | 14/14 (100%) | 18/23 (78%) | 20/24 (83%) | NS |
| | Myocardial infarction | 3/14 (21%) | 8/23 (35%) | 8/24 (33%) | NS |
| | No. of vessels diseased | 1.5±1.3 | 1.4±1.1 | 1.6±0.9 | NS |

| Risk factors | Hypertension | 4/14 (29%) | 10/23 (333%) | 11/24 (42%) | NS |
| | Family history | 5/14 (36%) | 6/23 (26%) | 7/24 (29%) | NS |
| | Diabetes | 2/14 (14%) | 1/23 (4%) | 1/24 (4%) | NS |
| | Obesity | 6/14 (43%) | 8/23 (35%) | 10/24 (42%) | NS |
| | Smoking (pack-years) | 16.8±13.9 | 25.2±20.6 | 25.0±19.9 | NS |

| Anti-Ischemic drugs | <beta>-Blocker | 9/14 (64%) | 18/23 (78%) | 17/24 (71%) | NS |
| | Ca antagonist | 10/14 (71%) | 15/23 (65%) | 14/24 (58%) | NS |
| | Nitrates | 11/14 (79%) | 12/23 (52%) | 14/24 (58%) | NS |
| | Triple therapy | 7/14 (50%) | 6/23 (26%) | 9/24 (38%) | NS |

NYHA indicates New York Heart Association and BMI, body mass index.

### TABLE 2. Cholesterol and Exercise-Induced Coronary Vasomotor Response: Serum Lipids

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 mg/100 mL</td>
<td>&gt;200-250 mg/100 mL</td>
<td>&gt;250 mg/100 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/100 mL</td>
<td>173.4±26.3</td>
<td>223.3±13.5</td>
<td>287.5±42.6</td>
<td>*&lt;.01</td>
</tr>
<tr>
<td>HDL cholesterol, mg/100 mL</td>
<td>42.6±8.1 (n=4)</td>
<td>43.7±10.4 (n=5)</td>
<td>40.6±7.4 (n=12)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mg/100 mL</td>
<td>133.5±20.1 (n=4)</td>
<td>145.9±17.0 (n=5)</td>
<td>205.1±58.8 (n=12)</td>
<td>↑&lt;.05</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>4.69±1.04 (n=4)</td>
<td>5.23±1.13 (n=5)</td>
<td>7.48±1.68 (n=12)</td>
<td>↑&lt;.05</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>3.26±1.10 (n=4)</td>
<td>3.52±1.10 (n=5)</td>
<td>5.14±1.46 (n=12)</td>
<td>↑&lt;.05</td>
</tr>
<tr>
<td>Triglycerides, mg/100 mL</td>
<td>118.1±71.8</td>
<td>133.9±56.0</td>
<td>224.0±153.1</td>
<td>↑&lt;.05</td>
</tr>
</tbody>
</table>

HDL and LDL cholesterol indicate high- and low-density lipoprotein cholesterol; total cholesterol/HDL, LDL/HDL, ratios of total to HDL cholesterol and LDL to HDL cholesterol, respectively.

*For differences between all groups; ↑for differences between groups 1 and 3 and between groups 2 and 3; differences between groups 1 and 2 not significant.
maximum exercise, and after sublingual nitroglycerin. Comparing coronary vasodilation in normal vessels within each group between patients with and without coronary artery disease showed the following: +37±31% (n=9) and +19±8% (n=5), respectively, in group 1 (NS); +15±12% (n=17) and +26±12% (n=6), respectively, in group 2 (NS); and +2±12% (n=22) and +14±13% (n=2), respectively, in group 3 (NS). Sublingual administration of nitroglycerin was associated with a similar increase in vessel size in all three groups, although vasodilation was slightly less in group 3 or 2 than 1 (Fig 1B).

Stenotic vessels were similar in size, with a mean percentage area stenosis of 58% to 77% in the three different groups. In contrast to the normal vessel segments, all three groups showed exercise-induced vasoconstriction ranging between −5% and −13%, with no significant differences between the three groups. Fig 1C shows changes in cross-sectional area from resting state to maximum exercise and to the situation after nitroglycerin.

**Influence of Hypercholesterolemia and Other Coronary Risk Factors on Coronary Vasomotion**

**Univariate analysis.** When total cholesterol, HDL cholesterol, LDL cholesterol, ratio of total cholesterol to HDL cholesterol, ratio of LDL cholesterol to HDL cholesterol, triglycerides, BMI, age, baseline normal luminal area, and pack-years of cigarettes smoked were related to exercise-induced vasomotor response, a significant correlation was found between total cholesterol (Fig 2), LDL cholesterol (Fig 3), ratio of total cholesterol to HDL cholesterol (Fig 4), and ratio of LDL cholesterol to HDL cholesterol, respectively, and exercise-induced vasomotion. There was also a significant correlation between the mean exercise-induced vasomotor response and the number of coronary risk factors (Fig 5). Among categorical coronary risk factors, only patients with a history of hypertension showed a significantly decreased exercise-induced vasomotor response compared with patients who were negative with regard to this risk factor (+6±12% vs +21±22% vasodilation, P = .0038).

**Multivariate analysis.** Stepwise multiple regression analysis revealed a negative correlation between exercise-induced vasomotion and total serum cholesterol (P = .0001) and a positive history of hypertension (P = .0032), respectively. The regression equation is as follows: exercise-induced vasodilation (percent increase from 100% at rest) equals 21.3% minus 13.1 (cholesterol group) plus 13.8 (history of hypertension) (present=1, absent=2; r = .68, P = .0001). All the other risk factors for coronary artery disease as well as the ratio of

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**Table 3. Cholesterol and Exercise-Induced Coronary Vasomotion: Exercise and Hemodynamic Data**

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol</th>
<th>C1 (&lt;200 mg/100 mL) (n=14)</th>
<th>C2 (200-250 mg/100 mL) (n=23)</th>
<th>C3 (&gt;250 mg/100 mL) (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upright bicycle exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work load (3 min), W</td>
<td>140.0±34.9</td>
<td>136.5±25.7</td>
<td>135.8±35.4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Work load, % of normal</td>
<td>89.8±20.0</td>
<td>93.7±14.0</td>
<td>91.8±19.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ST depression, mV</td>
<td>0.16±0.13</td>
<td>0.09±0.08</td>
<td>0.13±0.14</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris, %</td>
<td>9/14 (64%)</td>
<td>18/23 (62%)</td>
<td>20/24 (83%)</td>
<td>NS</td>
<td></td>
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<tr>
<td><strong>Supine bicycle exercise</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Work load (2 min), W</td>
<td>102.7±30.7</td>
<td>107.0±28.1</td>
<td>105.7±33.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Work load, % of normal</td>
<td>69.0±32.6</td>
<td>72.2±23.7</td>
<td>69.6±24.2</td>
<td>NS</td>
<td></td>
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<tr>
<td><strong>Heart rate, bpm</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Rest</td>
<td>67.2±10.2</td>
<td>65.5±10.8</td>
<td>67.0±9.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>115.5±29.0</td>
<td>106.9±17.1</td>
<td>119.0±17.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>After nitroglycerin</td>
<td>78.2±18.8</td>
<td>75.5±13.8</td>
<td>79.8±12.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>MPAP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>19.5±6.0</td>
<td>21.1±6.2</td>
<td>20.8±4.7</td>
<td>NS</td>
<td></td>
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<tr>
<td>Exercise</td>
<td>35.9±9.3</td>
<td>37.6±8.7</td>
<td>38.5±8.2</td>
<td>NS</td>
<td></td>
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<tr>
<td>After nitroglycerin</td>
<td>18.4±7.6</td>
<td>18.8±5.6</td>
<td>18.3±7.4</td>
<td>NS</td>
<td></td>
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<tr>
<td><strong>MAP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>98.6±12.6</td>
<td>97.5±14.9</td>
<td>93.8±16.6</td>
<td>NS</td>
<td></td>
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<tr>
<td>Exercise</td>
<td>104.3±13.1</td>
<td>110.8±19.9</td>
<td>114.5±18.5</td>
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<tr>
<td>After nitroglycerin</td>
<td>91.4±11.4</td>
<td>87.5±17.5</td>
<td>87.5±12.7</td>
<td>NS</td>
<td></td>
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<tr>
<td>LV ejection fraction at rest, %</td>
<td>61.6±9.6</td>
<td>64.7±7.6</td>
<td>63.7±8.5</td>
<td>NS</td>
<td></td>
</tr>
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</table>

MPAP indicates mean pulmonary artery pressure; MAP, mean aortic pressure; bpm, beats per minute; and LV, left ventricular.
Discussion

Previously it has been shown\textsuperscript{12,13,25} that endothelium-dependent vasodilation is impaired in atherosclerotic but also in angiographically smooth coronary arteries in the presence of hypercholesterolemia. A number of pharmacological agents such as serotonin, norepinephrine, vasopressin, papaverine, and mainly acetylcholine have been used to study the vasomotor response of coronary arteries.\textsuperscript{2-4,26} Our study protocol used a different approach to induce endothelium-dependent vasodilation: dynamic bicycle exercise. Although the physiological effect of exercise on vasomotion is probably more complex than that of the pharmacological compounds, this stimulus for coronary vasomotion reflects the daily activities of the investigated patients better than pharmacological interventions.

In clinical studies, intracoronary acetylcholine but also dynamic exercise constricts coronary arteries in the presence of atherosclerotic lesions but dilates normal coronary arteries.\textsuperscript{7,11,27,28} Variation in dose and rate of acetylcholine infusion may account in part for the reported heterogeneous response of angiographically normal vessels.\textsuperscript{10,27,28} Additionally, angiography is not a sensitive method for detection of early atherosclerosis. Undetected atherosclerosis in angiographically smooth vessels may account for insufficient vasodilator response.\textsuperscript{24} In the present study, however, a comparison between “normal” vessels of patients with angiographically defined coronary artery disease and vessels of patients with entirely smooth coronary arteries revealed normal exercise-induced vasodilation in the presence of normal serum cholesterol levels in both groups.

Pathophysiological Mechanisms of Abnormal Vasomotor Response and Hypercholesterolemia

The prevalent view for the development of atherosclerosis is the “response to injury” theory.\textsuperscript{29,30} In the early stages of the disease, injury to the endothelium may cause no morphological but only functional alterations of the endothelial cells.\textsuperscript{29} Later on, accumulation of lipids and migration and proliferation of smooth muscle cells occur, and a flow-limiting plaque finally results.

Functional changes of the vascular endothelium. There has been increasing emphasis in the literature on the functional impact of hypercholesterolemia on the vasculature.\textsuperscript{12,13,31,32} Cholesterol-fed animals showed attenuation of endothelium-dependent vasodilation before and after the development of histologically proven atherosclerosis.\textsuperscript{33,34} Even brief incubation of rabbit aorta with LDL cholesterol inhibits the vasodilator response to acetylcholine.\textsuperscript{35} Studies in humans have shown that hypercholesterolemia and other risk factors cause abnormal vasodilator responses not only in individuals with angiographically defined atherosclerosis but also in individuals with normal vessels.\textsuperscript{12,13} The present study is the first to demonstrate an impaired vasodilatory response of normal epicardial coronary arteries to a physiological stimulus such as exercise in patients with hypercholesterolemia. The alterations in the vasomotor response to exercise induced by hypercholesterolemia may implicate early changes in endothelial function with an attenuated release of endothelium-derived relaxing factors. However, although a number of experimental studies\textsuperscript{35,36} suggest that an impairment of endothelium-dependent relaxation in hypercholesterolemia (particularly LDL hypercholesterolemia) may be responsible for an abnormal vasomotor response, we cannot exclude in the present study early atherosclerosis not detectable by coronary arteri-
B

Mean cross-sectional area (mm²)

Group 1

Group 2

Group 3

C

Mean cross-sectional area (mm²)

Group 1

Group 2

Group 3
vessels was from resting vasodilation in these coronary arteries but with no evidence of atherosclerosis elsewhere in the coronary system; however, within each of the three groups, the degree of exercise-induced vasodilation in these angiographically normal arteries of patients with coronary artery disease was not statistically different from that of patients with completely normal coronary arteriograms. Intraoperative echocardiographic studies have, however, demonstrated that in vivo coronary atherosclerosis is far more extensive than predicted by coronary arteriography.

The effects of hypercholesterolemia on human vascular function without the potential confounding ef-

Fig 4. Scatterplot: The ratio of total cholesterol to high-density lipoprotein cholesterol (cholesterol/HDL-cholesterol, horizontal axis) and exercise-induced coronary artery vasomotion of angiographically normal vessels (delta-ex, vertical axis) are inversely and significantly related. Delta-ex is equal to the maximum exercise-induced increase (positive value) or decrease (negative value) in cross-sectional lumen area of the normal coronary artery in percent from resting state (100%).

Fig 5. Plot shows significant, inverse correlation between the number of coronary risk factors existing in a patient (number of risk factors, horizontal axis) and mean exercise-induced coronary artery vasomotion of angiographically normal vessels (delta-ex, vertical axis). Mean delta-ex in the five depicted groups with zero to four risk factors amounted to 24±11%, 25±34%, 20±17%, 10±13%, and 3±11%, with the exception of the differences of these values between the groups with zero to three risk factors. All differences between risk factor groups had P<.05 by ANOVA and Scheffé. For the calculation of the number of coronary risk factors, see text. Delta-ex is equal to the maximum exercise-induced increase (positive value) or decrease (negative value) in cross-sectional lumen area of the normal coronary artery in percent from resting state (100%).
fect of atherosclerosis were evaluated by Creager and coworkers in the forearm of patients with normal and with elevated serum LDL cholesterol levels. It is a well-known fact that the arteries of the forearm practically never develop atherosclerosis. The response of endothelium-mediated flow increases to metacholine was blunted in hypercholesterolemic patients compared with normal subjects. Thus, hypercholesterolemia in the absence of atherosclerosis is associated with abnormal vasomotion. Therefore, the observed alterations in coronary vasomotion in patients with hypercholesterolemia may not be necessarily associated with overt atherosclerosis.

In vitro studies with porcine epicardial and intramyocardial coronary arteries have shown that predominantly oxidized LDL cholesterol inhibits endothelium-dependent relaxation of coronary arteries. Oxidized LDL cholesterol appears to activate scavenger receptors on endothelial cells and inhibits the receptor-operated nitric oxide formation in epicardial coronary arteries.

Structural changes of the vascular endothelium. The basis for the development of atherosclerosis is damage to the arterial endothelium with accumulation of lipids, adhesion of monocytes, and platelet aggregation. Release of various growth factors leads to the later migration and proliferation of smooth muscle cells. An accelerated form of this proliferative process can be induced by a more denuding, deeper endothelial injury as it occurs during percutaneous transluminal coronary angioplasty, in patients undergoing coronary bypass grafting, or by an immune injury such as in patients undergoing heart transplantation. These chronic changes of coronary artery wall structure are known to be associated with profound functional impairments such as exercise-induced vasoconstriction. The nature of this phenomenon has not yet been elucidated but appears to be either related to endothelial dysfunction with impaired release of endothelium-derived relaxing factors, a Venturi mechanism with collapse of the atherosclerosis-free vessel wall within the stenosis, catecholamine-induced vasoconstriction, and/or enhanced platelet aggregation during exercise with release of thromboxane A2 and serotonin. An effect of hypercholesterolemia on coronary vasomotor response of the stenotic lesion (Fig 1C) was, however, not observed in the present study, suggesting that chronic, structural changes associated with atherosclerosis are probably not dependent on the actual serum cholesterol level. Thus, two different mechanisms of hypercholesterolemia in the pathobiology of coronary artery disease must be postulated: (1) a direct (toxic) effect of cholesterol on the endothelium of the coronary arteries and other vessels not prone to atherosclerosis such as arteries of the forearm (functional disorder) and (2) a more chronic effect of cholesterol on the development of atherosclerosis with an abnormal response of the stenotic vessel segment to exercise that is not influenced by the cholesterol level (anatomic or structural disorder).

Influence of Other Risk Factors on Coronary Vasomotion

In the present study, a history of hypertension was the only coronary risk factor other than hypercholesterolemia that independently predicted abnormal coronary vasomotor response to exercise. This finding is in agreement with experimental studies in animals where chronic and also acute elevation of blood pressure disturbed endothelium-dependent vasodilation. Furthermore, a very recently published clinical study has demonstrated impaired coronary blood flow increase to acetylcholine in hypertensive patients. Vita and coworkers in a study on the influence of multiple risk factors on coronary vasomotion in humans, have not found such a relation. The same group has, however, demonstrated recently that there is a relation between attenuated coronary vasomotor response to acetylcholine and the presence of hypertension.

Study Limitations

In the present study, total and HDL cholesterol values were determined on the basis of a single specimen measurement (two measurements per specimen). The total intraperson coefficient of variation (combination of intraindividual biological coefficient of variation and analytical coefficient of variation) in our clinical chemistry laboratory amounts to 5% for total cholesterol and to 7% for HDL cholesterol. Similar values have been reported in the literature. Since this was a retrospective study, only one specimen per patient at the time of catheterization was available.

Conclusions

This retrospective analysis demonstrates an inverse correlation between total serum cholesterol level or LDL cholesterol and exercise-induced vasomotor response in angiographically normal coronary arteries. Moreover, exercise-induced vasomotion can be predicted by the ratio of total cholesterol to HDL cholesterol or by the ratio of LDL cholesterol to HDL cholesterol. Apart from the total cholesterol level, a history of hypertension is another independent predictor for the amount of exercise-induced coronary artery vasomotor response. The number of coronary risk factors is strongly and inversely related to exercise-induced vasomotion. Total cholesterol level and other coronary risk factors are not related to exercise-induced vasomotion of stenotic coronary artery segments.

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