Reversal of Abnormal Coronary Vasomotion by Calcium Antagonists in Patients With Hypercholesterolemia

Philipp A. Kaufmann, MD; Jürgen Frielingsdorf, MD; Lazar Mandinov, MD, PhD; Christian Seiler, MD; Rosy Hug; Otto M. Hess, MD

Background—It has been shown that exercise-induced coronary vasodilation of angiographically normal coronary vessels is reduced in hypercholesterolemic patients. The purpose of this study was to evaluate the effect of calcium channel blockers on coronary vasomotion of angiographically smooth coronary arteries in hypercholesterolemic patients.

Methods and Results—A total of 57 patients were included in the present analysis. Vasomotion of angiographically normal coronary arteries was evaluated in 37 control subjects (group 1) without and 20 patients (group 2) with calcium blocker administration before physical exercise. Both groups were subdivided into subgroup A (normal cholesterol values: ≤5.5 mmol/L or 212 mg%) and subgroup B (elevated cholesterol values: >5.5 mmol/L or 212 mg%). Coronary luminal area at rest and during exercise was assessed by biplane quantitative coronary angiography. The normal vessels showed a significant increase in coronary luminal area during exercise in subgroup A (n=13) with normal cholesterol values (31%; P<.05) but not in subgroup B (n=24; 13%: P=NS). In contrast, all patients in group 2 showed similar vasodilation during exercise, namely, 22% (P<.05) in subgroups A (n=8) and B (n=12) (P<.05). Independent of the actual cholesterol level, the stenotic lesions showed coronary vasoconstriction during exercise in group 1 but vasodilation in group 2 after pretreatment with calcium antagonists.

Conclusions—Coronary vasomotor response to exercise is inversely related to actual serum cholesterol level in angiographically normal vessels. Administration of calcium antagonists normalizes exercise-induced vasodilation and thus eliminates cholesterol-induced abnormal vasomotion, probably by a direct effect on the smooth muscles of the vasculature. (Circulation. 1998;97:1348-1354.)

Key Words: vasodilation ■ angiography ■ endothelium ■ cholesterol ■ calcium channels

Coronary vasomotion plays an important role in the regulation of myocardial perfusion.1-3 Normal as well as stenotic arteries show vasomotion during exercise due to the fact that most lesions are eccentrically located and have a normal vessel segment within the stenosis.3 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.4-12 In angiographically normal coronary arteries of patients with coronary artery disease, both dilation and constriction have been demonstrated in response to flow changes and to acetylcholine.8 In patients without angiographic evidence of coronary artery disease, a correlation between the number of coronary risk factors and a loss of endothelium-dependent vasodilation has been reported.11 Similarly, an impairment of the vasodilatory response of angiographically normal coronary arteries to acetylcholine, papaverine, and cold pressor testing has been found in hypercholesterolemic patients.12 Sorensen et al13 described an impairment of endothelium-dependent dilation of the superficial femoral artery in children with familial hypercholesterolemia. Recently, Seiler and coworkers14 showed that hypercholesterolemia and hypertension impair the response of the coronary arteries to exercise, ie, they cause a reduction in exercise-induced vasodilation. The precise mechanism by which the impaired vasomotion of the normal coronary arteries is mediated remains unknown; a direct negative effect of hypercholesterolemia on endothelial function or early undetected atherosclerosis appears to be the most likely explanation. Thus, the purpose of the present study was to evaluate coronary vasomotor response to exercise in patients with hypercholesterolemia and to examine the effect of calcium channel blockers on exercise-induced vasomotion.

Methods

Study Population
Fifty-seven patients were included in the present analysis. Thirty-seven patients who had no pretreatment before exercise served as control subjects (group 1; 36 men, 1 woman; age, 54±7 years). Twenty male patients (age, 57±9 years) who were pretreated with a calcium channel blocker before exercise served as group 2. All but 7 of the 37 patients in group 1 had segmental coronary artery disease; on average, 1.8±1.1 vessels per patient were involved. Patients with coronary artery disease had a history of exercise-induced angina pectoris; 13 of them had previous myocardial infarction. The 7 patients with normal coronary arteriograms underwent coronary...
arteriography for exclusion of coronary artery disease in the presence of atypical chest pain.

Hypertension has been shown to be an important determinant of coronary vasomotion. Because hypertension was reported to be a confounding factor for the development of endothelial dysfunction, we excluded all hypertensive patients. Hypertension was defined as a history of high blood pressure (diastolic pressure $\geq 95$ mm Hg and/or systolic values $\geq 160$ mm Hg).

**Patient Subgroups**

Patients were subdivided into two subgroups, A and B, according to their actual serum cholesterol level at the time of coronary arteriography. Subgroup A consisted of patients with normal (<5.5 mmol/L or 212 mg%) cholesterol levels, and subgroup B consisted of patients with elevated (>5.5 mmol/L or 212 mg%) cholesterol levels according to the inclusion criteria in the 4S study. According to these criteria, 13 patients of group 1 were assigned to subgroup A and 24 to subgroup B. The respective numbers in group 2 were 8 and 12.

**Inclusion Criteria**

The subjects were selected from a group of 65 consecutive patients undergoing diagnostic coronary arteriography on the basis of (1) the presence of at least one angiographically normal coronary vessel, (2) exercise coronary arteriography, and (3) measurements of total serum cholesterol. Patients were not randomized but were included on a consecutive basis. First, control patients were studied, and in a second series of patients, a calcium channel blocker was administered before the exercise test. The two groups were well matched with regard to clinical characteristics.

**Determination of Serum Cholesterol**

Total serum cholesterol was determined in the Department of Clinical Chemistry at our hospital with the use of an enzymatic dye method (Chol-Pap method, Boehringer-Mannheim) on a blood sample obtained the day before cardiac catheterization.

**Coronary Risk Factors**

Hypercholesterolemia (>5.5 mmol/L according to Reference 16), cigarette smoking, family history (coronary artery disease in one of the patient’s parents or in a sibling <60 years old), obesity (body mass index $\geq 28$ kg/m$^2$), and diabetes mellitus (three patients with insulin-dependent diabetes mellitus, one with non-insulin-dependent diabetes mellitus) were evaluated in the present analysis.

**Cardiac Catheterization**

Patients underwent right and left heart catheterization for diagnostic purposes. Informed consent was obtained from all patients. Premedication consisted of 10 mg of chlordiazepoxide 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, followed by diagnostic coronary arteriography. An interval of at least 10 minutes was allowed for dissipation of the effect of the contrast material. A nonionic contrast material (Iopamiro 370: iopamidol 755.2 mg/mL, trometamol 1 mg/mL) was used for quantitative coronary angiography to minimize hyperemic reactions with transient changes in coronary blood flow. Quantitative coronary angiography was performed in the right and left anterior oblique projections, but in some patients, cranio-caudal angulation was necessary for proper visualization of the stenotic segment. Cine film was used as a data carrier (filming rate, 50 frames/s).

**Study Protocol**

At the end of diagnostic catheterization, biplane coronary arteriography was performed at rest with the patient’s feet attached to a bicycle ergometer (Siemens-Elema AG, model 380B). Exercise was begun at 50 to 75 W, and workload was increased every 2 minutes in increments of 25 to 50 W. Coronary arteriography was performed at the end of each exercise level with patients holding their breath during injection of the contrast medium. Arteriograms at maximum exercise level were used for analysis of coronary vasomotion. The average workload was similar in group 1 (98±30 W) and group 2 (93±30 W) ($P=NS$). In group 1, no vasoactive substances were administered before exercise. In group 2, a calcium channel blocker was given before exercise. Nine patients received 0.2 mg of intracoronary nicardipine over 30 seconds. In 11 patients, 2.5 mg of intracoronary diltiazem was administered. Immediately after the calcium channel blocker was administered, a second angiogram was acquired. Bicycle exercise was then begun as described above. The exercise test was terminated when angina pectoris, fatigue, or ST-segment depression $>0.2$ mV occurred; then, 1.6 mg of nitroglycerin was administered sublingually, and coronary angiography was repeated 5 minutes later. Nitroglycerin was administered routinely for clinical purposes to treat exercise-induced ischemia with ST-segment depression or to relieve angina pectoris (60% of all patients had angina). The doses were chosen to simulate the maximal coronary vasodilatation according to previously reported dose-finding studies for nicardipine, diltiazem, and nitroglycerin.

**Quantitative Coronary Angiography**

Quantitative evaluation of biplane coronary arteriograms was performed with a semiautomatic computer system. Evaluation was performed in a blinded fashion in both groups, that is, the observer was unaware of the actual study situation. The system is based on a 35-mm film projector (Tagarno A/S), a high-resolution slow-scan charged couple device camera (for image digitization) developed at the Institute for Biomedical Engineering in Zurich, and a computer workstation (Apollo DN 3000, Apollo Computer AG) for image storage and processing. Calibration was performed by the isocenter technique, which requires two orthogonal angiographic projections for the exact determination of the focus-image intensifier distance, and a reference point in the center of the two image intensifiers (2-mm lead marks). From these data, the exact calibration factor for each point of the image can be determined accurately. Contour detection was performed in the biplane projection by use of a geometric-densitometric edge-detection algorithm. The methodology for computerized analysis of coronary arteriograms has been described elsewhere.

Briefly, a three-dimensional model of the vessel was constructed by marking the center lines of the individual biplane tracings, assuming the vessel cross section to be elliptoidal. The reproducibility of luminal area measurements in coronary arteriograms has been reported to have an interobserver variability of 4.1% (standard error of estimate [SEE] in percent of the mean vessel cross-sectional area) and an intraobserver variability of 2.1%. The SEE for repeated measurements by one observer was 0.072 mm$^2$ in luminal area, and the SEE for interobserver variability was 0.137 mm$^2$ (see Reference 21).

Quantitative analysis was performed in a normal vessel segment of a coronary artery unaffected by luminal irregularities or stenoses. In the 50 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 cine frames without motion artifacts, (3) straightness of the vessel segment, and (4) biplane projection.

**Statistical Analysis**

Intergroup comparisons of clinical, hemodynamic, and angiographic data at rest and during exercise as well as after administration of a calcium channel blocker were performed by a one-way ANOVA for continuous variables followed by Scheffé’s test if the ANOVA test
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
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<th>Patient Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n=37)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>36 (97)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54±7</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.8±0.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4±2.2</td>
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<tr>
<td>EF, %</td>
<td>63±9</td>
</tr>
<tr>
<td>Patient history</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>30/37 (81%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13/37 (35%)</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>1.8±1.1</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>10/37 (27%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4/37 (11%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>7/37 (19%)</td>
</tr>
<tr>
<td>Smoking, pack years</td>
<td>28/37 (76%)</td>
</tr>
<tr>
<td>Anti-ischemic drugs</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>25/37 (68%)</td>
</tr>
<tr>
<td>Ca antagonist</td>
<td>22/37 (60%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>22/37 (60%)</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>12/37 (33%)</td>
</tr>
<tr>
<td>Serum lipids</td>
<td></td>
</tr>
<tr>
<td>Subgroup A</td>
<td>n=13</td>
</tr>
<tr>
<td>Total cholesterol, mg/100 mL</td>
<td>183±26</td>
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<tr>
<td>Triglycerides, mg/100 mL</td>
<td>52±28</td>
</tr>
<tr>
<td>Subgroup B</td>
<td>n=24</td>
</tr>
<tr>
<td>Total cholesterol, mg/100 mL</td>
<td>263±44*</td>
</tr>
<tr>
<td>Triglycerides, mg/100 mL</td>
<td>84±57*</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; BMI, body mass index; EF, ejection fraction; and CAD, coronary artery disease. According to the exclusion criteria, no hypertensive patients were included. *P<.01 vs subgroup A.

Results

**Patient Characteristics**

Sex distribution, age, functional classification according to the New York Heart Association, and body mass index were comparable in the two groups and the two subgroups. There were no differences among the study groups with regard to patient’s history, frequency of angina pectoris, myocardial infarction, and number of diseased vessels. Risk factors for coronary artery disease and the use of anti-ischemic and lipid-lowering drug therapy were evenly distributed among all groups. Because of the selection criteria, total serum cholesterol was significantly lower in subgroup A than in subgroup B in both groups. The respective subgroups of the two study groups showed similar cholesterol levels. See Table 1 for additional information.

**Hemodynamic and Exercise Data**

In the supine position, exercise workload was similar in groups 1 and 2. Changes in heart rate, mean pulmonary artery pressure, and mean aortic pressure were comparable during exercise after application of the calcium antagonist as well as after sublingual nitroglycerin. Heart rate and mean pulmonary artery pressure increased significantly during bicycle exercise, whereas mean aortic pressure remained unchanged in both groups (Table 2). The achieved workload was similar in normocholesterolemic and hypercholesterolemic patients in all groups and subgroups. With respect to ischemic symptoms, angina pectoris occurred in 73% of patients in group 1 but in only 25% of patients in group 2 (P<.05 versus group 1) during supine bicycle exercise test, although the incidence of angina pectoris was similar in the two groups during the upright bicycle exercise test (75% versus 65%; P=NS).

**Angiographic Data**

Normal vessels were similar in size, but the response to exercise was different in subgroups A and B in the two groups. In subgroup A of group 1 (n=13), there was a 31% increase in coronary artery luminal area during exercise (P<.01 versus rest), whereas in subgroup B of group 1 (n=24), only a mild increase of 13% was observed (P=NS versus rest; P<.05 versus subgroup A) (Fig 1). After sublingual administration of nitroglycerin, an increase to 42% in subgroup A and 30% in subgroup B was found. In group 2, after application of the calcium antagonist, a similar vasodilation was found in subgroups A (n=8; 22%; P<.05 versus rest) and B (n=12; 22%) that was slightly enhanced during exercise to 23% in subgroup A and 24% in subgroup B (P=NS versus subgroup A) (Fig 1). After sublingual nitroglycerin, the normal vessels dilated to 36% (P<.01) in subgroup A and 38% (P<.01) in subgroup B.

Stenotic vessels showed similar minimal luminal area and percent area stenosis in all groups and subgroups. In group 1, exercise-induced vasoconstriction was found in subgroups A (−10%; P<.05 versus rest) and B (−15%; P<.05 versus rest) (Fig 2). Sublingual nitroglycerin reverted constriction to dilation (12% in subgroup A and 20% in subgroup B). In group 2, administration of the calcium antagonist dilated the stenotic segment in subgroups A (12%) and B (8%); this effect was enhanced during subsequent exercise (A, 33%; B, 22%; P=NS for subgroup A versus subgroup B), thus preventing exercise-induced vasoconstriction (Fig 2). Sublingual nitroglycerin further enhanced coronary vasodilation in subgroups A (50%) and B (34%; P=NS versus subgroup A).

An additive effect between nitroglycerin and calcium antagonists was found, ie, maximal vasodilation after nitroglycerin was 40% in group 2 versus 14% in group 1 (P<.0001). This trend persisted in the two subgroups (50% versus 33%, P<.001 in subgroup A, and 34% versus 18%, P<.001 in subgroup B).

**Influence of Hypercholesterolemia on Coronary Vasomotion**

An inverse correlation between exercise-induced vasomotion of angiographically smooth coronary arteries and total cho-
lesterol was found ($r = -0.655, P < 0.001$). After pretreatment with the calcium channel blocker (group 2), this correlation was lost and all patients showed similar vasodilation during exercise regardless of total serum cholesterol level (Fig 3). When serum cholesterol level was $>$250 mg% ($n = 12$), exercise-induced vasodilation was no longer observed (3%; $P = \text{NS}$ versus baseline).

### Discussion

Impairment of endothelium-dependent vasodilation in angiographically normal coronary arteries has been reported in the presence of hypercholesterolemia.\cite{12,13,22} This has been attributed to a dysfunction of the endothelium via an attenuation of endothelium-derived relaxing factor release by oxidized cholesterol.

### Figure 1

Coronary vasomotion of the normal vessel segments in control subjects (group 1) and in patients pretreated with calcium antagonists (group 2). Delta-Ex indicates percent change of luminal cross-sectional area during exercise.

### Figure 2

Coronary vasomotion of the stenotic vessel segments in control subjects (group 1) and in patients pretreated with calcium antagonists (group 2). Note that there was stenosis constriction in control subjects that was prevented by calcium antagonists in group 2. Delta-Ex indicates percent change of stenosis cross-sectional area during exercise.
Seiler and coworkers reported that exercise-induced vasoconstriction of arteries with experimental hypercholesterolemia. Recently, the coronary arteries in the presence of an atherosclerotic lesion but to dilate normal coronary vessels. Exercise-induced coronary vasomotion of normal vessels. Del-ta-Ex indicates percent change of cross-sectional area; chol, cholesterol.

In contrast to most previous studies, a different approach was used in the present study to induce coronary vasodilation, namely, dynamic bicycle exercise. The effect of exercise on coronary vasomotion is probably more complex than that of a single pharmacological agent. However, dynamic exercise is a physiological stimulus and thus reflects the natural response of the coronary arteries to daily activities better than any pharmacological intervention. Intracoronary acetylcholine, as well as dynamic exercise, has been shown to constrict the coronary arteries in the presence of an atherosclerotic lesion but to dilate normal coronary vessels. Similar observations have been made in children with familial hyperlipidemia and in porcine coronary arteries with experimental hypercholesterolemia.

Pathophysiological Mechanisms of Abnormal Vasomotor Response to Hypercholesterolemia

In the development of atherosclerosis, injury to the endothelium results in a functional impairment without gross morphological alterations of the vessel wall. After accumulation of intracellular lipids, smooth muscle cells migrate and proliferate, and ultimately, a flow-limiting stenosis develops. Hypercholesterolemia and oxidized LDL interfere with the endothelium-dependent relaxation of the coronary arteries by attenuation of endothelium-derived relaxing factor release and/or stimulation of the expression of endothelin mRNA as well as the release of endothelin. These changes play an important role in the development of early atherosclerotic lesions, which is characterized by functional alterations of the endothelial cell before morphological changes can be detected. In the present study, no relationship between serum cholesterol and exercise-induced vasomotion of the stenotic vessel was found, in agreement with the study of Seiler et al. However, the normal vessel showed a decrease in exercise-induced vasodilation depending on the actual plasma cholesterol level, although normocholesterolemic and hypercholesterolemic patients achieved the same workload.

Hypercholesterolemia-Induced Endothelial Dysfunction: Influence of Calcium Channel Blockers

Reversal of hypercholesterolemia-induced endothelial dysfunction by l-arginine has been reported by Drexler and coworkers in cardiac transplant recipients. Beneficial effects of cholesterol-lowering therapy on coronary vasomotion and myocardial perfusion as well as on mortality have recently been reported. Habib and coworkers found preservation of endothelium-dependent relaxation in the cholesterol-fed rabbit by treatment with a calcium channel blocker. The present study is the first to demonstrate in humans that impaired coronary vasomotor response to physiological exercise is reversed by the administration of a calcium channel blocker (Fig 3). Because these drugs are strong vasodilators, the most likely explanation for the elimination of the cholesterol effect is the predilation of the coronary arteries by direct relaxation of the smooth muscle in the vasculature. The present data confirm this statement, because coronary vasodilation after administration of the calcium antagonist was found in stenotic (11%) as well as in normal (22%) coronary arteries.

Two different calcium antagonists were used in the present study, viz, a dihydropyridine (nicardipine) and a benzothiazepine-like substance (diltiazem). Differences among various calcium antagonists have been described with regard to contractility, peripheral vasodilator capacity, AV conduction, and cardioprotection. Dihydropyrimidines act mainly on the smooth muscle in the vasculature and have a negative inotropic action, with no effect on AV conduction, whereas benzothiazine-like substances elicit a similar pharmacological action but show an effect on AV conduction. Vasomotor response to exercise was similarly affected by these two groups, probably because of their strong vasodilator actions on the smooth muscle in the vasculature. Thus, these two classes of calcium channel blockers have comparable effects on coronary vasomotion, because there were no statistical differences between the two substances with regard to exercise hemodynamics and changes in coronary luminal area.

Several studies in humans have shown a beneficial effect of calcium channel blockers on progression of coronary atherosclerosis or on morbidity and mortality, whereas others have not. In a recent meta-analysis, not only was there a lack of a beneficial effect, but a dose-dependent increase in mortality was reported in coronary patients treated with nifedipine. However, our data confirm that calcium antagonists are potent coronary vasodilators even in hypercholesterolemic patients.
Clinical Implications

The present observations have important clinical implications because calcium antagonists are able to normalize the pathologic response of the coronary arteries to exercise in patients with hypercholesterolemia. There was a reduced coronary vasodilation of the angiographically normal vessels in hypercholesterolemia that was normalized after calcium channel blockers were administered. Furthermore, exercise-induced vasoconstriction was prevented by calcium antagonists. In this regard, Felder et al. have shown a decrease in regional coronary flow reserve during bicycle exercise but an increase during pharmacological vasodilation, suggesting that exercise-induced coronary vasoconstriction plays an important role in conditions of physiological stress.

Study Limitations

Serum cholesterol was measured several times, but only the values at the study date are reported in the present analysis. The accuracy of quantitative coronary arteriography has been established previously in our laboratory. Interobserver variability was found to be small, with an SEE for biplane data of 4.1% of the mean vessel area. This small variability is achieved by use of high-quality images and therefore requires careful selection according to the exclusion criteria, which could be a potential source of bias. However, the exclusion criteria were applied before the study to minimize any bias. The changes observed in our study are clearly larger than the reported angiographic resolution. Therefore, the observed changes after exercise or pharmacological intervention can be considered representative.

Repeated measurements with and without calcium antagonist treatment in each patient (using each patient as his or her own control) were not performed for ethical reasons. Repeated exercise testing would have prolonged the study own control) were not performed for ethical reasons. Repeated exercise testing would have prolonged the study. Repeated measurements with and without calcium antagonist treatment in each patient (using each patient as his or her own control) were not performed for ethical reasons.

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Circulation. 1998;97:1348-1354
doi: 10.1161/01.CIR.97.14.1348

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