Abnormal Coronary Vasomotion During Exercise in Patients With Normal Coronary Arteries and Reduced Coronary Flow Reserve

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A reduced coronary flow reserve has been reported in patients with ischemialike symptoms and normal coronary arteries. In 13 such patients, both coronary vasomotion and flow reserve were studied. The luminal area of the proximal and distal third of the left anterior descending and left circumflex artery were determined by biplane quantitative coronary arteriography using a computer-assisted system. Patients were studied at rest, during submaximal supine bicycle exercise (4.0 minutes, 116 W), and 5 minutes after sublingual administration of 1.6 mg nitroglycerin. Heart rate, mean pulmonary pressure, and mean aortic pressure as well as the percent change of both proximal and distal luminal area were determined. In 10 of the 13 patients, coronary sinus blood flow was measured by coronary sinus thermodilution technique at rest and after dipyridamole infusion (0.5 mg/kg in 15 minutes) 10±5 days after quantitative coronary arteriography. Coronary flow ratio (dipyridamole/rest) and coronary resistance ratio (rest/dipyridamole) were determined in these patients. Patients were divided into two groups according to the behavior of the coronary vessels during exercise (vasodilation, group 1; vasoconstriction, group 2). Coronary vasodilation of the proximal (luminal area +26%, p<0.001) and distal (+45%, p<0.001) artery was observed in seven patients (group 1) during exercise and after sublingual nitroglycerin (+46%, p<0.001; and +99%, p<0.001, respectively). In group 2 (n=6), however, there was coronary vasoconstriction of the distal vessel segments (−24%, p<0.001) during exercise, whereas the proximal coronary artery showed vasodilation (+26%, p<0.001) during exercise. After sublingual nitroglycerin, both vessel segments elicited vasodilation (distal coronary, +44%, p<0.001; proximal coronary artery, +47%, p<0.001). Coronary flow ratio amounted to 2.5 in group 1 and 1.2 in group 2 (p<0.05) and coronary resistance ratio to 2.7 in group 1 and to 1.2 in group 2 (p<0.05), respectively. Thus, among patients with ischemialike symptoms and normal coronary arteries, there is a group of patients (group 2) with an abnormal dilator response of the distal coronary arteries to the physiologic dilator stimulus of exercise and a reduced dilator capacity of the resistance vessels after dipyridamole (abnormal coronary vasodilator syndrome). The nature of this exercise-induced distal coronary vasoconstriction is not clear but might be due to an abnormal neurohumoral tone that may cause or contribute to the blunted vascular response during exercise. (Circulation 1989;79:516–527)

Myocardial ischemia in patients with normal coronary arteries and normal left ventricular function has been reported by many investigators. This condition with ischemialike symptoms, normal coronary arteries, and lactate production during atrial pacing has been called syndrome X. Several mechanisms have been considered possible causes of myocardial ischemia in patients with normal coronary arteries—abnormal affinity of red blood cells to hemoglobin, coronary arterial spasm, and coronary artery disease of the small vessels not visualized by coronary arteriography as well as abnormal neurohumoral regulation with abnormal vascular tone during various vasodilator influences. To further evaluate this syndrome in patients with isch-
emialike symptoms and normal coronary arteries, coronary artery vasomotion of the large and small epicardial arteries was studied at rest as well as under the physiologic stimulus of exercise by bplane quantitative coronary arteriography.

Methods

Patients

In 13 patients (mean age, 48 years; range, 40–60 years) with either angina pectoris (Table 1) or ST segment depression of 0.1 mV or greater (range, 0.1–0.2 mV) or both during upright bicycle exercise (Table 2), bplane coronary arteriography was performed at rest and during supine bicycle exercise. Patients were selected on a consecutive basis for the purpose of the present study. Eleven patients were men and two were women. All had normal coronary arteries; patients with coronary artery disease or wall irregularities were excluded. All patients were normotensive, and none had evidence of left ventricular hypertrophy in the standard 12-lead electrocardiogram. Angiographic muscle mass index determined according to the technique of Racleley and coworkers was 85 g/m² (range, 67–104 g/m²; upper limit of normality in our laboratory was 118 g/m² as reported by Corin et al). All drugs were discontinued at least 24 hours before catheterization.

Cardiac Catheterization

Patients underwent right and left heart catheterization in the fasting state. Informed consent was obtained from all patients. Premedication consisted of 10 mg chlordiazepoxide administered orally 1 hour before the procedure. Aortic pressure was measured with an 8F Judkins catheter introduced through the right femoral artery. Pulmonary artery pressure was measured with a 6F pacing catheter with a side lumen for pressure recordings introduced through the right femoral vein.

Study Protocol

The present study followed the same exercise protocol as it has been described previously. First, biplane left ventricular angiography was performed followed by the diagnostic coronary arteriography. An interval of at least 10 minutes passed after the last diagnostic coronary arteriogram had been performed; then simultaneous biplane coronary arteriograms were carried out in the 30° right anterior oblique and 60° left anterior oblique projections at a filming rate of 50 frames/sec using a nonionic contrast material (iopamidol 755.2 mg/ml, trometamol 1 mg/ml = Iopamiro 370®). In each patient, the segments of the vessels were selected for study on the basis of clear visualization without overlapping vessels. Control arteriography of the left coronary artery was carried out with the patient’s feet attached to the bicycle ergometer (model 380B, Siemens-Albis AG, Zurich). Aortic and pulmonary artery pressures were recorded immediately before coronary arteriography. Then, exercise was begun at a level of 50–75 W,

### Table 1. Clinical Data

<table>
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<td>p (group 1 vs. group 2)</td>
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T, typical exercise-induced angina; A, atypical chest pain.
†p<0.01; ‡p<0.001; NS, not significant.
which was increased every 2 minutes in increments of 25–50 W. Repeat biplane coronary arteriography with concurrent aortic and pulmonary artery pressure recordings was performed each 2 minutes and at the end of exercise. Exercise was terminated because of fatigue in all 13 patients. Sublingual nitroglycerin (1.6 mg) was given at the end of exercise test. Five minutes later, coronary arteriography was repeated. There were no complications related to the procedure in any of the patients studied.

**Quantitative Coronary Angiography**

Coronary arteriograms were projected on a large screen at 2.5-fold magnification for quantitative analysis with a Vanguard Model XR35 projector or an Angiogram Projection System Model CAP-35B (Weinberger AG, Zurich).16,17 The outlines of coronary arteries were traced and digitized with an electronic digitizer (Numonics Corp) interfaced with a computer (PDP 11/34). A portion of the catheter of known dimension, near its tip, was traced for each cine frame and provided a scaling factor. Pincushion distortion was found to be small for our system (Siemens Angioscope); measurements made at the periphery were 1.8±0.08% (horizontal and vertical axes, NS) larger than those made at the center.16 Therefore, a pincushion correction was not used in the present study.

The methodology for computerized analysis of coronary arteriograms was described previously.16–19 Briefly, a three-dimensional model of the vessel was constructed by matching center lines of the individual biplane tracings and assuming the vessel cross-section to be ellipsoidal.

Quantitative evaluation was carried out in a blinded fashion. The angiogram was projected and the tracings were made by an observer unaware of the particular study conditions (control, exercise, or sublingual nitroglycerin). For each vessel segment, six frames during mid-diastole to late diastole of one cardiac cycle were analyzed.

A proximal and distal vessel segment of the left anterior descending coronary artery and the left circumflex coronary artery were analyzed in all patients (Figure 1). When difficulties were encountered in visualization of the vessels in one of the two biplane views due to overlying vessels, a monoplane view was used in three of the 13 patients (23%). The exact location of the measuring site was identified in each patient. The length between the coronary ostium and the measuring site as well as the total length of the coronary artery were deter-
FIGURE 1. Coronary angiograms at rest (top), during supine bicycle exercise (middle), and after 1.6 mg sublingual nitroglycerin (bottom) in a 56-year-old man (group 2, patient 5). Distal luminal area decreased during exercise from 1.7 to 1.1 mm² (left anterior descending artery, LAD) and from 1.9 to 1.1 mm² (left circumflex artery, LCX), respectively, and increased to 2.6 mm² in both vessels after nitroglycerin. Proximal luminal area increased during exercise from 5.0 to 6.3 mm² (LAD) and from 4.2 to 5.9 mm² (LCX), respectively. There was a further increase after nitroglycerin to 7.8 (LAD) and 6.7 mm² (LCX). Arrows, vessel segments analyzed.
mained. The ratio (%) between these two lengths was calculated and used for identification of the measurement site. The proximal measuring site was at 23±3% of the left anterior descending and 27±4% of the left circumflex coronary artery; the distal measuring site was at 76±3% of the left anterior descending and 72±4% of the left circumflex coronary artery. There were no significant differences in regard to the measuring site between the two groups.

The effect of nonionic contrast agents on coronary vasomotion is small, and variations in vessel diameter after iopamidol were less than 5% of the control value.20 Thus, the effect of the contrast medium was considered to not contribute to the observed changes in coronary luminal area during exercise or after nitroglycerin.

Interobserver variability (n=22) has been evaluated previously in our laboratory.16,17,19 The SEE of the mean vessel area was 7.9% (0.30 mm²) for biplane and 9.3% (0.39 mm²) for monoplane coronary arteriography.

The range of luminal areas analyzed in the present study was from 0.9 to 4.5 mm² for distal and from 3.2 to 14.6 mm² for proximal segments of the coronary arteries. For each vessel segment, the results are expressed as mean±1 SD. On average, the standard deviation of mean values for the luminal area of the proximal and distal segments was 7.4%.

Coronary Blood Flow Measurements

Total coronary blood flow was measured by the coronary sinus thermodilution technique.10,13,21

Patients were studied 7–20 days (mean, 10 days) after coronary arteriography on an ambulatory basis. All drugs were discontinued at least 48–72 hours before catheterization. Catheterization was carried out in the fasting state under fluoroscopic control. A 7F thermodilution catheter (CCS-7U-90A or B, Webster Laboratory, Altadena, California) was introduced from the right femoral vein into the coronary sinus. Correct positioning was checked by measuring oxygen saturation and by injection of small amounts of contrast dye. Injection of cold saline into the superior vena cava was not associated with changes in the temperature curve of the thermistor in the coronary sinus.22 The signals of the external (mixing temperature of blood and saline) and internal (temperature of the injected saline) thermistors were recorded on an oscillograph (model VR-12, Electronics for Medicine) at a paper speed of 5 mm/sec. Then, room temperature saline was infused through the thermodilution catheter at a rate of 50 ml/min, and coronary sinus flow in milliliters per minute was calculated according to the formula of Ganz and coworkers.21 Normalization of coronary flow per 100 g muscle mass was carried out using left ventricular angiographic mass, which was determined in each individual patient. Coronary resistance (R, mm Hg·min·100 g/ml) was calculated according to the following equation:

\[ R = \frac{(AoP - CSP)}{CSBF} \]

where AoP is mean aortic pressure (mm Hg), CSP is mean coronary sinus pressure (mm Hg), and CSBF is coronary sinus blood flow per 100 grams of muscle weight (ml/min·100 g).

Coronary sinus outflow was determined at rest as well as after infusion of 0.5 mg/kg body wt dipyridamole over 15 minutes. This duration of infusion of dipyridamole was chosen to minimize the systemic effects of dipyridamole on heart rate and blood pressure. Mean aortic pressure remained unchanged after dipyridamole (111 and 110 mm Hg, respectively; NS), whereas heart rate increased (p<0.05) from 75 before to 88 beats/min after dipyridamole.

Coronary flow ratio (coronary flow reserve) was calculated as coronary sinus blood flow after dipyridamole infusion divided by the blood flow at rest. Coronary resistance ratio was determined from the resistance at rest divided by the resistance after dipyridamole infusion.

Patient Groups

Patients were divided into two groups according to the behavior of the coronary arteries during exercise: group 1 consisted of seven patients with coronary vasodilatation of all vessel segments and group 2 consisted of six patients with coronary vasoconstriction of the small (distal) epicardial vessels during exercise.

Statistical Analysis

The hemodynamic and angiographic data at rest in response to exercise and sublingual administration of nitroglycerin, expressed in absolute values and in percent of control, were compared by a two-way analysis of variance for repeated measurements. When data between group 1 and group 2 were compared, an unpaired t test was used. To compare coronary sinus blood flow before and after dipyridamole, a paired t test was used. The occurrence of typical and atypical chest pain within one group and between the two groups was compared by a χ² analysis. p value less than 0.05 was considered to be significant. In all tables, values are mean±1 SD; in all figures, values are mean±1 SEM.

Results

Clinical and Exercise Data

A history of angina pectoris was present in all patients; however, three patients in group 1 had atypical chest pain occurring not only during exercise but also at rest (Table 1).

There was no difference in regard to medical treatment between the groups: seven patients were on β-blockers (four in group 1 and three in group 2), seven were on calcium antagonists (three in group 1 and four in group 2), and eight were on long-acting nitrates (four in each group).
Mean pulmonary artery pressure (Figure 2) increased significantly only in group 2 (p<0.05), whereas mean aortic pressure remained unchanged compared with the resting value in both groups. Heart rate was slightly higher and mean aortic and pulmonary artery pressures were slightly lower in both groups after administration of sublingual nitroglycerin compared with the data obtained at rest.

**Quantitative Coronary Arteriography**

In Figure 1, coronary arteriograms are shown at rest, during supine exercise, and after sublingual nitroglycerin in a patient of group 2 with exercise-induced vasoconstriction of the distal vessels. In Figures 3 and 4, the effects of exercise and nitroglycerin on coronary luminal area are summarized. During supine exercise, an increase of the proximal vessel area was observed in both groups (group 1, +21%; group 2, +26%; p<0.001). In both groups, nitroglycerin produced a further increase in the mean luminal area of the proximal segment compared with the value during supine exercise (p<0.001). An increase in distal vessel area was observed in group 1 during supine exercise (+45%, p<0.001), whereas a decrease was observed in group 2 (~23%, p<0.001) during exercise. The response of the distal vessel segments to exercise was significantly different in the two groups (p<0.01). Nitroglycerin produced an increase in the mean luminal area of the distal coronary arteries in both groups compared with the values at rest and during supine exercise (p<0.001). There were no significant differences between the groups after sublingual nitroglycerin. The behavior of proximal and distal vessel segments of the left anterior descending and of the left circumflex coronary artery in the same patient did not differ during the various conditions of the study.

**Coronary Sinus Flow and Resistance**

After dipyridamole infusion, coronary sinus blood flow increased significantly (p<0.05) and coronary resistance decreased significantly (p<0.01) in group 1, whereas in group 2 no significant difference was found. Coronary sinus blood flow and coronary resistance ratio during dipyridamole were respectively lower in group 1 than in group 2 (p<0.05). Left ventricular muscle mass index was normal in both groups.

**Discussion**

Myocardial ischemia is believed to be the result of an imbalance between myocardial oxygen supply and demand. In the presence of normal coronary arteries, myocardial ischemia has been explained by several mechanisms ranging from abnormal affinity of red blood cells to hemoglobin, abnormal myocardial metabolism, coronary vasoconstriction, and abnormal neurohumoral regulation of coronary vasomotor tone. Most investigators have demonstrated myocardial ischemia...

**Hemodynamics**

During supine bicycle exercise, heart rate increased significantly in both groups (p<0.001 in group 1 and p<0.01 in group 2) but was significantly higher in group 1 than in group 2 (p<0.01) (Table 2). Heart rate–systolic pressure product was slightly but not significantly higher in group 1 than in group 2 during supine bicycle exercise.

**Left ventricular ejection fraction** was normal (mean, 67±10%; range, 55–87) in all patients. Mean body surface area was 1.86±0.12 m² (range, 1.67–2.02), and there was no significant difference between the groups (1.87 m² in group 1 vs. 1.85 m² in group 2). No ST segment elevation was observed in the upright exercise test before cardiac catheterization. The responses to upright bicycle exercise and intracatheterization supine bicycle exercise are listed in Table 2. In the upright exercise test, angina pectoris occurred in six of the 13 patients (three for each group) and in none during supine exercise (p<0.001). The total group of 15 patients achieved a mean work load of 146 W during upright exercise (95% of the predicted age-, sex-, and height-corrected physical working capacity) and of 116 W (74%) during the supine bicycle exercise (p<0.001). The maximal achieved mean heart rate was 137 and 108 beats/min, respectively (p<0.01). The mean heart rate–systolic blood pressure product was 234×10² mm Hg/min during the upright and 165×10² mm Hg/min during the supine exercise test (p<0.001).
FIGURE 3. Plots of changes in luminal area (mm^2) of each individual patient (n=13) and each vessel segment (n=52). Proximal and distal segments of the left anterior descending (LAD) and left circumflex (LCX) coronary arteries are depicted at rest, after 2 minutes of peak exercise, and 5 minutes after administration of 1.6 mg sublingual nitroglycerin at the end of the exercise test. Data of group 1 (left) and group 2 (right) are given separately. In group 1, all proximal (closed symbols) and distal (open symbols) vessel segments show vasodilation during exercise and after sublingual nitroglycerin. In contrast, distal vessel segments in group 2 showed a significant decrease in luminal area during exercise, which, however, increased after sublingual nitroglycerin. The proximal segments in group 2 as well as in group 1 showed an increase during exercise as well as after nitroglycerin. 2 min. Ex, 2 minutes of exercise; max. Ex, peak exercise; NTG s.l., 5 minutes after 1.6 mg sublingual nitroglycerin.

lactate production during pacing-induced ischemia in these patients with ischemialike symptoms and normal coronary arteries.\textsuperscript{1,4,5,9,10} Because the exact mechanism of this type of ischemia is not known, the disorder has been called syndrome X.\textsuperscript{1,3,10} The prognosis of syndrome X has been shown to be excellent with no occurrence of myocardial infarction or sudden death.\textsuperscript{1,3–5} To study further this syndrome, we evaluated coronary vasomotion of the large and small epicardial arteries at rest and during exercise in 13 patients with ischemialike symptoms and normal coronary arteries.

Coronary Vasomotion and Coronary Flow Reserve

Coronary luminal areas of the left anterior descending and left circumflex arteries were determined at rest and during supine bicycle exercise in 13 patients with normal coronary arteries but with histories of angina pectoris or ST segment depression or both during upright bicycle exercise test. In seven of the 13 patients (group 1), exercise was accompanied by vasodilation of the proximal and distal coronary arteries. However, in six patients (group 2), there was exercise-induced vasoconstriction of the distal coronary arteries (Figures 3 and 4). The small epicardial coronary arteries showed coronary luminal narrowing during exercise, whereas the proximal arteries showed exercise-induced vasodilation.

Coronary sinus flow was normal at rest in both groups, but there was only a slight and nonsignificant increase in flow after dipyridamole infusion in group 2, whereas dipyridamole led to a significant increase of flow in group 1. Thus, not only is coronary vasomotion of the small epicardial arteries abnormal but the dilator capacity of the resistance vessels is reduced in patients with exercise-induced vasoconstriction (group 2). Similarly, Opherk and coworkers\textsuperscript{9} have found a reduced dilator capacity of the resistance vessels in patients with normal coronary arteries and ischemia.

Possible Mechanisms of Impaired Dilator Response

The observation that lactate production may occur during exercise in patients with ischemialike symptoms and normal coronary arteries suggests that myocardial ischemia can be induced in these patients despite anatomically normal coronary arteries. Myo-
cardiac ischemia occurs when oxygen supply is inadequate to meet the metabolic demands of the myocardium. Normally, changes in blood flow are closely related to alterations in myocardial metabolism so that the balance between oxygen supply and demand is preserved in all circumstances. The following mechanisms that may cause ischemia in the presence of normal coronary arteries have to be considered.

First, an abnormal affinity of the red blood cells to hemoglobin has been suggested by some, but this finding has not been confirmed by others. If abnormal oxygen release would be responsible for ischemia in these patients, one would expect marked coronary vasodilation at rest to compensate for low tissue oxygen concentration.

Second, coronary arterial spasm has been discussed by some authors, but in none of these studies has ST segment elevation been reported at either rest or during pacing. Ergonovine testing was not associated with significant coronary luminal narrowing in 25 such patients studied by Cannon and coworkers, but coronary flow reserve was limited after dipyridamole infusion. These authors concluded that in these patients with ischemialike symptoms and normal coronary arteries, an exaggerated response of the coronary arteries to vasoconstrictor stimuli exists, which can result in myocardial ischemia during stress. Angina pectoris occurred in none of our patients during supine bicycle exercise. Mean pulmonary artery pressure increased significantly only in group 2 during exercise. The increase in mean pulmonary artery pressure was similar in group 1, but due to the larger variations in this group the increase was not significant. It has been reported that during submaximal bicycle exercise, mean pulmonary artery pressure averages between 20 and 29 mm Hg in normal subjects and that its rise from rest to exercise amounts to 15 mm Hg or less. Only one patient in group 2 showed an increase in mean pulmonary artery pressure of more than 15 mm Hg during exercise, and the average of the mean pulmonary artery pressure was within the range of normality in both groups. Thus, the hemodynamic changes in our patients do not suggest an exercise-induced ischemia.

Third, small vessel disease is an unlikely mechanism in patients with normal coronary arteries because endomyocardial biopsies of both left and

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Plots of response of proximal and distal vessel segments to dynamic exercise expressed in percent of the resting values. Proximal and distal vessel segments in group 1 (left) showed vasodilation of the proximal (+20%) and distal (+43%) left anterior descending coronary artery (LAD) and of the proximal (+23%) and distal (+47%) left circumflex coronary artery (LCX) during exercise. After sublingual nitroglycerin, there was a further increase in both proximal and distal vessel segments of both LAD and LCX. In group 2 (right), luminal area of the proximal vessel segments increased (LAD, +19%; LCX, +26%, respectively) during exercise but the distal vessel segments showed coronary vasoconstriction (LAD, −23%; LCX, −26%, respectively) during exercise. After sublingual nitroglycerin both proximal and distal vessel segments elicited coronary vasodilation. 2 min. Ex, 2 minutes of exercise; max. Ex, peak exercise; NTG s.l., 5 minutes after 1.6 mg sublingual nitroglycerin.
right ventricles have shown only nonspecific histologic abnormalities of the myocardium without alterations of the small vessels.\textsuperscript{9} Similar findings have been made by Richardson et al.,\textsuperscript{20} Shirey et al.,\textsuperscript{22} and Baandrup et al.\textsuperscript{28} However, Mosseri and coworkers\textsuperscript{29} reported evidence for small vessel disease in their group of six patients with normal coronary arteries and angina pectoris. Two of these patients had congestive heart failure, three had rhythm disturbances, and all showed ventricular hypertrophy with reduced compliance of both ventricles. These patients probably had myocardial disease of various etiology and cannot really be compared with our study group.

Fourth, an abnormal neurohumoral tone may cause or contribute to an abnormal vascular response during pacing.\textsuperscript{10–13} Cold pressure testing can increase coronary vascular resistance by vasoconstriction of the arterioles with only minimal luminal narrowing of the epicardial arteries.\textsuperscript{30} These changes in neurohumoral tone may be effective through reflexes enhancing \(\alpha\)-adrenergic tone, which can cause coronary vasoconstriction of the arterioles but also of the adjacent small epicardial coronary arteries.\textsuperscript{31,32,33} These reflexes can override autoregulatory vasodilator influences and thereby precipitate myocardial ischemia.\textsuperscript{11} Experimental studies\textsuperscript{34–36} have shown a different distribution of the \(\alpha\) and \(\beta\)-receptors in the coronary vessel segments and two different subtypes of \(\alpha\)-receptors (i.e., \(\alpha_1\) and \(\alpha_2\)-receptors). \(\alpha_2\)-Receptors appear to regulate mainly vasoconstriction of small resistance vessels rather than that of the large superficial coronary arteries.\textsuperscript{37,38} Thus, one may speculate whether an enhanced \(\alpha_2\)-adrenergic activity, predominantly effective in the small coronary arteries and arterioles, was at the origin of the vasoconstrictive response of the distal vessel segments during exercise in group 2.

Fifth, platelet aggregation with release of thromboxane \(A_2\) and serotonin during pacing or during exercise could be responsible for an abnormal dilator response of the small coronary arteries.\textsuperscript{39} Although this mechanism seems unlikely, Di Donato and coworkers\textsuperscript{40} have shown increased levels of thromboxane \(B_2\) in the coronary sinus of patients with spontaneous angina pectoris and normal coronary arteries.

Sixth, an increase in extravascular compression may be a cause of the abnormal vascular response observed in group 2.\textsuperscript{10} Increased extravascular compression can be caused by hypertrophy at rest or by tachycardia either during exercise or after dipyridamole. None of our patients had tachycardia or evidence of left ventricular hypertrophy by electrocardiographic criteria, and angiographic muscle mass index was well below the upper limit of normality. Moreover, angiographic mass did not differ between the two groups (82 g/m\(^2\) in group 1 vs. 89 g/m\(^2\) in group 2). However, it cannot be completely ruled out that \(\beta\)-blocker treatment that has been stopped 24 hours before catheterization had some influence on exercise hemodynamics or coronary vasomotion. When the patients were subdivided into two groups with (A) or without (B) previous \(\beta\)-blocker treatment (Table 1), the increase in heart rate (A, +38 ± 12 beats/min; B, +42 ± 15 beats/min; NS), mean aortic pressure (A, +14 ± 10 mm Hg; B, +7 ± 5 mm Hg; NS), or luminal area of the proximal coronary arteries (A, +17 ± 7%; B, +26 ± 12%; NS) during peak exercise was similar.

Considering these mechanisms, it appears most likely that an abnormal neurohumoral regulation of the small epicardial coronary arteries and the resistance vessels is responsible for the reduced dilator capacity in these patients with ischemialike symptoms. Similar conclusions have been reached by others.\textsuperscript{10–13} It is assumed that the small epicardial coronary arteries behave in a similar way as the arterioles because of the preferential distribution of the \(\alpha_2\)-receptors within the distal coronary arteries. The fact that the proximal vessel segments showed exercise-induced vasodilation may be due to the preferential distribution of the \(\beta\)-receptors within the proximal coronary arteries.\textsuperscript{36}

Limitations of the Study

The accuracy of quantitative coronary arteriography has been well established in our laboratory\textsuperscript{16,17,19} and in the extensive validation studies of Brown et al.\textsuperscript{40} and Gould et al.\textsuperscript{41} Coronary sinus thermodilution techniques were used to measure total coronary sinus blood flow. Although this method is unable to measure the perfusion in specific transmural layers or different left ventricular regions or rapid changes in coronary blood flow,\textsuperscript{42} Ganz and coworkers\textsuperscript{43} found a high correlation between coronary sinus flow measured by this technique and by timed collection of venous blood. According to Marcus and coworkers,\textsuperscript{44} this technique is adequate for measuring relatively slow and large changes (more than 30%) in coronary blood flow. The increase in coronary blood flow after dipyridamole was clearly larger than 30% in group 1 (154%), but only 21% in group 2 (Table 3). Thus, these observations lend evidence to the contention that there was a true increase of coronary blood flow after dipyridamole in group 1, whereas in group 2 coronary flow did not change.

It is possible that coronary blood flow during exercise did not increase in group 2 as much as in group 1 and, therefore, coronary vasodilation was less pronounced in group 2. However, the response to exercise was completely different in group 2 compared with group 1 because the distal epicardial coronary arteries exhibited exercise-induced vasoconstriction instead of exercise-induced vasodilation. Furthermore, it is unlikely that coronary blood flow was much different during exercise because the rate-pressure product was similar in both groups.

Dipyridamole was used in the present study to assess maximal vasodilator capacity as it has been done by others.\textsuperscript{9,13} The duration of dipyridamole infusion was 15 minutes to minimize the systemic
Table 3. Coronary Sinus Flow Before and After Dipyridamole

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p (C vs. D)  

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p (C vs. D)  

| p (group 1 vs. group 2) | NS | NS | NS | * | * | * | NS | * | * |

LMMI, left ventricle muscle mass index (g/m²); CSBF, total coronary sinus blood flow (ml/min); C, before dipyridamole; D, after dipyridamole; 100, CSBF/100 g muscle wt (ml/min·100 g); CR, coronary resistance (mm Hg·min·100 g/ml).  

*p < 0.05; †p < 0.01; NS, not significant.

Effects on heart rate and blood pressure as it was suggested by Strauer and coworkers\(^43\)-\(^45\) and Tauchert.\(^46\) At first glance, this prolonged administration of dipyridamole (rather than total administration within a few minutes) might eventually explain why the coronary flow ratios were generally low in the present study although the highest individual value was 4.3. The average value was 2.5 in group 1 and 1.2 in group 2. If group 1 is considered to be normal, then these flow ratios are somewhat small; however, similar values have been reported by others\(^10\)-\(^13\),\(^21\),\(^22\),\(^38\),\(^42\)-\(^47\) who administered dipyridamole between 0.5 and 0.75 mg/kg i.v. within 4 and 6 minutes. It should be recognized that approximately 10% of all patients do not achieve maximal hyperemia with the dose of dipyridamole administered in the present study\(^47\); this might explain in part the relatively low coronary flow ratios with dipyridamole.

In conclusion, among patients with ischemialike symptoms and normal coronary arteries, there is a group of patients (group 2) with both an abnormal dilator response of the distal coronary arteries during exercise and an abnormal dilator response of the resistance vessels after dipyridamole. Sax and coworkers\(^49\) reported that in patients with ischemialike symptoms and normal coronary arteries (microvascular angina), the impairment of vasodilator reserve affects not only the coronary circulation but also the peripheral arterial bed; they suggested that microvascular angina may be part of a more generalized disorder of regulation of vascular tone. The mechanism responsible for this disorder is yet to be elucidated, but it seems to be due to an abnormal neurohumoral tone that may cause or contribute to the abnormal vascular response.

Acknowledgments

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References


KEY WORDS • coronary vasomotion • quantitative coronary arteriography • supine bicycle exercise • coronary resistance vessels • abnormal neurohumoral tone • coronary flow reserve
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A S Bortone, O M Hess, F R Eberli, H Nonogi, A P Marolf, J Grimm and H P Krayenbuehl

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