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Epicardial Coronary Artery Tone and Reactivity in Patients With Normal Coronary Arteriograms and Reduced Coronary Flow Reserve (Syndrome X)

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The vasomotor response of proximal and distal angiographically normal coronary artery segments was studied in 12 patients with syndrome X, 17 age- and gender-matched patients with chronic stable angina and 10 control subjects with atypical chest pain and a normal coronary arteriogram. Ergonovine (300 μg by intravenous injection) and isosorbide dinitrate (1 mg by intracoronary injection) were administered to all patients. Computerized coronary artery diameter measurement (angiographically normal segments only) was carried out before and after the administration of ergonovine and nitrate.

Baseline intraluminal diameters (mean ± SEM) of proximal and distal coronary segments were not significantly different in control subjects and patients with syndrome X or coronary artery disease (proximal 2.88 ± 0.19, 3.01 ± 0.13 and 2.86 ± 0.13 mm; distal 1.57 ± 0.09, 1.70 ± 0.10 and 1.61 ± 0.06 mm, respectively). With ergonovine, proximal segments constricted by 10 ± 2%, 7 ± 2% and 11 ± 3% and distal segments by 12 ± 3%, 14 ± 3% and 14 ± 2% in control subjects and patients with syndrome X or coronary artery disease, respectively (p = NS). With isosorbide dinitrate, proximal coronary segments dilated by 11 ± 2%, 10 ± 2% and 8 ± 2% (p = NS) and distal segments by 15 ± 2%, 11 ± 3% and 13 ± 2% (p = NS) in control subjects and patients with syndrome X or coronary artery disease, respectively. Within groups, constriction in response to ergonovine and dilation in response to nitrate were not significantly different in proximal and distal segments.

The results of this study indicate that coronary diameters and the vasomotor response to ergonovine and isosorbide dinitrate of angiographically normal coronary artery segments at rest are not significantly different in patients with noncardiac chest pain, syndrome X or coronary artery disease. Although coronary flow reserve is impaired in patients with syndrome X, reactivity of large epicardial vessels to nitrate and ergonovine is within the physiologic range in these patients.

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Patients with microvascular angina (1) or syndrome X (2–4) have typical exertional angina that appears to be caused by an abnormal vasodilator capacity of the coronary microcirculation (1,3,5–7). In these patients, ergonovine can exacerbate limited coronary flow reserve during pacing in the absence of focal epicardial coronary artery spasm (7). Because a large proportion of patients with syndrome X have angina at rest and ischemia-like ST segment depression during ambulatory electrocardiographic (ECG) monitoring, which is not always preceded by an increase in heart rate, dynamic small vessel constriction has also been suggested (4) to play a role in the genesis of angina in these patients.

Recently, it was suggested (8) that patients with microvascular angina have an abnormal vasodilator reactivity that affects not only their coronary vascular smooth muscle, but also the systemic vasculature. Moreover, although most evidence indicates that the primary alteration responsible for microvascular angina or syndrome X lies in the coronary microcirculation, recent reports (9–11) suggest an alteration of the reactivity of epicardial coronary arteries in these patients. A diffuse abnormal epicardial coronary constrictor response to hyperventilation (9) and an "erratic" epicardial vasodilator response to nifedipine (10) have been reported in patients with syndrome X. It has also been shown (11) that in patients with normal coronary arteries and reduced coronary flow reserve, distal epicardial coronary arteries exhibit abnormal vasomotion during exercise.

We prospectively compared, using quantitative coronary arteriography, coronary artery diameters and reactivity of epicardial coronary arteries at rest in response to ergonovine and isosorbide dinitrate in patients with syndrome X, patients with chronic stable angina and individuals with atypical chest pain and a normal coronary arteriogram.

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Methods

Study patients. The study group comprised 39 patients; 10 had atypical chest pain and a normal coronary arteriogram (control group), 12 had syndrome X and 17 had chronic stable angina due to atheromatous coronary artery disease.

Control group. Five women and five men, aged 35 to 61 years (mean 49), were studied. These patients had atypical chest pain, a normal exercise test and angiographically normal coronary arteries. All had been referred for coronary arteriography by their treating physician. None of these patients had left ventricular hypertrophy, which was assessed by two-dimensional guided M-mode echocardiograms. Measurements were obtained according to American Society of Echocardiography recommendations (12). Left ventricular wall thickness was calculated as the arithmetic mean of both posterior and interventricular septal thickness, and left ventricular mass was calculated with the method proposed by Troy et al. (13). Left ventricular hypertrophy was excluded by using gender-specific normal limits from the Framingham study (14). Systemic hypertension (defined as a blood pressure >140/90 mm Hg in repeated readings), coronary artery spasm, cardiomyopathy, valvular heart disease or conduction disturbances were not present in any patient. In these individuals, chest pain was most probably of noncardiac origin. Coronary blood flow reserve in response to dipyridamole was assessed in 5 of the 10 patients, by positron emission tomography using oxygen-15–labeled water (15) and was found to be ≥3.5 in all (range 3.5 to 4.6), a finding consistent with normal values from our laboratory (3.95 ± 0.9 in normal volunteers) (16) and results obtained by other investigators (17) using a similar technique.

Syndrome X. Syndrome X was defined as typical exertional angina, a positive exercise test (≥2 mm of ST segment depression), abnormal coronary blood flow reserve and a completely normal coronary arteriogram. Eight women and four men, aged 36 to 67 years (mean 52), were included in the study. None of the patients had left ventricular hypertrophy, which was assessed as in the control group (left ventricular mass index ranged from 78 to 95 g/m^2 in the eight women and from 83 to 122 g/m^2 in the four men). Patients with conduction disturbances, systemic hypertension, coronary artery spasm, cardiomyopathy or valvular heart disease were not included. All patients with syndrome X included in the study had episodes of horizontal or downsloping ST segment depression during 24 h ambulatory ECG monitoring and eight had reversible regional perfusion abnormalities during exercise, as assessed by hexamibi technetium-99m scans in six and by positron emission tomography (rubidium-82) in the remaining two. Coronary blood flow reserve in response to intravenous dipyridamole, assessed by positron emission tomography, was reduced in all 12 patients (mean 2.2 ± 0.4), a finding also reported by Geltman et al. (17) using a similar technique.

Coronary artery disease. Seventeen patients (7 men and 10 women), aged 36 to 70 years (mean 51), with chronic stable exertional angina, an abnormal exercise test and angiographically documented single vessel coronary artery disease (≥50% fixed reduction in intraluminal diameter) were studied. They were age- and gender-matched with control patients and patients with syndrome X. No patient had left ventricular hypertrophy or a history of myocardial infarction and all had a normal baseline ECG and left ventricular function at rest.

Study Protocol

The study protocol was approved by the hospital's Ethics Committee. The nature of the study was explained to each subject before written informed consent was obtained.

Coronary arteriography. All antianginal medication was discontinued ≥48 h before the study, with the exception of sublingual nitrates, which were allowed for relief of anginal attacks. All patients were fasting and had not smoked or received nitrates for acute pain for ≥8 h before cardiac catheterization. After diagnostic coronary arteriography, orthogonal views of relevant coronary artery segments were obtained before the administration of ergonovine or nitrate (baseline control arteriograms). Only angiographically normal segments were considered for analysis. Ergonovine (300 μg) was administered intravenously to all patients and arteriograms were repeated 2 to 4 min after administration. In all patients, a second control coronary arteriogram was obtained 5 to 7 min after ergonovine administration, before the intracoronary injection of isosorbide dinitrate (1 mg). Arteriograms of the relevant coronary segments were repeated 2 to 4 min after administration of the nitrate.

Measurement of coronary artery diameters. Our technique to measure coronary artery diameters was reported in detail previously (18). Briefly, coronary lumen diameters were measured by an automated edge contour detection system (Coronary Angiography Analysis System [CAAS], Pie Data Medical). The stem of the Judkins coronary catheter was used for calibration to determine absolute measurements in millimeters, and correction was made for radiographic pincushion distortion. Arteriograms were analyzed by two independent observers and later reanalyzed without knowledge of previous findings to determine the reproducibility of the method. The repeatability of the measurements was quantified by calculating the difference of each vessel measurement from the average of the measurement of that vessel (intraobserver reproducibility of measurements = 98%). There were no statistically (analysis of variance) significant differences between observers ($F = 0.31$, $p = 0.70$).

All major coronary arteries were divided in thirds using the American Heart Association classification (19). For the purpose of the study, only angiographically normal segments located in proximal and distal locations were analyzed. Diseased segments in patients with coronary artery disease were excluded from analysis because in the three patient groups we tried to compare only the vasomotor response of

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Table 1. Coronary Diameter on Baseline Arteriograms and Arteriograms After Intravenous Ergonovine in 39 Patients

	Proximal Coronary Segments			Distal Coronary Segments		
	Baseline (mm)	Ergonovine (mm)	% Reduction	Baseline (mm)	Ergonovine (mm)	% Reduction
Control patients (n = 10)	2.88 ± 0.19	2.62 ± 0.2	−10 ± 2	1.57 ± 0.09	1.38 ± 0.08	−12 ± 3
Syndrome X (n = 12)	3.01 ± 0.13	2.80 ± 0.14	−7 ± 2	1.70 ± 0.10	1.46 ± 0.13	−14 ± 3
CAD (n = 17)	2.86 ± 0.13	2.54 ± 0.15	−11 ± 3	1.61 ± 0.06	1.39 ± 0.07	−14 ± 2

CAD = coronary artery disease.

coronary arteries that looked angiographically normal. In three patients who had multiple lesions in the diseased vessel, this artery was excluded from analysis altogether. The percent vasoconstriction in response to ergonovine and dilation in response to nitrate used to quantify changes in coronary artery diameter were calculated as follows:

$$\text{Constriction by ergonovine} = \{(\text{Control diameter} - \text{Diameter after ergonovine})/\text{Control diameter}\} \times 100\%.$$

$$\text{Dilation by nitrate} = \{(\text{Diameter after nitrate} - \text{Control diameter})/\text{Control diameter}\} \times 100\ (\%).$$

Data analysis. Coronary diameter data are presented as mean values ± SEM, and hemodynamic variables as mean values ± 1 SD. Differences between proportions were analyzed by the Yates corrected chi-square test. Paired and unpaired Student's *t* tests were used as appropriate to analyze continuous data. A p value < 0.05 was considered significant.

Results

Baseline and control coronary artery diameters. We analyzed 36 angiographically normal segments in 10 subjects in the control group, 34 segments in the 12 patients with syndrome X and 29 segments in the 17 patients with coronary artery disease. Mean baseline diameter of proximal and distal coronary segments was similar in patients with atypical chest pain (control group), syndrome X or coronary artery disease (proximal 2.88 ± 0.19, 3.01 ± 0.13 and 2.86 ± 0.13 mm, respectively; distal 1.57 ± 0.09, 1.70 ± 0.10 and 1.61 ± 0.06 mm, respectively) (Table 1, Fig. 1). Baseline coronary diameter of proximal and distal segments before ergonovine and baseline control diameter before isosorbide dinitrate were not significantly different in control subjects and patients with syndrome X or coronary artery disease (Tables 1 and 2).

Effects of ergonovine on coronary artery diameter (Table 1). The intravenous administration of ergonovine consistently caused a mild increase in systolic blood pressure, but heart rate did not change. The hemodynamic response to ergonovine was similar in the three patient groups. Compared with baseline values, systolic blood pressure increased by 7 ± 4, 9 ± 5 and 9 ± 4 mm Hg, respectively, whereas heart rate changed by 2 ± 3, 1 ± 4 and 3 ± 2 beats/min in control subjects and patients with syndrome X or coronary artery disease, respectively.

After the administration of ergonovine, all patients with coronary artery disease had mild diffuse coronary constriction. Segments with marked diameter reduction by atheromatous plaques constricted to an extent similar to that of angiographically normal segments, but coronary occlusion did not occur in any case.

Proximal coronary segments reduced their caliber by 10 ± 2%, 7 ± 2% and 11 ± 3% in the control subjects and patients with syndrome X or coronary artery disease, respectively (p = NS). Distal coronary segments in these three patient groups reduced their mean caliber by 12 ± 3%, 14 ± 3% and 14 ± 2%, respectively (p = NS) (Fig. 2 and 3).

Within groups, diameter reduction in response to ergonovine was not significantly different in proximal and distal segments (Table 1). However, in patients with syndrome X, distal coronary segments showed greater constriction than proximal segments (p = 0.09).

Response to intracoronary isosorbide dinitrate (Table 2). Vasodilation of proximal coronary segments after nitrate was 11 ± 2% in the control group, 10 ± 2% in those with syndrome X and 8 ± 2% in patients with coronary artery disease (p = NS) (Fig. 2 and 3). Dilation of distal segments after nitrate in these three groups was 15 ± 2%, 11 ± 3% and 13 ± 2%, respectively (p = NS) (Fig. 2 and 3).

Within groups, dilation of proximal and distal coronary segments was not significantly different. However, in pa-

Figure 1. Mean baseline coronary artery diameter of angiographically normal proximal and distal coronary artery segments in control subjects and patients with syndrome X or coronary artery disease (CAD). Basal coronary diameters were similar in the three groups.

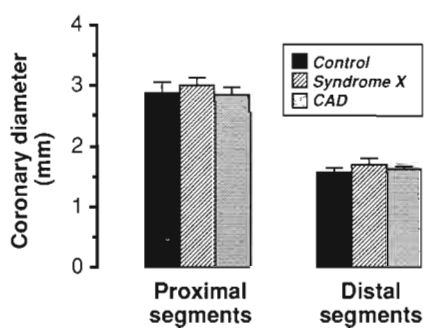


Table 2. Coronary Diameter on Baseline Arteriograms and Arteriograms After Intravenous Isosorbide Dinitrate in 39 Patients

	Proximal Coronary Segments			Distal Coronary Segments		
	Baseline (mm)	ISDN (mm)	% Dilation	Baseline (mm)	ISDN (mm)	% Dilation
Control patients (n = 10)	3.02 ± 0.14	3.40 ± 0.15	11 ± 2	1.59 ± 0.06	1.80 ± 0.07	15 ± 2
Syndrome X (n = 12)	2.8 ± 0.08	3.06 ± 0.07	10 ± 2	1.65 ± 0.07	1.82 ± 0.07	11 ± 3
CAD (n = 17)	2.84 ± 0.12	3.09 ± 0.12	8 ± 2	1.56 ± 0.05	1.76 ± 0.06	13 ± 2

CAD = coronary artery disease; ISDN = isosorbide dinitrate.

tients with coronary artery disease, coronary dilation in response to isosorbide dinitrate was greater in distal than in proximal segments ($p = 0.07$).

Discussion

This study demonstrates that mean basal coronary diameter is not significantly different in patients with atypical chest pain, syndrome X or coronary artery disease and that the response of proximal and distal angiographically normal coronary artery segments to nonendothelial-dependent vasoactive substances is similar in these three groups of patients.

Coronary response to ergonovine. Our findings with ergonovine are in agreement with observations of Cannon et al. (7) in patients with microvascular angina. These investigators found that the limitation in flow reserve caused by ergonovine, which resulted in myocardial ischemia, was not due to focal epicardial coronary spasm, because only mild diffuse epicardial constriction developed with ergonovine in their patients. In our study, the hemodynamic response to ergonovine was similar in the three patient groups and consistent with findings by others (20,21). In our patients with syndrome X, coronary constriction caused by ergonovine was within the physiologic range and similar to that in control patients and patients with chronic stable angina (20,21).

Our results do not confirm the findings by Bugiardini et al. (9) of marked diffuse generalized epicardial coronary constriction in response to vasoconstrictor stimuli in patients with syndrome X. We found that in our patients with angina, a normal coronary arteriogram and reduced coronary flow reserve, epicardial coronary reactivity to constrictor stimuli was within the physiologic range. Because the observations of Bugiardini et al. (9) were preliminary and a complete clinical description of their patients is lacking, it is possible that differences in patient selection may explain the different findings. In addition, the constrictor agents used differed in the two studies and quantitative computerized angiographic analysis was not carried out (9).

The distal coronary segments in our patients with syndrome X had greater (although the difference was not statistically significant) reactivity in response to ergonovine than did the proximal segments. This finding might be in agreement with the observation by Bortone et al. (11) that distal epicardial vessels constrict during exercise in patients with angina and normal coronary arteries, suggesting an abnormal behavior of these vessels in syndrome X. In our study, however, the mean diameter of small distal epicardial coronary vessels during baseline study and after nitrate administration was not significantly different in those with syndrome X, control subjects and patients with coronary artery disease. It is conceivable that the altered vasomotor response found by Bortone et al. (11) could be due to a diminished flow-dependent release of endothelium-derived relaxing factor, as also suggested by others (22).

Figure 2. Coronary artery vasodilation after intracoronary isosorbide dinitrate (**left**) and constriction after intravenous ergonovine (**right**) of angiographically normal proximal segments. No significant differences in the response to nitrate and ergonovine were observed in the control subjects and patients with syndrome X or coronary artery disease (CAD).

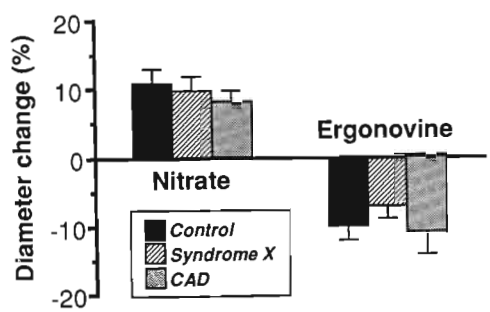
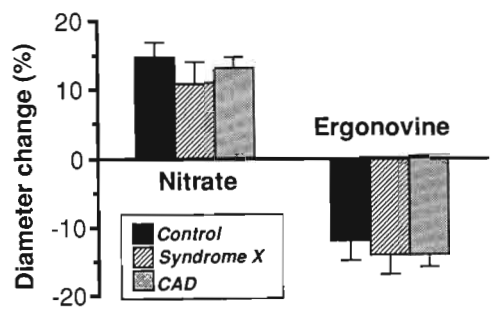


Figure 3. Coronary artery vasodilation after intracoronary isosorbide dinitrate (**left**) and constriction after intravenous ergonovine (**right**) of angiographically normal distal segments. Reactivity of distal epicardial coronary segments was not significantly different in control subjects and patients with syndrome X or coronary artery disease (CAD).



Coronary response to isosorbide dinitrate. In our study, epicardial coronary dilation with isosorbide dinitrate in patients with syndrome X was similar to that observed in the control group and in patients with coronary artery disease. Observations reported by Montorsi et al. (10) that the vasodilator response of coronary arteries to sublingual nifedipine is rather erratic in syndrome X were not confirmed in our study. Proximal and distal vessels consistently dilated in response to nitrate in all our patients with syndrome X. These differences could be explained by the greater potential of isosorbide dinitrate for dilation of epicardial coronary arteries in comparison with sublingual nifedipine (23). Moreover, because syndrome X is an ill defined patient category that in its broadest definition probably encompasses patients with different causes of their anginal pain, differences in patient selection could also explain the different findings. In addition to angina and an abnormal exercise test, our patients had reduced coronary flow reserve, whereas the Italian patients (10) were selected mainly on the basis of angina and an abnormal exercise test and it is not known whether they had an abnormal coronary flow reserve. In keeping with our findings, however, the response to nifedipine in the patients with syndrome X studied by Montorsi et al. (10) was, on average, similar to that of normal coronary branches in patients with classic effort angina previously reported by De Cesare et al. (24) from the same institution.

Conclusions. The results of our study indicate that despite the presence of an abnormal vasodilator capacity of the coronary microcirculation, epicardial coronary reactivity to nonendothelial-dependent vasoactive substances is normal in patients with syndrome X. Further studies to assess endothelial function in patients with this syndrome are necessary.

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