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Role of Adenosine in Pathogenesis of Syndrome X: Assessment With Coronary Hemodynamic Measurements and Thallium-201 Myocardial Single-Photon Emission Computed Tomography

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Objectives. **This study was performed 1) to examine the role of adenosine in the pathogenesis of syndrome X in patients with this syndrome and abnormal results on myocardial scintigrams during exercise, and 2) to determine the susceptibility to myocardial ischemia in this subset of patients with syndrome X.**

Background. **A role for adenosine in the pathogenesis of syndrome X has recently been postulated, but there are few clinical data supporting this hypothesis.**

Methods. **Exercise thallium-201 myocardial scintigraphy after intravenous administration of aminophylline, an adenosine receptor blocking agent, or saline solution and adenosine thallium-201 scintigraphy were performed in 26 patients with syndrome X. Hemodynamic variables during exercise and perfusion defect size after aminophylline and saline infusions were compared. At cardiac catheterization, coronary hemodynamic variables during separate infusions of adenosine and dobutamine were also examined and were compared among patients with abnormal or normal scintigrams and 10 control subjects.**

Results. **Perfusion abnormalities on exercise-thallium-201 scintigraphy occurred in 14 of 26 patients with syndrome X. Intravenous infusion of aminophylline suppressed the scintigraphic perfusion defect and prolonged the time to 1-mm ST segment depression in patients with syndrome X with abnormal exercise scintigrams. Intravenous infusion of adenosine induced a perfusion defect in the same myocardial area where the perfusion defect was observed at exercise in 7 of the 14 patients with syndrome X. At cardiac catheterization, patients with syndrome X with abnormal exercise scintigrams had lower coronary flow reserve and a greater frequency of myocardial lactate production and ST segment depression in response to the infusions of adenosine and dobutamine than did the other two groups. During adenosine infusion, great cardiac vein blood flow and oxygen content were significantly increased and myocardial oxygen consumption and lactate extraction were significantly reduced from baseline without a significant increase in rate-pressure product in this subset of patients with syndrome X.**

Conclusions. **Patients with syndrome X with abnormal exercise scintigrams have high susceptibility to myocardial ischemia during exercise or pharmacologic stress tests, probably owing to reduced coronary flow reserve. A heterogeneous response to endogenous adenosine may contribute to scintigraphic perfusion abnormalities and myocardial ischemia during exercise in this subset of patients with syndrome X.**

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Syndrome X comprises heterogeneous groups of patients with chest pain of cardiac or noncardiac origin (1–6). Recently a subgroup of patients with syndrome X—those whose syndrome is defined as chest pain, ST segment depression during exercise and normal coronary angiographic findings—has been studied (3–9) to evaluate whether the chest pain is due to myocardial ischemia. Several clinical studies (3–11) have proposed impaired coronary flow reserve as the pathogenesis of the syndrome in some of these patients and have demonstrated (12–14) perfusion abnormalities on thallium-201 myocardial scintigraphy in some. However, conclusive data on the mechanism or mechanisms responsible for myocardial ischemia in syndrome X have not been yet obtained.

Adenosine is endogenously released from myocardium during exercise or myocardial ischemia and acts as a vasodilator of resistance vessels (15–17). Adenosine is believed to provoke anginal pain (18,19) and even to produce myocardial ischemia during exercise or intravenous infusion in some patients with coronary artery disease (20–25). Several reports (5,26) suggest that adenosine may also be involved in the occurrence of chest pain and myocardial ischemia in syndrome X. However, there are few clinical data to prove a role of adenosine in syndrome X.

Thus, the aim of this study was to examine the susceptibility to myocardial ischemia in syndrome X in a subset of patients with abnormal findings on exercise scintigrams and to elucidate the role of adenosine in the pathophysiology of the syndrome

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Abbreviations and Acronyms
ECG = electrocardiogram
SPECT = single-photon emission computed tomography

in this subset. We therefore performed exercise thallium-201 single-photon emission computed tomography (SPECT) after administration of aminophylline, an adenosine receptor blocking agent, or 0.9% saline solution in 26 patients with syndrome X, and we compared measurements of hemodynamic variables during exercise and perfusion defect size obtained after infusion of aminophylline versus saline solution. Adenosine thallium-201 scintigraphy was also performed in these patients, and we compared the adenosine scintigraphic abnormalities with those on exercise scintigrams. Further, at cardiac catheterization, we measured coronary hemodynamic variables during infusion of adenosine and compared the results in the patients with abnormal and normal exercise scintigrams and in control subjects. We also measured coronary hemodynamic variables in the three groups during infusion of dobutamine, a relative $beta_1$-selective agonist that is often clinically used for pharmacologic stress testing as an alternative to exercise to stimulate cardiac oxygen demand.

Methods

Patients. Twenty-six consecutive patients (8 men and 18 women aged 39 to 76 years [mean 61]) with syndrome X (chest pain, ST segment depression during exercise and normal coronary arteriograms) and 10 control subjects (5 men and 5 women aged 41 to 75 years [mean 57]) were included in this study. All patients with syndrome X had positive exercise test findings for horizontal or downsloping ST segment depression ≥1 mm. Control subjects underwent diagnostic cardiac catheterization and exercise thallium-201 scintigraphy for evaluation of atypical chest pain. No control subject had chest pain or ST segment depression during exercise testing or abnormal findings on exercise scintigraphy. Coronary arteriograms in patients and control subjects showed no organic stenosis (>25%) in any coronary artery and showed no coronary artery spasm during provocative testing by intracoronary injection of acetylcholine (27). No patient or control subject had myocardial infarction, valvular heart disease, congenital malformation of the heart, cardiomyopathy and evidence of left ventricular hypertrophy or conduction defects that could interfere with interpretation of ST segment changes. Antianginal medications were discontinued >5 days before the study.

All participants gave written informed consent for inclusion in this study. This study protocol was in agreement with the guidelines of the ethical committee at our institution.

Thallium-201 myocardial scintigraphy in patients with syndrome X. *Exercise thallium-201 scintigraphy.* All patients with syndrome X underwent symptom-limited exercise thallium-201 scintigraphy just after intravenous administration of aminophylline (7 mg/kg body weight during 20 min) or 0.9% saline solution by way of a single-blind placebo-controlled protocol on different days; measurements of hemodynamic variables during exercise and perfusion defect size after aminophylline versus saline infusion were compared. The exercise test was performed with the patient upright on an electrically graded bicycle ergometer (380B, Siemens-Elema AB) with an initial work load of 25 W with 25-W increments every 3 min. A 12-lead electrocardiogram (ECG) and blood pressure were recorded at rest and during exercise. When anginal chest pain or exhaustion appeared, a bolus of 3 mCi of thallium-201 was injected through an indwelling intravenous infusion line and the patient was encouraged to continue exercising at the same level for 1 min more. Scintigraphic imaging began 5 min after completion of exercise and 4 h after the injection, as we (28,29) have previously described. The SPECT system used in this study consisted of a large field of view gamma camera with a general purpose, parallel hole collimator mounted on a gantry (GCA 7200A, Toshiba).

Adenosine thallium-201 scintigraphy. Adenosine thallium-201 myocardial scintigraphy was also performed on different days in all patients with syndrome X. Adenosine was infused through a peripheral vein at a rate of 50 μg/kg per min, followed by infusion at 75 and 100 μg/kg per min for 2 min each and finally 140 μg/kg per min, as previously reported (30,31). Three millicuries of thallium-201 was then injected at 3 min of the maximal infusion rate, and the maximal infusion rate was maintained for an additional ≥1 min after thallium-201 injection. Image acquisition began 5 min after injection in the manner described for the exercise scintigram. The infusion rate of adenosine was the same as that previously reported to be well tolerated and has been used for pharmacologic stress testing (30,31).

Quantitative analysis of defect size on the scintigram. The computerized thallium-201 tomographic method described in our previous reports (28,29) was used to quantify the size of the myocardial perfusion defect. An extent map of the defect was obtained by comparing normalized maximal count values for each point on the generated two-dimensional polar map with the corresponding lower normal limits at 2.0 SD below the mean value derived from 20 normal subjects. The extent polar map represents extent of count reduction, and the extent score for the size of perfusion defect was defined by calculating the number of points falling below the corresponding lower normal limits and by expressing this number as a percent of the total number of left ventricular points on the extent polar map. An extent of perfusion defect >5% of the total left ventricular area in the bull's-eye map was selected as the criterion for significant abnormality (32).

Measurement of coronary hemodynamic variables at cardiac catheterization in the patient and control groups. All patients and control subjects underwent cardiac catheterization with thermodilution measurement of great cardiac vein flow, in the manner previously reported (27), before and during intravenous adenosine or dobutamine infusion. Twelve ECG leads and arterial pressure were continuously monitored and recorded every minute to assess changes in ST segment

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depression and arterial pressure during the study. Blood samples were obtained from the aortic root and great cardiac vein and used to measure lactate concentration and oxygen saturation. Plasma lactate concentration was determined by an enzymatic method using determiner LA (Kyowa Medix, Tokyo, Japan). Myocardial lactate extraction ratio was calculated according to the formula: (Arterial lactate concentration − Venous lactate concentration) × 100/Arterial lactate concentration. Blood oxygen saturation was measured with an autoanalyzer (ABL-2, Radiometer, Copenhagen, Denmark), and myocardial oxygen consumption was calculated from the Fick equation: (Arterial oxygen content − Venous oxygen content) × Great cardiac vein blood flow. After baseline blood sampling and measurements of heart rate, blood pressure and great cardiac vein blood flow, adenosine was infused through the femoral vein at a rate of 50 μg/kg per min, followed by infusions at 75 and 100 μg/kg per min for 2 min each and finally at 140 μg/kg per min for 4 min in the same manner as performed during thallium-201 myocardial scintigraphy. During the last 1 min, coronary hemodynamic measurements and blood sampling were performed again.

Ten minutes after completion of the adenosine infusion (by which time coronary hemodynamic variables had returned to baseline levels), dobutamine was infused through the femoral vein at a rate of 5 μg/kg per min, followed by rates of 10 and 20 μg/kg per min for 3 min each and finally a rate of 30 μg/kg per min for 3 min. During the last 1 min, coronary hemodynamic measurements and blood sampling were performed again.

If chest pain or dyspnea associated with ST segment depression, serious arrhythmia or systolic blood pressure <80 or >250 mm Hg occurred before the maximal dose during each infusion, blood sampling and hemodynamic measurements were performed immediately, and thereafter the infusions were stopped.

Statistical analysis. Student paired *t* tests were used for intragroup comparison of coronary variables at baseline and at the end of the infusions. Unpaired *t* tests were used for intergroup comparison of exercise variables and scintigraphic defect size on exercise thallium-201 scintigraphy after aminophylline and after saline infusion between patients with abnormal and normal findings on exercise scintigrams. One-way analysis of variance was used to compare coronary hemodynamic variables at baseline and at the end of infusion among the three groups, and posthoc testing was performed with the Scheffé F test. Chi-square tests were used to compare the incidence of coronary risk factors and anginal pain and ST depression during each infusion of adenosine and dobutamine among the three groups. A p value <0.05 was considered statistically significant. Data are presented as mean value ± SD.

Results

Exercise-thallium-201 scintigraphy in patients with syndrome X. With saline infusion, a reversible perfusion defect appeared on exercise-thallium-201 scintigraphy in 14 of the 26 patients with syndrome X. The defect appeared in the anterior area in 8 of the 14 patients, in the posterior area in 4 and in both areas in 2. Chest pain occurred during exercise after saline infusion in six patients with normal results on exercise scintigraphy, in seven with abnormal results on exercise scintigraphy and in no control subject. The pain was significantly relieved during exercise after aminophylline infusion in all patients with syndrome X.

Table 1. Baseline Clinical Characteristics of Patients and Control Subjects

	Patients With Syndrome X		
	Abn Ex Scintigram (n = 14)	Norm Ex Scintigram (n = 12)	Control Subjects (n = 10)
Mean age (yr)	62 ± 12	61 ± 10	57 ± 12
Male	3 (23%)	4 (40%)	5 (50%)
Serum cholesterol (mg/ml)	179 ± 32	188 ± 31	196 ± 23
Systolic blood pressure (mm Hg)	135 ± 12	135 ± 20	138 ± 20
History of diabetes mellitus	0	0	1
Current smoker	5 (36%)	2 (17%)	4 (40%)

There were no significant differences among groups. Data presented are mean value ± SD or number (%) of patients. Abn Ex Scintigram = abnormal results on exercise scintigraphy; Norm Ex Scintigram = normal results on exercise scintigraphy.

Baseline clinical characteristics such as gender, age, smoking status, blood pressure, plasma levels of total cholesterol and incidence of diabetes mellitus were comparable in control subjects and the patients with abnormal and normal exercise thallium-201 scintigrams (Table 1). Values at rest for heart rate, systolic blood pressure and rate-pressure product after saline and aminophylline infusions were not significantly different between patients with abnormal and normal exercise scintigrams (Table 2). However, after saline infusion, values for heart rate and rate-pressure product at peak exercise were significantly higher in patients with normal than with abnormal exercise scintigrams. After aminophylline, these values were greater than those after saline infusion in both groups and did not differ significantly between groups. After saline infusion, the time to 1-mm ST depression during exercise was significantly shorter in patients with abnormal than with normal exercise scintigrams; the time to 1-mm ST depression was significantly greater after aminophylline infusion, than after saline infusion in the patients with abnormal exercise scintigrams but was unchanged in those with normal exercise scintigrams. The extent score of the perfusion defect was significantly lower after aminophylline than after saline infusion in the patients with abnormal exercise scintigrams (Fig. 1). The representative polar maps of myocardial distribution of thallium-201 during exercise are shown in Figure 2.

Adenosine thallium-201 myocardial scintigraphy in patients with syndrome X. Adenosine thallium-201 SPECT was also performed in all patients with syndrome X on a different

Table 2. Exercise Variables on Thallium-201 Myocardial Scintigraphy After Infusion of Saline Solution or Aminophylline in Patients With Syndrome X

	Rest			Peak Exercise			
Patient Group	HR	SBP	RPP	HR	SBP	RPP	Time to 1-mm ST ↓
Abn ex scintigram							
Saline	68 ± 10	135 ± 25	9,100 ± 1,900	124 ± 13	183 ± 27	22,400 ± 4,300	424 ± 162
Aminophylline	73 ± 10	130 ± 23	9,500 ± 2,300	135 ± 11 *	188 ± 30	27,500 ± 4,400 *	474 ± 147 *
Norm ex scintigram				*		*	*
Saline	66 ± 6	143 ± 21	9,600 ± 2,200	144 ± 20	207 ± 30	30,000 ± 7,200	542 ± 120
Aminophylline	76 ± 5	137 ± 17	9,900 ± 1,400	149 ± 23 *	211 ± 33	32,000 ± 8,000 *	552 ± 88 NS *

*$p < 0.05$. Data presented are mean value ± SD. HR = heart rate (beats/min); RPP = rate-pressure product (beats/min × mm Hg); SBP = systolic blood pressure (mm Hg); Time to 1-mm ST ↓ = exercise time to 1-mm ST segment depression; other abbreviations as in Table 1.

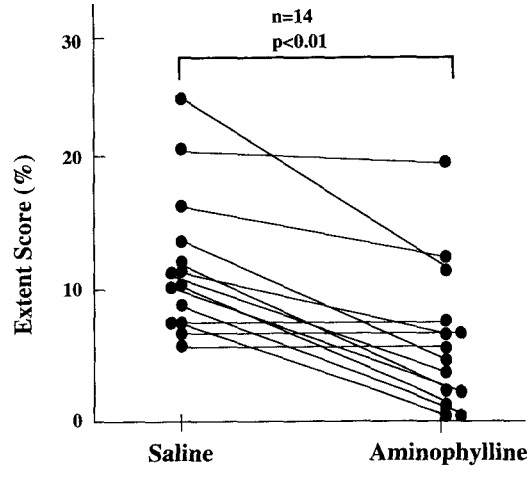
day within 2 weeks after exercise thallium-201 scintigraphy. It showed a reversible perfusion defect in 7 of the 14 patients with abnormal exercise scintigrams in the same myocardial region in which the defect appeared on the exercise scintigrams (Fig. 2); it showed no defect in any of the patients with normal exercise scintigrams. The extent score on adenosine thallium-201 scintigrams was not significantly different from that on exercise thallium-201 scintigrams after saline infusion.

Effects of adenosine and dobutamine infusions on coronary hemodynamic variables in patients with syndrome X and in control subjects (Table 3). The adenosine infusion was stopped at 100 μg/kg per min because of severe chest pain in one patient with syndrome X with normal exercise scintigrams and because of atrioventricular block in one patient with abnormal scintigrams and one control subject. All patients and control subjects tolerated the maximal dose of dobutamine. During adenosine infusion, chest pain occurred in 13 (93%) of the 14 patients with abnormal exercise scintigrams, in 11 (92%) of the 12 patients with normal exercise scintigrams and in 8 (80%) of the 10 control subjects. During dobutamine infusion, chest pain occurred in 5 (36%) of the 14 patients with abnormal exercise scintigrams, in 2 (17%) of the 12 patients with normal exercise scintigrams and in none of the 10 control subjects. The incidence of chest pain was not significantly different among the three groups during adenosine infusion, but it was significantly higher during dobutamine infusion in the patients with abnormal exercise scintigrams than in the control subjects ($p < 0.05$). ST segment depression during both infusions occurred more frequently in the patients with abnormal exercise scintigrams than in the remaining two groups (Fig. 3).

Heart rate was significantly increased, and systolic blood pressure was significantly decreased from baseline at the end of adenosine infusion in all three groups (Table 3). The rate-pressure product did not change significantly from baseline at the end of adenosine infusion in all three groups. Heart rate, systolic blood pressure and rate-pressure product increased significantly from baseline values at the end of dobutamine infusion in all three groups. Great cardiac vein blood flow increased significantly from baseline at the end of both infusions in all three groups, but the percent change in great cardiac vein blood flow at the end of the infusions was significantly lower in the patients with abnormal exercise scintigrams than in the other two groups (Fig. 4).

Oxygen content in great cardiac vein blood flow at the end of the infusions increased significantly from baseline in all three groups. Myocardial oxygen consumption during adenosine infusion was reduced from baseline in the patients with abnormal exercise scintigrams despite increased great cardiac vein blood flow, and the percent change in myocardial oxygen consumption from baseline after adenosine infusion was significantly less in the patients with abnormal exercise scintigrams than in the other two groups (Fig. 5). Myocardial oxygen consumption during dobutamine infusion increased from baseline in all three groups, but the percent change in myocardial oxygen consumption from baseline after dobutamine infusion was significantly less in the patients with abnormal exercise scintigrams than in the other groups. Myocardial lactate pro-

Figure 1. Comparison of the scintigraphic myocardial perfusion defect (extent score) during exercise between aminophylline and saline administrations in the 14 patients with syndrome X and abnormal exercise scintigrams. The extent score was significantly lower with aminophylline than with saline infusion (saline 12 ± 6% vs. aminophylline 6 ± 6%, $p < 0.01$).



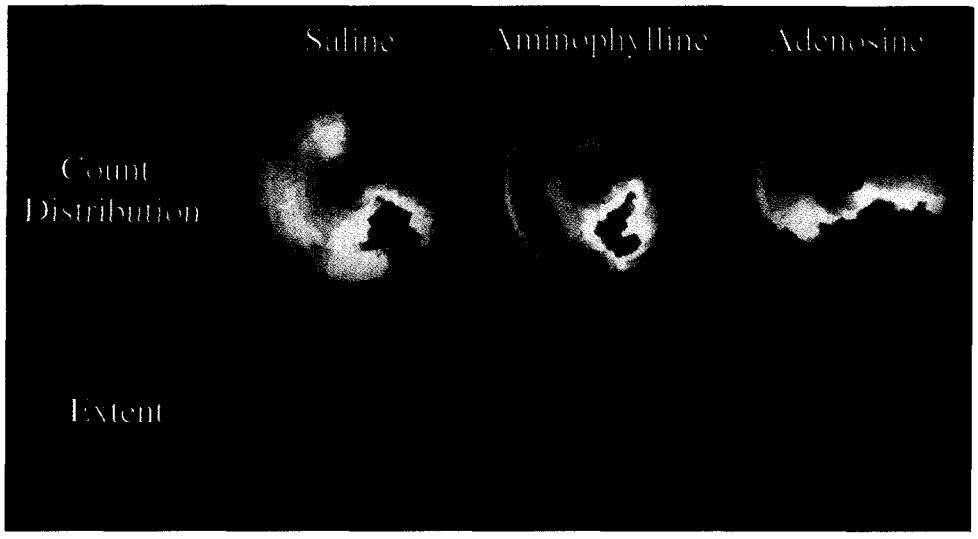


Figure 2. Polar representation of myocardial distribution of thallium-201 during exercise in combination with aminophylline or saline infusion and during adenosine infusions in one patient with syndrome X. Two-dimensional polar maps (**upper row**) represent three-dimensional myocardial count distribution on a scale ranging from **red** (high count) to **blue** (low count). The extent polar maps (**lower row**) represent binary maps on which points falling below the corresponding lower normal limits are shown as a **black region**, and the remaining points are shown as a **red region**.

duction occurred in 4 of the 14 patients with abnormal exercise scintigrams during adenosine infusion and in 4 of the 14 during dobutamine infusion, but it did not occur in any of the patients with normal exercise scintigrams or in control subjects. All four patients with myocardial lactate production during adenosine infusion had abnormal adenosine scintigrams, whereas three of four patients with myocardial lactate production during dobutamine infusion had abnormal exercise but normal adenosine scintigrams. Myocardial lactate extraction ratio significantly decreased from baseline after both infusions in all three groups (Table 3), but values after infusion were significantly lower in patients with abnormal than in those with normal exercise scintigrams or in control subjects.

Discussion

Susceptibility to myocardial ischemia in syndrome X. It is generally accepted that syndrome X encompasses several physiologic disease entities (1–6). Thus, it seems to be clinically important to determine whether the chest pain and ECG changes in individual patients with syndrome X are a consequence of myocardial ischemia. In this study, myocardial perfusion abnormalities in exercise thallium-201 scintigrams appeared in a high proportion of patients with syndrome X. An exercise thallium-201 perfusion defect indicates the presence of myocardial blood flow heterogeneity and does not always mean myocardial ischemia. However, myocardial lactate pro-

Table 3. Effect of Adenosine and Dobutamine Infusion on Coronary Hemodynamic and Metabolic Variables at Cardiac Catheterization in Patients With Syndrome X and Control Subjects

	HR (beats/min)	SBP (mm Hg)	RPP (beats/min × mm Hg × 10^{-2})	GCVF (ml/min)	O_2 Content (vol %)	$\dot{V}O_2$ (ml/O_2 per min)	LER (%)
Control subjects							
Baseline	75 ± 12	159 ± 38	119 ± 30	93 ± 29	5.4 ± 1.2	9.3 ± 2.4	38 ± 10
Adenosine	90 ± 17*	146 ± 43*	132 ± 47	266 ± 73*	11.4 ± 1.2*	10.2 ± 3.4	18 ± 8*
Dobutamine	121 ± 14*	192 ± 30*	219 ± 42*	243 ± 67*	8.1 ± 0.6*	17.1 ± 6.5*	17 ± 13*
Patients							
Norm ex scintigram							
Baseline	74 ± 13	158 ± 35	117 ± 30	85 ± 17	5.0 ± 0.9	8.5 ± 2.8	37 ± 15
Adenosine	88 ± 17*	148 ± 33*	131 ± 38	261 ± 74*	11.5 ± 1.3*	10.5 ± 4.6	16 ± 13*
Dobutamine	115 ± 19*	187 ± 44*	197 ± 59*	222 ± 86*	7.1 ± 1.4*	18.4 ± 6.7*	17 ± 11*
Abn ex scintigram							
Baseline	74 ± 13	153 ± 29	113 ± 31	91 ± 16	5.4 ± 0.9	10.3 ± 3.0	32 ± 12
Adenosine	85 ± 13*	142 ± 31*	128 ± 31	204 ± 52*	12.3 ± 0.9*	7.9 ± 2.4*	3 ± 9*†
Dobutamine	111 ± 19*	197 ± 54*	191 ± 33*	179 ± 66*	7.9 ± 1.0*	15.2 ± 5.4*	5 ± 10*†

*$p < 0.01$ versus respective baseline values. †$p < 0.01$ versus patients with normal results on exercise scintigraphy and control subjects. GCVF = great cardiac vein blood flow; LER = myocardial lactate extraction ratio; O_2 content = oxygen content in great cardiac vein; $\dot{V}O_2$ = myocardial oxygen consumption; other abbreviations as in Tables 1 and 2.

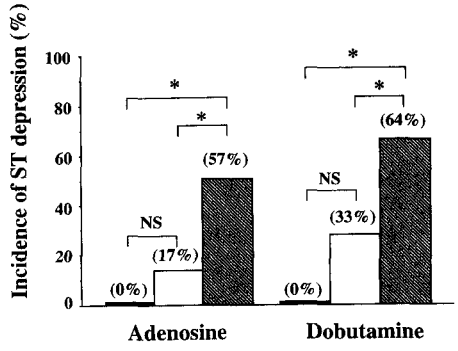


Figure 3. Incidence of ST segment depression during adenosine and dobutamine infusions in patients with syndrome X and normal (**open bars**) or abnormal (**hatched bars**) results on exercise scintigraphy and in control subjects (**solid bars**). *$p < 0.05$.

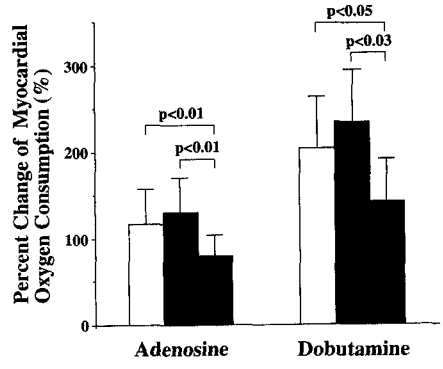
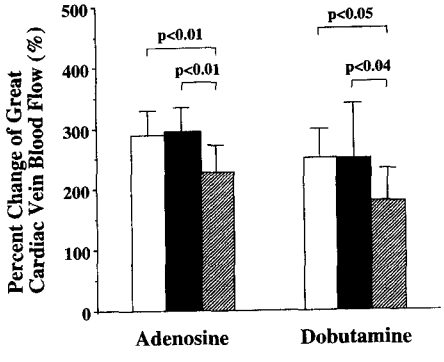


Figure 5. Percent change in myocardial oxygen consumption during adenosine and dobutamine infusions in patients with syndrome X and normal or abnormal results on exercise scintigraphy and in control subjects. Symbols as in Figure 4.

duction occurred during adenosine and dobutamine infusions in some patients with abnormal exercise scintigrams but in no control subject or patient with normal exercise scintigrams. Further, the incidence of ST segment depression during the infusions was higher in the patients with abnormal than with normal exercise scintigrams. The results suggest that patients with syndrome X with abnormal exercise scintigrams may have a greater susceptibility to myocardial ischemia in response to exercise or pharmacologic stress testing.

Myocardial ischemia in some patients with syndrome X has been postulated to be caused by abnormalities in the function of small coronary artery vessels (3–11). The present study showed that increases in great cardiac vein blood flow in response not only to adenosine but also to dobutamine, an inotropic agent, were lower in the patients with abnormal than with normal exercise scintigrams or in control subjects, suggesting that the abnormalities in coronary flow reserve may have contributed to the high incidence of myocardial ischemia and scintigraphic abnormalities in response to exercise or pharmacologic stress testing in the patients with abnormal exercise scintigrams.

Figure 4. Percent changes in great cardiac vein blood flow during adenosine and dobutamine infusions in patients with syndrome X and normal (**solid bars**) or abnormal results (**hatched bars**) on exercise scintigraphy and in control subjects (**open bars**).



Possible role of adenosine in syndrome X. The present study also showed that 1) aminophylline, an adenosine receptor blocking agent, reduced exercise-induced myocardial perfusion defect and prolonged the time to 1-mm ST depression in the patients with abnormal exercise scintigrams, and 2) that adenosine infusion produced a perfusion defect in the same myocardial region where the exercise-induced scintigraphic perfusion defect had been observed. Further, as described earlier, coronary flow reserve in response to adenosine was impaired in the patients with abnormal exercise scintigrams, and lactate production occurred during adenosine infusion in some of them. These results suggest that the heterogeneous response of coronary blood flow to adenosine may result in a perfusion defect and myocardial ischemia during both adenosine infusion and exercise.

It is notable that adenosine infusion induced myocardial lactate production in some patients with abnormal exercise scintigrams despite no significant change in rate-pressure product, an indicator of myocardial oxygen demand. However, during the infusion, great cardiac vein blood flow was significantly increased from baseline, great cardiac vein oxygen content was significantly high and myocardial oxygen consumption and lactate utilization were reduced in these patients. These findings suggest that patients with abnormal exercise scintigrams may possibly have myocardial blood "shunting," leading to myocardial ischemia. It has been demonstrated in some experimental and even clinical studies (23–26,33–36) that adenosine could induce myocardial blood flow shunting. Thus, one could speculate that coronary blood flow shunting around the scintigraphic perfusion defect area may have occurred during adenosine infusion, resulting in myocardial ischemia in the patients with abnormal exercise scintigrams.

In the present study, aminophylline did not completely lessen the extent of perfusion defect and ST depression, and adenosine did not always induce a perfusion defect and lactate production in patients with abnormal exercise scintigrams. Physiologic stress such as exercise has been shown to cause beta-adrenergic stimulation and endogenous release of aden-

osine, which concomitantly increase blood flow in the normal myocardial area (37), but the present dobutamine study suggests that the increase in blood flow in response to beta-adrenergic stimulation may also be blunted in the patients with abnormal exercise scintigrams. This abnormal vasodilator response to beta-adrenergic stimulation may intensify maldistribution of myocardial blood flow, leading to higher frequency of scintigraphic perfusion abnormalities during exercise than during adenosine infusion in the patients with abnormal exercise scintigrams. Previous findings showed that coronary blood flow reserve is reduced in response not only to adenosine but also to other vasodilators such as papaverine or acetylcholine (5,6,11). The present data indicate that patients with syndrome X may have a reduced response to beta-adrenergic stimulations as well as to vasodilators.

Conclusions. We conclude that 1) patients with syndrome X with abnormal exercise scintigrams have a high susceptibility to myocardial ischemia during exercise or pharmacologic stress tests, probably owing to reduced coronary flow reserve, and 2) endogenous adenosine may be involved in the origin of scintigraphic perfusion abnormalities and myocardial ischemia during exercise in this subset of patients with syndrome X.

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