Four-Year Follow-up Study in Patients With Angina Pectoris and Normal Coronary Arteriograms ("Syndrome X")

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In patients with typical stress-induced anginal pain, normal coronary arteries, and unimpaired left ventricular performance at rest ("syndrome X"), a reduced coronary dilatory capacity, abnormal lactate metabolism during stress, and reduction of left ventricular functional reserve have been described. A group of 40 patients with syndrome X was followed for several years to determine their long-term prognosis. In 27 patients pulmonary artery pressure and in 19 patients left ventricular ejection fraction were reassessed during rest and exercise approximately 4 years after the initial examination. In patients with stress-induced ST-segment depression, these variables did not change during the observation period. In patients with constant or rate-dependent left bundle branch block, however, there was significant deterioration of left ventricular performance during rest (pulmonary artery mean pressure, 16±3 vs. 17±4 mm Hg, p=NS; left ventricular ejection fraction, 62±5% vs. 55±5%, p<0.05) and exercise (pulmonary artery, 30±6 vs. 39±10 mm Hg, p<0.005; left ventricular ejection fraction, 59±6% vs. 49±5%, p<0.01). These findings suggest that in syndrome X two subgroups with distinctly different prognoses may be defined: In patients with stress-induced ST-segment depression during exercise, left ventricular performance remains well preserved; however, in patients with either constant or rate-dependent left bundle branch block, there is significant deterioration of left ventricular function within several years. (Circulation 1989;80:1610–1616)

In recent years, several studies have defined a syndrome that has been named "angina pectoris syndrome with normal coronary arteriogram," or "syndrome X." Typically, patients afflicted with this syndrome complain about stress-induced angina pectoris, and their electrocardiograms show corresponding ST-segment depression during exercise.

However, angiography is unable to demonstrate significant coronary artery luminal narrowing, and left ventricular (LV) performance at rest remains remarkably unimpaired.\(^1\)\(^\text{10}\) A previous study examined the results of endomyocardial biopsies, coronary dilatory capacity, and myocardial lactate metabolism in these patients.\(^1\)\(^\text{11}\) In the present study, a group of such patients was followed for several years to assess the late course of LV performance.

Methods

Control Examination of Patients With Angina but Normal Coronary Arteriograms (Syndrome X)

This group consisted of 40 patients (30 men, 10 women) with a chief complaint of typical stress-induced angina pectoris that was rapidly relieved by nitroglycerin. Patients with valvular heart disease, diabetes mellitus, hypertension, connective tissue disease, or congestive cardiomyopathy were excluded from the study group. It was suspected that patients who had syndrome X associated with left bundle branch block might constitute a separate, distinctive entity. Therefore, two subgroups were created on the basis of the electrocardiogram: group A comprised 25 patients with normal resting electrocardiogram and stress-induced ST-segment depression, and group B consisted of 15 patients with left bundle branch block or rate-dependent left bundle branch block.

The control group of 12 patients (eight men, four women) were referred for evaluation of atypical chest pain. They had normal exercise electrocardiogram, and coronary artery disease could be ruled out by cardiac catheterization.
TABLE 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>LVEDP (mm Hg)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>LV-EF (%)</th>
<th>CBF (ml/100 g×min)</th>
<th>CR (mm Hg/ml/100 g×min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n=12)</td>
<td>6.8±2.7</td>
<td>74±19.7</td>
<td>20±5.7</td>
<td>72±3.5</td>
<td>78±9.0</td>
<td>301±64</td>
</tr>
<tr>
<td>Syndrome X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
<td>Dipyrid</td>
</tr>
<tr>
<td>Group A (n=25)</td>
<td>9.6±3.2*</td>
<td>74±22.8</td>
<td>21±8.1</td>
<td>72±4.8</td>
<td>79±12.4</td>
<td>154±48.7†</td>
</tr>
<tr>
<td>Group B (n=15)</td>
<td>8.2±2.6</td>
<td>75±19.3</td>
<td>24±11.3</td>
<td>68±6.8</td>
<td>77±18.1</td>
<td>149±55.5†</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. Significantly different compared with the control group: *p<0.05, †p<0.001.

Coronary arteriography. Selective coronary angiography was performed with multiple projections of the right (at least three projections) and left (at least five, including hemiaxial projections) coronary arteries. LV volumes and ejection fraction (LV-EF) were calculated from the LV angiogram obtained in a 30° right anterior oblique projection. At control examination coronary blood flow was determined by the argon method at rest and after maximal vasodilation by dipyridamole (0.5 mg/kg i.v.).

Exercise electrocardiogram (n=40). A 12-lead standard electrocardiogram was obtained at rest and during maximal, symptom-limited exercise on a bicycle ergometer. ST-segment depression was measured 0.08 seconds after the J point; 1.5-mm ST-segment depression was defined as a positive result.

Echocardiography (n=21). Echocardiographic data were obtained in the standard way in 21 patients. In patients with left bundle branch block, no end-systolic dimensions were measured.

Pulmonary artery pressure (n=27). Pulmonary artery pressures were obtained by flow-directed, balloon-tipped catheters (Swan-Ganz catheter) during rest and maximal, supine exercise.

Gated blood pool scintigraphy (n=19). LV-EF was determined simultaneously by gated blood pool scintigraphy after application of autologous erythrocytes labeled with 25 mCi 99mTc.

Follow-up Examination

Patients were followed for a mean of 48±14 months. Severity of anginal pain was compared with the control examination. Stress testing, including exercise electrocardiogram (n=40), measurement of pulmonary artery pressure (n=27), and gated blood pool scintigraphy (n=19), was repeated under identical conditions as the control examination. In six patients in group B, in whom LV performance had deteriorated during the observation period, coronary and LV angiography were also obtained as the follow-up examination.

Statistics

Data were examined for statistical significance by Student’s t test for unpaired data, Mann-Whitney U test, or by analysis of variance (Schéffe).

Results

Control Examination

The average age of patients with syndrome X was 47.8±7.2 years; in the control group, it was 46.9±6.3 years (p=NS).

Coronary and left ventricular angiography, coronary blood flow (Table I). All patients included in the study group were totally free of angiographically detectable coronary artery disease. LV volumes were similar in all study groups. The LV end-diastolic pressure in group A, however, was slightly elevated compared with the control group (9.6±3.2 vs. 6.8±2.7 mm Hg, p<0.05). Under resting conditions, coronary blood flow was similar in all groups, but during maximal vasodilation with dipyridamole, it was significantly reduced in all patients with syndrome X (p<0.001). The corresponding minimal coronary resistance was significantly elevated in these patients compared with the control group (p<0.001).

Electrocardiogram (Table 2). The resting electrocardiogram was normal in the majority of patients with syndrome X (n=33); left bundle branch block was present in seven patients. During stress testing (133±30 W), there was significant ST-segment depression (0.15 mV or greater) in the left precordial lead in 20 patients. Five patients were unable to complete the test because of disabling anginal pain. In eight patients, a rate-dependent left bundle branch block developed during exercise.

Echocardiography (Figure 1). End-diastolic dimensions (EDD) were within normal limits in both

<table>
<thead>
<tr>
<th>Control study (n)</th>
<th>Follow-up (n)</th>
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<tbody>
<tr>
<td>Echocardiogram at rest</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Stress test</td>
<td>ST&lt;0.15 mV</td>
</tr>
<tr>
<td>ST≥0.15 mV</td>
<td>20</td>
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<tr>
<td>LBBB</td>
<td>15</td>
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LBBB, left bundle branch block; ST, ST-segment depression.
groups (group A, n=13, 51.0±3.3 mm; group B, n=8, 53.0±6.2 mm; p=NS).

**Pulmonary artery pressure** (Table 3, Figure 2). In group A, mean pulmonary artery pressure rose from 14±2 mm Hg at rest to 24±5 mm Hg during exercise. In group B, the corresponding values were 16±3 versus 30±6 mm Hg (significantly different compared with group A, p<0.001). Cardiac output was similar in both groups.

**Gated blood pool scintigraphy** (Table 3, Figure 3). In group A, resting LV-EF was 63±5% with no significant difference detected compared with the control group (65±6%). In the normal control group, LV-EF increased by 11±3% during maximal exercise. Such an increase, however, was not observed in either group A (63±5% vs. 65±8%; p=NS) or group B (62±5% vs. 59±6%; p=NS).

**Follow-up Examination**

The follow-up examination was performed approximately 4 years after the control examination.

**Clinical status.** Functional capacity was unchanged in 31 patients with syndrome X. Deterioration in symptoms by one or two degrees was reported by a total of nine patients (two in group A, seven in group B).

**Electrocardiogram** (Table 2). No significant change was observed in group A. In group B, rate-dependent left bundle branch block had progressed to constant left bundle branch block in five patients, increasing the number of patients with constant left bundle branch block from seven at control to 12 at follow-up. Only three patients continued to develop rate-dependent block during exercise.

**Echocardiography** (Figure 1). In group A, LV-EDD remained stable (51.0±3.3 vs. 51.6±3.6 mm), whereas in group B, it increased significantly (53.0±6.2 vs. 58.3±5.8 mm; p<0.05).

**Pulmonary artery pressure** (Table 3, n=27). In group A, pulmonary artery pressure during rest (14±3 mm Hg) and exercise (25±10 mm Hg) was unchanged from control examination (Figure 2). In group B, resting pulmonary artery pressure (17±4 mm Hg) had not changed significantly from control values (16±3 mm Hg, p=NS). However, there was a significant increase during maximal exercise (control 30±6 mm Hg, follow-up 39±10 mm Hg, p<0.05). At follow-up, pulmonary artery pressures in group B were significantly higher than in group A (p<0.001, Figure 2).

**Gated blood pool scintigraphy** (Table 3, n=19). In group A, LV-EF during rest (63±6%) and exercise (64±7%) was not significantly different from control examination (Figure 3). In group B, resting LV-EF had decreased from 62±5% to 55±5%, which was significantly different from the normal control group (p<0.01). During exercise, the LV-EF profile was clearly abnormal in every one of these patients, and a highly significant reduction from 55±5% to 49±5% (p<0.001) was observed. At follow-up, group B differed significantly from group A (p<0.001, Figure 3).

**Coronary and left ventricular angiography** (Figure 4, n=6). In six patients with syndrome X in whom there was obvious deterioration of LV performance during the observation period, coronary and LV angiography was repeated to rule out treatable cause; all of these patients belonged to group B. The average time interval from control examination was 51 months. No coronary artery disease had developed in any of these patients. However, end-diastolic volume had increased from 140±42 ml to 176±54 ml (p<0.05) and end-systolic volume from 46±23 ml to 95±23 ml (p<0.05), whereas LV-EF had deteriorated from 68±10% to 49±15% (p<0.005). In one patient, a second endomyocardial biopsy could be obtained, which showed a decrease of intracellular myofibril volume fraction from 57% to 45%. These patients received antiangiinal medication such as nitroglycerin and calcium blocking agents; none had experienced myocardial infarction during the observation period.

**Discussion**

Angina pectoris with normal coronary arteries is not an infrequent symptom in patients with arterial hypertension, valvular heart disease, dilated cardiomyopathy, or collagen disease with involvement of small intramyocardial vessels. Moreover, angina pectoris may also occur in normotensive patients in whom coronary artery disease has been ruled out by angiography and no associated heart disease has
been detected. In the literature this condition is known as syndrome X.1-11

The present study deals with a group of patients who presented with typical angina pectoris on exertion. In 33 patients, the initial resting electrocardiogram was within normal limits; in seven patients, there was left bundle branch block. During stress testing, eight additional patients developed rate-dependent left bundle branch block, whereas significant ST-segment depression occurred in patients without conduction block. Angiographically, all of these patients were found to be entirely free of coronary artery disease. To investigate the origin of their chest pain, several additional studies were performed, facilitating a more accurate definition of this particular group.10,11

First, myocardial blood flow was normal under resting conditions. However, the increase observed following vasodilation by dipyridamole was severely impaired; only 50% of the maximal myocardial blood flow observed in a normal control group was achieved in this group of patients.

Second, myocardial lactate uptake was studied in five patients of group B. It was found to be normal under resting conditions, but significant lactate production occurred during rapid atrial pacing, a finding well known from patients with obstructive coronary artery disease.11
Third, there was significant impairment of LV contractile reserve, as demonstrated by gated blood pool scintigraphy during rest and exercise.

Fourth, intramyocardial vessels were found to be normal in endomyocardial biopsies taken from the left ventricle in 18 patients of groups A and B, as described previously. No structural abnormality of the myocardiocytes could be demonstrated, with the exception of extensive mitochondrial swelling frequently associated with myelin figures. These findings were distinctly different from changes observed in dilated cardiomyopathy.

Several recent studies lend support to these findings: An abnormal vasodilator reserve in patients fitting our definition was demonstrated by Cannon et al., Greenberg et al., and others. In several reports, many of such patients were found to have a positive exercise electrocardiogram or an abnormal lactate metabolism during infusion of isoproterenol or atrial pacing. An impaired LV contractile reserve during exercise was detected by gated blood pool scintigraphy. All of these studies indicate that myocardial ischemia may be the underlying pathophysiologic mechanism despite normal epicardial coronary arteries.

With respect to the fate of these patients, it is generally accepted that their clinical course is favorable although no long-term studies are available in patients in whom coronary dilatory reserve has been measured. The purpose of the present study was to reexamine these patients after several years in order to assess the time course of LV performance. The results obtained after 4 years...
allow definition of two groups based on the presence of constant or rate-dependent left bundle branch block: Group A patients have syndrome X and stress-induced ST-segment depression, and group B patients have syndrome X and left bundle branch block.

At control examination, the two groups were indistinguishable with respect to their clinical status and LV functional reserve. In their subsequent course, however, they demonstrated considerable differences: Group A remained fairly stable over several years with no detectable impairment of LV functional reserve as determined by stress testing. In contrast, group B developed significant LV dysfunction, and LV performance at rest as well as during exercise was markedly compromised. These findings were confirmed by repeat angiography in six of the patients.

**Problems of Study**

Previously, Bramlet et al studied the effect of rate-dependent left bundle branch block on LV-EF. During exercise, the onset of the conduction defect may be associated with an abrupt decrease in LV performance, which cannot be attributed to myocardial ischemia or global LV dysfunction.\(^{30}\) Even in the presence of constant left bundle branch block, LV performance may be interfered with by the conduction defect itself. These facts must be taken into account when interpreting the results of stress testing in patients with left bundle branch block. At control examination eight patients in group B developed rate-dependent block during exercise, which may in part be responsible for the abnormal results. At follow-up, in all but three patients constant left bundle branch block was present; these three patients continued to develop rate dependent block during exercise. The results of stress testing (i.e., pulmonary artery pressure and LV-EF) were not changed appreciably if these patients were excluded from the data analysis. If it is assumed that LV dysfunction in patients with left bundle branch block is entirely caused by the conduction defect, it is still difficult to account for the deterioration of LV performance over time in patients with constant left bundle branch block at control and follow-up. In these patients, no change was noted in the electrocardiographic bundle branch block pattern, which might be interpreted as worsening of the conduction defect.

**Clinical Implications**

The results of this study suggest that not all patients with syndrome X belong to a homogeneous group with an essentially favorable long-term course. On the basis of electrocardiographic findings, it is possible to identify one subgroup, characterized by a left bundle branch block pattern, which is at considerable risk to develop LV dysfunction over the years. Retrospectively, these patients showed signs of a latent cardiomyopathy at the control examination.

**References**


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**TABLE 4.** Myocardial Lactate Uptake in Five Group B Patients

<table>
<thead>
<tr>
<th>Electrocardiogram</th>
<th>Lactate uptake ((\mu)mol/100 g/min)</th>
<th>Patient</th>
<th>Rest</th>
<th>Ex</th>
<th>Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>14</td>
<td>Normal</td>
<td>13.0</td>
<td>-21.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>Normal</td>
<td>5.3</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>Normal</td>
<td>5.6</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>LBBB</td>
<td>5.6</td>
<td>0.0</td>
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<tr>
<td></td>
<td></td>
<td>27</td>
<td>LBBB</td>
<td>32.5</td>
<td>-14.6</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td>11.7±12.3</td>
<td>-17.3±22.7</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>

LBBB, left bundle branch block.

KEY WORDS · angina · coronary vessels · bundle branch block · exercise · electrocardiography
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