Acute Effects of Nitrates on Exercise Testing in Patients With Syndrome X
Clinical and Pathophysiological Implications

Gaetano Antonio Lanza, MD; Alessandro Manzoli, MD; Elena Bia, MD; Filippo Crea, MD; Attilio Maseri, MD

Background Sublingual nitrates are much more effective in relieving angina pectoris in patients with coronary artery disease than in patients with syndrome X, but it is not known whether their effect on exercise tolerance is also different in these two groups of patients.

Methods and Results Treadmill exercise testing was performed before and after administration of sublingual isosorbide dinitrate (ISDN, 5 mg) in 18 patients with syndrome X (effort angina and normal coronaries, group X) and in 33 patients with documented coronary artery disease (group C). As a selection criterion, all patients had ST-segment depression ≥1 mm on the control exercise test. Compared with the control test, the main differences in the two groups observed during the exercise test after administration of ISDN were (1) heart rate at 1-mm ST-segment depression was higher (126±25 versus 104±15 beats per minute [bpm], P<.01) in group C, whereas it was not different (125±15 versus 126±16 beats per minute) in group X; (2) the rate-pressure product at 1-mm ST-segment depression, the time to 1-mm ST-segment depression, and the exercise duration were significantly improved in group C (P<.01 for all) but were worsened in group X (18 047±4159 versus 20 535±4507 bpm · mm Hg, P=.014; 268±312 versus 429±214 seconds, P<.01; 494±279 versus 622±194 seconds, P=.013, respectively); (3) a normalization of the ECG (no ST-segment depression) was obtained in 10 patients (30%) of group C but in only 1 (5%) of group X (P<.01); (4) angina was prevented in 10 of 19 patients of group C but in no patient of group X (P<.01).

Conclusions In patients presenting with anginal chest pain, the effects of sublingual nitrates on exercise testing appear to be clinically useful to distinguish patients with coronary artery stenoses from patients with syndrome X. Indeed, worsening of exercise tolerance is highly predictive of normal coronary arteries. Furthermore, the failure of nitrates to improve exercise tolerance in patients with syndrome X suggests that a deficiency in coronary prearteriolar nitric oxide production is unlikely to play a key role in the pathophysiology of the syndrome. (Circulation. 1994;90:2695-2700.)

Key Words • nitrates • syndrome X • exercise • tests

Syndrome X is diagnosed in patients with effort angina and ST-segment depression on the exercise ECG who are found to have normal epicardial coronary arteries at angiography.1,2 Myocardial ischemia caused by abnormalities in the function of small coronary arterial vessels has been hypothesized to be the cause of the syndrome.2,3 Indeed, a reduced coronary flow reserve, as indicated by an impaired response to vasodilator stimuli, has been demonstrated in a group of such patients,3-5 although the mechanism(s) of the microvascular abnormality are not known for the moment.

Chest pain in patients with syndrome X is often indistinguishable from that occurring in patients with stable angina and atherosclerotic coronary disease.6 Also, the accurate analysis of noninvasive tests such as ECG exercise testing,7-9 Holter monitoring,10 and radionuclide techniques11-13 does not allow a reliable prediction of coronary stenosis in patients coming to medical attention because of effort anginal pain.

It is well known that the acute administration of sublingual nitrates is highly effective in both relieving and preventing chest pain in patients with coronary artery disease. Furthermore, sublingual nitrates also have powerful effects on angina and ECG signs of myocardial ischemia induced by exercise testing in these patients.14 Conversely, several anamnestic and epidemiological studies have reported that sublingual nitrates promptly relieve chest pain in no more than 40% to 50% of patients with syndrome X.15-16 Moreover, possible detrimental effects of sublingual or intracoronary administration of isosorbide dinitrate (ISDN) have recently been found in a study.17

The present study aimed to evaluate the effects of the acute administration of nitrates on ECG changes and symptoms induced by exercise stress test in a carefully selected group of patients with syndrome X. We also compared the effects of nitrates on exercise testing in these patients and in a group of patients with stable angina and coronary artery stenoses in order to evaluate whether they can be useful in distinguishing between the two groups. Furthermore, the study of the effects of nitrates on exercise testing also could provide valuable information about the pathophysiological mechanisms of the microvascular dysfunction in syndrome X.

Methods

Patients

The main general data of patients are summarized in Table 1.
Table 1. Main Clinical Data of Patients

<table>
<thead>
<tr>
<th></th>
<th>Group X</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/14</td>
<td>25/8</td>
</tr>
<tr>
<td>Age (mean±SD), y</td>
<td>56±8</td>
<td>60±9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5 (28%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>12 (36%)</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Vessel disease</td>
<td></td>
<td>10 (30%)</td>
</tr>
<tr>
<td>2-Vessel disease</td>
<td></td>
<td>14 (43%)</td>
</tr>
<tr>
<td>3-Vessel disease</td>
<td></td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Left main disease</td>
<td></td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Group X indicates patients with syndrome X (effort angina and normal coronaries); group C, patients with documented coronary artery disease.

Patients With Syndrome X (Group X)

Eighteen patients (4 men, 14 women; age, 56±8 years) were included in this group. The diagnosis of syndrome X was based on the presence of strict criteria, including typical effort angina, reproducible ST-segment depression on exercise testing, and totally normal coronary arteries at angiography, which was performed within 1 month of the study. Other cardiac or systemic diseases were excluded by full clinical and laboratory investigations. No patient had a history of hypertension, diabetes, or glucose intolerance. Five patients (28%) had increased blood cholesterol levels (between 220 and 280 mg/dL); the ECG at rest showed no alterations that could interfere with the interpretation of ST-segment changes, and left ventricular hypertrophy was also excluded by echocardiography. Eight patients (44%) had occasional episodes of angina at rest. Intravenous ergonovine maleate (50+100+200 µg) caused no evidence of myocardial ischemia in any patient. Exercise 201Tlc myocardial scintigraphy and/or 99mTc angioscintigraphy were performed in 15 patients and showed abnormal findings in 13 and doubtful results in 2. Patients were studied either off therapy or after discontinuing active drugs for at least 48 hours.

Patients With Coronary Artery Disease (Group C)

Thirty-three patients (25 men, 8 women; age, 60±9 years) with stable effort angina, ST-segment depression during exercise testing, and significant coronary stenosis at angiography were included in this group. Twelve patients (36%) had a previous myocardial infarction (>3 months) and 9 (27%) had a history of mild hypertension. All patients had significant coronary stenosis (≥75% reduction of lumen diameter) in at least one main coronary artery: 10 patients had one-vessel disease, 14 two-vessel disease, 8 three-vessel disease, and 1 patient had a left main coronary stenosis. No patient had ECG alterations that could interfere with the interpretation of ST-segment changes. Therapy was discontinued in the 48 hours before the study in patients taking active drugs.

ECG Stress Test

All treadmill exercise tests were performed in the morning, according to a symptom-limited Bruce or modified Bruce protocol. The Bruce protocol was used in 5 patients of group X (28%) and 8 of group C (24%). Three ECG leads (V1, aVF, and V6) were continuously monitored during the test, and up-to-date averaged QRS complexes of all ECG leads were continuously displayed on the screen. A standard 12-lead ECG was printed and blood pressure measured by a cuff manometer at the onset of the test, at the end of each stage, and at peak exercise as well as at 1-mm ST-segment depression, when chest pain occurred, and when it was clinically indicated. Several 12-lead ECG ST-segment strips were printed when ST-segment depression started to appear on the screen in order to time exactly when 1-mm ST-segment depression occurred. A recovery time was allowed of either 7 minutes or until ST-segment normalization was achieved, with ECG and blood pressure being recorded every minute.

The exercise test was terminated when one or more of the following end points were reached: (1) physical exhaustion; (2) progressive angina; (3) ST-segment depression ≥3 mm; and (4) the occurrence of other harmful conditions such as hypotension, severe arrhythmia, and dyspnea. Myocardial ischemia was diagnosed when a horizontal or downsloping ST-segment depression of 1 mm at 0.08 seconds from the J-point was observed in at least one lead.

All patients needed to have a positive basal exercise stress test to be included in the study. The test was repeated in the same session after sublingual administration of 5 mg of ISDN. The second test was started after 30 minutes from both ST-segment normalization and return of heart rate and blood pressure to basal values and 5 minutes after the complete sublingual absorption of the drug. The same type of protocol (Bruce or modified Bruce) was used in each patient. The ECG strips of both tests were evaluated independently in a blind fashion by two cardiologists; in case of disagreement, the matter was resolved by consensus.

To evaluate the response to ISDN of each patient, we compared the duration of exercise, the time to 1-mm ST-segment depression, the time to angina, and the rate-pressure product (heart rate · systolic blood pressure) at both 1-mm ST-segment depression and at angina observed on the two tests of each patient. The values at the peak of exercise were used for statistical analysis when ST-segment depression and/or angina did not occur during the second exercise test.

The following criteria were fixed in order to judge the effects of ISDN on the exercise variables: (1) the time to 1-mm ST-segment depression, the time to angina, and the duration of exercise were considered improved when they were prolonged by at least 120 seconds, whereas they were judged to be worse when they were decreased by 60 seconds or more compared with the control exercise test; (2) the rate-pressure product at 1-mm ST-segment depression and rate-pressure product at angina were considered to be improved when they were increased by ≥2500 bpm · mm Hg compared with the basal value, whereas they were considered worsened when they were decreased by ≤2500 bpm · mm Hg compared with the basal value.

The effect of ISDN on the exercise stress test was considered to be negligible (that is, to have no effect) in the case of intermediate values. All the parameters of exercise testing were considered improved after ISDN if there was no ST-segment depression on the ECG and the test had to be stopped because of exhaustion, in the absence of any symptoms.

Statistics

The comparison of continuous variables within groups was made with a paired t test when they showed a normal distribution, whereas a Wilcoxon signed rank test was used when the data did not fit to a normal distribution, as evaluated by the Kolmogorov-Smirnov test. Comparisons between groups were done by the unpaired t test. Discrete variables were compared by Fisher’s exact test. Correlation analyses were done by Spearman’s test. A value of P<0.05 was considered as the level of significance. Values are reported as mean±SD.
The main results of the exercise test before and after ISDN in group X patients are summarized in Table 2. Compared with the basal test, after ISDN the resting heart rate and the rate-pressure product increased ($P<.01$ for both), whereas the systolic blood pressure decreased ($P<.01$). At peak exercise there were no differences between the two tests for heart rate, blood pressure, and rate-pressure product, but the exercise duration was reduced after ISDN (622±194 versus 494±279 seconds, $P=.01$).

The control test was terminated because of fatigue in 13 patients, progressive angina in 2, ST-segment depression ≥3 mm in 2, and dyspnea in 1, whereas the test after ISDN administration was ended because of fatigue in 12 patients, angina in 1, ST-segment depression in 2, dyspnea in 2, and ventricular arrhythmia in 1. Eight patients (44%) developed angina on the control test, and all had angina on the second test.

Seventeen patients (94%) had ST-segment depression on both exercise tests. Heart rate at 1-mm ST-segment depression was similar (126±16 versus 125±15 bpm), whereas systolic blood pressure (163±27 versus 143±24 mm Hg, $P<.01$) and rate-pressure product (20 535±4507 versus 18 047±4159 bpm · mm Hg, $P=.014$) were lower after ISDN. Furthermore, the time to 1-mm ST-segment depression (429±214 versus 268±312 seconds, $P=.048$) was reduced after ISDN. In 5 patients (28%), the administration of ISDN produced a significant degree of ST-segment depression associated with a marked increase in heart rate before the beginning of the test. There was no significant difference in the entity of ST-segment depression, whereas the time to recovery of ST segment was longer in the second test ($P<.04$).

In the 8 patients who developed angina, there were no differences between the two tests in heart rate, blood pressure, and rate-pressure product at the onset of angina and in time to angina. No differences were observed in the behavior of exercise variables between patients who had and patients who did not have a history of chest pain at rest.

### Results

#### Patients With Syndrome X

The main results of the exercise test before and after ISDN in group X patients are summarized in Table 2. Compared with the basal test, after ISDN the resting heart rate and the rate-pressure product increased ($P<.01$ for both), whereas the systolic blood pressure decreased ($P<.01$). At peak exercise there were no differences between the two tests for heart rate, blood pressure, and rate-pressure product, but the exercise duration was reduced after ISDN (622±194 versus 494±279 seconds, $P=.01$).

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### Patients With Coronary Artery Disease

The main results of the exercise test before and after ISDN in group C are reported in Table 3. Compared with the basal test, resting heart rate increased ($P<.01$), systolic blood pressure decreased ($P<.01$), and the rate-pressure product remained unchanged after the administration of ISDN.

At peak exercise, heart rate was higher (117±21 versus 130±24 bpm, $P<.01$) after ISDN, whereas there was no difference in systolic blood pressure. The rate-pressure product (19 475±4737 versus 21 327±5627 bpm · mm Hg, $P<.01$) and the exercise duration (473±223 versus 673±212 seconds, $P<.01$) were both improved significantly by ISDN.

The control test was terminated because of fatigue in 8 patients, progressive angina in 14, and ST-segment depression ≥3 mm in 11; the test after ISDN was terminated because of fatigue in 17 patients, angina in 7, and ST-segment depression in 9.

Heart rate and rate-pressure product at 1-mm ST-segment depression and the time to 1-mm ST-segment depression were all significantly improved by ISDN. Similarly, the severity of ST-segment depression and the time to recovery of the ST segment were both improved by ISDN. The time to angina and heart rate and rate-pressure product at angina were all improved by the nitrate.

### Individual Response to ISDN in Syndrome X and Coronary Patients

The individual response of the exercise variables to ISDN in the two groups is synthesized in Figs 1 and 2. After ISDN, all variables were improved in most group C patients but were either worsened or not improved in group X patients. Worsening of one or more of the exercise variables after ISDN was always associated with normal coronaries. Thus, the time to 1-mm ST-segment depression was shortened in 11 patients (61%)
TABLE 3. Results of Exercise Stress Test in Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Basal values</th>
<th>Control Test</th>
<th>Test After ISDN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>75±13</td>
<td>87±18</td>
<td>.000</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>136±17</td>
<td>118±19</td>
<td>.000</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>84±9</td>
<td>78±11</td>
<td>.000</td>
</tr>
<tr>
<td>RPP, bpm · mm Hg</td>
<td>10 332±2673</td>
<td>10 436±2964</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values at 1-mm ST depression

<table>
<thead>
<tr>
<th>Values at peak exercise</th>
<th>Control Test</th>
<th>Test After ISDN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>117±21</td>
<td>130±24</td>
<td>.000</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>166±20</td>
<td>163±22</td>
<td>NS</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>94±11</td>
<td>89±12</td>
<td>.022</td>
</tr>
<tr>
<td>RPP, bpm · mm Hg</td>
<td>19 475±4737</td>
<td>21 327±5627</td>
<td>.000</td>
</tr>
</tbody>
</table>

Duration of exercise, s

<table>
<thead>
<tr>
<th>Duration of exercise, s</th>
<th>Control Test</th>
<th>Test After ISDN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to 1 mm, s</td>
<td>329±213</td>
<td>599±247</td>
<td>.000</td>
</tr>
<tr>
<td>(median)</td>
<td>(300)</td>
<td>(576)</td>
<td></td>
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</tbody>
</table>

Values at angina

<table>
<thead>
<tr>
<th>Values at angina*</th>
<th>Control Test</th>
<th>Test After ISDN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>108±17</td>
<td>123±27</td>
<td>.000</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>160±18</td>
<td>159±18</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>90±13</td>
<td>87±13</td>
<td>NS</td>
</tr>
<tr>
<td>RPP, bpm · mm Hg</td>
<td>17 305±3532</td>
<td>19 855±5383</td>
<td>.004</td>
</tr>
</tbody>
</table>

Time to angina, s

<table>
<thead>
<tr>
<th>Time to angina, s</th>
<th>Control Test</th>
<th>Test After ISDN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(median)</td>
<td>(340)</td>
<td>(588)</td>
<td></td>
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</tbody>
</table>

ISDN indicates isosorbide dinitrate; HR, heart rate; bpm, beats per minute; BP, blood pressure; and RPP, rate-pressure product.

*Referred to 19 patients with angina on the control test.

Discussion

The results of this study show that in most patients with syndrome X, sublingual ISDN had no beneficial effects and even had detrimental effects on exercise testing, in sharp contrast with the significant improvement in exercise tolerance in the majority of patients with coronary artery disease. As a consequence, the response of exercise testing to sublingual nitrates appears to be useful to differentiate among patients with anginal pain and exercise-induced ST-segment depression, those with angiographically normal coronary arteries. Furthermore, the lack of beneficial effects of nitrates in patients with syndrome X also has some pathophysiological implications.

Clinical Implications

Often, patients with syndrome X cannot be distinguished clinically from patients with coronary artery disease, and the results of an ECG exercise test do not provide reliable evidence of the presence or absence of obstructive coronary disease in patients with anginal chest pain even when a multivariate approach is used. Also, in several patients with syndrome X, stress myocardial scintigraphic techniques often show perfusion defects and/or regional contractile alterations similar to those found in patients with coronary artery disease.

Our data show that in patients with effort angina and exercise-induced ischemic ST-segment depression, the response to sublingual nitrates of exercise testing can be useful to predict the presence or the absence of obstructive coronary lesions. Indeed, in our study groups, a
significant reduction of the time or the rate-pressure product to 1-mm ST-segment depression after ISDN was invariably associated with angiographically normal coronaries. Conversely, a complete prevention of angina by ISDN was always associated with the presence of coronary artery disease; moreover, normalization of the ECG during exercise by ISDN was observed in 10 of 33 patients (30%) with coronary artery disease but in only 1 of 18 patients (5%) with syndrome X. Between these two extremes, an improvement in exercise tolerance after ISDN was more frequently associated with coronary stenoses, whereas a lack of improvement was more frequently associated with normal coronary arteries at angiography.

Our findings are consistent with the clinical observation that sublingual nitrates fail to relieve angina in a sizable number of patients with syndrome X15,16 and with the reported reduction in ischemic threshold during atrial pacing after the sublingual or intracoronary administration of ISDN.7

Pathophysiological Mechanisms

There are several possible explanations for the negative effects of nitrates in patients with syndrome X. Effort angina in these patients is usually believed to be due to small coronary vessel disease,2,3 although the site (ie, arteriolar or prearteriolar)21,28 and the pathophysiological mechanisms of the dysfunction remain unknown and may not be the same in all patients.

The mechanism(s) of the adverse effects of nitrates on exercise ischemic threshold in syndrome X are similarly not clear. To explain dipyridamole-inducible angina and ischemic ST-segment changes, a primary increase in prearteriolar vasoconstriction has been hypothesized as the probable main cause of the syndrome.2,18 An abnormal adrenergic reactivity, which has been reported previously in patients with syndrome X19,20 and is suggested in our study by the consistent increase in basal heart rate after ISDN administration, could contribute to enhancement of vascular constriction of dysfunctional prearterioles through α-stimulation. On the other hand, the observation that nitrates fail to improve and may even worsen exercise tolerance in patients with syndrome X does not support the hypothesis that a defective production of the endothelium-derived relaxing factor nitric oxide (NO) by small coronary vessels is a major cause of syndrome X. This possible mechanism has been proposed based on the observation of an impaired coronary vasodilator response to acetylcholine of both epicardial21 and resistance vessels22-24 in some patients with syndrome X.

Exogenous nitrates exert their endothelium-independent vasodilator effect on epicardial and also on prearteriolar resistance vessels through the release of NO from their molecules.25 Thus, if a reduced NO production was the only or the main cause of the microvascular dysfunction in syndrome X, one would expect the dysfunction to be corrected by the administration of ISDN because the vasodilator response of vascular smooth muscle to the administration of exogenous nitrates has been shown experimentally to be strongly enhanced in the presence of a deficient NO production.26,27 In fact, the impaired vasodilator response to intracoronary acetylcholine found in previous studies may be due to mechanisms different from a deficient NO generation, including a defective endothelial release of the vasodilator endothelial hyperpolarizing factor,28 a direct vasconstrictor effect of acetylcholine,29 a release of endothelin,30 and a primary increase in microvascular tone with a reduced vasodilator response of vascular smooth muscle cells to NO.31

Our findings, however, do not exclude that a deficient NO generation in arteriolar vessels may be implied in syndrome X because the effects of nitrates on these vessels are negligible, owing to the poor ability of arterioles to convert exogenous nitrates to NO (or to its nitrosothiolic derivative).32 However, the possibility that the microvascular abnormality resides in arterioles has been questioned,21,28 and preliminary data suggest that the regulation of coronary blood flow by NO is likely to be mainly operating in prearteriolar rather than in arteriolar vessels.32

Our findings also were compatible with a non-ischemic origin of chest pain and ST-segment depression such as a dishomogeneity in cellular potassium currents in different parts of the myocardium33 or an increased stimulation of myocardial Al adenosine receptors.34,35 Indeed, adrenergic activation, consequent to sublingual ISDN administration, could increase potassium concentrations33 and interstitial adenosine,36 facilitating the appearance of ECG alterations and symptoms.

Study Limitations

Our method of performing the two exercise tests before and after ISDN, always in the same order and with an interval of only 30 minutes, might have introduced some bias; however, it seems unlikely that the negative effects observed after ISDN in syndrome X may be related to this study method because opposite effects were found in patients with coronary disease.

The significant increase in resting rate-pressure product after ISDN administration in syndrome X patients may have contributed to the shorter duration of exercise; however, the rate-pressure products at 1-mm ST-segment depression and at angina are unlikely to be influenced negatively by the change in basal rate-pressure product induced by ISDN.

Although striking, our data have been obtained in a limited number of carefully selected patients. Therefore, more extensive data will be required to better define the actual sensitivity and specificity of nitrate exercise testing in distinguishing patients with angiographically normal coronary arteries from those with flow-limiting stenoses.

Conclusions

Our data show that in patients with anginal chest pain and exercise-induced ST-segment depression, worsening of the results of exercise testing after the administration of sublingual nitrates is highly predictive of the presence of normal coronary arteries at angiography. The failure of nitrates to improve exercise tolerance in patients with syndrome X suggests that a reduction in NO generation at the prearteriolar level is unlikely to have by itself a major pathophysiological role in the syndrome.
References


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