Combined Effects of Nitrates on the Coronary and Peripheral Circulation in Exercise-Induced Ischemia

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We compared the effects of isosorbide dinitrate (ISDN) administered by intracoronary and intravenous routes in 10 patients with severe coronary artery disease, stable effort angina, and very low exercise tolerance. Supine bicycle ergometer exercise was performed under four conditions: 1) control, 2) after intracoronary administration of 0.4 mg ISDN, 3) 1 hour later (control 2), and 4) after administration of intravenous 4 mg ISDN. At rest, intracoronary ISDN caused no significant hemodynamic effects, whereas intravenous infusion of ISDN resulted in a decline in left ventricular (LV) systolic pressure (−20±5 mm Hg), LV end-diastolic volume (−27±3%), and LV end-systolic volume (−30±4%). After intracoronary infusion of ISDN, ST segment depression and the increase in LV end-diastolic pressure and LV end-systolic volume induced by exercise were significantly less abnormal than during control (0.20±0.09 vs. 0.14±0.08 mV, 36±7 vs. 24±8 mm Hg, and 91±40% vs. 40±29%, respectively). When exercise was performed after intravenous infusion of ISDN, the above-mentioned parameters were significantly improved even further: ST segment depression to 0.05±0.07 mV, end-diastolic pressure to 14±7 mm Hg, and LV end-systolic volume to 5±11% (all p<0.01 compared with intracoronary ISDN). Thus, in patients with severe coronary artery disease, it is suggested that intracoronary nitrates increase coronary blood supply during effort-induced ischemia, based on significant improvements in the indirect measures of ST segment depression, LV end-diastolic pressure, and LV volume. More marked effects on these measures were observed after intravenous administration, when coronary and peripheral effects are combined.

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The mechanisms by which nitrates improve myocardial ischemia in chronic effort angina are not fully understood. Peripheral venous dilatation resulting in decreased myocardial oxygen consumption by preload reduction has been clearly established, but whether nitrates also increase coronary blood flow to the ischemic myocardium by relieving coronary vasoconstriction remains controversial.3–9

This study was designed to assess the relative contribution of peripheral and coronary vasodilatation induced by nitrates in improving exercise-induced ischemia. We approached this problem by comparing the hemodynamic effects of intracoronary and intravenous isosorbide dinitrate (ISDN) at rest and during effort-induced ischemia in a group of patients with severe coronary artery disease and very low exercise tolerance.

Methods

Patients

Of 35 consecutive patients with chronic stable effort angina, we selected 10 who had a very limited coronary flow reserve. In four patients, previous myocardial infarction was documented by the patient’s history and also by electrocardiographic (ECG) and angiographic criteria. We excluded patients with valvular heart disease, cardiomyopathy, unstable angina pectoris, or a history of acute myocardial infarction within the previous 6 months.

All patients underwent exercise testing according to a standardized modified Bruce protocol.10 Blood pressure measurements and 12-lead ECGs were obtained at 1-minute intervals throughout the test. In addition, three ECG leads (usually III, V2, and V5) were continuously monitored before, during, and after exercise. A computer-assisted system (Marquette CASE, Marquette Electronics Inc., Milwaukee, Wisconsin) was used for analysis of the ECG, and the trends of heart rate, rate-pressure product, and ST
segment level in the three monitored leads were obtained.

Patients were selected for study if exercise-induced rectilinear or downsloping ST segment depression of at least 0.1 mV was observed in at least two ECG leads after less than 5 minutes of exercise (4 METS). Patients with resting ST segment abnormalities were excluded.

Before the hemodynamic study, patients underwent selective coronary angiography by the femoral approach. A high-resolution video playback was used to identify the most critical stenoses and the coronary artery in which nitrates were to be administered. Reading of collateral filling was performed with the scale proposed by Rentrop and colleagues: 0 = no visible filling of collateral channels, 1 = collateral filling of branches of the stenotic vessel without any depth reaching the epicardial segment of this vessel, 2 = partial collateral filling of the epicardial segment of the stenotic vessel, and 3 = complete collateral filling of the stenotic vessel.

Protocol

Immediately after coronary angiography, patients underwent four consecutive bicycle ergometer exercise tests in the supine position (Figure 1). Approximately 30 minutes for recovery was allowed between each exercise test. The first test was performed without any medication and was considered to be the control test. Two exercise levels of 3 minutes each were chosen according to the results of the preliminary treadmill test so that ischemia could be expected to develop during the first or the second exercise level. After the patients had recovered from symptoms and the ECG and hemodynamic parameters had returned to basal values, 400 μg ISDN (Cedocard, Isoket, Pharma Schwarz, Mannheim, FRG) were selectively infused into the ischemia-related coronary artery. The vessel to be injected was selected according to the location of ECG changes observed during the assessment treadmill exercise and according to coronary anatomy. The most stenotic but still patent vessel was injected. The drug was infused into the left coronary artery in six patients, into the right coronary in two, and into both arteries in the remaining two (double dose). Care was taken to slowly infuse the drug during a 5-minute interval to avoid any bolus effect.

After administration of ISDN, the ECG, hemodynamic parameters, and left ventricular volumes were measured during 5 minutes at rest; the second exercise test was then started. The same work loads were used, but if the occurrence of symptoms and/or ST segment changes were delayed, the patients were asked to begin a further stage at an increased work load. This was followed by a second recovery period (at least 30 minutes) not only to allow for the regression of ischemia but also to ensure clearance of the effects of nitrates.

A third exercise test was then performed to assess the reproducibility of the hemodynamic response to exercise under control conditions. Finally, after a further period of recovery, 4 mg ISDN was given intravenously and followed by the last exercise test.

ECG, Hemodynamic, and Left Ventricular Volume Measurements

Two ECG leads were continuously monitored throughout the study; one was used for QRS gating, and the second was used to follow ST segment changes. The lead showing the most significant changes was selected according to the results of the preliminary stress test performed in the assessment phase. Left ventricular pressure was also continuously monitored throughout the study through a 7F pigtail catheter.

Red blood cells were labeled by a standard in vivo technique. Four milligrams of stannous pyrophosphate (Pyrolite, New England Nuclear, Billerica, Massachusetts) was given intravenously and after 20 minutes was followed by an injection of 740 MBq (20 mCi) $^{99m}$Tc.

To optimize visual separation of right and left ventricles, a mobile gamma camera (model 215 M, Elscint, Haifa, Israel) was positioned over the patient’s chest in the 40–50° left anterior oblique position with a 10–30° craniocaudal tilt. Nuclear data were continuously acquired in list mode before, during, and after drug administration as well as during exercise tests on a Hewlett-Packard 1000 computer (2 × 80 Mbyte Winchester disk, Hewlett-Packard, Cupertino, California).

A program developed at our institution was used for further data processing. Briefly, after QRS recognition and image reconstruction from the list-mode nuclear data, a single region of interest was drawn around the left ventricle. Background radioactivity was then subtracted, and corrections were made for the decay of $^{99m}$Tc during the study period. The beat-to-beat activity curve in the left ventricular region of interest was obtained by mobile averaging for 13 beats to increase the statistics of nuclear data.
TABLE 1. Preliminary Exercise Test and Angiographic Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Exercise duration (min)</th>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>ST segment depression (mV)</th>
<th>Left ventricular ejection fraction (%)</th>
<th>Coronary angiography (% stenosis)</th>
<th>Collateral grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>111</td>
<td>140</td>
<td>0.31</td>
<td>50</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>108</td>
<td>135</td>
<td>0.29</td>
<td>58</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>140</td>
<td>140</td>
<td>0.30</td>
<td>59</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>115</td>
<td>130</td>
<td>0.24</td>
<td>68</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>84</td>
<td>140</td>
<td>0.31</td>
<td>74</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>117</td>
<td>150</td>
<td>0.30</td>
<td>54</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>120</td>
<td>130</td>
<td>0.30</td>
<td>50</td>
<td>70*</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>118</td>
<td>130</td>
<td>0.20</td>
<td>44</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>98</td>
<td>100</td>
<td>0.25</td>
<td>70</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>100</td>
<td>150</td>
<td>0.41</td>
<td>61</td>
<td>100</td>
<td>90</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; Cx, circumflex artery; RCA, right coronary artery.

*70% stenosis of left main artery.

This program allows continuous recording of beat-to-beat time-activity curves that are proportional to changes in left ventricular volume. The volume changes observed during the two control exercises were expressed as the percent changes relative to resting values. For the two exercise tests performed after intracoronary or intravenous administration of ISDN, results were expressed as the percent changes relative to predrug resting values.

Data Analysis

ECG, left ventricular pressure, and left ventricular volume curves were continuously acquired, beat by beat, on the same computer. The following parameters were derived from the original waveforms on a beat-by-beat basis: heart rate (beats/min), ST segment level at the J-point and 60 msec after the J-point (mV), left ventricular systolic and end-diastolic pressures (mm Hg), rate-pressure product (beats/min×mm Hg), and left ventricular end-diastolic and end-systolic volumes (% changes relative to resting values).

For each patient and for the entire study group, the beat-to-beat values of the various derived parameters were averaged over 10-second periods and plotted versus time in a trend format. Selected regions of the recording were identified from the resulting printouts to obtain the relevant measurements during the different phases of the study.

Data were compared for the same exercise duration and equivalent work loads. The level of exercise chosen for comparative purposes was always the maximal one achieved during the first control exercise test. This level was used for all further comparisons between exercise test data even if patients were able to sustain higher work loads after drug administration.

Statistical Analysis

Student's paired t tests with Bonferroni correction were used for comparison of heart rates, ST segment depression, exercise duration, left ventricular pressure, and rate-pressure product. One-way analysis of variance was used for comparison of the percent volume changes between exercise tests.

Results

Baseline Assessment of Coronary Flow Reserve and Angiographic Data

On the modified Bruce protocol, all patients exhibited severe impairment of effort tolerance with very

TABLE 2. Data Collected at Rest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control 1</th>
<th>IC</th>
<th>Control 2</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>73±11</td>
<td>74±12</td>
<td>75±10</td>
<td>91±19*†</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>141±22</td>
<td>137±25</td>
<td>139±24</td>
<td>119±24*†</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>17±5</td>
<td>15±3</td>
<td>17±4</td>
<td>8±2*†</td>
</tr>
<tr>
<td>LV end-diastolic volume changes (%)</td>
<td>-2±3</td>
<td>-27±3*</td>
<td>-2±3</td>
<td>-30±4*</td>
</tr>
<tr>
<td>LV end-systolic volume changes (%)</td>
<td>-2±3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricular; IC, intracoronary; IV, intravenous.

Values are mean±SEM.

*p<0.01 vs. Control 2.

†p<0.01 vs. IC.
low exercise duration (3.2±1.1 minutes; range, 1.5–5 minutes), marked ST segment depression (0.29±0.05 mV; range, 0.2–0.4 mV), and low rate-pressure product levels at peak exercise (14,972±2,711 [beats/min]×mm Hg; range, 9,800–19,600 beats/min×mm Hg).

At coronary angiography, eight patients had three-vessel disease (one had significant left main coronary artery stenosis), and two had two-vessel disease. Despite the severity of coronary artery disease, mean left ventricular ejection fraction was 59±10% (range, 44–74%). Details of the individual patient's responses to exercise testing as well as angiographic data are summarized in Table 1.

**Hemodynamic and Left Ventricular Volume Data at Rest**

The resting values of heart rate and left ventricular systolic and end-diastolic pressures and volumes were similar before the beginning of both control exercise tests. Relative to control, intracoronary infusion of 0.4 mg ISDN did not produce any significant changes in the parameters mentioned above. Conversely, intravenous administration of 4 mg ISDN resulted in a significant increase in heart rate, a small decrease in left ventricular systolic pressure, and a decline in left ventricular end-diastolic pressure, end-diastolic volume (–27±3%, p<0.01), and end-systolic volume (–30±4%, p<0.01). Details of hemodynamic and volume data obtained at rest are given in Table 2 and in Figures 2 and 3.

**ECG, Hemodynamic, and Left Ventricular Volume Data During Exercise**

For the same work loads, heart rate, ST segment depression, left ventricular systolic and end-diastolic pressures, and rate-pressure product were similar

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**FIGURE 2.** Line plots of left ventricular end-diastolic pressure (y axis, mm Hg) at rest and during exercise (EX) (same work loads). ISDN, isosorbide dinitrate; IC, intracoronary; IV, intravenous.

**FIGURE 3.** Line plots of left ventricular end-systolic volume changes (y axis, %) (same work loads). EX, exercise; ISDN, isosorbide dinitrate; IC, intracoronary; IV, intravenous.
Table 3. Data Collected During Exercise for Same Work Loads

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control 1</th>
<th>IC</th>
<th>Control 2</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST segment depression (mV)</td>
<td>0.20±0.09</td>
<td>0.14±0.08*</td>
<td>0.20±0.09</td>
<td>0.05±0.07†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>107±14</td>
<td>109±15</td>
<td>109±14</td>
<td>120±21‡</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>172±29</td>
<td>173±32</td>
<td>171±22</td>
<td>150±25†</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>36±7</td>
<td>24±8*</td>
<td>35±8</td>
<td>14±7†</td>
</tr>
<tr>
<td>Rate-pressure product [mm Hg×(beats/min)×10³]</td>
<td>18.3±3.4</td>
<td>18.9±4.8</td>
<td>18.7±3.9</td>
<td>18.1±4.6</td>
</tr>
<tr>
<td>End-systolic volume changes (+%)</td>
<td>91±40</td>
<td>40±29*</td>
<td>88±39</td>
<td>5±11†</td>
</tr>
<tr>
<td>End-diastolic volume changes (+%)</td>
<td>50±16</td>
<td>29±14*</td>
<td>48±15</td>
<td>6±13†</td>
</tr>
</tbody>
</table>

LV, left ventricular; IC, intracoronary; IV, intravenous. Values are mean±SEM. *p<0.05 vs. Control 1 †p<0.01 vs. Control 2 and IC. ‡p<0.05 vs. Control 2 and IC.

during the two control exercise tests. The percent increases in left ventricular systolic and end-diastolic volumes were also similar.

The level of rate-pressure product attained after intracoronary ISDN was similar to that observed, for the same work load, during the first control exercise. However, at this level, a noticeable improvement in all ischemic end points was observed: ST segment depression was less severe (from 0.20±0.09 to 0.14±0.08, p<0.05), increase in left ventricular end-diastolic pressure was markedly reduced (from 36±7 mm to 24±8 mm, p<0.05), and increase in left ventricular volume was also markedly reduced (end-systolic volume from 91±40% to 40±29%, p<0.05; end-diastolic volume from 50±16% to 29±14%, p<0.05).

Intravenous infusion of 4 mg ISDN did not affect rate-pressure product, as the slight reduction in systolic pressure was accompanied by an increase in heart rate. For the same work load and for equivalent levels of rate-pressure product, all signs of ischemia were significantly reduced during exercise: Mean ST segment depression was 0.05±0.07 mV (range, 0–0.19 mV), and left ventricular end-diastolic pressure was 14±7 mm Hg (range, 9–32 mm Hg) (Table 3).

All ischemic end points were significantly improved, both when compared with those observed during the second control exercise and with those recorded during the exercise performed after intracoronary ISDN dosing. Details of the results obtained during the four exercise tests are shown in Table 3 and in Figures 2–4.

Discussion

Our study shows that in patients with severe coronary artery disease, the beneficial effects of nitrates in preventing or reducing exercise-induced myocardial ischemia could be at least partially mediated by coronary vasodilatation. In all patients, slow intracoronary infusion of a small dose of ISDN resulted in reduction of ECG and hemodynamic signs of acute myocardial ischemia induced by exercise.

Compared with control, ST segment depression and impairment of left ventricular function, as assessed by the increase in left ventricular end-diastolic pressures and volumes, were less severe after intracoronary administration of nitrates. The effect occurred for equivalent levels of external work load and rate-pressure product and in the absence of significant hemodynamic changes before the onset of exercise. Despite the fact that we did not measure coronary blood flow or coronary artery diameter, these findings strongly suggest that the anti-ischemic effect of ISDN was the consequence of improved perfusion of the ischemic areas by dilatation of epicardial coronary artery stenoses, by increased collateral flow, or both.

Our data are at variance with those obtained by Ganz et al who found that intracoronary administration of nitroglycerin had no effect in preventing or reducing pacing-induced ischemia. Two factors may contribute to the discrepancy. First, in the study performed by Ganz et al, the 75-µg nitroglycerin bolus transiently exposed the coronary circulation to almost 200 times the pharmacologically active dose. Such a high concentration may redistribute coronary blood flow from the subendocardium to the subepicardium and from ischemic to nonischemic areas as a result of arteriolar vasodilatation and a drop in poststenotic pressure. Second, exercise but not pac-

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Line plots of ST segment depression (y axis, MV) during exercise for individual patients (same work loads). CI, control 1; IC, postintracoronary dinitrate (ISDN); C2, control 2; IV, postintravenous ISDN.
ing may cause coronary vasoconstriction,\textsuperscript{14} which could be prevented or reduced by nitrates.

Our conclusions are consistent with more recent studies. Brown et al\textsuperscript{9} showed that nitrates can induce an 18% and a 36% increase in luminal area in normal and stenotic epicardial vessels, respectively, and cause a 38% reduction of the estimated transtentnic resistance. Liu et al\textsuperscript{8} assessed thallium-201 regional distribution during pacing with single-photon emission computed tomography. Intracoronary infusion of nitrates produced an increase in coronary blood flow to the ischemic areas that was more pronounced in the mildly to moderately underperfused regions. Kaski et al\textsuperscript{9} found a variable response to sublingual nitrates in patients with chronic stable effort angina. Approximately one third of the patients who were tested dramatically improved their exercise capacity, achieving significantly less ST segment depression.

As expected, intravenous administration of ISDN resulted in a greater improvement in exercise tolerance presumably because of summation of the effects on the coronary and systemic circulations. It seems reasonable to assume that the relative contributions of coronary and systemic effects of nitrates are likely to vary in different patients depending on the prevailing pathophysiological mechanisms responsible for ischemia. In this respect, coronary vasodilatation by nitrates could play an even greater therapeutic role when coronary flow reserve is not as limited as in our patients and when dynamic changes in stenotic severity are more important in limiting effort tolerance.

\section*{Limitations}

Despite the fact that the small hemodynamic changes with intracoronary administration of nitroglycerin were not significant at rest, the small reduction observed in end-diastolic pressure and end-systolic volume at rest in some patients could be explained by different factors. Vasodilatation at the site of a severe stenosis could relieve some degree of ischemia already present at rest and thus reduce ventricular filling pressures and volumes. However, we cannot exclude the possibility that this small reduction in pressure and volume signify a small decrease in systolic wall stress and, hence, \textit{Mvo}_{2} or, alternatively, that they may lead to improved subendocardial perfusion. During exercise, although the observed changes in ventricular pressures and volumes are more likely consequences of stenotic vasodilatation, we cannot totally exclude the possibility that a small systemic effect could have been present after intracoronary nitrate infusion with decreased venous return. Although our data suggest that increased perfusion was dominant after intracoronary infusion, this evidence is based on indirect measurements and in the absence of myocardial blood flow measurements.

The mechanism of the improvement in myocardial perfusion is also a matter of speculation. It could result from minimal, perhaps not angiographically detectable, dilatation of critical stenoses; from dilatation of collateral vessels not visible angiographically; or from dilatation of distal coronary vessels.

In conclusion, this study indicates that exercise-induced ischemia is relieved mainly by the peripheral effect of nitrates. However, in our patients with severe coronary artery disease and very limited exercise capacity, intracoronary nitrate infusion results in significant beneficial effects on both symptoms and signs of ischemia and suggests a direct effect on coronary blood supply.

\section*{References}

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\textbf{Key Words} • nitrates • exercise • angina
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