Preferential Dilation of Recipient Coronary Arteries of the Collateral Circulation by Intracoronary Administration of Nitroglycerin

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Objectives. The purpose of this study was to test the hypothesis that the sensitivity to nitroglycerin of collateral vessels and recipient arteries is greater than that of donor arteries of the collateral circulation.

Background. The collateral circulation responds vigorously to nitroglycerin. However, the mechanisms of the efficacy of nitroglycerin for improving collateral circulation are not fully elucidated.

Methods. The diameter of donor and recipient arteries of the collateral circulation was measured with a computer-assisted analysis system in eight patients with well-developed collateral vessels. Coronary angiography was repeated before and after the intracoronary injection of 50 μg of nitroglycerin.

Results. After nitroglycerin, the mean diameter ± SD of donor arteries increased to 1.61 ± 0.53 from 1.29 ± 0.39 mm (p < 0.01), whereas the diameter of recipient arteries increased to 1.59 ± 0.50 from 1.10 ± 0.49 mm (p < 0.01). The change in the diameter of recipient arteries was significantly greater than that of donor arteries (52.3 ± 24.6% vs. 24.7 ± 11.5%, p < 0.05). These changes induced by the intracoronary injection of nitroglycerin were accompanied by a decrease in pacing-induced ST segment depression (0.16 ± 0.06 to 0.06 ± 0.04 mV, p < 0.01), suggesting increased flow reserve through collateral channels.

Conclusions. These findings indicate that the sensitivity to nitroglycerin of recipient arteries of the collateral circulation is significantly greater than that of donor arteries. This observation may explain the strong response of the collateral circulation to nitroglycerin in patients with functionally significant collateral channels.

(J Am Coll Cardiol 1994;24:631-5)
ischemia-related coronary artery and to evaluate the extent of collateral circulation with the use of a Philips 6-in. (15-cm) image intensification system. Films were exposed at a rate of 60 frames/s with an Arriflex 35-mm cine camera. A pacing catheter was then positioned in the high right atrium. When left ventricular pressure returned to baseline after coronary angiography, right atrial pacing was begun at an initial rate of 90 beats/min that was increased by 10 beats/min every 2 min until the patient had severe chest pain in association with significant ST segment depression in the 12-lead electrocardiogram (ECG). The rapid atrial pacing provoked angina without the appearance of second-degree atrioventricular block in all eight patients. The lead showing the maximal ST depression was selected for subsequent analysis. Three observers who had no knowledge of patient data assessed the extent of ST depression visually and reached a consensus. After an adequate recovery time to allow left ventricular pressure and ECG changes to return to baseline, 50 µg of nitroglycerin (Nihon Kayaku) dissolved in 5 ml of warmed 0.9% saline solution was injected into a major donor artery of the collateral circulation with the use of a computer-based coronary analysis system (CARDIO 500, Kontron Electronik, Germany) as previously described (13). Known dimensions of the angiographic catheter filled with contrast medium allowed calculation of a magnification factor and, thus, of absolute diameter dimensions. To evaluate the response of similar-sized coronary segments to nitroglycerin, we measured a segment from the middle or distal portion of the donor artery and a segment from the middle portion of the recipient artery. An observer who had no information about the data assessed the coronary cineangiograms.

**Statistical analysis.** For comparison of coronary diameters, a two-way repeated measures analysis of variance was used. ST segment changes were analyzed by paired t test. A p value < 0.05 was considered significant. All results are expressed as mean value ± SD.

**Results**

**Hemodynamic variables and left ventricular function (Table 2).** Left ventricular function at rest was normal in our eight patients with chronic stable effort angina. There were no detectable differences from control values in any hemodynamic variable after the intracoronary administration of 50 µg of nitroglycerin.

**Coronary artery diameter (Fig. 2).** Donor and recipient arteries were comparable in diameter under control conditions. After the intracoronary administration of nitroglycerin, the diameter of donor arteries increased from 1.29 ± 0.39 to 1.61 ± 0.53 mm (p < 0.01), whereas that of recipient arteries increased from 1.10 ± 0.49 to 1.59 ± 0.50 mm (p < 0.01). The change in diameter was significantly greater in recipient than in donor arteries (52.3 ± 24.6% vs. 24.7 ± 11.5%, p < 0.05) (Fig. 2). Although the size of collateral vessels could not be compared quantitatively before and after nitroglycerin administration, these vessels were more clearly visualized in all patients after nitroglycerin (Fig. 1).
Table 2. Hemodynamic and Overall Left Ventricular Functional Data Before and After the Intracoronary Administration of Nitroglycerin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nitroglycerin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>66 ± 1</td>
<td>68 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LVPSP</td>
<td>145 ± 24</td>
<td>136 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP</td>
<td>10 ± 4</td>
<td>9 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>MAP</td>
<td>107 ± 16</td>
<td>98 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>CI (liters/min per m²)</td>
<td>3.0 ± 1.2</td>
<td>9.0 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>74 ± 24</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>LVESVI</td>
<td>31 ± 13</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>61 ± 7</td>
<td>-</td>
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</tbody>
</table>

CI = cardiac index determined by the thermodilution method; HR = heart rate; LVPSP = left ventricular end-systolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; MAP = mean aortic pressure; — = not measured.

Discussion

A salient finding of the present study is that the recipient artery of a well developed collateral circulation responds more markedly to nitroglycerin than does a donor artery of similar diameter.

Effects of nitrates on collateral vessels. Farnum and McGregor (3) showed that nitroglycerin causes a marked increase in retrograde collateral flow and peripheral coronary pressure in dogs with chronic occlusion of one major branch of the left coronary artery, indicating that increased collateral indexes result from vasodilation of collateral channels and large conductance coronary arteries. Cohen et al. (4) demonstrated, using anesthetized open chest dogs with well developed collateral vessels, that regional myocardial dysfunction induced by the reduction in the perfusion pressure of the source artery was attenuated by a small dose of intracoronary nitroglycerin as a result of the increased collateral blood flow. Kumada et al. (5) also demonstrated the favorable effects of isosorbide dinitrate on exercise-induced myocardial dysfunction in the collateral-dependent zone in dogs with long-term implantation of ameroid constrictors around the left circumflex coronary artery. In contrast to these investigators, who used experimental models in which collateral vessels were fully dilated by the ischemic stimulus, Fujita et al. (6) studied the effects of nitroglycerin in dogs with newly developed collateral vessels 5 to 7 days after cessation of repetitive coronary occlusion, when there was a clearly demonstrable functional regression of previously demonstrated adequacy of collateral perfusion. They found that a small dose (5 µg/kg) of intravenous nitroglycerin increased collateral flow and decreased myocardial dysfunction in the collateral-dependent zone during coronary occlusion.

Goldstein et al. (7) evaluated the effect of intravenous nitroglycerin on collateral circulation in patients undergoing saphenous vein bypass surgery; they found that nitroglycerin elicited large increases in retrograde flow and, therefore decreases in calculated collateral resistance. Elsewhere, we (8) have evaluated, in patients with recent myocardial infarction,
the effects of administration of a sublingual dose of 0.3 mg of nitroglycerin on myocardial function in regions perfused exclusively by collateral channels. In patients with significant collateral circulation, this treatment resulted in significant improvement in both left ventricular ejection fraction and regional wall motion in the infarct zone. In contrast, in patients without significant collateral perfusion, there were no detectable changes in either global function or regional wall motion. Using stress thallium-201 myocardial scintigraphy, Aoki et al. (9) demonstrated that nitroglycerin reduces exercise-induced myocardial ischemia in the collateral-dependent area in patients with well developed collateral channels and effort angina due to total or subtotal occlusion of the proximal left anterior descending coronary artery. Although the beneficial effect of nitroglycerin on cardiac size, and therefore myocardial oxygen demand, cannot be ignored, these results suggest that nitroglycerin improves collateral function during exercise.

Study design. In the present study, to eliminate the systemic effects of nitroglycerin, we injected a small dose (50 µg) of nitroglycerin into the donor artery alone. Thus, we excluded the effects of this agent on aortic and left ventricular end-diastolic pressure, which may affect the extent of the collateral circulation.

Previous studies. Feldman et al. (14) reported that the size of an artery before the administration of nitroglycerin is the principal determinant of the extent of vasodilation, with smaller segments dilating more than larger ones. Therefore, in our study, we compared the response to nitroglycerin in donor and recipient coronary arteries of similar size. We found that the 50-µg intracoronary dose of nitroglycerin increased the recipient artery diameter by 52%, which was significantly larger than the 25% increase in the diameter of the donor artery.

These results are not in agreement with those of another study in which Feldman et al. (15) reported that a 150-µg dose of intracoronary nitroglycerin dilated collateral-filled arteries by 38% and comparably sized distal coronary segments by 34%. The difference may be at least partly due to differences in dose of nitroglycerin used and study patients, as well as the small number of observations in each study. Patients in the earlier study predominantly had multivessel disease, whereas our patients had no severe disease in more than one vessel. In other earlier studies (16,17), nitroglycerin was injected into the ischemia-related coronary artery, making it impossible to compare our data with those.

Pacing stress test. In the present study, atrial pacing was performed before and after intracoronary nitroglycerin to recognize the recruitment of collateral channels. The treatment with nitroglycerin alleviated myocardial ischemia, as evidenced by the reduced ST segment depression at a similar rate-pressure product, implying an increase in collateral blood flow. It is most likely that the increased collateral conductance was achieved by the reduction in the resistance of collateral and recipient coronary arteries. Pupita et al. (10) hypothesized that the constriction of collateral vessels or distal coronary arteries, or both, may cause myocardial ischemia in patients who are similar to those in our study. Our data suggest that nitroglycerin is more effective in the presence of impaired endothelial function of these vessels, presumably due to decreased basal endothelium-derived relaxing factor.

Mechanisms of the enhanced response of the recipient artery to nitroglycerin. Although the precise mechanism of the marked increase in diameter of the recipient artery is not clear, one possible explanation is that vascular ischemia of distal parts of the severely stenosed ischemia-related coronary artery may impair a variety of endothelial functions, including the ability to release the endothelium-derived relaxing factor with appropriate stimuli (18,19). Indeed, Sellke et al. (11) have disclosed that endothelium-dependent vascular relaxation of the collateral and recipient arteries is impaired in dogs with well developed collateral vessels induced by the implantation of amiodar constrictors. Thus, in the presence of impaired endothelial function, the sensitivity of these vessels to the endothelium-independent vasodilation induced by nitroglycerin may have been increased. Alternatively, it is possible that flow-dependent vasodilation of the recipient artery occurred as a result of increased collateral blood flow in response to the nitroglycerin-induced dilation of collateral channels (20).

Study limitations. To clearly demonstrate the effect of nitroglycerin on the collateral circulation, we limited our study patients to those who had non jeopardized well developed collateral vessels and whose noninfarct collateral-dependent zone was exclusively perfused by collateral vessels. These strict inclusion criteria resulted in a relatively small number of patients. However, each donor or recipient coronary artery served as its own control, and the changes produced by the intracoronary injection of nitroglycerin were consistent among the patients. It may be questioned whether the intracoronary injection of 50 µg of nitroglycerin used in our study can achieve
complete coronary artery dilation. A larger dose of nitroglycerin might have produced different findings.

We thank Kumiko Tsuura for preparation of the manuscript.

References