The Mechanisms of Nitroglycerin Action: Stenosis Vasodilatation as a Major Component of the Drug Response

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SUMMARY The effect of sublingual or intracoronary nitroglycerin (NTG) on luminal caliber in normal and diseased portions of epicardial coronary arteries was determined in 85 lesions from 57 typical patients with ischemic heart disease. Measurements were made from coronary angiograms, using a computer-assisted method and a carefully blinded protocol for analysis of the pre- and post-NTG angiograms. Luminal area in the "normal" portion of the diseased segment and at its maximum constriction and an estimate of flow resistance in the stenosis were computed. Luminal area increased 1.27 mm² (p < 0.001) in the "normal" regions, an average increase of 18% over the control area. Dilation with NTG depended strongly on vessel size; area increased 35% in normal vessels of 1.6–2.3 mm luminal diameter and only 9% in vessels 4.0–5.0 mm in diameter. Lesions were grouped into four levels of severity by percent stenosis. Minimum luminal area increased 0.35 mm² (p < 0.01) at the narrowest point in moderate lesions, a 22% area increase, and 0.14 mm² (p < 0.001) in severe lesions, a 36% area increase. Stenosis dilation resulted in an average 25% reduction (p < 0.01) in estimated stenosis flow resistance in moderate lesions and a 38% reduction (p < 0.001) in severe lesions. A statistically significant resistance reduction of greater than 20% occurred in 15 of 20 severe stenoses; only two of 20 showed no measurable dilation. We reviewed recent literature on hemodynamic responses to NTG and determined that changes of this magnitude are among the largest reported. We conclude that vasodilatation of epicardial coronary stenoses is usually a major component of the beneficial response to NTG. We support that conclusion by demonstrating a striking improvement in ischemic left ventricular compliance abnormalities after low-dose intracoronary NTG.

Nitroglycerin (NTG) affords dramatic relief of angina pectoris in patients with coronary artery disease; yet its mechanisms of action are complex and, in certain respects, controversial. NTG is said to reduce the myocardial oxygen requirement by diminishing systolic wall tension through reduced systemic pressure (afterload) and reduced left ventricular (LV) diastolic pressure and cavity size (preload). By reducing intraventricular diastolic pressure, it improves the transmural distribution of myocardial perfusion by reducing extrinsic diastolic compression of the subendocardial vessels. Although NTG does not appear to dilate the coronary arteriolar resistance bed, it dilates coronary collaterals and the undiseased large coronary arteries. The early studies by Winbury and the angiographic observations of Sones, Gensini and Likoff and co-workers suggested that coronary arterial dilation played an important role in the NTG effect. However, angiograms of diseased coronary arteries did not demonstrate readily discernible changes in stenosis caliber in most cases. In 1972, Ganz and Marcus demonstrated that intracoronary NTG failed to relieve pacing-induced angina. These observations appeared to refute the stenosis-dilation hypothesis of angina relief.

In recent years, coronary angiographic quality has improved substantially and objective methods for analysis of coronary angiograms have been developed. We therefore reexamined the hypothesis that NTG causes a hemodynamically significant dilation of the atherosclerotic coronary lesion. Our approach includes computer-assisted measurements of the response of the diseased lumen to NTG, an attempt to separate the systemic hemodynamic from the direct coronary effects of the drug, and a comprehensive review of the literature to assess the relative magnitude of other potentially beneficial hemodynamic responses to NTG. We believe that, in most cases, an important component of the beneficial effect of NTG derives from direct stenosis dilation.

Methods

Patient Studies — Sublingual NTG

Forty-six male veterans underwent cardiac catheterization to evaluate symptomatic ischemic heart disease. None had variant angina, although eight had exertional angina that had progressed to intermittent...
rest pain with associated ST-segment depression. Premedication was usually avoided; all cardiac medications were discontinued at least 10 hours before the procedure. Sublingual NTG was available as needed, but if it was used within 4 hours of catheterization, the patient was excluded from the study. After routine LV and coronary angiography, one or two lesions of interest and their best pair of angiographic projections were selected by review of the videotape. NTG was given sublingually as 0.4 mg, 0.6 mg or 0.8 mg. Aortic pressure and heart rate were monitored. Coronary angiograms were repeated in the selected views approximately 30 seconds after the aortic systolic pressure nadir (4.0 ± 1.1 minutes after NTG administration). In 14 patients, the first injection of an artery was repeated 4 minutes later in the same angiographic projection without intervening drug to determine if Renografin alone caused significant arterial caliber changes. The pre- and post-NTG and pre- and post-Renografin angiograms were later reviewed. When image quality was satisfactory, arterial segments containing clearly visualized stenoses were analyzed.

Patient Studies — Intracoronary NTG

Seventeen additional patients with severe narrowing in one of the major arteries in the left coronary distribution were selected for having an abnormally elevated LV filling pressure. Myocardial contraction was present on the angiogram (although sometimes hypokinetic) in the distribution of this diseased vessel. Aortic, right atrial and pulmonary capillary wedge pressures, cardiac output and heart rate were determined in the resting state, then after a steady 2-3-minute infusion of 0.050 mg of NTG into the left coronary artery and after 0.4 mg of sublingual NTG. A glass syringe was used for the intracoronary infusion. A subgroup of 11 of these patients was further selected because aortic systolic pressure was unchanged after intracoronary NTG or fell by no more than 9 mm Hg. The most severe left coronary lesion in nine of these 11 cases was visualized well enough for computer analysis.

Quantitative Angiography

Analysis of the 85 coronary lesions was performed using a computer-assisted method. Coronary cineangiograms were obtained using Judkins' technique in multiple projections, including cranial angulation views. For each left anterior oblique (LAO) view, a perpendicular right anterior oblique (RAO) view was filmed. The General Electric Fluoricon 300 system, coupled with individually adjusted film processing, provided high-quality arterial images. Films were projected at about fivefold magnification and cineframes were selected for lesion clarity at comparable points in the cardiac cycle in each view of a perpendicular projection pair. The borders of the selected stenosis images were digitized by telephone from a terminal in Los Angeles to a time-sharing PDP 11/45 digital computer in Seattle, Washington. The computer program reduces the lesion image to true scale by compensating for pin-cushion distortion, x-ray beam divergence and magnification. Figure 1 shows a hard-copy computer printout of a typical processed lesion. From this representation, the computer calculates and prints vessel diameter and cross-sectional area in the "normal" proximal and distal segments and at the point of maximum narrowing. Percent diameter and area stenosis are calculated, as well as lesion length, atheroma mass and stenosis flow resistance. Formulas by which these calculations are made have been presented. The accuracy of this method is within 0.08 mm for measurement of known dimensions; its variability averages ± 3% (SD) for percent stenosis estimates and 0.10 mm for minimum diameter estimates. Sixty-two percent of lesions studied were not adequately visualized in two perpendicular projections. In these cases, the measurements were made from a single angiographic view that was carefully repeated for the drug studies.

Angiographic Data Analysis

To eliminate observer bias in the angiographic analysis, a strategy for blinding was used to prevent those performing each step of lesion processing from knowing which of the four possible study conditions (drug control, NTG, Renografin control, post-Renografin) they were analyzing. The blinding was monitored by an assistant who randomly assigned a "code" (x,y,z,w) to each of the different study conditions, ran the projector so as to conceal the injection sequence, and coordinated the efforts of the two observers performing the sequence of steps in lesion analysis. For each study condition, four frame pairs were selected; frame numbers were concealed from the observer and recorded by the assistant. Because noticeable differences in arterial caliber after NTG might have suggested the identity of the study condition, a delay of at least 4 hours, and usually of 1 day or more, separated the selection and tracing of lesions from each different study condition. This delay was sufficient to erase the memory, already dulled by this tedium, of arterial caliber in the preceding condition. The lesion, as seen in each of the four selected frame pairs, was traced independently by two blinded experienced observers. The resulting eight tracings of the lesion in a given condition were then digitized in a similarly blinded fashion. The computer-processed data was stored on magnetic discs. Data on any lesion measurement were retrievable as the mean ± SD of the eight computed values of that measurement for a given condition. Comparative data were available for all measurements in figure 1, but a detailed analysis of the effects of NTG was made only for normal luminal area, minimum area, "percent stenosis," and stenosis flow resistance estimated at an assumed flow of 1 ml/sec.

Other Effects of NTG — A Literature Survey

To gain a perspective on the importance of the direct effects of NTG on diseased coronary arteries
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compared with the systemic hemodynamic effects, we made a detailed survey of *Index Medicus* from 1960–1980. One hundred fifty-four reports of the systemic NTG response were reviewed. The various partial determinants of myocardial perfusion and oxygen demand are listed in table 1. Two to six articles were selected as representative, careful studies of the response of each of these determinants to sublingual NTG; from these, the average response was calculated as a percentage change from the control state. Data from animal models were avoided except when patient data were not available and the animal model seemed appropriate. Evidence relating to the transmural distribution of perfusion comes largely from animal studies. Determination of coronary flow by precordial coincidence counting of radioisotopes may be in error in the setting of heterogeneous regional perfusion;24 we therefore excluded data obtained with these methods.

**Results**

**Effects of Contrast Medium**

Fourteen coronary segments were analyzed, using the single-view mode, from the first contrast injection into an artery and again from an injection repeated 4 minutes later in the same view. The average value of the ratio of postcontrast/precontrast normal luminal area was 1.01 ± 0.10 (± SD). Minimum area and stenosis flow resistance were also unchanged. Thus, the contrast medium did not cause residual dilation of large coronary arteries at 4 minutes. Changes after NTG therefore could not be attributed to contrast effects.

**Effects of Sublingual Nitroglycerin**

Mean aortic pressure fell 14% (p < 0.05) and 18% (p < 0.05) after 0.4 and 0.8 mg of sublingual NTG. Heart rate rose 4% and 8% (NS).

Figure 2 illustrates a typical lesion response to sublingual NTG. As was usually the case, the visual impression is one of no change. However, careful scrutiny of the true-scale images suggests what quantitative analysis confirms. In this case, there is a 46% increase in luminal cross-sectional area in the normal portions of the lesion, a 29% increase in minimum luminal area, and a resulting 37% reduction in predicted stenosis flow resistance. Because both the normal and the diseased portions of the lumen dilate, the percent diameter reduction (percent stenosis) did not change significantly, contributing to the visual impression of no change.

Luminal cross-sectional areas in normal and in narrowed portions of diseased vessels dilated consistently (fig. 3). Here, arterial segments are grouped into four levels of disease severity (minimal, mild, moderate and severe narrowing). The normal portions of all segments studied dilated an average of 1.27

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**Figure 1.** Hard-copy printout of computer analysis of a coronary stenosis. The left anterior oblique (LAO) and right anterior oblique (RAO) views of this segment are reduced to actual scale in the 3 × 3 cm panels. These views are matched at the point of greatest luminal narrowing and stretched to true length in the center panels. Luminal diameter and cross-sectional area are computed in the "normal" portions and at the point of greatest narrowing. Percent diameter and area reduction, lesion length, atheroma mass, two flow resistance functions, estimates of stenosis pressure loss, and the angles of lumen convergence and divergence are among the variables computed from this 3-dimensional representation of the stenosis.
mm², or 18% of the control luminal area. The magnitude of NTG-induced dilation in normal vessels was a strong function of vessel size. Intermediate-sized vessels of the caliber of moderate diagonal and marginal branches and the mid-LAD, with normal luminal area less than 4 mm² and averaging 2.1 ± 0.2 mm (± sd) luminal diameter increased luminal area by 35% after NTG. Vessels with an area of 4–8 mm², with average diameter 2.9 ± 0.5 mm, dilated in luminal area by 21%. Vessels with a normal area of 8–12 mm², with average diameter 3.4 ± 0.2 mm, dilated by 13%. Vessels of the caliber of the left main coronary, with normal area 12 mm², or more, averaging 4.5 ± 0.7 mm diameter, dilated in luminal area by only 9%.

Minimally diseased segments dilated by 1.00 mm², or 16% of initial area, whereas severely diseased segments dilated only 0.14 mm² at the point of greatest narrowing. While the absolute area increase is much less for severely than for minimally diseased stenoses, it represents a larger percentage (36%) increase from the original luminal area. This percentage increase in minimum area for the severely narrowed group differs significantly from that for the three less-diseased groups (p < 0.01).

The effect of NTG on predicted stenosis flow resistance is summarized in figure 4. Each point on the plot represents a lesion. The percent reduction in flow resistance with NTG is plotted against severity of stenosis. Although there is considerable variability in the lesion responses to NTG, physiologically and statistically significant reductions in predicted flow resistance occur in most cases at all levels of disease severity. There is no apparent difference in the spectrum of vasodilatory responses for those cases in which NTG was given in excess of the standard dose, 0.4 mg. Group average estimated stenosis flow resistance in minimal lesions was 0.6 mm Hg/ml/sec

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**Table 1. Averaged Values of Reported Hemodynamic and Coronary Vascular Responses to Sublingual Nitroglycerin that Relate to the Mechanisms of Benefit**

<table>
<thead>
<tr>
<th></th>
<th>Beneficial</th>
<th>Potentially adverse</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic wall tension × time product⁴⁰</td>
<td>-8% (-7%)†</td>
<td></td>
<td>2,6,8,43,44</td>
</tr>
<tr>
<td>Peak systolic LV pressure</td>
<td>-10%</td>
<td></td>
<td>1,3</td>
</tr>
<tr>
<td>LV cavity diameter</td>
<td>-5%</td>
<td></td>
<td>1,2,3,4,6,43</td>
</tr>
<tr>
<td>Heart rate</td>
<td>+13%</td>
<td></td>
<td>1,2,3,4,6,43</td>
</tr>
<tr>
<td>Myocardial contractility⁴¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak velocity of LV shortening</td>
<td>+19% (40%)</td>
<td></td>
<td>2,46*</td>
</tr>
<tr>
<td>Ventricular stroke volume⁶²</td>
<td>-7% (+2%)</td>
<td></td>
<td>2,43,44</td>
</tr>
</tbody>
</table>

**Responses affecting myocardial oxygen demand**
(pct change from control value)

<table>
<thead>
<tr>
<th></th>
<th>Beneficial</th>
<th>Potentially adverse</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central aortic pressure</td>
<td></td>
<td></td>
<td>-11%</td>
</tr>
<tr>
<td>Coronary flow in CAD patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total flow (coronary sinus)</td>
<td>-11%§</td>
<td></td>
<td>6,7</td>
</tr>
<tr>
<td>Flow in nondiseased vessels</td>
<td>-32% [-6%];§</td>
<td></td>
<td>6,8,[47];§</td>
</tr>
<tr>
<td>Small vessel resistance</td>
<td>+17%</td>
<td></td>
<td>6,7,8</td>
</tr>
<tr>
<td>Resistance in significant stenoses</td>
<td>-25% to -38%</td>
<td></td>
<td>6,7,8</td>
</tr>
<tr>
<td>Coronary collateral function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collateral flow</td>
<td>0,[8%]</td>
<td></td>
<td>9,[52]</td>
</tr>
<tr>
<td>Collateral resistance</td>
<td>-28% [-15%]</td>
<td></td>
<td>9,[52]</td>
</tr>
<tr>
<td>Subendocardial flow distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo/epi flow ratio</td>
<td>([+20%])</td>
<td>([−42%])</td>
<td>[48],[49]</td>
</tr>
<tr>
<td>LV filling pressure</td>
<td>-32% (−40%)</td>
<td></td>
<td>7,50,[51]</td>
</tr>
<tr>
<td>LV end-diastolic pressure</td>
<td>-47% (−62%)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Blood oxygenation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial oxygen pressure</td>
<td>-14%</td>
<td></td>
<td>50,53,54</td>
</tr>
<tr>
<td>Oxygen content</td>
<td>-2%</td>
<td></td>
<td>50,<em>53</em></td>
</tr>
</tbody>
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*Values estimated from data provided.
†Values in parentheses reflect responses during regional myocardial ischemia.
‡Values in brackets reflect measurements made in animal models likely to correspond to human disease.
§Reduced flow is here regarded as beneficial, reflecting reduced myocardial oxygen demand.

Abbreviations: LV = left ventricular; CAD = coronary artery disease.
in the control state; in mild lesions it was 2.1 mm Hg/ml/sec; in moderate lesions, 4.8 mm Hg/ml/sec; and in severe lesions, 48.5 mm Hg/ml/sec. After sublingual NTG, stenosis resistance fell an average of 25%, 14%, 25%, and 38%, respectively, in these four groups. Lesions measured as 75–85% stenosis were usually overestimated as 90–99% by the angiographers, as previously noted.22,23 Thus, lesions of the greatest clinical severity are included in the “severe” group.

Because NTG dilates both normal and diseased portions of arteries in relatively equal proportion, the “percent stenosis” measurement changes very little. The average change in percent stenosis in this group of lesions was 0.6 ± 5.7%.

**Effects of Intracoronary NTG**

Eleven of 17 patients with severe stenoses in the left coronary distribution and with resting LV compliance abnormalities were included in this subgroup because...
their systemic arterial pressure (afterload) did not change after low-dose intracoronary NTG. The hemodynamic and coronary caliber responses are listed in table 2 and figure 4. Intracoronary NTG had no effect, in this selected group, on aortic and right atrial pressures and cardiac index. However, the elevated pulmonary capillary wedge pressure fell from 20 ± 8 to 11 ± 4 mm Hg (p < 0.01). Subsequent sublingual NTG caused typical reduction in systemic and right atrial pressure and a small, nonsignificant additional reduction in the wedge pressure. Nine lesions, averaging 68 ± 9% stenosis, were analyzed. After intracoronary NTG, luminal caliber dilated in the normal and diseased arterial segments, with an average 40 ± 26% reduction (p < 0.05) in predicted stenosis flow resistance. The resistance changes, illustrated individually in figure 4, are comparable to those after sublingual NTG.

**Discussion**

These measurements quantify the well-established observation that normal segments of coronary arteries dilate in response to sublingual NTG, increasing an average of 18% in cross-sectional area. We have also demonstrated that segments narrowed by the atherosclerotic process commonly dilate after NTG. The magnitude of stenosis dilation is small in terms of increased luminal dimensions, but is substantial when considered in terms of the reduction of stenosis flow resistance, the appropriate physiologic index of vasodilation. An average increase in luminal diameter of 0.15 mm in moderately diseased and 0.12 mm in severely diseased segments reduced predicted stenosis flow resistance an average of 25% and 38%, respectively. Such precise estimates are impossible by the visual assessment of stenosis severity, but we are confident of the measured changes because they were made under a carefully blinded protocol and they are within the resolving power of the quantitative angiographic technique: In these studies, the average standard deviation for minimal diameter estimates was 0.09 mm for moderate stenoses and 0.06 mm for severe stenoses.

What is the importance of stenosis dilation compared with other hemodynamic benefits reported for NTG? These direct effects on the arterial stenosis are compared to certain indirect systemic hemodynamic effects in table 1. These data, representing the averaged responses to NTG from the studies listed, suggest that not all responses are beneficial to myocardial oxygenation. Blood pressure falls, heart rate and myocardial shortening velocity increase, collateral flow may decrease, and blood oxygenation is decreased. Among the largest potentially beneficial responses are the peripherally mediated reduction in flow requirement (11–32%), reduced ventricular filling pressure (32%) and reduced stenosis flow resistance (25–38%).

If this NTG-mediated stenosis dilation plays an important role in the clinical response to NTG, why did intracoronary NTG fail to relieve pacing-induced angina within 1 minute? The 75-µg bolus used in that study transiently exposed the coronary vessels to almost 200 times the pharmacologically effective NTG concentration. In normally perfused vessels, this dose caused a 45% reduction in coronary vascular resistance as flow nearly doubled for an average of 45 seconds. By comparison, clinically effective NTG doses decrease coronary flow in response to a metabolically mediated arteriolar constriction (table 1). Thus, in pharmacologic concentrations, NTG dilates large coronary arteries and their diseased segments without affecting the microvascular autoregulatory mechanisms. In higher concentrations, the large vessel response undoubtedly persists, but is accompanied by a comparable dilation of the resistance bed. To relieve angina, pacing-induced or otherwise, the perfusion pressure distal to the coronary stenosis (fig. 5) must increase above the threshold for adequate subendocardial perfusion. As a fraction of aortic pressure, the poststenotic pressure is (1 + Rs/Rv)⁻¹,

<table>
<thead>
<tr>
<th>Hemodynamic responses</th>
<th>Arteriographic responses</th>
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<tbody>
<tr>
<td>Blood pressure (sys/dia, mm Hg)</td>
<td>Cardiac index (l/min/m²)</td>
</tr>
<tr>
<td>Control</td>
<td>131/78, 100</td>
</tr>
<tr>
<td>Intracoronary nitroglycerin (50 µg/2–3 min)</td>
<td>127/78, 87§</td>
</tr>
<tr>
<td>Sublingual nitroglycerin (0.4 mg)</td>
<td>105/70, 85‡</td>
</tr>
</tbody>
</table>

Statistical comparison by paired t test, with preceding condition (i.e., intracoronary nitroglycerin vs control; sublingual nitroglycerin vs intracoronary nitroglycerin):

*p < 0.05.

‡p < 0.01.

§p < 0.001.

Abbreviation: ND = not done.
where $R_s$ is the stenosis resistance and $R_v$ is the resistance of the vascular bed distal to the stenosis. From this expression, interventions that comparably affect stenosis resistance and vascular bed resistance, such as bolus intracoronary NTG, clearly will not improve the poststenotic pressure or the subendocardial perfusion. A convincing example of this principle is i.v. dipyridamole, a coronary vasodilator which causes mild-to-severe angina in 40% of patients with coronary disease, and thallium-201 scintigraphic perfusion defects beyond most coronary stenoses of 40% or greater narrowing. Dipyridamole reduces small-vessel resistance by 63% and more than doubles coronary flow in patients, but has no significant effect on stenosis resistance.

By extension of this reasoning, a small, steady infusion of intracoronary NTG approximating pharmacologically effective concentrations could be more effective in improving subendocardial perfusion than a larger bolus. The study of intracoronary NTG described above was designed to test this hypothesis. The systemic hemodynamic effects were well-separated from the direct stenosis effects in a subset of 11 patients selected for severe coronary stenosis in the left coronary distribution and resting LV compliance abnormalities. In these patients, improvements in both the compliance abnormality and LV function were clearly associated with dilation of the epicardial coronary stenosis, and not with alterations in systemic hemodynamics.

Figure 5 is a summary of the principal mechanisms of NTG benefit. These pressure curves are those of a hypothetical patient with 70% stenosis of the left anterior descending coronary artery (LAD) and easily provoked angina. The LAD flow at rest is 68 ml/min, the average normal great cardiac vein flow. Normal basal flow is maintained by vasodilation in the arteriolar resistance bed beyond the stenosis to compensate for pressure lost in flow through the stenosis. McMahon et al. averaged the predicted stenosis pressure-flow characteristics from 10 such patients. Stenosis hemodynamic theory is based on classic fluid mechanics, and is consistent with observations in experimental and postmortem stenoses. The responses to NTG in the patient of figure 5 are in every respect those of the averaged data of table 1. In the usual setting, ischemia results from inadequate subendocardial perfusion. The mechanics and dynamics of the coronary vasculature are such that the inner layer of myocardium is at greatest jeopardy when the blood supply becomes limited. Subendocardial ischemia occurs when the perfusion gradient for subendocardial flow (the stippled area between the distal coronary and the ventricular diastolic pressure curves in figure 5) falls too low to support local myocardial oxygen demands despite full dilation in the subendocardial vascular bed. Moir and Debra and Wyatt et al. have demonstrated that subendocardial perfusion and contractile function in the resting state remain adequate until pressure distal to a coronary stenosis falls below about 60 mm Hg. In figure 5, an exercise-related 2.4-fold increase in systolic pressure times heart rate should drive coronary flow to 163 ml/min. But the total LAD resis-

**Figure 5.** Typical hemodynamic response to exercise and sublingual nitroglycerin in a hypothetical patient with 70% left anterior descending coronary artery (LAD) stenosis. The responses are those listed in table 1. Aortic, left ventricular, and poststenotic coronary pressure are shown. The cross-hatched area is the pressure lost, $\Delta P$, in the flow, $Q$, of blood through the stenosis, as estimated from 10 such patients. $\Delta P$ is in mm Hg and $Q$ in ml/sec. The stippled area between the poststenotic and left ventricular diastolic pressure contours is one determinant of subendocardial perfusion per beat. Subendocardial ischemia occurs when the threshold for adequate perfusion is crossed, as with exercise in this example. Nitroglycerin improves the mean gradient for subendocardial perfusion (from 56 to 61 mm Hg) despite a 12-mm Hg fall in aortic pressure. $HR =$ heart rate.
tance and available aortic pressure limit coronary flow to 120 ml/min (assuming a maximum fourfold dilation of the LAD arteriolar resistance bed). At that flow rate, stenosis pressure loss becomes 56 mm Hg. As the threshold for subendocardial ischemia is crossed, LV compliance and contractile function worsen, filling pressure rises, and the gradient for subendocardial perfusion is further compromised to an inadequate 24 mm Hg. After relief of ischemia with NTG, the resting hemodynamics are actually improved compared with the original resting state. With stenosis dilation, the predicted pressure loss for a given stenosis flow is reduced by 38%. Combined stenosis dilation plus an 11% reduction in stenosis flow result in a 52% improvement, from the resting state, in pressure loss through the stenosis. LV diastolic pressure falls to below the resting values. Thus, with NTG, the subendocardial perfusion gradient is 5 mm Hg greater than in the resting state, despite a 12-mm Hg fall in aortic mean pressure.

We conclude that no single “peripheral” or “coronary” response mediates the NTG benefit. In fact, some of the effects of NTG are predictably detrimental to myocardial oxygenation. If the goal in therapy of ischemia is to improve the subendocardial perfusion gradient, three principal responses contribute: (1) NTG directly dilates coronary stenoses with an average 38% resistance reduction in severely narrowed segments. (2) NTG reduces coronary flow requirement an average of 11% in response to a peripherally mediated decrease in myocardial oxygen demand, which is doubly rewarded because of the dominant Q² term in the stenosis pressure-flow relationship. (3) NTG decreases ventricular filling pressure (the lower end of the subendocardial perfusion gradient) by peripheral venous pooling, and by improving ischemic abnormalities of ventricular diastolic compliance.

Finally, these observations contradict the popular misconception that the stenotic coronary lumen is circumscribed by a calcified, cholesterol-laden, fibrotic, and thus rigidly immobile shell of athersclerosis. Stenosis morphology is actually variable; some diseased segments fit this description and have little potential for vasodilation. But many lesions are formed by an atheroma arising from only one side of the vessel; the lumen is then eccentrically located and partially circumscribed by an arc of relatively normal vessel wall. In such a morphologic setting, the potential for stenosis vasomobility is not only maintained, but in certain cases is even greatly enhanced.²⁷ ²⁸

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