The Effects of Intracoronary Nitroglycerin on Left Ventricular Systolic and Diastolic Function in Man

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SUMMARY The effects of intracoronary (IC) nitroglycerin (NTG) on left ventricular (LV) function were evaluated in 13 patients with significant coronary artery disease. LV cineangiograms were performed in the 40° right anterior oblique projection before and 2 minutes after 0.15 mg NTG was injected directly into the left main coronary artery, and angiographically derived volume and dimensional data were related to simultaneously measured high-fidelity pressures. The diameter of the proximal left anterior descending (LAD) coronary artery was measured from 3-ml injections of contrast material before and after drug administration, and hemodynamic measurements were made 1 and 2 minutes after IC NTG. There was a 22% increase in diameter of the LAD, a small (but significant) and transient rise in heart rate, a more sustained increase in maximal dP/dt and no change in LV end-diastolic pressure, LV systolic pressure or LV volumes. NTG produced no change in global systolic LV function, quantitated as ejection fraction and mean normalized systolic ejection rate, or in regional systolic LV function, measured as 1) shortening velocity and percentage shortening of basal, middle and apical transverse diameters, and 2) segmental ejection fraction. There was also no change in diastolic function evaluated in terms of 1) volume stiffness: slope k of the linear relation between logarithmic pressure and volume, and 2) muscle stiffness: slope α of the linear relation between logarithmic wall stress and midwall circumference. LV geometry, assessed by ratios of basal, middle and apical transverse diameters to the long axis and slope and intercept of the linear relation between middle diameter/long-axis ratio and volume throughout diastole, likewise was not affected. These results with IC NTG contrast with the previously demonstrated significant effects of sublingual NTG on hemodynamics, systolic and diastolic LV function and LV geometry, and suggest that the major cardiac actions of the drug are indirect.

ALTHOUGH NITRITES and their derivatives have been the dominant treatment of angina pectoris for longer than a century,1 the cardiac actions of this group of drugs are unknown or controversial. The basic pharmacologic property of nitrates is to relax smooth muscle, and their well-documented hemodynamic effects generally have been held to be secondary to actions on vascular smooth muscle.2 3 In a recent study4 we found that sublingual nitroglycerin (NTG) has significant effects on both systolic and diastolic left ventricular (LV) function, but it was not clear whether the effects were indirect (peripheral) or direct (cardiac). The present investigation was undertaken in an effort to resolve this problem. To avoid peripheral actions of the drug, NTG was injected directly into the coronary circulation. Few previous reports have been based on intracoronary injection of NTG in man.5–7

Patients and Methods

Thirteen male patients, mean age 45 years (range 24–56 years), underwent cardiac catheterization for evaluation of chest pain. All had significant obstruction (≥ 75%) of the left anterior descending (LAD) coronary artery with or without involvement of the other major vessels. In seven, obstruction was confined to the LAD. Two others had involvement of the LAD and left circumflex, one involvement of the LAD and right, and three involvement of the LAD, left circumflex and right coronary arteries. No patient had sustained a prior myocardial infarction, and none had areas of akinesis by ventriculography.

All patients were in sinus rhythm and none had significant valvular disease. All cardiac medications, including nitrates, were stopped before study.

Catheterization was performed 1 hour after oral premedication with 10 mg diazepam. A micromanometer catheter* was advanced into the left ventricle via a right brachial arteriotomy. Using percutaneous techniques, we introduced a pigtail catheter† into the left ventricle from the left femoral artery and a Judkins left coronary catheter‡ into the aorta from the right femoral artery. Midchest level was used as zero reference for pressure measurements. To correct for any baseline drift of the high-fidelity catheter, the pressure signal was superimposed on that obtained by the conventional system.8

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LV cineangiography was performed in the control state and 2 minutes after injection of NTG directly into the left main coronary artery (LMCA). All patients gave informed consent for this intervention. A NTG solution was prepared by dissolving a 0.5-mg tablet in saline. This was then passed through a milli-pore filter to render it bacteriologically sterile. An aliquot containing 0.15 mg was used for intracoronary injection. It was assumed that if dilatation of the coronary tree occurred, a pharmacologically effective dose of NTG had been administered. Intracoronary dosages as low as 0.075 mg have been shown to have a significant effect on the coronary circulation.

The basic catheterization protocol was as follows: 3 ml of contrast material was injected into the LMCA to measure the diameter of the proximal LAD. One minute later, the first ventriculogram was obtained in the 40° right anterior oblique projection at 80 frames/sec by injection of 40 ml contrast agent through the pigtail catheter. After an interval of 15 minutes, 0.15 mg NTG was injected into the LMCA within 15 seconds. This was followed after 2 minutes by a repeat ventriculogram. In the first seven patients a second 3-ml dye injection for measuring coronary diameter was performed 1 minute after intracoronary NTG (1 minute before the second ventriculogram); in the last six patients a second 3-ml dye injection was made 30 seconds after the repeat ventriculogram. Neither the patient nor the x-ray equipment was moved between the paired angiograms or before the correction factor for x-ray magnification was derived, as previously described. After the second angiogram, selective coronary arteriography was performed using the Judkins technique.

High-fidelity LV pressure was monitored via the catheter micromanometer and during ventriculography was sampled synchronously with frame exposure and displayed on the corresponding cine frame in digital form. LV pressure and its first derivative (dP/dt) were also recorded on a strip chart at a paper speed of 250 mm/sec, in conjunction with aortic pressure and a cine frame marker. Hemodynamic measurements, taken from three beats and averaged, were made at 1 and 2 minutes after NTG administration. The second set was recorded immediately before the second angiogram.

For evaluation of systolic LV function, projected end-diastolic and end-systolic silhouettes were traced by hand. Volumes were calculated by a modified area-length method, where the long axis was defined from the aortic-mitral valve junction to the apex. Volumes were not corrected by a regression equation but were normalized for body surface area. Premature beats and the first postextrasystolic beat were not analyzed.

Global systolic function was assessed by ejection fraction (EF) and mean normalized systolic ejection rate (MNSER).

Regional systolic function was evaluated in two ways: 1) in terms of shortening velocity and percentage shortening of basal, middle, and apical transverse diameters, and 2) in terms of segmental ejection fraction (SEF), representing percentage change in area of five angular segments. A computerized system superimposed end-diastolic and end-systolic silhouettes by aligning the long axes (mid-aortic valve to apex) and fixing their midpoints. The five angular segments were defined from this midpoint, beginning at the left aortic valve margin: 1 = anterobasal, 2 = anterolateral, 3 = apical, 4 = diaphragmatic, and 5 = posterobasal. SEF for any segment was determined as (end-diastolic area - end-systolic area) · 100/end-diastolic area.

For evaluation of diastolic LV function, cine films were projected to a video camera and ventricular silhouettes were outlined with a light pen on a video screen. A computer system* calculated volumes every 25 msec using a multiple-slice technique (50 perpendicular slices with long axis defined from aortic-mitral junction to apex) and applying Simpson's rule.

Diastolic function was analyzed in terms of so-called volume stiffness and muscle stiffness. For the former, pressure-volume relations were determined from the lowest diastolic pressure to the beginning of the "a" wave. The natural logarithm of pressure was used in linear regression analysis of pressure and volume from which a slope k was derived. Changes in k were taken as changes in volume stiffness.

Ideally, muscle stiffness should be assessed in terms of stress-strain analysis, but there are practical problems with this approach. Calculation of Lagrangian strain requires determination of resting length, which is difficult to measure in the intact heart. However, if certain assumptions are made, stress-circumference analysis can be shown as the mathematical equivalent of stress vs strain: The logarithmic stress-circumference relationship is linear with slope α; changes in α closely approximate changes in slope of the stress-strain relations. For these reasons, we assessed muscle stiffness in terms of midwall circumferential stress–midwall circumference relations (α).

Wall thickness at the LV equator was traced on the last diastolic frame. From this and simultaneous volume measurements, the computer calculated LV mass, and assuming constant mass, back-calculated wall thickness at each diastolic volume. Midwall circumferential stress was calculated by the formula of Sandler and Dodge from simultaneous pressure, wall thickness and computer-derived major and minor semiaxes. This formula is based on a thin-walled model, but yields values agreeing closely with those obtained using more complex thick-walled models. The natural logarithm of stress was used in linear regression analysis of stress and midwall circumference, from which slope α was derived.

Drug effects on LV geometry were determined at end-diastole and end-systole in terms of the ratios of minor axes (basal, middle and apical) to long axis.

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These axes were defined as for evaluation of regional systolic LV function. Drug effects on LV geometry throughout diastole were evaluated in terms of slope, q, and intercept, r, of the linear relation between middle minor axis/long axis ratio and volume.4

From the projected left coronary arteriograms obtained with injection of 3 ml contrast material, the diameter of the LAD distal to the stenosis (but limited to proximal and middle segments) was measured at five or more anatomic sites. Measurements were made by hand with a vernier caliper accurate to 0.05 mm.26 For each patient, the percentage change in diameter at each site after drug intervention was calculated, and then percentage changes from all sites were averaged.

Observations before and after NTG administration were analyzed statistically using the paired t test (two-tailed). A p value < 0.05 was considered significant.

Results

Hemodynamics, LV Volumes and Global Systolic Function

The effects of intracoronary NTG on hemodynamics, volumes and global systolic LV function are summarized in table 1. Heart rate increased slightly but significantly 1 minute after drug administration but was not significantly different from control values at 2 minutes. Maximal dP/dt was significantly increased both at 1 and 2 minutes. There was no change in end-diastolic pressure, LV systolic pressure, end-diastolic volume index, end-systolic volume index, EF or MNSER.

Regional Systolic LV Function

The effects of intracoronary NTG on regional systolic LV function are summarized in table 2. There was no significant change in mean shortening velocity or percentage shortening of basal, middle or apical diameters. Also, there was no significant change in SEF of any of the five defined segments.

Diastolic LV Function

The effects of intracoronary NTG on volume stiffness (k) and muscle stiffness (α) are summarized in table 2. There was no change in either parameter. Plots of logarithmic pressure vs volume and loga-
It was interesting to compare the degree of coronary vasodilatation induced by intracoronary NTG in the present study with that induced by the dose of sublingual NTG used in our earlier study. Therefore, in another seven patients, change in diameter of the LAD was determined 5 minutes after administration of 0.8 mg NTG sublingually. Identical techniques were followed. Percentage change in diameter from at least five sites in the proximal and middle segments was calculated, and all changes in each patient were averaged. Sublingual administration resulted in an increase in diameter of the LAD of 17 ± 3% (SD).

Discussion

In this study we used quantitative angiographic techniques that are subject to a variety of potential errors. These have been discussed in an earlier paper in which similar methods were used and will not be reviewed in detail here. In this study, as in the previous one, the majority of errors should have been consistent and, because only within-patient comparisons were made, any observed directional changes should be valid. Pressure-derived parameters were measured from high-fidelity pressure signals, and all pressure-volume or stress-circumference analyses were based on simultaneously determined pressures and dimensions.

There is considerable controversy as to the best method for defining diastolic LV function. The model in the present analysis is very simple and assumes a purely elastic myocardium and ignores various properties both extrinsic (e.g., pericardium, right ventricular overload) and intrinsic (e.g., viscous properties, diastolic suction, completeness of ventricular relaxation) to the left ventricle.

In our earlier study, we found that sublingual NTG 1) reduces determinants of LV preload and afterload, 2) enhances velocity indexes of global systolic LV function in both normals and patients with coronary artery disease (CAD), 3) enhances velocity indexes of regional systolic LV function uniformly in normals but not uniformly in patients with CAD, 4) alters passive elastic properties of the myocardium in terms of muscle stiffness but not volume stiffness in both normals and CAD patients, and 5) alters one index of diastolic configuration, an effect that may mask any changes in volume stiffness induced by the drug. From that study we could not conclude whether the demonstrated effects were direct (cardiac) or indirect (peripheral). In this investigation we used similar analytical methods but used intracoronary administration of NTG in order to study actions of the drug on the heart uncomplicated by its effects on the systemic circulation.

The sublingual dose of NTG used in our earlier study, 0.8 mg, produced an average increase in diameter of the LAD of 17%. The intracoronary dose of NTG given in the present study, 0.15 mg, produced an average increase in LAD diameter of 22%. Despite producing a greater degree of coronary vasodilatation, intracoronary administration resulted in fewer other cardiac effects than did sublingual. We observed a
 transient increase in heart rate, a more sustained increase in maximal dP/dt, but no change in LV end-diastolic pressure, LV systolic pressure or LV volumes. It is interesting to consider possible mechanisms for the increase in heart rate. One possibility would be a direct action of NTG on the sinus node, but in only five of the 13 patients did the blood supply to the sinus node arise from the left coronary system. Another possibility is that a NTG-induced increase in coronary flow provoked a reflexly mediated increase in heart rate. In experimental animals, increases in coronary flow have been shown to trigger reflex increases in cardiac sympathetic discharges, but these were not associated with any change in heart rate. That NTG by the intracoronary route is capable of increasing coronary flow even in patients with CAD has been documented. In five patients with CAD, Ganz and Marcus observed no change in heart rate within 30 seconds after intracoronary injection of NTG despite a 39% increase in coronary sinus blood flow. In dogs, 15-30 seconds after intracoronary administration of NTG, Gaasch and Bernard noted no change in heart rate but did observe a significant increase in coronary blood flow. At 1 minute, heart rate had significantly increased, but at this time coronary flow had returned to control values. Thus, there appears to be no direct relation between coronary blood flow and heart rate, and the mechanism by which intracoronary NTG elicits a transient increase in heart rate remains uncertain.

In our study, the increase in maximal dP/dt without apparent changes in determinants of preload and afterload suggests a positive inotropic effect of NTG. On the other hand, the increase in dP/dt might have been related to the increase in heart rate. The other indexes of global systolic function evaluated (EF and MNSER) failed to reflect improved performance. Other investigations into the actions of NTG on the contractile state of the myocardium have yielded conflicting results, the effects varying with the experimental preparation or model studied, the dose, route of administration and time. Some studies have suggested a negative inotropic action, either direct or due to an adrenergic blocking effect, whereas others have suggested a positive inotropic action, either direct or indirect. Increases in coronary blood flow per se are known to be associated with increases in myocardial contractility, including NTG-induced increases in coronary flow in anesthetized, areflexic dogs. But in conscious dogs Vatner et al. found no early enhancement of contractile state by NTG despite an increase in coronary blood flow (although a late reflex increase in contractility was noted). In contrast, Strauer and co-workers demonstrated a pronounced direct positive inotropic effect of NTG on the myocardium, independent of coronary flow. Enhanced contractility by NTG was also suggested by our study; its clinical importance is doubtful, however, because EF and MNSER were not affected. Our investigation revealed intracoronary NTG had

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<th>Table 2. Effects of Intracoronary Nitroglycerin on Regional Systolic and Diastolic Left Ventricular Function</th>
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<tr>
<td><strong>Basal</strong></td>
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<tr>
<td></td>
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<tr>
<td>$V$ (circ/sec)</td>
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<tr>
<td>Control</td>
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<tr>
<td>2 min after NTG</td>
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<td>$p$</td>
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Values represent group means ± s.d.
Abbreviations: $V$ = mean shortening velocity; S = percentage shortening of basal, middle and apical transverse diameters; k = slope of diastolic logarithmic pressure-volume relation; $\alpha$ = slope of diastolic logarithmic stress-midwall circumference relation (see text); NTG = nitroglycerin; n = number.

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<th>Table 3. Effects of Intracoronary Nitroglycerin on Left Ventricular Geometry</th>
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<td><strong>DB/L</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>$q$ (m$^{-2}$)</td>
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<td>Control</td>
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<td>2 min after NTG</td>
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<td>n</td>
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Values represent group means ± s.d.
Abbreviations: $DB/L$, $DM/L$, $DA/L$ = ratios of basal, middle and apical diameters, respectively, to long axis; q = slope and r = intercept of linear plot of $DM/L$ vs volume throughout diastole; ED = end-diastole; ES = end-systole; n = number.
no effect on parameters of regional systolic LV function. It should be remembered that all patients studied had at a minimum \( \geq 75\% \) obstruction of the LAD. Thus, there was no effect by intracoronary NTG on wall motion in post-stenotic segments in the distribution of the LAD. Of course, wall motion in these segments was normal. Whether intracoronary NTG would have improved abnormal post-stenotic segmental function is not known. The one previous investigation on the influence of intracoronary NTG on regional wall motion also revealed no improvement.\(^7\)

In regard to diastolic function, we found no effect by intracoronary NTG on indexes of either volume or muscle stiffness. There have been no other studies on the effects of intracoronary NTG on LV stiffness in man. In dogs, using intraaortic injection of NTG, Templeton et al.\(^46\) observed no effect on volume stiffness. Also in dogs, Gaasch and Bernard\(^46\) noted a significant increase in diastolic wall thickness in response to intracoronary NTG. Although LV compliance was not quantitated, they presumed that an increase in stiffness had occurred as a result of vascular engorgement (the “erectile” effect of Salisbury et al.\(^46\)). It should be noted that Gaasch and Bernard used a relatively large dose of intracoronary NTG, which produced an average increase in coronary blood flow of about 260\%. The relatively smaller dose used in the present study might account for the lack of a measurable effect on LV stiffness. In our earlier investigation on the effects of sublingual NTG,\(^4\) we noted an increase in muscle stiffness but not volume stiffness. The failure of volume stiffness measurements to reflect effects of sublingual NTG appeared to be related to drug-induced changes in ventricular geometry. In the present study, we could not attribute the lack of an effect by intracoronary NTG on either volume or muscle stiffness to geometric changes induced by the drug. In any case, the observations in our two studies are consistent with the concept that NTG influences LV stiffness primarily through peripheral mechanisms. The nature of what these might be is unclear. A logical possibility is that sublingual NTG, by reducing LV volumes and pressures and altering LV configuration, reduces wall stress, which secondarily lessens the resistance to coronary filling and favors engorgement. Intracoronary NTG, not reducing LV volumes and pressures or altering geometry, lacks this effect.

We conclude that intracoronary NTG significantly dilates the major coronary vasculature and significantly increases maximal \( \text{dP/dt} \) but has few other hemodynamic effects and no measurable effect on several parameters of global and regional systolic LV function, diastolic LV function or geometry. These results contrast with the previously demonstrated significant effects of sublingual NTG on hemodynamics, systolic and diastolic LV function and LV geometry and suggest that the major cardiac actions of the drug are indirect rather than direct.

Acknowledgment

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References


Table 2. (Continued)

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<tr>
<th>Segmental ejection fraction (%)</th>
<th>k (ml(^{-1}))</th>
<th>(\alpha) (cm(^{-1}))</th>
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<tr>
<td>1</td>
<td>53 \pm 10</td>
<td>46 \pm 7</td>
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<tr>
<td>2</td>
<td>55 \pm 5</td>
<td>47 \pm 9</td>
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<td>3</td>
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<td>4</td>
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<td>5</td>
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<td>(NS)</td>
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