Coronary Reactivity to Nitroglycerin: Intravascular Ultrasound Evidence for the Importance of Plaque Distribution

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Objectives. This study was designed to assess the extent and timing of vasodilation after intracoronary administration of nitroglycerin using intravascular ultrasound. We also sought to relate the magnitude of nitroglycerin-induced dilation to the distribution of atherosclerotic plaque.

Background. Although previous angiographic studies have shown that nitroglycerin can dilate both normal and stenotic coronary arteries, it remains uncertain whether atherosclerotic vessels can respond to nitroglycerin to the same extent as normal arteries in the clinical setting.

Methods. We analyzed a total of 48 segments from 48 patients by means of a multielement 3.5F to 5.5F 20-MHz intravascular ultrasound system before and after intracoronary administration of nitroglycerin (250 μg). Videotaped images were digitized, and the lumen cross-sectional area was measured with an electronic cursor. In noncircumferential lesions, the perimeters of the normal and diseased portions were measured separately to compare the reactivity to nitroglycerin in each portion.

Results. Of 48 sites examined 14 were normal by ultrasound, and 34 revealed atherosclerotic lesions. In the 14 normal segments nitroglycerin produced a large increase in cross-sectional area (31 ± 16% [mean ± SD]) within 60 s after injection. In the 34 atherosclerotic segments, nitroglycerin-induced dilation was impaired, and the cross-sectional area increased only 12 ± 8% (p < 0.01). In 15 of 34 atherosclerotic segments, a none circumferential lesion was identified, and the cross-sectional area after nitroglycerin increased an average of 17 ± 6%. In the remaining 19 sites, circumferential disease was present, and the cross-sectional area increased by only 8 ± 7% (p < 0.05 vs. normal or noncircumferential atherosclerotic segments). In noncircumferential lesions, the increase in the perimeter of the normal portion of the wall was significantly greater (14 ± 6%) than the increase in the diseased portion (5 ± 3%, p < 0.05).

Conclusions. These data indicate that vasoreactivity after nitroglycerin administration is reduced in segments with atherosclerosis by ultrasound. We suggest that nitroglycerin-induced vasodilation at the stenotic segments can be produced primarily by expansion of the nondiseased portion of the vessel wall.

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of the presence or absence of an angiographically apparent lesion and permits continuous measurement of changes in vascular dimensions after nitroglycerin administration. Using intravascular ultrasound, the coronary reactivity to vasoactive drugs was examined in transplanted hearts with accelerated vasculopathy (16–18). However, no data exist regarding vascular behavior of naturally occurring atherosclerosis in the native vessels. The current study used intravascular ultrasound to clarify the action of nitroglycerin on coronary artery segments at sites with and without atherosclerotic lesions. We attempted to determine the magnitude and time course of coronary dilation in response to nitroglycerin and to examine whether the extent of dilation was similar in diseased and normal vessel sites. We also examined the mechanism of nitroglycerin-induced dilation of the stenoses.

Methods

Study patients. A total of 59 patients admitted for coronary angiography for the diagnosis of chest pain were entered into the present protocol. Patients with significant (>50%) left main coronary artery stenosis, clinically unstable angina or active treatment with nitrates were excluded from the study. All patients taking long-acting calcium channel blocking agents were excluded study because of the uncertain effects of these drugs on coronary artery vasoreactivity.

Written informed consent was obtained from all subjects using an Institutional Review Board-approved consent form. Although not a consecutive series, the study group represented all recruitable patients for whom informed consent was obtained. Among the registered patients, we were unable to complete the full protocol in nine because of clinical or technical difficulties. These included malfunction of the ultrasound catheter in seven patients and unexpected elevation of systemic blood pressure to >200 mm Hg in two. Accordingly, complete studies were performed in the remaining 50 patients (31 men, 19 women; mean age 54 years, range 27 to 72). Twenty-eight patients had classical exertional angina, with or without previous myocardial infarction, and 22 exhibited chest pain with some atypical features. None had a history of typical variant angina.

Ultrasound imaging device. The imaging system used in the present study has been described in detail elsewhere (11,13). Briefly, the intravascular ultrasound imaging probe consists of a 32- or 64-element transducer, and the maximal diameter of the device is 3.5F or 5.5F (1.67 or 1.83 mm) (Endosonics Corp.). The transducer operates with a center frequency of 20 MHz and a bandwidth of 10 MHz. The ultrasound images are displayed using at a 512 × 512-pixel resolution with an 8-bit gray scale (256 levels) and are recorded on Super-VHS video cassette tape for review and analysis.

Study protocol. To avoid any possible effect of circadian morning increases in coronary artery tone (19), all catheterization procedures were performed in the afternoon. With the exception of sublingual nitroglycerin, all vasodilators, including nitrates, regular calcium channel blockers and other vasodilating antihypertensive agents, were withheld for at least 9 h before the procedures. No patient received sublingual nitroglycerin within 4 h of ultrasound examination.

After routine diagnostic coronary angiography and left ventriculography, a 7F or 8F left Judkins guiding catheter (Superflow, Schneider Inc.) was advanced into the coronary artery. In all patients the study segment was located in the proximal left anterior descending, left circumflex or right coronary artery.

A 0.014-in. (0.036 cm) angioplasty guide wire was advanced through the ultrasound catheter and fluoroscopically guided into the distal coronary arteries. The ultrasound imaging catheter was subsequently advanced over the guide wire into the vessel and fixed at a site that yielded high quality images enabling identification of the entire intimal leading edge. The operator sought to maneuver the ultrasound catheter to a central location in the lumen, primarily by catheter rotation and guide wire movement. For the initial 16 patients, sites with normal findings on both angiography and ultrasound were examined. In the 34 remaining patients, diseased sites were studied.

A cineangiogram was performed with the radiopaque ultrasound transducer in situ to document the precise angiographic location. Injection of small amount of contrast medium assisted in the recognition of the intimal leading edge border of the site examined. This injection of contrast medium also provided a method to ensure that insertion of the ultrasound catheter probe had not induced coronary vasospasm. During these procedures, the vessel lumen was also observed by ultrasound to detect possible vasospasm.

An intracoronary nitroglycerin solution was prepared within 10 min before administration. One milliliter of nitroglycerin solution (American Regent Laboratories, Inc.) containing 5 mg of nitroglycerin, 30% ethanol with 30% propylene glycol and water was mixed with 19 ml of 0.9% normal saline solution. The final nitroglycerin concentration of this solution was 250 μg/ml. The guiding catheter was cleared of contrast material and filled with 1 ml (250 μg) of the nitroglycerin solution, which was subsequently injected through the guiding catheter into the left or right main coronary artery as a bolus over 3 s. In five patients, another 500 μg of nitroglycerin was added 5 min after the initial injection to examine the dose dependency of coronary vasodilation by nitroglycerin.

The intravascular ultrasound image was observed continuously and recorded on videotape for at least 2 min after nitroglycerin administration. Heart rate and systemic blood pressure were also monitored continuously during the procedure. At the conclusion of the procedure, a contrast injection was performed to reconfirm the angiographic location of the imaging site. After the procedure, the cineangiographic findings at the location examined were classified as normal or abnormal for at least six different orthogonal views. Angiographic findings at the sites of examination were further evaluated by consensus of two observers according to the criteria of Austen et al. (20).
Ultrasound measurements. Videotaped ultrasound images were analyzed by two investigators (J.K. and S.K.) in a blinded manner using an off-line digitizing system (Mipron, Kontron Electronics or PC-9801, NEC Corp, Tokyo, Japan). The operators reviewed 10-s sequences and selected the frame with the largest lumen size and optimal delineation of the blood-intimal border. For each selected site, ultrasound measurements of wall morphology were performed at baseline. Subsequently, the lumen was measured at baseline and every 10 s for 2 min after nitroglycerin administration.

Assessment of wall morphology consisted of measurement with an electronic cursor of the maximal thickness of the intimal leading edge and underlying sonolucent zone. The intimal leading edge was taken as the bright echo signal at the innermost lumen-wall interface, and the adventitia was identified as the next bright layer extending about the circumference of the vessel. The maximal thickness of the intimal leading edge was measured by placing the electronic cursor at the border between the vessel lumen and the intimal leading edge and at the border of the leading edge and sonolucent zone. Maximal thickness of the sonolucent zone was determined by measuring the distance from the trailing edge of intima to the leading edge of the adventitia.

There are differences in the appearance of intravascular ultrasound images using multielement and mechanical systems. For both ultrasound devices, the thickness of the intimal leading edge or sonolucent zone does not necessarily represent the thickness of histologic intima or media, respectively (21). However, the total thicknesses of the intimal leading edge with sonolucent zone can represent the actual thickness of the intima-media complex and are thus comparable to histologic measurements (21, 22).

At each site examined, the lumen cross-sectional area was determined by tracing the acoustic interface between the lumen and the intimal leading edge. In patients with noncircumferential atherosclerotic lesions, the perimeters of the diseased and normal portions of the vessel wall were measured separately to compare the nitroglycerin vasoreactivity of both segments of the vessel wall. The arc of the diseased portion was defined as that portion of the circumference with an intimal thickness exceeding the 95% confidence limits for previously studied normal segments (13). Because the cross-sectional area in systole is greater by ~10% than that in diastole (23), we measured the maximal cross-sectional area during systole. All measurements were performed for two consecutive cardiac cycles and the final data obtained by averaging these values.

Classification of wall morphology. As reported previously (13), the criteria for abnormality define atherosclerosis as a maximal thickness of intimal leading edge >0.3 mm or a sonolucent zone thickness >0.2 mm, or both. The predominant lesion morphology by ultrasound was defined using previously published criteria (12) in which plaques less echogenic than the adventitia are termed soft, whereas more echogenic plaques are termed hard. Calcification was identified as dense plaques with sufficient acoustic impedance to obstruct transmission of high frequency ultrasound, thereby shadowing underlying structures.

Intraobserver and interobserver variability. Cross-sectional areas of 10 randomly selected sites were measured by two independent observers and by one observer at two separate times. These data were used in the assessment of interobserver and intraobserver variabilities. The result was expressed as a linear regression between the two measurements and as a percent error that was derived as the absolute difference between measurements divided by the initial measurements.

Statistics. All data are expressed as mean value _ 1 SD. All simple group comparisons used an unpaired or paired Student t test. For analysis of nitroglycerin responses at different times after administration, we used multiple regression analysis with dummy variables (24); p < 0.05 was considered significant.

Results

Measurable images were obtained at 50 sites. However, transient minor lumen narrowing by ultrasound was observed in two sites associated with catheter insertion, although angiography did not show evident vasospasm. We excluded these two patients from measurement, which resulted in 48 evaluable segments. Thirty-one sites were obtained from the left anterior descending, nine from the left circumflex and eight from right coronary artery.

Systemic hemodynamic effects. Before nitroglycerin injection, mean blood pressure was 92 _ 10 mm Hg, and heart rate was 72 _ 11 beats/min. Blood pressure declined slightly 60 s after intracoronary nitroglycerin injection, averaging 86 _ 9 mm Hg (p < 0.01), but heart rate remained essentially unchanged at 74 _ 12 beats/min.

Vascular wall morphology. Among 48 segments, 26 segments were normal by angiography; 22 segments exhibited minor lumen irregularity (<25% stenosis). By intravascular ultrasound, 14 of 26 angiographically normal segments demonstrated a thin leading edge (0.18 _ 0.06 mm) and sonolucent zone (0.16 _ 0.05 mm), which met the criteria for normal morphology (group I) (Fig. 1, left). The remaining 34 segments

![Figure 1. Intravascular ultrasound images from a normal coronary segment of the proximal left anterior descending coronary artery. Left, Before intracoronary injection of nitroglycerin, the cross-sectional area was 6.1 mm². Right, Sixty seconds after intracoronary injection of nitroglycerin, the area was 8.9 mm², an increase of 46%.](image-url)
exhibited evidence of atherosclerosis by ultrasound (group II) (Fig. 2, left and Fig. 3, middle), although angiography showed lumen irregularities in only 22 of 34 segments (Fig. 3, left).

The sites with disease by ultrasound exhibited a maximal thickness of intimal leading edge averaging 0.38 ± 0.09 mm and a sonolucent zone averaging 0.60 ± 0.22 mm. In these diseased segments, a “soft” plaque was evident at 16 sites (Fig. 2, left), more dense “hard” plaques at 8 sites (Fig. 3, middle) and calcification at 8 sites. Only four of the eight segments with calcification by ultrasound also exhibited angiographic evidence of calcium.

Observer variability. Interobserver variability for area measurement (standard deviation) was ±4.2% with a correlation coefficient of r = 0.93 (linear regression analysis). Intraobserver variability was ±3.5% with a correlation coefficient of r = 0.96.

Vascular reactivity to nitroglycerin. Before nitroglycerin injection, the mean cross-sectional area of the segments examined in group I ranged from 6.0 to 15.9 mm² (mean 9.3 ± 2.6). Subsequently, the cross-sectional area was determined every 10 s for 2 min after nitroglycerin injection. The vessel lumen began to dilate almost immediately after nitroglycerin injection and was larger than that at baseline (increasing 18 ± 10%) at 20 s after injection. Nearly maximal vasodilation was obtained at 40 s after injection (27 ± 11%) and remained almost constant at 60 s (12.1 ± 3.0 mm², or 31 ± 16% [Y = b₀ + Σ bᵢDᵢ + b₁₄Vᵣ, where b₀ (control valve) = 0; bᵢ = the value for each patient; Dᵢ (dummy variable) = 1 if patient i (i < 14), -1 if patient 14, and 0 otherwise; and b₁₄ of Vᵣ (time of measurement) = 0.62, p < 0.0001 (Fig. 4)]. No further dilation occurred after additional dosing of nitroglycerin (32 ± 12%, n = 5). Therefore, we compared the cross-sectional area before with that 60 s after injection of 250 μg of nitroglycerin.

The cross-sectional areas of the group II segments before nitroglycerin injection ranged from 3.1 to 15.1 mm² (mean 9.6 ± 3.2, p = NS vs. the cross-sectional areas of the segments group I). Sixty seconds after nitroglycerin injection, group II segments dilated to a lesser extent (mean 10.9 ± 3.5 mm² [Fig. 2, right and Fig. 3, right], an average increase of 12 ± 8%, p < 0.01 compared with group I [Fig. 5]).

Noncircumferential and circumferential disease. In the 34 segments with atherosclerotic disease by ultrasound, there was considerable variability in the augmentation of cross-sectional area after nitroglycerin, ranging from 0% to 34% (Fig. 5). We hypothesized that the differences in the distribution of atherosclerotic plaque might be one reason for the high variability. Accordingly, we divided the diseased segments into subgroups according to the distribution of plaque. A lesion was defined as circumferential if the entire 360° wall was abnormal (i.e.,
thickness values exceeded the 95% confidence limits for the previously studied normal cohort) and noncircumferential if wall abnormalities involved only a portion of the vessel perimeter.

The changes in cross-sectional area for segments with circumferential disease (n = 19) were compared with those with noncircumferential atherosclerosis (n = 15). Segments with noncircumferential disease dilated to a much greater extent, from 9.8 ± 2.0 to 11.7 ± 2.7 mm² (an average increase of 17 ± 6%), compared with segments with circumferential disease, which increased from 9.3 ± 3.0 to 10.1 ± 3.2 mm², or 8 ± 7% (p < 0.05 by unpaired t test) (Fig. 6).

Mechanism of enlargement. To further examine the mechanism by which noncircumferential atherosclerotic segments respond to nitroglycerin, the changes in perimeter of normal and diseased portions of the vessel wall were compared. In the 15 segments with noncircumferential atherosclerosis, the perimeter of the undiseased portion was 5.9 ± 1.9 mm (range 3.4 to 9.8), and that of the diseased portion was 5.1 ± 1.4 mm (range 3.8 to 7.7) just before nitroglycerin injection. Sixty seconds after nitroglycerin injection, the perimeter of the nonsclerotic portion increased to 6.6 ± 1.9 mm (range 4.2 to 10.6, p < 0.0001), whereas that of the diseased portion increased only slightly (to 5.4 ± 1.5 mm, range 3.8 to 8.0) (Fig. 7). Thus, the percent change in the normal portion of the vessel circumference after nitroglycerin was significantly greater than the increase in perimeter of the atherosclerotic portion (14 ± 6% vs. 5 ± 3%, p < 0.05) (Table 1).

Table 1. Perimeter Changes of Normal and Atherosclerotic Portions of Noncircumferential Lesions Before and After Nitroglycerin Administration

<table>
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<tr>
<th>Pt No./ Gender</th>
<th>Age (yr)</th>
<th>Before (ram)</th>
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*p < 0.0001, †p < 0.05. F = female; M = male; Pt = patient.
Discussion

Comparison with previous studies. Pathologic studies (25) have demonstrated that many stenotic coronary lesions are circumscribed by fibrotic or calcified tissue. It would seem unlikely that this rigidly immobile shell of atherosclerosis could dilate after nitroglycerin administration. However, clinical studies using quantitative angiography have indicated that the reactivity of the angiographically determined atherosclerotic segments to nitroglycerin is highly variable. Brown et al. (4) demonstrated that maximal nitroglycerin-induced vasodilation in stenotic segments was similar to that in angiographically normal segments (as much as 36% over baseline). However, other investigators (3,7,8) reported a large range for the magnitude of stenosis dilation (0% to 30%). The present ultrasound study also showed large variability in percent change in cross-sectional area of atherosclerotic segments, ranging from 0% to 34% (Fig. 5).

Experimentally, the reactivity of the atherosclerotic human coronary artery to nitroglycerin in vitro is also controversial. Bossaller et al. (26) showed that isolated atherosclerotic human coronary arteries could respond to nitroglycerin. However, Berkenboom et al. (27) found markedly impaired vasoreactivity in atherosclerotic human coronary arteries to nitroglycerin and other endothelium-independent vasodilators, such as isoprenaline (28). The severity of the preexisting atherosclerosis could have been different in each study, thus resulting in variation in nitroglycerin action on the atherosclerotic vessels.

Mechanism of impaired vasoreactivity to nitroglycerin in vivo. Several mechanisms might explain impairment of nitroglycerin-induced vasodilation in the clinical setting. Potentially important factors include the effect of medial smooth muscle atrophy, a feature characteristic of advanced atherosclerotic lesions (29,30). However, we were unable to evaluate the precise thickness of the media using the present ultrasound system. Another possible mechanism could be the hemodynamic effects of nitroglycerin on coronary blood flow. Nitroglycerin can increase coronary blood flow by ~40%, which may result in flow-mediated endothelium-dependent vasodilation (31). Thus, impairment of vasoreactivity in diseased segments may partially be due to disordered flow-mediated vasodilation because this mechanism is impaired in the presence of atherosclerosis (32).

Our study provides a possible explanation for the variability of nitroglycerin-induced vasodilation in atherosclerotic segments. The stenosed segments with noncircumferential atherosclerosis tended to vasodilate nearly as much as normal segments, whereas sites with circumferential disease were markedly insensitive to intracoronary nitroglycerin. This suggests that the circumferential distribution of plaque is one of the critical factors in determining the response to nitroglycerin. The present investigation also provides insight into the time course of nitroglycerin response. The onset of nitroglycerin-induced vasodilation in normal segments was almost immediate, and the percent increase in ultrasound cross-sectional area in these normal segments was somewhat greater than that reported for angiography. Differences between the present investigation and previous angiographic studies could be related to the observation that angiographically normal segments frequently contain occult atherosclerotic lesions detected only by intravascular ultrasound (10-13). Thus, previous angiographic studies probably included some sites with angiographically inapparent disease, which resulted in lower average changes in cross-sectional area after nitroglycerin.

Clinical implications. One of the most important advantages of intravascular ultrasound is its ability to determine the circumferential extent of atherosclerotic disease. This feature enabled examination of the mechanism of vasodilation in atherosclerotic segments. We found an increase in the perimeter of the uninvolved normal portions of the vessel wall, a finding that explains most of the capacity of atherosclerotic lesions to vasodilate. Conversely, the presence of circumferential plaque results in a marked blunting of the ability of the segment to vasodilate. These findings support and amplify previous angiographic studies (4) demonstrating that segments with minor lumen irregularities often retain the capacity to vasodilate.

Even for atherosclerotic segments with circumferential disease, nitroglycerin-induced vasodilation exhibited a broad range, 0% to 20%, indicating the presence of other factors in the variability of vessel reactivity to nitroglycerin. This may be explained by differences in the composition of atherosclerotic lesions, including other characteristics of plaque morphology, such as the presence of “hard” or “soft” plaque. Recently, Pinto et al. (16) and Anderson et al. (18) observed by intravascular ultrasound that nitroglycerin could dilate the diseased segments of transplanted hearts without tissue rejection to the same extent as normal segments. However, another study (17), also with transplanted hearts, demonstrated that vasodilation by nitroglycerin was impaired in the presence of such transplant vasculopathy, similar to our observations. The controversy in transplanted heart studies may also be explained by differences in the composition of the diseased segments, although the numbers of patients enrolled in the current study did not permit subgrouping by plaque composition.

Variation of the values of baseline cross-sectional area may also affect vessel reactivity to nitroglycerin (3), although only proximal coronary segments were studied.

Study limitations. There remain several important limitations to the present study. Intravascular ultrasound images represent a thin (1 to 2 mm) tomographic cross section of the vessel. Accordingly, this method examines the vasoreactivity of a very short axial length of the vessel and cannot simultaneously evaluate changes in adjacent segments. The ultrasound catheters used in this study were relatively large (1.17 to 1.83 mm), which precluded measurements within high grade stenoses. Therefore, the exact mechanism of nitroglycerin-induced vasodilation at sites of severe stenosis still remains unclear.

In measurements of normal and diseased arcs in noncircumferential lesions, we determined the border between these
two arcs by referring to the normal values of wall thickness by visual inspection. Therefore, a small overlap may exist in the determination of the border zones. Use of an automated border detection system may further improve the accuracy of these measurements (17).

It is possible that 9 h of no therapy with nitrates or calcium channel blockers might not be enough time to guarantee complete absence of pharmacologic effects, although patients who were given extra long-acting time-release calcium channel blockers were excluded from the study. It is also possible that other drugs, such as nonvasodilating antihypertensive or lipid-lowering agents, may have influenced vasoreactivity to nitroglycerin, although we consider this possibility remote.

We used nitroglycerin, an endothelium-independent vasodilator, to examine coronary reactivity in the presence or absence of atherosclerosis. There were slight changes in blood pressure after nitroglycerin injection. Therefore, the direct coronary vasodilator effects of nitroglycerin might have been slightly underestimated in this study. However, this phenomenon would not affect vessel reactivity in the presence or absence of atherosclerosis because there was no difference in the decrease in blood pressure in each patient in each group. Further study using another agent, such as acetylcholine, which is an endothelium-dependent vasodilator (33), may more sensitively demonstrate functional impairment of atherosclerotic coronary segments when examined by intravascular ultrasound.

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References