Coronary Artery Disease

Coronary Artery Distensibility in Diabetic Patients With Simultaneous Measurements of Luminal Area and Intracoronary Pressure
Evidence of Impaired Reactivity to Nitroglycerin

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OBJECTIVES
This study investigated whether noninsulin dependent diabetes mellitus (NIDDM) adversely affects the elastic properties of the coronary arteries in patients with coronary artery disease (CAD) and NIDDM.

BACKGROUND
Attenuated vascular smooth muscle dilation to exogenous donors of nitric oxide, such as nitroglycerin, has been observed with forearm blood flow studies in patients with NIDDM.

METHODS
Twenty patients with CAD and NIDDM (diabetics), and 20 patients with only CAD (nondiabetics) were evaluated. Intracoronary ultrasound (ICUS) imaging with simultaneous intracoronary pressure (P2) recordings were performed at the imaging site with 0.014 in fiber-optic high fidelity pressure monitoring wire. The same wire was used as guide wire for the ICUS catheter. Sites with less than 50% luminal stenosis by ICUS were studied. Recordings were done before and after 300 mg of intracoronary nitroglycerin (IC-NTG). Electrocardiographic tracings recorded simultaneously with ICUS images were used for timing. Systolic and diastolic cross-sectional lumen area (CSLA) and coronary artery distensibility (C-DIST) were measured, C-DIST = [(systolic CSLA-diastolic CSLA)/{(intracoronary pulse pressure)}^3] * (diastolic CSLA)] × 1,000.

RESULTS
Diabetics had smaller CSLA (diabetics = 8.6 ± 0.6 mm², nondiabetics = 11.5 ± 0.5 mm², p < 0.01). Although C-DIST was similar before IC-NTG in the two groups, it became significantly lower in diabetics after IC-NTG (diabetics C-DIST = 4.21 ± 0.15 mm Hg⁻¹, nondiabetics C-DIST = 3.02 ± 0.14 mm Hg⁻¹, p < 0.01). Degrees of circumference involved, total plaque burden and composition were similar in both groups.

CONCLUSIONS
Noninsulin dependent diabetes mellitus reduces C-DIST after IC-NTG administration. (J Am Coll Cardiol 1999;34:1075–81) © 1999 by the American College of Cardiology

Patients with diabetes mellitus have increased morbidity and mortality due to cardiovascular disease (1). Coronary artery disease (CAD) is a common complication of diabetes mellitus, which frequently results in myocardial infarction and ischemic heart disease (2).

Several mechanisms have been implicated in the pathogenesis of CAD in patients with diabetes mellitus, such as elevated blood glucose level, insulin resistance with hyperinsulinemia and hyperlipidemia (3). In addition to these mechanisms, decreased availability or activity of nitric oxide in the coronary arterial bed of diabetic patients may play an important role (4). Attenuated vasodilation to exogenous donors of nitric oxide, such as nitroglycerin, has been observed in patients with noninsulin dependent diabetes mellitus (NIDDM), suggesting impaired vascular function in this group of patients (5).

Experimental and clinical studies have demonstrated that the increase in angiographic cross-sectional lumen area (CSLA) of normal coronary arteries after nitroglycerin administration can reach 30% to 50% from that at baseline (6). However, angiographic studies on coronary vasoactivity to nitroglycerin in vivo have provided some conflicted data, probably as a result of the limitations of angiography to study vessel wall morphology and coronary artery dimensions (7). Recent advances in intracoronary ultrasound (ICUS) imaging technology have enabled real-time evaluation of coronary lumen size and wall morphology in vivo (8,9). Intracoronary imaging enables identification of the atherosclerotic disease regardless of the presence or absence

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Abbreviations and Acronyms

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<td>C-DIST</td>
<td>coronary artery distensibility</td>
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<td>CSLA</td>
<td>cross-sectional lumen area</td>
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<td>D-BP</td>
<td>diastolic intracoronary pressure</td>
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<td>ECG</td>
<td>electrocardiographic tracings</td>
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<td>IC-NTG</td>
<td>intracoronary nitroglycerin</td>
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<td>ICUS</td>
<td>intracoronary ultrasound</td>
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<td>NIDDM</td>
<td>noninsulin dependent diabetes mellitus</td>
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<tr>
<td>P₁</td>
<td>aortic pressure</td>
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<tr>
<td>P₂</td>
<td>intracoronary pressure</td>
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<tr>
<td>PTCA</td>
<td>percutaneous transluminal coronary angioplasty</td>
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<tr>
<td>S-BP</td>
<td>systolic intracoronary pressure</td>
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of an angiographically apparent lesion and permits continuous measurement of changes in vascular dimensions after nitroglycerin administration (10).

Furthermore, there are several studies that used ICUS to assess pulsatile changes and thus elastic properties of the coronary arterial wall in normal and diseased coronary segments. However, in all these studies coronary lumen changes were not related to simultaneous intracoronary pressure recordings at the imaging site, and whenever intracoronary pressures were measured, they were restricted in the very proximal coronary segment (11–13).

Therefore, in this study, we attempted to evaluate coronary artery distensibility (C-DIST) in diabetic and nondiabetic patients, before and after intracoronary nitroglycerin (IC-NTG) injection, using a method that related pulsatile coronary lumen changes to the simultaneously obtained intracoronary pressure at the imaging site. Thus, we determined accurately C-DIST at different coronary segments in both groups of patients.

METHODS

Patient population. The study patients were obtained from 60 consecutive patients with NIDDM who underwent diagnostic heart catheterization or percutaneous transluminal coronary angioplasty (PTCA) and 50 consecutive patients without NIDDM who underwent similar procedures. Among them were 23 patients with NIDDM and 22 patients without NIDDM who met the study criteria of one- or two-vessel CAD. One- or two-vessel CAD was defined as luminal stenosis in one or two vessels equal to or more than 50% angiographically. In all patients, the coronary artery that had no significant disease by angiography was evaluated by ICUS. In case of one-vessel disease, the coronary artery with the least luminal stenosis was selected. Two patients with extreme tortuosity of the coronary segment that we attempted to study (one diabetic and one nondiabetic) and three others who had poor guiding catheter support (two diabetics and one nondiabetic) were excluded for further evaluation. Thus, 20 patients (diabetics) with NIDDM and CAD and 20 patients with CAD (nondiabetics) were studied. Angina pectoris was present in all nondiabetics (duration of symptoms 8 ± 1 months) and in 12 diabetics (duration of symptoms 7 ± 2 months). None had a history of typical variant angina. All patients had abnormal exercise stress test.

In the diabetics, 10 sites in the proximal and 3 in the middle-left anterior descending coronary artery and 2 sites in the proximal and 5 in the middle-right coronary artery were evaluated. In the nondiabetics, 8 sites in the proximal and 3 in the middle-left anterior descending coronary artery and 2 sites in the proximal and 7 in the middle-right coronary artery were studied.

All diabetics were followed at the diabetes outpatient clinic and had documented fasting hyperglycemia (blood glucose more than 7.7 mmol liter⁻¹) on more than one occasion. There was no history of ketoacidosis in any of the diabetic patients. Diabetic control was achieved by diet alone or diet and oral hypoglycemic agent treatment. Average duration of diabetes was 4.2 ± 2 years. Data were confirmed by interviewing the patient and reviewing the medical records.

Written informed consent was obtained from all patients and the study protocol was approved by the Human Research Committee of our hospital. All the above procedures were in accordance with the institutional guidelines.

Methods. Using standard PTCA techniques after insertion of an 8 F guiding catheter, intravenous heparin (10,000 U) was given before guide wire manipulations. An 0.014-in. fiber-optic high-fidelity pressure monitoring wire (Pressure-guide wire) was used as a guide wire to obtain intracoronary pressure from its pressure sensor, which was located at the transition of the radiopaque floppy tip. This fiber-optic pressure wire (14) is connected with a pressure analyzer to show continuously mean or systolic and diastolic intracoronary pressure (P₂). The pressure analyzer was connected to a DC-coupled pressure monitor system (Electronics for Medicine DR-12, Honeywell, Phoenix) through a high-level analogue output for screen display and recording of the P₂ wave forms.

On the screen of the Electronics for Medicine DR-12 system, in addition to the pressure guide wire tracings, electrocardiographic tracings (ECG) as well as aortic pressure (P₁) wave forms were simultaneously displayed. A fluid-filled catheter interfaced with a Statham P23D transducer was used to obtain P₁ wave forms from the guiding catheter. After calibration of the fiber-optic pressure guide wire, the pressure-guide wire was advanced through the ultrasound catheter until the flexible distal part with the pressure sensor appeared just beyond the tip of the ultrasound probe. The ultrasound catheter was used as a protective sheath to advance the wire into the guide catheter and up to the ascending aorta. The fiber-optic pressure monitoring guide wire was then advanced beyond the ultrasound catheter, up to the tip of the guiding catheter. At that point,
equality of pressures that were registered by the guiding catheter and the fiber-optic wire was verified.

The wire was then positioned under fluoroscopic guidance into the distal part of the coronary artery and the ultrasound catheter was advanced over the wire. Guide wire P2 was recorded before and after the advancement of the ultrasound catheter to detect any changes. The ultrasound catheter that displayed continuous intracoronary images was immobilized in the most proximal coronary artery site that appeared without significant disease by angiography. The pressure guide wire was subsequently withdrawn under fluoroscopic guidance to the point where the pressure sensor that is located at the transition of the radiopaque floppy tip was just beyond the ultrasound catheter tip into the coronary arterial lumen (Fig. 1). At that point using an on-off signal, simultaneous ECG and P2 of ten cardiac cycles were recorded. The on-off signal was used to correlate electrocardiographic cycles displayed on the ultrasound console monitor with the P2 tracings and ECGs recorded on the strip chart by the Electronics for Medicine DR-12 system (Fig. 2). Subsequently, 300 μg IC-NTG were given, and 1 min after IC-NTG administration using the on-off signal another ten cycles were recorded.

Attempts were made to position the ultrasound catheter in the center of the lumen. Sites of side branches, vessel bifurcations or angular segments where the imaging plane of the ultrasound catheter was oblique were not selected. Coronary arteries less than 2.5 mm in diameter at their proximal segments, by angiography, were not evaluated because manipulations of the ultrasound catheter would have been limited.

Angiographic findings were evaluated and determined by consensus of two observers using at least six orthogonal views.

None of the patients received medications for at least 8 h before the study, and all procedures were performed in the afternoon to avoid any possible circadian morning effect on the coronary arteries.

The ICUS catheters (Endosonics, Rancho Cordova, California) that were used during this study were of a synthetic aperture array electronic transducer design with a 20-MHz operating frequency and were 1.16 mm in diameter (15). The images were stored on a 1.27 mm super VHS videotape for later review. Electrocardiographic tracings were continuously displayed on the console screen during the study.

Plaque was defined by ICUS as an eccentric or concentric echo-reflectant zone delimited internally by the lumen and externally by the echo-lucent area containing the media. A segment showing concentric or eccentric atherosclerotic plaque was considered diseased. The plaque composition was assessed visually. Soft plaque tissue was less dense than the reference adventitia. Dense fibrous tissue produced echoes that were as bright as, or brighter than, the reference adventitia but without acoustic shadowing. Calcified tissue produced bright echoes with acoustic shadowing.

At the end of the study left ventricular end diastolic pressures were recorded in all patients through a fluid-filled pigtail catheter because left ventricular end diastolic pressures can alter coronary flow and conceivably affect C-DIST.

Measurements. The CSLA was defined as the area circumscribed by the ultrasound leading-edge interface between lumen and plaque or lumen and intima. Cross-sectional area of the vessel was defined as the area inside the echo-dense perimeter of the adventitia, including the lumen area and the plaque area. Cross-sectional atherosclerotic plaque burden was defined as the sum of plaque plus media cross sectional area which was calculated by the difference of vessel cross sectional area-lumen cross-sectional area. A
Clinical and angiographic characteristics were considered the results significant when p < 0.05. The criteria for abnormality defined atherosclerosis as a maximal thickness of intimal leading edge > 0.3 mm or a sonolument zone thickness > 0.2 mm, or both. Although a single-end diastolic frame was used for measurement, review of the dynamic imaging sequence was routinely used to confirm the location of the intimal leading edge.

The formula used for C-DIST was: C-DIST = (systolic CSLA – diastolic CSLA)/[(intracoronary pulse pressure) × (diastolic CSLA)] × 1,000. Intracoronary pulse pressure was obtained from the strip-chart recording. For the determination of the largest CSLA (systolic luminal area) and the smallest CSLA (diastolic luminal area), the ECG guidance was used (16). All reported measurements represent the average of three consecutive beats. Because (systolic CSLA – diastolic CSLA)/(intracoronary pulse pressure) could be influenced by a change in blood pressure, the stiffness index (beta) (13), which is considered to be independent of the changes in blood pressure, was obtained, essentially by normalizing dimension change to the diastolic mean diameter according to the following formula: beta = {ln [systolic intracoronary pressure (S-BP)/D-BP]}/[(difference between systolic and diastolic mean diameters)/ (diastolic mean diameter)]. The systolic and diastolic mean diameters were calculated from those areas with the assumption that the cross section was circular [diameter = 2(area/π)^1/2], where π = 3.14.

**Interobserver and intraobserver variabilities.** The CSLA of 10 randomly selected sites were measured by two independent observers and by one observer two separate times. These data were used to obtain the inter- and intra-observer variability. The results were expressed as a linear regression between the two measurements and as a percent error that was derived as the absolute difference between measurements derived by the initial measurements (17).

**Statistical analysis.** Data are expressed as mean ± SD. The relation between two parameters was evaluated with a linear regression analysis. Paired t test was used to compare the data of the same segments before and after nitroglycerin injection. Pooled-variance t test or Mann-Whitney U test was used for comparisons between diabetics and nondiabetics where appropriate. Discrete data were compared by chi-square analysis. Analysis of covariance was used to detect significant differences of a dependent variable (distensibility) between the categories of a factor (diabetes mellitus: diabetics, nondiabetics) after controlling for a number of variables that were used as covariates. Statistical analyses were performed by use of the SPSS version 8.0 statistical package (SPSS Inc., Chicago, Illinois). We considered the results significant when p < 0.05.

**Results.** Clinical and angiographic characteristics were similar in the two groups, except fasting blood sugar (Table 1).

**Intracoronary ultrasound measurements.** In the diabetics, diastolic CSLA was 8.6 ± 0.6 mm² (range 6.98 to 10.65 mm²), atherosclerotic plaque burden was 4.45 ± 0.37 mm² (range 3.7 to 5.21 mm²) and luminal stenosis was 33 ± 3%. The arc of the circumference affected by the plaque was 120 ± 20°. The maximum intima plus media thickness at the nonplaque containing portion of the circumference was 0.9 ± 0.15 mm. There were 12 fibrotic plaques, 5 soft and 3 with calcium deposits.

In the nondiabetics, diastolic CSLA was 11.5 ± 0.5 mm² (range 9.2 to 13.6 mm²), atherosclerotic plaque burden was 4.25 ± 0.29 mm² (range 3.67 to 4.81 mm²) and luminal stenosis was 27 ± 5%. The arc of the circumference affected by the plaque was 111 ± 30°. The maximum intima plus media thickness at the nonplaque containing portion of the circumference was 0.8 ± 0.2 mm. Ten plaques were fibrotic, nine were soft and one had calcium deposits.

**Observer variability.** Interobserver variability for area measurements as depicted by standard deviation was ± 3.9% whereas the correlation coefficient was r = 0.95. Intraobserver variability was ± 3.1% with a correlation coefficient of r = 0.96.

**Coronary distensibility.** In the diabetics, S-BP was 136 ± 12 mm Hg (range 110 to 155 mm Hg) and D-BP was 76 ± 11 mm Hg (range 52 to 93 mm Hg). Mean pulse pressure was 60 ± 12 mm Hg. After IC-NTG injection, S-BP was 121 ± 20 mm Hg (range 100 to 155 mm Hg), and D-BP

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### Table 1. Clinical Characteristics

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<th>Nondiabetics</th>
<th>Diabetics</th>
<th>P Value</th>
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<td>Patients</td>
<td>20</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Men/women</td>
<td>13/7</td>
<td>15/5</td>
<td>NS</td>
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<tr>
<td>Age (yr)</td>
<td>54 ± 2</td>
<td>53 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
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<td>Cholesterol (mmol/liter)</td>
<td>7.13 ± 1.05</td>
<td>7.43 ± 1.55</td>
<td>NS</td>
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<td>High density lipoproteins (mmol/liter)</td>
<td>0.88 ± 0.18</td>
<td>0.86 ± 0.15</td>
<td>NS</td>
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<td>Triglycerides (mmol/liter)</td>
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<td>2.2 ± 1.5</td>
<td>NS</td>
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<tr>
<td>Fasting blood glucose (mmol/liter)</td>
<td>4.1 ± 1.1</td>
<td>8.3 ± 1.2</td>
<td>&lt; 0.01</td>
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<td>Glycated hemoglobin (%)</td>
<td>9.1 ± 0.6</td>
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<td>Coronary artery disease</td>
<td></td>
<td></td>
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<tr>
<td>One-vessel</td>
<td>12</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>8</td>
<td>9</td>
<td>NS</td>
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<tr>
<td>Angiographic stenosis at the imaging site (%)</td>
<td>29 ± 5</td>
<td>30 ± 3</td>
<td>NS</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>55 ± 4</td>
<td>53 ± 3</td>
<td>NS</td>
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1. Vavuranakis et al. 
2. JACC Vol. 34, No. 4, 1999
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was 75 ± 11 mm Hg (range 50 to 87 mm Hg). Mean pulse pressure was 46 ± 10 mm Hg.

Mean systolic CSLA increased from 9.5 ± 0.7 mm² to 10.6 ± 0.78 mm² after IC-NTG and mean diastolic CSLA increased also from 8.6 ± 0.6 mm² to 9.3 ± 0.8 mm². Thus, IC-NTG induced a 11.5% ± 6% increase in systolic CSLA and a 8.1% ± 7% in diastolic CSLA. Consequently, C-DIST increased from 1.73 ± 0.1 mm Hg⁻¹ (range 1.56 mm Hg⁻¹ to 1.84 mm Hg⁻¹) to 3.02 ± 0.14 mm Hg⁻¹ (range 2.83 mm Hg⁻¹ to 3.31 mm Hg⁻¹) after IC-NTG (p < 0.01), whereas beta decreased from 11.2 ± 1 (range 9.8 to 13) to 7.1 ± 0.4 (range 6.3 to 8) (p < 0.001). Mean left ventricular end diastolic pressure at the end of the study was 6.3 ± 2 mm Hg.

Before IC-NTG in the nondiabetics, S-BP was 128 ± 12 mm Hg (range 108 to 158 mm Hg) and D-BP was 76 ± 7 mm Hg (range 55 to 95 mm Hg). Mean pulse pressure was 52 ± 12 mm Hg. After IC-NTG injection, S-BP was 111 ± 12 mm Hg (range 90 to 125 mm Hg) and D-BP was 71 ± 10 mm Hg (range 50 to 85 mm Hg). Mean intracoronary pulse pressure was 40 ± 10 mm Hg.

Mean systolic CSLA increased from 12.5 ± 0.9 mm² to 13.7 ± 0.8 mm² after IC-NTG. Mean diastolic CSLA increased from 11.5 ± 0.5 mm² before IC-NTG to 11.7 ± 0.9 mm² after IC-NTG. Thus, IC-NTG induced a 9.6% ± 10% increase in systolic CSLA and 2% ± 1% in diastolic CSLA. Therefore, C-DIST increased from 1.68 ± 0.12 mm Hg⁻¹ (range 1.42 mm Hg⁻¹ to 1.95 mm Hg⁻¹) to 4.21 ± 0.15 mm Hg⁻¹ (range 4.0 mm Hg⁻¹ to 4.5 mm Hg⁻¹) after nitroglycerin injection (p < 0.01) whereas beta decreased from 11.7 ± 3 (range 8.3 to 15.7) to 3.8 ± 0.5 (range 3.0 to 4.9) (p < 0.001). Mean left ventricular end D-BP at the end of the study was 5.8 ± 2.1 mm Hg.

Thus, before IC-NTG there was no difference in S-BP (p = 0.06) and D-BP (p = 0.8) between diabetics and nondiabetics. After IC-NTG, S-BP decreased significantly in diabetics (p < 0.01) and in nondiabetics (p < 0.01), but absolute values of S-BP remained similar among the two groups (p = 0.07). However, D-BP decreased significantly after IC-NTG only in the nondiabetics (p = 0.04). Percent changes in systolic CSLA induced by IC-NTG were similar between the two groups, whereas percent changes in diastolic CSLA were smaller in the nondiabetics. Although C-DIST (p = 0.1) and beta (p = 0.8) were similar between diabetics and nondiabetics at baseline, C-DIST increased and beta decreased significantly in both groups after IC-NTG. Furthermore, C-DIST was greater (p < 0.01) and beta was smaller (p = 0.001) in the nondiabetics compared with the diabetics after IC-NTG. There was a good inverse correlation between atherosclerotic plaque burden and changes in C-DIST after IC-NTG in the nondiabetic patients (r² = 0.746, p = 0.0001, Fig. 3) but not in the diabetics, (r² = 0.19, p = 0.06, Fig. 4).

Although diabetics had coronary arteries with smaller systolic and diastolic CSLA before and after IC-NTG administration compared with nondiabetes (p < 0.01), there was no significant difference in atherosclerotic plaque burden, plaque characteristics and arc of the circumference affected by the atherosclerotic plaque. However, the degree of luminal stenosis was greater in diabetics compared with nondiabetics (p = 0.002).

No correlation was observed between changes in C-DIST after IC-NTG and known duration of diabetes, high density lipoprotein cholesterol, fasting glucose and glycated hemoglobin levels.

Analysis of covariance revealed that C-DIST after IC-NTG was significantly different between diabetics and nondiabetics (p = 0.021) after correction for a number of variables that were used as covariates (age, S-BP, D-BP, pulse pressure, plaque burden, CSLA).

In the whole patient population, C-DIST was inversely correlated with plaque burden (p = 0.033, r² = 0.113).
DISCUSSION

Coronary artery distensibility and diabetes. Our findings provide evidence for impaired augmentation of C-DIST after IC-NTG, an endothelium independent vasodilator, in patients with NIDDM. Previous studies in diabetics using forearm blood flow measurements reported reduced responsiveness of the arterial smooth muscle to intrabrachial nitroglycerin infusion (7). Our study documented similar changes in the coronary arterial bed. This is not unexpected because coronary arteries are affected and damaged by diabetes more frequently than the forearm arteries. Both impairment of the nitric oxide pathway, through which nitroglycerin acts, and dysfunction of the arterial smooth muscle cells would produce the same result (18). Studies in diabetics implicate increased inactivation of nitric oxide by oxygen-derived free radicals or advanced glycosylation end products and abnormal response of vascular smooth muscle to nitric oxide, involving either the receptor for guanylate cyclase or subsequent signal transduction, as the main mechanisms (19).

Subtle differences in the elastic properties of the coronary arterial wall between the two groups might not have been detected by our technique before IC-NTG in the presence of an impaired biologic effect of nitric oxide due to atherosclerosis (20,21). These subtle differences may have been revealed only after IC-NTG, an exogenous donor of ample amounts of nitric oxide. Indeed, structural changes in diabetics (22) may alter intrinsic vessel wall properties and increase coronary artery stiffness. The relative short duration of diabetes and its mild clinical course may have produced only mild alterations in C-DIST, which were detected only after IC-NTG. Combination of the ICUS study with tissue characterization of the arterial wall will be necessary to clarify the role of intrinsic factors in determining vessel distensibility. Age and calcification of the vessel wall may also affect distensibility (23).

In the nondiabetics, smaller percent changes in diastolic CSLA induced by IC-NTG may be due to the significant decrease in D-BP. Absolute levels of blood pressure will also affect vessel distensibility (24). However, changes in beta were in accordance with those of C-DIST.

Severe atherosclerosis in coronary artery segments is characterized by medial smooth muscle atrophy (25). Such structural changes may severely impair C-DIST and mask differences between diabetics and nondiabetics. Because our purpose was to study the effect of NIDDM on C-DIST, we selected segments without significant CAD. Furthermore, total atherosclerotic plaque burden was not significantly different between the two groups of patients. We used total atherosclerotic plaque burden as an index of the arterial wall encroachment by the atherosclerotic process. Thus, we assumed that we compared distensibility in coronary segments that should have responded similarly to IC-NTG injection if NIDDM had not been present.

A good correlation between atherosclerotic plaque burden and changes in C-DIST was observed only in nondiabetics. This correlation was poor in diabetics, which implies that other factors are more important determinants of C-DIST in diabetics. However, we found a poor correlation between increases in C-DIST after IC-NTG and known duration of diabetes, high density lipoprotein cholesterol, fasting glucose and glycated hemoglobin levels, which supports the hypothesis that the mechanical property of the coronary arterial wall that is represented by C-DIST is independent of these factors. Systolic and diastolic CSLA was smaller in diabetics at baseline, and although total plaque burden and circumference of the artery involved appeared similar in both groups, there may be more diffuse atherosclerosis in the diabetics. Similarly, the larger CSLA in nondiabetics may have influenced our results. However, analysis of covariance revealed that C-DIST after IC-NTG differed significantly between diabetics and nondiabetics even after correcting for CSLA.

Our study supports the view that the presence of diabetes mellitus is associated with reduced arterial elasticity (24) and provides evidence that this also applies to the coronary arteries (12). It is possible that the impaired elastic properties of the coronary arterial wall may play an important role in the development of elastic recoil and restenosis after coronary angioplasty in diabetics.

Study limitations. Images of ICUS represent a thin tomographic cross-section of the artery and cannot be used to evaluate changes simultaneously in adjacent segments. The size of the ultrasound catheter (1.17 mm) excluded segments with severe stenosis from evaluation. Measurements of CSLA performed at diastole and systole may not refer to the same coronary site precisely, because the position of the transducer with respect to vessel-wall landmarks may change during the cardiac cycle.

Although it has been shown that the distribution of the atherosclerotic plaque affects regional augmentation of CSLA after IC-NTG administration (13), we determined only total vessel distensibility. This was because the intima-media thickness at the nonplaque containing arc was beyond the reported upper normal limits and could not be assumed to be free of atherosclerotic changes.

We compared segments with similar total plaque burden. However, despite the similar total atherosclerotic plaque burden, an identical effect on the elastic behavior of the coronary arterial wall can only be assumed.

The interval that the medications were on hold before the study may not be enough to guarantee complete absence of pharmacologic effects. It is also possible that other drugs, such as lipid lowering agents, may have influenced vasoreactivity to nitroglycerin, although we consider this possibility remote.

Conclusions. Our findings help to elucidate the mechanisms by which nitroglycerin acts on the coronary arteries of diabetic patients. The results of this study indicate that coronary arteries of diabetics may not respond as well as the
coronary arteries of nondiabetics to nitroglycerin, a therapeutic agent used routinely to treat ischemic heart disease.

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REFERENCES