

Determinants of Coronary Compliance in Patients With Coronary Artery Disease: An Intravascular Ultrasound Study

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Objectives. The aim of this study was to elucidate determinants of coronary compliance in patients with coronary artery disease.

Background. Intravascular ultrasound potentially enables in vivo evaluation of coronary artery compliance.

Methods. Twenty-seven patients (mean age [\pm SD] 57 ± 11 years, three women) undergoing coronary angioplasty were studied with intravascular ultrasound imaging. A mechanical intravascular ultrasound system (4.8F, 20 MHz) was used. A total of 58 different coronary segments (proximal to the target angiographic lesion) were studied. Of these, 35 were located in the left anterior descending, 9 in the left main, 8 in the left circumflex and 6 in the right coronary arteries. During intravascular ultrasound imaging, 22 segments (38%) appeared normal, but 36 (62%) had plaque (24 fibrotic, 3 lipidic and 9 calcified). Systolic-diastolic changes in area (ΔA) and pressure (ΔP) with respect to vessel area (A) were used to study normalized compliance (Normalized compliance = $[\Delta A/A]/\Delta P$ [$\text{mm Hg}^{-1} \times 10^3$]).

Results. Lumen area and plaque area were 12.6 ± 5.7 and 3 ± 3 mm^2 , respectively. Plaque was concentric (more than two

quadrants) at 10 sites, but the remaining 26 plaques were eccentric. Compliance was inversely related to age ($r = -0.34$, $p < 0.05$) but was not related to other clinical variables. Compliance was greater in the left main coronary artery (3.9 ± 2.1 vs. 1.8 ± 1.2 mm Hg^{-1} , $p < 0.05$) and in coronary segments with normal findings on ultrasound imaging (2.9 ± 1.9 vs. 1.6 ± 1.1 mm Hg^{-1} , $p < 0.01$). Moreover, at diseased coronary segments compliance was lower in calcified plaques than in other types of plaques (1.2 ± 0.7 vs. 2.3 ± 1.6 mm Hg^{-1} , $p < 0.01$) but was similar in concentric and eccentric plaques (1.6 ± 1.5 vs. 1.6 ± 0.9 mm Hg^{-1}). Plaque area ($r = -0.38$, $p < 0.01$) was inversely correlated with compliance. On multivariate analysis, only age and plaque area were independently related to compliance.

Conclusions. Intravascular ultrasound may be used to evaluate compliance in patients with coronary artery disease. Compliance is reduced with increasing age and is mainly determined by the arterial site and by the presence, size and characteristics of plaque on intravascular ultrasound imaging.

(*J Am Coll Cardiol* 1994;23:879-84)

Intravascular ultrasound imaging is a new technique for tomographic real-time visualization of the coronary arteries (1,2). Recent studies have demonstrated its usefulness for analyzing coronary vessel wall morphology and measuring lumen dimensions and area (1-5). Pathologic studies have also demonstrated that this technique provides new insights concerning the extent of coronary artery disease and unique in vivo information about atherosclerotic plaque composition (6,7). In addition, by measuring the changes in vessel lumen area resulting from systolic-diastolic changes in pressure, intravascular ultrasound has the capability to determine vessel compliance. Compliance of peripheral arteries in humans has been evaluated by ultrasound imaging (8). However, only preliminary data suggest the value of intra-

vascular ultrasound imaging for assessing compliance of coronary arteries in patients (9).

In this prospective investigation we attempted to elucidate determinants of coronary artery compliance in vivo, using intravascular ultrasound to study patients with angiographically proved coronary artery disease.

Methods

Patients. Twenty-seven consecutive patients with good quality intravascular ultrasound recordings obtained immediately before coronary angioplasty were included. Patients were considered eligible for intravascular ultrasound imaging when the proximal segment of the artery that was going to be dilated was large on angiography (>2.5 mm) and nontortuous. Mean age of the group was 57 ± 11 years, and three patients were women. Reasons for coronary angioplasty included unstable angina in 20 patients and stable angina in 7. Five patients had a prior history of myocardial infarction, nine had multivessel disease, and mean left ventricular ejection fraction was $65 \pm 16\%$. Thirteen patients were hypertensive, and 6 had diabetes mellitus. In five

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Manuscript received June 14, 1993; revised manuscript received November 1, 1993, accepted November 4, 1993.

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patients coronary angioplasty was attempted at more than one angiographic site, but intravascular ultrasound studies were performed only in one of the major coronary arteries.

Procedures. Coronary angioplasty procedures were performed in the standard manner (10,11). A conventional balloon coronary angioplasty was performed in 16 patients, 7 patients underwent coronary atherectomy and 4 patients underwent coronary stenting (Palma-Schatz stent) electively for restenosis. Coronary angioplasty was attempted in 19 lesions in the left anterior descending coronary artery, 3 in the left circumflex coronary artery and 5 in the right coronary artery.

Intravascular ultrasound catheter. Intravascular ultrasound studies were always performed with a 4.8F mechanical intravascular ultrasound catheter (Boston Scientific). This catheter includes a single-element piezoelectric crystal transducer (20 MHz, 1.75-mm aperture) at its distal tip, which is rotated 900 rpm. The catheter has a polyethylene outer shaft with a single distal port to be advanced over a 0.014-in. (0.036-cm) guide wire. Catheters were connected to an image console (Diasonics), and intravascular ultrasound images were displayed in real time during the procedure and also were stored on a 0.5-in. (1.27-cm) VHS videotape for subsequent playback and analysis.

Imaging protocol. All patients gave informed consent to the procedure and received 0.2 mg of intracoronary nitroglycerin before undergoing intravascular ultrasound imaging. Intravascular ultrasound catheters were advanced through large lumen (≥ 0.78 in. [1.98-cm] inner diameter) guiding catheters to facilitate the advancement of the system and to allow injection of contrast material to monitor the location of the transducer (radiopaque) with respect to angiographic landmarks. Special care was taken to avoid occlusive catheters producing changes in the aortic pressure while engaging the ostium. Intravascular ultrasound catheters were advanced under continuous fluoroscopic monitoring while imaging and subsequently slowly pulled back manually to study the coronary artery proximal to the target angiographic lesion. Gain settings were adjusted to optimize visualization of the plaque and the boundaries of the coronary lumen and to highlight particular regions of interest. At sites where a relatively central catheter position was obtained and optimal visualization of the entire lumen-wall interface was achieved, the movement of the catheter was stopped. At this moment aortic pressure was recorded through the guiding catheter. Arterial pulsatility was analyzed by continuously recording systolic and diastolic changes in the lumen area. Sites near the takeoff of side branches, near the lesion that was going to be dilated, and sites where the imaging catheter was wedged into the plaque, resulting in a small residual lumen, were excluded.

Qualitative and quantitative analysis. The presence and morphologic characteristics of atherosclerotic plaque were analyzed jointly by two experienced observers. Agreement was reached by consensus. Plaques were defined as well visualized structures of different echogenicity on the vessel

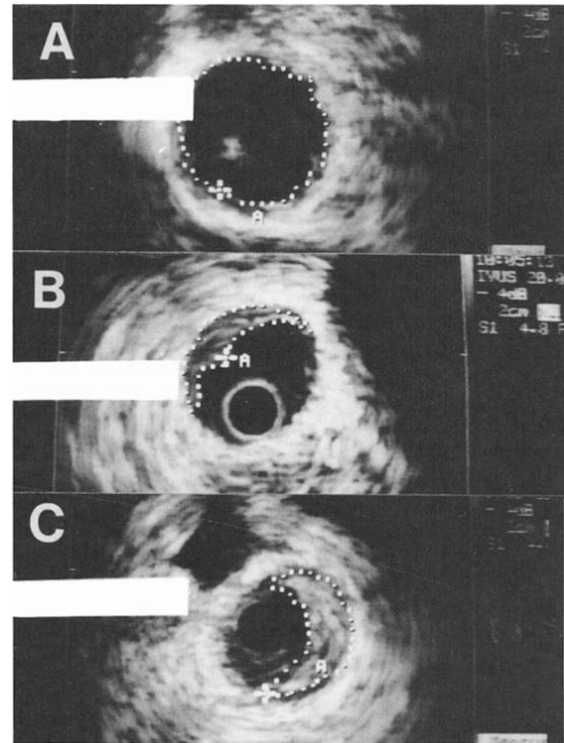


Figure 1. Measurements of lumen area and plaque area. A, Lumen area traced within the dotted line. B and C, Measurements of plaque area (dotted line) in two fibrous plaques with different shape and size.

wall, either protruding into the vessel lumen or disrupting normal coronary wall architecture. Plaques were classified as hypoechogenic or fibrotic, considering their predominant echorefectivity, according to previously suggested criteria (12,13). Calcification was considered present in plaques with bright reflecting areas inducing distal shadowing. The number of quadrants with plaque was analyzed to determine plaque distribution along the entire perimeter of the coronary lumen. Plaques affecting one or two quadrants of the coronary lumen were considered eccentric.

Quantitative analysis of intravascular ultrasound images was performed off-line with a specific computer software (Hewlett-Packard Sonos 1000 system). Measurements included cross-sectional lumen area and plaque area (Fig. 1). Plaque area was also normalized to vessel area. The outer boundaries of plaque were determined following the internal elastic lamina (12,13). Maximal and minimal lumen areas at the selected sites were identified by frame by frame playback analysis. Vascular pulsatility was determined as both the absolute change in area in mm^2 and also as percent (difference between planimetered large and small areas divided by small area times 100). Absolute compliance was determined from systolic-diastolic changes in area resulting from pressure changes (Absolute compliance = Change in area/Change in pressure [$\text{mm}^2/\text{mm Hg} \times 10^3$]). Subsequently, compliance was also normalized to reference vessel area [Normalized compliance = (Change in area/Vessel area)/

Table 1. Location and Extension of Plaque According to Plaque Characteristics

Segments (no.)	Vessel				Quadrants			
	LM	LAD	LCx	RCA	1	2	3	4
Calcified (9)	0	6	1	2	7	2	0	0
Fibrotic (24)	4	15	3	2	4	11	8	1
Hypoechoic (3)	0	1	0	2	2	0	0	1
Normal (22)	5	13	4	0	—	—	—	—

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; RCA = right coronary artery.

Change in pressure ($\text{mmHg}^{-1} \times 10^3$). To assess interobserver and intraobserver variability for measurements of lumen area and plaque area, a random subset of 10 diseased coronary segments was reanalyzed in a blinded manner.

Statistical analysis. Data are presented as mean value \pm SD for continuous variables and as a percent for categorical variables. Discrete variables were compared with the chi-square test or the Fisher exact test. Continuous variables were compared with a two-tailed Student *t* test. Analysis of variance (Newman-Keuls test) was used to compare means within groups. Correlations were determined by linear regression analysis. Variables that were associated with absolute and normalized compliance on univariate analysis were included in a logistic regression analysis to determine independent predictors of coronary compliance. Accordingly, both absolute and normalized compliance were dichotomized into two categorical variables (upper compliance and lower compliance groups) using two different percentiles (tertiles [33% percentile] and the 50% percentile). Variables with independent predictive value and able to improve the value of discrimination criteria were selected. A *p* value $<$ 0.05 was considered statistically significant.

Results

Intravascular ultrasound findings. A total of 58 different coronary segments with optimal systolic and diastolic images were analyzed. Of these, 35 were located in the left anterior descending, 9 in the left main, 8 in the left circumflex and 6 in the right coronary artery. During intravascular ultrasound imaging, 22 coronary segments (38%) appeared normal, but the remaining 36 segments (62%) had plaque (24 fibrotic, 3 hypoechoic, 9 calcified). Plaque involved a single quadrant of the vessel perimeter in 13 cases and involved two quadrants in 13 cases. Ten plaques were considered concentric (more than two quadrants). Table 1 shows the distribution of different types of plaques within the coronary tree and the number of quadrants of the vessel perimeter affected by plaque. All nine calcified plaques were eccentric (seven involving only one quadrant). The distribution of the normal coronary segments during intravascular ultrasound imaging is also presented in Table 1.

On quantitative analysis, maximal lumen cross-sectional

Table 2. Vessel Area and Pulsatility

	Area (mm^2)	Pulsatility	
		mm^2	%
LM	$15.8 \pm 2.2^*$	$3.55 \pm 2.1^+$	$22.4 \pm 12^+$
LAD	13.2 ± 6.4	1.41 ± 1.1	11.0 ± 7
LCx	9.7 ± 3.4	0.91 ± 0.4	10.4 ± 6
RCA	$8.2 \pm 2.9^+$	1.16 ± 0.9	13.6 ± 9

**p* $<$ 0.01 (vs. all other vessels). +*p* $<$ 0.05 (vs. all other vessels). Abbreviations as in Table 1.

area was $12.6 \pm 5.7 \text{ mm}^2$, minimal lumen cross-sectional area $11 \pm 5.2 \text{ mm}^2$ and mean plaque area $3 \pm 3 \text{ mm}^2$. Coronary pulsatility was $1.6 \pm 1.5 \text{ mm}^2$ or $15 \pm 14\%$. Lumen area and vessel pulsatility according to type of vessel are listed in Table 2. Correlation for measurements of plaque area between observers was $r = 0.94$, SEE = 0.09 mm^2 , and for lumen area $r = 0.96$, SEE = 0.09 mm^2 . Within the individual observer, correlation for plaque area was $r = 0.95$, SEE = 0.07 mm^2 , and for vessel lumen area $r = 0.97$, SEE = 0.04 mm^2 .

Determinants of absolute coronary compliance. Absolute coronary compliance for the 58 sites studied was $26.6 \pm 24.5 \text{ mm}^2/\text{mm Hg}$. Compliance was reduced in arteries of diabetic patients (17 ± 16 vs. $29 \pm 25 \text{ mm}^2/\text{mm Hg}$, $p <$ 0.05) but was not significantly reduced in coronary segments of hypertensive patients (24 ± 19 vs. $29 \pm 28 \text{ mm}^2/\text{mm Hg}$, $p = \text{NS}$) and was not related to age ($r = -0.22$, $p = \text{NS}$). Compliance was strongly related to arterial pulsatility ($r = 0.91$, $p <$ 0.001) and moderately related to maximal lumen area ($r = 0.34$, $p <$ 0.01), but it was inversely related to plaque area ($r = -0.36$, $p <$ 0.01) and to normalized plaque area ($r = -0.42$, $p <$ 0.01). The relation between coronary compliance and the type of vessel is presented in Figure 2. Compliance was greater in the left main coronary artery, but no differences were found among the other three large epicardial vessels. Compliance was greater for coronary vessels appearing normal on ultrasound imaging than for diseased coronary segments (Fig. 3), but there was no relation between coronary compliance and the number of quadrants with plaque. In fact, compliance was similar in eccentric and concentric plaques (19 ± 13 vs. $16 \pm 16 \text{ mm}^2/\text{mm Hg}$, $p = \text{NS}$). In contrast, the type of plaque (hypoechoic, fibrotic, calcified) was related to arterial compliance. Segments with calcified plaques had a reduced compliance as compared with that of noncalcified plaques (Fig. 4).

Normalized compliance. Compliance was normalized to vessel area to avoid the influence of vessel size on arterial compliance as previously determined. Normalized compliance had an inverse relation with age ($r = -0.34$, $p <$ 0.05) but was not related to other clinical variables. However, the same anatomic features previously found to be associated with absolute compliance were related to normalized compliance. Normalized compliance was greater in the left main coronary artery (3.9 ± 2.1 vs. $1.8 \pm 1.2 \text{ mm Hg}^{-1}$, $p <$ 0.05)

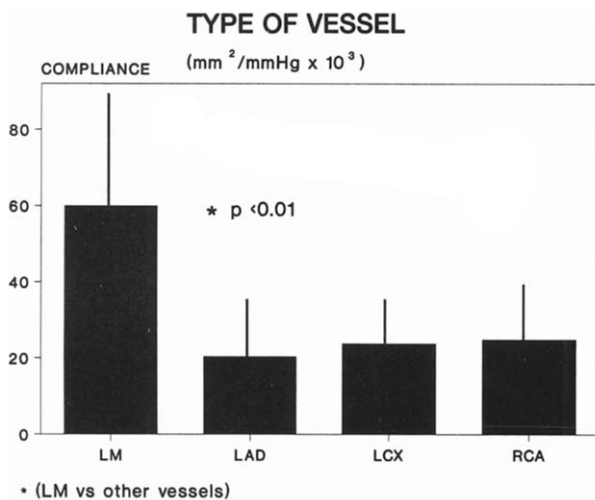


Figure 2. Coronary artery compliance according to the vessel studied. Compliance was greater in the left main coronary artery (LM) than in other vessels. LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

and in coronary segments appearing normal on intravascular ultrasound imaging (2.9 ± 1.9 vs. 1.6 ± 1.1 mm Hg⁻¹, $p < 0.01$). Normalized compliance was lower in segments with calcified plaques (1.2 ± 0.7 vs. 2.3 ± 1.6 mm Hg⁻¹, $p < 0.01$) than in segments with other type of plaque, but was similar in concentric and eccentric plaques (1.6 ± 1.5 vs. 1.6 ± 0.9 mm Hg⁻¹). Plaque area was also inversely related to normalized compliance ($r = -0.38$, $p < 0.01$).

Independent correlates of compliance and normalized compliance on multivariate analysis were similar when tertiles or the 50% percentile were used to separate vessels with higher and lower compliance (Table 3). Only age and plaque area appeared as independently related to normalized compliance.

Figure 3. Compliance in diseased coronary segments and in coronary segments appearing normal on intravascular ultrasound imaging.

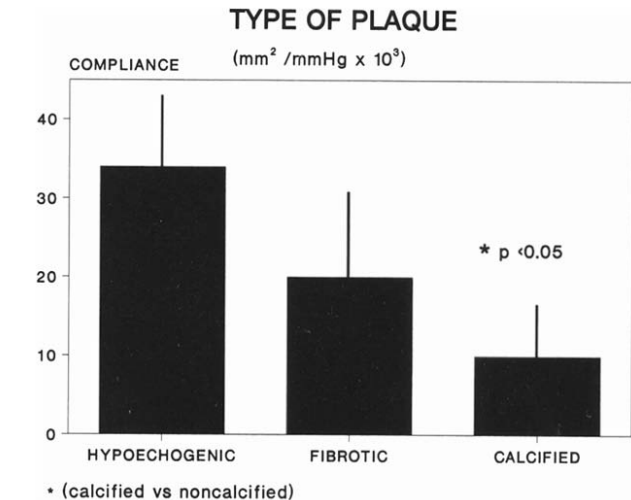
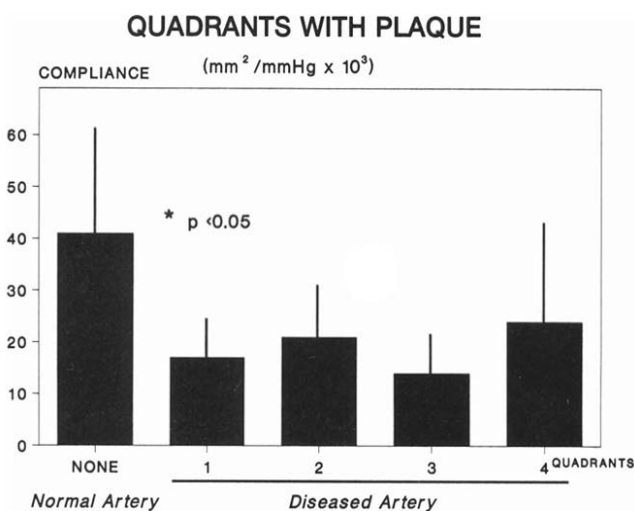


Figure 4. Coronary artery compliance in different types of plaque as determined with intravascular ultrasound imaging.

Procedural results. No complications were related to the intravascular ultrasound examination. All coronary angioplasty procedures were completed with success, although in one patient who initially underwent balloon dilation, stent implantation was eventually required (for an occlusive dissection) to achieve a satisfactory angiographic result.

Discussion

Intravascular ultrasound is a new technique providing the unique opportunity to study lumen dimensions and area as well as the severity and extent of atherosclerotic disease in vivo (1-5). Unlike coronary angiography, which only portrays a silhouette of the coronary lumen, intravascular ultrasound allows accurate measurements of lumen cross-sectional area and gives some insights concerning plaque characteristics (1-5). Moreover, by measuring systolic and diastolic changes in lumen area corresponding to systolic and diastolic changes in pressure, this technique potentially enables the study of coronary compliance in patients. However, to date only limited information supports the value of intravascular ultrasound imaging to determine coronary artery compliance (9). In this prospective investigation we attempted to evaluate the feasibility and usefulness of intra-

Table 3. Results of Multivariate Analysis

Compliance		Normalized Compliance	
Variable	p Value	Variable	p Value
Diabetes	NS	Age	0.022
Vessel area	NS	Left main coronary artery	NS
Left main coronary artery	NS	Normal vessel on IVUS	NS
Normal vessel on IVUS	NS	Calcium	NS
Calcium	NS	Plaque area	0.029
Normalized plaque area	0.018		

IVUS = intravascular ultrasound imaging.

vascular ultrasound imaging to assess coronary compliance in patients with coronary artery disease. In addition, we sought to identify determinants of coronary artery compliance *in vivo*.

Clinical determinants of compliance. Our results suggest that with currently available technology the study of coronary artery compliance is feasible at selected coronary sites, where intravascular ultrasound measurements have a good intra- and interobserver variability. Because arteries of different sizes but with similar elastic properties may respond with different absolute changes in area in response to the same distending pressure, compliance should be normalized to lumen area. In this investigation, coronary artery compliance, as absolute change in area, was significantly reduced in diabetic patients. However, when compliance was normalized for vessel size, an inverse relation between compliance and age was found, but compliance was no longer reduced in patients with diabetes. This observation suggests that the reduced changes in area seen in our diabetic patients may be a consequence of their smaller arteries. Megnien et al. (8) studied compliance of large human arteries and suggested that diabetes mellitus may induce intrinsic alterations on the elastic properties of the arterial walls. Nissen et al. (14) suggested that coronary intimal thickening increases with age. All of our patients had proved coronary artery disease in the imaged vessel because all of them underwent the intravascular ultrasound examination immediately before intervention. Furthermore, all of our patients had normal blood pressure during the intravascular ultrasound study; this fact is relevant because an elevation in blood pressure stretches the arteries and, as compliance is a nonlinear function of blood pressure in a given arterial segment, increased blood pressure reduces vessel distensibility (8). Pharmacologic modifications of aortic pressure during intravascular ultrasound studies will be required to fully elucidate the effect of different levels of pressure on coronary pulsatility.

Anatomic factors. Our findings suggest that anatomic factors are the major determinants of coronary artery compliance in patients with coronary artery disease. Moreover, all anatomic factors that were associated with a reduced compliance in absolute values were also determinants of reduced normalized compliance. In the present study, compliance was greater in the left main coronary artery, but no significant differences were found among the three other large epicardial vessels. It is well established that the left main coronary artery has an elevated content of elastic fibers, which may predispose to elastic recoil after coronary angioplasty (15), and this may explain the greater compliance of this vessel. Nevertheless, some methodologic factors should also be considered. It seems reasonable that the pressure waveform recorded from the guiding catheter will be a more accurate correlate of the actual pressure within the vessel lumen in large proximal coronary segments (such as the left main stem) than in smaller vessels. Although in our study we tried to diminish this potential limitation by select-

ing relatively large and proximal coronary segments (which on intravascular ultrasound imaging showed a well preserved coronary lumen surrounding the imaging catheter), we cannot rule out the possibility of some pressure damping induced by the imaging system. An artifactual decrease in pressure will decrease pulsatility even in coronary segments with preserved elastic properties.

Our results also suggest that coronary segments manifesting disease on intravascular ultrasound imaging have a reduced compliance compared with that of segments appearing normal on imaging. The sensitivity of intravascular ultrasound imaging for detecting atherosclerotic plaque is by far superior to that of conventional coronary angiography, and plaque is commonly detected with intravascular ultrasound studies in coronary segments that are normal on angiography (1,5,16). In addition, because intravascular ultrasound imaging constitutes a valuable tool to assess plaque characteristics (6,7), it provides a unique opportunity to correlate the morphologic features of the plaque with coronary compliance. In this regard, calcified plaques in our study had a reduced compliance, as compared with that of noncalcified plaques. An unexpected finding was the lack of association between the number of quadrants with plaque and coronary compliance. In other words, compliance was similar in arteries with eccentric and concentric plaques. However, all calcified plaques that we analyzed were confined to one or two quadrants, an observation that may explain the reduced compliance of eccentric plaques in our series.

Our findings suggest that plaque area is a more important determinant of vessel compliance than are other anatomic factors. In fact, plaque area was an independent determinant of arterial compliance in our series. Reddy et al. (9) found that coronary atheroma reduced distensibility in nondilated vessels. They also suggested that plaque fracture produced after coronary angioplasty increased vessel distensibility. Brogan et al. (17) recently suggested that by altering plaque compliance, as the result of reducing plaque mass, rotational atherectomy may facilitate coronary balloon angioplasty in lesions that cannot be dilated. We did not attempt to analyze compliance at the target angiographic lesion, because we believe that with our methodology and current technology analysis of compliance at sites with severe lumen narrowing may suffer from important limitations (18). Finally, other investigators (19) have suggested that arterial bifurcations are an independent cause of local stiffening. However, we excluded coronary sites near the takeoff of side branches to avoid the potential influence of this factor.

Limitations. Several potential limitations in the study of human coronary compliance *in vivo* apply to the present investigation:

- 1) Our study includes a small number of patients and only provides some insights on the elastic properties of coronary vessels. To precisely assess compliance, curves depicting changes in volume according to several pressure conditions are needed for every coronary segment.

2) We did not measure intracoronary pressure. Assuming that the pressure recorded with the guiding catheter represents a valid estimation of the pressure at the imaging site may not be correct in some cases and may also modify the temporal relation between pressure changes and changes in lumen area. Accordingly, the use of miniaturized pressure catheters to monitor pressure changes at the selected sites has been advocated (20). However, at present this approach is technically cumbersome in coronary vessels and is limited by inaccuracies in the position of the catheters, nonsimultaneous sampling and profile differences between pressure and intravascular ultrasound catheters. In this regard, the use of currently available 3.5F catheters would be more appropriate to avoid potential attenuations of intracoronary pressure induced by the catheter.

3) In our study, only cross-sectional coronary segments were used to analyze compliance. This methodology does not take into account the potential tethering effect induced by either long atherosclerotic plaques or neighbor plaques. Intravascular ultrasound studies with three-dimensional reconstruction capabilities will be required to determine the influence on compliance of focal versus diffuse coronary disease.

Conclusions and clinical implications. Coronary compliance may be determined in vivo and is dependent on clinical and anatomic factors. Compliance decreases with age and with increasing plaque area. It is greater in the left main coronary artery and is reduced in diseased coronary segments, mainly at calcified sites. The study of coronary artery compliance may provide complementary information on coronary artery disease (to that of the severity of lumen narrowing) and may have prognostic and therapeutic implications. The study of compliance may also prove useful in guiding selection of the coronary angioplasty device best suited for each type of lesion, in determining changes in compliance after interventions and, on theoretic grounds, it could also be related to the subsequent development of elastic recoil and restenosis.

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