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Morphology of Vulnerable Coronary Plaque: Insights from Follow-up of Patients Examined by Intravascular Ultrasound Before an Acute Coronary Syndrome

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OBJECTIVES To determine the morphologic features of coronary plaques associated with acute coronary syndrome, we prospectively followed patients with atherosclerotic disease identified by intravascular ultrasound (IVUS).

BACKGROUND Although clinical evaluation of the vulnerable atherosclerotic plaque is important, few data exist regarding the morphology of the vulnerable plaque in clinical settings.

METHODS We examined 114 coronary sites without significant stenosis by angiography (<50% diameter stenosis) in 106 patients. All the sites exhibited atherosclerotic lesions by IVUS. These lesions consisted of 22 concentric and 92 eccentric plaques with a percent plaque area averaging 59 ± 12%.

RESULTS During the follow-up period of 21.8 ± 6.4 months (range 1 to 24), 12 patients had an acute coronary event at a previously examined coronary site at an average of 4.0 ± 3.4 months after the initial IVUS study. All the preexisting plaques related to the acute events exhibited an eccentric pattern and the mean percent plaque area was 67 ± 9%, which was greater than plaque area in the other 90 patients without acute events (57 ± 12%, $p < 0.05$). There was no statistically significant difference in lumen area between two patient groups (6.7 ± 3.0 vs. 7.5 ± 3.7 mm^2). Among 12 coronary sites with an acute occlusion, 10 sites contained the echolucent zones, eight of these shallow and two deep, likely representing a lipid-rich core. In 90 sites without acute events, an echolucent zone in the shallow portion was seen at only four sites ($p < 0.05$).

CONCLUSIONS Large eccentric plaque containing an echolucent zone by IVUS can be at increased risk for instability even though the lumen area is preserved at the time of initial study. Compensatory enlargement of vessel wall due to remodeling may contribute to the relatively small degree of stenosis by angiography. (J Am Coll Cardiol 2000;35:106–11) © 1999 by the American College of Cardiology

Necropsy studies and intracoronary angioscopy have demonstrated that most acute coronary syndromes, including acute myocardial infarction (AMI) and unstable angina, are the consequence of rupture or erosion of a preexisting atherosclerotic plaque with subsequent local thrombus formation (1–4). Prior angiographic studies in patients who present with an AMI demonstrate that the coronary lumen is preserved until just before the acute occlusion, often showing a relatively minor stenosis, typically less than a 50% reduction in luminal diameter (5–7). Ambrose et al. (7) reported that minor to moderate luminal irregularities with an irregular ulcerative contour were the most prominent angiographic finding predictive of subsequent occlusion. However, elucidation of the precise morphology of the atherosclerotic plaque associated with acute coronary syndromes has remained difficult, because angiography provides only a silhouette of the vessel lumen, not precise intramural plaque morphology (8).

Intravascular ultrasound (IVUS) enables assessment of the morphology and distribution of atherosclerotic plaque in vivo (9,10). Nissen et al. (11) demonstrated that IVUS

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Abbreviations and Acronyms
AMI = acute myocardial infarction
IVUS = intravascular ultrasound
MI = myocardial infarction

could potentially differentiate stable from vulnerable plaque by showing a thin intimal leading edge and large intimal echolucent zones within the plaque. However, it remains unclear whether IVUS-derived plaque characteristics can be used to predict subsequent acute coronary events.

Development of a method for prospective identification of vulnerable plaque would have major clinical implications, potentially allowing application of coronary interventions techniques, to prevent subsequent acute occlusion (12). Therefore, we performed this study to prospectively identify plaque features associated with subsequent acute coronary syndromes. In coronary disease patients, a descriptive classification of their atherosclerotic plaques was performed using IVUS. Patients were subsequently followed for occurrence of an acute coronary syndrome. In those patients with and without subsequent acute coronary events, plaque characteristics by IVUS were compared to identify morphologic features of preexisting atherosclerotic plaques predictive of rupture.

METHODS

Patients. From April 1994 to March 1996, informed consent for the present protocol was obtained in 112 patients who were admitted for diagnostic or interventional cardiac catheterization. The principal indications for coronary angiography and IVUS in this cohort were diagnosis of chest pain (13), effort angina in 88 patients and rest angina in 24 patients. Because of the requirement for informed consent, these patients were not consecutive series. There were 92 men and 20 women with a mean age of 56 years.

IVUS study protocol. After routine catheterization procedures were completed, coronary sites with atherosclerotic disease were systematically examined by IVUS. The ultrasound transducer (30 MHz, 3.5F, Sonicath or 3.2F, Ultracross, Boston Scientific Corporation, Boston, Massachusetts) was advanced as distally as possible over a guidewire (0.014 in.) and withdrawn by a slow manual or mechanical (1 mm/s) pullback. Wherever a significant atherosclerotic plaque was observed, pullback was temporarily interrupted and the plaque carefully examined. Criteria for inclusion of a plaque in the study database included all of the following: 1) an atheroma thickness >0.5 mm (14), 2) an angiographically insignificant (<50% diameter) stenosis, and 3) a lesion not requiring intervention. We included only sites with focal or segmental lesions, avoiding diffuse atherosclerotic disease, because of the difficulty in selecting specific individual sites from a diffusely diseased artery. However, if IVUS demonstrated the multiple lesions in a single coronary artery, all such sites were identified and classified.

Precise localization of each interrogated site was accomplished using fluoroscopy to identify the IVUS transducer within the vessel. Identification of the side branches by IVUS and the presence of a calcified lesion were also helpful to localize the position of the IVUS transducer. In 72 patients in whom an automatic pullback system was used for IVUS interrogation, measurement of time from various landmarks to the target lesion provided a distance measurement—1 mm × time (s). Using the aforementioned techniques, the angiographic location of all examined sites was documented. Intravascular ultrasound images were recorded into s-VHS videotape for measurements.

IVUS measurements. After the procedure, the lesions were planimetered by the measurement software incorporated in the ultrasound system (M2400A, Hewlett Packard or Clearview, Boston Scientific, Boston, Massachusetts). Lumen area was determined by tracing the boundary between the lumen and the intimal leading edge. Total vessel area was determined by tracing the leading-edge of the media-adventitia boundary. Percent plaque area was computed using the formula: {(total vessel area − lumen area)/total vessel area} × 100. At the studied sites, the maximal and minimal thickness of the vessel wall was measured and an atheroma eccentricity index calculated by the formula: {(maximal thickness − minimal thickness)/maximal thickness}. The plaque was defined as concentric if this index was <0.5 and as eccentric if the atheroma eccentricity index was ≥0.5 (14). Calcified lesions were defined by the presence of echogenic plaque with acoustic shadowing (15).

Because presence of the lipid-rich core may be an important requisite for the plaque vulnerability (16), we particularly searched an intraplaque echolucent zone, defined as an area of low echogenicity with a thickness >0.3 mm (17). However, we did not classify a plaque as containing a lipid-rich core if attenuation or acoustic shadowing produced the echolucent zone. The position of the echolucent core within the plaque was defined as "shallow" if the echolucent zone occupied the half of plaque depth closest to the lumen, and defined as "deep" if the echolucent zone was present within the deeper half of the plaque. Although the thickness of the fibrous cap of the plaque also may play a role in atheroma vulnerability (3), we did not measure the thickness of fibrous cap because trailing edge measurement by ultrasound are confounded by limitations in axial resolution and ultrasound beam divergence.

Follow-up imaging. We defined the study end points as the occurrence of an acute coronary syndrome including myocardial infarction (MI) or unstable angina. All patients presenting with an acute coronary syndrome during the follow-up period were subjected to repeat coronary angiography to determine the site of acute occlusion and some of these patients underwent emergent interventional proce-

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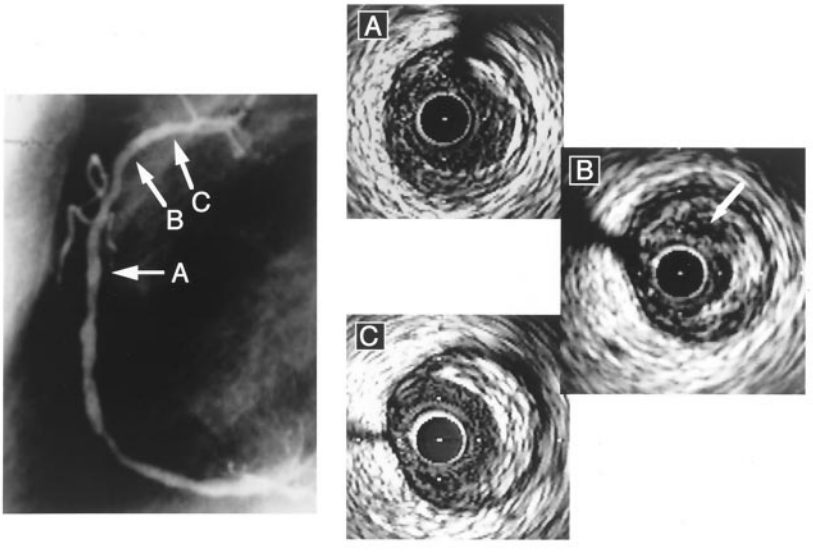

Figure 1. Representative intravascular ultrasound image of vulnerable atherosclerotic plaque. **(Left)** The right coronary angiography showed multiple luminal irregularities. **(Right) (A)** At the distal portion, there existed mild concentric lesion. **(B)** In the proximal portion there was a significant eccentric lesion in which the echolucent area with percent plaque area of 67% was seen **(arrow)**. **(C)** At the very proximal of this artery, there was also eccentric lesion with relatively high echo density. All three lesions were examined at follow-up.

dures. Patients without acute coronary syndrome were followed for 24 months after the initial IVUS study. We retrospectively reviewed the original IVUS images at the examined coronary sites to evaluate the presence of vessel remodeling (compensatory enlargement). The total vessel area at each site and an adjacent proximal reference segment were measured. The presence of compensatory enlargement was defined as the total vessel area at the disease site that was at least 10% larger than the total vessel area at the corresponding proximal reference site.

Intra- and interobserver variability. The vessel area and lumen areas of 10 randomly selected disease sites were measured by two observers and by one observer at two separate sessions. We also studied 16 other sites to determine interobserver agreement in the assessment of the presence of an echolucent zone within the plaque. Results were expressed as a linear regression correlation coefficient between the two measurements. Percent error was determined from the absolute difference between two measurements divided by the initial measurements.

Statistical analysis. Data are expressed as mean ± standard deviation. Unpaired Student *t* test was used for continuous variables and the chi-square test for categorical variables. A Cox's proportional hazard model was used for the end point of acute coronary syndrome with backward entry of the following covariates: percent plaque area, history of smoking, history of hypertension, hypercholesterolemia and history of diabetes mellitus. A McNemar chi-square test was used for determining the interobserver agreement of IVUS evaluation of intraplaque echolucent zone. We considered the results significant when the p value was <0.05.

RESULTS

Analyzed coronary segments. We finally examined 114 coronary sites from 106 patients who met all inclusion criteria. The remaining six patients were excluded because of the incomplete follow-up. Among the included patients, three different coronary sites were examined from one patient and two different sites from six patients. There were 90 men and 16 women, and mean age was 54 ± 10 years. Eighty-seven patients had stable angina pectoris at the time of the initial examination. Nineteen patients had a history of unstable angina and 44 patients had previous MI.

Coronary risk factors included hypertension (systolic pressure >160 mm Hg and diastolic pressure >90 mm Hg) in 73 patients, hypercholesterolemia (>250 mg/100 ml) in 60, glucose intolerance in 58 and smoking in 78. The examined vessels consisted of 64 left anterior descending arteries, 32 right coronary arteries and 10 left circumflex arteries. Ultrasound morphology consisted of 92 eccentric and 22 concentric lesions. Mean percent plaque area was 59 ± 12%.

Acute coronary syndromes. During the follow-up period of 21.8 ± 6.4 months (range 1 to 24 months), 16 patients experienced an acute coronary syndrome. In 12 of these patients angiography revealed a culprit lesion at the same sites where the preexisting atherosclerotic disease had been demonstrated by the IVUS (Figs. 1 and 2). The remaining four patients showed a culprit lesion in a different vessels than the artery originally studied at enrollment. The mean

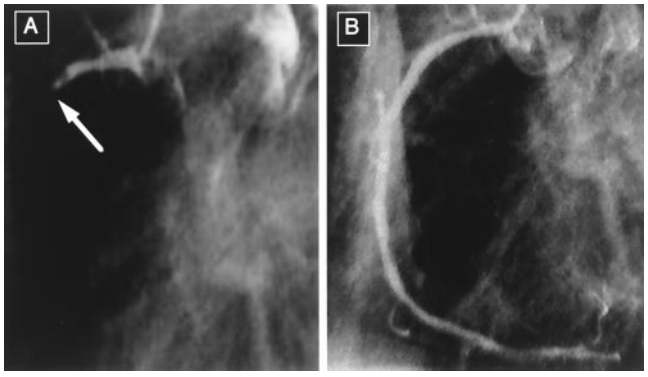

Figure 2. Coronary angiography before and after emergent angioplasty. Three months after registration, the patient had acute inferior myocardial infarction. Under these conditions **(A)** the coronary artery was totally occluded at the portion where the eccentric plaque with echolucent area had been seen by ultrasound. **(B)** Emergent balloon angioplasty that was done at the site of total occlusion resulted in complete recanalization of this artery.

follow-up period of these 12 patients was 4.0 ± 3.4 months (range 1 to 8 months). Among these 12 patients, 3 patients had the history of stable effort angina pectoris, and 9 patients had the history of previous MI at another coronary site.

Patients with acute coronary syndromes. Since the behavior of various plaques within the same patient are likely not to be independent, we compared only one coronary site per patient. Therefore, in the one patient who had acute coronary syndrome at one site out of three examined sites, the remaining two originally imaged sites were excluded for comparison. The four patients whose acute coronary syndromes occurred at a coronary site not examined at the original IVUS study were also excluded. In the six patients without an acute coronary syndrome in whom two sites were examined at the original IVUS study, we averaged the percent plaque area of the two different sites.

In the 12 patients with acute coronary syndrome, the preexisting disease showed eccentric lesions with the percent plaque area of 67 ± 9%. An echolucent zone within the plaque was found in 10 of 12 sites (Fig. 1). The position of echolucent zone in this group was shallow in eight sites and was deep in two sites. A calcified plaque was present at five coronary sites. At the time of the initial IVUS examination, the lumen area in this group was 6.7 ± 3.0 mm^2. Compensatory enlargement was observed in 7 of 12 coronary sites.

Patients without acute coronary syndromes. In 90 patients without an acute coronary syndrome, at IVUS examination there were 67 eccentric and 23 concentric lesions. The percent plaque area of these sites was 57 ± 12%, which was significantly smaller than the culprit sites in patients with an acute coronary syndrome ($p < 0.05$). The lumen area in the stable subgroup was 7.5 ± 3.7 mm^2 at the time of initial IVUS study. There was no statistically significant difference in lumen area between the patients with or without acute coronary syndrome. An echolucent zone was observed in 19 out of the 90 sites. Strikingly, however, an echolucent zone located in the shallow portion of the plaque was observed in only four patients ($p < 0.05$ compared with the unstable group). With respect to clinical history in the patients with an echolucent zone within the plaque, 10 patients had effort angina pectoris, and nine patients had MI (NS).

There was no statistical difference regarding the risk factors between two groups. However, nearly all the examined patients had at least one risk factor. Analysis using Cox's proportional hazard model also revealed that the percent plaque was the significant determinant for the occurrence of acute coronary syndrome during follow-up period (Parameter estimate = 0.070, Standard error = 0.033, Wald chi-square = 4.533, p chi-square = 0.033).

Observer variability. Interobserver correlation coefficient and the percent error for the total vessel area was r = 0.99 and 2.3 ± 2.0%, respectively. Values for lumen area were r = 0.99 and 5.4 ± 6.6%, respectively. The intraobserver correlation coefficient and the percent error were 0.99 and 3.5 ± 2.3% for the total vessel area and 0.98 and 4.9 ± 4.7% for the lumen area. As for the accuracy for determination of intraplaque echolucent zone by IVUS, there was no statistical significance in interobserver agreement (p = 0.803).

DISCUSSION

In this study, we prospectively followed patients who had undergone systematic IVUS interrogation of a major epicardial coronary vessel to determine atherosclerotic plaque morphology. The goal of this study was determination of the morphologic appearance of the plaque that subsequently would result in an acute coronary syndrome. Although the lumen area was preserved at the time of initial examination, plaques that ultimately caused an acute coronary syndrome exhibited a relatively large plaque volume and were strikingly eccentric in plaque distribution. Furthermore, we frequently observed an echolucent zone close to the luminal surface (shallow location) in plaques that ultimately became unstable.

Necropsy studies have suggested that among the determinants of the plaque vulnerability, the size of plaque area was less significant than the presence of lipid-rich core (16). However, a recent angiographic study demonstrated that coronary stenosis rapidly increased prior to the onset of acute coronary syndrome (18,19). Under these conditions, the severity of the preexisting atherosclerotic disease may be an important factor in accelerating luminal occlusion. According to the concept of coronary remodeling originally proposed by Glagov et al. (20), the coronary lumen is usually preserved until the plaque involvement reaches about 40% of the vessel circumference. Lim et al. (21) demonstrated that compensatory enlargement occurs in approximately 80% patients examined by IVUS, as observed in this study. Therefore, it remains possible that the coronary stenosis

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becomes unstable when the plaque volume exceeds the capacity of compensation (22). Under these conditions, a remodeled atheroma may be vulnerable to mechanical forces leading to plaque rupture (23,24). In the presence of vessel remodeling, it is reasonable that angiography underestimates the disease severity.

We frequently observed an echolucent zone within the plaques that eventually became unstable. A recent clinicopathologic study indicated that the echolucency of the plaque could represent the presence of a lipid-rich core (17) where metaloproteinases are associated with erosion of the fibrous cap (25). Therefore, one might speculate that the presence of the echolucent zone might be indicative of plaque vulnerability. Other methods such as analysis of plaque composition by ultrasonic tissue characterization (26), atheroma temperature (27) or tissue reflection in the near infrared spectrum (28) may prove helpful to identify the lipid-rich core and plaque vulnerability.

The eccentric plaque distribution appears to be more vulnerable than the concentric disease (1–3). This is likely related to the mechanism of the plaque rupture. We previously reported that the eccentric plaque had heterogeneous vessel wall distensibility (29) that could represent a mechanical factor in plaque rupture (30).

Clinical implications and limitations. The ability to identify vulnerable plaque has major clinical implications, since acute coronary syndromes including sudden death represent the leading cause of morbidity and mortality in modern civilizations. The present data demonstrate the increased risk of rupture for an eccentric atheroma with a relatively large plaque burden and a shallow echolucent zone which are observed by IVUS. If confirmed by further studies, this observation may allow selection of specific patients for very aggressive risk factor interventions to reduced morbidity and mortality (31).

There remain limitations of our study. First, the precise mechanism of the acute coronary event remains unclear, because we did not perform the IVUS examination at the time of the acute coronary syndrome. The repeated IVUS examination in the setting of an evolving acute coronary syndrome may demonstrate the mechanism of the occlusion, although we did not believe it appropriate to perform intracoronary examination prior to reperfusion.

Second, in view of the intervals ranging one to eight months between the initial IVUS examination and the development of acute coronary syndromes, the lesions may have changed in composition during these periods. Accordingly, it remains possible that a plaque could increase in the size or the echolucent zone could expand through intraplaque necrosis. Conversely, the size of these lipid-rich zones may decrease as plaque fibrose or calcify. Serial IVUS observation in such patients would be required to demonstrate changes in the plaque composition during the disease process. To statistically account for the variable length of follow-up, we applied Cox's proportional hazard model with percent plaque area and patients' risk factors as variables. However, the small number of patients who exhibited acute coronary syndrome limits any conclusions from this analysis, although this analysis revealed importance of percent plaque area for possible occurrence of acute coronary syndrome.

Finally, this study was not performed in a truly randomized fashion, because we could only examine the patients in whom informed consent was obtained. Further study with multicenter, randomized design will be required to fully elucidate IVUS morphology in the atherosclerotic plaque associated with acute coronary syndrome.

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