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Attenuated Plaque Detected by Intravascular Ultrasound

Clinical, Angiographic, and Morphologic Features and Post-Percutaneous Coronary Intervention Complications in Patients With Acute Coronary Syndromes

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Objectives We evaluated the clinical significance of attenuated plaque (hypoechoic plaque with deep ultrasound attenuation).

Background Attenuated plaques are unusual intravascular ultrasound (IVUS) findings in patients with acute coronary syndrome (ACS).

Methods We reviewed clinical presentations and angiographic and pre-intervention IVUS findings in 293 ACS patients undergoing percutaneous coronary intervention (PCI) without a distal protection device: 187 with non–ST-segment elevation myocardial infarction (NSTEMI) and 106 with ST-segment elevation myocardial infarction (STEMI).

Results Attenuated plaque was observed in 75 patients (25.6%): 39.6% of STEMI versus 17.6% of NSTEMI ($p < 0.001$). (We also reviewed 100 randomly selected patients with stable angina and pre-intervention IVUS; none had attenuated plaque.) Overall, in ACS patients with attenuated plaques: 1) the level of C-reactive protein was higher; 2) angiographic thrombus and initial coronary flow Thrombolysis In Myocardial Infarction flow grade <2 were more common; and 3) IVUS lesion site plaque burden and remodeling index were significantly greater, lesion site luminal dimensions significantly smaller, and thrombus, positive remodeling, and plaque rupture were more common. No-reflow (26.7% vs. 4.6%, $p < 0.001$) and deteriorated post-PCI coronary blood flow (8.0% vs. 2.8%, $p = 0.001$) were higher. In ACS patients with normal coronary blood flow at baseline, deterioration in the coronary blood flow post-PCI was more common in lesions with attenuated plaque.

Conclusions Attenuated plaque was more common in ACS patients with STEMI than NSTEMI. Attenuated plaque in ACS patients was associated with a higher C-reactive protein level, more severe and complex lesion morphology, reduced coronary blood flow before PCI, and *especially* no-reflow after PCI. (J Am Coll Cardiol Intv 2009;2:65–72) © 2009 by the American College of Cardiology Foundation

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Intravascular ultrasound (IVUS) can be used to identify high-risk or unstable lesion morphologies. For example, IVUS data have indicated that acute coronary syndrome (ACS) lesions more often have positive remodeling (1–3), plaque rupture (4,5), and hypoechoic (soft) plaque (1,6–8) compared with non-ACS lesions. IVUS characteristics that can predict no-reflow and/or increased creatine kinase-MB after percutaneous coronary intervention (PCI) (9–12) include a larger plaque burden (13,14), intracoronary mobile mass (15), lipid pool-like plaque characteristics (16,17), and, most recently, attenuated plaque (defined as deep ultrasound attenuation without calcification) (18). However, attenuated plaques have not been studied in detail in patients with ACS. Therefore, we report the frequency; clinical, angiographic, and morphologic features; and post-PCI complications of IVUS-detected attenuated plaques in patients with ACS.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CSA = cross-sectional area
CTFC = corrected Thrombolysis In Myocardial Infarction frame count
EEM = external elastic membrane
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
P&M = plaque and media
RCA = right coronary artery
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Methods

Patient population. We identified 293 patients with ACS (187 patients with non–ST-segment elevation myocardial infarction [NSTEMI] and 106 patients with ST-segment elevation myocardial infarction [STEMI]) treated with PCI who had undergone pre-intervention IVUS imaging between January 2006 and March 2007 at the Washington Hospital Center. During this time period, PCI was performed in 1,306 ACS patients of whom 39.1% had IVUS guidance. We excluded 217 patients with target lesions that were restenotic, graft vessel disease, lesions located at the side branch, lesions that were pre-dilated before IVUS, lesions treated with any distal protection or thrombectomy device, and IVUS image acquisition using below 40 MHz transducers. The clinical, angiographic, and IVUS feature of these 293 patients are the basis of this report. The study protocol was approved by the internal review board at MedStar Research Institute at Washington Hospital Center.

An experienced research nurse obtained clinical demographics at the time of the procedure. Demographic information included gender, age, presence of hypercholesterolemia (treated or >240 mg/dl), diabetes mellitus (dietary glycemic control or oral agent or insulin-treated), hypertension (medication-treated), family history of coronary artery disease, and current or experienced smoking.

Angiographic analysis. Angiograms were analyzed by an independent operator (S.W.K.) using standard methodology and blinded to the clinical and IVUS findings (19). Angiographic coronary blood flow was assessed at baseline and after PCI based on Thrombolysis In Myocardial Infarction (TIMI) flow grade (20) and corrected Thrombolysis In Myocardial Infarction frame count (CTFC) (21). Angiographic no-reflow was defined as a post-PCI decrease from baseline in final TIMI flow grade <2 after PCI without identified mechanical obstruction. Presence or absence of intracoronary thrombus (discrete intraluminal filling defect), intimal flap (discrete intraluminal filling defect), and calcification were also evaluated.

IVUS analysis. All IVUS studies were performed before any intervention and after intracoronary administration of 200 μg of nitroglycerin using a commercial scanner (Boston Scientific Corporation, Maple Grove, Minnesota) that consisted of a 40-MHz transducer mounted on the tip of a flexible shaft rotated at 1,800 rpm within a 2.6 to 3.2-F monorail sheath. The IVUS catheter was advanced beyond the lesion followed by automatic transducer pull back (at 0.5 mm/s) to the aorto-ostial junction. IVUS images were recorded onto 0.5-inch high-resolution s-VHS videotape or digitally onto a CD or DVD for offline analysis.

Qualitative analysis was performed blind to clinical data according to criteria of the American College of Cardiology clinical expert consensus document on IVUS (22). Lesion site was at the minimum lumen cross-sectional area (CSA). Distal and proximal references segments were the most normal looking cross sections within 10 mm distal and proximal to the lesion site, respectively. Using planimetry software (TapeMeasure, INDEC Systems, Mountain View, California), we measured external elastic membrane (EEM) and lumen CSA (mm^2) at the lesion site and at the proximal and distal reference segments. If EEM circumference could not be identified because of attenuation, we interpolated the EEM area. Plaque and media (P&M) CSA was calculated as EEM minus lumen CSA. Plaque burden was calculated as P&M divided by EEM CSA. Plaque eccentricity was calculated as maximum P&M thickness minus minimum P&M thickness divided by maximum plaque plus media thickness. Remodeling index was defined as the lesion site EEM CSA divided by mean reference-segment EEM CSA. Positive remodeling was defined as a remodeling index >1.0, intermediate/negative remodeling as a remodeling index <1.0 (22).

Lesion plaque composition at the culprit lesion was assessed visually (22). IVUS plaque rupture was defined as the presence of a cavity that communicated with the lumen with an overlying residual fibrous cap fragment (23). Thrombus was an intraluminal lobulated mass with evidence of blood flow (microchannels) within the mass,

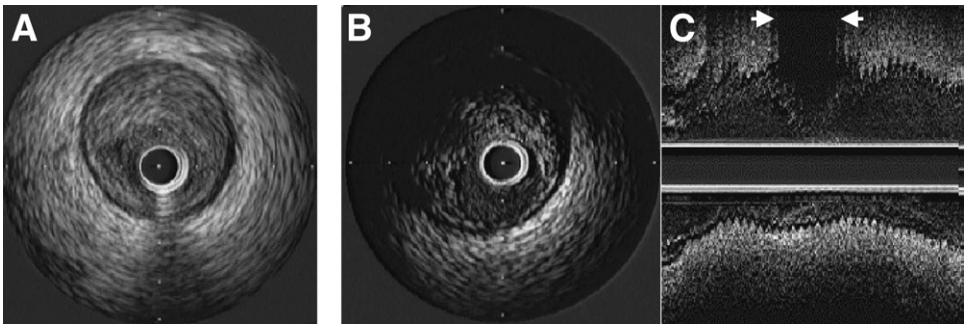

Figure 1. Normal Versus Attenuated Plaque in IVUS

Cross-sectional intravascular ultrasound (IVUS) images of plaque without attenuation **(A)** and plaque with attenuation **(B)** in cross-sectional images and longitudinal reconstruction **(C, between the white arrows)**. Ultrasound attenuation occurred despite the absence of calcium.

mobility, and sparkling or scintillation appearance (24). Attenuated plaque was defined as hypoechoic plaque with deep ultrasound attenuation without calcification or very dense fibrous plaque (Figs. 1 and 2). Attenuated plaque required the agreement of 2 independent, experienced observers (S.Y.L. and N.J.W.); lesions in which these 2 observers disagreed were excluded. With motorized transducer pullback, we measured the distance from each attenuated plaque back to the respective coronary ostium (pullback speed multiplied by number of seconds). Calcification was identified as very bright echoes (brighter than the adventitia) with acoustic shadowing of deeper tissue zones (25). Fibrotic plaques can also produce shadowing or attenuation; however, their echoreflectivity distinguishes them from attenuated plaques.

Statistics. Statistical analysis was performed with StatView 5.0 (SAS Institute, Cary, North Carolina). Continuous variables were expressed as mean ± SD and compared with Student unpaired *t* test. Categorical variables were expressed as frequencies and compared with chi-square statistics. A p value <0.05 was considered statistically significant.

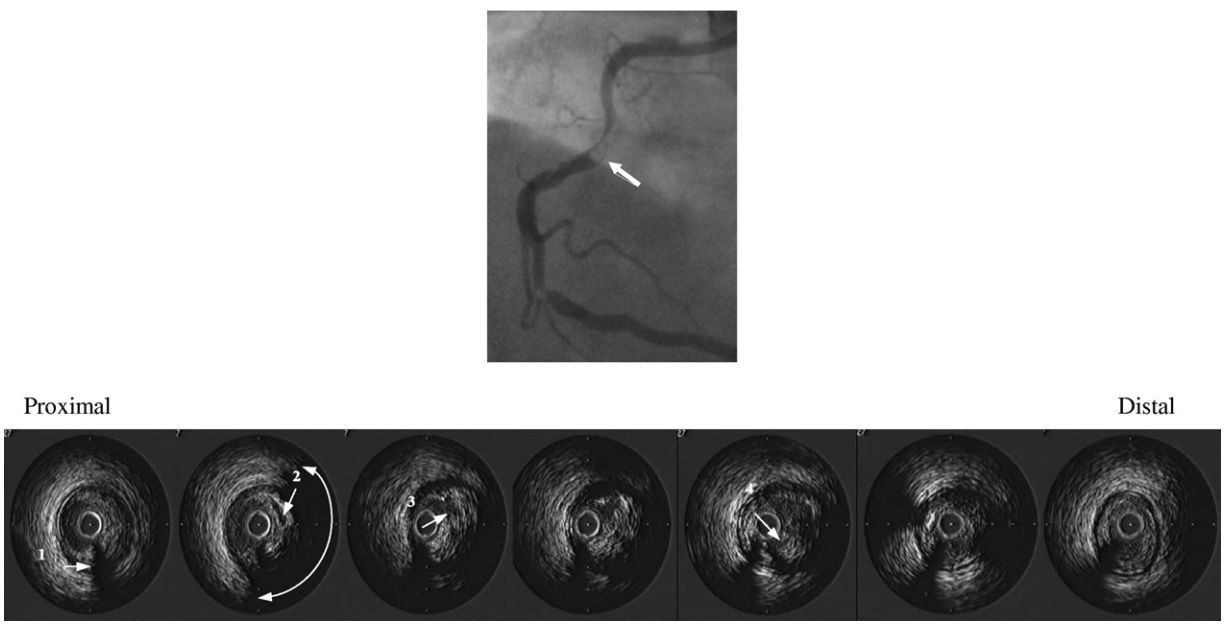

Figure 2. IVUS Findings in Angiographic Thrombotic Lesion

Angiogram shows a right coronary artery with lesion containing a filling defect **(arrow)**. In the corresponding intravascular ultrasound (IVUS) imaging run with cross sections 0.5 mm apart, double-headed curved **white arrows** outline the echo attenuation with an angle of 155°, **arrow 1** indicates guidewire-induced artifact, **arrow 2** indicates lipid pool, **arrow 3** indicates plaque rupture, and **arrow 4** indicate thrombus.

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Results

Attenuated plaque was observed in 75 of 293 (25.6%) ACS patients; 42 of 106 (39.6%) STEMI patients, and 33 of 187 (17.6%) NSTEMI patients ($p < 0.001$). Three lesions were excluded because of disagreement between observers; these 3 lesions were located adjacent to calcium. For the purposes of comparison, we also reviewed a random sample of 100 patients with stable angina undergoing pre-PCI IVUS between January 2006 and March 2007 selected from our database; none of them had attenuated plaques.

Patient baseline characteristics are shown in Table 1. There were no significant differences in cardiac risk factors in ACS patients with attenuated plaques except that attenuated plaques were observed more often in male patients ($p = 0.002$) and in patients with a high C-reactive protein level ($p = 0.03$). There were no significant differences in use of thrombolytics in STEMI patients or use of direct thrombin inhibitors or glycoprotein IIb/IIIa inhibitors comparing the 2 groups.

Baseline angiographic and IVUS data. Angiographic data are shown in Table 2. Most lesions with attenuated plaque were detected in the left anterior descending coronary artery (LAD) and right coronary artery (RCA); 80% were located in proximal and midcoronary artery segments of the LAD and RCA. One patient with NSTEMI had 2 attenuated plaques: 1 was located in the mid-RCA and the other in the proximal RCA (Fig. 3). Angiographic thrombus was more frequently found in target lesions with attenuated plaque, and angiographic calcification was less common. Baseline TIMI flow grade was reduced, and CTFC was higher in ACS patients with attenuated plaque compared with that in patients without attenuated plaque.

IVUS data are summarized in Table 3. Lesion site plaque burden, plaque eccentricity, and remodeling index were significantly greater, and lesion site lumen area and minimal lumen diameter was significantly smaller in lesions with attenuated plaque. IVUS target lesion thrombus, positive remodeling, and plaque rupture were more common in lesions with attenuated plaque. By IVUS analysis, attenuated plaques were predominately located at the proximal portions of a coronary artery—specifically, within 40 mm from the ostium in 62 (82.7%) patients (Fig. 4). Echo attenuation was located at the minimal lumen CSA site in 65 of 75 patients (86.7%) and proximal to it in 6 (8.0%) patients. Attenuated plaques were more frequently found in

Table 1. Clinical and Laboratory Data

	Patients With Attenuated Plaque (n = 75)	Patients Without Attenuated Plaque (n = 218)	p Value
Age (yrs)	61.9 ± 13.8	65.2 ± 14.1	0.08
Male, n (%)	56 (74.7)	121 (55.5)	0.002
STEMI/NSTEMI, n	42/33	64/154	<0.001
Hypertension, n (%)	65 (86.7)	174 (79.8)	0.1
Diabetes mellitus, n (%)	21 (28.0)	64 (29.4)	0.34
Hypercholesterolemia, n (%)	59 (81.9)	173 (78.3)	0.24
Smoking, n (%)	30 (40.0)	76 (34.9)	0.43
Family history of coronary disease, n (%)	35 (46.7)	78 (35.8)	0.06
LV ejection fraction <30%, n (%)	13 (17.3)	40 (18.3)	0.49
Primary or rescue PCI, n (%)	30 (40.0)	67 (30.7)	0.015
Use of thrombolytics in STEMI patients, n (%)	14 (33.3)	18 (28.1)	0.12
Use of glycoprotein IIb/IIIa inhibitors, n (%)	10 (13.3)	46 (21.1)	0.09
Use of direct thrombin inhibitors, n (%)	47 (54.7)	107 (49.1)	0.24
C-reactive protein (mg/dl) at admission	33.1 ± 70.8	10.8 ± 15.6	0.03
CK-MB (mg/dl) at admission	24.1 ± 42.1	29.2 ± 56.1	0.47
Peak CK-MB (mg/dl) after PCI	30.5 ± 65.9	26.1 ± 48.9	0.55
Duration of hospital stay, days	4.79 ± 3.47	4.40 ± 2.28	0.27

CK = creatine kinase; LV = left ventricular; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Angiographic Data

	Attenuated Plaque (n = 75)	No Attenuated Plaque (n = 218)	p Value
Artery, n (%)			0.25
Left main		2 (0.9)	
LAD	36 (48.0)	112 (51.4)	
LCX	9 (12.0)	39 (17.9)	
RCA	30 (40.0)	65 (29.8)	
Location			0.9
Proximal	23 (30.7)	71 (32.6)	
Mid	44 (58.7)	122 (56.0)	
Distal	8 (10.7)	25 (11.5)	
Thrombus, n (%)	35 (46.7)	40 (18.3)	<0.001
Intimal flap, n (%)	4 (5.3)	8 (3.7)	0.32
Calcification, n (%)	2 (2.7)	32 (14.7)	0.014
Multivessel disease, n (%)	45 (60.0)	123 (56.4)	0.3
Baseline TIMI flow grade, n (%)			<0.0001
0/1	10 (13.3)	15 (6.9)	
2	27 (36.0)	13 (6.0)	
3	38 (50.7)	190 (87.2)	
CTFC	36.6 ± 19.2	25.1 ± 11.25	<0.001
Post-PCI TIMI flow grade, n (%)			<0.001
0/1	2 (2.7)	3 (1.4)	
2	18 (24.0)	7 (3.2)	
3	55 (73.3)	208 (95.4)	
CTFC	27.3 ± 10.7	22.9 ± 8.0	<0.001

CTFC = corrected Thrombolysis In Myocardial Infarction (TIMI) frame count; LAD = left anterior descending coronary artery; LCX = left circumflex artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

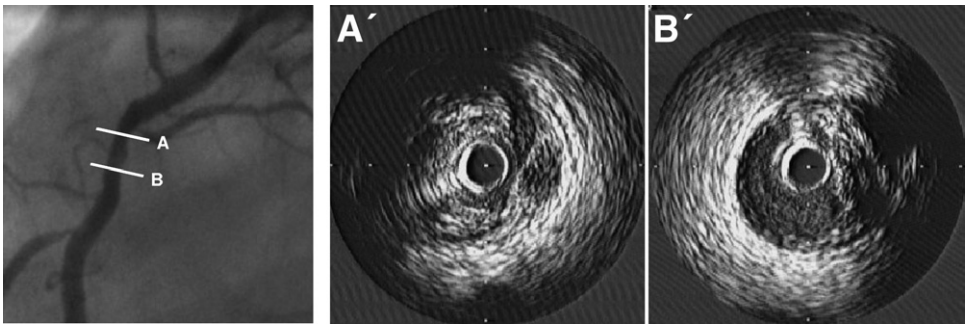

Figure 3. Two Attenuated Plaques in Lesion at Mid-RCA

Angiogram shows a right coronary artery (RCA) with lesions containing luminal haziness **(B)** with corresponding intravascular ultrasound imaging run **(A', B')**. Two attenuated plaques 6.4 mm apart were seen in this RCA.

lesions with plaque ruptures compared with those seen in lesions without plaque ruptures (42.4% vs. 18.8%, p = 0.001).

Outcomes. A total of 311 stents were implanted; but there were no significant differences in stent number (1.14 ± 0.42 vs. 1.05 ± 0.34 per lesion, p = 0.08), stent size (3.23 ± 0.47 vs. 3.19 ± 0.43 mm, p = 0.4), or stent length (21.5 ± 7.8 vs. 20.3 ± 7.4 mm, p = 0.2) comparing the 2 groups (with vs. without attenuated plaques).

Post-PCI coronary flow was restored to normal in 89.7% of ACS patients, but it deteriorated compared with that seen in baseline in 4.1% of ACS patients. No-reflow (26.7% vs. 4.6%, p < 0.001) and deteriorated post-PCI coronary blood flow (8.0% vs. 2.8 %, p = 0.001) were more common, and CTFC (Table 2) was higher in ACS patients with attenuated plaque compared with that in patients without attenuated plaque. In patients with TIMI flow grade <2 at baseline, improvement of coronary blood flow post-PCI (75.7% vs. 89.3%, p = 0.3) was not different between the 2 groups; but in lesions with normal coronary blood flow (TIMI flow grade 3) at baseline, deterioration in the coronary blood flow post-PCI (13.2% vs. 3.2%, p = 0.021) was more common in lesions with attenuated plaque. There were no significant differences in peak levels of creatine kinase-MB after PCI, and the duration of hospital stay was similar comparing the 2 groups (Table 1).

Table 3. IVUS Data at Lesion Site

	Attenuated Plaque (n = 75)	No Attenuated Plaque (n = 218)	p Value
EEM CSA (mm^2)	12.0 ± 3.9	11.6 ± 4.8	0.57
Lumen CSA (mm^2)	2.1 ± 0.9	2.6 ± 1.4	0.003
P&M CSA (mm^2)	9.9 ± 3.8	9.1 ± 4.6	0.13
Plaque burden (%)	81.8 ± 8.4	75.8 ± 11.2	<0.001
Minimum lumen diameter (mm)	1.39 ± 0.23	1.57 ± 0.38	0.001
Remodeling index	1.00 ± 0.25	0.91 ± 0.27	0.007
Positive remodeling, n (%)	36 (48.0)	63 (28.9)	0.008
Plaque eccentricity	0.65 ± 0.23	0.56 ± 0.28	0.019
Lobulated mass, n (%)	29 (38.7)	29 (13.3)	0.001
Plaque rupture, n (%)	36 (48.0)	49 (22.5)	0.001

CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; P&M = plaque and media.

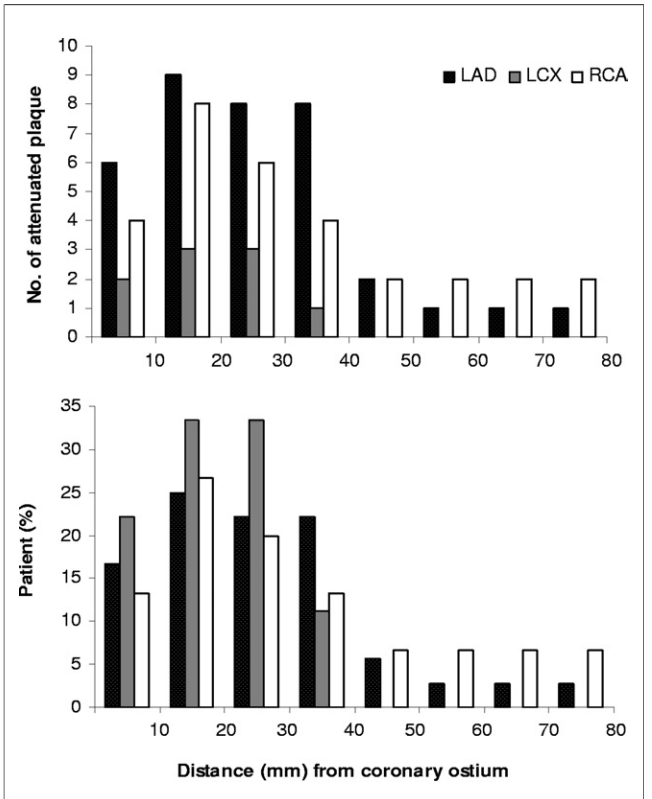

Figure 4. Locations of Attenuated Plaques

The locations of 75 attenuated plaques according to distance from each coronary ostium are shown for the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA).

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Discussion

In this analysis of 293 ACS patients who underwent pre-PCI IVUS examination, we found attenuated plaque in 25.6%, more commonly in STEMI than in NSTEMI patients. This study suggests that attenuated plaque is not unusual in patients with ACS and may be part of the unstable lesion morphometric spectrum.

In a recent angiographic study, Wang et al. (26) analyzed 208 patients with STEMI to determine the location of epicardial coronary artery thrombosis. Occlusions tended to cluster in the proximal one-third of the major epicardial coronary arteries. In a 3-vessel IVUS study, Hong et al. (27) evaluated the axial location of plaque rupture in 392 patients. Plaque ruptures occurred mainly in proximal segments of the LAD, the proximal and distal segments of the RCA, and the proximal left circumflex artery. The location of attenuated plaques in the current study is similar to the location of acute occlusions or plaque ruptures in these previous 2 studies, especially with regard to proximal distribution in the LAD and RCA. Thus, "hot-spots" for thrombotic occlusion, plaque rupture, and attenuated plaque are in similar locations. Proximally located "hot-spots" may lead to more myocardial damage, but also (potentially) early detection and localized directed preventive strategies.

Recent pathological reports have studied the mechanisms of ultrasound attenuation in plaques that were not densely fibrotic (28–30). In human cadaver coronary arteries, Hara et al. (28) reported ultrasound attenuation was associated with Von Kossa-positive granules within the fibrous plaque, interpreted to indicate microcalcification. In another report also from human cadaver coronary arteries (29), dense fibrofatty tissue and necrotic core were more common in plaques with ultrasound attenuation. Directional coronary atherectomy specimens from attenuated plaques showed very advanced atherosclerosis consisting predominantly of hyalinization with scattered, small areas of calcification (30). Calcium is a reflector of ultrasound; the extent of image attenuations might be related to the distribution and volume of calcification. However, the sensitivity of IVUS (using 30-MHz transducers) for microcalcification is only 64% for calcium particle size <0.05 mm (31). The current study also showed that attenuated plaque was associated with target-lesion thrombus assessed using either angiography or IVUS. An animal experiment (32) suggested that white thrombi may produce an attenuated ultrasound pattern compared with a nonattenuated pattern for red thrombi; white thrombi contain more densely homogenous cellular elements. These findings support the hypothesis that microcalcification and thrombus with underlying advanced atherosclerosis maybe the mechanism of echo attenuation in unstable plaques.

Previous IVUS studies have shown that culprit lesions in ACS patients typically contain, at most, spotty calcium. Similarly, recent plaque imaging with multislice computed tomography (33,34) has also described plaques with minimal calcification in unstable lesions. However, it is not clear whether multislice computed tomography studies can separate the ultrasound-attenuated plaques reported in the current study from merely noncalcified plaques.

In the present study, only 1 patient had multiple attenuated plaques. However, this was not a 3-vessel IVUS study; therefore, the exact frequency of multiple-attenuated plaques cannot be determined. Although the exact frequency of multiple ruptured plaques is the subject of debate, in several IVUS studies secondary ruptured plaques have been found at sites remote from the culprit lesion, evidence of the systemic nature of plaque vulnerability (35,36).

A recent IVUS study by Okura et al. (18) in 110 ACS patients with 73 lesions showed that attenuated plaque was related to a transient deterioration in coronary blood flow and poor outcome such as larger infarct size and higher incidence of fatal arrhythmia after PCI. The current study showed an incidence of 26.7% of no-reflow after PCI in ACS patients with attenuated plaque. In addition, even in the presence of normal baseline coronary blood flow, there was a high incidence of deterioration in the coronary blood flow post-PCI if lesions had attenuated plaque. In the current study, attenuated plaque was also associated with more severe and complex lesion morphology, IVUS predictors for no-reflow (13–17). Distal protection device use—especially routine use—in patients with ACS is still controversial (37–39); our results and those of others suggest a more selective use of these devices during primary PCI in patients with ACS according to plaque morphology and morphometry.

Study limitations. This was a retrospective study of patients from a single center. It identified the relationship between attenuated plaque PCI complications, but additional prospective studies will need to be conducted to determine its relative value versus other parameters that may cause complications. Almost 90% of patients had TIMI flow grade >1; therefore, ACS patients presenting with totally occluded vessels and angiographic thrombus-containing lesions were typically not imaged, and the current results cannot be extrapolated to such patients. We excluded ambiguous plaque with ultrasound attenuation (i.e., attenuation located adjacent to significant calcium or at a side branch). The presence of acoustic shadowing of the EEM at the site of attenuated plaques may interfere with calculation of remodeling and plaque burden. The lag between symptom onset and IVUS imaging and PCI may have influenced attenuation if attenuated plaque changes dynamically. IVUS examinations using low-frequency IVUS transducers (below 40 MHz) were excluded; we did not find any attenuated plaques in the 43 patients studied using such instruments presumably because of greater degrees of penetration with 20- versus 40-MHz transducers. Similarly, Yamada et al.

(29) exclusively used 40-MHz transducers to detect attenuated plaques.

Conclusions

Attenuated plaque was detected in 25.6% of patients with ACS. Attenuated plaque was more common in ACS patients with STEMI than in those with NSTEMI. Attenuated plaque was associated with a higher C-reactive protein level, more severe and complex lesion morphology (thrombus and plaque rupture), reduced coronary blood flow before PCI, and *especially* no-reflow after PCI.

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