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Plaque ruptures in stable angina pectoris compared with acute coronary syndrome

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Abstract

Background: Plaque rupture is more frequently observed in patients with acute coronary syndrome (ACS) rather than in patients with stable angina pectoris (SAP). Consequently, studies regarding plaque rupture, which occurred in SAP patients, are rare. Therefore, we evaluated the frequency and axial location of plaque ruptures in SAP patients and compared them with those in ACS patients.

Methods: Three hundred ninety-two patients (231 ACS and 161 SAP patients) who were scheduled for coronary intervention underwent three-vessel intravascular ultrasound (IVUS) study. IVUS criteria for plaque rupture were a plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. Using motorized IVUS transducer pullback in all three coronary arteries, the distance between each coronary plaque rupture segment and the respective coronary ostium was measured.

Results: Plaque ruptures were detected in 206 of 392 patients who underwent three-vessel intravascular ultrasound examination. At least one plaque rupture in any coronary artery was noted in 48 (30%) SAP and 158 (68%) ACS patients ($p<0.001$). In both ACS and SAP patients, plaque ruptures were clustered mainly in the proximal segments of the left anterior descending artery and in the proximal and distal segments of the right coronary artery.

Conclusions: At least one plaque rupture in any coronary artery was noted in 30% of SAP patients. Like in ACS patients, plaque ruptures were clustered mainly in the proximal segments of the left anterior descending artery and in the proximal and distal segments of the right coronary artery in SAP patients.

Keywords: Ultrasonics; Plaque; Coronary disease

1. Introduction

Plaque rupture and subsequent thrombus formation is the most important mechanism leading to an acute coronary syndrome (ACS) [1,2]. Recent intravascular ultrasound (IVUS) studies have reported the occurrence of multiple plaque ruptures in ACS patients [3–5]. Plaque rupture has usually reminded us of exclusively ACS patients. However, plaque rupture was sometimes observed in stable angina pectoris (SAP) patients. The clinical characteristics or pathophysiology of plaque rupture which occurred in SAP patients is elusive because of limited data about plaque rupture in SAP patients. Therefore, the purpose of this study was to evaluate the frequency and axial location of plaque ruptures in SAP patients and to compare them with those in ACS patients.

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2. Materials and methods

Three hundred ninety-two patients who were scheduled for coronary intervention underwent three-vessel IVUS study [6]. The frequency of plaque rupture in the first cohort of 235 patients [3], and the axial location of plaque ruptures in the overall cohort of 392 patients [6], who underwent three-vessel IVUS examination, was previously reported. The overall cohort of 392 nonconsecutive series of patients consisted of 231 ACS and 161 SAP patients. Three-vessel IVUS examination detected at least one plaque ruptures in 206 of the 392 patients. Of these 206 patients, 158 had ACS [including 136 acute myocardial infarction (AMI) and 22 Braunwald ACS classification IIIB]; and 48 had SAP. A total of 273 plaque ruptures (197 culprit/target lesions and 76 non-culprit/non-target lesions) were detected. Definitions of AMI and SAP, identification of culprit/target lesions, and exclusion criteria for three-vessel IVUS imaging were described previously [3]. IVUS examinations of all three major epicardial arteries were performed before any intervention and after intracoronary administration of 0.2 mg nitroglycerin using motorized transducer pullback system (0.5 mm/s) and a commercial scanner (Boston Scientific Corp./SCIMED) consisting of a rotating 30 MHz transducer within a 3.2 Fr imaging sheath. Qualitative and quantitative analyses were performed according to criteria of the clinical expert consensus document on IVUS [7]. IVUS criteria for plaque rupture were a plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment [8]. The diagnosis of plaque rupture required independent review and agreement by two of the authors (M-K.H. and Y-H.K.). In all three coronary arteries in each of the patients studied, the transducer was advanced into the distal coronary artery; and an imaging run was performed back to the aorto-ostial junction. Using motorized transducer pullback, we measured the distance from each plaque rupture back to the respective coronary ostium (pullback speed multiplied by number of seconds). Quantitative IVUS analysis was performed using computerized planimetry at the plaque rupture site. Quantitative measurements included external elastic membrane (EEM) and lumen cross-sectional area (CSA). The intraplaque cavity was measured and extrapolated to the ruptured capsular area [4]. Using the guiding catheter for magnification-calibration and an on-line system (ANCOR V2.0, Siemens, Germany), minimal luminal diameter (MLD) of lesions with plaque rupture and reference segment lumen diameter were measured before coronary intervention. The lesion morphology was classified according to the modified American College of Cardiology/American Heart Association (ACC/AHA) grading system [9]. Statistical analysis was performed with SPSS program. Comparison was performed with a Chi-square test and unpaired Student's *t*-test. A *p*-value <0.05 was considered statistically significant.

Table 1
Baseline clinical characteristics of all patients and IVUS measurements of culprit/target lesions

	SAP patients	ACS patients	*P*-value
Number of patients	161	231	
Age (years)	58±10	57±10	0.23
Male gender	114 (71%)	176 (76%)	0.28
Hypertension	68 (42%)	84 (36%)	0.29
Diabetes mellitus	48 (30%)	32 (14%)	<0.001
Cigarette smoking	70 (44%)	105 (46%)	0.8
Lipid profiles			
Total cholesterol (mg/dl)	178±31	191±36	<0.001
LDL cholesterol (mg/dl)	107±30	115±30	0.046
Triglyceride (mg/dl)	154±92	159±109	0.6
HDL cholesterol (mg/dl)	41±10	43±11	0.21
CRP level (mg/dl)	0.4±0.7	0.9±1.4	<0.001
Number of diseased vessels			0.5
1	97 (60%)	126 (55%)	
2	42 (26%)	65 (28%)	
3	22 (14%)	40 (17%)	
IVUS measurements			
Proximal reference segment			
EEM CSA (mm^2)	14.3±3.6	15.6±3.7	0.001
Lumen CSA (mm^2)	8.4±2.1	9.2±2.3	0.001
Lesion segment			
Plaque cavity CSA (mm^2)	2.6±1.0	2.3±0.8	0.062
EEM CSA (mm^2)	13.2±3.7	15.5±4.0	<0.001
Lumen CSA (mm^2)	2.2±0.4	2.2±0.5	0.5
Positive remodeling (%)	72 (45%)	160 (69%)	<0.001
Calcium arc (°)	44±68	36±64	0.3
Distal reference segment			
EEM CSA (mm^2)	12.3±3.7	13.2±3.7	0.020
Lumen CSA (mm^2)	7.6±2.4	7.9±2.2	0.23

ACS: acute coronary syndrome, CRP: C-reactive protein, CSA: cross-sectional area, EEM: external elastic membrane, IVUS: intravascular ultrasound and SAP: stable angina pectoris.

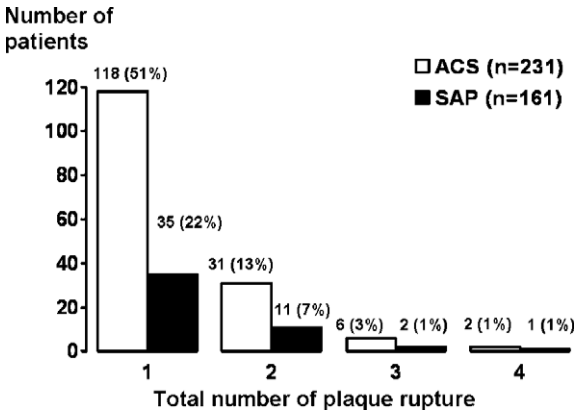

Fig. 1. The frequency of single and multiple plaque rupture between acute coronary syndrome (ACS) and stable angina pectoris (SAP).

3. Results

Baseline clinical characteristics and culprit/target lesion IVUS measurements of 161 SAP and 231 ACS patients are shown in Table 1. SAP patients had more diabetes mellitus while total cholesterol and C-reactive protein level were significantly higher in ACS patients. IVUS measurements of proximal reference EEM and lumen CSA, and distal

Table 2
Angiographic analysis of ruptured plaque lesions between SAP and ACS patients

	SAP patients	ACS patients	*P*-value
Total number of lesions	67	206	
Culprit/target lesions	44	153	
Lesion morphology			0.13
A			
B1	16 (36%)	33 (22%)	
B2	12 (28%)	56 (36%)	
C	16 (36%)	64 (42%)	
Lesion length (mm)	17.9±5.3	18.0±5.7	0.9
Reference vessel size (mm)	3.2±0.5	3.3±0.5	0.5
Minimal lumen diameter (mm)	0.8±0.6	0.6±0.6	0.03
Diameter stenosis (%)	75±17	83±17	0.03
Non-culprit/non-target lesions	23	53	
Lesion morphology			0.5
A	4 (17%)	11 (21%)	
B1	9 (39%)	15 (28%)	
B2	7 (31%)	12 (23%)	
C	3 (13%)	15 (28%)	
Lesion length (mm)	14.0±5.2	16.0±6.0	0.2
Reference vessel size (mm)	3.1±0.6	3.3±0.6	0.18
Minimal lumen diameter (mm)	1.6±0.7	1.6±0.6	1.0
Diameter stenosis (%)	49±20	51±19	0.6

ACS: acute coronary syndrome and SAP: stable angina pectoris.

reference and lesion site EEM CSA were also significantly larger in ACS patients along with more positive lesion site remodeling.

Plaque rupture was noted in the culprit/target lesions of 44 SAP patients (27%) versus 153 ACS patients (66%) ($p<0.001$). Non-culprit/non-target lesions (secondary) plaque ruptures occurred in 11 SAP patients (7%) versus 36 ACS patients (16%) ($p=0.014$). Multiple plaque ruptures (≥2 plaque ruptures) were observed in 13 SAP patients (8%) versus 40 ACS (17%) ($p=0.044$). Therefore, at least one plaque rupture in any coronary artery was noted in 48 (30%) SAP vs. 158 (68%) ACS patients ($p<0.001$) (Fig. 1). Angiographic analysis of ruptured plaque lesions in culprit/target and in non-culprit/non-target lesions between SAP and ACS patients are shown in Table 2.

A total of 273 plaque ruptures (67 plaque ruptures in SAP and 206 plaque ruptures in ACS patients) were detected in 247 coronary arteries: 143 ruptures (43 and 100 plaque ruptures, respectively) in 128 left anterior descending arteries (LAD), 40 ruptures (5 and 35 plaque ruptures, respectively) in 38 left circumflex arteries (LCX), and 90 ruptures (19 and 71 plaque ruptures, respectively) in 81 right coronary arteries (RCA). In these 247 arteries with at least one plaque rupture, the total length of the coronary artery imaged by IVUS was 83±14 mm in the LAD (88±13 mm in SAP patients versus 81±14 mm in ACS patients, $p=0.007$), 77±12 mm in the LCX (81±5 mm versus 76±13 mm, respectively, $p=0.4$), and 101±22 mm in the RCA (111±18 mm versus 98±22 mm, respectively, $p=0.038$).

When both target/culprit and non-target/non-culprit plaque ruptures were combined and considered together, LAD plaque ruptures were predominantly located in the segment between 10 and 50 mm from the LAD ostium in both ACS and SAP patients (Fig. 2). LCX plaque ruptures were evenly distributed throughout the entire tree in ACS patients (Fig. 2), but it was difficult to determine the distribution pattern of LCX plaque ruptures in SAP patients due to small study population (n=5). Most RCA plaque ruptures were located in the segments between 10 and 40 mm and in the segments beyond 70 mm from the coronary ostium in both ACS and SAP patients (Fig. 2).

When only the target/culprit plaque ruptures were considered, the clustering of LAD plaque ruptures in culprit/target lesion was similar in ACS and SAP patients.

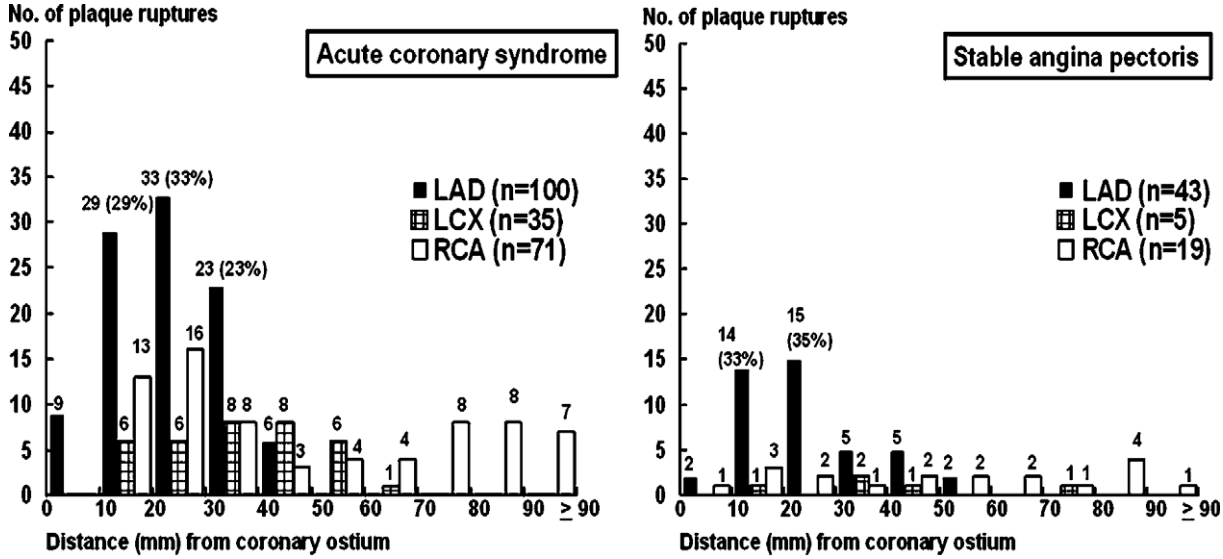

Fig. 2. The clustering of both culprit/target and secondary (non-culprit/non-target) plaque ruptures in patients with acute coronary syndromes and stable angina pectoris (illustrated separately) according to distance from each coronary ostium is shown for the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA).

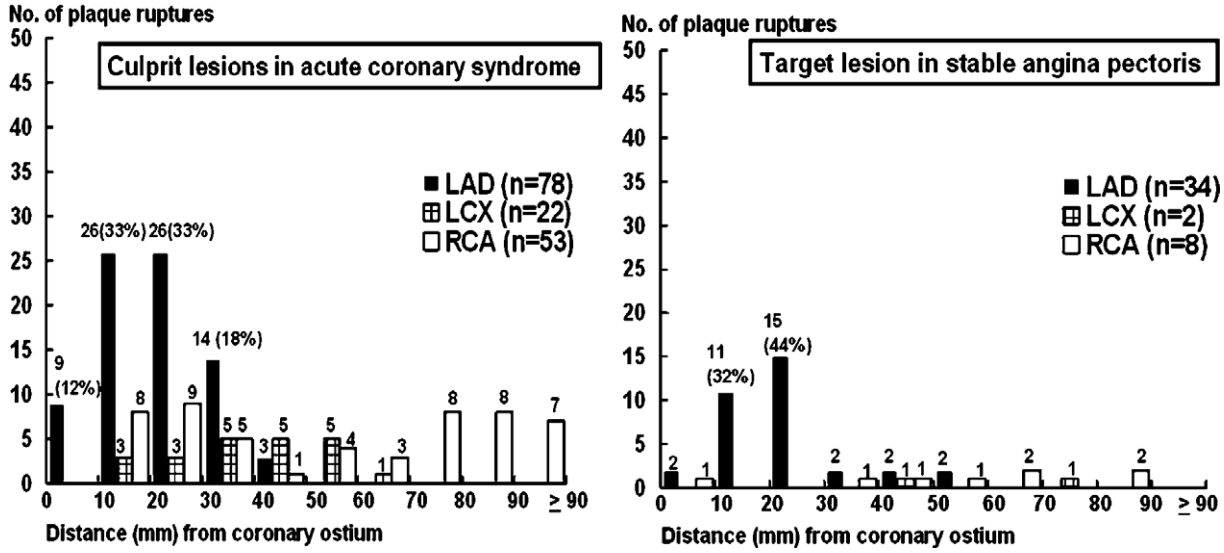

Fig. 3. The clustering of just the culprit lesion plaque ruptures in patients with acute coronary syndromes and just the target lesion plaque ruptures in patients with stable angina pectoris (illustrated separately) according to distance from each coronary ostium is shown for the LAD, LCX, and RCA. Abbreviations as in Fig. 2.

Most LAD plaque ruptures in culprit/target lesions were located in the segments between 10 and 30 mm from the coronary ostium in both groups (Fig. 3). Because the number of LCX ($n=2$) and RCA ($n=8$) target lesion plaque ruptures in SAP patients was small, it was difficult to determine the axial distribution pattern of plaque ruptures in these arteries in SAP patients. However, in ACS patients, the distribution pattern of LCX and RCA plaque ruptures were similar to those of overall cohort of ACS patients (Fig. 3).

4. Discussion

The current study showed that 30% of lesions in SAP patients had features of plaque rupture. While this may seem surprising, Maehara et al. reported that 22% of plaque ruptures occurred in patients with stable angina or no symptoms [5]. Plaque rupture may be one of the mechanisms of stenosis progression in some patients. As shown by Fujii et al., clinical symptoms may depend on the severity of the original and/or co-existing stenosis or on thrombus formation, not just on plaque rupture [10]. Furthermore, in the study by Fujii, 32.5% of the plaque ruptures were in patients with stable symptoms.

A recent angiographic study showed that acute coronary occlusion tended to occur within the proximal third of each of the coronary arteries in patients with acute myocardial infarction [11]. The importance of plaque rupture clustering (plaque rupture was the presumed substrate for acute occlusion) was emphasized in this angiographic study of AMI patients. Conversely, similar data in SAP patients are rare. The current study indicates that the location of plaque ruptures in SAP patients was similar to ACS patients confirming the importance of plaque rupture clustering in both groups. The current study showed that proximal segments of the LAD and the proximal and distal segments of the RCA before the crux were the most common sites of plaque ruptures. There was one noticeable discrepancy between the current findings and the angiographic report of Wang et al. [11]. Wang et al. found that RCA occlusions occurred in the proximal RCA while we found that plaque ruptures occurred in the proximal and distal RCA. Because the RCA has few branches, retrograde clot propagation could explain the dissociation between distal plaque rupture location and proximal angiographic occlusion.

This study has several limitations. Use of pre-intervention IVUS and the decision to do three-vessel IVUS was at the operator's decision. Therefore, selection bias cannot be completely excluded. SAP patients who undergo coronary angiography is a minority of the SAP patients, therefore the true incidence of plaque rupture may be underestimated or overestimated depending on the selection criteria for performing coronary angiography. It was not evaluated for the onset of plaque rupture to be recent or remote in SAP patients and in the non-culprit lesion of ACS patients. Compared with angiography, IVUS imaging is limited by distal lesion location, small vessel size, and confounding IVUS morphology (thrombus may obscure the ruptures).

In conclusion, at least one plaque rupture in any coronary artery was noted in 30% of SAP patients. Like in ACS patients, plaque ruptures were clustered mainly in the proximal segments of the LAD and in the proximal and distal segments of the RCA in SAP patients.

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