—Report on Experiments and Clinical Cases—

Significance of Plaque Disruption Sites in Acute Coronary Syndrome

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Abstract

Coronary plaque disruption and subsequent thrombosis occur in both unstable angina (UA) and acute myocardial infarction (AMI). However, it is unclear why UA and AMI have different clinical courses. The purpose of this angiographic study was to examine whether the longitudinal plaque disruption site is a factor that can be used to distinguish these two conditions. Seventy-two patients with AMI or UA in whom ischemia- or infarct-related arteries and plaque disruption sites could be determined were enrolled. The plaque disruption sites were classified as upstream type or downstream type. The upstream type and downstream type were defined as plaque rupture site located proximal and distal, respectively, to the maximum stenosis on angiography. The frequency of the upstream type was significantly higher in patients with AMI (60.0%) than in patients with UA (18.5%). On the other hand, the frequency of the downstream type was higher in patients with UA (81.5%) in patients with AMI (40.0%; $p<0.01$). The longitudinal plaque disruption site may thus be a factor that can be used to distinguish these two diseases.
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Key words: acute coronary syndrome, myocardial infarction, unstable angina, plaque disruption

Introduction

Coronary plaque disruption followed by thrombus formation is considered an important factor in the pathogenesis of acute coronary syndrome (ACS), including acute myocardial infarction (AMI) and unstable angina (UA), and results in progression of coronary stenosis, which can be confirmed with several kinds of studies such as pathologic examination , angiography , intravascular ultrasonography, and angioscopy[1–4]. Plaque disruption occurs mainly at so-called shoulder lesions showing focal accumulation of foam cells, a thin fibrous cap, and/or a large lipid pool and high circumferential stress on the plaque[4,5].

Although the depth of plaque disruption, the condition of the thrombus, and an interruption of blood flow may help differentiate AMI from UA[3], it remains unclear why these two clinical conditions arise from similar pathological conditions. The aim of this study was to identify an additional factor that can be used to distinguish AMI from UA. The basic principle at issue in this study is that the plaque disruption site may influence the clinical presentation of ACS. There is a possibility that

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plaque rupture at a proximal site of plaque and thrombus formation might strongly interfere with the regulation of blood flow, in comparison to a plaque rupture at a distal site. We hypothesized that thrombus accompanied by plaque rupture at a proximal site might cause total occlusion and thus result in AMI. On the other hand, thrombus accompanied by plaque rupture at a distal site might induce nontotal occlusion and result in UA. To verify this hypothesis, we investigated plaque rupture sites in patients with ACS using coronary angiography.

Methods

We evaluated 348 consecutive patients who underwent coronary angiography and were diagnosed with AMI or UA from May 1997 through March 2004 at our institution. Patients in whom ischemia- or infarct-related arteries (IRAs) and plaque rupture sites could not be determined with angiography were excluded. Finally, 72 patients in whom IRAs and plaque rupture sites could be clearly determined with angiography were enrolled. Then we evaluated the locations of plaque rupture and compared clinical characteristics and angiographic findings between AMI and UA. Informed consent was obtained from all patients enrolled in this study.

Criteria of AMI and UA

UA was defined as either an exacerbation of angina that was previously stable, such as angina occurring at rest, or the new onset of chest pain occurring at rest. The diagnosis of AMI was based on a characteristic history of prolonged chest pain, diagnostic electrocardiographic changes, an elevation in the serum creatine kinase level, the creatine kinase MB fraction ($\geq$2 times the upper limit of the normal value), and/or elevation of troponin T levels ($\geq$0.1 ng/m*l*).

Coronary Angiography

Coronary angiography was performed with standard procedures from the femoral or radial arteries. After 2,000 units of heparin was administered, qualifying and quantitative angiography was performed to assess lesion morphology and the severity of stenosis. Each coronary artery was closely observed with at least two projections in the right coronary artery and three projections in the left anterior descending artery and left circumflex artery. Quantitative coronary angiograms were analyzed with a computer-assisted, automated edge-detection algorithm (CMS, Medical Imaging System, Nuenen, The Netherlands) by one angiographer. The qualitative morphologic analyses of all angiograms were performed by two experienced angiographers who were blinded to clinical presentation.

Evaluation of Ischemia- or Infarct -Related Arteries and Lesions

IRAs were defined as arteries originally perfusing an area distal to the lesion on a specific coronary artery on the basis of the distribution of transient or persistent ischemic ST-T changes on 12-lead electrocardiography, transient or persistent asynergic area on two-dimensional echocardiography, left ventriculography, and scintigraphy. After the locations of IRAs were determined, ischemia- or infarct-related lesions (IRLs) could be identified. IRLs were the most severe lesions or complex lesions in the IRAs.

Evaluation of Plaque Disruption Sites

We classified the coronary angiographic morphology of AMI and UA into six categories, which included total occlusion, simple lesions (type I), and four variable degrees of luminal narrowing (types IIa, IIb, IIc, IId)[6] (**Fig. 1**). Type I lesions represent luminal narrowing resulting from negative endoluminal images with smooth borders and broad necks. Type IIa lesions represented irregular, poorly defined, or hazy borders with sharp leading or trailing edges that either overhung or were perpendicular to the vessel walls. Type IIb lesions, including ulcerative lesions, were characterized by focal external eversion or protrusion of contrast media and diffuse luminal irregularities. Type IIc lesions included luminal narrowing with ellipsoid contrast pooling adjacent to the diseased portion, i.e., so-called extraluminal contrast pooling, and single or

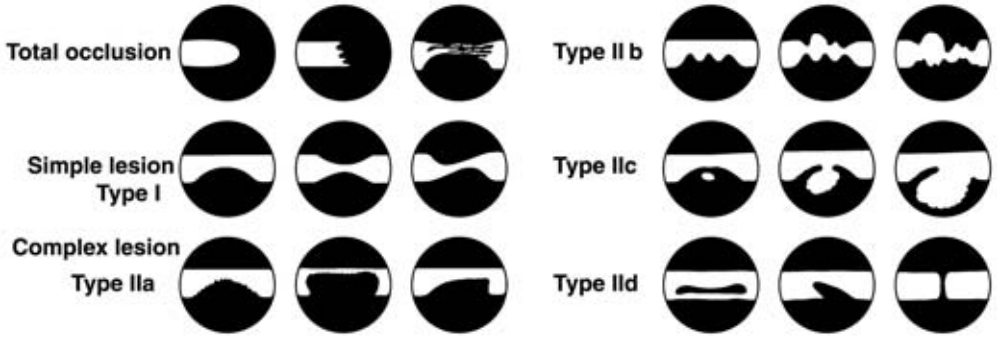

Fig. 1 Angiographical morphologies of plaque disruption site

paired short, thin, linear radiolucency with or without a variable degree of outpouching, and definite outpouching with or without radiolucency. Type IId lesions included variable forms and grades of linear or club-shaped intraluminal radiolucency caused by membranous or band-like structures. These radiolucent lesions may be parallel, spiraled, angulated, or perpendicular to the vessel wall. An angiographic plaque rupture was defined as an ulceration and an angle between the plaque shoulder and the vessel wall, for example a narrow neck.

According to the definition of IRLs, plaque rupture sites were divided into two groups, namely an upstream type and a downstream type. If the plaque rupture site was at the proximal portion of the maximum stenotic site, it was defined as an upstream type, and if the plaque rupture site was at the distal portion, it was defined as a downstream type. However, we could not determine the upstream or downstream part in cases of total occlusion, simple lesions, multiple ulcerations, or slit lesions or in cases with ulceration in the middle of stenosis.

Statistical Analysis

Data are expressed as the means ± SD. categorical variables were analyzed with the chi-square test or Fisher's exact provability test. Whether data were normally distributed or not was examined with the Kolmogrov-Sminov test. If data were normally distributed, an unpaired Student's *t*-test or Welch's *t*-test was used to compare groups. Otherwise, the Mann-Whitney U test was used. Differences were considered to be statistically significant at $p<0.05$.

Results

Plaque Disruption Site

Two hundred twenty patients, including 121 patients with simple lesions and 99 patients with total occlusion, were excluded from this study because plaque rupture sites could not be diagnosed. Forty-seven patients with complex lesions were also excluded because the upstream or downstream part of the plaque rupture could not be determined. Nine patients with small or thin anatomic coronary structures could not be evaluated with the coronary angiography equipment. Finally, 72 patients in whom the upstream or downstream plaque rupture sites could be clearly identified were included in this study.

Of the 72 patients with clearly identified plaque rupture sites, 45 had AMI and 27 had UA. In the AMI group, 27 sites were categorized upstream type and 18 as downstream. In the UA group, 5 sites were categorized as upstream and 22 as downstream. The frequency of upstream sites was significantly higher in patients with AMI than in those with UA. On the other hand, the frequency of downstream sites was higher in patients with UA than in those with AMI. Between the AMI group and the UA group, there were no significant differences in percent diameter stenosis, minimum lumen diameter, or lesion length (**Table 1**).

Cases of the upstream type and downstream types are shown in **Figure 2, 3**, respectively.

Baseline and Angiographic Characteristics

The baseline and angiographic characteristics of

Table 1 Lesion Characteristics on Angiogram

	Acute Myocardial Infarction n=45	Unstable Angina n=27	*P*
Disruption Site			
Upstream	27 (60.0)	5 (18.5)	<0.05
Downstream	18 (40.0)	22 (81.5)	
QCA Analysis			
Percent Diameter Stenosis, %	88 ± 13	89 ± 11	0.76
Minimal Lumen Diameter, mm	0.98 ± 0.55	0.96 ± 0.26	0.72
Lesion Length, mm	6.77 ± 2.64	8.24 ± 1.40	0.15

Values are n (%) or the mean ± SD. QCA indicates quantitative coronary angiography.

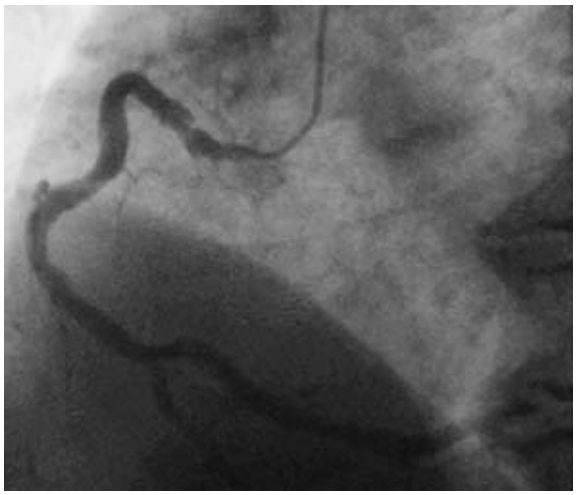

Fig. 2 Plaque disruption at upstream site in patient with AMI

the AMI group and the UA group are summarized in **Table 2**. There were no significant differences in age, gender, body mass index, plasma lipid levels, or the frequencies of diabetes mellitus, hypertension, or smoking habit. In addition, no significant differences were observed in the location of culprit coronary arteries or the number of diseased vessels.

Angiographic Morphology of Plaque Disruption Sites

There were no significant differences in the angiographic morphology of plaque rupture sites between the AMI and UA groups. However, type IIa lesions, which demonstrated irregular, poorly defined, or hazy borders with sharp leading or trailing edges that hung over the vessel walls, were a major morphological finding in each group. A type IIc lesion was observed in only one patient with UA, whereas type IId lesions were observed in 6 patients with AMI and in 9 patients with UA **(Table 3)**.

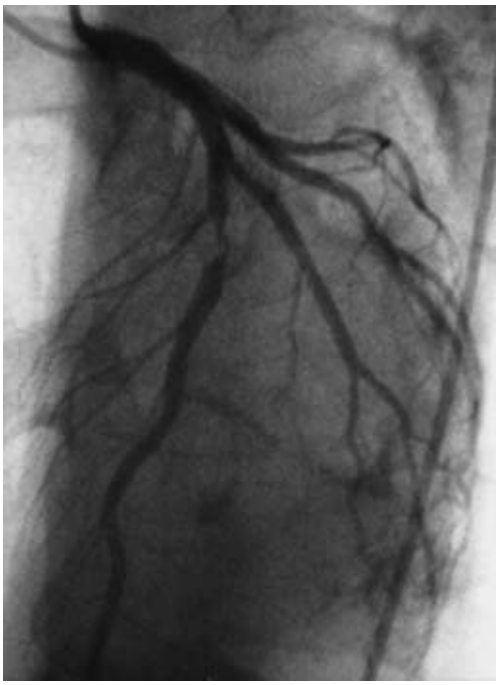

Fig. 3 Plaque disruption at downstream in patient with UA

Differentiation of Plaque Disruption Sites in Patients with AMI

The AMI group included 34 patients with ST elevation myocardial infarction and 11 patients with non-ST elevation myocardial infarction. There were no significant differences in plaque rupture sites between the groups **(Table 4)**. There were no significant differences in other baseline characteristics between the groups.

Discussion

To the best of our knowledge, this is the first study to find that AMI arises from a plaque

Table 2 Baseline Characteristics

	Acute Myocardial Infarction n = 45	Unstable Angina n = 27	*P*
Age, yr	65.1 ± 10.4	62.6 ± 9.7	0.37
Male, Female	31 (68.8)	17 (65.9)	0.39
Diabetes Mellitus	15 (33.3)	6 (22.2)	0.23
Hypertension	22 (51.1)	14 (51.8)	0.49
Hyperlipidemia	23 (53.1)	13 (48.1)	0.49
Serum Lipid Levels			
Total Cholesterol, mg/d*l*	200.3 ± 36.7	185.1 ± 31.7	0.13
Triglycerides, mg/d*l*	147.3 ± 138.0	117.6 ± 58.1	0.33
High-density Lipoprotein Cholesterol, mg/d*l*	43.8 ± 12.7	43.8 ± 12.7	0.28
Smoking History	33 (75.0)	16 (59.2)	0.16
Body Mass Index, Kg/mm^2	23.7 ± 2.8	24.9 ± 4.0	0.19
Distribution of Culprit Lesions			
Right Coronary Artery	10 (22.2)	10 (37.0)	0.38
Left Descending Artery	21 (46.6)	11 (40.7)	
Left Circumflex Artery	14 (31.1)	6 (22.2)	
Number of Diseased Vessel			
1 Vessel	23 (51.1)	11 (40.7)	0.42
2 Vessels	17 (37.7)	10 (37.7)	
3 Vessels	5 (11.1)	6 (22.2)	

Values are n (%) or the mean ± SD.

Table 3 Angiographic Morphology of the Plaque Disruption Site

	Acute Myocardial Infarction n=32	Unstable Angina n=23	*P*
IIa	28	15	0.11
IIc	0	1	
IId	4	7	

Values are n (%) or the mean ± SD.

Table 4 Differentiation of the Plaque Disruption Site in patients with MI

	ST elevation MI n=34	Non-ST elevation MI n=11	*P*
Upstream	21	6	0.73
Downstream	13	5	

Values are n (%). MI indicates myocardial infarction

disruption of the upstream part and that UA arises from a plaque disruption of the downstream part in most cases. A disruption of the vulnerable plaque exposes the thrombogenic contents of an atheroma to flowing coronary blood and initiates thrombus formation, which may lead to either a blood-flow limitation or total occlusion[3,7]. The degree of flow interruption is influenced by several factors, such as the magnitude of plaque rupture, the severity of pre-existing coronary stenosis, the amount of thrombus adhering to the plaque rupture site, the lability of the thrombus, the balance of coagulability, and the severity of coronary spasm. All these factors may influence on the clinical setting of AMI and UA.

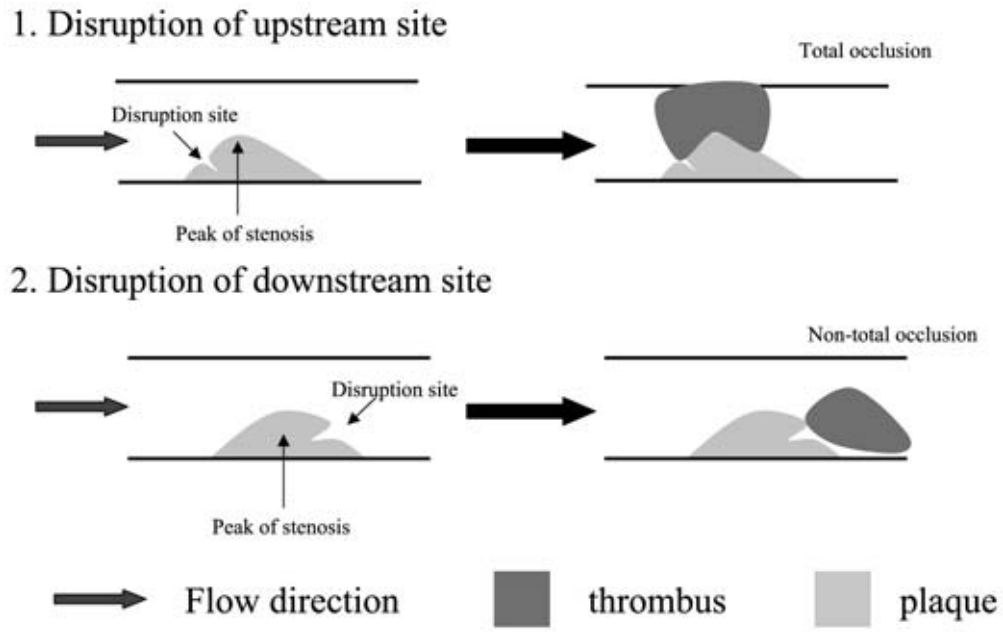

Fig. 4 Relation between the Plaque Disruption Site and Flow Interruption

Previous Mechanisms to Differentiate AMI and UA

A disruption of the atheromatous plaque following thrombus formation is believed to be the initial step in the onset of ACS. Fuster et al. have proposed the following explanation for differences between AMI and UA[3,8]. In UA with progressive symptoms, but without chest pain at rest, a plaque rupture with a change in the geometric configuration of the plaque, but without any overlying thrombus, can increase the severity of pre-existing stenosis. However, in the case of UA with chest pain at rest, the plaque rupture and pre-existing stenosis are both less severe, and, therefore, thrombosis is transient or labile. An incomplete interruption of blood flow leads to UA. In AMI, the plaque disruption is deeper than in UA, and the thrombus, which is anchored to a large rupture site, is more firmly fixed. The duration of coronary artery occlusion in AMI is also longer than in UA[9].

In terms of an interruption of blood flow, our previous angioscopic study revealed occluded red thrombi, which are formed by blood stasis, in patients with AMI. On the other hand, nonoccluded white thrombi, which are formed through incomplete interruption of blood flow, were observed in patients with UA[10]. In addition to the severity of blood flow limitation, other mechanisms that might be used to distinguish AMI from UA are vessel wall injury and hypercoagulability[11,12].

Plaque Disruption Sites

Plaque disruption often occurs on a thin fibrous cap that is composed of abundant inflammatory cells and scant smooth muscle cells (SMCs). Recently, Dirksen et al. investigated the relationship between blood-flow direction and the cellular composition of carotid plaques in a consecutive autopsy series of 45 patients. They found that the upstream shoulder of plaques tended to contain more macrophages than did the downstream shoulder. They also found that many rupture sites were located in the upstream part of the plaque[13]. Experimental studies have shown that high shear stress increases expression of endothelial adhesion molecules, such as intercellular adhesion molecule and vascular cell adhesion molecule, thus resulting in enhanced leukocyte adherence[14,15]. The upstream shoulder is exposed to high shear stress, which activates endothelium-derived nitric oxide (NO) synthesis and NO production. This chronically enhanced NO production inhibits SMC protein synthesis and SMC proliferation[16,17]. Conversely, the downstream shoulder part of the plaque, which has a relatively

low shear stress, shows larger SMC-rich areas than does the upstream part. Since the upstream shoulder of the plaque contains many inflammatory cells and few SMCs, it is more fragile than the downstream shoulder, which contains many SMCs.

Mechanical stress might also influence the development of plaque rupture. Richardson et al. investigated plaque disruption sites in autopsy cases. In cases with extracellular lipid pools in the intima, many plaque disruptions occurred at the junction of the plaque cap and the center of the plaque cap. The differentiation of the plaque disruption site was influenced by the degree of circumferential stress and shear force in the arterial wall and by the presence of a calcified plate within the intima[5]. From the viewpoint of mechanical stress, the downstream plaque shoulders could rupture more easily owing to the effects of such stress.

If the maximum stenotic site is located distal to plaque disruption, then the part of the disrupted plaque with thrombus may cause either severe stenosis or occlusion in the artery. This condition may lead to AMI. On the other hand, if maximum stenosis site is proximal to plaque disruption, then plaque disruption followed by thrombus might not induce total occlusion (**Fig. 4**). This study thus suggests that the plaque rupture site might be an important factor for distinguishing UA and AMI.

Study Limitations

We excluded totally occluded lesions and very small arteries on angiograms, because their rupture sites were unclear. In this study, the plaque ruptures in 119 of 348 patients (34.1%) and plaque rupture sites in 72 of 348 patients (20.6%) were clearly detected by angiograms. Rioufol et al. could identify plaque ruptures in 9 of 24 (37.5%) patients with ACS using intravascular ultrasound[18]. It is difficult to identify plaque disruption sites with angiography, as with other modalities, because of superimposed thrombi. The findings of Rioufol et al. are consistent with the small percentage of patients in whom plaque rupture sites could be accurately determined in our study.

Conclusions

The frequency of upstream disruption was higher in patients with AMI, whereas the frequency of downstream disruption was higher in patients with UA. This angiographic study showed that plaque disruption site might be used to distinguish UA and AMI.

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