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Multiple Atherosclerotic Plaque Rupture in Acute Coronary Syndrome

A Three-Vessel Intravascular Ultrasound Study

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Background—To test the hypothesis of general atherosclerotic plaque destabilization during acute coronary syndrome (ACS), the present study sought to analyze the 3 coronary arteries by systematic intravascular ultrasound scan (IVUS).

Methods and Results—Seventy-two arteries were explored in 24 patients referred for percutaneous coronary intervention after a first ACS with troponin I elevation. Fifty plaque ruptures (mean, 2.08 per patient; range, 0 to 6) were diagnosed by the association of a ruptured capsule with intraplaque cavity. Plaque rupture on the culprit lesion was found in 9 patients (37.5%). At least 1 plaque rupture was found somewhere other than on the culprit lesion in 19 patients (79%). These lesions were in a different artery than the culprit artery in 70.8% and were in both other arteries in 12.5% of these 24 patients. Complete IVUS examination of all 3 coronary axes in patients who had experienced a first ACS revealed that multiple atherosclerotic plaque ruptures were detected by IVUS; these multiple ruptures were present simultaneously with the culprit lesion; they were frequent and located (in three quarters of cases) on the 3 principal coronary trunks; and the multiple plaque ruptures in locations other than on the culprit lesion were less severe, nonstenosing, and less calcified.

Conclusion—Although one single lesion is clinically active at the time of ACS, the syndrome seems nevertheless associated with overall coronary instability. (*Circulation*. 2002;106:804-808.)

Key Words: ultrasonics ■ atherosclerosis ■ plaque ■ coronary disease

Acute coronary syndromes (ACS) are clinical events that cause considerable immediate morbidity and mortality and a high risk of a further coronary accident within a year.^{1,2} Atherosclerotic plaque rupture or erosion is recognized to be the prime motivating factor in ACS, and it is the associated local thrombosis activation that gives the acute incident its potential immediate seriousness.³⁻⁵

Intravascular ultrasound (IVUS) is a safe clinical device¹² that provides reliable information on the coronary wall,¹³ and it is our institution's policy to use IVUS in routine diagnosis. To test this hypothesis of overall destabilization throughout the coronary tree in ACS, the present study sought to analyze all 3 coronary arteries in patients admitted for ACS.

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Methods

Patients

Between February and August of 2000, IVUS examinations were systematically performed after coronarography in patients referred for a first ACS (with or without ST-segment elevation) with a duration of <4 weeks and >3 days whenever an indication for percutaneous coronary intervention (PCI) was accepted and all 3 epicardial coronary arteries proved suitable for IVUS. A further inclusion criterion was that the culprit lesion be clearly identifiable. The coronary artery and the lesion underlying the atherosclerotic event (ie, the culprit lesion) were identified by the association of pre- and intercrisis electrocardiographic signs, possible left ventricle segment kinetics anomalies, and lesion aspect on coronary angiography as specified below.

A number of angiographic studies have reported a surge in the incidence of coronary atherosclerosis in the months after a coronary accident, with a worsening of not only the culprit lesion when it has not been treated by angioplasty, but also of other lesions initially deemed insignificant; this pattern appears in 20% of cases, as compared with <5% in cases of stable angina.⁶⁻¹⁰ Such a rapid development of atherosclerosis probably involves diffuse destabilization of atherosclerotic plaques, leading to the concept of "pancoronaritis" in ACS, as suggested in recent angiographic and angioscopic studies.^{2,11}

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Coronary Angiography

Angiographic quantification of lesions used the AdvantX software (General Electric Medical Systems). A coronary stenosis was considered clinically significant if it was >50% in diameter. Multivessel disease was presumed when >1 coronary artery presented a significant coronary stenosis. The classification of Ambrose et al⁶ was adopted for qualitative analysis after 2 orthogonal views. Briefly, concentric lesions have symmetric narrowing with smooth borders, type I or II eccentric lesions are asymmetric with a broad neck and may or may not be irregular, and the term multiple irregularities refers to serial stenosis or severe diffuse irregularities. Type I or II eccentric lesions and multiple irregularities are considered complex lesions. Complex coronary stenosis was identified by consensus of 2 independent angiographers when a complex lesion was associated with a stenosis of >50% diameter.²

IVUS Imaging Protocol

The IVUS system used was a commercially available mechanical sector scanner (Intravascular Imaging System, Hewlett-Packard) with 40-MHz single-element ultrasound catheters (Boston Scientific). After the administration of 200 µg of intracoronary nitroglycerine, IVUS exploration began from the coronary artery contralateral to the artery housing the culprit lesion, continued to the second artery, which was not implicated in the recent clinical event, and finished in the culprit artery before any percutaneous coronary intervention (PCI) was performed. The transducer was introduced at least two thirds of the way up each artery explored, and the artery was imaged in retrograde using a motorized pullback at 0.5 mm/s. Each ruptured coronary plaque detected was precisely located on the angiogram. IVUS exploration of the 3 arteries took an average 10 minutes.

IVUS Quantitative Analysis

Quantitative analysis (I²DP Data Processing) was conducted on 2 specific cross-sections¹⁴ for each ruptured plaque detected: the IVUS reference segment, defined as the first normal or the least pathological segment not more than 10 mm from the rupture, and the section on which lumen cross-sectional area (LCSA) was the smallest within the plaque rupture. Cross-sectional images were quantified for lumen cross-sectional area (mm²), external elastic membrane cross-sectional area (EEM CSA, mm²), and plaque (P)+media (M) cross-sectional area (P+M CSA=EEM CSA-LCSA, mm²). Plaque burden was defined as PB(%)=[(EEM CSA-LCSA)/EEM CSA]×100. Lesion length was derived from the duration of the pullback.

IVUS Definitions

The IVUS classification by Ge et al¹⁵ for atherosclerotic plaque rupture was adopted. Atheromatous plaque rupture was diagnosed on the basis of the appearance of either a ruptured capsule associated with intraplaque cavity, possibly enhanced by intracoronary saline injection, or of plaque excavation by atheromatous extrusion with no visible capsule. The intraplaque cavity was measured and extrapolated to the ruptured capsule area. Close attention was paid to possible artifacts,¹⁶ especially in bifurcation areas. Plaque rupture diagnosis required the agreement of 2 trained operators (Drs Rioufol and Finet). Significant stenosis was defined as minimum lumen area <3 mm².¹⁷ Arterial remodeling was determined by comparing the EEM area at the center of the lesion with the EEM area at the proximal reference segment. Positive remodeling was defined as a relative ratio ≥1.0 and negative remodeling was defined as <1.0. The eccentricity ratio was calculated as [(maximum P+M thickness-minimum P+M thickness)/maximum P+M thickness]×100. Calcifications were measured in terms of the degree of arc with respect to the center of the coronary lumen.

PCI and Clinical Follow-Up

PCI was performed using stent and antiglycoprotein IIb/IIIa at the discretion of the operators. In case of coronary stenting, clopidogrel was systematically added to aspirin for at least 1 month. A 6-month

TABLE 1. Patient Characteristics

Male sex	23 (96)
Age, y	61±10
Smoker	18 (75)
Diabetes mellitus	6 (25)
Hypercholesterolemia	17 (71)
ACS	
ST elevation	9 (37.5)
No ST elevation	15 (62.5)
LVEF, %	60±9
Coronary artery disease	
1 vessel	7 (29)
2 vessels	11 (46)
3 vessels	5 (21)
LMA lesion	2 (8)
Multiple complex coronary stenoses	9 (37.5)

Values are n (%) or mean±SD (n=24). LVEF indicates left ventricular ejection fraction; LMA, left main artery.

follow-up was conducted; repeat PCI, bypass surgery, ACS, and death were considered major outcome events.

Statistics

Statistical analysis was performed with StatView 4.5 MDSU statistical software (Abacus Concept, Inc). Data are presented as mean±SD. Continuous quantitative data were compared by matched Student's *t* test and discontinuous quantitative data by χ^2 test. *P*<0.05 was considered statistically significant.

Results

Population

Twenty-four consecutive patients were included at a mean of 2.3±1.5 weeks after ACS. The majority (62.5%) did not present with ST-segment elevation but had high troponin I levels. For purely anatomic reasons of IVUS feasibility, the population corresponded to 20% of all referrals for first ACS assessment during the study period and was in all other ways similar to the overall population referred during the same period. Patients' clinical features are summarized in Table 1.

Coronary Atherosclerotic Plaque Rupture

Seventy-two major epicardial coronary arteries were explored by IVUS without incident, and 50 distinct plaque ruptures were detected (mean, 2.08 per patient; range, 0 to 6). Nine cases of plaque rupture in 9 patients (37.5%) were clearly identified as being located on the culprit lesion itself, and 41 cases of plaque rupture were located on arteries other than the culprit. Culprit lesions with (n=9) or without (n=15) plaque rupture had the same clinical aspect on angiography and IVUS from all other points of view. For example, similar minimum LCSAs (3.8±3.7 mm² versus 1.8±1.1 mm², *P*=NS), plaque burdens (81±15% versus 87±6%, *P*=NS), and remodeling ratios (1.08±0.17 versus 1.05±0.12, *P*=NS) were found. As they were characterized by the same physiopathological event, it was therefore considered reasonable to pool their data. Among the 24 patients, 19 (79%) had at least 1 plaque rupture somewhere other than on the culprit lesion (Figure 1), 17 (70.8%) had at least 1 rupture diagnosed in an

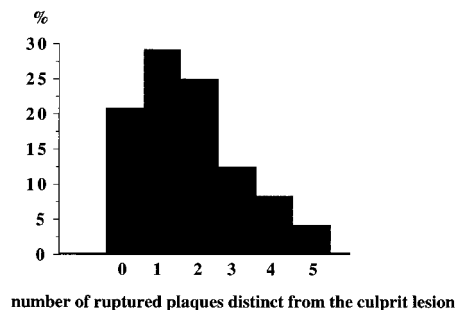


Figure 1. Percentage distribution of coronary atherosclerotic plaque ruptures other than the culprit lesion. In 79% of cases, at least 1 such plaque rupture was found.

artery other than the culprit artery, and 3 (12.5%) had at least 1 rupture in all 3 arteries (Figure 2). Plaque rupture incidence in the left coronary trunk, the left anterior descending artery, the circumflex artery, and the right coronary arteries was 8%, 30%, 20%, and 42%, respectively. The incidence of plaque rupture did not differ between patients presenting ACS with and without ST-segment elevation (respectively 2.2 ± 1.9 and 1.7 ± 1.3 ruptures, $P=NS$).

On qualitative angiographic analysis, 62.5% of culprit lesions met complex coronary lesion criteria, compared with 41.5% of the other distinct plaque ruptures ($P=0.1$). Except in the case of culprit lesions, which IVUS sometimes failed to detect, no complex coronary lesions were ever detected on angiography that were not also found by IVUS on ruptured plaques.

Quantitative Angiography and IVUS Analysis

Quantitative analysis of the culprit lesions revealed significantly greater stenosis than in the case of the distinct lesions associated with plaque rupture (Table 2). The coronary remodeling was positive overall in both types of lesion (1.05 ± 0.15 for culprit lesions versus 1.04 ± 0.12 for distinct

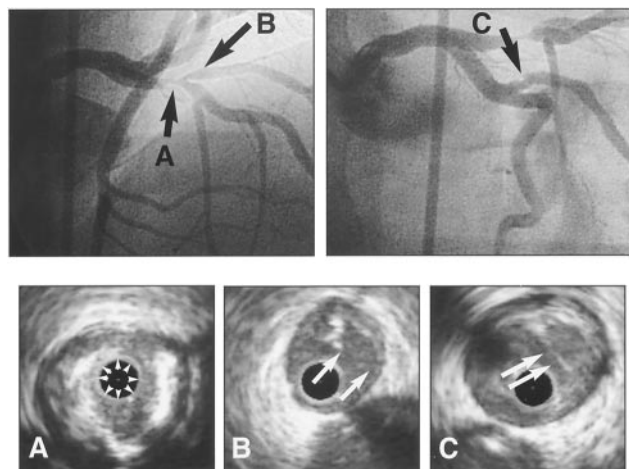


Figure 2. Angiographic and intravascular ultrasound images of typical multiple unstable coronary lesions. The culprit lesion was subocclusive in the left anterior descending artery (A; arrows underline the arterial lumen); IVUS found 2 other plaque ruptures in the diagonal artery (B) and in the marginal artery (C). C was the only lesion detected on angiography. The double arrows underline the fibrous capsule rupture edges.

lesions, $P=NS$). Positive remodeling indices >1.05 were observed in 39% of culprit lesions and in 42% of distinct lesions with plaque rupture. This difference was not significant. Culprit lesions presented more calcification than the other ruptured plaques.

Percutaneous Coronary Intervention

Twenty-two patients were treated by angioplasty, one received medical treatment in the absence of significant coronary stenosis criteria, and another was referred directly to surgery in view of a much greater left coronary trunk stenosis than had been suggested by angiography alone. In 3 cases, the culprit lesion did not require stenting, as spontaneous local thrombolysis left no significant residual stenosis. Particularly in patients presenting multiple complex coronary plaques, however, several concomitant lesions were able to be treated on preprocedural angiographic and IVUS criteria (minimum lumen diameter <1.5 mm, minimum LCSA <4 mm²). Excluding the patient who was managed surgically, 23 plaque ruptures (48.9% of detected ruptures) underwent no specific procedure (Table 3).

Clinical Follow-Up

Mean clinical follow-up of interventional or medically managed patients ($n=23$) was 10 ± 3 months. During follow-up, all patients took antiplatelet inhibitors (clopidogrel, 22%), all but one (96%) had statin therapy, and 10 (43%) received β -blockers. No death occurred, but 5 combined events were noted, 4 restenoses and 1 subacute stent thrombosis, all proved by angiography. There was no recurrence of ACS.

Discussion

Complete IVUS examination of all 3 coronary arteries in patients with first ACS very frequently revealed 1 or more atherosclerotic plaque ruptures associated with the culprit lesion (79% of cases). According to our observations, 70% of patients had at least 1 atherosclerotic lesion presenting rupture criteria on IVUS examination in an artery distinct from the culprit artery. Despite this overall coronary instability, current strategies and PCI seem to provide a satisfactory outcome.

Plaque Rupture

It has been learned from numerous postmortem studies that atherosclerotic plaque rupture with a broken or eroded capsule seems to be the trigger for acute coronary thrombotic accidents.^{3,18-21} The same studies suggest that isolated or multiple ruptures can be found in control subjects and may be involved in the natural development of the atherosclerotic plaque.^{19,22,23} Coronary angiography is ill suited for the precise detection of ruptured coronary plaques, as it probably identifies only the largest lesions.¹³ Ge et al¹⁵ found that angiography pointed to coronary ulceration in only 35% of the cases diagnosed as such by IVUS and that type II (Ambrose) eccentric lesions were noted in about half of the cases whether or not there was a plaque rupture. Similar data were found in our present study, inasmuch as coronary ruptures distinct from the culprit lesion were suspected on angiography in only 41.5% of cases.

TABLE 2. Quantitative Analysis of the Culprit Lesions and Other Distinct Plaque Ruptures

	Culprit Lesion (n=24)	Other Ruptured Plaque (n=41)	P
QCA			
Minimum lumen diameter, mm	1.09±0.22	2.23±0.16	<0.001
Stenosis, %	70±5	39±3	<0.0001
IVUS			
ML CSA, mm ²	2.52±0.51	8.45±0.64	<0.001
Plaque burden, %	85±2	59±2	<0.0001
Lesion length, mm	14±2	10±1	<0.01
Remodeling ratio	1.05±0.03	1.04±0.02	0.27
Plaque cavity, mm ²	1.7±1.9	1.4±0.9	0.27
Eccentricity ratio, %	50.9±10.2	52.9±16.5	0.62
Presence of calcifications,* %	83.3	59.5	<0.05
Degree of calcified arc, degrees	98±88	38±46	<0.05

Values are mean±SD except presence of calcifications.

QCA indicates quantitative coronary angiogram; IVUS, intravascular ultrasound; and ML CSA, minimum endoluminal cross-sectional area.

*Percentage of plaques.

The Culprit Lesion

In our present study, IVUS found only 37.5% of plaque ruptures to be on the culprit lesion (which, by definition, was identified unambiguously by the correlation of clinical data and angiography rather than by IVUS). Fukuda et al²⁴ have recently reported similar percentages, with 37% of subtle plaque dissections on the infarct-related lesions in 59 patients. These discrepancies in anatomopathology findings can probably be accounted for by the relatively constant presence of a larger or smaller thrombus in culprit lesions. Thrombi are of mixed echogenicity and thus are generally impossible to differentiate from an ordinary plaque, thereby covering and effectively masking the underlying ulcerations or ruptures. Lacking specific imaging criteria for the diagnosis of thrombus,^{13,14} IVUS discriminates the culprit lesion poorly for purposes of analysis, whereas angiography using Ambrose's criteria shows a complex lesion in 62.5% of cases, a figure which matches Ambrose's princeps data classifying 71% of culprit lesions as type II eccentric.⁶ Positive coronary remodeling is recognized to be associated with such ruptured plaques.^{25–28} Schoenhagen et al²⁵ reported a remodeling index of 1.06±0.02 in a population of 85 patients suffering unstable angina or recent infarction, and Von Birgelen et al²⁸ reported an remodeling index of 1.09±0.13 in 29 ACS patients, both of which are in agreement with our data (1.05±0.03).

Multiple Ruptures

To the best of our knowledge, there have been no previous studies using IVUS in all of the main coronary trunks for invasive exploration of ACS. It is, however, noteworthy that in a recent study, Asakura et al¹² took a similar approach using coronary angiography. Over the 4 weeks after infarction, angiographic examination of the 3 coronary trunks (2.9 per patient) revealed yellow plaques not only on 90% of the culprit lesions, but even more so diffusely (3.2±1.7 per artery) in all 3 coronary axes. In contrast, intracoronary

thrombus other than that found at the culprit lesion site was exceptional (2%). The question nevertheless remains open as to the possible vulnerability of these yellow plaques, which are much more frequent and diffuse in the case of ACS.²⁹ Despite differing techniques, it is legitimate to set these findings beside our own multiple rupture data, in which an average of 2 distinct ruptures were diagnosed per patient, 70.8% in arteries other than those implicated in the ACS. The lower number of distinct ruptures found on IVUS compared with the large diffusion of yellow plaques on angiography may be explained by the simple fact that these yellow plaques are merely vulnerable but not actually ruptured. This hypothesis has the merit of accounting for the remarkably high rate of 60% for yellow plaque incidence in stable coronary subjects, in whom IVUS estimates plaque rupture incidence at some 10% to 20%,¹⁵ a figure close to anatomopathology findings.^{4,5,19} The distinct multiple ruptures observed show positive remodeling to the same degree as the culprit lesion. The distinct ruptures, moreover, are found on lesions that are looser and less calcified than the culprit lesion, suggesting a less chronic atheromatous process and thus the possibility of younger lesions subsequently developing.

Development and Prognosis

ACS with complex coronary lesions as detected on angiography is of poor clinical prognosis, particularly in terms of

TABLE 3. Percutaneous Coronary Intervention Characteristics

Number of patients with PCI	22 (91)
Stenting on the culprit lesion	19 (86.4)
Stenting on other sites	16 (72.7)
Untreated plaque rupture	13 (59)
Glycoprotein IIb/IIIa inhibitors	5 (23)
Clopidogrel (≥1 month)	22 (100)

Values are n (%).

recurrent ACS episodes.² In our study, prognosis remained excellent, with no subsequent accidents. Although 59% of the patients still had coronary plaque ruptures that had not been treated by angioplasty, the only events recorded were strictly related to the interventional cardiology procedures. So positive a development as compared with the 24% recurrent ischemia observed by Goldstein et al² was probably due to a number of factors, including the fact that >70% of our patients had several coronary stents fitted during the procedure itself, with angioplasty performed on all complex coronary plaques found, and the lesions observed on angiography with ruptures detected by IVUS were less severe (with a mean 39% stenosis in terms of diameter) than in the study by Goldstein et al, in which multiple complex plaques by definition had to be associated with at least 50% stenosis. Asakura et al¹² found yellow plaques disseminated in all 3 trunks on angiography in the month after infarction in 20 patients but still reported no atherothrombotic events in coronary arteries explored over 2-year follow-up. There again, the associated angiographic lesions were relatively mild ($19 \pm 13\%$ stenosis on average). It would seem to be the association of significant stenosis with plaque rupture or cracking that can cause acute coronary thrombotic accidents^{18,20} and that can be a factor of clinical seriousness in itself. Further studies are needed to assess the development of atherosclerosis, which may be associated with such lesions, as anatomopathological examination would suggest.^{23,30}

Conclusion

This 3-coronary vessel IVUS study of ACS showed that IVUS detects multiple atherosclerotic plaque ruptures; these ruptures are present simultaneously with the culprit lesion; they are frequent and can be located in all 3 main coronary trunks; and these other multiple ruptured plaques are less severe, less stenosing, and less calcified than the culprit lesion. Thus, although a single lesion is clinically the culprit at the moment of ACS, ACS would also seem to be associated with pancoronary destabilization.

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Notice of Retraction

For the paper by Rioufol, et al., “Multiple Atherosclerotic Plaque Rupture in Acute Coronary Syndrome: A Three-Vessel Intravascular Ultrasound Study,” *Circulation*. 2002;106:804–808, the editors have discovered that the authors violated *Circulation’s* Ethical Policy, as stated in our Instructions for Authors:

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2. The previous publication of some material in the *Archives Des Maladies Du Coeur Et Des Vaisseaux’* paper was not acknowledged within the *Circulation* manuscript, and no permission from the original copyright holder for the material’s use in the *Circulation* paper was provided.

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