Evolution of Spontaneous Atherosclerotic Plaque Rupture With Medical Therapy Long-Term Follow-Up With Intravascular Ultrasound

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Background—Ruptured coronary atheromatous plaque is generally considered to involve a high risk of subsequent clinical events. Few data are available on the natural evolution of non–culprit-lesion ruptured plaque. We therefore used serial intravascular ultrasound (IVUS) to study how such lesions, detected in the context of a first acute coronary syndrome with elevated troponin I levels, develop.

Methods and Results—Fourteen patients with 28 distinct plaque ruptures (2±1 per patient) without significant associated stenosis (minimal lumen cross-sectional area >4 mm²) were included and systematically treated with 40 mg statin and antiplatelet agent (clopidogrel and aspirin for ≥9 months). Mean clinical and IVUS follow-up was 22±13 months (median, 22 months). No clinical event related to the lesion under study occurred. On final IVUS examination, half (14 of 28) of the ruptured plaques had healed, and the degree of stenosis tended to diminish (stenosis, 22±17% versus 29±17% at baseline; P=0.056). No healing-prediction criterion could be identified.

Conclusions—Nearly 2 years of follow-up found that spontaneous coronary atheromatous plaque rupture without significant stenosis detected on first acute coronary syndrome healed without significant plaque modification in 50% of cases with medical therapy. (Circulation. 2004;110:2875-2880.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ catheterization ■ imaging ■ ultrasonics

O ur knowledge of the natural history of coronary atherosclerosis leads us to expect acute coronary syndrome (ACS) in case of early diagnosis of atheromatous plaque(s) involving a high risk of thrombosis and/or rapid development of stenosis. A recently published consensus study of the concept of vulnerable or at-risk plaque1 identifies several diagnostic criteria, including the visualization of injured plaque, deemed a major criterion. Our own team2 and then others3–7 have recently used intravascular ultrasound scanning (IVUS) to demonstrate the existence of multiple ruptured coronary atheromatous plaques other than the culprit lesion, especially in the context of ACS.

There is a close correlation between ruptured atheromatous plaque and complex lesions visualized on coronary angiography,8 and multiple complex coronary lesions have been shown to be a negative prognostic factor in ACS.9,10

Currently, it is not known how ruptured plaques other than the culprit lesion as visualized on IVUS develop, which raises treatment issues in view of the associated risk of thrombosis.11,12 In a significant number of cases, angioscopy continued to find thrombus on the culprit lesion at 6 months after myocardial infarction (MI),13 which underscores the importance of prolonged (>12 to 18 months) follow-up in studying the natural history of atherothrombosis.

We therefore conducted the present ≈2-year prospective clinical and IVUS study of patients referred for coronary angiography for ACS in whom ruptured non–culprit-lesion plaques were diagnosed on IVUS but not treated by either interventional cardiology or CABG.

Methods

Inclusion Criteria

The study inclusion criteria have been previously reported.2 Briefly, all patients referred for coronary angiography secondary to a first ST-elevation MI (STEMI) or non-STEMI (NSTEMI) and in whom IVUS detected ≥1 atheromatous plaque rupture apart from the culprit lesion were considered for inclusion. Non–culprit-lesion ruptures were managed by interventional cardiology only when the minimum endoluminal area was <4 mm².14 All other cases went without further intervention and were included in the follow-up study.

Follow-Up

Follow-up was conducted by telephone every 6 months. Given the potential seriousness of such ruptured lesions and the unpredictable nature of coronary accidents,15 a coronary angiography plus IVUS...
checkup was systematically advised at 12 months at the latest or at any time in case of suspect developments. All patients provided written informed consent.

Clinical End Points
Because the aim of this prospective study was to assess the development of ruptured plaque, the assessment criteria adopted were the following: angina on effort, NSTEMI or STEMI associated with the ruptured plaque under study, and target lesion revascularization.

IVUS Imaging Protocol
Before the procedure, 200 μg IC nitroglycerin was injected, and a 40-MHz IVUS (Boston Scientific) catheter was advanced >10 mm beyond the lesion. On first IVUS, each plaque was located with precision by the 0.5-mm/s pullback data and immediate anatomic relations to enable precise comparison during follow-up. Qualitative and quantitative IVUS measurements were performed through the use of published definitions, especially for ruptured plaques.2,6,15 On follow-up, the IVUS protocol was rigorously the same, and the initial arterial segment of interest was painstakingly found.

IVUS Definitions
Atheromatous plaque rupture was diagnosed on the basis of a visual aspect of either a ruptured capsule associated with intraplaque cavity, possibly enhanced by intracoronary saline injection, or plaque excavation by atheromatous extrusion with no visible capsule. The intraplaque cavity was measured and extrapolated to the ruptured capsule area.

On follow-up, an initially ruptured plaque was considered to have healed if the initial intraplaque cavity at its precise anatomical location had disappeared, the intima presented no area of discontinuity, and systematic saline flush confirmed the absence of intraplaque cavity. Plaque rupture diagnosis and potential healing required the agreement of 3 trained operators (G.R., M.G., and G.F.). The atheromatous plaques were classified as hypoechoic, hyperechoic, or mixed.

Quantitative IVUS Analysis
Quantitative analysis was conducted on 2 particular cross sections for each ruptured plaque detected: (1) the IVUS reference segment, defined as the first normal or the least pathological segment not >10 mm from the rupture, and (2) the section on which the lumen cross-sectional area was the minimum (ML-CSA) within the plaque rupture.

Cross-sectional images were quantified for lumen CSA (L-CSA, mm²), external elastic membrane CSA (EEM-CSA, mm²), and plaque plus media (P+M) CSA (P+M CSA=EEM-CSA−L-CSA, mm²). A number of parameters were calculated: (1) Plaque burden was defined as [(P+M CSA)/EEM-CSA]×100; (2) percentage stenosis was defined as (ML-CSA reference−ML-CSA ruptured)/ML-CSA reference)×100; (3) significant stenosis was defined as ML-CSA ≤ 4 mm²; (4) 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); (5) eccentricity ratio was calculated as (maximum−minimum/maximum) P+M thickness×100; (6) calcifications and disease-free arterial wall were measured in terms of the degree of arc with respect to the center of the coronary lumen; and (7) relative intraplaque cavity volume with respect to the particular atheromatous plaque was defined as percent cavity area/plaque ratio=(cavity/P+M CSA)×100. Comparisons between initial and follow-up data were expressed as percentage variation.

Statistical Analysis
Statistical analysis was performed with StatView 4.5 statistical software (Abacus Concept, Inc). Data are presented as mean±SD. Continuous quantitative data were compared by matched Student t test or nonparametric Wilcoxon test if numbers were <30; and discontinuous quantitative data were compared by χ² test. P<0.05 was considered statistically significant.

Results
Between June 2000 and June 2001, 14 patients presenting with first ACS and nonstenotic nonculprit IVUS-detected ruptured plaques were prospectively enrolled. Six were patients from our previous study,2 which had simply looked at the clinical and IVUS criteria on initial post-ACS checkup. This population represents ~10% of all patients referred to our institution for first ACS and 30% of all IVUS examinations performed during the study period. Table 1 presents the demographic data of our population.

Twenty-eight distinct ruptured plaques (2±1 per patient) were diagnosed and given only medical management, with a mean follow-up of 22±13 months (median, 22 months). All patients had IVUS control examinations without incident.

Clinical
During the whole follow-up, no ruptured plaque–related clinical event or target lesion revascularization occurred. All patients received statin and, for at least the first 9 months after ACS, continual antiplatelet bitherapy followed by uninterrupted antiplatelet monotherapy (aspirin, 13; clopidogrel, 1). During clinical follow-up, ultrasensitive C-reactive protein and LDL cholesterol levels fell nonsignificantly (0.75±0.68 to 0.42±0.44 mg/dL and 114±41 to 101±22 mg/dL, respectively).

Follow-Up of Ruptured Coronary Atherosclerotic Plaque
By the end of IVUS follow-up on the 28 ruptured plaques, 14 (50%) had healed. The remodeling index was unchanged and

TABLE 1. Patient Characteristics at Baseline (n=14)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>64±10</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>ACS, n (%)</td>
<td></td>
</tr>
<tr>
<td>ST elevation</td>
<td>3 (21)</td>
</tr>
<tr>
<td>No ST elevation</td>
<td>11 (78)</td>
</tr>
<tr>
<td>LVEF, mean±SD, %</td>
<td>58±13</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>1 Vessel</td>
<td>6 (43)</td>
</tr>
<tr>
<td>2 Vessels</td>
<td>7 (50)</td>
</tr>
<tr>
<td>3 Vessels</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Ruptured plaque location, n (%)</td>
<td>28</td>
</tr>
<tr>
<td>LAD</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Circumflex</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>13 (47)</td>
</tr>
<tr>
<td>Left main</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Stenosis, mean±SD, %</td>
<td>29±17</td>
</tr>
<tr>
<td>Angiographic complex plaque, n (%)</td>
<td>14 (50)</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; LAD, left anterior descending. n=14.
considerably positive (1.10±0.08), with a tendency toward reduced plaque burden and increased endoluminal area (9.1±3.3 versus 8.3±2.5 mm² at baseline; \( P=0.08 \)), entailing less severe stenosis. Plaque eccentricity tended to diminish, whereas the calcification arc increased significantly (15°±30° versus a baseline of 10°±27°; \( P=0.03 \)) (see Table 2). Angiography detected only half of the IVUS-detected ruptured plaques, and angiographic complexity significantly decreased on follow-up (\( P=0.04 \)).

**Healed and Unhealed Ruptures**

Univariate analysis failed to reveal any morphological baseline predictors of spontaneous ruptured plaque healing. Over comparable follow-up periods for healed and unhealed plaques, quantitative analyses proved that similar—notably cavity area (1.6±2.0 versus 1.8±1.6 mm²; \( P=0.68 \)) and plaque burden (61.9±10.1 versus 59.3±8.1; \( P=0.73 \))—and qualitative data remained the same, particularly the type (central or lateral) of rupture and plaque composition (see Table 3). Moreover, neither clinical data (age, diabetes, hypertension, number of ruptured plaques per patient) nor biological markers (C-reactive protein, LDL cholesterol) at baseline or follow-up managed to pinpoint any predictive factor for plaque healing (Figures 1 and 2).

**Discussion**

Nearly 2 years of clinical and IVUS follow-up showed that spontaneous coronary atheromatous plaque rupture without significant stenosis detected on first ACS healed spontaneously in 50% of cases.

**Ruptured Plaque and IVUS Characteristics**

Several studies have addressed the IVUS characteristics of nonculprit ruptured plaques, and our analysis of the 28 ruptured plaques at baseline was very much in line with the literature. In terms of minimum lumen area, the nonculprit ruptured plaques typically presented no significant stenosis criteria; mean ML-CSA was 8.3±2.5 mm² (range, 4.1 to 13.8 mm²), comparable to the 8.5±0.6 mm² previously reported and a little greater than in other studies (5±3 mm² from Mintz et al., 5.3±2.6 mm² from Gössl et al., and 6.2±2.8 mm² from Fujii et al.). Our strict inclusion criteria probably account for this difference, because only nonsignificant stenoses with ML-CSA >4 mm² were followed up prospectively. Mean intraplaque cavity area was 1.7±1.8 mm² with a ratio of cavity area to plaque of 11±8% compared with 2.8±1.9 mm² and 19.9±10%, respectively, for Fujii et al. They did not report their indications for non–culprit artery IVUS, which doubtless derived from suspicious aspects on angiography, favoring detection of the largest ruptures.

**Ruptured Plaque and Development of Stenosis**

Anatomopathological studies have shown that when subclinical coronary plaque ruptures heal, they can contribute to stenosis and that the number of healed ruptures increases with severity of stenosis. Such healed ruptures are especially found in association with fatal atherothrombotic accident or history of MI.
Angiographic follow-up studies have shown 38% of non-culprit lesions to have stenosis with a mean progression from 12% to 45% during the first month after MI, although rarely when the initial stenosis was <50% on angiography. Likewise, Kaski et al with a mean follow-up of 8-3 months, found that 10% of stenoses <50% progressed on average from 37±11% to 45±14%, notably in medically controlled unstable angina, especially when the lesions were complex (P=0.002) and when there was >1 complex lesion in the coronary tree (P<0.01).

No prospective IVUS follow-up study has previously been performed for this kind of coronary lesion. In our population, we found a mean of 2±1 ruptured lesions per patient with a mean stenosis of 29±17% (range, 5% to 65%). Over follow-up, stenosis tended to diminish by 13% (P=0.056). This tendency can be accounted for by the nonsignificant −3±8% reduction in plaque burden with no change in remodeling index. The lack of lesion progression is in disagreement with the findings on angiographic series. However, management at the time of those studies involved only aspirin and rarely statins. More recently, Lee et al found that angiographically complex lesions associated with the culprit lesion after acute MI showed no significant change in percentage stenosis (74±15% versus 72±15%; P=0.40), although follow-up was only 6 months. Statin was prescribed in only 29% of cases, and longer-term angiographic development

Figure 1. Example of spontaneously healed plaque. At baseline, angiogram discloses ulceration of second segment of right coronary artery (arrow) with corresponding IVUS image (A, B). There is central plaque rupture with ruptured capsule (double arrow). Cavity size is 7.8 mm². At 19 months’ follow-up, ulceration has disappeared from angiogram, and IVUS image (C, D) confirms cicatricization. L-CSA is very similar at both examinations (9.0 and 9.4 mm²), whereas EEM-CSA has increased from 40.1 to 44.0 mm². B, D, Schematization of contours. *Wire echo.

Figure 2. Example of nonhealed plaque. At baseline, angiogram discloses ulceration of second segment of right coronary artery (arrow) with corresponding IVUS image (A, B). There is central plaque rupture with ruptured capsule (double arrow). At 21 months’ follow-up, ulceration remains present on angiogram, and corresponding IVUS image (C, D) confirms that plaque has not healed; instead, plaque rupture has become lateral (double arrow). L-CSA and EEM-CSA have increased from 9.2 to 9.8 mm² and from 28.3 to 34.6 mm², respectively. Cavity size has increased from 2.9 to 4.7 mm². B, D, Schematization of contours. *Wire echo.
remained undetermined. In contrast, our patients received aspirin plus clopidogrel platelet aggregation bitherapy for ≥9 months, followed by monotherapy, and all patients systematically received statin (40 mg pravastatin ×9, and 40 mg simvastatin ×5). This regimen probably explains the stability (or improvement) observed in the coronary lesions.

Ruptured Plaque and Healing

Anatomopathological studies demonstrate that although ruptured plaques commonly heal,17,18 ruptured lesions other than the culprit lesion21 or lesions in subjects dead from noncardiovascular causes are frequently observed.22 In the present study, IVUS showed that 50% of detected ruptures healed spontaneously over 2 years of follow-up and that the others remained stable without significant change in plaque or cavity parameters. No IVUS healing-prediction criterion could be found.

Regardless of whether ruptures healed or not, the reduction in stenosis observed here was the same, ∼15%. This finding is in disagreement with the anatomopathological data17,18 but is comprehensible in view of the variety of stages of coronary atherosclerosis and analysis techniques. There are no IVUS data on the natural history of ruptured atheromatous plaque; the few old coronary angiography series that are available are limited by the poor sensitivity of angiography for the detection of ruptured plaque.2,15 They seem to show that if a lesion is complex (ie, liable to rupture), it tends to remain so or lead to occlusion.23,24 Regardless of the initial clinical aspect, the percentage of complex stenoses that smooth out over angiographic follow-up is low, ranging from 2% to 6% for a follow-up ranging from 6 to 8 months10,25 to several years. Analysis specifically concerning ulcerated lesions on angiography is even more piecemeal, with a few data here and there on healing or stability over time.23,24 In contrast, in the present highly selected population, most (9 of 14) unstable nonstenotic plaques became smooth over follow-up (P = 0.04). The exhaustive statin plus antiplatelet regimen probably accounts for this difference from pre–statin era studies.

Culprit lesions with a complex aspect on angiography are generally agreed to entail a high risk of a significant future coronary event.26,27 More recently, it has been shown that the 6-month10 and 1-year9 prognoses after STEMI are poor in case of multiple complex coronary lesions, with a higher rate of percutaneous coronary interventions on noninfarcted arteries (14.5% versus 3.5% and 17% versus 4.6%, respectively) and of recurrent ACS (19% versus 2.6%,9). Such complex lesions by definition have associated ≥50% stenosis, but clinical data on complex coronary plaques with no significant associated stenosis are not as well established. After a mean of 8 ± 4 months of follow-up of 85 medically stabilized unstable angina patients, Chen et al26 found that 16% of coronary events (4 of 25 patients) occurred on nonculprit and initially nonsignificant (stenosis, 44 ± 11%) coronary lesions, with no details as to their complexity or otherwise. Moreover, Kaski et al,20 with a mean of 8 ± 3 months of follow-up, showed coronary events to be more likely in case of unstable angina and complex lesions and demonstrated that initially nonsignificant lesions (stenosis, 37 ± 11%) are liable to develop rapidly toward complete occlusion. Unlike in these pre–statin era studies, our population was systematically managed with statin and platelet aggregation treatment (including ≥9 months of bitherapy). With a mean of 22 ± 13 months of clinical follow-up, we show that a nonculprit ruptured plaque with no significant stenosis (29 ± 17%) secondary to ACS entails no risk of further events. Such ruptured plaques would seem to have lost whatever thrombotic potential they may have had and to have become passive.28 These findings agree with the retrospective PURSUIT study analysis, which assessed the use of eptifibatide in ACS without ST elevation.29 Of the 5767 patients undergoing coronary angiography, 696 (12%) presented with stenosis <50% (without details as to whether complex or not) and had a very low risk of death/nonfatal MI as an end point at 30 days or 6 months (1.1% and 2.2% versus 10% and 13.4%, respectively, in case of significant stenosis; P < 0.001 in both cases).

We report here on a small series underpowered to reliably detect any clinical event even with 2 years of follow-up, so our results merely suggest that a lesion destabilized by plaque rupture but without significant associated stenosis (ML-CSA > 4 mm²) may be managed medically with systemic high doses of statin and antiplatelet therapy, sparing the patient the inherent risks of interventional cardiology.30 Larger-scale studies are needed to confirm the present findings. The natural evolution of an unstable lesion with ≥50% stenosis and the role of stenting in such a clinical situation also remain to be assessed.

References

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