Extensive Development of Vulnerable Plaques as a Pan-Coronary Process in Patients With Myocardial Infarction: An Angioscopic Study

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**OBJECTIVES** To test our hypothesis that the development of vulnerable plaques is not limited to the culprit lesions, but is a pan-coronary process, we directly observed all three major coronary arteries by angioscopy and evaluated the prevalence of yellow plaques in patients with myocardial infarction (MI).

**BACKGROUND** Although pathologic studies have suggested that the disruption of atheromatous plaque plays a major role in the development of acute MI, the prevalence of yellow plaques in the whole coronary arteries of patients with MI has not been clarified.

**METHODS** Thirty-two patients undergoing follow-up catheterization one month after the onset of MI were prospectively and consecutively enrolled in this study. The prevalence of yellow plaques and thrombus in the major coronary arteries was successfully evaluated in 20 patients (58 coronary arteries, 21 culprit lesions) by coronary angioscopy. The diameter stenosis (DS) of the culprit lesions and the maximal diameter stenosis (maxDS) of nonculprit segments were angiographically measured for each coronary artery.

**RESULTS** The DS of the culprit lesions and maxDS were 27 ± 17% and 19 ± 13%, respectively. Yellow plaques and thrombus were detected in 19 (90%) and 17 (81%) of 21 culprit lesions, respectively. Yellow plaques were equally prevalent in the infarct-related and non–infarct-related coronary arteries (3.7 ± 1.6 vs. 3.4 ± 1.8 plaques/artery). However, thrombus was only detected in the nonculprit segments of one (2%) coronary artery.

**CONCLUSIONS** In patients with MI, all three major coronary arteries are widely diseased and have multiple yellow though nondisrupted plaques. Acute MI may represent the pan-coronary process of vulnerable plaque development. (J Am Coll Cardiol 2001;37:1284–8) © 2001 by the American College of Cardiology

Pathologic and angioscopic studies (1–8) have revealed that thrombus covers the disrupted intracoronary atheromatous plaques in patients with acute myocardial infarction (MI) and have suggested that disruption of the plaques may play a major role in the development of acute MI. However, the prevalence of atheromatous plaques in the nonculprit segments of the infarct-related coronary arteries and in the noninfarct-related coronary arteries of patients with acute MI has not been clarified. Goldstein et al. (9) demonstrated, using coronary angiography, the existence of additional unstable lesions other than the culprit lesions in 21% of patients with MI; these lesions were defined as total or subtotal occlusion with evidence of thrombus or as stenosis with clear ulceration, fissuring and/or intraluminal filling defects. They suggested that plaque instability may not represent a mere random “vascular accident,” but may perhaps reflect a “pan-coronary” process. However, acute MI is frequently caused by angiographically normal to mildly stenotic lesions (10) that cannot be identified by coronary angiography as the vulnerable lesions. Angioscopy may be more useful than angiography to detect vulnerable plaques, because vulnerable plaques are easily detected as yellow plaques (4–8,11,12). We hypothesized that MI occurs accidentally at one of the multiple vulnerable plaques prevalent throughout the coronary arteries. To test this hypothesis, we evaluated, using coronary angioscopy, the prevalence of yellow plaques in all three major coronary arteries in patients with MI.

**METHODS**

**Study patients and protocol.** From September 1997 to August 1998, we prospectively and consecutively enrolled 32 patients undergoing follow-up catheterization one month after the onset of MI. Angioscopic studies of all three major coronary arteries were performed to evaluate the prevalence of yellow plaques and thrombus. Myocardial infarction was confirmed by creatine kinase-MB fraction elevation and demonstration of coronary artery occlusion in the acute phase by angiography. In all patients, reperfusion therapy was successfully performed by balloon angioplasty with or without stenting or thrombolysis. Informed, written consent was obtained from all patients. The patients’ characteristics were also collected. This study protocol was approved by the Osaka Police Hospital Ethical Committee.

Twelve patients were excluded from analysis because two...
or more coronary arteries were not successfully observed by angioscopy due to arterial tortuosity or stenosis. Therefore, 20 patients (15 men and 5 women, age 59 ± 10 years) were included in the present study. In 2 of 20 patients, the right coronary artery (RCA) was not successfully observed. In one patient, inferior acute MI occurred during follow-up of anterior MI, and two lesions in the left anterior descending coronary artery (LAD) and RCA were regarded as culprit lesions. Therefore, 58 coronary arteries, including 21 culprit lesions, were analyzed in those 20 patients. Stenting and thrombolysis were performed in two patients and one patient, respectively. Table 1 describes the characteristics of the study patients. A representative case is shown in Fig. 1.

**Angiographic analysis.** Catheterization was performed by the femoral artery approach using an 8F sheath and catheters. The coronary angiogram was recorded with the Advantx Medical System (General Electric, Milwaukee, Wisconsin). The left coronary arteries were evaluated from at least four views, and the RCAs from at least two views. The diameter stenosis (DS) of the culprit lesions and the maximal diameter stenosis (maxDS) of each coronary artery, excluding the culprit lesion, were determined by quantitative coronary angiography. The vessel contour (smooth, irregular, ulcerative or hazy) was also evaluated. On the angiogram, thrombus was defined as the filling defect of mobile fragments or haziness, although the filling defect of the mobile fragments is usually detected in the acute stage of acute coronary syndromes (ACS), and only haziness was actually detected in the present study.

**Angioscopic procedures and evaluations.** We used the angioscope MC-800E (Nihon Kohden, Tokyo, Japan) and the optic fiber AS-003 (Nihon Kohden). The angioscopic observations were made while the blood was cleared away from the view by the injection of 3% dextran-40, as described previously (7). We continuously examined the whole coronary artery from the distal segment to the ostium of all three major coronary arteries if the lumen diameter was ≥2 mm, and we evaluated the existence of yellow plaques and thrombus. There was no complication associated with the angioscopic procedures. Yellow plaque was simply defined as the yellow area on the lumen surface, which may have a smooth or irregular surface with or without protrusion into the lumen. Thrombus was defined as white or red material that has a cotton-like or ragged appearance or fragmentation, which may be protruding into the lumen or adhering to the lumen’s surface. The prevalence of yellow plaques and thrombus was determined for the culprit and nonculprit segments separately, and the number of yellow plaques in each coronary artery, excluding or including the culprit lesions, was counted. Evaluations of the angioscopic images were performed by two angioscopy specialists who had no knowledge of the clinical data, and in case of disagreement, the third reviewer decided the interpretation. The interobserver and intraobserver reproducibilities for interpretation of the angioscopic images were 96% and 100% for plaque color and 94% and 91% for thrombus, respectively.

**Determinants for the number of yellow plaques.** The number of yellow plaques in a coronary artery was compared between: 1) infarct–related and noninfarct–related coronary arteries; 2) men and women; 3) LAD and left circumflex coronary arteries; 4) diabetes with and without hypertension; 5) type 1 with type 2 diabetes mellitus; 6) diabetic and nondiabetic smokers; 7) high and low total cholesterol; 8) high and low HDL cholesterol; 9) high and low triglyceride; 10) high and low body mass index; 11) high and low systolic blood pressure; 12) high and low diastolic blood pressure; 13) high and low low-density lipoprotein cholesterol; 14) high and low high-density lipoprotein cholesterol; 15) high and low C-reactive protein; 16) high and low serum lipoprotein (a).

[Table 1. Patients’ Characteristics (n = 20)]

<table>
<thead>
<tr>
<th>Angioscopic observations (n)</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary arteries</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>20</td>
</tr>
<tr>
<td>LCx</td>
<td>20</td>
</tr>
<tr>
<td>RCA</td>
<td>18</td>
</tr>
<tr>
<td>Culprit lesions</td>
<td>21</td>
</tr>
<tr>
<td>LAD</td>
<td>10</td>
</tr>
<tr>
<td>LCx</td>
<td>5</td>
</tr>
<tr>
<td>RCA</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>75%</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59 ± 10</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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</tr>
<tr>
<td>Hyperlipidemia</td>
<td>60%</td>
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<tr>
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<td>56%</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
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</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>46 ± 10</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>169 ± 122</td>
</tr>
</tbody>
</table>

Data are presented as the number of patients, percentage of patients or mean value ± SD.

HDL = high density lipoprotein; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Figure 1. A representative patient (58-year-old man) with anterior myocardial infarction. Angioscopic images of the culprit lesion (nos. 8 and 9) and of all the yellow plaques in the nonculprit segments are presented. Thrombus was detected over the yellow plaque in the culprit segment.

**Abbreviations and Acronyms**

- ACS = acute coronary syndrome
- DS = diameter stenosis
- HDL = high density lipoprotein
- IVUS = intravascular ultrasound
- LAD = left anterior descending coronary artery
- maxDS = maximal diameter stenosis
- MI = myocardial infarction
- RCA = right coronary artery
coronary artery and RCA; and 4) patients with and those without hypertension, hypercholesterolemia, diabetes mellitus or a smoking habit. The relationship between the number of yellow plaques and the patient's age or serum levels of total cholesterol, high density lipoprotein (HDL) cholesterol or triglycerides was also evaluated.

**Coronary events.** The data on cardiac events (death, ACS, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty) were collected from the clinical records after the angioscopic study, by the end of September 2000. The follow-up period was 931 ± 107 days.

**Statistical analysis.** All data were presented as the mean value ± SD. The number of yellow plaques in an infarct–related coronary artery and a noninfract-related coronary artery was determined separately for each patient by calculating the average if there were two or more infarct-related or noninfarct-related coronary arteries, and the difference between the infract-related and noninfract-related coronary arteries was analyzed by the paired $t$ test. The difference in the number of yellow plaques between three coronary vessels was analyzed by the paired $t$ test. The average number of yellow plaques in a coronary artery was determined for each patient by calculating the average of all major coronary arteries, and the difference of this average number of yellow plaques between the groups, defined by various risk factors (hypertension, hypercholesterolemia, diabetes mellitus and smoking) or gender, was analyzed by using the unpaired $t$ test. The correlation between the number of yellow plaques and the patient's age or serum levels of total cholesterol, HDL cholesterol or triglycerides was assessed by linear regression analysis using the least squares method. The value $p < 0.05$ was regarded as significant.

**RESULTS**

**Culprit lesions of MI.** The DS of the culprit lesions was 27 ± 17% (range 0% to 55%). On the angioscopic images, we observed yellow plaques and thrombus in 19 (90%) and 17 (81%) culprit lesions, respectively. Slight haziness was detected by angiography in 4 (19%) culprit lesions, and thrombus was angioscopically detected in all of them. However, thrombus was also detected by angiography in 13 culprit lesions (62%) with a smooth contour on the angiogram. Therefore, angiography could detect thrombus in only 24% of the culprit lesions in which thrombus was detected by angiography. Yellow plaques were found in 6 culprit lesions (29%) with mild stenosis on the angiogram; irregular or ulcerative contour was found in 9 culprit lesions (43%) with mild stenosis and smooth contour and in 4 culprit lesions (19%) without stenosis and with smooth contour. Both stented culprit lesions, where angiography revealed no stenosis, irregularity or haziness, had yellow plaque and thrombus.

**Distribution of yellow plaques in the whole coronary arteries.** The maxDS of the nonculprit segments was 19 ± 18% (range 0% to 65%). Twenty-three coronary arteries (40%) did not have either lumen stenosis or vascular wall irregularity by coronary angiography. In the nonculprit segments of all patients, 17 mildly stenotic lesions (one with hazy contour and 16 with smooth contour) were detected by angiography, and 185 yellow plaques were detected by angioscopy. Although 16 (94%) of those 17 lesions had yellow plaque, 169 (91%) of 185 yellow plaques were found in the site where angiography was completely normal. Even after knowing the existence of yellow plaque, no specific angiographic sign was detected for them. Yellow plaques were observed in the nonculprit segments in 55 (95%) of 58 coronary arteries. Thrombus was detected in the nonculprit segment only in 1 coronary artery (2%) in the segment of angiographic haziness with mild stenosis where yellow plaque was also detected.

The mean number of yellow plaques detected in a coronary artery, excluding the culprit lesion, was 3.2 ± 1.7 (the distribution is presented in Fig. 2). Yellow plaques were equally prevalent in the infract–related and non–infarct-related coronary arteries (3.7 ± 1.6 vs. 3.4 ± 1.8 plaques/artery, including the culprit lesion; $p = \text{NS}$). Significantly more yellow plaques were detected in the right as compared with the left circumflex coronary artery or LAD (4.4 ± 2.1 vs. 2.8 ± 1.3 or 3.5 ± 1.5 plaques/artery, including the culprit lesion; $p < 0.05$). However, the number of yellow plaques had no significant relationship with the rest of the factors (age, gender, hypertension, hypercholesterolemia, diabetes mellitus, smoking or serum levels of total cholesterol, HDL cholesterol or triglycerides).

**Coronary events.** No death or bypass surgery was observed among the enrolled patients. Acute MI was observed in one patient; however, because the culprit lesion was in the distal segment of the RCA, it had not been observed by angioscopy, and whether the MI occurred at the yellow plaque was not determined. Percutaneous transluminal coronary angioplasty was performed in four patients because of restenosis of the culprit lesion (three of them had yellow plaque).
DISCUSSION

Our previous report demonstrated that the yellow plaques were detected in the culprit lesions in 93% of patients with acute MI and suggested that yellow plaques play a major role in the development of MI. However, so far, no reports have evaluated the prevalence of yellow plaques in the whole coronary arteries, especially in the nonculprit segments. In the present study, on the angioscopic images, we observed all three major coronary arteries in patients with MI, revealing that yellow plaques exist not only in the culprit lesions but also in the nonculprit segments, both in the infarct-related and noninfarct-related coronary arteries. This finding clarified that all three major coronary arteries are similarly diseased and have multiple yellow plaques in patients with MI.

Vulnerability of yellow plaques. Thieme et al. (12) validated angioscopic observations with histologic assessment of the material removed by coronary atherectomy, and they suggested that the yellow plaque color is closely related to degenerated plaque or atheroma and is associated with ACS. Waxman et al. (13) demonstrated that yellow plaques are associated with the risk of adverse outcomes after balloon angioplasty, and they suggested that yellow plaques may have an increased thrombogenic potential. We previously reported that yellow plaques were observed in only 64% of patients with stable angina who had no history of MI, but in 93% of patients with acute MI and in 95% of patients with unstable angina. Thieme et al. (12) also demonstrated that yellow plaques were detected in only 57% of patients with stable angina, but in 89% of patients with unstable angina. These results support the idea that the presence of yellow plaques is closely associated with the vulnerability of the lesions and unstable symptoms, and that yellow plaques likely cause ACS, although the natural course of yellow plaque development and disruption has not been established. On the basis of these reports, the present study suggests that whole major coronary arteries in patients with MI are extensively diseased and have multiple vulnerable plaques that have a possibility to cause another ACS.

The combination of these modalities may increase the sensitivity of angioscopy to detect vulnerable plaques. Although some of the angioscopic findings may be a sign of vulnerability, intravascular ultrasound (IVUS) imaging may also be useful to identify the highly vulnerable plaques among the yellow plaques, because IVUS gives us additional information on the sectional images of the plaques. Compensatory enlargement of the arterial segments, as detected by IVUS, has been associated with unstable clinical events. However, some of the characteristic appearances observed in the culprit lesions of ACS may be acquired by the disruption of the plaque, and the appearance of vulnerable plaques before imminent disruption may be different. To test whether various angioscopic findings can be a sign of vulnerability in the plaques before disruption, prospective clinical trials may be required.

Although no event of ACS was observed to result from the yellow plaques during ~2.5 years of follow-up among the enrolled patients, intensive treatment with beta-blockers, antiplatelets and lipid-lowering therapy might have prevented the occurrence of ACS. To evaluate the vulnerability of yellow plaques, patients who are not intentionally treated or a larger number of patients should be studied.

Detection of vulnerable plaques by angioscopy. The sensitivity of angioscopy to detect vulnerable plaques may be high because: 1) the culprit lesions of ACS appear to be predominantly yellow; 2) thrombus is five times more likely to be found in association with yellow as compared with white lesions (16); 3) angioscopically demonstrated yellow plaque has been shown to have a large lipid core and a thin fibrous cap and has been associated with unstable clinical situations; and 4) it is extremely easy to find the yellow lesions on the white lumen surface. However, there is little information on its specificity. However, because all yellow plaques may not be vulnerable, further research is required to find out the characteristics of the highly vulnerable plaques among the yellow plaques. The culprit plaques of ACS (7,17) have a similar appearance of: 1) vividly yellow color that is sometimes glistening; 2) an irregular surface, sometimes with the protrusion of the plaque content; 3) adherence of the predominantly white thrombus, revealing a ragged or cotton-like appearance; and 4) intramural hemorrhage manifested as a blood-red discoloration of the lumen’s surface. Glistening yellow color (18) has been reported to be predictive of ACS, and the existence of thrombus is known to be a risk factor of adverse cardiac events. However, some of the characteristic appearances observed in the culprit lesions of ACS may be acquired by the disruption of the plaque, and the appearance of vulnerable plaques before imminent disruption may be different.
specificity of the angioscopic study to identify the highly vulnerable plaques, and may be able to identify patients who have a high risk of developing acute MI in the early stage of plaque formation, when angiography cannot detect any abnormal sign.

Study limitations. This study has two limitations: the study group was small and the small vessels (diameter <2 mm) were not included. The prevalence of yellow plaques in patients with stable effort angina or in patients without coronary artery disease remains to be established, because we observed the coronary arteries only in patients with MI. The prevalence of yellow plaque or thrombus at the culprit lesions may possibly differ after different reperfusion therapy. However, plaque color is not likely to be altered by stents that are usually not covered by the neointima as long as 45 days after implantation (21).

Conclusions. Whole coronary arteries are diseased and have multiple yellow plaques in patients with MI, and the development of MI may reflect the pan-coronary process of vulnerable plaque formation. Therefore, once the patients present with acute MI, they must have additional vulnerable plaques, which possibly cause another ACS, so they should be treated intensively to prevent the next coronary event.

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REFERENCES