Change of multiple complex coronary plaques in patients with acute myocardial infarction: A study with coronary angiography

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Background Patients with acute myocardial infarction (AMI) may have multiple complex coronary plaques that are not limited to the culprit lesions. However, it is unknown whether they tend to progress in severity, regress, or remain stable. The aim of this angiographic study is to evaluate the natural history of these lesions.

Methods We consecutively enrolled 229 patients who underwent coronary angiography at the time of their hospitalization to treat AMI with primary angioplasty. Baseline and follow-up (mean follow-up duration, 192 ± 33 days) coronary angiographic data in patients with multiple complex coronary plaques characterized by thrombus, ulceration, plaque irregularity, and impaired flow were compared.

Results Single complex coronary plaques were identified in 167 patients (73%), and multiple complex plaques were identified in the other 62 patients (27%). Among the patients with multiple complex plaques (62 patients, 83 non-culprit complex plaques), the angiographic examinations were reviewed simultaneously in 43.5% (27 patients, 35 non-culprit complex plaques). Of 35 non-culprit complex lesions, 29 lesions (82%) remained complex without changing into smooth lesions, 1 lesion became totally occluded, and 4 lesions regressed. The severity of non-culprit complex lesions between baseline and follow-up angiography is equal (maximal diameter stenosis, 74% ± 15% vs 72% ± 15%, $P = .4$). Long-term cardiac events after discharge were more likely to develop in patients with multiple complex plaques than in patients with single complex plaques (24% vs 10%, respectively; $P < .01$).

Conclusions In patients with AMI, little angiographic change occurred during 6 months of follow-up in the non-culprit complex plaques. (Am Heart J 2004;147:281–6.)

Histopathologic and angioscopic studies indicate that most coronary artery lesions resulting in acute myocardial infarction (AMI) are thrombi superimposed on disrupted atherosclerotic plaques.[1–3] However, whether the predominant mechanism for plaque disruption is local or systemic is not clear. Recently, Goldstein et al reported that in patients with AMI, coronary arteries have multiple complex plaques, and the presence of these lesions was independently predictive of future adverse clinical outcomes.[4] Asakura et al also demonstrated that vulnerable yellow plaques exist not only in the culprit lesions, but also in the non-culprit segments on the angioscopic images.[5] They suggested that plaque instability is not merely a local vascular accident, but may reflect more generalized pathophysiologic processes.

However, little data are available on the natural history of these lesions. It is assumed that the severity or complexity of non-culprit complex lesions might be changed with time in accordance with their different clinical outcomes. Therefore, clarifying these natural history issues can have important implications on preventive and therapeutic interventions and regarding our basic understanding of subsequent acute coronary events after AMI.[6,7] We attempted to answer these questions by studying the angiograms of 229 patients with AMI who had sequential coronary angiograms.

Methods

Study patients

The study population consisted of consecutive 229 patients who underwent coronary angiography at the time of their hospitalization to treat AMI with primary angioplasty from

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Table I. Baseline clinical characteristics

	Single (n = 167)	Multiple (n = 62)	P
Age	58 ± 12	59 ± 9	.4
Male (%)	133 (80)	48 (77)	.7
Risk factor			
Total cholesterol (mg/dL)	190 ± 49	159 ± 33	.5
Hypertension (≥140/90 mm Hg) (%)	45 (27%)	12 (19%)	.24
Smoking (%)	76 (46%)	22 (35%)	.18
Diabetes mellitus (%)	24 (14%)	13 (21%)	.23
Multi-vessel disease (≥2) (%)	44 (26%)	51 (82%)	<.001
Ejection fraction	55% ± 10%	52% ± 12%	.07
Infarct-related artery			
Left anterior descending	84	30	
Left circumflex	2	5	
Right	81	27	
Drug use (%)			
Aspirin	147 (88)	56 (90)	.92
β-Blockers	105 (63)	41 (66)	.26
ACE inhibitors	55 (33)	24 (34)	.55
Fibrates	10 (6)	4 (7)	.60
Statins	53 (32)	18 (29)	.16

Data are presented as the number of patients (%) or mean value ± SD.

June 1997 to December 2000. The inclusion criteria were typical chest pain lasting >30 minutes, presentation within 12 hours after the onset of symptoms, and ST-segment elevation ≥0.1 mV in ≥2 limb leads or ≥0.2mV in ≥2 consecutive precordial leads. Exclusion criteria were previous administration of thrombolytic agents for the index infarction and previous percutaneous transluminal coronary angioplasty. All patients received conventional drug therapy in accordance with standard clinical practice. All patients gave their written, informed consent to participate in the study.

Angiographic analysis

Baseline (at the time of their hospitalization) and follow-up (an interval >6 months) coronary angiographic data in patients with multiple complex coronary plaques were reviewed simultaneously by 2 independent experienced investigators, who wre blinded to patient identity and group. By means of χ^2 analysis, a highly significant correlation of the 2 angiographers' interpretations was demonstrated (χ^2, 47.6; P <.001). Follow-up angiography was routinely performed on every patient undergoing primary angioplasty. Paired frames of the same view at end diastole were compared. Artifactual causes of complexity were excluded. These included poor opacification, streaming of contrast material, presence of overlying structures (especially small branches that, on a single frame, might be easily confused with irregularity), tortuosity, and foreshortening of the segment. The percent-diameter stenosis was estimated from a view demonstrating the most severe narrowing. A lesion morphology was considered smooth when it had smooth borders and no filling defects, whether it was concentric or eccentric. Lesions were considered complex when they caused at least 50% stenosis and had ≥2 described features (intraluminal filling defect consistent with thrombus, plaque ulceration, plaque irregularity, and impaired flow). The location of the infarct-related plaque was determined from the admission electrocardiogram and wall-motion abnormalities. An anatomically remote plaque was defined as one: in a different artery from the artery containing the infarct-related plaque; in the same artery as that containing the infarct-related plaque, but in a different branch; or in the same artery and branch as the infarct-related plaque, but at least 5 cm from the infarct-related plaque, with an intervening segment of disease-free vessel. Non-culprit lesion changes at the narrowest point defined progression or regression when exceeding 0.27 mm validated by Gibson et al.[8] The principle angiographic end points were the changes in percent-diameter stenosis and morphology. The mean follow-up period was 192 ± 33 days (range, 154–625 days).

Coronary events

The data on cardiac events (death, nonfatal reinfarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty) were collected from the clinical records after primary angioplasty. Nonfatal myocardial reinfarction was defined as the occurrence of acute occlusion in the non-culprit complex lesions. Data from patients in whom a second intervention was performed were analyzed to determine whether the later intervention was performed on the index culprit lesion or on a remote plaque.

Statistical analysis

Data were expressed as the mean plus or minus SD for continuous variables and as frequencies for the categorical variables. These variables were compared with the χ^2 test when applicable and otherwise with the Fisher exact test. Within-subjects analysis of variance and unpaired and paired Student t test, as appropriate, were used to analyze the data. A P value <.05 was considered to be statistically significant.

Results

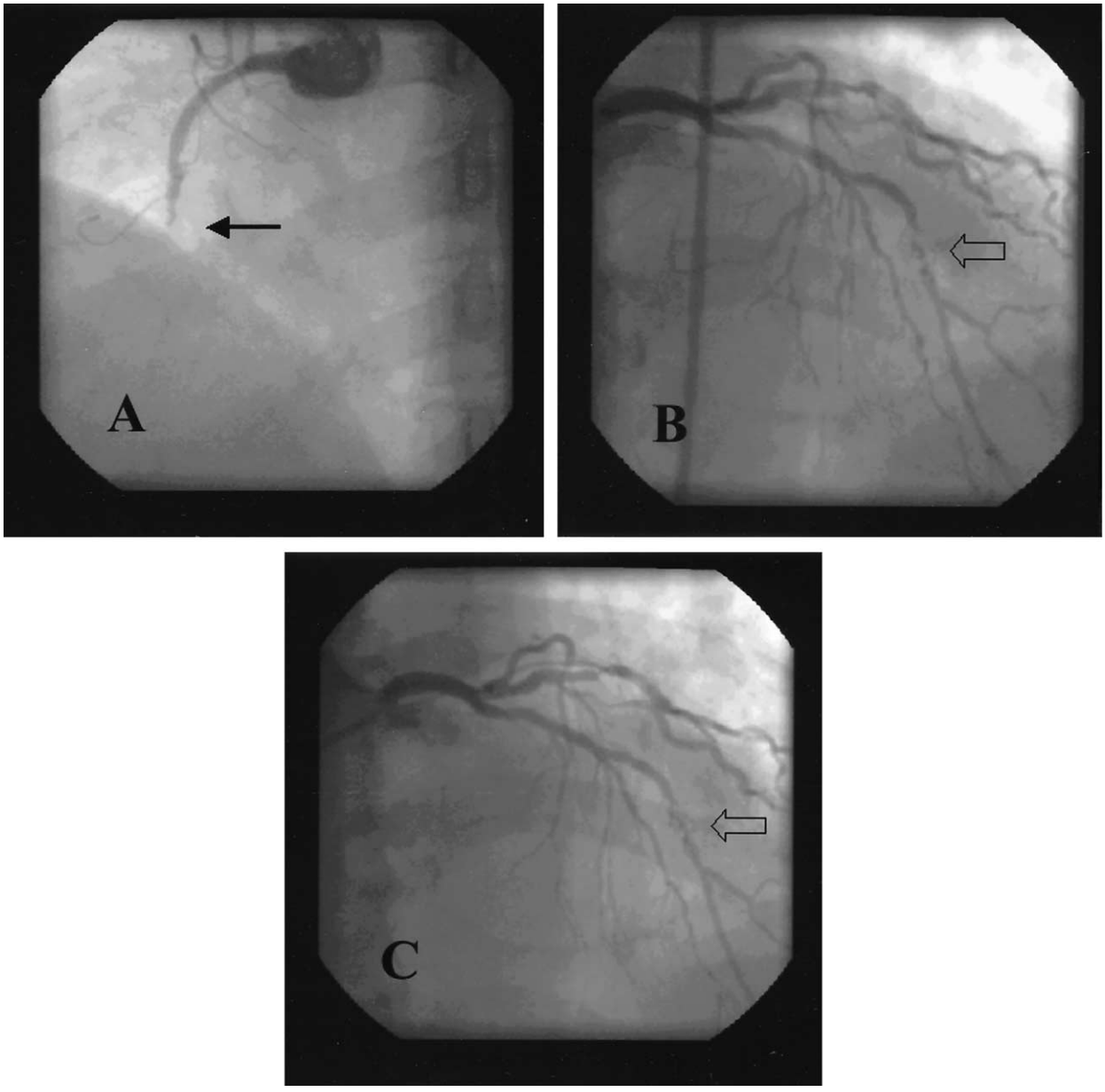
Patients characteristics

Multiple complex plaques were identified angiographically in 62 patients (27%; Table I). Patients with single and multiple complex plaques did not differ significantly in mean age, sex, the frequency of risk factors, mean ejection fraction, or the use of antiplatelet agents, angiotensin-converting enzyme inhibitors, and statins, except that patients with multiple complex plaques were more likely to have multivessel disease (82% vs 26%, P <.001). Among the patients with multiple complex plaques, 41 patients (67%) had 2 complex plaques, and 21 patients (33%) had ≥3 complex plaques.

Coronary angiographic findings

The culprit complex plaque responsible for the AMI was identified in all patients with multiple complex plaques. Figure 1 shows a representative example of serial arteriograms with the corresponding case histo-

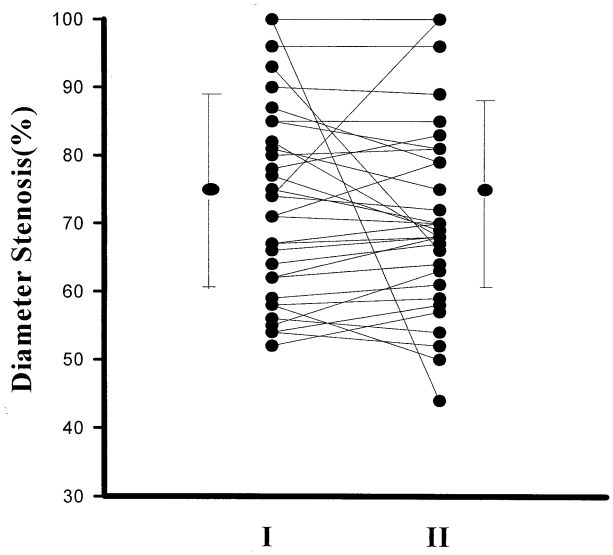
Figure 1



Representative angiograms from a patient with acute inferior myocardial infarction. **A,** Angiogram showing a culprit lesion in the right coronary artery with a total occlusion (*solid arrow*). **B,** Angiogram showing a cranial view of the left anterior descending artery in the same patient, demonstrating a complex irregular, ulcerated, tight stenosis with haziness (*open arrow*). **C,** Angiogram showing no change in the same lesion (*open arrow*) at 6-month follow-up angiography.

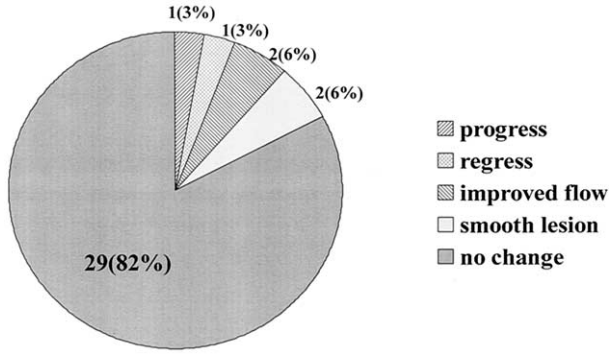
ries. Among the patients with multiple complex plaques (62 patients, 83 non-culprit complex plaques), planned staged angioplasty was performed on a documented non-culprit complex plaques in 20 patients, and follow-up angiography was not performed in 15 patients. The pairs of angiographic tests were reviewed simultaneously in 44% of patients (27patients, 35 non-culprit complex plaques). Of 35 non-culprit complex lesions, 29 (82%) remain complex without changing into smooth lesions, 1 became totally occluded, and 4 regressed (Figure 2). The severity of non-culprit complex lesions between baseline and fol-

Figure 2



The change in diameter stenosis of the non-culprit lesions in patients with multiple complex coronary plaques at first (*I*) and follow-up (*II*) coronary angiography. Two dots with vertical bars represent the mean diameter-percent stenosis and SD for all lesions evaluated.

Figure 3



Pie chart showing the changes of morphology of complex lesions (n = 35).

low-up angiography is equal (maximal diameter stenosis, 74% ± 15% vs 72% ± 15%, $P = .4$; Figure 3).

Clinical outcomes during follow-up

The rate of successful primary angioplasty was similar between patients with a single complex plaque and patients with multiple complex plaques. During the hospitalization period, the incidence of cardiac death was similar in the 2 groups (1% vs 1%, P = not significant). Patients with multiple complex plaques required urgent bypass graft surgery more frequently than patients with a single complex plaque (6% vs 0%, $P < .05$). Long-term cardiac events after discharge occurred more frequently in patients with multiple complex plaques than in patients with a single complex plaque (24% vs 10%, respectively; $P < .01$), mainly because of a higher incidence of coronary bypass graft surgery and angioplasty for the treatment of recurrent ischemia associated with non-culprit complex plaques (Figure 4).

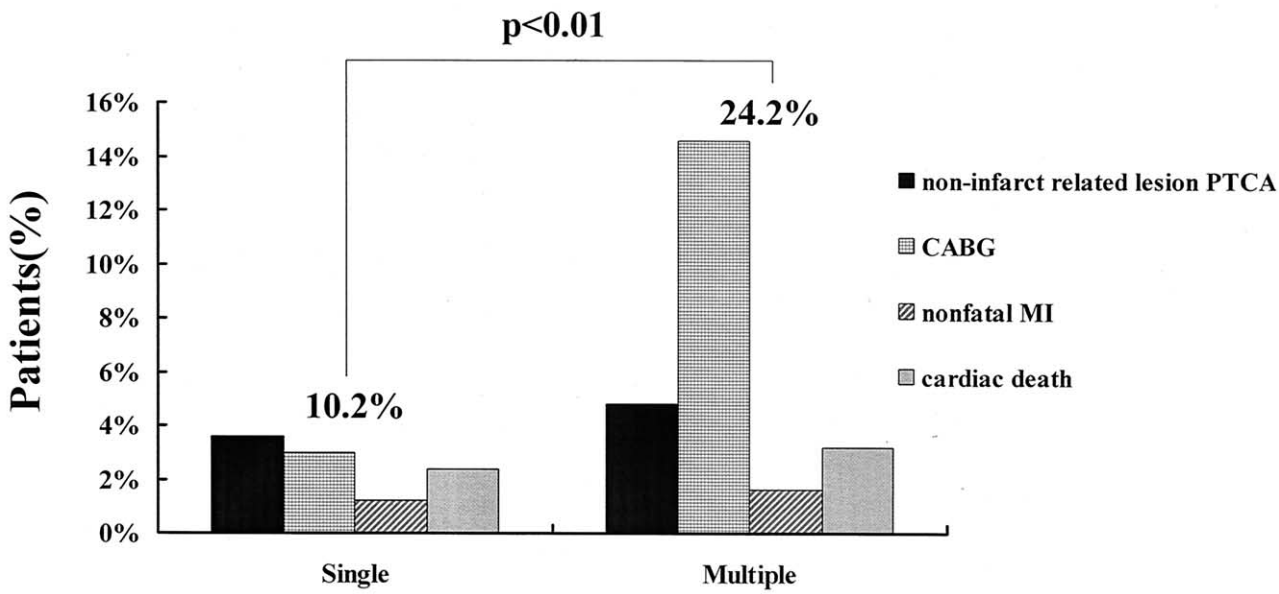
Discussion

In this serial angiographic study of complex lesion morphology in patients with AMI, we found that in most cases, a complex lesion did not change its morphology with time.

Comparison with previous studies

From angiographic observations and postmortem histologic examinations, the occurrence of myocardial infarction has been regarded as being caused by plaque disruption and subsequent thrombus formation and dissolution that may evolve in minutes or days.[1-3] Recently, Goldstein et al suggested that plaque instability may reflect a "pan-coronary" process.[4] Their concept of multifocal plaque instability was supported by angiographic natural history studies in patients with acute coronary syndrome, in whom rapid progression of both culprit and non-culprit complex lesions have been demonstrated.[9-11] However, we did not find a progression of complex lesions or a conversion to non-complex morphologies, except in rare instances. Rather, we found that, in most cases, a complex lesion would remain complex for several months without changing. This contrasts sharply with findings from previous angiographic studies. First, the study by Guazzi et al included matching control patients who were not enrolled consecutively; the time between presentation and coronary angiogapy ranged from 3 to 5 days. Accordingly, it is assumed that the angiographic findings do not represent a index finding at the time of AMI; although a greater proportion of lesions progressed angiographically within a short period, only a small number of patients was associated with clinical events.[9] These make it likely that differences could be attributed to a selection bias or systemic error. Second, in the studies by Moise et al and by Kaski et al, an enhanced progression in non-culprit complex lesions was shown in unstable angina.[10,11] However, angiography was performed after the clinical event, and the time course of progression before the

Figure 4



Long-term clinical outcomes of patients with AMI and single and multiple complex coronary plaques after discharge.

event is not known. Furthermore, unstable angina is not synonymous with AMI.

Clinical outcomes and angiographic changes

All the differences in the incidence of adverse events during follow-up between the patients with a single complex plaque and patients with multiple complex plaques came from an increased incidence of coronary bypass graft surgery. This would appear to be natural because nearly all the patients with multiple complex plaques had multivessel disease and probably had an indication for coronary bypass graft surgery independent of any new ischemic events. The incidence of myocardial infarction or cardiac death were essentially unchanged in the 2 groups.

Detection of vulnerable plaque is difficult with conventional angiography. Kerensky et al reported that an angiographic culprit lesion could not be identified in more than one third of patients with non-Q–wave myocardial infarction.[12] Thus, most complex plaques are not sufficiently changed grossly to be detected angiographically. Furthermore, we cannot assume that even most of complex lesions were culprit lesions. Second, individual atherosclerotic lesions have a heterogeneity in both their composition and appearance. Two recently developed intracoronary imaging tools have the potential to provide these insights. Intracoronary ultrasound scanning imaging provides information about plaque size and composition, and intracoronary angioscopy is an accurate means of detecting the presence of vulnerable yellow plaque and thrombus.[13–16] The results of this study suggest that in identifying the vulnerable plaque in patients with complex plaque, angiographic change or morphology should be used in conjunction with other objective evidence. There is a also increasing need for biochemical markers or a higher-resolution imaging technique that can better define the vulnerable plaque and for pharmacologic interventions designed to stabilize plaques.[6,7,17]

Study limitations

Several potential limitations of our study should be acknowledged. First, this study was performed in a subset of patients with AMI selected for primary angioplasty, and angiographic follow-up was not performed in all patients with multiple complex plaques. Thus, we preclude the generalization of the findings to all patients with AMI. However, we took advantage of the current situation in our clinical care system, in which patients who require primary angioplasty are consecutively put on angiographic lists at the time of AMI. Second, with this angiographic study it is difficult to explain the association between initial obscured lesions and new narrowing development or sudden marked stenosis progression in patients with a clinical event.[18,19] However, the incidence of significant progression might be low. Third, it is possible that had the interval between angiograms been longer, we

would have found persistence of complex lesions to be less common. However, this is unlikely, because other studies reported complex lesions in unstable angina to be stable in serial angiograms with as long as 5 to 7 years between studies.[20] Finally, progression of lesions may be related to pharmacologic therapy, such as statins, angiotensin-converting enzyme inhibitors, and antithrombotic agents.

Despite these limitations, this is the first report, to our knowledge, to evaluate the angiographic changes of multiple complex plaques in the largest sample of patients with AMI. In conclusion, this study provides valuable insight in understanding of plaque instability for patients with AMI.

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