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The Natural History of Unheralded Complex Coronary Plaques

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Objectives. **This study sought to assess the behavior of unheralded complex lesions in patients with no previous history of acute coronary ischemia.**

Background. **Angiographically complex coronary stenoses appear to originate from plaque disruption and are associated with rapid progression early and late after acute coronary events. Complex lesions may occur without symptoms, but neither the incidence nor the behavior of these unheralded complex lesions is known.**

Methods. **We studied 222 patients with chronic stable angina who were on a waiting list for single-vessel percutaneous transluminal coronary angioplasty of an unoccluded lesion and underwent repeat angiography immediately before the procedure as part of routine practice or shortly after a coronary event. Patients with a previous episode of myocardial infarction or unstable angina were not included. Angiograms were analyzed quantitatively and qualitatively using established methods. A change of ±15% stenosis severity or total coronary occlusion defined categoric change.**

Results. **At first angiography, there were 52 unheralded complex target lesions (23%) and 170 smooth target stenoses (77%). Stenosis severity did not differ between complex and smooth target lesions at first and second angiography at a mean (±SD) interval of 7 ± 4 months. At follow-up, seven complex lesions had progressed (14%) compared with six smooth lesions (4%, $p < 0.02$). Total occlusion developed in four complex lesions and one smooth lesion. Overall, complex stenoses progressed by 3 ± 13% compared with 0.5 ± 7% in the smooth stenoses ($p = 0.15$). Complex stenoses were 4.2 times more likely to progress than smooth stenoses (95% confidence interval 1.2 to 15.2 [Cornfields method]). Clinical events developed in seven patients. One complex lesion regressed and became smooth, and three smooth stenoses became complex at follow-up.**

Conclusions. **Morphologically complex stenosis can develop without an episode of acute coronary ischemia and are relatively common in patients awaiting single-vessel angioplasty. Our study demonstrates that like their clinically heralded counterparts, these unheralded complex stenoses are at higher risk of progression than smooth stenoses.**

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Angiographic complex coronary stenoses are common and frequently lead to adverse clinical outcomes (1–6). Complex lesions are frequently seen at angiography after an acute coronary event (4,7) and are thought to arise from plaque disruption (8,9). However, coronary plaque disruption can occur without symptoms (10–12), and we have seen that complex stenoses may develop without causing acute coronary syndromes (13). Neither the incidence nor the behavior of complex lesions in patients without a previous history of acute ischemia has been systematically investigated. We therefore assessed the incidence and morphologic appearances and progression of the intended angioplasty target lesions in a consecutive series of patients with single-vessel disease and no previous history of acute coronary syndromes who were awaiting percutaneous transluminal coronary angioplasty.

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Methods

Patients. The use of the waiting list for routine coronary angioplasty for assessing the evolution of coronary artery disease has been previously described (6,13,14). The study group was derived from all patients (n = 420) with single-vessel disease who underwent routine coronary angioplasty for chronic stable angina from January 1, 1988 through December 31, 1992. Clinical details were obtained at the time of initial referral for diagnostic angiography, at the time of the diagnostic angiogram and at the time of the angioplasty procedure. The notes were reviewed blinded as to the study objectives. Details were recorded and included age; presence of hypertension (sytolic blood pressure >145 mm Hg or diastolic blood pressure >90 mm Hg, or both, on two separate occasions or patients being treated for hypertension) or diabetes mellitus; a family history of coronary artery disease (documented coronary artery disease in a first-degree relative); and a history of smoking (one or more cigarette per day); and plasma lipids were obtained. Excluded from analysis were patients who had undergone previous coronary intervention (n = 29); patients undergoing coronary angioplasty for total coronary occlusion (n = 6) and patients who had evidence of previous acute coronary ischemia (n = 131). The latter group included patients with a clear diagnosis of a previous episode of acute

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coronary syndrome according to World Health Organization or Braunwald criteria (15). Patients with a "borderline" diagnosis of acute ischemia were also excluded (n = 26). A borderline diagnosis was made in the presence of a clinical history suggestive of myocardial infarction or unstable angina but without documentation and included patients admitted to the hospital or accident and emergency departments with a "query" diagnosis of acute coronary syndrome. Six patients who were placed on the waiting list during the same period were lost to follow-up and were not analyzed.

The study group therefore included 222 patients. All patients had stable angina for at least 2 months before the diagnostic angiogram and had a single nonoccluding stenosis (target stenosis) requiring angioplasty for symptom control. All patients were placed on a routine waiting list and had a second angiogram immediately before the angioplasty procedure (n = 215) or within 10 days of an acute coronary event (n = 7).

Stenosis morphologic analysis. *Lesion morphology.* The morphologic appearance of each lesion was independently assessed by two experienced investigators (L.J., M.R.C.) at separate sittings using a previously described method (6,13,16). The lesions were evaluated in orthogonal projections during end-diastole and were qualitatively classified as *complex* or *smooth*. The presence of one or more of the following criteria in one or more projection defined complex stenoses: 1) irregular or scalloped borders; 2) poorly defined or hazy borders; 3) abrupt edges to the lesion that were perpendicular to the vessel wall or were overhanging; 4) ulceration (i.e., outpouchings within the stenosis); or 5) the presence of a filling defect consistent with thrombus. The last category was noted separately. Stenoses where these features were absent were categorized as *smooth*. Discrepancies were dealt with by consensus with a third observer (J.C.K.). The observers had no knowledge of the clinical histories and were not aware of the study objectives.

Quantitative analysis of target stenoses. Quantitative assessment of stenosis diameter reduction for each lesion was carried out using a previously validated computer-assisted technique (17–20). Briefly, the angiograms were projected in blinded manner with regard to the clinical characteristics of the patients, and the best views of the lesions of interest were selected for subsequent analysis using an automated edge contour detection system (Coronary Angiography Analysis System [CAAS], Pie Medical Data). The contour of the selected arterial segment was determined automatically by the computerized system, with minimal interactive correction. End-diastolic frames were used for measurement of coronary diameters and the projection showing the stenosis at its most severe was used for analysis (17). Absolute minimal lumen diameters were measured in millimeters, and the percent stenosis was derived by comparing the minimal stenotic diameter with an angiographically "normal" (reference) segment. The size of the stem of the coronary catheter was used to calibrate the system, and correction was made for pincushion distortion. We studied the reproducibility of our measurements using this system by calculating the accuracy (defined as the signed difference between the measured and true value) and the precision (defined as the standard deviation of these differences) of the system. The accuracy was 0.08 mm, and the precision was 0.10 mm. Coronary diameters were measured by two independent observers, and the angiograms were also reanalyzed in blinded manner at a later time to ascertain the interobserver and intraobserver variability. Intraobserver variation (SEE) was 0.09 mm, and interobserver variation was 0.08 mm (13).

The presence or absence of well-developed collateral channels was noted.

Statistical analysis. Data are expressed as mean value ± SD, unless otherwise stated. Change in stenosis severity was entered both as a continuous variable (without log transformation) and as a categoric variable. As previously described, we used an arbitrary cut point of 15% change in stenosis severity or the development of total coronary occlusion to define categoric change (13). This value is equal to 2 SD of repeated measures and was not selected post hoc to enhance differences. Intergroup comparisons were performed as appropriate using the Student *t* test or the chi-square test with Yates correction. All statistical comparisons were two-tailed, and $p < 0.05$ was considered significant for the primary comparison between complex and smooth stenosis progression. We used the Bonferonni correction for multiple intergroup comparisons.

Results

Patients. Patients were dichotomized according to the morphologic appearances of the intended target stenosis at the time of the first diagnostic angiogram. The target stenosis was smooth in 170 patients (77%, Group 1) and complex in the remaining 52 (23%, Group 2). Two of the complex stenoses had additional features consistent with thrombus. The clinical features of the two groups and intergroup comparisons are given in Table 1. Group 1 patients had a mean age of 59 ± 9 years compared with 60 ± 8 years ($p = 0.72$) in Group 2 patients. There were more smokers in Group 2 than in Group 1 ($p < 0.02$). Otherwise, there were no intergroup differences with respect to gender, history of hypertension, diabetes mellitus, family history of coronary artery disease or medical therapy. Total plasma cholesterol (6.4 ± 1.1 vs. 6.4 ± 1.1 mmol/liter, $p = 0.99$) and plasma triglyceride levels (2.1 ± 1.1 vs. 2.4 ± 1.9 mmol/liter, $p = 0.33$) did not differ between Groups 1 and 2, respectively. The interval between the first and second angiograms was 7 ± 4 months for both groups. The reference diameter on the first and second angiograms was the same in both groups (Group 1: 3.2 ± 0.7 mm; Group 2: 3.2 ± 0.8 mm, $p = 8$ for intergroup differences).

Stenosis morphology and angiographic evolution. Seven (13.5%) of the 52 complex stenoses progressed compared with 6 (3.5%) of the 170 smooth stenoses ($p < 0.02$). The odds ratio of the relative likelihood of complex stenosis progression was 4.2 (95% confidence interval [CI] 1.2 to 15.2 [Cornfields method]). Stenosis severity of complex and smooth lesions at

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Table 1. Features at Diagnostic Angiography in 222 Patients Without a Previous Episode of Acute Coronary Syndrome

	Smooth Stenoses (n = 170)	Complex Stenoses (n = 52)	p Value
Male	112 (66)	32 (61)	0.80
Risk factors			
Family history*	23 (14)	12 (23)	0.15
Smoker†	50 (29)	25 (48)	0.02
Hypertension‡	47 (29)	15 (28)	0.99
Diabetes mellitus	19 (12)	6 (11)	0.84
Antianginal medication			
Beta-blockers	110 (65)	29 (56)	0.32
Long-acting nitrates	102 (60)	36 (69)	0.30
Calcium channel blockers	94 (55)	21 (40)	0.09
≥2 antianginal therapies	170 (99)	51 (98)	0.99
Aspirin	162 (95)	50 (96)	0.91
Lipid-lowering therapy	41 (24)	16 (31)	0.44

*First-degree relative with documented coronary artery disease. †One or more cigarette per day. ‡Treatment for hypertension or systolic blood pressure >145 mm Hg or diastolic blood pressure >90 mm Hg. Data presented are number (%) of patients.

initial angiography and follow-up did not differ; nor did the mean change in stenosis severity during follow-up differ between complex and smooth stenoses (Table 2). In the 13 progressing lesions the complex stenoses progressed from 62 ± 9% to 95 ± 9% stenosis severity ($p < 0.01$), and the smooth stenoses progressed from 62 ± 8% to 91 ± 10% stenosis severity ($p < 0.01$). Total coronary occlusion occurred in six patients (evolution from complex lesions in four and from a smooth target lesion in one and a new occlusion in one). Only one lesion that was complex at the first angiogram regressed and became smooth. The appearance of thrombus present in two complex stenoses at the first study had resolved at the second. Three originally smooth target stenoses developed a complex appearance at follow-up, one of which was associated with the development of unstable angina.

The clinical features of the 13 patients with target stenosis progression and the 208 patients who did not show target stenosis progression are shown in Table 3. Aside from complex morphology, none of the baseline characteristics predicted progression.

Clinical events during follow-up. Clinical events were uncommon, affecting only seven patients (3%). Myocardial infarction occurred in the one patient with new total coronary occlusion from an angiographically normal segment at initial angiography, and unstable angina developed in six patients. The intended target lesion was clearly responsible in only four patients (evolution from complex target stenoses in 2, from smooth target stenoses in 2), and a new lesion was responsible in one. In the remaining two patients, a new hemodynamically significant stenosis had developed during follow-up, and the culprit lesion responsible for the episode of acute ischemia was not identifiable with certainty. In view of the rarity of clinical events associated with individual target lesions, statistical comparisons were not performed.

Well developed collateral channels were seen in only a minority of patients with very severe stenoses (n = 6 [3%]) and were equally prevalent in patients with complex and smooth stenoses.

Table 2. Quantitative Analysis of Complex and Smooth Target Stenoses at First and Second Angiogram

	1st Angiogram (%)*	2nd Angiogram (%)*	Δ (%)	1st Angiogram (mm)†
Smooth (n = 170)	66 ± 7	66 ± 9	0.5 ± 7‡	1.22 ± 0.4
Complex (n = 52)	66 ± 9	69 ± 13	2.6 ± 13§	1.22 ± 0.4
p value	0.91	0.09	0.15	0.93

*Percent diameter reduction. †Minimal lumen diameter. ‡$p > 0.4$, §$p > 0.2$, one-sample t test. Data presented are mean value ± SD. Δ = change.

Table 3. Clinical Features in 13 Patients With and 208 Patients Without Target Stenosis Progression

	Progression (n = 13)	No Progression (n = 208)	p Value
Age (yr)	58 ± 6	59 ± 9	0.63
Male	8 (62)	136 (65)	0.97
Risk factors			
Family history	3 (23)	32 (15)	0.72
Smoking	6 (46)	68 (33)	0.50
Hypertension	3 (23)	59 (28)	0.93
Diabetes mellitus	0	25 (12)	—
Cholesterol (mmol/liter)	6.7 ± 0.6	6.4 ± 1.2	0.48
Triglycerides (mmol/liter)	2.8 ± 1.1	2.2 ± 1.5	0.36
Lipid-lowering therapy*	3 (23)	54 (26)	0.92
Angiography			
Interval between angiograms (mo)	8 ± 5	7 ± 4	0.53
Stenosis diameter reduction at 1st angiogram (%)	63 ± 8	66 ± 7	0.21

*Patients starting lipid-lowering therapy after initial angiogram (progression, n = 0; no progression, n = 3). Data presented are mean value ± SD or number (%) of patients.

Discussion

It has been shown that complex coronary stenoses are more likely to progress than smooth stenoses in stable angina (13) early after acute coronary syndrome (1–4) and late after an episode of unstable angina (6). We (6,14) and others (1,5,21) have shown that unstable angina is an important predictor of future progression.

Angiographic complex morphology and acute coronary ischemia are closely associated (22,23). Thus, the inclusion of patients with a previous history of acute ischemia in previous studies complicates the task of assessing the role of complex morphology in stenosis progression. To our knowledge, this is the first study to systematically assess the behavior of complex coronary lesions in patients without a documented history of acute coronary ischemia. We took advantage of the routine waiting list to compare angiographic progression of complex

and smooth stenoses in a well defined study group of patients with a single target lesion and troublesome stable angina requiring routine coronary angioplasty. We excluded patients with multivessel disease because the analysis would have been considerably more complicated, without improving the validity of the study. Three main observations emerge from the study: 1) Symptomatic stenoses with a complex angiographic appearance may arise without an episode of manifest acute ischemia; 2) such unheralded stenoses are common; 3) like their clinically heralded counterparts, these unheralded complex stenoses behave differently from smooth stenoses. The study also confirms earlier observations that the likelihood of an individual lesion progressing in patients with stable angina is very small (2,13,20,24).

"Unheralded" origin of complex stenoses. Levin et al. (8) and Hangartner et al. (9) have demonstrated that what has been termed complex morphology is the angiographic legacy of plaque disruption. Studies of human atherosclerotic plaque obtained from patients dying of noncardiac causes (11) and from patients undergoing atherectomy (10) have shown that not only does plaque disruption usually underlie acute ischemia, but that disruption frequently occurs in the absence of a history of acute coronary ischemia. Thus, plaque disruption can lead to a spectrum of outcomes with rapid vessel obstruction and symptomatic acute coronary syndrome at one extreme and a hemodynamically insignificant and clinically "silent" outcome at the other (25). It is likely then that the complex stenoses in our study arose through an episode of plaque disruption that was unheralded by acute ischemia. Consistent with this is the observation that two lesions that were smooth at the initial angiogram developed complex features unaccompanied by acute ischemia. Moreover, Davies et al. (26) has shown that some initially complex lesions become smooth through organization and remodeling in the first few weeks after plaque disruption. In our study, thrombus was seen in two complex stenoses at the initial angiogram even though the patients were clinically stable, and another complex stenosis became smooth and regressed during follow-up. This suggests that the appearance of these three stenoses at the initial angiogram were recent.

Our study shows that angiographic complex stenoses that evolve without clinically manifest acute ischemia are common in patients with chronic stable angina with single-vessel disease and who are put on a waiting list for routine coronary angioplasty. However, the origin of the lesions in our study is speculative, and our observation refers only to angiographic appearances and should not be interpreted as evidence that major "silent" plaque disruption is common. Other techniques such as intravascular ultrasound may provide an insight into the origins of the unheralded complex lesions in our study.

Mechanisms of rapid stenosis progression. The short time interval between angiograms in our study suggests that the observed change in stenosis severity is due to rapid stenosis progression. Waters et al. (27) have shown that angiographic stenosis progression, whether silent or associated with acute coronary syndrome, is an important predictor of future coronary events. Why complex plaques should be particularly vulnerable to rapid stenosis progression is speculative. Certainly the abnormal geometry may promote plaque disruption through shear stress and oscillatory stress (28,29). In addition, complex lesions are associated with increased platelet activation (30) and are more prone to vasoconstriction (31). The pathogenetic basis for rapid stenosis progression after plaque disruption is likely to involve platelet aggregation, thrombosis and vasospasm in the acute phase (25) and intimal proliferation (32) in the subacute phase. Whether the pathogenesis of rapid progression in unheralded complex stenoses is the same as that in heralded complex stenoses is not known. A power calculation, based on the data in the present study and data recently observed in clinically stabilized complex plaques (6), shows that >2,000 patients would be required to have a 90% probability of showing a difference in rates of progression between heralded and unheralded complex stenoses in patients with stable angina. The choice of a cut point to define progression is necessarily arbitrary. In early studies we and others used ≥20% to define progression (6,20,24), whereas others have used 10% (33). The choice of 15% in the present study was based on widely accepted criteria and was used in a recent study by our group (13). Analysis of the data with a 20% cut point shows that 6 of 170 smooth stenoses progressed compared with 6 of the 52 complex stenoses ($p < 0.06$), whereas using a 10% cut point, 8 complex compared with 6 smooth stenoses progressed ($p < 0.01$).

Previous clinical history. The lack of clinical evidence of previous acute coronary ischemia is an important feature of our study design. To avoid the inclusion of patients with a missed diagnosis, we excluded patients with a "borderline" diagnosis a priori. Whether a patient receives a diagnosis of acute coronary syndrome is dependent on a number of factors such as the severity of myocardial ischemia, symptom recognition and illness behavior. Myocardial ischemia varies considerably and is dependent on the dynamic relation between the severity of lumen encroachment, the presence of collateral supply and microvascular redistribution on the supply side, and metabolic demand on the other. In our study very few patients had good collateral channels at angiography, although their presence at plaque disruption cannot be excluded. To diagnose manifest ischemia, the symptoms must be sufficient to prompt the patient or their physician to seek and confirm the diagnosis. Thus, patients who experience atypical pain and those with a high pain threshold might confuse the diagnostic process (34). Furthermore, demonstrable myocardial ischemia commonly occurs in the absence of pain (35). Insofar as these factors might explain the presence of disrupted plaques in patients without a history of acute coronary syndrome, they do not compromise the validity of the study. In contrast, illness behavior is a potentially important confounding factor. It is possible to explain our findings if all patients with complex plaques in the event-free group had had a major symptomatic clinical event and deliberately ignored it. Denial is a common and important psychoprotective mechanism, and it is impossible to positively exclude this explanation. However, all the

patients sought medical advice for troublesome angina and were willing to undergo coronary angioplasty for symptom relief without any prospect of improving longevity. Furthermore, patient records did not indicate a reluctance to visit clinics or participate in investigations.

The clinical event rate during follow-up in the present study (3%) was somewhat lower than we have reported previously in patients awaiting coronary angioplasty (14). This might be the result of excluding high risk patients, patients with multivessel disease and patients with previous acute ischemic episodes.

Conclusions. Unheralded complex plaques are relatively common in patients with chronic stable angina requiring single-vessel coronary angioplasty. Our study reemphasizes that angiographic complex lesions are at higher risk for progression irrespective of their clinical origins. Further research into the identification, causes and consequences of subclinical plaque disruption is warranted.

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