Differential Progression of Complex and Smooth Stenoses Within the Same Coronary Tree in Men With Stable Coronary Artery Disease

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Objectives. We sought to compare the evolution of complex and smooth stenoses within the same coronary tree in patients with stable coronary artery disease.

Background. Progression of coronary stenosis has prognostic significance and may be influenced by local and systemic factors. Stenosis morphology is a determinant of disease progression, but no previous study has systematically assessed progression of complex and smooth stenoses within the same patient.

Methods. We studied 50 men with stable angina who 1) had one complex coronary stenosis and one smooth stenosis in different noninfarct-related coronary vessels at initial coronary angiography, and 2) had a second angiogram after a median interval of 9 months (range 3 to 24). Patients with lesions ≥10 mm long, at a major branching point or with >85% diameter reduction were not included. Coronary lesions were measured quantitatively from comparable end-diastolic frames. Stenosis morphology was determined qualitatively by two independent observers.

Results. All patients remained in stable condition during follow-up. Progression, defined as an increase in diameter stenosis by ≥15% was seen in only eight complex stenoses (16%) but in no smooth lesions (p < 0.01). The severity of complex stenoses changed more than that of corresponding smooth stenoses (mean ± 1 SD 5.8 ± 13% vs. −0.06 ± 6%, p < 0.01). On average, the annual rate of growth was 11.4 ± 28% and 1.5 ± 14% for complex and smooth lesions, respectively (p < 0.01).

Conclusions. Few coronary stenoses progress rapidly in stable angina. Complex and smooth coronary stenoses progress at different rates within the same coronary tree. Complex stenosis morphology itself is an important determinant of progression of stenosis in patients with apparently clinically stable coronary artery disease.

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Recently it has been shown (1) that clinical and subclinical progression of angiographic coronary stenosis is an important predictor for subsequent coronary events. Coronary stenosis progression and the development of acute coronary syndromes are influenced by both local and systemic factors (2,3). Of the local factors, stenosis location and severity as well as lesion length and morphology appear to play a role in disease progression (4–7). Coronary stenoses with an angiographically complex morphologic appearance are associated with increased risk of adverse clinical events in a variety of circumstances (5,6,8–14). Previous angiographic studies focused attention on the role of stenosis morphology in disease progression in different patients, many with a change in clinical status between angiograms. The marked interindividual variability of systemic risk factors for progression of coronary stenosis complicates the task of evaluating the relative role of local coronary factors in such progression. With the exception of a retrospective study of patients with acute syndromes by Taeymans et al. (15), no previous examination of the role of lesion morphology on progression of coronary stenosis has systematically minimized the influences of interindividual variability of systemic risk factors in patients with stable angina. In this study we compared the rates of progression of angiographic complex lesions and smooth lesions in different noninfarct-related vessels within the same coronary tree in patients with clinically stable coronary artery disease.

Methods

Patients

We analyzed the coronary angiograms of 198 consecutive male patients with chronic stable angina at presentation who were put on a nonurgent waiting list for coronary revascularization and underwent a second comparable angiogram in our hospital between January 1, 1988 and December 31, 1989. Thus, we did not include patients who were in unstable condition at presentation or those who underwent revascularization without a second angiogram. Of the 198 patients, 171 were routinely restudied before undergoing coronary angioplasty and 27 were restudied before undergoing coronary

Table 1. Fasting Plasma Lipids and Angiographic Stenosis Severity in the Study Group and the Total Consecutive Series

	Study Group (n = 50)		Total Consecutive Series (n = 198)	
	Mean	SD	Mean	SD
Age (yr)	59	8.4	57.6	9.6
Total cholesterol (mmol/liter)	6.3	1.2	6.3	1.2
Triglyceride (mmol/liter)	2.3	1.5	2.3	1.2
HDL cholesterol (mmol/liter)	0.3	0.5	0.4	0.2
Stenosis diameter reduction (%)				
Smooth stenoses	49.6	9.46	48.4	13.0
Complex stenoses	61.6*	12.3	59.5†	12.9

*† p < 0.01 within-group Student t test. There were no differences between groups using the t test and Wilcoxon rank sum test. Data are expressed as mean value ± 1 SD from the t test. HDL = high density lipoprotein; Study Group = the 50 study patients with stable angina and one complex and one smooth coronary stenosis. Total Consecutive Series = 198 consecutive patients who underwent routine coronary angiography before revascularization twice during the same period.

artery bypass surgery because they had been on the waiting list for >1 year. We selected consecutive patients (n = 50) who had only one of each morphologic type of stenosis (one complex and one smooth), with a diameter reduction of 30% to 85%, in different noninfarct-related coronary arteries on initial angiographic study. We excluded patients with a nonoccluding stenosis that was located at a major branching site or had >85% diameter reduction or was ≥10 mm long. Patients with an occlusion were included if the occluded vessel was different from the two arteries containing the lesions of interest. Clinical details at initial presentation and follow-up were collected for all patients and included age, previous history of myocardial infarction, hypertension and diabetes mellitus, family history of coronary artery disease, history of smoking and fasting plasma lipids (Table 1).

Coronary Angiographic Analysis

Lesion morphology. The morphologic appearance of each lesion was independently assessed by two investigators at separate sittings using a previously described method (13,16). The lesions were evaluated in orthogonal projections during end-diastole and were qualitatively classified as complex or smooth. Complex stenoses were defined by the presence of one or more of the following criteria in one or more projections: 1) irregular or scalloped borders; 2) abrupt edges to the lesion that were perpendicular to the vessel wall or were overhanging; 3) ulceration (i.e., outpouchings within the stenosis); or 4) the presence of a filling defect consistent with thrombus. The presence of haziness of a lumen border was not sufficient in itself to define complexity. Stenoses without these features were categorized as smooth. Five patients were excluded because there were discrepancies between the data of observers; that is, stenoses could not be clearly defined as either

complex or smooth at the first analysis. The reproducibility of the morphologic classification was determined by repeat analysis of the films at >3-month intervals independently by both observers without knowledge of the classification at the first reading. No discrepancies arose. Stenoses located in coronary arteries <1 mm in diameter were not included in the analysis as the Coronary Angiography Analysis System (CAAS) is less reliable under these circumstances (17).

Quantitative analysis. Quantitative assessment of stenosis diameter reduction for each lesion was carried out by using a previously validated computer-assisted technique (CAAS) (17–22). Briefly, the angiograms were projected without knowledge of the clinical characteristics of the patients, and the best views of the lesions of interest were selected for subsequent analysis with the use of an automated edge contour detection system (CAAS, Pie Medical Data). The contour of the selected arterial segment was determined automatically by the computerized system; because lesions at branching points were excluded from analysis, interactive correction was rarely required. End-diastolic frames were used to measure coronary diameters; the frame showing the stenosis at its most severe was used for analysis (19). Absolute minimal lumen diameter was measured in millimeters, and 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.

Repeatability of measurements. Measurements were repeated without knowledge of earlier results, and the mean value was used for analysis. No systematic differences were observed between paired measurements (mean difference = 0.89 ± 6.1%, t value = 0.74, p = 0.47). Regression of absolute difference between measurements on mean measurement gave F = 0.14, p = 0.71.

Statistical analysis. Statistical comparisons between the total consecutive series of 198 patients and the final study group of 50 patients were two-tailed using the Student t test. The Fisher exact test was used to compare categoric stenosis progression and regression between morphologic types. A ≥15% change in stenosis severity between angiograms (equal to >2 SD for repeat measurements using the CAAS system in this study) was used to define stenosis progression or regression (1). This definition was chosen before the data were reviewed and was not selected to maximize post-hoc differences between groups. All other statistical comparisons were two-tailed pairwise comparisons using the paired Student t test. A p value <0.05 was considered statistically significant. Pairwise comparisons were repeated using the Wilcoxon signed rank test and gave similar levels of significance. Data are expressed as mean value ± 1 SD of the mean unless otherwise stated.

Results

Study group. Clinical, biochemical and angiographic features in the total consecutive series and in the 50 patients in the

Table 2. Clinical Features of the Study Group and the Total
Consecutive Series at First Angiographic Study

	Study Group	Total Consecutive Series
Stable angina >3 mo	50 (100%)	198 (100%)
Previous myocardial infarction (≥3 mo)	27 (54%)	88 (44%)
Smoking	20 (40%)	87 (44%)
Hypertension	15 (30%)	45 (23%)
Diabetes mellitus	5 (10%)	24 (12%)
Family history of coronary artery disease	6 (12%)	32 (16%)
Antianginal medication		
Beta-blockers	48 (96%)*	138 (70%)
Long-acting nitrates	26 (52%)	121 (61%)
Calcium channel blockers	28 (56%)†	108 (55%)
Two or more antianginal therapies	50 (100%)	190 (96%)
Aspirin	47 (94%)	178 (90%)
Lipid-lowering therapy	12 (24%)‡	45 (23%)

†‡During follow-up, one patient stopped beta-blockers, one† started
calcium channel blocking therapy, and a third‡ started lipid-lowering therapy 3
weeks before the second angiogram. Definitions of the Study Group and the
Total Consecutive Series as in Table 1.

final study group at study entry are shown in Tables 1 and 2. No
patient in the study group experienced an acute coronary event
during follow-up (median interval 9 months, range 3 to 24).
Only 3 of the 50 patients had a change in medication: One
stopped treatment with a beta-adrenergic-blocking agent be-
cause of claudication, another added calcium channel blocking
agents to previous therapy and a third started lipid-lowering
medication within 3 weeks of the second angiogram.

Angiographic analysis. We analyzed 50 complex stenoses
and 50 smooth stenoses. The components of the criteria used
to define complexity were as follows: irregular or scalloped
borders (n = 38), abrupt edges to the lesion (n = 18),
ulceration [outpouchings within the stenosis] (n = 15), the
presence of a filling defect consistent with thrombus (n = 1),
haziness of a lumen border (n = 16). The anatomic distribu-
tion of stenoses was as follows: 1) left anterior descending
coronary artery (n = 41 [21 complex, 20 smooth]); 2) left
circumflex coronary artery (n = 35 [20 complex, 15 smooth]);
and 3) right coronary artery (n = 24 [9 complex, 15 smooth]).
Complex stenoses were more severe than smooth stenoses at
study entry and at follow-up (Table 3).

Percent stenosis severity change in complex and smooth
stenoses at initial angiography and at follow-up is shown in
Figure 1. The mean change in complex stenosis severity and
minimal lumen diameter at follow-up was greater than in the
corresponding smooth stenosis (5.8 ± 13% vs. −0.06 ± 6%,
and −0.2 ± 0.4 mm vs. 0.01 ± 0.3 mm, respectively, p < 0.01)
(Table 3). Eight complex stenoses (16%) but no smooth lesions
progressed ≥15% (p = 0.006). One of each type of lesion
regressed ≥15% and the majority of stenoses changed by
≤15%. There were no differences in the initial severity of the
stenoses, patient age, interval between studies, plasma choles-
terol or triglyceride levels or other risk factors between the
patients with and without lesion progression. There were also

Table 3. Percent Stenosis Diameter Reduction and Absolute
Minimal Lumen Diameter of Smooth and Complex Lesions at First
and Second Angiographic Studies

| Lesion Type	First Angiogram		Second Angiogram		p Value
	% Stenosis	MLD (mm)	% Stenosis	MLD (mm)	
Smooth	50 ± 9	1.5 ± 0.5	50 ± 11	1.5 ± 0.3	<0.005*
Complex	61 ± 12	1.1 ± 0.5	67 ± 14	0.9 ± 0.3	
p value	<0.01	<0.01	<0.01	<0.01	

*Difference in change in percent stenosis diameter reduction and minimal
lumen diameter (MLD) between complex and corresponding smooth stenoses.
Differences were compared using the one sample t test and the Wilcoxon signed
rank test. Values shown are mean value ± 1 SD (by t test).

no systematic differences between the features of the progress-
ing and the nonprogressing complex stenoses. The components
of the criteria used to define complexity in the eight progress-
ing stenoses were as follows: irregular or scalloped borders
(n = 6); abrupt edges to the lesion (n = 4); ulceration (i.e.,
outpouchings within the stenosis) (n = 3); presence of a filling
defect consistent with thrombus (n = 0); haziness of a lumen
border (n = 3). None of these aspects was more predictive of
progression than another. The relative pairwise change in
stenosis severity at follow-up is presented in Figure 2. A small
group of patients (n = 7) exhibited relative progression ≥15%,
all from complex stenoses, at initial angiography (p < 0.05,
Fisher exact test).

The mean annual rate of progression (derived from the
change in stenosis severity or minimal lumen diameter and the
interval between angiograms) was >7 times greater in com-
plex than in smooth stenoses (11.4 ± 28% vs. 1.5 ± 14% and
−0.4 ± 0.8 mm vs. −0.001 ± 0.2 for stenosis severity and
minimal lumen diameter, respectively, p < 0.01).

Stenosis severity at first study. The mean severity of
complex stenoses was greater than that of smooth lesions at
study entry (61 ± 12% vs. 50 ± 9%, respectively, Table 3).
However, when each pair of lesions was compared, the initial
severity of the more rapidly progressing lesion did not differ

Figure 1. Change in severity of complex and smooth stenoses at
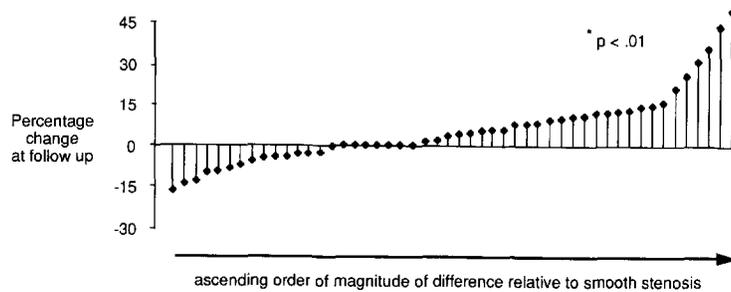second angiogram plotted against initial severity.
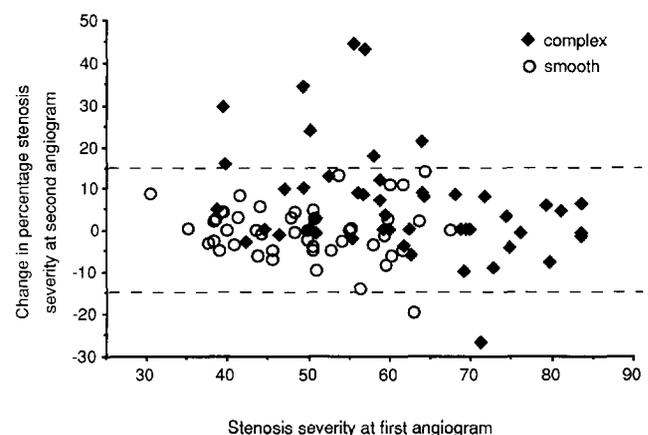
Figure 2. Change in severity of the complex stenosis at follow-up relative to that of the corresponding smooth stenosis for each of the 50 patients. The data are arranged in order of magnitude of relative differences. *Fisher exact test.

from the corresponding, more slowly progressing lesion (56 ± 13% vs. 55 ± 12%, respectively, mean difference 0.23%, p = 0.8). Furthermore, the mean severity of the eight complex stenoses that progressed >15% was similar to that of the corresponding smooth stenosis (52 ± 9% vs. 51 ± 11%, respectively, mean difference 1%, p = 0.9).

Subclinical total coronary occlusion developed in two patients from moderately severe complex stenoses (57% and 56%, respectively). Both patients had well developed collateral circulation at the second, but not the first, angiographic study. Three smooth stenoses (6%) had developed complex features at follow-up but without a further reduction in coronary diameter. No complex stenosis became smooth. One new lesion (35% complex stenosis) developed from a previously angiographically normal segment.

Discussion

In this study we used the waiting lists for routine nonurgent coronary revascularization in our hospital in the late 1980s to assess angiographic progression of stenosis in patients with stable angina. Patients were admitted from the routine waiting list at different intervals on the basis of nonclinical factors, such as bed availability, cancellations and rescheduling of admission dates. Subclinical progression of stenosis is well recognized in clinical practice; therefore, angiograms were routinely repeated before the revascularization procedure was performed. We have shown for the first time that, in individual patients with apparently clinically stable coronary artery disease, angiographically complex and smooth coronary stenoses progress at different rates.

Although the precise mechanism underlying progression of coronary stenosis remains elusive, it is clear that disease progression is a consequence of complex interactions among multiple local and systemic factors (3). Important systemic risk factors for coronary artery disease such as plasma lipids (23) and hemostatic factors (24) exhibit marked interindividual variation. Taeymans et al. (15) were the first to retrospectively compare morphologic features of stenoses responsible for myocardial infarction with control segments in individual patients. They found that although complexity did not predict the development of myocardial infarction, the angle of the inflow and outflow angle did. Unlike patients in the present study, those in the study of Taeymans et al. were selected by

having an angiogram both before and during or shortly after an acute myocardial infarction. Thus, the different observations in the two studies might be explained by differences in patient and outcome selection. Previous studies (5,6,8–14) of the role of stenosis morphology in angiographic progression of stenosis were subject to the confounding influences of interindividual variability of systemic risk factors. It cannot be excluded that risk factors may have a different influence on two lesions in the same patient depending on blood rheologic features. However, by comparing complex and smooth stenosis progression in the same coronary tree, we have eliminated systemic factors as the *primary causes* of differential stenosis progression in this group. We also excluded other local anatomic factors that are known to influence coronary stenosis progression (long lesions [>10 mm], coronary stenoses ≥85% and lesions at major branching points). This study does not diminish the importance of systemic factors in the pathogenesis of coronary stenosis progression; it only raises questions regarding the relative importance of local and systemic risk factors and their interaction in the pathogenesis of progression of coronary stenosis.

Stenosis morphology and progression. Previous longer-term angiographic studies of the morphologic features of stenoses (5,6,8–14) suggested a greater tendency of complex than of smooth lesions to progress over time. Whether long-term progression is predominantly due to "slow linear" or "episodic rapid" progression or a combination of both is not known (25,26). The relatively short follow-up interval between angiograms in our study means that the difference we observed in disease progression between complex and smooth stenoses was largely due to a differential tendency of the two lesion types to develop rapid stenosis progression. The precise mechanism leading to rapid disease progression in our patients is speculative. Investigators (11,25,27,28) have stressed the role of episodic rapid progression of stenosis, particularly in patients with subsequent coronary events. Plaque rupture and thrombosis are key steps in the pathogenesis of rapid stenosis progression associated with an acute coronary syndrome (29–31), where typically the culprit lesion is angiographically complex (4,16). It is tempting to speculate that similar, predominantly thrombotic, plaque events underlie rapid progression in complex stenoses whether or not progression is associated with the development of an acute coronary syndrome.

Stenosis severity and progression. At initial angiographic study, complex stenoses were more severe than smooth steno-

ses. The relation between stenosis severity and tendency to stenosis progression is controversial. Some investigators (6,32) have shown that stenosis severity of >90% diameter reduction is a risk factor for progression. A more recent study (33) indicates that stenoses of <50% severity progress more rapidly than do those of ≥50% severity, whereas an analysis of the Coronary Artery Surgery Study (CASS) data base (34) revealed that stenoses of >50% severity predict myocardial infarction. In our patients with stenosis progression, there was no difference in initial stenosis severity between the progressing (complex) stenoses and the corresponding nonprogressing (smooth) stenoses. Thus, the different rates of progression of complex and smooth coronary stenoses in our study cannot easily be explained by differences in stenosis severity on initial angiography.

Study limitations. Because our patients were selected, by study design, to include only subjects with clinically stable disease who had the two different morphologic types of stenosis, they may not be representative of patients as a whole. No patient in our study group had an unstable coronary syndrome at initial angiography or during follow-up. Thus, it is possible that the outcome of our study was influenced by the failure of the design to include patients who might be likely to have an acute event during follow-up. However, the study design is appropriate to test the hypothesis that complex stenosis morphology in itself is an important determinant of coronary stenosis growth, and our findings are likely to apply to patients with clinically stable coronary artery disease. Moreover, the patients were selected consecutively over a fixed period on the basis of strict criteria determined before the study, and their clinical features at study entry were closely similar to those in the consecutive series of 198 patients from which our patients were drawn (Table 2). Nevertheless, the inclusion and exclusion criteria for the study probably influenced our results. These factors probably explain why the annual incidence of stenosis progression in our study is greater than that in two recent angiographic follow-up studies (1,35) whose patients had mild to moderate coronary disease and were not candidates for coronary revascularization.

The interval between the first and second angiograms in our study was dictated by the dynamics of the waiting list, as explained earlier, and therefore was not the same for all patients. However, this variability cannot explain the findings because pairs of stenoses within individual patients were effectively acting as their own controls.

Conclusions. This angiographic follow-up study of patients with clinically stable coronary artery disease demonstrates that coronary stenoses with a complex morphologic appearance grow more rapidly than do smooth stenoses within the same coronary tree. Thus, complex stenosis morphology itself is an important determinant of disease progression. It cannot be ascertained from this study whether the risk of progression in complex stenoses is homogeneously spread throughout the group of complex lesions or whether the tendency to progression is confined to a high risk subgroup. Further research on this subject is warranted. Similarly, whether the complexity of a stenosis promotes progression or whether the appearance reflects abnormalities within the plaque that predispose to progression remains to be answered.

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