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Pathology of Unstable Plaque: Correlation With the Clinical Severity of Acute Coronary Syndromes

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Objectives. **The aim of this study was to relate the various clinical presentations of acute coronary syndromes to the underlying plaque morphology as assessed from histopathologic analysis of plaque fragments obtained by directional coronary atherectomy (DCA).**

Background. **Autopsy studies have shown that unstable angina and infarction are related to plaque instability and involve events such as fissure or rupture of the fibrous cap, thrombosis and inflammation. The clinical severity and prognosis of acute coronary syndromes can be estimated by the Braunwald classification of unstable angina. Whether plaque morphology can be related to the Braunwald classification has not been evaluated.**

Methods. **Plaque fragments were obtained by DCA in 75 patients: 38 with unstable angina, 19 with stable angina and 18 with no symptoms after infarction. The presence of fibrous tissue, thrombus, high cellularity, inflammatory cells, atheroma, neovessels and "stellar-shaped" smooth muscle cells was evaluated in 7-μm thick sections by appropriate staining. The patients were classified according to clinical presentation without knowledge of the results of pathologic examination, and a plaque instability score was assigned. The risk of further cardiac events was classified as low, medium or high.**

Results. **Increasing severity of the score of unstable angina was associated with increasing prevalence of thrombus, high cellularity, atheroma and neovessels. Plaque from patients with unstable angina considered to be at low risk of further events appeared very similar to that of patients with stable angina, whereas the specific morphologic characteristics of plaque instability were more frequently observed as the clinical score and the risk of further events increased. After thrombolyzed infarction, plaque morphology depends on the delay between the acute event and DCA. Within 1 week after infarction, plaque still showed the morphologic characteristics of instability, whereas late DCA provided samples with morphologic features similar to those observed in patients with stable angina.**

Conclusions. **The morphologic features of plaque fragments vary at different stages of acute coronary disease. The specific features of plaque instability correlate with the clinical scoring system of the Braunwald classification.**

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Current concepts about the pathophysiology of acute coronary syndromes stem from postmortem pathologic examinations that have shown that thrombi frequently cover fissures in lipid-rich plaque (1–3). The application of invasive imaging techniques has allowed verification of previous autopsy findings in vivo. Therefore, occluding thrombi are now the recognized cause of acute myocardial infarction (MI) and represent the leading cause of unstable angina (3,4). Indeed, at coronary angiography, stenoses responsible for unstable angina often appear irregular and contain filling defects (5–7) likely to represent thrombus, which has indeed been found on intracoronary angioscopy (8–10).

If thrombus formation is a consequence of plaque disruption, healing of the disrupted fibrous cap covering the lipid core also occurs as a result of the production of new connective tissue by proliferating smooth muscle cells and the colonization of residual thrombus by capillary vessels (2). Thus, the atherosclerotic coronary plaque seems to undergo cycles of disruption and repair, the major plaque events corresponding to the periods of clinical instability (11).

In this study we attempted to verify this concept in vivo. Because histologic analysis cannot be performed repeatedly in the same patients, we studied the underlying morphologic features of plaque fragments retrieved by directional coronary atherectomy (DCA) in patient groups with a well characterized clinical presentation of either stable or acute coronary artery disease. For comparison, we also studied asymptomatic patients in whom DCA of the culprit lesion was performed at various time intervals after recovery from acute MI. Given the heterogeneous spectrum of unstable conditions, we used the

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Abbreviations and Acronyms

CK = creatine kinase
DCA = directional coronary atherectomy
MI = myocardial infarction
Post-MI = free of symptoms after myocardial infarction

clinical classification of unstable angina proposed by Braunwald (12). This classification, based on the severity, time sequence and circumstances of symptoms, was shown to correlate with the angiographic appearance of the culprit lesion, in particular the presence of intracoronary thrombus and stenosis complexity (13), as well as with patient outcome (14,15).

Methods

Selection and classification of patients. A total of 75 consecutive patients (65 men, mean age ± SD 58 ± 6 years) treated by DCA after May 1992 in our center in Brussels were included in this study. Patients were included when the culprit lesion was clearly identifiable at angiography, successfully treated percutaneously by DCA and if at least two fragments of tissue were retrieved. Patients were then classified as having stable disease (n = 19), unstable angina (n = 38) or no symptoms after MI ("post-MI," n = 18). In post-MI patients, the diagnosis of a previous MI was based on conventional enzymatic and electrocardiographic criteria. Classification in the Braunwald unstable angina class (12) was performed routinely on admission by the attending physicians and entered in the data base at the time of patient discharge. We verified the adequacy of the classification by checking the data base and the source documents (patient records). Patients were considered to present with stable angina if they did not fulfill any of the Braunwald criteria. A positive stress test result or other evidence for ischemia was required to justify the coronary intervention. Clear indications permitting patient classification were available in all cases and no post hoc alterations were made. The Braunwald categories of unstable angina were also grouped according to the score established by Ahmed et al. (13) in classes with increasing symptom severity. The presence of risk factors for coronary artery disease was compared among groups. Arterial hypertension was considered to be present when long-term treatment was required. Hypercholesterolemia was defined as total cholesterol ≥200 mg/100 ml.

Protocol. Approval for the use of DCA in these patient groups was granted by the local Ethics Review Committee when the lesion was deemed suitable for this procedure by the operator (J.P.R. or W.W.). Before and during DCA, patients with unstable angina received intravenous heparin. The majority of patients with MI had received thrombolytic treatment. In the post-MI group, DCA was performed within 1 week (range 1 to 6 days, median 3.5) after MI in 11 patients ("elective post-MI" group) and between 2 weeks and 3 months (range 10 to 90 days, median 3 weeks) after the initial event in the remaining 7 ("late post-MI" group). All patients with unstable angina were receiving intravenous heparin at the time of the procedure. The other patients received a bolus of 10,000 IU of heparin and 500 mg of aspirin intravenously before DCA. No patient was treated with glycoprotein IIb/IIIa receptor blocking agents.

Atherectomy cuts with use of the Simpson device followed by complementary balloon angioplasty were performed, as previously described (16). The number of fragments and the amount of tissue retrieved were comparable among groups. The fragments were promptly retrieved from the DCA catheter, rinsed in saline solution, then fixed in 4% formaldehyde and separately embedded in paraffin. Fragments were then cut in 7-μm thick sections. Each fragment was investigated with use of specific staining and immunocytochemistry methods. The following staining methods were used: hematoxylin-eosin saffron for the analysis of cellularity, fibrosis, neovessels and inflammatory cells; periodic acid–Schiff reaction for extracellular matrix, atheroma (foam cells, cholesterol clefts or debris) and lamina interna; phosphotungstic acid–hematoxylin for thrombus, "stellar-shaped" fibromyocytes (i.e., muscle cells with dendritic processes) and media; von Kossa for calcium deposits; and Verhoeff-van Gieson for the presence of collagen. In each case, immunocytochemistry was used to further characterize the cellular population of the plaque. Macrophages and smooth muscle cells were detected by using the HAM 56 and anti-smooth muscle alpha-actin antibodies (Dako, Denmark), respectively. Sections were incubated with the specific antibody for 60 min, then washed for 5 min with phosphate-buffered saline solution and finally incubated for 60 min with a rat anti-mouse IgG light chain antibody. After washing, peroxidase activity was revealed with use of a commercial kit (3-amino-9-ethylcarbazol, Dako) with 0.1% H_2O_2. Sections were rinsed in water, counterstained in Mayer's hematoxylin for 2 min and mounted with an aqueous mounting medium (Dako).

Stained sections were examined by light microscopy at various magnifications with a Zeiss microscope. Thrombus was defined as successive layers of red blood cells and platelet-fibrin aggregates (Fig. 1c). Inflammatory process was characterized by the presence of clusters of macrophages and lymphocytes (Fig. 1d). Among these variables, the percent of fibrosis and cellularity was measured quantitatively by morphometry on a Visopan planimeter (Reichert) at ×25 magnification with use of a 100-square grid on the whole surface of each section. The number of square intersections crossed by either fibrosis or smooth muscle cells was reported as a percent of surface. Plaque was considered to be fibrous (or sclerotic) when >75% of the surface was covered by fibrosis (dense extracellular matrix); plaque was considered to be cellular (or proliferative) when >10% of the surface was covered by cellular hyperplasia. When present, the media was not included in the planimetry measurements. The other variables (thrombus, atheroma, inflammation, stellar-shaped smooth

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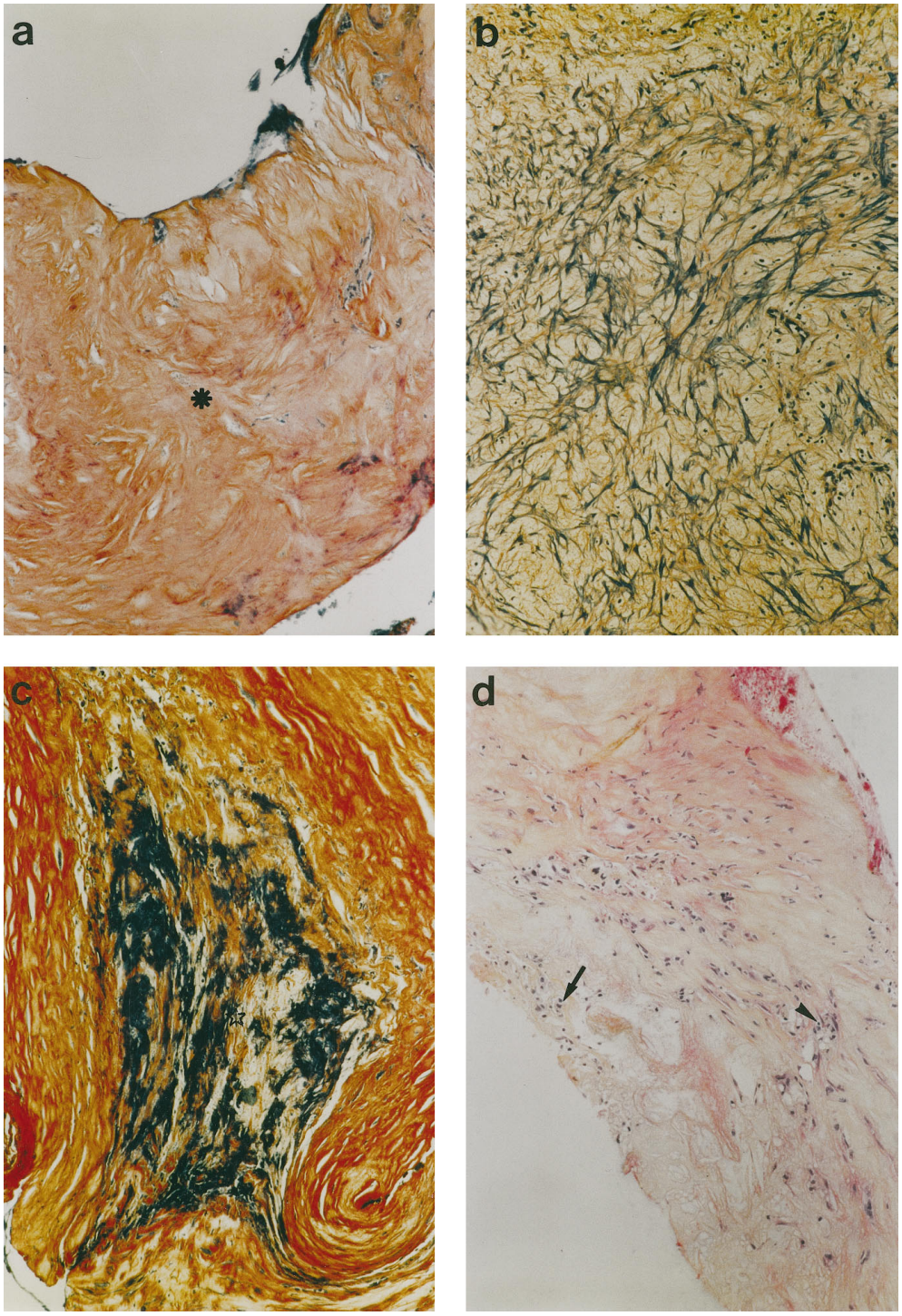

Figure 1. Light microscopic images illustrating various morphologic features found in atherosclerotic fragments obtained by DCA: fibrosis **(asterisk, panel a)**, cellular hyperplasia with "stellar-shaped" fibromyocytes **(panel b)**, thrombus **(panel c)** and inflammation with macrophages **(arrow, panel d)** and lymphocytes **(arrowhead, panel d)**. Original magnification, ×25. Phosphotungstic acid-hematoxylin, **panels a to c**; hematoxylin-eosin saffron, **panel d.**

muscle cells, calcium, neovessels and media) were analyzed qualitatively (present or absent) and expressed as percent of prevalence in each group.

Data analysis and statistics. The percent of surface of all specimens covered by fibrosis or cellular hyperplasia was averaged per patient. The percent of cases presenting with each of the different morphologic features described was calculated in the following patient groups: stable angina, unstable angina and post-MI; as stated earlier, patients in the post-MI group were further classified in an elective or late post-MI group. In patients with unstable angina, results are given for each Braunwald class, for each score as well as for the three following subgroups with increasing severity of symp-

Table 1. Clinical Characteristics and Risk Factors in Patients With Stable Angina

Pt No.	Age (yr)/ Gender	HTA	Smoker	Chol	Vessel Treated	CAD
1	53/M	−	+	−	LAD	1 VD
2	46/M	+	+	+	LAD	1 VD
3	38/M	+	+	−	LAD	2 VD
4	70/F	+	+	+	LAD	2 VD
5	52/M	−	+	−	LAD	1 VD
6	47/M	+	−	−	LAD	1 VD
7	60/F	+	−	+	LAD	1 VD
8	61/M	−	+	+	RCA	2 VD
9	52/M	−	+	+	LAD	1 VD
10	28/M	+	+	+	LCx	1 VD
11	67/M	+	−	+	LAD	1 VD
12	70/M	−	−	+	LAD	1 VD
13	47/M	−	−	−	RCA	1 VD
14	59/M	+	+	−	LAD	1 VD
15	78/M	−	−	−	LAD	1 VD
16	66/M	−	−	+	RCA	1 VD
17	48/M	+	−	−	LAD	1 VD
18	47/F	−	+	−	LAD	1 VD
19	46/M	−	−	−	LAD	1 VD

CAD = coronary artery disease; Chol = hypercholesterolemia; F = female; HTA = arterial hypertension; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = male; Pt = patient; RCA = right coronary artery; VD = vessel disease; + = present; − = absent.

toms: low (IA, IIA IIIA, IB), medium (IIB, IIIB), high (all C) scores.

Continuous variables are presented as mean value ± SD. Statistically significant differences between groups were calculated by using the Fisher exact test, and a Bonferroni p adjustment was performed for multiple comparisons. A p value < 0.05 was considered significant.

Results

Patient characteristics. Arterial hypertension was found in 47% of patients with stable angina, 44% of post-MI patients and 63% of patients with unstable angina. Smoking habits were found in 53%, 44% and 68% of patients from these groups, respectively. Hypercholesterolemia was found in 47% of patients with stable angina, 39% of post-MI patients and 55% of patients with unstable angina (Tables 1 to 3). The levels of total cholesterol were comparable among groups (mean 210 mg/100 ml, range 120 to 310/100 ml). No significant differences in demographic data, number of diseased coronary arteries or culprit vessel were present among groups (Tables 1 to 3).

Of the 38 patients with unstable angina, only 1 patient was in class A, 27 (71%) were in class B and 10 (26%) were in class C. The small number of class A patients probably reflects the low need for revascularization in such patients once the extracardiac cause of plaque instability is corrected. Table 2 also indicates which thrombolytic drugs were used in post-MI patients and the delay between thrombolysis and DCA whenever applicable. The peak value of creatine kinase (CK) was 3,000 ± 1,000 IU/liter in post-MI patients, in contrast to 1,500 ± 700 IU/liter in patients with unstable angina after MI (class C, $p < 0.05$).

Morphologic characteristics. The morphologic characteristics of the plaque fragments retrieved in the various patient groups are summarized in Table 4 and Figures 2 to 4. As shown in Figure 2a, all plaque fragments retrieved from patients with

Table 2. Clinical Characteristics and Risk Factors in Patients With a Previous Myocardial Infarction

Pt No.	Age (yr)/ Gender	HTA	Smoker	Chol	Vessel Treated	CAD	Delay (days)	Thromb
1	64/M	−	−	+	LAD	2 VD	4	SK
2	64/F	+	−	−	LAD	1 VD	4	SK
3	30/M	+	−	−	RCA	2 VD	23	None
4	66/M	−	+	−	RCA	3 VD	6	None
5	55/M	−	+	+	LAD	1 VD	2	UK
6	48/M	−	+	+	RCA	1 VD	10	SK
7	78/M	−	−	−	LAD	2 VD	4	SK
8	71/M	+	+	−	RCA	1 VD	3	rt-PA
9	57/M	−	+	−	RCA	1 VD	3	rt-PA
10	64/M	−	−	−	LAD	1 VD	1	SK
11	66/M	+	−	−	LAD	3 VD	5	None
12	63/F	+	−	+	LAD	2 VD	13	None
13	51/M	−	+	−	RCA	2 VD	2	SK
14	63/M	+	−	−	LAD	1 VD	3	rt-PA
15	66/M	−	−	−	RCA	1 VD	25	rt-PA
16	44/M	+	+	+	LAD	2 VD	48	SK
17	58/M	+	−	+	LCx	1 VD	14	UK
18	42/M	−	+	+	LAD	2 VD	90	UK

Delay = delay between acute myocardial infarction and directional coronary atherectomy; rt-PA = recombinant tissue-type plasminogen activator; SK = streptokinase; Thromb = thrombolytic therapy; UK = urokinase; other abbreviations and symbols as in Table 1.

Table 3. Clinical Characteristics and Risk Factors in Patients With Unstable Angina

Pt No.	Age (yr)/ Gender	HTA	Smoker	Chol	Vessel Treated	CAD	Infarct	Thromb	Braunwald Class
1	59/M	+	+	+	RCA	1 VD	Inf	SK	IC
2	71/F	+	+	+	LAD	2 VD	No	None	IB
3	60/M	+	+	+	RCA	1 VD	No	None	IB
4	52/M	+	+	+	LAD	2 VD	Inf	SK	IB
5	51/M	−	−	+	LAD	1 VD	No	None	IIB
6	53/M	−	+	−	RCA	1 VD	Inf	rt-PA	IIIC
7	52/M	+	−	−	LAD	1 VD	Ant	rt-PA	IIC
8	40/M	−	+	+	LAD	3 VD	Inf	None	IIC
9	71/M	−	+	−	LAD	1 VD	No	None	IIB
10	66/M	+	+	−	RCA	2 VD	No	None	IIB
11	38/M	−	+	+	LAD	1 VD	No	None	IIIB
12	72/M	+	−	−	LAD	1 VD	Ant	SK	IIIC
13	66/M	+	−	−	LAD	3 VD	No	None	IIB
14	49/M	+	+	+	RCA	2 VD	No	None	IIIB
15	58/M	−	−	+	LAD	1 VD	No	None	IIB
16	72/M	+	−	−	RCA	1 VD	No	None	IB
17	61/M	−	+	+	LAD	2 VD	No	None	IIB
18	54/M	−	−	−	LAD	1 VD	No	None	IIB
19	54/M	+	+	+	RCA	2 VD	Inf	UK	IIIB
20	36/M	−	+	−	LAD	1 VD	Ant	None	IC
21	43/M	−	−	−	LAD	1 VD	Ant	SK	IIIC
22	57/F	+	+	+	LAD	2 VD	Ant	None	IIC
23	54/M	−	+	+	RCA	1 VD	Inf	rt-PA	IC
24	58/M	+	+	+	LCx	2 VD	No	None	IB
25	45/M	+	+	−	LAD	1 VD	No	None	IB
26	43/M	+	−	+	LAD	3 VD	No	None	IB
27	60/M	+	+	−	LAD	1 VD	No	None	IB
28	62/M	+	−	+	LAD	2 VD	Inf	SK	IB
29	55/M	+	+	−	LAD	2 VD	Inf	SK	IIC
30	66/M	+	+	+	LAD	1 VD	No	None	IB
31	66/M	+	−	−	LAD	2 VD	Ant	None	IIA
32	54/M	+	+	+	RCA	1 VD	No	None	IB
33	57/F	+	+	−	LAD	1 VD	No	None	IIB
34	50/M	−	−	+	LAD	1 VD	No	None	IB
35	36/M	−	+	+	LAD	1 VD	No	None	IB
36	73/M	+	+	−	LAD	1 VD	No	None	IB
37	52/M	+	+	+	LAD	1 VD	No	None	IIIB
38	56/F	−	−	+	LAD	1 VD	No	None	IIB

Ant = anterior; inf = inferior; Infarct = infarction; other abbreviations and symbols as in Tables 1 and 2.

stable angina were fibrous, whereas cellularity increased in patients with unstable angina in proportion to severity of the plaque instability score. Plaques from asymptomatic post-MI patients were more often fibrous as the delay from the acute event increased (Table 4). The area of the specimen covered by fibrosis was 92 ± 5%, 85 ± 4% and 64 ± 8% of total surface in the stable angina, post-MI and unstable angina groups, respectively ($p < 0.05$, unstable angina group vs. the other two groups). Conversely, the area of the biopsy specimen covered by cellular hyperplasia was 4 ± 1%, 8 ± 3% and 14 ± 2% of total surface in the stable angina, post-MI and unstable angina groups, respectively ($p < 0.05$, unstable angina group vs. the other two groups). The remaining surface of the samples was mainly covered by atheroma or thrombus, which represents a relatively small percent of the total surface in the three groups. When patients with unstable angina were classified according to the Braunwald scheme, the prevalence of cellular plaques in patients with a low instability score was not different from that in patients with stable angina, whereas values of cellularity found in medium and high score groups were significantly higher ($p < 0.05$ vs. stable angina and low instability) (Fig. 2B). There was also a striking difference in plaque cellularity between patients in the elective post-MI and late post-MI subgroups; cellularity in the elective group was similar to that in patients with medium and high score instability, whereas cellularity in the late group was identical to that in patients with stable angina and low score instability (Table 2).

As expected from previous studies (17–20), the prevalence of thrombus was significantly higher in patients with unstable angina than in patients with stable angina (Fig. 3a). The overall group of post-MI patients also showed a high rate of intracoronary thrombosis (Table 4). Again, the percent of thrombus

Table 4. Prevalence of Morphologic Features of Plaque in the Different Groups

Groups	Fibr	Cell	Thr	Infl	Ath	Calc	Media	NV	SSC
Stable angina (n = 19)	100	0	5	33	20	22	17	17	5
Post-MI (n = 18)	89	6	33*	22	50*	39	11	33*	33*
Unstable angina (n = 38)	67*	16*	19*	22	19	33	8	37*	41*
Class IIA (n = 1)	—	—	—	—	—	—	—	—	—
Class IB (n = 13)	78	7	14	43	14	43	14	36*	29
Class IIB (n = 10)	60*	40*	50*	10	40	20	10	30	60*
Class IIIB (n = 4)	50*	50*	25*	25	50	50	0	25	50*
Class IC (n = 3)	66*	33*	33	66	100	33	0	66*	33
Class IIC (n = 4)	75*	25*	75*	25	50	50	0	75*	75*
Class IIIC (n = 3)	66*	33	66*	33	33	0	33	100*	66*
All class B (n = 27)	66*	16*	21*	21	21	26	8	24	31*
All class C (n = 10)	70*	20*	60*	40	60	30	10	80*	60*
Score 3 (n = 14)	80	7	13	40	13	40	13	33	27
Score 4 (n = 13)	61*	38*	46*	23	54*	23	8	38*	54*
Score 5 (n = 8)	62*	38*	50*	25	50*	50	0	50*	63*
Score 6 (n = 3)	66*	33*	66*	33	66*	0	33	100*	66*
Elective post-MI (n = 10)	75*	36*	45*	27	63†	45	18	27	45
Late post-MI (n = 8)	100	0	10	14	28	28	0	42*	10

*$p < 0.05$ versus values in patients with stable angina. †$p < 0.05$ versus values in patients with low risk unstable angina. Data are presented as percent of patients in each group. The Braunwald classification is presented from class IIA to class IIIC; then patients are grouped in classes B and C. The patients are also grouped according to severity score (3 to 6) and status in elective or late post-MI groups (see Methods for definitions of post-MI groups). Ath = atheromatosis; Calc = calcium; Cell = cellularity of ≥10% of plaque surface; Fibr = fibrosis of ≥75% of plaque surface; Infl = inflammatory cells; Media = medial cuts; NV = neovascularization; SSC = stellar-shaped cells; Thr = thrombus.

was not different among patients in the stable angina, low score unstable angina or late post-MI groups. The highest prevalence was found in patients with post-MI angina (Braunwald class C), despite thrombolytic treatment in 7 of 10 patients in this group (Table 2). Lytic drugs were given to the majority of asymptomatic post-MI patients in both the elective (9 of 11) and late (5 of 7) subgroups, but evidence of residual thrombus had virtually disappeared only in the latter subgroup (Table 4).

The presence of atheroma was not different between patients in the stable and unstable angina groups, but it was significantly more frequent in post-MI patients ($p < 0.05$). Again, the prevalence of atheroma was significantly higher in medium and high risk groups than in the group with low risk unstable angina and in the group with stable angina (Fig. 3B). The prevalence was higher in class C than in class B patients (Table 4). Atheroma was also significantly more frequent in the elective post-MI group than in the late post-MI group ($p < 0.05$), whose rate of atheroma did not differ from that of patients with stable plaque.

The prevalence of plaque neovascularization was greater in the high risk unstable angina and post-MI groups than in the stable angina group (Table 2). Unlike the previous morphologic criteria, there was no statistical difference between patients in the stable angina and unstable angina groups with either a low or a medium risk score. However, plaque from patients with post-MI instability (class C) displayed a significantly higher percent of neovascularization (Fig. 4A).

Stellar-shaped fibromyocytes were found more frequently in patients in the unstable angina and post-MI groups than in the patients with stable angina (Table 4). An increasing proportion of positive findings was found when comparing low, medium and high risk score patients with unstable angina (Fig. 4b). Similarly, a significant difference was found between elective post-MI patients (who had results similar to those of patients with unstable angina) and late post-MI (whose results were similar to those of patients with stable angina).

Other morphologic characteristics such as the presence of inflammatory cells, calcium deposits or medial cuts were not significantly different among the groups studied (Table 4).

Discussion

Correlation between clinical and pathologic spectra of instability. To summarize, our data show that the clinical classification of severity of unstable angina is correlated with an increasing prevalence of the following morphologic characteristics within plaque: high cellularity, thrombus, atheroma, stellar-shaped smooth muscle cells and neovessels. More specifically, in patients with a low instability score, plaque has the same characteristics as that of patients with stable angina. When the instability score and the risk of further events increase (14,15), so does the prevalence of the specific morphologic features of instability. These findings demonstrate a strong correlation between the clinical presentation of unstable angina as assessed by the Braunwald classification and the histologic structure of the culprit coronary lesion. These observations therefore provide additional support for the validity of the clinical classification proposed by Braunwald (12,13).

Also of interest are the differences in plaque morphology among patients with previous MI without residual angina, in relation to the delay between the acute event and DCA.

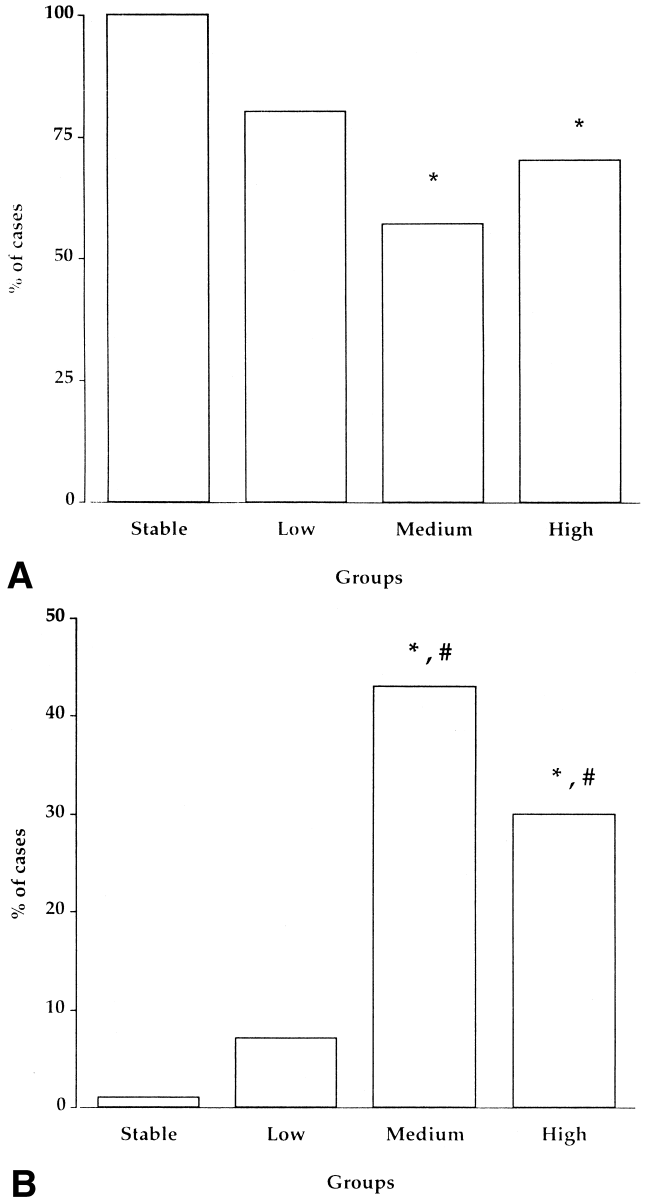

Figure 2. Prevalence of fibrosis (**A**) and cellularity (**B**) in patients with stable angina (Stable) and in patients with unstable angina at increasing risk of further cardiac events (low, medium and high risk). Plaque was considered fibrosclerotic when >75% of the surface was covered by dense extracellular matrix. Plaque was considered fibrocellular when > 10% of the surface was covered by smooth muscle cells. *p < 0.05 versus patients with stable angina. #p < 0.05 versus patients with unstable angina at low risk.

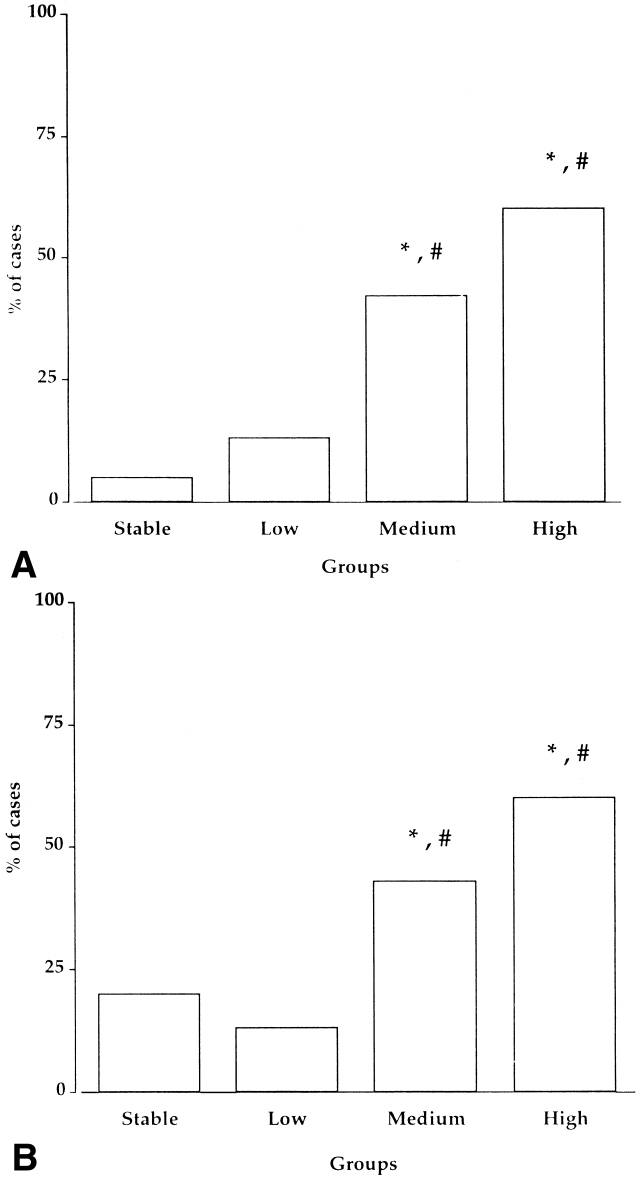

Figure 3. Prevalence of thrombus (**A**) and atheroma (**B**) in patients with stable angina (Stable) and in patients with unstable angina at increasing risk of further cardiac events (low, medium and high risk). Cases were considered positive when the specific morphologic feature was found to be present. *p < 0.05 versus patients with stable angina. #p < 0.05 versus patients with unstable angina at low risk.

Indeed, patients in whom DCA was performed early after MI have plaque characteristics that are similar to those of patients with unstable angina at high risk for further cardiac events. In contrast, plaque obtained late after MI shows morphologic features of healing and appears similar to stable plaque, except for the high prevalence of neovessels. The high prevalence of neovessels in post-MI plaque implies thrombus colonization and repermeabilization, as suggested from autopsy studies (2,21). It is obviously not possible to obtain serial samples from the same lesion in order to study the evolutionary changes in plaque structure from stable to unstable and toward stability again through plaque healing (11). However, the striking similarity between plaque features in late post-MI and stable angina groups suggests that both extremes of the spectrum join in a circle that is likely to represent the cycle of disruption and repair that individual lesions undergo. This observation supports current efforts to stabilize the unstable plaque medically rather than to attempt immediate performance of interventional revascularization.

Morphologic characteristics of plaque instability. Our data are mostly in agreement with previous reports (18–

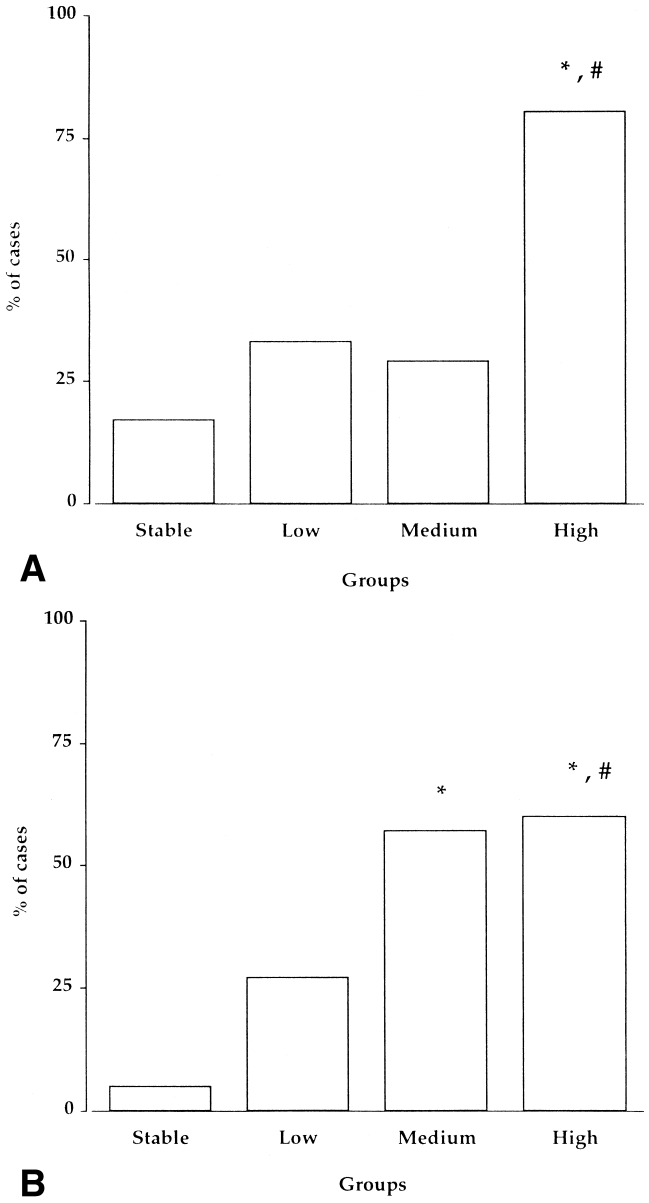

Figure 4. Prevalence of neovessels (**A**) and "stellar-shaped" cells (**B**) in patients with stable angina (Stable) and in patients with unstable angina at increasing risk of further cardiac events (low, medium and high risk). Cases were considered positive when the specific morphologic feature was found to be present. *$p < 0.05$ versus patients with stable angina. #$p < 0.05$ versus patients with unstable angina at low risk.

20,22,23) showing the differences between stable and unstable plaque with respect to cellularity, fibrosis and thrombosis. However, in earlier studies, plaque morphology was not correlated with the clinical presentation in well characterized patient groups. The high prevalence in unstable plaque of stellar-shaped smooth muscle cells, which is the predominant cell phenotype within restenotic lesions (17,18), has not been reported previously. The results are in agreement with the classification of advanced types of atherosclerotic lesions reported by Stary et al. (24). Plaque morphology in patients with stable angina corresponds to type IV of Stary et al. In low-risk unstable angina, lesions are identical to type V, whereas advanced grades of instability reproduce the lesions seen in type VI. An intriguing observation is the lack of correlation between plaque instability and the presence of inflammatory cells, which are considered to play an important role in plaque rupture (25–27). Indeed, activated inflammatory cells release inducible enzymes, such as metalloproteinases, that can digest the extracellular matrix and favor plaque rupture by weakening of the fibrous cap (28). Preliminary results suggest that macrophages present in the plaque need first to be activated before producing mediators of plaque instability and such activation does not seem to happen in atherosclerotic plaque from patients with stable angina (29). We looked only at the presence or absence of inflammatory cells, whereas their presence within critical areas of the plaque may be more important than their abundance (25,26).

Thrombogenesis in various stages of instability. The most sensitive method to detect intraluminal thrombus is coronary angioscopy, and recent studies reported a 40% to 61% prevalence of red thrombus in acute coronary syndromes (8–10). Consistent with previous reports analyzing samples obtained by DCA, we found a relatively low prevalence of thrombus (19%) in the overall population of patients with unstable angina (19,20,22). However, taking into account the severity of the unstable condition, we found thrombus prevalence ranging from 46% to 66% in medium and high risk patients, values identical to findings in the reports based on angioscopy. These observations confirm the diversity of the acute coronary syndromes and further support the importance of careful classification of unstable angina. Also, it remains possible that part of the mural thrombus becomes dislodged during the manipulations of the atherectomy device and embolizes distally. This hypothesis is supported by the rather high prevalence of increased CK release after seemingly uncomplicated DCA (30). Another possibility relates to the obvious limitation of the current atherectomy technique, which is neither truly directional nor guided such that random samples of plaque fragments are retrieved. Lastly, it is noteworthy that "thrombolysis" after MI seems to continue over the next weeks as the prevalence of thrombus decreases with time from 45% to 10%. This observation is consistent with earlier angiographic data (31) showing a decrease in stenosis severity over time when measured by quantitative coronary angiography.

Study limitations. As already acknowledged, the morphologic analysis of DCA fragments provides only small biopsy specimens of the plaque. One has to assume that the retrieved fragments are representative of the underlying plaque. This assumption can be occasionally verified when deep cuts also permit retrieval of media. In an attempt to limit sampling errors, we included only cases in which two or more samples were retrieved. Because of this limitation, we could not determine accurately the location of all morphologic features inside the plaque or quantitate their abundance, but only assess their presence or absence. As discussed previously, this limitation could explain the lack of significant correlation

between inflammation and plaque instability. Finally, only a relatively small number of patients could be studied, precluding an even more precise correlation between clinical subgroups and morphologic findings.

Conclusions. The morphologic pattern of coronary atherosclerotic lesions varies at different stages of acute coronary syndromes. The clinical severity of unstable angina assessed by the Braunwald classification is correlated with an increasing prevalence of the following morphologic characteristics: thrombus, atheroma, neovessels and cellular hyperplasia. Plaque composition late after MI in patients without residual angina evolves toward a quiescent pattern similar to that found in lesions from patients with stable angina.

References

1. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to myocardial infarction and/or sudden death. Circulation 1985;712: 699–708.
2. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 1990;82 Suppl II:II-38–46.
3. Fuster V. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. Circulation 1994;90:2126–46.
4. Mac Isaac AI, Thomas JD, Topol EJ. Toward the quiescent coronary plaque. J Am Coll Cardiol 1993:1228–41.
5. Ambrose JA, Winters SL, Stern A, et al. Angiographic morphology and the pathogenesis of unstable angina pectoris. Am J Cardiol 1985;5:609–16.
6. Gotoh K, Minamino T, Katoh O, et al. The role of intracoronary thrombus in unstable angina: angiographic assessment and thrombolytic therapy during ongoing anginal attacks. Circulation 1988;77:526–34.
7. Freeman MR, Williams AE, Chisholm RJ, Armstrong PW. Intracoronary thrombus and complex morphology in unstable angina. Circulation 1989;80: 17–23.
8. Terstein PS, Schatz RA, DeNardo SJ, Jensen EE, Johnson AD. Angioscopic versus angiographic detection of thrombus during coronary interventional procedures. Am J Cardiol 1995;75:1083–7.
9. White CJ, Ramee SR, Collins TJ, et al. Coronary thrombi increase PTCA risk: angioscopy as a clinical tool. Circulation 1996;93:253–8.
10. Waxman S, Sassower MA, Mittleman MA, et al. Angioscopic predictors of early adverse outcome after coronary angoplasty in patients with unstable angina and non-Q wave myocardial infarction. Circulation 1996;93:2106–13.
11. Davies MJ. Acute coronary thrombosis—the role of plaque disruption and its initiation and prevention. Eur Heart J 1995;16 Suppl L:3–7.
12. Braunwald E. Unstable angina: a classification. Circulation 1989;80:410–4.
13. Ahmed WH, Bittl JA, Braunwald E. Relation between clinical presentation and angiographic findings in unstable angina pectoris, and comparison with that in stable angina. Am J Cardiol 1993;72:544–50.
14. Calvin JE, Klein LW, VandenBerg BJ, et al. Risk stratification in unstable angina: prospective validation of the Braunwald classification. JAMA 1995; 273:136–41.
15. Van Miltenburg AJM, Simoons ML, Veerhoek RJ, Bossuyt PMM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. J Am Coll Cardiol 1995;25:1286–92.
16. Umans V, Haine E, Renkin J, de Feyter P, Wijns W, Serruys PW. One hundred attempts at directional atherectomy: the early and combined experience of two European centers using quantitative angiography to assess their results. Eur Heart J 1992;13:918–24.
17. Johnson DE, Hinohara T, Selmon MR, Braden LJ, Simpson JB. Primary peripheral arterial stenoses and restenoses excised by transluminal atherectomy: a histopathologic study. J Am Coll Cardiol 1990;15:419–25.
18. Garratt KN, Edwards WD, Kaufmann UP, Vlietstra RE, Holmes DR. Differential histopathology of primary atherosclerotic and restenotic lesions in coronary arteries and saphenous vein bypass grafts: analysis of tissue obtained from 73 patients by directional atherectomy. J Am Coll Cardiol 1991;17:442–8.
19. Escaned J, Van Suylen RJ, McLeod DC, et al. Histologic characteristics of tissue excised during directional coronary atherectomy in stable and unstable angina pectoris. Am J Cardiol 1993;71:1442–7.
20. Rosenschein U, Ellis SG, Haudenschild CC, et al. Comparison of histopathologic coronary lesions obtained from directional atherectomy in stable angina versus acute coronary syndromes. Am J Cardiol 1994;73:508–10.
21. Depre C, Havaux X, Wijns W. Characterization of transmural neovascularization in human coronary atherosclerotic lesions. Cathet Cardiovasc Diagn 1996;39:215–20.
22. Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of coronary arterial plaques in isolated unstable angina pectoris with pain at rest. Am J Cardiol 1990;66:562–7.
23. Arbustini E, De Servi S, Bramucci E, et al. Comparison of coronary lesions obtained by directional coronary atherectomy in unstable angina, stable angina, and restenosis after either atherectomy or angioplasty. Am J Cardiol 1995;75:675–82.
24. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. Circulation 1995;92:1355–74.
25. Van der Wal AC, Becker AE, Van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89:36–44.
26. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JF. Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. Circulation 1994;90:775–8.
27. Libby P. Molecular basis of acute coronary syndromes. Circulation 1995;91: 2844–50.
28. Galis SZ, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest 1994;94:2493–503.
29. Depre C, Havaux X, Renkin J, Wijns W. Expression of inducible nitric oxide synthase in coronary plaque fragments from patients with unstable angina [abstract]. Circulation 1996;94 Suppl I:I-588.
30. Lefkovits J, Blankenship JC, Anderson KM, et al. Increased risk of non-Q wave myocardial infarction after directional atherectomy is platelet dependent: evidence from the EPIC trial. J Am Coll Cardiol 1996;28:849–55.
31. Serruys PW, Wijns W, Van Den Brand M, et al. Is transluminal coronary angioplasty mandatory after successful thrombolysis? Br Heart J 1983;50: 257–65.