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A new look at coronary angiograms: plaque morphology as a help to diagnosis and to evaluate outcome

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Abstract

Characterization of plaque morphology can provide useful information beyond those generally yielded by the more traditional methods of interpretation of coronary angiograms based on assessment of severity of stenoses and number of diseased vessels. Focus on the culprit coronary lesion in acute myocardial infarction and in unstable angina allows recognition of the complex plaque and of presence of endoluminal thrombi that are closely associated to the mechanisms of the disease. Response to treatment in these clinical situations, and the healing process can be assessed by repeated opacifications of the lesion. The presence of a residual thrombus is associated with a worse clinical outcome and also a higher risk of complication if coronary angioplasty is performed. The prognostic information derived from the morphologic analysis extends to the chronic phase of the disease. The extent score of disease, defined as the sum of coronary artery segments showing a narrowing of any severity marks more severe disease and predicts future progression. Severity of stenosis is also a predictor. More severe lesions will occlude more frequently but most often without clinical consequences. Occlusion of less severe stenosis, on the other hand, leads to acute myocardial infarction or to the other manifestations of acute coronary syndromes. Other morphologic features are also associated with a higher risk of myocardial infarction. These include a geometry favoring blood flow separation and turbulence such as acute inflow and outflow angles of the stenosis and presence of a division within its vicinity. This new look at coronary angiograms may help orient therapy. Patients with angina and a significant stenosis will profit from a corrective intervention. Others with a high extent score should receive a comprehensive program for control of risk factors. Patients with a lesion of borderline significance at risk of activation should be closely monitored, and when clinical symptoms evolve, receive more intensive antithrombotic therapy. Quantification of the morphologic characteristics of the plaque, coupled to new techniques for endovascular imaging should lead in the future to better diagnostic and better risk stratification.

Introduction

The severity of coronary atherosclerosis is classically assessed by coronary arteriography and expressed in terms of number of diseased vessels with 50% or more of diameter stenosis. Many studies have correlated cardiac mortality with the number of diseased vessels [1–5]. For example, among 20,088 patients in the Coronary Artery Surgery Study Registry, the 4-year survival with medical management was 97, 92, 84 and 68% respectively with zero-, single-, double- and triple-vessel disease, defined by visual appreciation of diameter stenosis 70% or greater [5]. Stenoses with less than 50% are ordinarily not treated by coronary angioplasty or coronary bypass surgery because they are not considered severe enough to cause myocardial ischemia. However, lesions in this range cause a substantial proportion of myocardial infarctions when they occlude [6].

The morphologic features of coronary lesions are usually ignored in the clinical classification of coronary disease. This is so for several reasons. First, the clinical significance of different morphologic features and their prognostic importance have not been defined as explic-

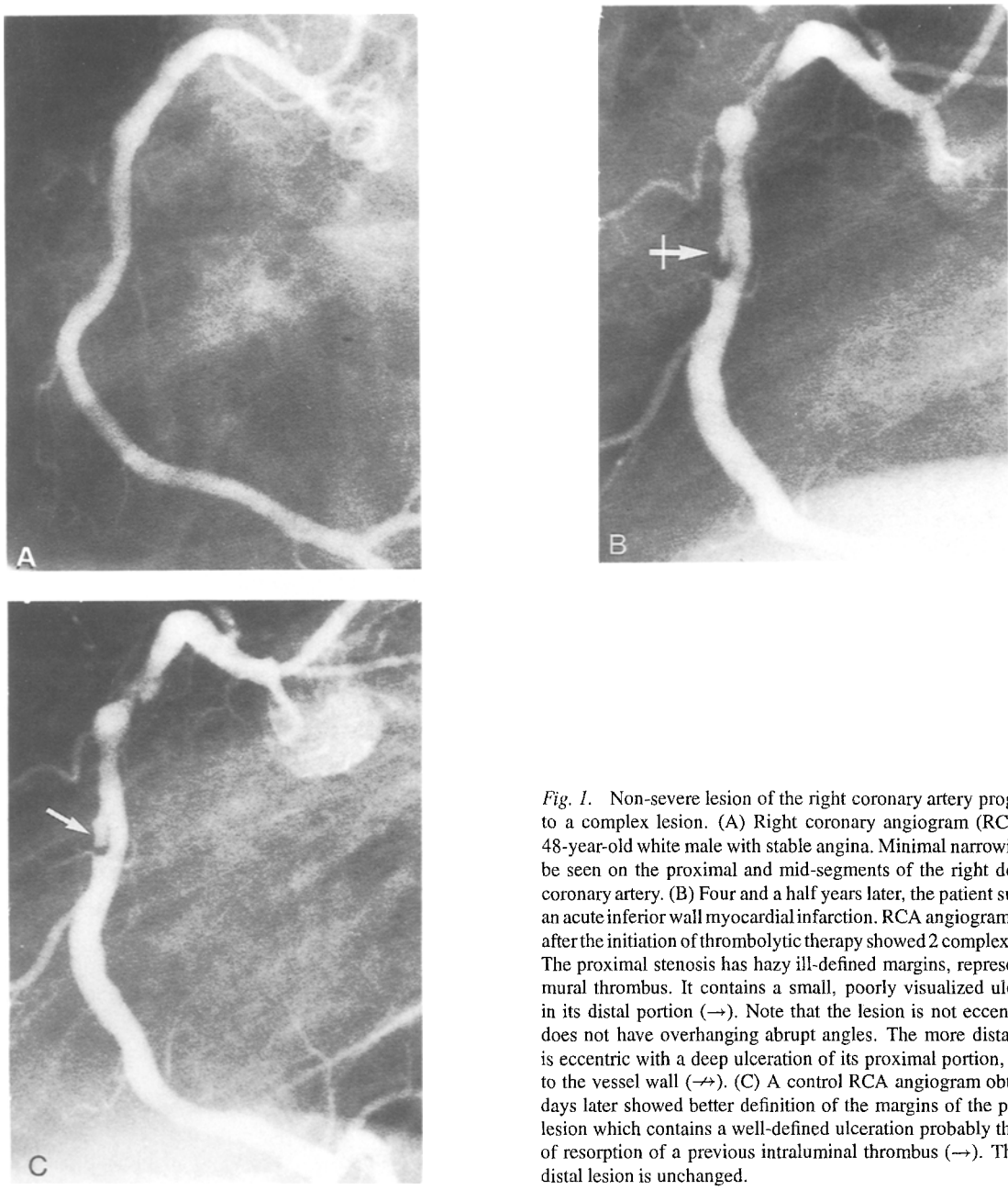


Fig. 1. Non-severe lesion of the right coronary artery progressing to a complex lesion. (A) Right coronary angiogram (RCA) in a 48-year-old white male with stable angina. Minimal narrowings can be seen on the proximal and mid-segments of the right dominant coronary artery. (B) Four and a half years later, the patient sustained an acute inferior wall myocardial infarction. RCA angiogram 2 hours after the initiation of thrombolytic therapy showed 2 complex lesions. The proximal stenosis has hazy ill-defined margins, representing a mural thrombus. It contains a small, poorly visualized ulceration in its distal portion (→). Note that the lesion is not eccentric and does not have overhanging abrupt angles. The more distal lesion is eccentric with a deep ulceration of its proximal portion, parallel to the vessel wall (↛). (C) A control RCA angiogram obtained 6 days later showed better definition of the margins of the proximal lesion which contains a well-defined ulceration probably the result of resorption of a previous intraluminal thrombus (→). The more distal lesion is unchanged.

itly as have other measurements, such as the number of diseased vessels. Also, different descriptors of morphologic characteristics exist in the literature and the assessment of lesion morphology is both subjective and associated with a high degree of interobserver variability. Many of these characteristics are not readily amenable to quantitative angiography. Quantitative angiography has another purpose; it is an exquisite tool to objectively and accurately measure lesions; these lesions, however, must first be recognized and interpreted by a knowledgeable and experienced physician.

Any qualitative or quantitative evaluation of a coronary angiogram is plagued by inherent radiographic limitations. A comprehensive report by Whiting et al. identified 6 technical factors limiting the quantitation of coronary artery stenoses [7]; most of them are related to radiographic distortion and the 2 most important are image blur and quantum noise, resulting from focal

spot unsharpness of the x-ray tube and image intensifier and limited resolution and motion caused by the movement of the beating heart. These factors affect overall resolution causing as much as 0.3 mm blur in a 2-mm coronary artery stenosis [7].

These limitations lead to the implicit belief that minor border irregularities of lesions would not be seen at cineangiography, resulting in a low sensitivity for diagnosis. On the other hand, the identification of plaque irregularities and intraluminal lucencies would almost always represent true-positive findings, and a high specificity.

This manuscript reviews the morphologic features of coronary lesions that could be useful in clinical practice to evaluate diagnosis and prognosis of coronary artery disease. The various morphologic aspects of lesions are described as well as the clinical circumstances in which they are most commonly encountered. The relevance of these various changes to disease progression and clinical outcome is also reviewed.

Correlation between angiography and pathology

Levin et al. obtained post-mortem coronary arteriography in patients who died following myocardial infarction or bypass surgery and compared the angiographic and pathologic findings; 73 lesions with a 50 to 99% reduction of the luminal diameter were characterized [8, 9]. Thirty-eight stenoses had irregular borders or intraluminal lucencies at angiography; 30 of these were 'complicated' on histologic sections, with plaque rupture, plaque hemorrhage, superimposed partially occluding thrombus, or recanalized thrombus. Conversely, 35 lesions had smooth borders, an hourglass configuration and no intraluminal lucencies at arteriography; only 4 of them had a 'complicated' histology. These results suggest that post-mortem angiography is quite sensitive and specific for the detection of the complex lesion. By extrapolation, the accuracy of coronary arteriography in living patients could be assumed to be similar. Conversely, however, a series of autopsy studies performed at the National Institute of Health shed doubt on the validity of coronary angiography in vivo by describing more severe and more extensive coronary artery disease at histology, more frequent complex plaques and less intraluminal thrombi [10, 11].

The recent development of coronary angioscopy has provided a means to compare angiographic features with the surface pathology of lesions in living patients. Although large series have not yet been reported, observations in small numbers of patients indicate that coronary arteriography may be insufficiently sensitive to detect subocclusive thrombi and other features of complex plaques. In the study of Sherman et al. [12], angiography correctly identified the absence of a complex plaque and thrombus in 22 vessels, but detected only 1 of the 4 complex plaques and 1 of the 7 thrombi. In 10 unstable angina patients studied by Mizuno et al. [13], only 2 had thrombus at angiography, but 9 were detected by angioscopy. The sensitivity of coronary arteriography to detect thrombus may be higher in acute myocardial infarction, where the thrombus is more likely to be totally occlusive [14]; the thrombus is reddish in myocardial infarction but grayish-white in unstable angina.

Taken together, the available data suggest that coronary arteriography is quite specific to detect the complex lesion, but not very sensitive, particularly with respect to subtle abnormalities such as small amounts of thrombus or shallow ulcerations.

Plaque morphology

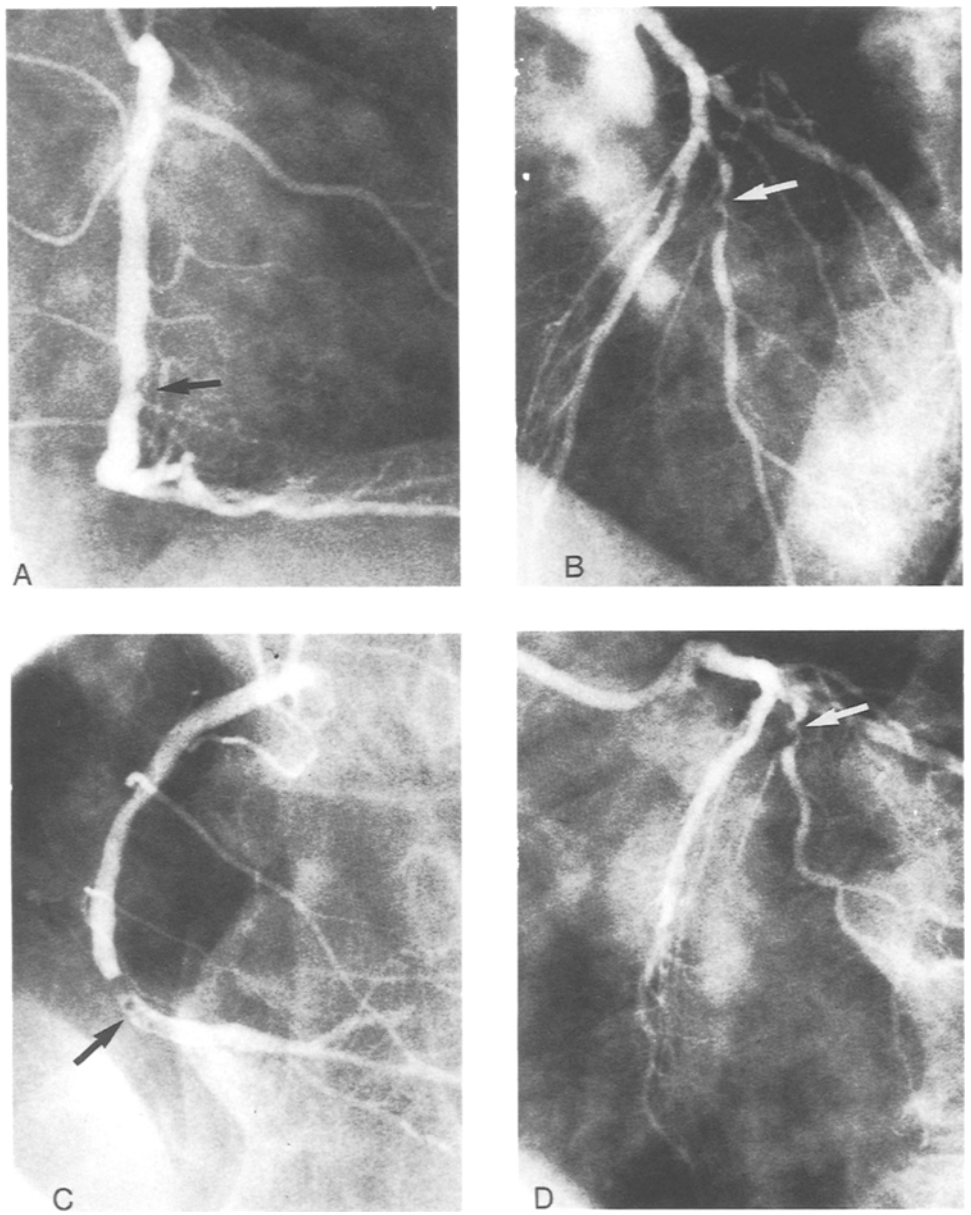
A complex plaque is defined by the presence of 1 or more of the following features.

Eccentricity

Eccentricity defines lesions with a lumen lying in the outer quarter of the main lumen diameter of the artery [15]. Eccentricity per se has little significance when the edges of the lesion are smooth [16]. However, eccentric lesions with abrupt or overhanging edges or with steep inflow or outflow angles, are often associated with acute coronary syndromes [16, 17] (Figs. 1B, 2C, 2E, 4 and 5A). The *inflow angle* is defined by the angle formed by the main axis of the vessel and a line from the proximal border of the lesion to its maximal narrowing [15, 18, 19]. Steep lesions have an angle of less than 135°. The *outflow angle* is the equivalent measure at the outlet of the stenosis.

Irregularities

The endoluminal edges of the lesions can be smooth and regular, or coarse and rough giving a so-called 'saw-tooth' appearance [15, 16]. Irregular lesions often lack definition because of hazy margins. Their identification is partly subjective. The lesions illustrated in Figs. 1B, 2B and 8 are coarse and irregular and the



lesions in Figs. 2A and 6B, smooth. Irregular lesions may represent a partially resorbed thrombus, healed ulcerations or remodelled plaques. They are rarely seen in patients with stable angina; reported incidences were 1.5% in one study [20] and 3.5% in another [15].

Ulcerations

Ulcerations correspond to contrast-medium-opacified craters within the area of a stenosis. They presumably are the consequence of plaque rupture [16, 18, 21, 22]. Figs. 1B, 1C, 2B and 6A are examples of ulcerations of different shapes and sizes. Their aspect may vary with time in the same patient in relation to the degree of filling of the rupture by the thrombus and to subsequent healing with plaque remodelling. An index of ulcerations was defined by Wilson et al. [22] as the ratio of the diameter measured at the site of the least severe stenosis to the maximum intralesional diameter (Fig. 9). This ratio was independent of the severity of the stenosis and allowed separation of patients with unstable angina from patients with stable coronary artery

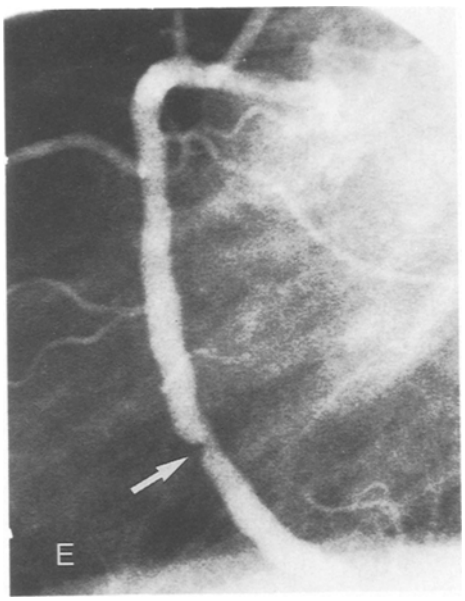


Fig. 2. A moderately severe non-complex lesion progressing to near-complete occlusion. (A) RCA angiogram in a 62-year-old white male admitted for stable angina: multiple but mild narrowings can be seen in the proximal and mid-segments of the right coronary artery. The smooth, eccentric 40% stenosis on mid-RCA segment has an inflow angle measured at 145°, thus greater than the $\leq$135° criterion for an abrupt proximal face as proposed by Davies et al. [19]. (B) The LCA angiogram reveals an eccentric and possibly ulcerated 70% diameter stenosis superimposed on a proximally irregular first diagonal branch (→) supplying a large territory, a lesion considered at high risk. (C) The patient was admitted 2.5 months later for an acute inferior wall infarction. The RCA showed a rapid progression of the 40% stenosis to an 80% with appearance of a complex morphology including eccentricity, acute inflow angle almost perpendicular to the long axis of the vessel and endoluminal distal filling defects. These aspects are characteristic of a large thrombus (→). The flow is delayed with only partial distal opacification (TIMI grade 2). (D) The LCA angiogram showed no progression of the previously severe and ulcerated stenosis of the first diagonal branch (→). (E) Control RCA angiogram obtained 6 days after myocardial infarction and thrombolytic therapy showed restoration of a TIMI-3 antegrade flow. The distal filling defects had completely disappeared. A short, eccentric 40–50% diameter stenosis persists.

disease. Davies et al. [19] modified this index, as the ratio of the maximal to the minimal intralesional diameter (Fig. 9) and used it as a predictor of early clinical instability following thrombolytic therapy.

Filling defects

Filling defects are defined as intraluminal radiotranslucent images, subopacified as compared to the adjacent lumen [23]. The filling defects may be of various sizes and completely (Figs. 5B and 7A) or partly occlusive (Figs. 2C and 4); they are usually ovoid (Fig. 4) or polypoid in shape (Fig. 2C) and attached to the underlying plaque. When smooth and well-delineated by the contrast media, filling defects are pathognomonic of intraluminal thrombi (Figs. 2C and 4). Occlusive thrombi usually show a squared off or a convex upstream termination, creating a stump (Fig. 5B). Older thrombi may have the appearance of adherent intraluminal mass with irregular or angular borders creating a very eccentric lumen (Fig. 3A). More chronic obstruction usually tapers smoothly to supply a terminal side branch which assures the run-off; collaterals are then usually well developed.

Contrast medium stagnation

Stagnation of the contrast medium expressing blood flow stagnation can be manifested by impregnation of the clot (Fig. 5B) but more often by stagnation proximal to the thrombus (Fig. 7B). This blood stagnation sets the stage for upstream extension of the thrombus which will be interrupted at the nearest branch assuring run-off.

Multiple irregularities

Multiple irregularities are defined as 3 or more serial and closely spaced severe stenoses or as severe diffuse narrowing in a coronary artery (Fig. 8) [15, 16].

Quantification of complex morphology

The description of ulceration indices by Wilson et al. [22] and Davies et al. [19] represented early attempts to quantify morphologic features (Fig. 9).

More recently, Kalbfleisch developed a novel method of quantification based on mathematical techniques describing vectors and on fractal analyses quantifying the complexity of continuous curves [24]. Five morphometric parameters were evaluated: peaks, summed maximum error, integrated error, number of major features and scaled edge length ratio. The first 4 parameters allowed differentiation of unstable and stable angina patients ($p < 0.01$). No correlation existed between these parameters and the degree of luminal narrowing, showing that they indeed added independent information to the traditional methods of measurement. This line of investigation could be useful in the future.

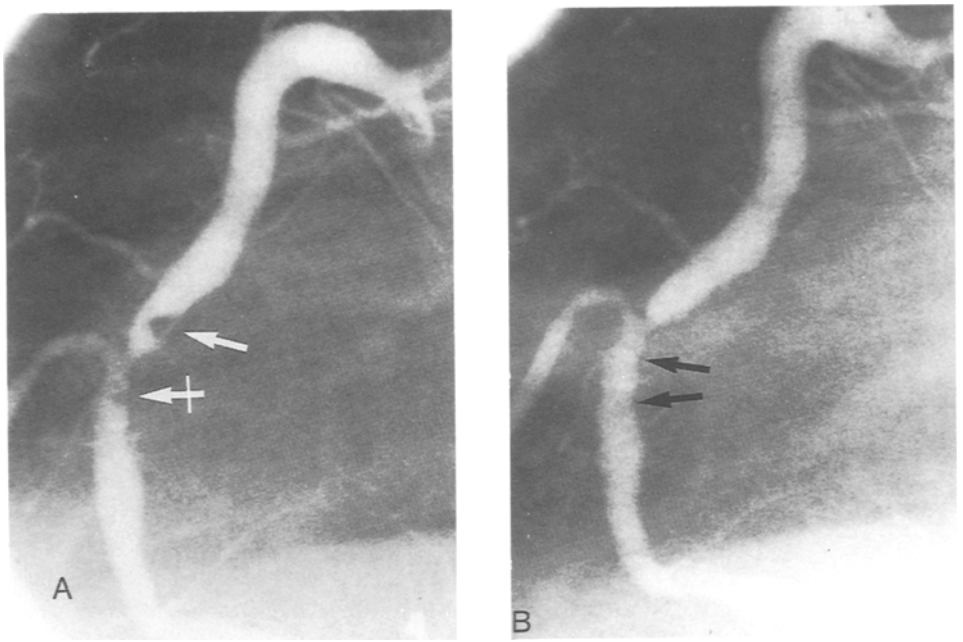


Fig. 3. Presence of a division branch as a risk factor for thrombosis. (A) RCA obtained within 2 hours of the onset of chest pain in a 43-year-old white male with an acute inferior myocardial wall infarction: an intraluminal filling defect with angular borders, proximal to a concentric 70% lumen diameter stenosis of the mid-segment of the RCA is present. This narrowing strongly suggesting a mural thrombus (→), is immediately proximal to a large acute marginal branch. Numerous poorly defined small intraluminal filling defects are present distal to the stenosis (↛). (B) RCA angiogram of the same patients 6 days after thrombolytic therapy: the endoluminal filling defects have completely disappeared, and the severity of the stenosis has not changed. Note the discrete mural irregularities distal to the stenosis (→).

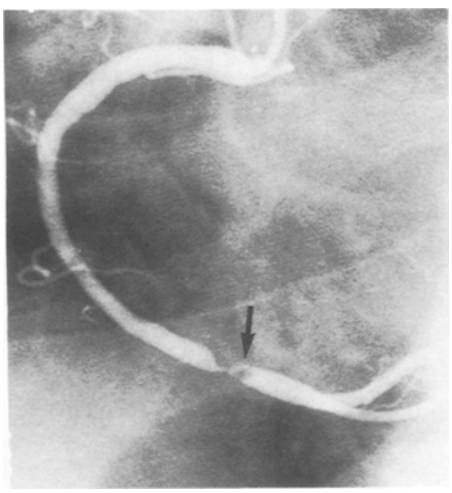


Fig. 4. Right coronary angiogram obtained in a 56-year-old patient admitted for *unstable angina*. The figure demonstrates a smooth, eccentric severe (75%) stenosis of the distal RCA with abrupt, steep inflow angle (120°), and a well-circonscribed endoluminal filling defect just distal to the stenosis. This aspect is characteristic of a thrombus forming on a complex plaque.

Angiographic morphology associated with acute coronary syndromes

Only 1 decade back, coronary angiograms of patients with unstable angina, myocardial infarction and stable angina were believed to share the same characteristics [25]. This was partly so because patients with acute myocardial infarction were usually catheterized only past the acute phase and also because the analysis of the angiograms focused on the number and severity of stenoses. In 1980, De Wood et al. opened a new era by describing total coronary artery occlusion in 84% of patients catheterized within 6 hours after the onset of acute myocardial infarction [26]. From then, identification of the culprit lesion, responsible for an acute event, and characterization of its morphology and complexity became an investigative tool. The initial observations made in patients with Q-wave myocardial infarction were subsequently extended to include other acute coronary syndromes such as non-Q-wave myocardial infarction and unstable angina. The morphologic features were used as a help to better understand the basic

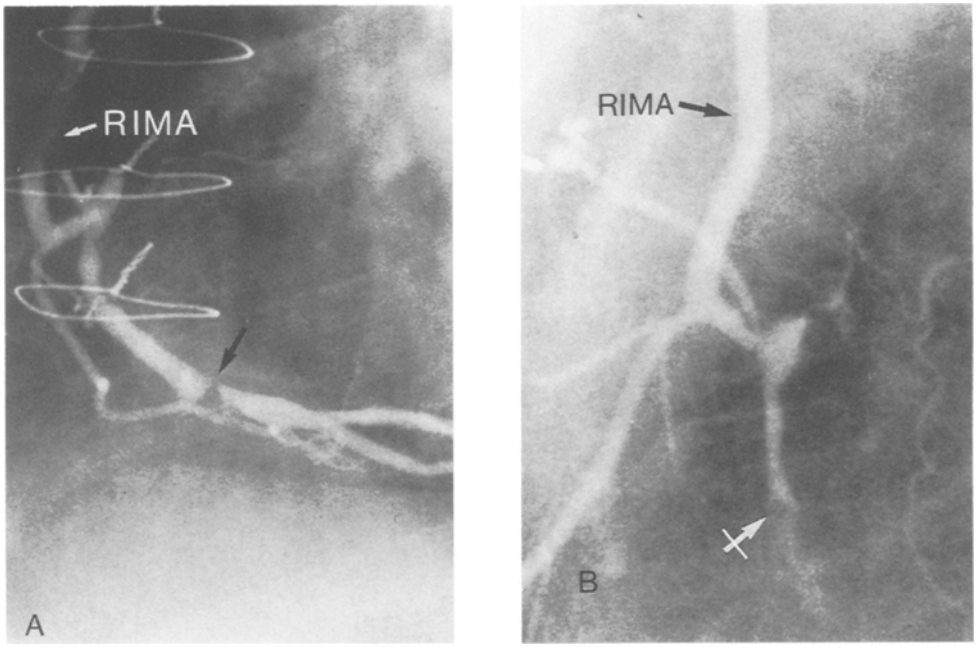


Fig. 5. Lesion morphology in unstable angina culminating to myocardial infarction. (A) Contrast injection of a right internal mammary artery (RIMA) grafted on the marginal branch of a distal right dominant RCA 8 years previously, in a 63-year-old patient admitted for unstable angina. A very eccentric lesion (⇀) can be seen in the distal third of the native artery, with a 75% lumen diameter obstruction. The lesion is discrete, abrupt and has steep inflow and outflow angles but regular contours; no thrombus can be seen at this time. (B) Angiogram repeated 6 days later, after the onset of an acute Q-wave myocardial infarction. The distal right coronary artery is now completely occluded at the site of the previous narrowing by an endoluminal filling defect surrounded with dye impregnation. This defect has an upstream convex shape (⇀↽), characteristic of a thrombus. Wall motion abnormalities had now appeared in postero-lateral and diaphragmatic left ventricular segments.

pathophysiologic mechanisms involved. Angiography was subsequently applied to evaluate the natural evolution of the disease and the success of interventional therapy, using repeated injections of the culprit coronary artery. This process coupled to major development in interventional cardiology and to availability of thromboactive drugs has completely modified the clinical approach to management of acute coronary syndromes. Table 1 summarizes the complex morphology that has been described in acute coronary syndromes.

Acute Q-wave myocardial infarction

Cardiac catheterization has now become nearly a routine procedure to evaluate the success of thrombolysis or to determine the need to perform angioplasty.

The angiographic morphologic descriptor of acute myocardial infarction is an abrupt cut-off of intraluminal flow by a semi-translucent, often convex image, representing the intraluminal occlusive thrombus (Figs. 2C, 5B, 7). Collateral flow is usually absent. The quality of flow is described by the Thrombolysis in Myocardial Infarction (TIMI) grading system. The grading is based on blood flow through the culprit coronary artery lesion [27]. TIMI grade 0 describes an absence of flow beyond the proximal aspect of the thrombus and, TIMI grade 1, a penetration of the blood clot by the dye but without opacification of the distal artery. In TIMI grade 2, the opacification of the distal artery is fainter and significantly delayed. TIMI grade 3 represents a complete and rapid opacification of the distal bed. A progressive improvement in flow can often be observed on repeated dye injections. The rapidity by which a better TIMI flow is achieved is an important determinant of subsequent recovery of left ventricular function [28]. TIMI grade 3 is associated with better improvement of function and better survival and should now be the target for optimal therapy; TIMI grade 2 flow results in suboptimal clinical success [28, 29]. Intravenous streptokinase restores a TIMI-2 or 3 grade flow at 90 minutes in 40% of patients, tissue plasminogen activation (t-PA) in 70% of patients [27] and front-loaded t-PA plus heparin in more than 80%

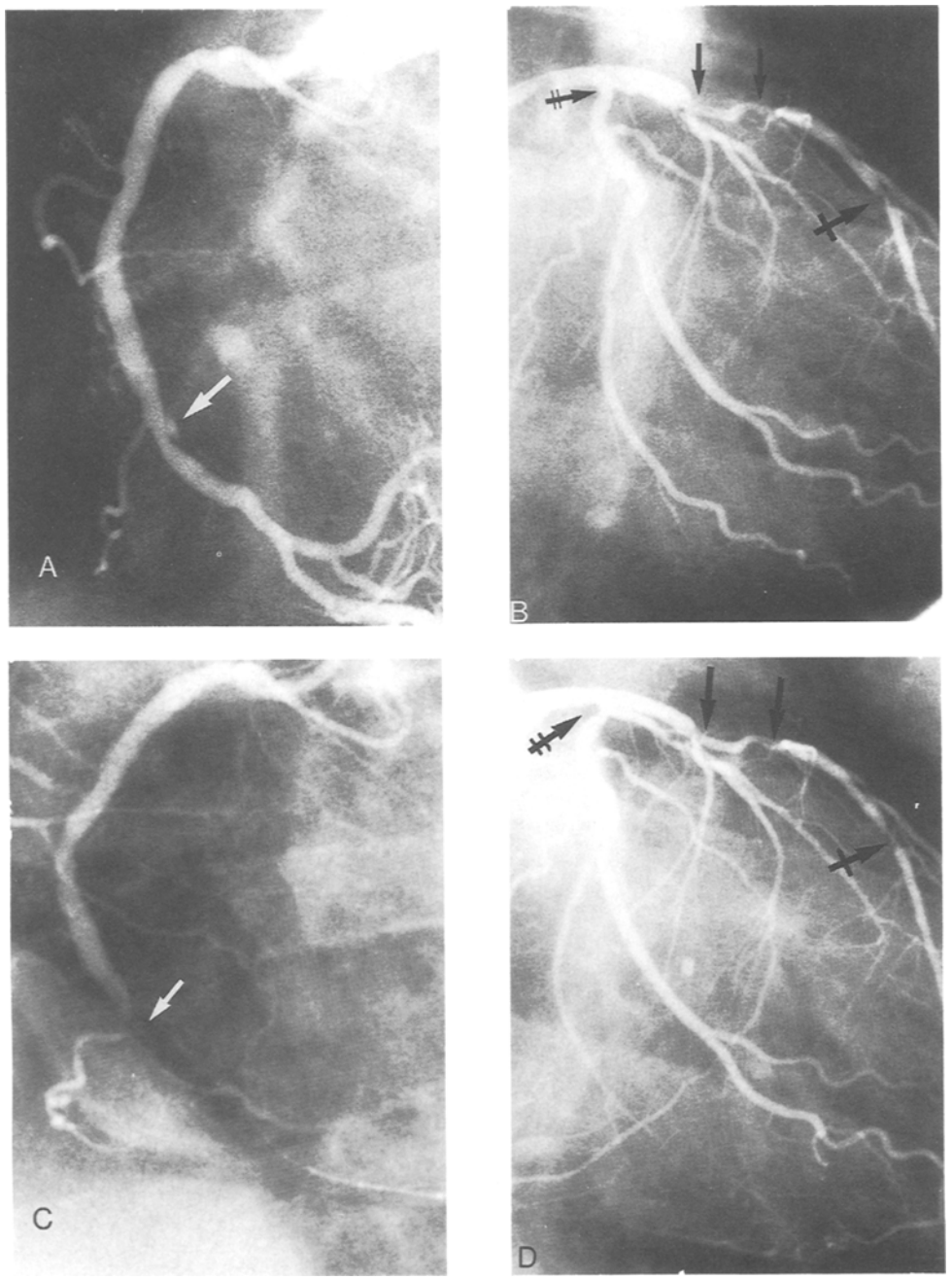


Fig. 6. Lesion morphology in unstable angina progressing to myocardial infarction. RCA (A) and LCA (B) coronary angiograms obtained 3 days after a non-Q-wave inferior wall myocardial infarction. The right coronary angiogram demonstrates a lesion of moderate severity (50% lumen diameter reduction) with an ulceration (→) and a side branch. It can be postulated that this lesion transiently developed a thrombus which has resolved. The left angiogram showed a 60% lumen diameter stenosis on the proximal left anterior descending artery (LAD) (→) and an 80% stenosis on its midportion (↛). A 30% narrowing on the proximal left circumflex artery is also seen (↛). What were the lesions at risk of progression in the following years in this patient? The angiograms shown in C and D were obtained 4 years later, shortly after an acute Q-wave inferior wall myocardial infarction. The distal right coronary artery is now completely occluded (→) at the site of the previously moderately stenotic but ulcerated lesion. The 60 and 80% stenoses of the LCA have surprisingly remained unchanged whereas the stenosis on the proximal left circumflex artery has progressed from 30 to 60% lumen diameter reduction.

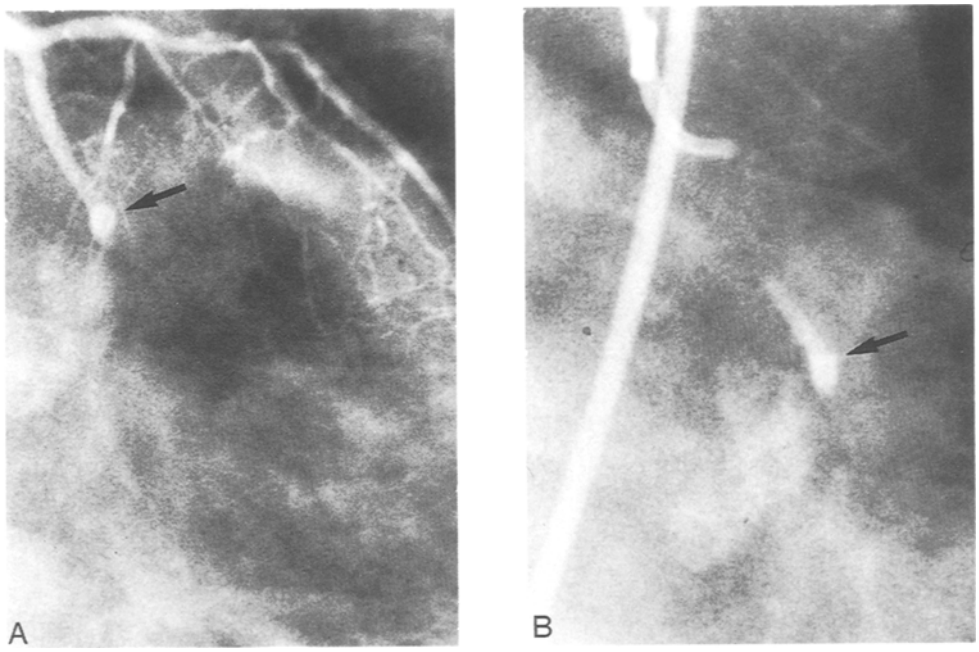


Fig. 7. Dye stagnation in acute myocardial infarction. (A) An abrupt cut-off of the left circumflex coronary artery in the acute phase of myocardial infarction. This lesion typically represents an occlusive thrombus (→). (B) Stagnation of the contrast medium proximal to the site of the abrupt occlusion (→). In more chronic obstruction, the occlusion tapered smoothly just distal to a terminal side branch assuming runoff of the dye.

Table 1. Complex morphology in acute coronary syndromes.

Author	Clinical condition	No. pts	Morphologic features	Incidence
Ambrose et al. [16] (1985)	UA	63	Type II eccentric lesion	71% vs 16%
	SA	47		
Bresnahan et al. [35] (1985)	UA	67	Intracoronary thrombus	35% vs 2.5%
	SA	201		
Capone et al. [36] (1985)	UA	119	Intracoronary thrombus	37% vs 0%
	SA	35		
Ambrose et al. [40] (1986)	UA	25	Type II eccentric lesion	71% vs 0%
	SA	21		
Williams et al. [37] (1988)	UA	101	Complex lesions	61%
Cowley et al. [38] (1989)	UA	69	– Complex lesions	26% vs 10%
	SA	20	– Thrombus	58% vs 5%
			– Overall evaluation	84% vs 15%
TIMI IIIA [39] (1993)	UA	209	– Apparent thrombus	35%
	non-Q MI	97	– Possible thrombus	40%
			– Ulcer	12%
			– Hemorrhage	4%
			– Eccentricity	45%

UA = unstable angina; SA = stable angina; MI = myocardial infarction.

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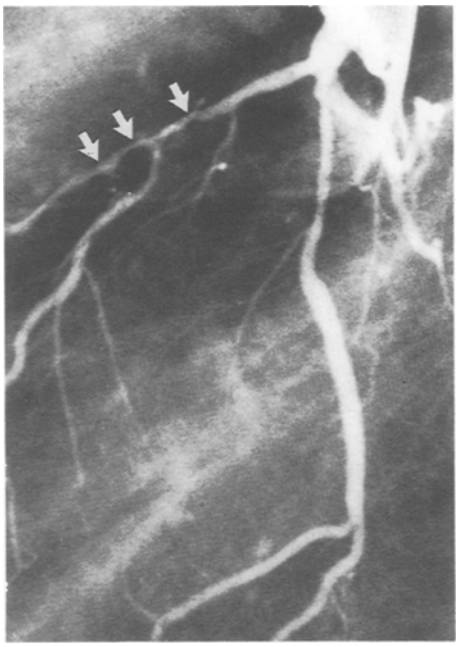

Fig. 8. Multiple irregularities and diffuse narrowing. LCA angiogram in a 50-year-old white male showing a severe and diffuse disease with multiple irregularities involving the proximal and mid-segments of the LAD (→).

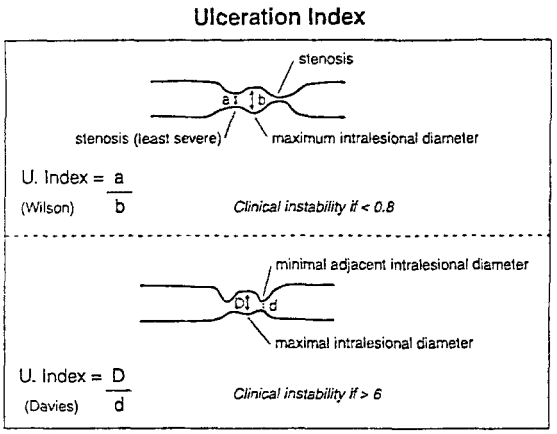

Fig. 9. Quantitative morphologic analysis of an ulceration index (bottom), method described by Wilson et al. (top) [22], methods described by Davies et al. [19]. Two related methods for quantifying the degree of ulceration. The indices derived can be useful to identify unstable angina and higher risk patients.

of patients [30]. Spontaneous reperfusion is observed in up to 40% of patients after 24 hours.

Control angiograms obtained after a few days, document reocclusion in 10 to 20% of patients initially

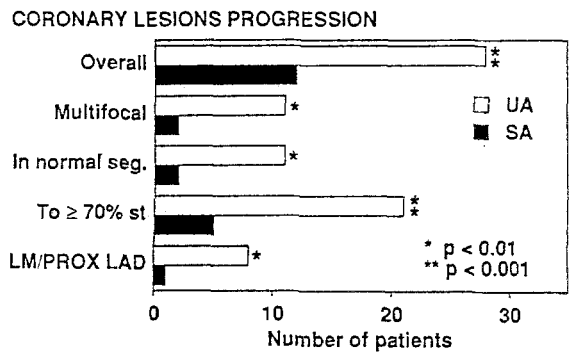

Fig. 10. Progression of coronary artery lesions in 38 patients with unstable angina (UA) and in 38 matched control patients with stable angina (SA). Overall progression, multifocal progression and progression in normal segments or to a significant ≥ 70% stenosis (st) were all more frequent in patients with unstable angina. Progression in the left main or in the proximal left anterior descending coronary artery (LM/PROX LAD) was also more frequent. From Théroux P, Moisea, Waters DD. Coronary angiography in unstable angina. In: Hugenholtz PG, Goldman BS (eds.). Unstable Angina. New York: Schattauer Stuttgart, 1985: 45–7, with permission of the authors and the editor. [84].

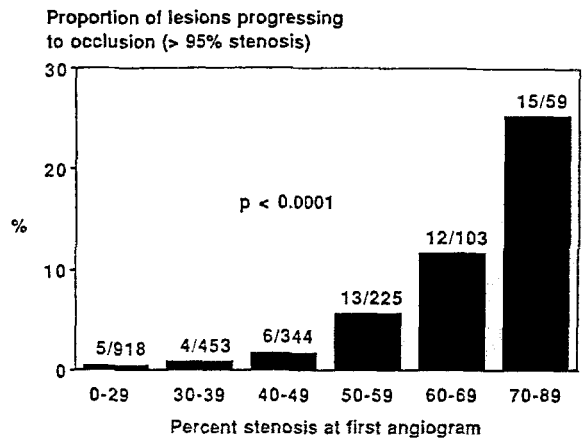

Fig. 11. Data from the Nicardipine study [51] on progression of coronary disease which has 383 enrolled patients in a double-blind placebo controlled trial. A coronary angiogram was obtained at baseline and a repeated angiogram after 2 years in 335 patients. The risk of occlusion increased exponentially with the degree of severity of the initial stenosis from stenoses less than 50% to stenoses 50–59%, 60–69% and above 70%.

successfully reperfused, indicating secondary failure of treatment and often, further deterioration of left ventricular function and a worse prognosis [31]. Most patients, however, will improve lumen diameter; 33% of the patients have a stenosis less than 50% lumen diameter reduction after 1 week and 66%, less than

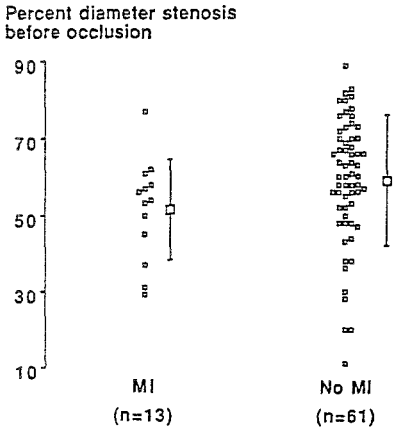

Fig. 12. Among the 335 patients from Fig. 11 with repeat arteriography after a 2-year interval, 58 had developed 74 new coronary occlusions, but only 13 of the occlusions had caused an interim myocardial infarction. All but one of these 13 narrowings that went on to cause infarction were < 70% diameter stenosis. Stenoses that occluded and caused infarction tended on average to be less severe than stenoses that occluded silently (p not significant).

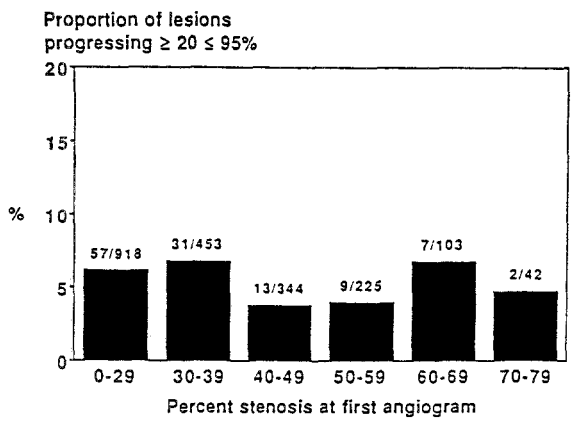

Fig. 13. Same study as in Figs. 12 and 13 showing that progression without occlusion was independent of the severity of the initial stenosis.

60% [32]. Davies et al. documented a decrease in the ulceration index with heparin therapy [18]. Nakagawa et al. also showed resorption of thrombus and remodelling of the mural architecture with rigorous anticoagulation over the following month [21]. Plaque features may help evaluate prognosis: in one series, 11 of the 15 patients with an ulceration index > 6 developed early clinical instability requiring urgent intervention; only 8 of the 57 stable patients had an index in this range [19].

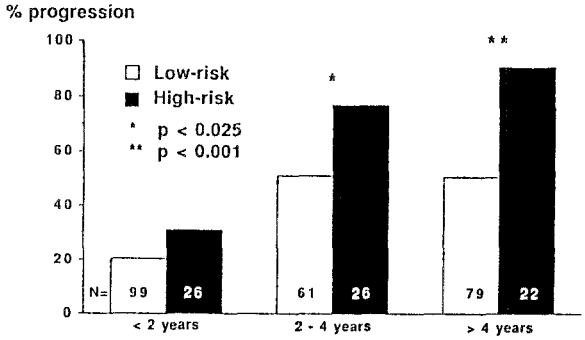

Fig. 14. Angiographic definition of patients at higher risk of progression of coronary artery disease. Patients were classified at the time of the baseline angiogram by the extent score, defining the sum of segments showing any degree of lumen diameter reduction. The high risk group shown by the dark bars included patients aged less than 50 years and an extent score of 4 or more. Patients older than 50 years old were also at higher risk when the initial extent score was 5 or more (see text). From Moise, A, Théroux P, Taeymans Y, Waters DD, Lespérance J, Fines P, Descoings B, Robert P. Clinical and angiographic factors associated with progession of coronary artery disease. J Am Coll Cardiol 1984; 3: 659–67, with permission of the authors and the American Heart Association [50].

Typical angiographic findings in acute myocardial infarction are shown in Figs. 2C, 5B and 7A. A residual intraluminal thrombus is most often present (Fig. 3A) and the site of plaque rupture can often be identified (Fig. 1B). The severity of the underlying stenosis can be better appreciated when the thrombus has completely resorbed (Figs. 1C, 2E and 3B). Plaque morphology, however, may not then be the same as it was before the acute rupture, because of plaque remodelling and possibly also because the process has lead to accelerated atherosclerosis [33].

Non-Q-wave myocardial infarction and unstable angina

Non-Q-wave myocardial infarction is less frequently associated with the presence of a coronary artery thrombus; complete occlusion was found in only 26% of patients studied within the first 24 hours with an incidence increasing to 42% in the following 72 hours [34].

Clinically, non-Q-wave myocardial infarction resembles unstable angina; the angiographic findings are also similar. In 1985, Ambrose et al. attempted a classification of coronary artery associated with unstable angina [16]. Coronary artery lesions were classified as:

(1) *concentric*, a symmetric narrowing with smooth or only slightly irregular borders;
(2) *type I eccentric*, an asymmetric stenosis with smooth borders and a broad base;
(3) *type II eccentric*, an asymmetric stenosis usually in the form of a convex intraluminal obstruction with a base narrowed by overhanging edges, or with very irregular or scalloped borders; and
(4) *multiple irregularities*, severe serial stenoses, or severe diffuse disease of an entire segment.

The analysis included 147 stenoses with lumen diameter reductions varying from 40% to subtotal in 110 patients, 47 with stable and 63 with unstable angina. Fifty-four percent (54%) of the 92 lesions in unstable patients were type II eccentric, and only 7% of the 55 lesions in stable patients. Concentric, type I eccentric, and multiple irregularities were all more frequent in stable angina patients. When the lesion responsible for the clinical syndrome could be identified, it was type II eccentric in 71% of the 41 unstable and in 16% of the 25 stable angina patients. The authors postulated that the type II eccentric lesion represented a ruptured plaque or a partially occlusive thrombus [16, 17].

Bresnahan et al. examined retrospectively 268 consecutive coronary arteriograms [35]. A thrombus was identified in 35% of 67 patients with unstable angina and in only 2.5% of the 201 with stable angina patients. Capone et al. also described intracoronary thrombus in 37% of 119 unstable angina patients and in none of 35 patients with stable angina patients [36]; a thrombus was present more likely in angiograms obtained within 24 hours after the last episode of chest pain, marking a more acute disease. Williams et al. [37] and Cowley et al. [38] described thrombi and complex plaques in 61 and 84% of patients with unstable angina respectively.

The TIMI-3A study was designed to characterize the anatomy of the culprit coronary artery lesions in unstable angina and non-Q-wave myocardial infarction within 24 hours after the onset of pain and again 24 hours after treatment with tissue plasminogen activator plus heparin or with heparin alone [39]. Ninety-seven of the 306 patients enrolled had a non-Q-wave myocardial infarction. A perfusion grade TIMI-0 was observed in 18% of patients and was rarely caused by a chronic occlusion (< 3%). Collaterals were seldom well developed. A thrombus was apparent in 35% of the culprit lesions and possible in 40%; it was more frequent in patients with non-Q-wave myocardial infarction. Twelve percent of the culprit lesions were ulcerated and 45% eccentric. A thrombus was frequently associated with an ulceration but was rarely seen in very eccentric plaques. Examples of apparent and possible thrombi are shown in Figs. 2 to 7 and of plaque ulceration in Figs. 1 and 6.

In the TIMI-3A study, t-PA plus heparin resulted in no significant further improvement compared to heparin alone. However, the improvement was greater with t-PA in lesions containing apparent thrombus (36 versus 15%, $p < 0.01$) and in patients with a non-Q-wave myocardial infarction (33 versus 8%, $p < 0.005$).

The appearance of unstable angina is a clinical indicator that an underlying coronary lesion has progressed. In a previous study [33], progression of coronary lesions could be documented in 29 of 38 patients with unstable angina as compared to 12 of 38 matched patients with stable angina. The progression was often proximal, involving major vessels; it was also often in previously normal or minimally stenosed segment and could be multifocal, indicating accelerated atherosclerosis (Fig. 10). Fig. 1 illustrates such an example. Ambrose et al. described similar findings [40] with progression observed in 76% of 25 unstable angina patients and 33% of 21 stable patients ($p < 0.001$); in this study, 18 of the 25 stenoses which progressed had less than 50% lumen diameter reduction at the first angiogram; the progression was to complete coronary occlusion in 8 instances and 12 of the remaining 17 lesions showed a type II eccentric lesion. Plaque rupture with superimposed thrombus, often at the site of a mild lesion, thus accounts for the abrupt worsening of myocardial ischemic symptoms.

Angiographic studies performed during the acute phase have the obvious limitation of describing events once they have occurred. Further, the angiographic description is of single moment of a dynamic pathophysiologic process. The findings of angiography may thus vary depending on the time it is performed in relation to the acute event. Questions that can be appropriately asked are: (1) What are the angiographic features of the plaque at risk of progression and of occlusion? (2) What are the evolving changes during the acute process and what are their clinical and prognostic significance? (3) What are the consequences of the remodelling of the plaque?

Angiographic morphology preceding the acute event or the lesion at risk

The differentiation of lesions at higher risk of provoking an acute clinical event from more benign lesions would represent a clear clinical progress and help ori-

Table 2. Usefulness of coronary angiography to predict disease progression, occlusion and myocardial infarction.

Predictors of occlusion	
Extent score	Moise et al. [41]
Severity of stenosis	Moise et al. [41]
	Ambrose et al. [46]
	Waters et al. [20]
	Alderman et al. [42]
	Jost et al. [43]
Predictors of occlusion with myocardial infarction	
Extent score	Moise et al. [41]
Disease progression	Moise et al. [53]
	Bissett et al. [55]
	Waters et al. [56]
More severe lesion	Ellis et al. [15]
	Alderman et al. [42]
Less severe stenosis (± 50% stenosis)	Singh et al. [44]
	Ambrose et al. [46]
	Taeymans et al. [6]
	Little et al. [45]
	Waters et al. [20]
	Giroud et al. [47]
Lesion morphology	
Lesion roughness	Ellis et al. [15]
Conditions favoring flow turbulence	Taeymans et al. [6]
	Ellis et al. [15]
Predictors of progression without occlusion	
Extent score	Moise et al. [49]
	Nikkuta et al. [52]
Size of vessel (> 2 mm)	Jost et al. [61]
Right coronary artery	Jost et al. [61]
	Alderman et al. [42]
Not related to the severity of initial stenosis	Waters et al. [20]

ent the treatment of patients. Attempts have been made in that direction using descriptors of lesion severity, extent score of disease and lesion morphology. One should realize that the descriptors of progression may not be necessarily the same in less severe and in more severe lesions (Table 2) and also in progression to occlusion with or without a clinical event (Table 3).

Lesion severity

Progression to occlusion

Moise et al. described, in a large series of 313 patients with iterative coronary arteriograms, 39 ± 25 months apart, that the initial degree of obstruction could predict the new coronary occlusions that were found in 98 patients [41]. Alderman et al. in a recent review of data from the CASS study [42], and Jost et al. [43] in a prospective study also correlated progression to occlusion with the initial severity of the stenoses.

Progression to occlusion and myocardial infarction

In a prospective more recent trial, 335 patients had coronary arteriograms 2 years apart [20]. A new angiographic occlusion occurred in 58 patients (17%); the risk of occlusion could also be correlated with the severity of the initial stenosis, as illustrated in Fig. 11. The risk was less than 1% with initial stenosis less than 40% and increased to 1.7, 5.8, 12 and 25% for lesions 40–49%, 50–59%, 60–69% and > 70 diameter stenosis respectively. The new occlusion was, however, associated with a myocardial infarction in only 13 patients (22%); in these patients, the stenosis was less severe at the first angiogram as compared to patients who developed occlusion without infarction (Fig. 12).

Another study by Singh et al. also showed that 48% of the new occlusions that cause an acute clinical syndrome occurred in previously normal or minimally diseased segments [44]. Little et al. reported 42 consecutive patients who had an arteriogram at some point before their myocardial infarction, with a restudy within 1 month after the infarction [45]; a newly occluded artery was found in 29 patients; 19 of these new occlusions had occurred in lesions with less than 50% lumen diameter reduction on the first angiogram and in all but 1, at a site of a stenosis less than 70% lumen diameter reduction. Interestingly, the new thrombotic occlusion was at the site of the most severe stenosis in the same patient in only 10 of the 29 patients. Ambrose et al. studied 38 patients with progression of coronary artery disease between 2 cardiac procedures, 23 with an interim myocardial infarction and 15 without an interim clinical event [46]. Progression or occlusion associated with a myocardial infarction occurred in previously normal segments (30% of patients) or in segments with less than 70% narrowing (78% of patients). Conversely, occlusions without myocardial infarction occurred mostly in segments with a previous significant lesion with more than 70% lumen diameter reduction (61% of segments). Giroud et al studied 92 patients who had undergone coronary angiography before and after an acute myocardial infarction without intervening bypass surgery or angioplasty. The median time between the first coronary angiography and the infarction was 26 months (range 1 to 144). Most

Table 3. Comparison of lesions that occlude to produce infarction to control lesions in the same patient.

	Occlusive lesions (n = 38)	Control lesions (n = 64)	p value
Qualitative features			
Division of branch	29 (76%)	33 (52%)	< 0.05
Irregular contours	18 (47%)	43 (67%)	0.05
Asymmetry	24 (57%)	41 (64%)	NS
Intraluminal defects	0 (0%)	0 (0%)	...
% stenosis (visual analysis)	53.7 ± 21	43.6 ± 19.4	< 0.01
Quantitative measurements			
Minimal diameter (mm)	1.55 ± 0.6	1.76 ± 0.6	NS
Length of stenosis (mm)	7.16 ± 3.1	7.09 ± 3.1	NS
Lumen diameter reduction (%)	47.5 ± 17.8	41.0 ± 12.5	< 0.05
Asymmetry index	0.46 ± 0.28	0.44 ± 0.29	NS
Inflow angle (°)	21 ± 10	16 ± 7	< 0.05
Outflow angle (°)	20 ± 10	16 ± 8	< 0.05

From Taeymans Y, Théroux P, Lespérance J, Waters D. Quantitative angiographic morphology of the coronary artery lesions at risk for thrombotic occlusion. Circulation 1992; 85: 78–85, with permission of the authors and the American Heart Association [6].

patients had 1- or 2-vessel disease at first angiography and 78% of segments responsible to the infarction were not significantly stenosed, particularly when the interval between the first angiogram and the infarction was long [47].

Progression to occlusion thus can occur in minimally or severely diseased vessels but is more frequent in the latter. Occlusions leading to myocardial infarction clearly occur at sites of less severe stenosis whereas progression to total occlusion but no infarction usually occurs in segments with more severe stenosis. Possible explanations can be the presence of protecting collateral circulation in most severe stenoses and their absence in less severe stenoses and also the preconditioning effect of repeated episodes of transient ischemia. An alternative explanation could be different pathophysiologic mechanisms for progression in less severe and in more severe stenoses with more frequent acute plaque rupture and thrombus formation in the former. It should also be noted that most of the studies concerning the evolution of coronary artery lesions are based on patients who have undergone two coronary angiograms, many of them for clinical reasons, introducing a selection bias which significance is difficult to quantitate. Many of the patients with a high risk significant lesion possibly were more likely to be treated by a revascularization procedure and thus were excluded from the cohort of patients subsequently submitted to a second angiography. Also, the number of non-significant lesions is always greater than the number of significant lesions, shifting the likelihood of an event to non-significant lesions.

Progression without occlusion

Progression of disease without new occlusion appears, on the other hand, unrelated to the initial severity of stenosis and occurs as frequently in less severe as in more severe stenosis (Fig. 13) [20]. The explanation could be the multifactorial factors involved in atherosclerosis. The acute coronary syndromes mark plaque activation and rapid progression of disease, expressing the extreme of the von Rakitowsky incrustation hypothesis of thrombosis as the precipitating event for atherosclerosis. Lipids and other risk factors are critical in subclinical progression as expressed by the Virchow hypothesis of lipid infiltration for the etiology of atherosclerosis. Coronary angiography in these circumstances will not identify the cellular events leading to atherosclerosis. It will image its consequences, the appearance and progression of the atherosclerotic plaque. An extent score of the disease and morphologic features of the plaque have been used to describe this process.

Extent score

Coronary angiography remains the gold standard to evaluate the significance of coronary artery lesions. It allows identification of the more severe stenosis that causes angina and helps decide optimal therapy and the feasibility of coronary angioplasty. Left main disease, or equivalents, is associated with impaired prognosis which is improved by bypass surgery. This important clinical impact of coronary angiography resulting in interventions with immediate benefit for the patients has obscured other important information that angiography can provide on the extent of atherosclerosis. Various semi-quantitative methods of evaluation have been proposed to account for these findings, including the Friesinger [48] and the Gensini [49] scores; most of these scores, however, emphasized mainly the severity of lesions.

An extent score was shown to be extremely useful to predict progression of coronary artery disease and long-term prognosis in various clinical circumstances [50]. This score is formulated as the simple mathematical addition of all diseased coronary artery segments with a stenosis 75% or less lumen diameter reduction. Thus, a patient with a 40% stenosis in each of the 3 major coronary arteries and with no other lesions, would have an extent score of 3 but zero-vessel disease according to the standard clinical classification.

This extent score defining the number of mild to moderate lesions with a potential for progression or occlusion is not based on a hemodynamic concept but rather reflects the extent of atherosclerotic angiographic involvement and possibly the severity of the underlying disease process. It seems obvious that a patient with 8 or 10 non-occluded stenoses is at higher risk than a patient with 1 or 2. In the original analysis of 313 medically-treated patients with iterative coronary angiographies, only 2 baseline clinical variables could independently predict progression of disease; these were a younger age and a higher extent score [50]. The combination of these 2 variables could identify a high risk group defined by a score ≥ 4 and an age < 50 years (Fig. 14). The 74 patients in this group, compared to the remaining 239 patients had a relative risk of progression at 2 years of 1.52 (95% confidence limits, 0.76–3.06), between 2 and 4 years of 1.51 (1.09–2.09, $p < 0.05$) and after 4 years of 1.6 (1.25–2.02, $p < 0.001$). Fig. 6 is an example of a patient with a high extent score.

Extent score and age can be combined in various ways to stratify risk. A higher score and a younger age increased risk. Higher risk subsets include age < 50 years and score of ≥ 4, age 51 to 60 years, and score ≥ 5 and age 60 to 70 and score ≥ 6. Recent prospective studies have used the higher risk categories to enroll patients in intervention trials aimed at reducing angiographic progression; in one of the trials, 43% of patients showed disease progression over a period of 2 years [51]. The extent score was also the best predictor of long-term progression of disease following coronary angioplasty, past the critical 6-month restenosis period [52]. The INTACT study which included 348 patients in an angiographic progression study also related progression of disease at 3 years to the number of lesions at the baseline angiogram [53].

Prognostic significance of angiographic progression

Angiographic progression marks more active disease, and should therefore herald a worse prognosis. Indeed, the original extent score study involving 313 patients with iterative coronary angiograms, documented that progression was an independent predictor of long-term prognosis [54]. Four-year survival without myocardial infarction was 89% when progression was absent and 73% when it was present ($p < 0.001$). The Program on Surgical Control of the Hyperlipidemias (POSCH) followed 838 patients for a period of 9.7 years [55, 56]. The reduction in blood lipids achieved in this study by partial ileal bypass resulted in significantly lower death and non-fatal myocardial infarction rates compared to placebo. The reduction could not be detected after 3 years, yet coronary angiography, demonstrated a large difference ($p = 0.0008$) in coronary artery progression. Coronary death or myocardial infarction however, in the following 7 years occurred in 25.8% of the 240 patients with progression observed at 3 years as compared to only 11.2% of the non-progressors ($p < 0.001$), for a relative risk of 2.3 and 95% confidence limits of 1.65–3.22 ($p < 0.00000$).

Progression also predicted coronary events in a subsequent 44 ± 10-month follow-up in another trial of 335 patients submitted to coronary angiography after a 2-year placebo-controlled intervention with a calcium antagonist: the relative risk of a coronary event with progression compared to no progression, was 7.34 (95% confidence limits 2.18–2.47) for cardiac death, 2.29 (1.26–4.19) for cardiac death or myocardial infarction, and 1.69 (1.24–2.31) for any coronary event [57]. The independent predictors of cardiac events by Cox multivariate stepwise regression model

were angiographic progression ($p < 0.001$) and ejection fraction ($p = 0.001$).

Thus, extent score predicts progression and progression predicts future cardiac events. Interpretation of coronary angiograms should account for these new descriptive features considering that it is now possible to delay disease progression with an aggressive program of control of risk factors [58–60]. Prevention of disease progression may also be more marked in stenoses 50% or less lumen diameter reduction, coinciding with the critical degree of stenosis for myocardial infarction to occur [61].

Lesion morphology

The relation existing between lesion morphology, progression of disease and future coronary events have been examined in only a few studies. Some plaque features may however have a prognostic value.

Ellis et al. used the data bank of the Coronary Artery Surgery Study to compare 118 medically-treated patients who developed an anterior myocardial infarction within 3 years of follow-up and 141 patients matched for similar coronary anatomy who did not infarct [15]. The left anterior descending lesions were compared in the 2 study groups using 17 different morphologic characteristics. Luminal roughness was the strongest predictor of subsequent occlusion and infarction. The multivariate analysis also retained lesion length and severity of baseline stenosis as risk factors. Although ulceration and thrombus were also predictive, these were infrequent findings usually associated with lesion roughness, and were not retained as independent predictors.

A study from the Montreal Heart Institute looked at a series of patients who had coronary angiography before and shortly after an acute myocardial infarction to compare the 38 coronary artery lesions which provoked an infarction to 64 control lesions in the same patients which did not occlude [6]. Lesions were analyzed both qualitatively and quantitatively. The results of the various comparisons are listed in Table 3. The mean diameter reduction of lesions that occluded was greater than lesions that did not, but was in the range of non-significant lesion, 47.5 ± 17.8 versus $41.0 \pm 12.5\%$ for the control lesions. The inflow and outflow angles were significantly steeper in lesions that occluded. The presence of a division branch within the vicinity of the stenosis was also more frequent and observed in 76% of the lesions that occluded compared to 52% of the control lesions ($p < 0.05$). The morphologic features of the stenosis at risk thus shared common characteristics that increased shear stress and flow separation, enhancing the risk of plaque rupture and fissure and subsequent occlusion. Examples of a division branch in the stenosis can be seen in Figs. 3 and 6A.

Other features associated with a higher risk of occlusion have been described. These are longer and more irregular lesions and lesions located at sites of an angulation or bending of 45° or more [15]. Progression may also be more frequent in larger (> 2 mm) arteries, in stenoses located in a proximal or mid-artery position and more particularly in the right coronary artery [42, 62].

The predictive value of many of these findings remains to be documented in prospective studies. Although the correlation is statistically significant, the overlap is sometimes important, limiting the clinical usefulness for individual patients. In addition, systemic factors such as smoking and hypercholesterolemia, coagulation factors, platelet function and fibrinolytic activity, as well as other local morphologic factors not appreciated by arteriography, such as the integrity and durability of the fibrous cap, and the composition of the plaque, contribute to the risk of coronary occlusion [63]. These various factors have been reviewed in depth by Fuster [64]. Bogaty et al. recently tested the hypothesis that the clinical manifestations of ischemic heart disease did not occur randomly on similar pathologic background; they compare the angiographic findings of 55 patients with acute myocardial infarction as first manifestation of disease, and of 47 patients with stable angina for at least 2 years after the angiogram [65]. Patients with unheralded myocardial infarction in this study were younger and, by definition, had a shorter duration of clinical disease. At angiography, they had fewer diseased vessels and less extensive disease compared to patients with uncomplicated stable angina.

Angiographic morphology following the event

Morphologic changes and prognostic significance of complex lesions

The presence of complex lesions or of angiographic evidence of thrombus has been correlated with in-hospital outcome in patients with unstable angina. In a first series of 101 consecutive patients with unstable angina reported by Williams et al., the complex features carry a higher risk of in-hospital death, myocar-

dial infarction, and revascularization procedures, independently of the number of diseased vessels [37]. These authors subsequently reported in a study involving randomization to early or delayed angiography, that the presence of an intracoronary thrombus required more often urgent arteriography because of recurrent symptoms [23]. Cardiac events occurred in 73% of patients with thrombus, 55% of patients with complex morphology and in 58% of patients with multivessel disease, compared to respectively 17, 31 and 7% of patients without these features.

In another study which included patients with lesions 50% or more lumen diameter reduction, the presence of a complex morphology in 58 unstable angina patients resulted in an unfavorable clinical outcome in more than half the patients and its absence in 30 patients resulted in events in only 6% [66]. The presence of silent ischemia on Holter monitoring further impaired prognosis in this study. The ulceration index of Davies et al. predicted clinical instability to require urgent intervention in 11 of the 15 patients with an index greater than 6; 49 of the 57 patients with an index smaller than 6 had an uncomplicated course [19].

Reocclusion after successful thrombolysis is an important clinical problem associated with a 3-fold increase in in-hospital mortality and further deterioration of left ventricular function [67]. Early suboptimal reperfusion as determined by a TIMI-2 flow [67, 68] or intermittent patency [68] is associated with a higher risk of reocclusion at 1 week [67] and of recurrent ischemic events during the hospital course [68]. Failure of a lesion to achieve a concentric configuration within 24 hours after thrombolysis was also associated in a small study with a higher risk of clinical events [69]. A large study of 192 patients however failed to show a correlation between in-hospital ischemic events present in 21% of patients and the prospectively described angiographic findings 90 minutes after onset of thrombolytic therapy of TIMI flow grade, % diameter stenosis, minimal diameter, presence of a thrombus, diffuse disease or ectasia in the infarct-related artery or Ambrose morphology [70]. These observations may not be surprising considering that the morphology of the culprit lesion during the acute phase can be highly variable and largely determined by the rapid change in plaque composition associated with the acute phase of myocardial infarction and with thrombolysis. Occlusion may also occur after hospital discharge; angiography performed after 3 or 6 months have demonstrated late reocclusion in 25 to 30% of infarct-related arteries [71, 72]. One study of thrombolysis followed by angioplasty documented reocclusion in 71% of patients with a residual thrombus visualized before the angioplasty procedure compared to 4% of patients with no apparent thrombus [73].

The risk of acute complication of coronary angioplasty is also enhanced in complex lesions. Among 1,423 consecutive angioplasty patients from the Thoraxcenter [74], occlusion during the procedure occurred in 5.6% of patients and in an additional 1.7% within 24 hours. The 3 independent predictive variables were unstable angina before angioplasty, multivessel disease and complex lesions. In another series of 1000 lesions in 533 consecutive patients treated by angioplasty, the presence of an intracoronary thrombus was the only independent morphologic predictor of complications [75]. In the report from the Mayo Clinic, complete occlusion complicated the procedure in 11 of 15 cases with an intracoronary thrombus with no intimal dissection visualized, whereas complete occlusion developed in only 18 of 223 patients with no thrombus, most of these patients showing an intimal tear [76].

Intravascular ultrasound to visualize vessel wall

Coronary arteriography provides only a view of the morphologic features of coronary lesions defined by the endovascular boundaries. Coronary angioscopy may reveal more subtle features of surface pathoanatomy, such as presence of subocclusive thrombus [77] and more information based on tissue visualization [78]. Intravascular ultrasound goes a step further, by revealing the structures throughout the entire thickness of the vessel wall [79]. Intravascular ultrasound images obtained in vitro correlate well with both histology and quantitative angiographic measurements [80, 81]. Morphologic features as assessed by ultrasound in angioplasty patients appeared useful in predicting clinical outcomes [82, 83]. Future studies will determine whether lesion characteristics as defined by intracoronary ultrasound can predict plaque rupture, progression or regression of the lesion. An exciting approach for the future that could provide information on the fine structure could be tissue characterization using vascular magnetic resonance imaging.

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