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Angiographic Morphology and the Pathogenesis of Unstable Angina Pectoris

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In 110 patients with either stable or unstable angina, the morphology of coronary artery lesions was qualitatively assessed at angiography. Each obstruction reducing the luminal diameter of the vessel by 50% or greater was categorized into one of the following morphologic groups: concentric (symmetric narrowing); type I eccentric (asymmetric narrowing with smooth borders and a broad neck); type II eccentric (asymmetric with a narrow neck or irregular borders, or both); and multiple irregular coronary narrowings in series. For the entire group, type II eccentric lesions were significantly more frequent in the 63 patients with unstable angina ($p < 0.001$), whereas concentric and type I eccentric lesions were seen more frequently in the 47 patients with stable angina ($p < 0.05$).

Type II eccentric lesions were also present in 29 of 41 arteries in patients with unstable angina compared with 4 of 25 arteries in those with stable angina ($p < 0.0001$) in whom an "angina-producing" artery could be identified. Therefore, type II eccentric lesions are frequent in patients with unstable angina and probably represent ruptured atherosclerotic plaques or partially occlusive thrombi, or both. A temporary decrease in coronary perfusion secondary to these plaques with or without superimposed transient platelet thrombi or altered vasomotor tone may be responsible for chest pain in some of these patients with unstable angina.

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In unstable angina pectoris, patients often present with acute onset of chest pain or rapid progression of symptoms. In some cases, these presentations may indicate a decrease in coronary blood flow rather than an increase in myocardial oxygen demand as the primary mechanism for chest pain. Even though the clinical manifestations and pathophysiology of ischemia in unstable angina may differ from those of stable angina (1), quantitative coronary anatomic variables are similar. Angiographic comparisons of the coronary anatomy in patients with unstable angina have shown no significant differences from patients with stable angina in terms of the number of diseased vessels and the degree of obstruction (2,3).

Although differentiation on the basis of quantitative variables has not proven helpful, the qualitative appearance of coronary lesions in unstable angina is unknown. The qualitative appearance of coronary lesions on postmortem angiography as demonstrated by Levin and Fallon (4) has provided important information concerning the pathologic significance of various coronary lesions. Qualitative analysis of coronary morphology at cardiac catheterization may provide a foundation for the angiographic stratification of patients with coronary artery disease on the basis of clinical presentation.

Methods

Patient selection. Between June and September 1983, the history and coronary angiograms of all patients referred to cardiac catheterization for evaluation of angina pectoris or for angioplasty were prospectively reviewed. The history was obtained before catheterization by either one of two cardiologists. The coronary angiograms were reviewed by three experienced angiographers unaware of the historical data. The criteria for exclusion of patients with coronary artery disease or angina pectoris from the study included the following: normal coronary arteries or nonobstructive coronary artery disease (<50% obstruction), concomitant

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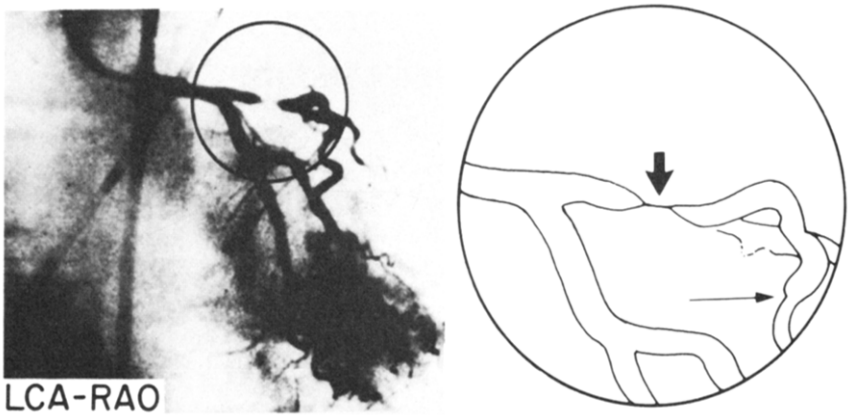

Figure 1. Representative left coronary angiogram (LCA) and schematic diagram of a concentric coronary stenosis. There is a severe stenosis of the proximal left anterior descending artery as seen in the right anterior oblique (RAO) projection. The **thick arrow** indicates the concentric lesion; the **thin arrow** indicates the distal left anterior descending artery.

valvular or nonischemic cardiomyopathy, acute infarction with entry into a streptokinase reperfusion trial or atypical or unclear history.

Patient classification. Patients were classified as having stable angina pectoris if they manifested one of the following: 1) typical exertional angina (class I or II) relieved by rest or nitroglycerin with stable symptoms; 2) slowly progressive exertional angina (increasing by less than two Canadian Heart classifications) without pain at rest; or 3) severe stable angina (class III to IV), including chronic pain at rest (>6 months' duration) and no recent change in symptoms.

Patients were classified as having unstable angina pectoris if they manifested one of the following: new onset of chest pain at a low work load (class III) or at rest (class IV) of less than 6 months' duration, crescendo angina defined as an *abrupt increase* in angina (≥ two Canadian Heart classifications) within 6 months of catheterization or in a patient with previous stable angina or recent (< 2 weeks) well documented subendocardial or transmural infarction and recurrent anginal pain at rest in the hospital without serum enzyme evidence of additional infarction.

Study patients. Of the 143 patients who met the criteria for admission into the study, 110 were entered. This included 47 patients with stable angina and 63 patients with unstable angina; no patient had variant angina. All patients were categorized into anginal subsets without knowledge of the coronary anatomy. The most common reason for elimination of the other 33 patients was the inability to clearly

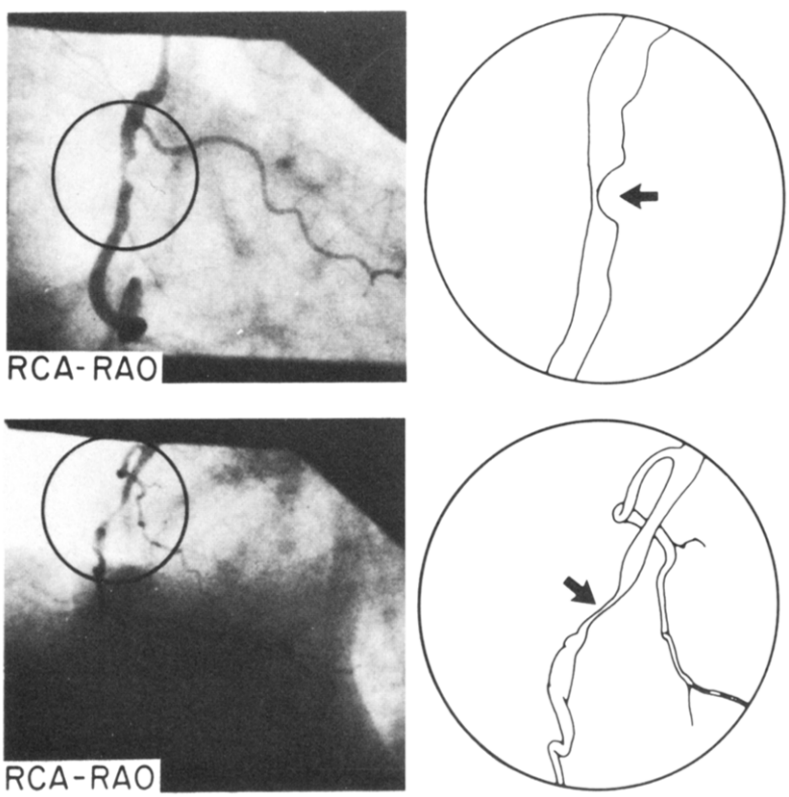

Figure 2. Representative right coronary angiograms (RCA) and schematic diagrams of two different right coronary arteries with type I eccentric lesions. The **arrows** indicate the type I eccentric lesion.

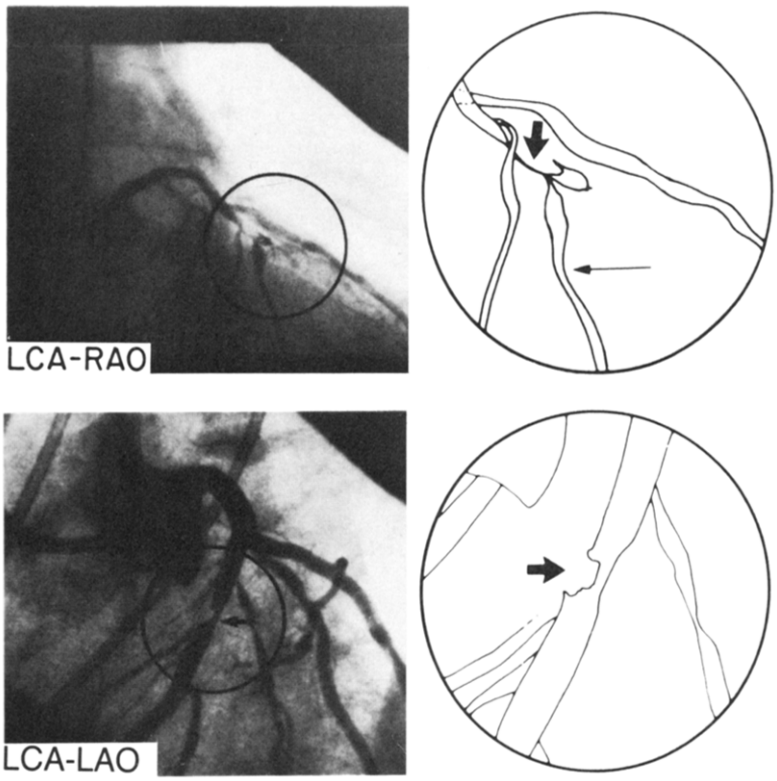

Figure 3. Representative left coronary angiograms (LCA) and schematic diagrams of two different left anterior descending arteries with type II eccentric lesions. The **thick arrows** indicate the lesions; the **thin arrow** indicates the distal left anterior descending artery. LAO = left anterior oblique projection, RAO = right anterior oblique projection.

delineate coronary morphology because of poor film quality or overlapping vessels (21 patients). We were unable to classify the anginal history in only five patients. In high quality coronary angiograms in two patients, it was impossible to classify the morphology of the coronary lesion.

There were no age or sex differences in the 47 patients with stable angina as compared with the 63 patients with unstable angina. Risk factors for coronary artery disease were equally distributed among both groups.

Coronary arteriography. All coronary angiographic studies were performed from either the brachial or femoral approach using standard catheters and techniques. Each coronary artery was selectively viewed in at least two projections. Nitroglycerin was not used routinely during each procedure. Left ventriculography was performed in the right anterior oblique projection, and five standard left ventricular wall segments were qualitatively analyzed as normal, hypokinetic, akinetic or dyskinetic.

All coronary obstructions were traced on transparent paper in two views by the same angiographer, and each obstruction was measured with a millimeter ruler and compared with the "normal" proximal, juxtaposed segment. The percent stenosis of an obstruction was taken as the more severe of the two measurements. Only obstructions reducing the diameter of the coronary artery by 50% or greater and occurring in the major coronary branches were tabulated. When more than one stenosis was present in the same artery, both were measured and the most severe obstruction was

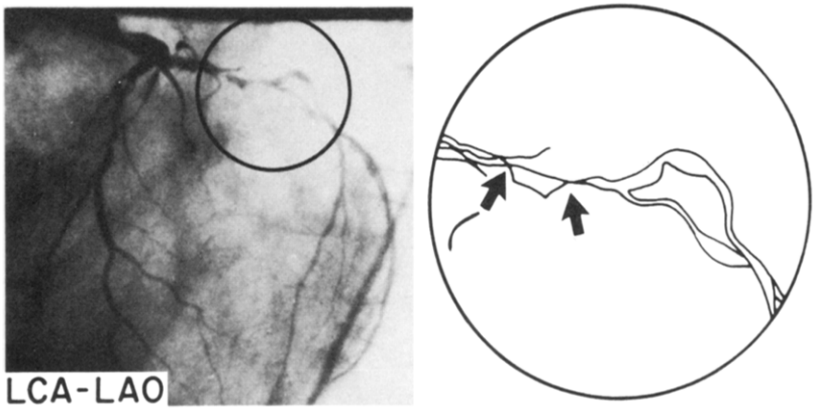

Figure 4. Representative left coronary angiogram (LCA) and schematic diagram of multiple irregularities in the left circumflex artery. The **arrows** indicate severe obstructions in the proximal portion of the left circumflex artery. LAO = left anterior oblique projection.

Table 1. Angiographic Characteristics of 110 Patients With Stable or Unstable Angina Pectoris

	Stable Angina Pectoris (n = 47)	Unstable Angina Pectoris (n = 63)
No. of vessels with ≥ 50% obstruction	91	121
Distribution of coronary artery disease		
One vessel	12 (25%)	22 (35%)
Two vessel	22 (47%)	25 (40%)
Three vessel	13 (28%)	16 (25%)
Distribution of coronary arteries with ≥ 50% stenosis		
Left main	5 (6%)	4 (3%)
Left anterior descending	36 (40%)	45 (37%)
Left circumflex	25 (27%)	29 (24%)
Right	25 (27%)	43 (36%)
No. of totally obstructed vessels	36 (40%)*	29 (24%)
No. of vessels with ≥ 50% and < 100% obstruction	55 (60%)	92 (70%)
Mean % of stenosis (±SD) in vessels with ≥ 50% and < 100% obstruction	79.7 ± 13.7	79.8 ± 11.8
Presence of collateral vessels	21 (23%)	18 (28%)
Calcified obstructions	6 (7%)	16 (25%)

*p < 0.05 by Student's *t* test. SD = standard deviation.

utilized. Calcification of coronary obstructions as well as the presence of any coronary collateral vessels filling the vessel distal to the obstruction were recorded. The same cinefilm viewer (Tagarno) was used for viewing all coronary angiograms.

Coronary morphology. Coronary lesions were morphologically classified as follows by a consensus of the same three angiographers on the basis of qualitative analysis of each lesion in at least two projections:

1) *Concentric stenosis*: symmetric narrowing of a coronary artery. The borders of this lesion were smooth or only slightly irregular (Fig. 1).
2) *Eccentric stenosis*: asymmetric narrowing of a coronary artery. Two subgroups of eccentric lesions were categorized:
   a. *Type I eccentric lesion*: any asymmetric stenosis with smooth borders and a broad neck (Fig. 2).
   b. *Type II eccentric lesion*: an asymmetric stenosis usually in the form of a convex intraluminal obstruction with a narrow base or neck due to one or more overhanging edges or borders that were very irregular or scalloped (Fig. 3).
3) *Multiple irregularities*: three or more serial and severe (≥ 70%) closely spaced obstructions in a coronary artery. This classification also included coronary arteries with severe diffuse irregularities or arteries in which the segment of a coronary artery between two severe obstructions also exhibited significant diffuse luminal irregularities (Fig. 4).

Reproducibility for classifying a stenosis in its morphologic subset was determined by repeat evaluation of 54 films without knowledge of the first reading. Ninety-seven percent of all stenoses, including all type II eccentric lesions, were read in an identical fashion. In the other 3%, the second reading was utilized for analysis of data.

"Angina-producing" coronary artery. In all patients, an attempt was made to localize the coronary artery with 50% or more and less than 100% obstruction that was responsible for the anginal syndrome and characterize its morphology. This artery was classified as the "angina-producing" artery. Determination of this presumed angina-producing coronary artery was possible in 66 of the 110 study patients.

This artery was characterized in the following manner. In the 32 patients with significant one vessel disease, this vessel was designated as the "angina-producing" artery. An angina-producing artery was also identifiable in 34 patients with multivessel disease by one of the following criteria: reversible ST-T changes on electrocardiograms obtained during anginal episodes at rest localized the angina-producing artery in 13 patients, while reversible thallium

Table 2. Angiographic Morphology of Coronary Artery Obstructions ≥ 50% and < 100% in All 110 Patients

	Stable Angina Pectoris (n = 47)	Unstable Angina Pectoris (n = 63)
No. of vessels	55	92
Concentric	26 (47%)†	24 (26%)
Type I eccentric	19 (35%)*	16 (17%)
Type II eccentric	4 (7%)	50 (54%)‡
Multiple irregularities	6 (11%)*	2 (2%)

*p < 0.05, †p < 0.01, ‡p < 0.001 by Student's *t* test.

Table 3. Angiographic Characteristics of Coronary Obstructions ≥ 50% and < 100% in "Angina-Producing" Arteries

	Stable Angina Pectoris (n = 25)	Unstable Angina Pectoris (n = 41)
Distribution of coronary artery disease		
One vessel	9 (36%)	20 (49%)
Multivessel	16 (64%)	21 (51%)
Mean % stenosis (± SD)	85.0 ± 9.9	84.0 ± 10.2
Presence of collaterals to "angina-producing" arteries	2 (8%)	4 (10%)
Calcified obstructions	7 (16%)	5 (12%)

SD = standard deviation.

perfusion defects on exercise testing localized this artery in 4 additional patients. In patients with a significant obstruction in a left anterior descending artery without obstruction in a large circumflex branch, isolated anterior precordial ST-T changes localized the left anterior descending artery as the angina-producing vessel. In patients with a significant obstruction in a dominant right coronary artery without obstruction in a large circumflex branch or in a left anterior descending artery that "wrapped" completely around the apex, isolated inferior ST-T changes localized the right coronary artery as the angina-producing vessel.

Angiographic analysis localized this artery in the remaining 17 patients. Eight of these patients had a prior history of myocardial infarction and one or more totally occluded arteries subserving akinetic myocardium. The remaining vessel with a significant obstruction was designated as the angina-producing artery if it supplied normal myocardium. In the remaining nine patients, all coronary obstructions of a given patient had the same morphology. The artery with the most severe obstruction was arbitrarily chosen as the angina-producing artery. In no patient with two significant obstructions in a single vessel was this vessel included as an angina-producing artery if the morphologic classifications differed.

Statistical analysis. All analyses between groups were performed using the two tailed Student's *t* test or chi-square analysis. Significance was defined as a probability (p) value of less than 0.05.

Table 4. Angiographic Morphology of ≥ 50% and < 100% Coronary Artery Obstructions in "Angina-Producing" Arteries

	Stable Angina Pectoris (n = 25)	Unstable Angina Pectoris (n = 41)
Concentric	12 (48%)*	6 (15%)
Type I eccentric	8 (32%)	6 (15%)
Type II eccentric	4 (16%)	29 (71%)†
Multiple irregularities	1 (4%)	0

*$p < 0.005$, †$p < 0.001$ by Student's *t* test.

Results

Coronary arteriographic findings. The findings at coronary arteriography in all 110 patients with stable and unstable angina are listed in Table 1. There were 91 vessels with significant obstruction in the stable angina group compared with 121 significantly obstructed vessels in the unstable angina group (1.9 coronary obstructions/patient in both groups). There were more totally occluded vessels in the stable than in the unstable angina group ($p < 0.05$); however, the incidence of one, two and three vessel disease and the distribution of coronary obstructions were similar. In addition, the percent stenosis for all nontotally occluded arteries in the stable and unstable angina groups was not significantly different.

Coronary morphology. Morphologic findings at coronary arteriography in vessels with less than 100% obstruction are listed in Table 2. Two by four chi-square analysis revealed a significant difference in the coronary morphology between the groups with stable and unstable angina ($p < 0.001$). Concentric and type I eccentric lesions were more frequent in patients with stable angina, whereas in the group with unstable angina type II eccentric lesions were present in 50 (54%) of 92 vessels ($p < 0.001$).

"Angina-producing" coronary artery. Presumed angina-producing arteries were identifiable in 25 patients with stable angina and 41 patients with unstable angina. The distribution of coronary obstructions and their morphology in these two groups are listed in Tables 3 and 4, respectively. The percent stenosis of the angina-producing artery was similar in both groups. The left anterior descending artery was the most common angina-producing vessel in both groups.

Analysis of coronary morphology revealed that significant differences were present between the two groups (two by four chi-square analysis, $p < 0.001$). Concentric lesions were more prevalent in the group with stable angina ($p < 0.005$). Type II eccentric lesions were present in 29 (71%) of 41 arteries in the unstable angina group and in only 4 (16%) of 25 arteries in the stable angina group ($p < 0.001$). Of the 12 patients in the unstable angina group without type II eccentric lesions in the angina-producing artery, only 2

patients had type II eccentric lesions in other coronary vessels with 50% or more obstruction. The presence of calcium within a coronary obstruction and the presence of coronary collateral vessels to the angina-producing artery were not significantly different between the two groups.

In the unstable angina group, 14 patients had crescendo angina, 23 patients had new onset angina and 4 patients had had a recent myocardial infarction (Fig. 5). Type II eccentric lesions were equally prevalent in new onset and crescendo angina and as frequent in unstable angina of less than 2 months' duration as in unstable angina of longer duration, in patients with or without chest pain at rest and in patients with one vessel versus multivessel disease. In addition, within the group with unstable angina, there were no demographic or angiographic differences in the 29 patients with type II eccentric lesions compared with the 12 patients without these lesions. Finally, within the group of 29 patients with significant one vessel disease and an identifiable angina-producing artery, 16 of 20 in the unstable angina group had type II eccentric lesions compared with 1 of 9 in the stable angina group ($p < 0.001$).

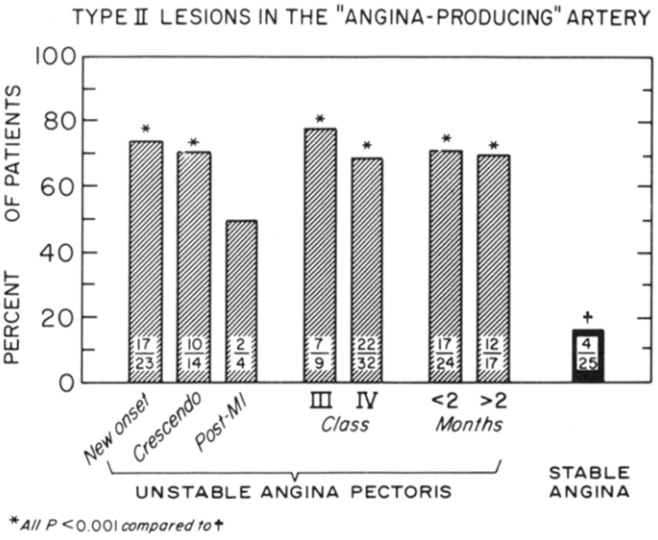

Figure 5. Graph showing the distribution of type II eccentric lesions in different subgroups of patients with unstable angina. The numbers within the **bars** indicate the number of eccentric lesions and the number of patients in each subgroup. MI = myocardial infarction.

Discussion

Unstable angina is a clinical syndrome characterized by the new onset of chest pain at a low work load or at rest, crescendo angina or any prolonged anginal pain at rest without infarction (5). Analysis of coronary anatomy in unstable angina revealed the distribution of coronary lesions, number of diseased vessels and percent stenosis to be similar to those in patients with stable angina. However, because these studies did not identify the coronary anatomy before the onset of unstable angina, their significance is unclear. Recently, Moise et al. (6) found progression of coronary artery disease in 29 (76.3%) of 38 patients with stable angina restudied after an episode of crescendo angina with progression in a previously healthy segment in 11 of 38 patients.

Different coronary morphology in unstable versus stable angina. The qualitative appearance of coronary lesions in coronary artery disease has not been well studied. The appearance of coronary lesions on postmortem angiography has been correlated with pathologic findings, but only in patients dying from complications of myocardial infarction or coronary artery bypass surgery (4). Our data suggest a specific morphology on routine coronary angiography in the majority of patients with unstable angina presenting with either new onset or crescendo angina. For the entire group of 110 patients, 54% of coronary obstructions in patients with unstable angina were type II eccentric lesions compared with only 7% of such lesions in patients with stable angina. This type of lesion was also found in 71% of angina-producing coronary arteries in those with unstable angina but in only 16% of arteries in those with stable angina. Furthermore, the type II eccentric lesion was the only significant angiographic marker for patients with either new onset or crescendo unstable angina, while the distribution of coronary artery lesions, percent stenosis and presence of collateral vessels were similar between patient subgroups. Because the number of patients with unstable angina after myocardial infarction was small, the relevance of this lesion in this group requires further study.

Cause of eccentric coronary morphology. The significance of these different morphologies is unknown. On the basis of postmortem angiographic and pathologic correlations by Levin and Fallon (4), stenoses with irregular borders often demonstrate plaque rupture or partially occlusive thrombi. Therefore, it is not unreasonable to postulate that a type II eccentric lesion might represent a ruptured atherosclerotic plaque. Rupture of a plaque could then account for the acute progression of coronary artery disease in these patients as reported by Moise et al. (6). It is also possible that partially occlusive intraluminal thrombi could explain the angiographic appearance of most type II eccentric lesions. Intraluminal thrombi have been described (7,8) in a few patients with unstable angina and nontotally occluded vessels. Recently, Mandelkorn et al. (9) demonstrated dissolution of intraluminal filling defects with streptokinase in a small subset of patients with unstable angina and severe coronary stenoses. However, these thrombi have usually been located just distal to the coronary narrowing and this pattern was present in only two of our patients with unstable angina.

Progression to myocardial infarction. Myocardial infarction is a common sequela of unstable angina, and an-

giographic progression from severe coronary obstruction to total occlusion has been documented (10). Although the mechanisms involved in this progression are unknown, pathologic studies (11,12) in patients dying from acute infarction have revealed a high incidence of thrombus overlying a disrupted atherosclerotic plaque. Our study suggests a possible mechanism for this progression in that the exposed intimal surfaces of these irregular stenoses may be foci for platelet aggregation with subsequent thrombus formation (13,14) or possible vasospasm secondary to release of thromboxane A_2, or both (15,16). Furthermore, as the percent stenosis and presence of collateral vessels were similar among patients with stable or unstable angina, transient platelet aggregates or vasospasm on an exposed intimal surface, or both, might be responsible for episodes of ischemic pain at rest in the absence of myocardial infarction. Conceivably, a decrease in perfusion in arteries with these eccentric lesions could be due solely to a decrease in the coronary distending pressure (passive vasomotion) without implicating vasospasm or platelet thrombi (17).

Limitations of the study. *Patients.* In this study, patients with unstable angina were limited primarily to those with new onset or crescendo angina. This included most patients with pain at rest, but excluded a small group (11 patients) with a long history of severe angina and chronic pain at rest (> 6 months' duration) that was included in the stable group. In this latter group, coronary angiography revealed multivessel disease in 8 of 11 patients and there was only 1 patient with a type II eccentric lesion. Therefore, the morphologic findings in new onset or crescendo angina are not applicable to all patients with ischemic pain at rest.

Angiographic analysis and coronary morphology. Our analysis of coronary morphology was purely descriptive. All previous angiographic analyses in unstable angina have not commented on the appearance of coronary lesions. As noted previously, Levin and Fallon (4) performed postmortem angiography in patients dying from complications of myocardial infarction or during coronary artery bypass surgery. They noted that coronary lesions with irregular borders or intraluminal lucencies that were termed "complicated lesions" exhibited plaque rupture or partially occlusive thrombi on pathologic sectioning. Their definition of complicated lesions would probably have included our classification of type II eccentric and multiple irregularities. However, since patient selection and angiographic techniques were not comparable, these differences in morphologic description cannot be resolved at the present time.

Although we suspect that these type II eccentric lesions represent ruptured plaques or thrombi, the significance of the other morphologic subtypes is unclear. Although coronary lesions classified as multiple irregularities may have contained plaque rupture or thrombi, no correlation to new onset or crescendo angina was found. In addition, the length of the stenosis, the minimal cross-sectional area or the effects of serial stenoses were not considered in this study. Therefore, further study in this area appears warranted.

"Angina-producing" artery. The concept of an "angina-producing" artery was developed to localize the coronary obstruction responsible for angina pectoris in patients with single and multivessel disease. Since no patient had variant angina, chest pain was assumed to originate only from vessels with significant obstructions. In the majority of patients (49 of 66), either a single obstruction or ischemic area localized by noninvasive tests was present, whereas in the other 17, indirect methods were utilized. Therefore, the angina-producing artery was probably correctly identified in all patients.

Clinical implications. Unstable angina is intermediate in its presentation between stable angina and myocardial infarction. Although the risk of a subsequent coronary event is higher in unstable angina than in stable angina, the greatest period of risk appears to be soon after the change in symptoms (18). Identification of this patient group at risk for a subsequent coronary event would be extremely important in planning appropriate therapy.

We have shown that the type II eccentric lesion is a common angiographic finding in the majority of patients with either new onset or crescendo unstable angina. We suspect that this lesion is caused by a ruptured plaque or a partially occlusive thrombus, or both, which acutely compromises the coronary circulation and plays an important role as the source of the unstable ischemia. Unfortunately, the natural history of type II eccentric lesions in this study is unknown since most patients with unstable angina had an intervention after angiography. As progression to complete coronary occlusion and myocardial infarction is thought to be related to thrombus formation, the "thrombogenicity" of various morphologic lesions should be a topic of future study. Analysis of coronary sinus blood for the presence of various vasoactive substances may identify the group at highest risk for a subsequent coronary event. It may be prudent, however, in the absence of these data to administer anticoagulants to all patients with new onset or crescendo unstable angina using either antiplatelet or heparin-like agents because most of these patients will have type II lesions. Two recent studies (19,20) that showed a decreased incidence of subsequent coronary events in patients with unstable angina treated with either low dose aspirin or heparin would support this suggestion.

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