Quantitative angiographic morphology of coronary stenoses leading to myocardial infarction or unstable angina

ROBERT F. WILSON, M.D., MYRL D. HOLIDA, B.S., AND CARL W. WHITE, M.D.

ABSTRACT Identification of a characteristic morphology of a coronary stenosis likely to result in myocardial infarction would facilitate the prospective evaluation of infarct prevention strategies and identification of high-risk patients. We postulated that coronary lesions associated with recent myocardial infarction or unstable angina would have an angiographic morphology suggesting disruption of an atherosclerotic plaque and would appear morphologically different from lesions associated with chronic stable angina. To test this hypothesis, quantitative coronary angiography (Brown-Dodge method) was performed in 15 patients 4 to 30 days after myocardial infarction, in 10 patients with the abrupt onset of unstable angina and single-vessel coronary disease, and in 15 patients with chronic stable angina without prior myocardial infarction. Serial arterial diameters (20 to 40) within each lesion were determined and the degree of luminal irregularity was quantitated by calculation of an “ulceration” index. The majority of all lesions analyzed resulted in severe luminal stenosis (mean 78% area stenosis, all groups). Despite small differences in mean lesion severity among groups, overlap in the degree of luminal compromise prevented precise classification of lesions associated with myocardial infarction or unstable angina based on percent stenosis or minimum luminal cross-sectional area. The mean ulceration index of lesions in patients with unstable angina and in the infarct-related vessel in those with acute myocardial infarction was 0.62 ± 0.05 (± SEM) and 0.61 ± 0.03, respectively. These were significantly different from the mean ulceration indexes of lesions in patients with stable angina (0.96 ± 0.01, p<.05) or from indexes of lesions in the noninfarct-related vessel of patients with acute infarction (0.90 ± 0.02, p<.05). None of 10 lesions associated with unstable angina and 14 of 15 infarct-related lesions had an ulceration index less than 0.78. All lesions associated with stable angina and each lesion in the noninfarct-related vessel in patients with infarction had an ulceration index of greater than 0.83. The ulceration index did not vary significantly with the degree of luminal stenosis or prior treatment with thrombolytic agents. These data provide quantitative evidence that lesions associated with myocardial infarction or the abrupt onset of unstable angina are of a similar characteristic angiographic morphology that is suggestive of plaque disruption and not commonly seen in lesions associated with chronic stable angina. The ulceration index may provide a mechanism for the prospective identification of high-risk coronary lesions.


ACUTE MYOCARDIAL INFARCTION usually occurs as a discrete event caused by sudden occlusion of a single coronary artery. Although the occlusion often occurs at the site of a severe atherosclerotic lesion, many patients with acute myocardial infarction have coronary stenoses of equal or greater severity in other coronary vessels that have not occluded. Methods for predicting the occurrence of myocardial infarction have focused primarily on the anatomic distribution of atherosclerotic coronary lesions and, to a lesser extent, on the degree of coronary luminal compromise produced by each lesion. In individual patients, however, the distribution and overall extent of coronary artery disease are only weak predictors of subsequent myocardial infarction and death. Hence, efforts to predict the likelihood that a single coronary lesion will eventuate in myocardial infarction have been generally unsuccessful. This inability to predict the occurrence...
of total occlusion of an individual coronary lesion has hampered our assessment of infarct prevention strategies.

We hypothesized that coronary lesions associated with acute myocardial infarction would be morphologically different from lesions associated with stable angina pectoris. Pathologic studies of coronary stenoses associated with sudden death or myocardial infarction have demonstrated that atherosclerotic plaque disruption (fissuring or hemorrhage) is present in up to 100% of recently thrombosed lesions. Since the angiographic appearance of coronary lesions should reflect their anatomic structure, we postulated that a detailed quantitative evaluation of coronary stenoses associated with these syndromes might reflect underlying disruption of atherosclerotic plaque. The use of thrombolytic therapy for acute infarction has now provided a patient population in whom detailed angiographic evaluation of the morphology of coronary lesions associated with recent acute infarction is now possible. Since patients with the abrupt onset of very unstable angina are known to have a high incidence of rapid progression to myocardial infarction, we also postulated that coronary lesions associated with unstable angina might have a similar morphology to those associated with acute infarction. Recent studies by Falk, in which an 80% incidence of atherosclerotic plaque disruption in patients with unstable angina was found have pioneered this concept.

Angiographic features of atherosclerotic plaque disruption have been qualitatively described. Autopsy specimens of coronary arteries with atherosclerotic plaque disruption have a "complicated" angiographic appearance characterized by irregular arterial borders and intraluminal filling defects. Similar qualitative irregularities of the arterial lumen can be seen on coronary angiograms obtained from patients with unstable angina. Visual interpretation of coronary angiograms obtained in vivo, however, is fraught with marked intraobserver and interobserver variability and prior qualitative studies have not provided an objective basis for the evaluation of the morphology of a stenosis. Moreover, prior angiographic analysis of the morphology of a stenosis in vivo have dealt primarily with lesions associated with unstable angina. In this study, we used Brown-Dodge quantitative coronary angiography to quantitatively define the "irregular" appearance of lesions leading to infarction or unstable angina.

In a preliminary study, we divided coronary stenoses into angiographically complicated and uncomplicated lesions according to the postmortem angiographic definitions of Levin and Fallon. An uncomplicated lesion was defined as one with only one area of narrowing per lesion. A complicated lesion contained multiple areas of narrowing within the same lesion. After these preliminary studies, we found that most coronary lesions contained some degree of luminal irregularity and were, therefore, complicated to some extent. We reasoned that, if the angiographically complicated lesions were the site of a fissured atherosclerotic plaque as pathologists have suggested, then the depth of the fissure (or angiographic ulceration) could be quantitated by comparing the maximal arterial diameter at the site of plaque disruption to the diameter of the vessel just adjacent to the disruption. In addition, we related this angiographic index of ulceration to quantitative measurements of the degree of luminal narrowing.

Methods

Patient characteristics. Patients (n = 40) were selected in a retrospective manner by review of all consultations performed by one of the authors (R. F. W.) from 1982 to 1983. All patients meeting the clinical criteria for study defined below and who underwent coronary angiography within 2 weeks of consultation were included. Each patient had received nitroglycerin (intracoronary or sublingual) before angiography. Five patients were excluded from the study because their angiograms were of insufficient quality for quantitative angiographic analysis. Three angiograms were excluded because they appeared to contain intraluminal thrombus.

Three patient subgroups were studied. The first subgroup comprised 15 patients who underwent coronary angiography within 1 month of acute myocardial infarction and were found to have a patent vessel supplying the infarcted area. Angiograms from 12 of these patients were obtained during routine follow-up coronary angiography performed 4 to 12 days after thrombolytic therapy for acute Q wave myocardial infarction. Three additional patients underwent coronary angiography 14 to 30 days after non-Q wave myocardial infarction, but had not received thrombolytic therapy. Infarction was documented by the triad of a classical clinical history, threefold elevation in total creatine kinase with an elevated creatine kinase-MB fraction, and evolutionary electrocardiographic changes consistent with acute myocardial infarction. The acutely occluded vessel was the left anterior descending in nine patients, the circumflex artery in one patient, and the right coronary artery in five patients. In six of the patients, another stenosis adequate for quantitative studies (i.e., stenosis with patent lumen demonstrated in orthogonal views) was present (two left anterior descending, two circumflex, two right coronary artery).

The second subgroup comprised 10 patients with abrupt onset of unstable angina and with only one coronary lesion with more than 50% diameter stenosis (unstable angina associated with single-vessel coronary artery disease). Unstable angina was specifically defined as (1) the new onset of angina pectoris with angina occurring frequently at rest or (2) the abrupt worsening of previously stable angina pectoris by two New York Heart Association functional classes with angina at rest. The lesion was in the left anterior descending in five patients, in the circumflex artery in four patients, and in the right coronary artery in the remaining patient.

The third subgroup comprised 15 patients with a history of
stable angina, no prior history of myocardial infarction, and with at least one coronary stenosis judged visually to have more than 50% luminal diameter stenosis. The lesion analyzed was in the left anterior descending in nine patients, the circumflex artery in three, and the right coronary artery in three.

**Angiographic analysis.** Angiographic analysis was carried out by two observers who were blinded to the clinical history, electrocardiogram, and left ventriculographic findings. Each coronary angiogram was projected onto a rectilinear grid at 5× magnification and analyzed by quantitative angiography (Brown-Dodge method). Each observer independently traced the outline of each coronary stenosis in two orthogonal projections (e.g., right anterior oblique 60 degrees, left anterior oblique 30 degrees) during three portions of the cardiac cycle. In patients with recent myocardial infarction, we traced the coronary stenosis that had been the site of prior occlusion (the “infarct related” lesion) and, in addition, any other stenosis in a major coronary vessel that appeared to have more than 50% luminal diameter stenosis (the “noninfarct related” lesion). In patients with unstable angina and single-vessel disease, we traced the only significant coronary lesion. In patients with chronic stable angina the most severe coronary stenosis in any major coronary vessel was analyzed.

Each lesion was outlined, digitized, and computer corrected for radiographic pincushion and magnification distortion. An arterial centerline was computer determined. Twenty to forty serial arterial diameters were measured from the onset of luminal narrowing to the end of the lesion. The minimum cross-sectional area, maximal percent area stenosis, and length of each lesion were then calculated by averaging values obtained from each portion of the cardiac cycle. The length of each lesion was measured as the distance between proximal and distal ends of the lesion, beginning and ending with a 10% deviation from the normal vessel area.

To assess the extent of angiographic ulceration, we calculated an “ulceration index.” The ulceration index was defined as the diameter of the least severe narrowing within the lesion (the downward “lip” of the ulcer) divided by the maximum intraluminal diameter (presumably the maximal diameter of the “ulcerated” portion of the vessel; figure 1). This index of ulceration is inversely related to the extent of angiographic ulceration. We calculated this ulceration index for each coronary lesion in all six angiographic frames analyzed. Since the most severe ulceration may be apparent in only one view, the lowest ulceration index obtained from any of six frames analyzed per patient was used for data analysis.

**Data analysis.** Interobserver correlation was determined by the linear regression equation (least square method). Group differences between minimum lesion cross-sectional area, maximum lesion percent stenosis, lesion length, and ulceration index were tested by analysis of variance. A p value of less than .05 was considered statistically significant. Data are reported as mean ± SEM.

**Results**

**Interobserver variability.** Measurements of the maximum percent area stenosis, minimum cross-sectional area, ulceration index, and lesion length made by observer A were highly correlated with those made by observer B: percent area stenosis, r = .90, SEM = 1.9%, slope = 0.87; minimum cross-sectional area, r = .87, SEM = 0.11 mm², slope = 1.05; length, r = .83, SEM = 0.59 mm, slope = 1.09; ulceration index, r = .87, SEM = 0.03, slope = 0.76.

**Quantitative assessment of arterial narrowing.** The degree of luminal compromise produced by the lesions in each group is shown in table 1. The majority of all lesions analyzed resulted in severe luminal stenosis (figure 2). In patients with myocardial infarction, the mean percent area stenosis of lesions in the infarct-related vessel was not significantly different than that of lesions in the noninfarct-related vessel. The mean percent area stenosis of the lesions in patients with unstable angina was similar to that of the lesions in patients with stable angina. The stenoses in those with unstable angina, however, were significantly more severe than lesions in either the infarct-related or noninfarct-related vessels of patients with acute infarction. Despite small differences in mean lesion severity among the groups, there was considerable overlap in the range of luminal compromise produced by individual lesions such that analysis of lesion severity was unable to provide a means of predicting which lesions were associated with unstable angina or acute infarction.

The minimum cross-sectional area of lesions in each group showed the same trends as percent stenosis, but the group differences were not significant (figure 3). This was probably related to variation in the normal size of the vessels studied.

**Ulceration index.** Figure 4 shows the ulceration index calculated for each lesion studied. In patients with myocardial infarction the mean ulceration index of lesions in the infarct-related vessel was 0.61 ± 0.03 and was significantly less than the ulceration index of lesions in the noninfarct-related vessel (0.90 ± 0.02). Hence, in the same patient, lesions which had caused myocardial infarction could be angiographically separated from the other lesions which were not related to the infarction.

The ulceration index in the infarct-related vessel was nearly identical to that found in lesions associated with myocardial infarction in the noninfarct-related vessel. The majority of all lesions analyzed resulted in severe luminal stenosis (figure 2). In patients with myocardial infarction, the mean percent area stenosis of lesions in the infarct-related vessel was not significantly different than that of lesions in the noninfarct-related vessel. The mean percent area stenosis of the lesions in patients with unstable angina was similar to that of the lesions in patients with stable angina. The stenoses in those with unstable angina, however, were significantly more severe than lesions in either the infarct-related or noninfarct-related vessels of patients with acute infarction. Despite small differences in mean lesion severity among the groups, there was considerable overlap in the range of luminal compromise produced by individual lesions such that analysis of lesion severity was unable to provide a means of predicting which lesions were associated with unstable angina or acute infarction.

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TABLE 1
Morphologic features of coronary lesions

<table>
<thead>
<tr>
<th>Group</th>
<th>Ulceration index</th>
<th>Area stenosis (%)</th>
<th>Minimum cross-sectional area (mm²)</th>
<th>Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct-related vessel (n = 15)</td>
<td>0.61 ± 0.03abc</td>
<td>74 ± 3b</td>
<td>1.5 ± 0.20</td>
<td>16.0 ± 1.2abc</td>
</tr>
<tr>
<td>Noninfarct-related vessel (n = 6)</td>
<td>0.90 ± 0.02abc</td>
<td>67 ± 7b,c</td>
<td>2.2 ± 0.42</td>
<td>8.8 ± 1.1b</td>
</tr>
<tr>
<td>Unstable angina (n = 10)</td>
<td>0.62 ± 0.05abc</td>
<td>86 ± 2</td>
<td>0.89 ± 0.15</td>
<td>13.7 ± 1.1</td>
</tr>
<tr>
<td>Stable angina (n = 15)</td>
<td>0.96 ± 0.01c</td>
<td>81 ± 2</td>
<td>1.16 ± 0.12</td>
<td>11.1 ± 0.7</td>
</tr>
</tbody>
</table>

*p < .05 vs myocardial infarction–noninfarct-related vessel; *p < .05 vs unstable angina; c*p < .05 vs stable angina.

with the abrupt onset of unstable angina (0.62 ± 0.05). The mean ulceration index of lesions associated with stable angina (0.96 ± 0.01, p<.01), however, was significantly greater. Moreover, 14 of 15 lesions in the infarct-related vessel, and 9 of 10 associated with unstable angina had ulceration indexes of less than 0.78, whereas all lesions in noninfarct-related vessels and all lesions associated with stable angina had ulceration indexes of greater than 0.83. The ulceration index did not vary significantly with the degree of luminal compromise, the vessel studied, or prior thrombolytic therapy.

Lesion length. Lesions in vessels associated with recent infarction were significantly longer than lesions associated with stable angina (table 1, figure 5). The average length of lesions in the infarct-related vessel was 44% longer than the average length of lesions associated with stable angina and 81% longer than lesions in the noninfarct-related vessel. Lesions causing unstable angina tended to be longer than those associated with stable angina, but the difference was not statistically significant.

Discussion
In this study we have shown that coronary lesions leading to myocardial infarction have a specific angiographic morphology that is uncommon in lesions of similar severity in the noninfarct-related vessel or in
FIGURE 3. Minimum cross-sectional area of lesions in each group. No significant differences exist between groups.

FIGURE 4. Calculated ulceration index (UI) of lesions in each group. The ulceration index of lesions involved in myocardial infarction (MI) or unstable angina (UA) is significantly less than that of lesions uninvolved in infarction or associated with stable angina (SA) (p<.01).
vessels of patients with chronic stable angina pectoris. This morphology is similar to that seen in lesions associated with the abrupt onset of unstable angina.

There are two likely causes of the angiographic morphology we describe — disruption of atherosclerotic plaque and intraluminal thrombus. Either or both of these causes may be responsible. The type of angiographic morphology we identified is clearly consistent with rupture of atherosclerotic plaque. Disruption of the intima of the plaque would allow angiographic contrast material to enter and, in some angiographic views, give the appearance of stenosis ulceration. A previous autopsy study by Levin and Fallon demonstrated that atherosclerotic plaque disruption could be identified by visual inspection of plane-film postmortem angiograms obtained in coronary vessels dissected free from the heart. In their study, 79% of the lesions angiographically characterized by irregular borders and intraluminal lucencies were found to contain atherosclerotic plaque disruption, whereas only 11% of lesions with angiographically smooth borders demonstrated these same pathologic findings. The coronary lesions we observed from cineangiograms obtained from patients with infarction or unstable angina had characteristics similar to those of plaque disruption. Our angiographic analysis quantifies these qualitative observations and provides a quantitative basis for assessing the presence of luminal irregularities previously reported in patients with unstable angina.

The second line of evidence supporting plaque disruption as a cause of this angiographic morphology comes from autopsy studies that have shown a high incidence of plaque disruption in patients with acute myocardial infarction or sudden ischemic cardiac death. Chapman studied longitudinal sections of 19 coronary vessels found to be occluded with thrombus at the time of autopsy and found that “in each of 19 cases, a recent thrombus was found adherent to the torn intimal surface of an atherosclerotic plaque.” Other investigators, employing careful histologic techniques, have also found a high incidence of plaque disruption in coronary arteries associated with acute infarction. Davies and Thomas have additionally reported that 74 of 100 patients suffering sudden ischemic cardiac death had thrombus present in a coronary vessel and that, in 93% of the deaths associated with intracoronary thrombus, atherosclerotic plaque fissuring was evident at the site of thrombus formation.
These studies support the concept that myocardial infarction and intracoronary thrombosis are associated with atherosclerotic plaque disruption.

Intracoronary thrombus might mask rather than produce the angiographic ulceration we observed. Evidence for this is derived from studies of vessels of patients that have undergone thrombolytic therapy for acute infarction. Immediately after thrombolysis, coronary lesions often appear smooth, presumably because thrombus still coats the inside of the vessel. The minimum cross-sectional area of the totally occluded lesion in patients with acute infarction usually increases in the first 10 days after thrombolysis, suggesting that further dissolution of thrombus occurs with time.\(^1^5\) Figure 6 illustrates how thrombus can reside in and disguise plaque disruption. In this angiogram obtained from a patient with acute infarction (before thrombolysis), the thrombus appears to be attached to the coronary wall (right anterior oblique 45 degree view), but plaque ulceration is not evident. Ten days after thrombolysis, however, the ulceration can be clearly seen at the site the thrombus once occupied. Hence, intraluminal thrombus could, in some patients, occupy a plaque fissure and hide its existence on the coronary angiogram. If the morphology we describe resulted from intraluminal thrombus, then the ulceration index of lesions in infarct-related vessels that had undergone thrombolysis should have been higher than that seen in infarct-related vessels of patients who did not receive thrombolytic therapy. Although the numbers of patients in the latter group was small, the ulceration index of both subgroups was nearly identical. Nonetheless, thrombus within coronary vessels studied after myocardial infarction could produce an irregular luminal outline.

An unexpected finding of this study was that coronary lesions associated with unstable angina as a group produced greater luminal narrowing than lesions that had resulted in thrombosis and infarction. Two factors may account for this difference. First, bias in patient selection may have decreased the apparent severity of lesions associated with myocardial infarction. Patients with transmural infarction undergoing initially successful thrombolytic therapy may experience rethrombosis of previously lysed coronary lesions, especially if the residual cross-sectional area of the remaining

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**FIGURE 6.** Coronary angiograms obtained from a patient with acute myocardial infarction. During the initial study a large thrombus can be seen adherent to the vessel wall (right anterior oblique 45 degree view). Ten days later, after thrombolysis, an apparent plaque ulceration is present at the site where the thrombus was attached to the vessel wall. (Figure courtesy of Greg Brown, M.D., Ph.D., University of Washington, Seattle.)
lesion (after thrombolytic therapy) is less than 0.4 mm². Hence, we may have been unable to analyze the morphology of some of the most severe coronary lesions leading to infarction because they had rethrombosed by the time of follow-up angiography. Likewise, lesions having a complicated morphology, but which are not associated with severe restriction of the vessel lumen, might result in unstable angina infrequently. Such lesions, not intrinsically severe, could remain asymptomatic unless thrombosis supervenes. Thus, the population with unstable angina may be limited to patients with severe coronary lesions, while acute infarctions may result from lesions of a wider range of luminal stenosis.

The presence of an unrecognized intraluminal thrombus, laminated against the vessel wall, might also account for these differences in luminal narrowing. McMahon et al. studied coronary stenoses associated with non-Q wave infarction or unstable angina in patients not receiving thrombolytic therapy. The minimum cross-sectional area of lesions causing unstable angina was similar to what we observed in patients with similar clinical histories. McMahon et al., however, observed that lesions associated with non-Q wave infarction (not treated with thrombolytic agents) produced even greater luminal narrowing than lesions associated with unstable angina. Our data show that coronary lesions in infarct-related vessels yield less severe residual stenoses after thrombolysis than lesions that are associated with unstable angina. This suggests that lesions associated with unstable angina are on average more severe than lesions that result in total thrombotic occlusion. Unrecognized laminated intraluminal thrombus, therefore, might be present in lesions associated with unstable angina or non-Q wave infarction. In any event, the finding that coronary lesions associated with the abrupt onset of unstable angina are associated with greater luminal compromise than lesions that lead to myocardial infarction deserves further study.

Our findings also show that coronary lesions leading to unstable angina or myocardial infarction tend to be longer than lesions associated with stable angina. Although there are theoretical reasons to support the concept that longer lesions are prone to thrombosis, residual intraluminal thrombus might have artifactually increased the apparent length of the lesion in the vessels we studied. This finding will require direct anatomic correlation.

Current methods for quantitating the extent of coronary artery disease have not been successful in predicting the subsequent occurrence of coronary occlusion. The clinical importance of specific morphologic features of individual coronary lesions has received little attention, in part because quantification of stenosis geometry has been cumbersome. Detailed evaluation of morphology of stenosis with the use of automated quantitative angiography may, however, soon become clinically feasible. Identification and follow-up of the morphology of stenosis associated with unstable angina or infarction should facilitate prospective evaluation of infarct prevention strategies.

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