Quantitative Angiographic Morphology of the Coronary Artery Lesions at Risk of Thrombotic Occlusion

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Background. Coronary angiography in acute myocardial infarction has revealed complicated atherosclerotic plaque and a high rate of thrombotic occlusion. However, the characteristics of lesions at high risk of subsequent occlusion are not well known.

Methods and Results. In the present study, the qualitative and quantitative angiographic features of 38 coronary artery lesions that occluded within 3 years to cause an acute myocardial infarction were compared with 64 control segments from the same patients that did not occlude. Compared with control lesions, the lesions that occluded were more likely to have a division branch originating within the stenosis (76% versus 52%, p<0.05). The percent lumen diameter reduction was more severe (47.5±17.8% versus 41±12.5%, p<0.05) and the inflow (21±10° versus 16±7°, p<0.05) and outflow (20±10° versus 16±8°, p<0.05) angles of the stenosis were steeper. Time to myocardial infarction after the angiogram interacted with the importance of these features (p<0.02). Thus, paired analysis of the lesions that occluded within 3 months and of the most severe control lesion from each patient showed percent lumen diameter reduction of 62.1±11.5% and 46.4±11.4%, respectively (p<0.001). The length of the stenosis, its asymmetry, and the irregularity of the contours did not help differentiate occlusive from control segments.

Conclusions. Coronary artery lesions at high risk of thrombotic occlusion share common characteristics that favor higher shear stress and flow separation. (Circulation 1992;85:78–85)

Characterization of the morphology of the coronary artery lesions associated with acute myocardial infarction and unstable angina have improved our understanding of the underlying pathophysiological mechanisms.1–4 The major role of coronary artery thrombus formation as the cause of the acute obstruction has been recognized. The mechanism triggering thrombus formation appears to be local and related to rupture of an atherosclerotic plaque.5,6 However, most of our observations are based on studies performed after coronary occlusion has occurred, so the characteristics of the lesions at high risk for thrombotic occlusion are in large part unknown. Identification of such lesions would help explain the pathophysiological mechanisms triggering thrombosis and identify stenoses for which a more aggressive treatment would be warranted. Efforts made in this direction have been limited7–9 and have suggested that stenosis severity could be less important7,8 and morphological features of the plaque9 could be more important than previously recognized. The present study was designed to investigate further whether high-risk lesions could be recognized using qualitative and quantitative angiographic analyses of coronary lesions that later occluded to provoke an acute myocardial infarction. These lesions were compared with control lesions from the same patients that did not occlude.

Methods

Study Population

The study population was selected from a pool of patients catheterized during the acute phase of myocardial infarction. Mean time to catheterization after the acute infarct was 15.1±12 days. The clinical diagnosis of myocardial infarction was based on the presence of chest pain more than 30 minutes in duration with diagnostic enzyme elevation, evolving ischemic ST-T changes, and new Q wave formation. The patients were considered for the study if they had a coronary angiogram performed in our institution within the previous 3 years and they had

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been without intervening coronary events such as bypass surgery, coronary angioplasty, congestive heart failure, unstable angina, or myocardial infarction. Of approximately 1,400 patients catheterized during acute infarction, 86 qualified for the study on the basis of these selection criteria. The selection process was then extended to require unequivocal identification of a well-defined coronary artery segment responsible for the infarction by the demonstration of a complete occlusion or of an intracoronary lumen defect suggestive of thrombus and corresponding to the electrocardiographic site of the new Q wave, usually with a new wall motion abnormality on the left ventriculogram. The 38 patients responding to these entry criteria formed the study population. Excluded were 28 patients with previous myocardial infarction and diffuse coronary artery lesions precluding exact identification of the culprit lesion, four patients without a coronary lesion in a control segment, and 16 patients with angiograms technically unsuitable for quantitative analysis.

Coronary Angiography

Coronary angiography was performed using standard techniques, including special angulated views. Left ventriculography was obtained in the 30° right anterior oblique position. The angiogram performed after the acute infarct was used as a reference to establish the site of the new occlusion and localize the preexisting lesion. For this purpose, the two angiograms for each patient were projected simultaneously and visualized by an experienced radiologist and a cardiologist to identify the occlusive and control segments to be analyzed. Overall, a total of 217 coronary lesions were identified in the 38 patients on the first angiogram. Excluded were 29 lesions showing either complete or partial occlusion related to previous myocardial infarction and 86 lesions with poor definition or image superposition. This first coronary angiogram, preceding the infarct, was reanalyzed at a later time by visual inspection as well as by a computer-assisted procedure using the Cardiovascular Angiography Analysis System (CAAS) (Pie Data Medical, B.V.). This latter analysis of the 38 segments that subsequently occluded to cause the qualifying myocardial infarction and of the 64 diseased segments that did not represent the goal of the present study and was performed completely blindly; the second angiogram was not available, and the analysis involving cine frames was identified by numbers alone.

The qualitative description of the first angiogram included identification of the location and the severity of all coronary artery narrowings and of the presence or absence of a division branch originating within them. Severity of stenoses was expressed as percent lumen diameter reduction. Morphological features of each lesion noted were regular or irregular contours, symmetry of the stenosis, and presence of intraluminal defects.

The quantitative analysis was performed on each of the coronary artery narrowings suited for such an analysis, excluding control segments with suboptimal contrast opacification, stenoses with overlapping vessels, and occlusions or stenoses related to a previous myocardial infarction. Measurements were made in a single projection. The cine frame showing the stenosis at its most severe in a projection as perpendicular as possible to the axis of the radiographic beam was selected. Lesions of the right coronary artery were best visualized in the left or right anterior oblique projection, lesions of the left anterior descending coronary artery were best visualized in the same projections with cranial angulation, and lesions of the circumflex coronary artery were best visualized in the right anterior oblique position with or without caudal angulation. Analyses of the frames were performed at the time of best filling, during diastole whenever possible.

Minimal diameter, length of stenosis, percent diameter reduction, asymmetry index, and inflow and outflow angles were measured. Contours of the arterial segment were determined automatically by the computer system and corrected interactively by the user when they seemed inappropriate, as might occur when division branches are present in the area of interest. The percent diameter reduction was computed from the minimal diameter of the diameter function and the mean normal diameter at a user-indicated reference position, avoiding areas of poststenotic dilatation. This method was preferred to the semiautomated method, which requires a more ideal stenosis with a proximal normal segment. The asymmetry index was measured from the predefined centerline of the vessel and given a value between 0 and 1, with 1 representing a perfectly concentric lesion and 0 representing the most severe case of eccentricity. The inflow angle of stenosis was defined by the average slope of the diameter function over the section bounded by the position of the minimal diameter and the proximal boundary of the stenotic segment. The outflow angle represented the same measurement from the minimal diameter to the distal boundary of the stenotic segment. Figure 1 illustrates a typical example and the methods used for the various measurements. The intraobserver and interobserver variabilities of these methods of measurement are very small.

Statistical Analyses

The characteristics of the 38 coronary artery segments that subsequently occluded and of the 64 coronary artery segments that remained patent were compared using SYSTAT 4.0 and BMDP softwares. $\chi^2$ analyses were performed for discrete variables and an analysis of variance with unbalanced design for the continuous variables. The patients were stratified in three groups according to the time between the first coronary angiogram and the myocardial infarction: 3 months or less, 3–18 months, and more than 18 months. A paired analysis of variance for repeated
measures was done with lesions being the repeated factor and time from baseline to infarction being the grouping factor. In a very conservative analytic approach, the patient’s control lesion showing the greater amount of abnormality was used for this analysis. Discrete data were compared by the McNemar’s test, selecting at random one of the patient’s control lesions for the paired comparison with the occlusive lesion and repeating the random procedure 20 times; the number of experiments with a significant difference was reported as x divided by 20.

Results

Clinical Evaluation

The study included 38 patients (30 men and eight women). Age ranged from 35 to 65 years, with a mean of 53 years. A previous myocardial infarction had occurred in 14 patients. The interval between the two angiograms was 10.3 ± 11.2 months, with a range of 0.12–36 months; the interval was 3 months or less in 21 patients, between 3 and 18 months in 11 patients, and more than 18 months in 10 patients. The qualifying myocardial infarction involved the anterior wall in half the patients and the inferior wall in the other half. The mean peak creatine kinase elevation was 1,717 ± 1,213 IU/l (range, 167–5,000 IU/l). Ejection fractions were 58.5 ± 13% at the first angiogram and 52 ± 7.5% at the second. Thirteen of the 38 segments with thrombotic occlusion were located in the right, eight in the left circumflex, and 17 in the left anterior descending coronary artery; the occlusion was complete in 26 segments, subtotal in eight, and greater than 70% in the remainder. The distribution of the control lesions was similar, with 27 in the right, 16 in the left circumflex, and 21 in the left anterior descending coronary artery.

Qualitative Assessment

The results of the morphological evaluation of the lesions are shown in Table 1. A division branch originating within the stenosis was present in 29 of the 38 lesions (76%) that occluded and in 33 of the 64 control lesions (52%, p < 0.05). All 20 paired comparisons selecting a control lesion at random had a probability value of less than 0.05. This higher frequency was present irrespective of the time interval after the first angiogram, but it was more conspicuous during the first 18 months (Figure 2A). Lesions with irregular contours and more asymmetric lesions were observed slightly more frequently in the control group (p=NS) and, in
TABLE 1. Qualitative and Quantitative Evaluation of Lesions at Risk

<table>
<thead>
<tr>
<th>No. of lesions</th>
<th>Occlusive lesions (n=38)</th>
<th>Control lesions (n=64)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Division branch</td>
<td>29 (76%)</td>
<td>33 (52%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Irregular contours</td>
<td>18 (47%)</td>
<td>43 (67%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>24 (57%)</td>
<td>41 (64%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraluminal defects</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>. .</td>
</tr>
<tr>
<td>Percent stenosis (visual analysis)</td>
<td>53.7±21</td>
<td>43.6±19.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Quantitative measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal diameter (mm)</td>
<td>1.55±0.6</td>
<td>1.76±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stenosis (mm)</td>
<td>7.16±3.1</td>
<td>7.09±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen diameter reduction (%)</td>
<td>47.5±17.8</td>
<td>41.0±12.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Asymmetry index</td>
<td>0.46±0.28</td>
<td>0.44±0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Inflow angle (°)</td>
<td>21±10</td>
<td>16±7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Outflow angle (°)</td>
<td>20±10</td>
<td>16±8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

the paired random analysis, were more frequent in the occlusive segment in only two of the 20 comparisons. Intraluminal defects on the first angiogram were not detected in this series of patients. The severity of stenosis estimated visually at the time of the first angiogram was 53.6±21.3% for the occluded segments and 43.6±19.4% for the controls (p<0.01).

Quantitative Assessment

The minimal diameter of the stenosis, its length, and the asymmetry index could not differentiate segments that subsequently occluded from those that did not. However, percent stenosis and inflow and outflow angles of the stenosis significantly discriminated between the two groups. The values for the various quantitative measurements are listed in Table 1.

Percent stenosis was 47.5±17.8% in the occluded segments and 41±12.5% in the controls (p<0.05). The paired analysis of variance showed a significant interaction between occluded and control segments stratified as a function of time with more severely stenosed segments occluding earlier (p<0.001) (Figure 2). All 11 coronary artery segments with a 60% or greater stenosis that occluded did so in the first year, as did 17 of the 19 stenoses with a 50% or greater stenosis. Among 17 cases with infarction within the first 3 months, only one control lesion was more severe than the occlusive lesion and two were of comparable severity; overall, 19 of the 36 stenoses were 50% or greater occluded, and seven of the 21 had stenoses with 50–60% occlusion.

The inflow angle discriminated between the occluding and the control segments (p<0.05) and also had a significant interaction with time (p<0.001) (Figure 2). Of the 21 lesions with inflow angle of 25° or greater, 14 occluded, 12 of the 14 during the first year. The outflow angle was also significantly steeper in segments that occluded (20° versus 16°, p<0.05), with some interaction with the time of follow-up.

Discussion

In the present morphological and quantitative angiographic analysis of coronary artery stenoses at high risk for thrombotic occlusion that will cause an acute myocardial infarction, three predictors of subsequent occlusion could be identified: the presence of a division branch originating within the stenosis, the severity of the stenosis as assessed by percent lumen diameter reduction, and the steepness of the stenosis inflow and outflow angles. These characteristics share the common property of directly influencing blood flow rheology, in particular, shear stress and flow separation.

The main determinant of higher shear stress is the severity of the stenosis; other geometric factors of the stenosis play a less important role.15-17 In the present study, the length of the stenosis, its asymmetry index, and its irregularity did not influence outcome. Shear stress increases as percent stenosis increases to reach a maximal value near the site of maximal stenosis.15 Wall stress drops sharply at the point of widening of the stenosis, resulting in deceleration of flow, recovery of pressure, and flow separation.15,18 Experimental studies indicate that flow separation can occur even in a relatively mild constriction, below that required to limit coronary flow under resting conditions.16-19 Elevated plasma and whole blood viscosity, found in some patients with coronary artery disease, may also contribute to higher shear stress and an enhanced tendency to thrombosis.20 Branching vessels are sites of predilection for atherosclerosis21 and modify flow separation in a complex way, depending on many factors, including flow velocity, angle of the division branch, its curvature, and its diameter.18,22-24 These branching points have also been shown to be more sensitive to acetylcholine-mediated vasoconstriction.25

Extrapolation of in vitro and in vivo experimental research to diseased coronary arteries is further complicated by any active vasomotor tone that is present in the epicardial arteries proximal and distal
to the stenosis as well as, to varying degrees, at the site of the stenosis.\textsuperscript{26-28} This dynamic aspect may in part explain some of the variability in the results and why outcome was more directly related to percent stenosis than to absolute minimum diameter.\textsuperscript{29} Also, percent stenosis in part accounts for blood flow velocity in the diseased segment, and minimal diameter does not (e.g., a 0.4-mm minimal diameter will not cause much turbulence in a 2-mm artery [20% stenosis] but will in a 0.5-mm artery [80% stenosis]). The statistically significant association between severity of the stenosis, the inflow angle, and the presence of a collateral branch strongly suggest that shear stress and flow separation may be the most
important determinants of outcome of the plaque. These two factors are associated with trauma to the vascular wall, development and progression of atherosclerosis, platelet deposition, and thrombus formation.

Previous angiographic studies have described specific lesions associated with the acute phase of myocardial infarction and unstable angina. Thus, a high incidence of coronary artery thrombus is found in patients catheterized acutely to decrease subsequently, presumably because of spontaneous lysis. Later, lesions appear to be eccentric with a narrow neck or irregular borders, representing either a disrupted atherosclerotic plaque or a partially occlusive or lysed thrombus. Quantitative morphological analysis of these lesions shows a high degree of lumen irregularity, suggesting plaque ulceration and disruption in accordance with the pathological finding of a high incidence of thrombus formation and plaque fissure in unstable angina, sudden death, and myocardial infarction.

These angiographic and pathological observations have all been obtained after the acute event, and it is not known to what extent they are the consequence rather than the cause of the acute occlusion. The absence of eccentric and irregular lesions before occlusion in the present study suggests that these features do not play an important etiologic role. Furthermore, the findings do not determine whether plaque fissuring and thrombus formation are random processes or are associated with specific characteristics of the plaque.

Studies performed before the occurrence of acute coronary events have yielded more controversial results. The distribution and extent of coronary artery obstructive lesions have been shown to be weak predictors of ischemic events. In a 5-year follow-up of patients with one-vessel coronary artery disease, the anatomic location of the lesion did not influence the rate of ischemic events, and the severity of the stenosis was a weak predictor of subsequent infarction. In a report from the Coronary Artery Surgery Study (CASS) registry of 118 patients with left anterior coronary artery disease, the 3-year risk of anterior infarction was 2% with stenosis of less than 50%, 6% with stenosis of 50% or greater, and 11% with two or more stenoses of 50% or greater. Stenoses of 90–98% had a 15% 3-year risk.

In a further analysis of the morphology of coronary lesions that caused myocardial infarction, the CASS investigators matched the 118 patients to a control group without infarction and the same extent of left anterior descending coronary involvement. A multivariate analysis revealed edge roughness as the most potent predictor of subsequent infarction; the length of the stenosis and the presence of a branching point at the site of the stenosis during the first year were also predictive. The poor reproducibility of the method for edge roughness measurement in their study (72% intraobserver agreement, \( p = 0.07 \)) and the absence of angiographic phy to document the site of occlusion limit the validity of their conclusions. In the present study, edge roughness, defined as irregular contours, was diagnosed in 47% of the infarct lesions and in 67% of the control lesions compared with 16.1% and 3.5%, respectively, in the aforementioned study. This large difference suggests important interobserver differences in the evaluation of this qualitative parameter and might explain the absence of predictive value in our analysis. In a study by Little et al., an angiogram performed 706±685 days before an acute infarct was not predictive of the site of infarction as determined by repeat angiography shortly after the infarct. Ambrose et al. also using angiographic confirmation of the site of infarct, reported more frequent myocardial infarction with proximal stenoses of 50% or more in severity; percent stenosis, left anterior descending coronary involvement, and type 2 eccentric lesions were not predictive.

The observations made in the present study document that thrombotic occlusion of a coronary artery at the site of an atherosclerotic plaque is not a completely random process but is influenced by hemodynamic disturbances related to the geometry of the plaque and to local blood flow. These observations should stimulate a more in-depth analysis of coronary atherosclerotic lesions in an attempt to predict which lesions at higher risk of occlusion would benefit from more aggressive treatment.

The sensitivity and specificity of the plaque’s geometric features to predict subsequent occlusion are, however, relatively low, suggesting that other critical characteristics of the plaque not detected by angiography could be operative and possibly also the state of activation of platelets and of the blood factors. Thus, plaques that undergo disruption tend to be softer, with high concentrations of cholesterol and cholesterol ester. Fissuring is frequently observed at the lateral margin of plaques containing an eccentric pool of extracellular lipid in the intima and in plaques with caps infiltrated with macrophages.

**Study Limitations**

As in all retrospective analyses, case selection may have introduced biases so that the results of the present study may not accurately reflect reality. The computer-assisted measurement method may introduce further bias because unmeasurable stenoses were excluded. Another limitation of the present study is that the characteristics of the plaque were analyzed only once before the infarction; an evolution of the lesion between the time of angiography and the time of the myocardial infarction cannot be ruled out. A history of worsening angina before infarction is reported by many patients and may correspond to this process.

Many other parameters not analyzed in these studies, more specifically, clinical factors, could also have considerably influenced the outcome of the plaque. Thus, risk factors such as smoking, hypertension, lipid...
disorders, and other blood coagulation or platelet abnormalities could have been determinants of occlusion for some plaques.\textsuperscript{41,45} The design of the present study may minimize the importance of these factors because lesions that occluded were compared with lesions that did not occlude in the same patients. However, different lesions in the same patient can behave differently by constricting or dilating in response to the same stimulus.\textsuperscript{25} Interrelations between clinical factors, plaque geometry and characteristics, and outcome represent an exciting field for further investigation, with the challenge to better identify high-risk lesions.

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