Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions

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Background—Acute coronary occlusions leading to ST-segment elevation myocardial infarctions (STEMIs) are due primarily to rupture of atherosclerotic plaques. Present “vulnerable plaque” detection technology focuses on identifying individual plaques with no clear therapeutic plan beyond conventional risk factor reduction. We developed a spatial map of the distribution of acute coronary occlusions to test our hypothesis that plaque ruptures do not occur uniformly throughout the coronary tree.

Methods and Results—We analyzed 208 consecutive patients who presented to the Brigham and Women’s Hospital with STEMI and mapped the location of the acute coronary occlusion. These occlusions were not uniformly distributed throughout each of the major epicardial coronary arteries but tended to cluster within the proximal third of each of the vessels (right coronary artery, \( P = 0.001 \); left anterior descending artery, \( P = 0.003 \); left circumflex artery, \( P = 0.001 \)). Furthermore, Poisson regression showed that for each 10-mm increase in distance from the ostium, the risk of an acute coronary occlusion was significantly decreased by 13% in the right coronary artery, 30% in the left anterior descending artery, and 26% in the left circumflex artery.

Conclusions—Acute coronary occlusions leading to STEMI tend to cluster in predictable “hot spots” within the proximal third of the coronary arteries. Identification of these high-risk zones for acute coronary occlusions will lead to future advances in vulnerable plaque detection technology and potentially locally directed preventive strategies. (Circulation. 2004;110:278-284.)

Key Words: coronary disease • myocardial infarction • plaque

The abrupt and persistent thrombotic occlusion of a major epicardial coronary artery or its large branches, usually within a discrete segment marked by ≥1 mural atherosclerotic plaques, has been established as the cause of the common myocardial infarction.1 It is widely held that the proximate cause of sudden coronary thrombosis is erosion or frank rupture of an underlying plaque, leading to a pathological cascade of platelet adherence and thrombus formation on the exposed plaque surface.2–4 Efforts to identify patient factors and to modify coronary plaque biology include patient-based diagnostic tests5,6 and systemic preventive strategies such as \( \beta \)-blockade, statin, and ACE inhibitor therapy; optimum diabetes control; behavior modification such as smoking cessation, exercise, and psychological stress reduction7; and even bypass surgery.8

In contrast to these patient-based and systemic approaches, new proposed strategies target the coronary plaque itself and aim to identify the preprothrombotic plaque, called “vulnerable plaque,” through a variety of diagnostic and imaging techniques (eg, direct thermography, intravascular ultrasound, and optical coherence tomography or spectroscopy).9–20 Once detected, there has been some suggestion that the identified unstable plaque might also be modified directly, or neutralized, via percutaneous intervention.21,22

Our present understanding of the physical characteristics that make an atherosclerotic plaque vulnerable to thrombosis (ie, thin fibrous cap,23,24 large lipid core,25–27 and the abundance of inflammatory cells28–29) is derived from histopathological studies. Whether such physical characteristics can accurately be measured to identify high-risk plaques in vivo before plaque rupture remains untested. Moreover, if such a population of plaques could be identified within any given patient, a hierarchical scheme to determine which plaques might be most vulnerable to thrombosis would be required to conserve any planned percutaneous prophylactic interventions.

We hypothesized that most plaque ruptures occur in predictable clusters or “hot spots” along the coronary artery tree. To investigate this hypothesis, we measured the location of acute coronary occlusions in patients presenting to...
Brigham and Women’s Hospital with ST segment elevation myocardial infarctions (STEMIs) and mapped the portions of the coronary tree at highest risk.

Methods

Patient Selection
From January 1, 2001, to August 31, 2002, all adult patients who presented to the Brigham and Women’s Hospital with STEMI, defined as chest pain associated with ST elevations of ≥1 mm in 2 contiguous ECG leads, and underwent coronary angiography were identified (n=496). Patients were excluded if they had a history of coronary artery bypass surgery, if there was no clear culprit lesion identified on coronary angiography, or if the patient was the recipient of an orthotopic heart transplant. In addition, patients who presented within 30 days of an elective angioplasty or had subacute stent thrombosis were excluded. For the period examined, the medical records of 208 patients who met these criteria were obtained and reviewed. In addition to basic demographics (eg, age, gender, and cardiac risk factors), laboratory values (eg, peak creatine kinase, peak serum creatinine, peak troponin-I, and left ventricular ejection fraction) were recorded.

Angiographic Analysis Methods
Quantitative coronary angiographic analysis to determine the location of epicardial thrombosis was performed with a standard software package (system version 5.1, Cardiology Medis System) and published techniques for calibration and measurement of coronary dimensions. Standardized angiographic projections were chosen for the measurement of each arterial segment within the infarct-related artery to minimize foreshortening (Table 1). For each patient studied, the segment lengths of the infarct-related vessel and side branches were measured. We used the coronary artery map from the Bypass Angioplasty Revascularization Investigation (BARI) and Coronary Artery Surgery Study (CASS) (with the addition of branch segments for the diagonal, marginal, and ramus intermedius vessels; Figure 1 and Table 1) for vessel classification.

Distance to the lesion was defined as the distance from the ostium of the involved coronary segment to the site of thrombosis. The thrombosis site was defined as the point of angiographic occlusion or, if TIMI grade 1 or more flow was present, the minimal luminal diameter within the culprit lesion. Two measures for the location of thrombosis were examined. The first measure was the absolute distance from the ostium (ostium analysis) of the coronary artery, which was defined as the sum of the coronary segments proximal to the site of the coronary occlusion plus the distance to the lesion. The second normalized the distance to the lesion to the length of the involved segment (normalized segment analysis).

Statistical Analysis
All analyses were performed with SAS version 8e. Continuous variables were reported as mean±SD and binary variables as

| TABLE 1. Standardized Projections Used for the Coronary Artery Segments |
|-------------------|-----------------|
| Vessel Segment    | BARI Classification | Projection |
| Left main         | 11               | AP CAU     |
| Ramus intermedius | 28               | LAO CRA    |
| Proximal RCA      | 1                | Straight LAO |
| Mid RCA           | 2                | Straight LAO |
| Distal RCA        | 3                | Straight LAO |
| Posterior descending | 4         | LAO CRA    |
| Posterior lateral segment | 6     | LAO CRA    |
| Proximal LAD      | 12               | RAO CAU    |
| Mid LAD           | 13               | RAO CRA    |
| Distal LAD        | 14               | RAO CRA    |
| Diagonal 1 branch | 15               | LAO CRA    |
| Diagonal 2 branches | 16            | LAO CRA    |
| Proximal LCx       | 18              | RAO CAU    |
| Mid LCx           | 19               | RAO CAU    |
| Distal LCx         | 19a              | RAO CAU    |
| Obtuse marginal 1  | 20               | RAO CAU    |
| Obtuse marginal 2  | 21               | RAO CAU    |

AP indicates anterior posterior; CAU, caudal; LAO, left anterior oblique; CRA, cranial; and RAO, right anterior oblique.
percentages. Cumulative frequency distribution curves were constructed for the ostium analysis. To determine whether the coronary occlusions were randomly distributed across the normalized distances within each segment, we first divided the vessel distances into 10-mm categories. If acute coronary occlusions are equally likely across the vessel distance categories, then we would expect the observed number of occlusions to be approximately uniformly distributed. We tested this assumption using a \( \chi^2 \) test. We also estimated a Poisson regression model to estimate the risk of a coronary occlusion as a function of distance from the ostium.

**Results**

Two hundred eight patients with STEMI were analyzed. The mean age of the cohort was 62 years; 73% were male. The prevalence of a prior myocardial infarction was 13.5%, and 24.5% had diabetes mellitus (Table 2). Most myocardial infarctions occurred in the right coronary artery (RCA; \( n=92, 44\% \)) and left anterior descending artery (LAD; \( n=81, 39\% \)) (Table 2). There was 1 thrombosis each in the left main and ramus intermedius segments.

**Right Coronary Artery**

All RCAs in this study gave rise to the posterior descending artery, and thrombosis was most common in the mid segment of the right coronary. The clustered nonuniform distribution \( (P=0.001) \) of thromboses within the RCA is further supported by the ostium analysis (Figure 2A) and normalized segment analysis (Figure 2B), with 50% of coronary occlusions occurring within 45 mm of the RCA (by cumulative frequency distribution of thrombotic locations from ostium of RCA).

**Left Anterior Descending Artery**

All LAD thromboses observed in this cohort were located within the proximal or mid vessel. In addition, there were 2 thromboses in the first diagonal and 1 myocardial infarction in the second diagonal. The ostium analysis and normalized segment analysis showed a high degree of clustering of thromboses within the proximal vessel \( (P=0.003; \text{ Figure 3A and 3B}) \). The cumulative frequency curve demonstrates that 50% of myocardial infarctions within the LAD occurred within the first 25 mm, and 90% occurred within the first 40 mm of the LAD (Figure 3C).

**Table 2. Patient Characteristics and Myocardial Infarction Vessel Location**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic profile</strong></td>
<td></td>
</tr>
<tr>
<td>Mean±SD age, y</td>
<td>61.7±12.6</td>
</tr>
<tr>
<td>Male, n</td>
<td>152 (73.1)</td>
</tr>
<tr>
<td><strong>Medical history, n</strong></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>28 (13.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>132 (63.5)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>110 (52.9)</td>
</tr>
<tr>
<td>IDDM</td>
<td>10 (4.8)</td>
</tr>
<tr>
<td>NIDDM</td>
<td>41 (19.7)</td>
</tr>
<tr>
<td>Present smoker</td>
<td>73 (35.1)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>53 (25.5)</td>
</tr>
<tr>
<td>Positive family history</td>
<td>88 (42.3)</td>
</tr>
<tr>
<td>Presented with CHF</td>
<td>44 (21.2)</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline creatinine, mg/dL</td>
<td>0.99±0.5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>47.7±11.1</td>
</tr>
<tr>
<td><strong>Myocardial infarct vessel location</strong></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Ramus intermedius</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>RCA</td>
<td>92 (44.2)</td>
</tr>
<tr>
<td>LAD</td>
<td>81 (38.9)</td>
</tr>
<tr>
<td>LCx</td>
<td>33 (15.9)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. IDDM indicates insulin-dependent diabetes mellitus; NIDDM, non–insulin-dependent diabetes mellitus; CHF, congestive heart failure; and LVEF, left ventricular ejection fraction.
The ostium analysis and normalized segment analysis of the left circumflex coronary artery (LCx) demonstrated proximal clustering of thromboses ($P=0.001$; Figure 4A and 4B). The cumulative frequency curve for the ostium analysis demonstrated that 50% of infarctions occurred within the first 25 mm of this vessel (Figure 4C), which included the native circumflex or an obtuse marginal branch, depending on the individual LCx anatomy.

**Left Circumflex Artery**
The ostium analysis and normalized segment analysis of the left circumflex coronary artery (LCx) demonstrated proximal clustering of thromboses ($P=0.001$; Figure 4A and 4B). The cumulative frequency curve for the ostium analysis demonstrated that 50% of infarctions occurred within the first 25 mm of this vessel (Figure 4C), which included the native circumflex or an obtuse marginal branch, depending on the individual LCx anatomy.

**Nonuniformity of Thrombosis Distribution Within the Coronary Tree**
Poisson regression showed that for each 10-mm increase in distance from the ostium, the risk of a coronary occlusion was significantly decreased by 13% in the RCA [relative risk (RR), 0.87; 95% CI, 0.83 to 0.92; $P<0.001$], 30% in the LAD (RR, 0.70; 95% CI, 0.62 to 0.78; $P<0.001$), and 26% in the LCx (RR, 0.74; 95% CI, 0.63 to 0.87; $P<0.001$).

**Discussion**
The present study examines the geographical distribution of occlusive thromboses throughout the coronary tree and demonstrates that such occlusions are clustered within the proximal portions of the major epicardial arteries. Specifically, we report the first detailed study of the spatial distribution of coronary thromboses causing STEMI and suggest that these thromboses are clustered in discrete coronary segments. Combined with the notion that acute coronary thromboses are caused by unstable plaque erosions or ruptures, these findings support a focalized approach to diagnostic and therapeutic...
modalities designed to identify and prevent coronary plaque thrombosis.

**Myocardial Infarction Prevention at the Focal Plaque**

Systemic strategies to prevent coronary thrombosis aim to mitigate the chronic atherosclerosis process by reducing inflammatory triggers, eg, aspirin, statin, ACE inhibitor therapies, or smoking cessation. Local coronary thrombosis preventive strategies aim to reduce factors that might lead to erosion or rupture of an already formed and unstable arterial plaque, eg, shear stress reduction with antihypertensive therapy and plaque biology modification through statin or β-blockade therapy. An emerging local preventive approach aimed at radially modifying the unstable pre-erosion, pre-rupture plaque biology, once an unstable plaque can be identified, is percutaneous coronary intervention.8,21 The coronary intervention would physically disrupt the delicate vulnerable anatomic components of the plaque through high-pressure compression (with or without a stent) and subsequently replace the surface plaque with a vascular scar, possibly incapable of supporting atherosclerotic pathology. In addition, local antiatherosclerosis drug therapy via intracoronary catheters could also be spatially directed. Armed with the knowledge of high-probability zones of coronary thrombosis through spatial distribution mapping, we can envision focal percutaneous treatments as a complement to systemic and local pharmacological treatments.

**Spatial Distribution of Coronary Thromboses**

The well-known propensity for acute coronary thrombosis to occur within large epicardial arteries rather than within smaller branches downstream has been responsible for the high morbidity and mortality associated with acute myocardial infarction, because the proximal large-caliber coronary vessels subtend a substantial myocardial territory. Although this conclusion may suffer from verification bias resulting from the possibility that small distal occlusions (ie, non-STEMIs) may be not be detected as frequently, there is good evidence that a large portion of small myocardial infarctions are still the result of transient occlusions of the major epicardial vessels or large branches.36 Paradoxically, the more proximal location of acute coronary thromboses has made percutaneous interventions more feasible. A pathological study by Fawal et al37 of 59 patients who died of myocardial infarction in Glasgow supports the notion that thromboses are distributed in the proximal coronary vessels. Likewise, the relative confinement of thromboses to the epicardial arteries has partially explained the benefit of coronary bypass surgery in the BARI trial (diabetic patients with 2- and 3-vessel disease), because the bypass insertion sites are often within the distal coronaries.8

The present study reports that acute STEMIs are highly clustered within the proximal portions of large epicardial coronaries. The finding of a lack of uniform distribution across the major epicardial vessels suggests a propensity for plaque erosion or rupture to occur in certain high-frequency regions within the coronary tree. These hot spots tend toward the proximal vessel, especially in the LAD. Because of their relative confinement to discrete segments (eg, 50% of LAD thromboses occurred within the first 25 mm of the vessel; Figure 3B), diagnostic and therapeutic approaches designed to diagnose unstable plaques or to prevent subsequent thrombosis should focus on these high-risk locations for better yield and contrast. Furthermore, randomized clinical trials might be designed to test percutaneous treatments used in such high-frequency coronary segments, with or without complementary plaque diagnostics, in patients with obstructive coronary disease elsewhere who also have high risk of myocardial infarction (such as diabetic patients with 2- or 3-vessel coronary disease).

**Theoretical Explanations for the Nonuniform Distribution of Coronary Thromboses**

Multiple mechanical and hemodynamic stresses have been proposed as contributing factors in the rupture of a vulnerable plaque. The constant stresses from each cardiac cycle are individually insufficient to induce plaque rupture, but over time, these stresses can weaken the fibrous cap and ultimately lead to rupture. This “cap fatigue” secondary to the constant stretching, compression, bending, and flexion that occur with each cardiac cycle can cause weakening of the fibrous cap over time, leading to its failure.38,39 Many theories could potentially explain the clustering of plaque rupture found in the present study. The segments with high-frequency thromboses we identified might be points of high shear stress (>70 dynes/cm²) where endothelial damage, platelet deposition, and cap fatigue may contribute to plaque rupture.40

**Clinical Implications of the Clustering of Epicardial Thrombotic Occlusions**

The finding that coronary thromboses are generally confined to proximal zones is attractive for the potential of catheter-based plaque modification. Theoretically, application of a low-restenosis-risk stent such as a proven drug-eluting stent or a specialized modification could modulate the high-risk coronary segment zone by focal plaque compression and replacement by controlled neointimal vascular scar. The extremely low frequency of thrombosis occurring in stented segments suggests that the scarred stented coronary segment generally does not provide the adequate milieu for local atherosclerotic plaque.41,42 Similar to the risk reduction for myocardial infarction seen with arterial bypass graft surgery compared with conventional percutaneous coronary intervention for diabetic patients at high risk of myocardial infarction,43 in which the bypass grafts themselves provided a parallel, more stable conduit beyond the proximal native coronaries at risk for future thrombosis,8 the use of prophylactic stenting might provide a similar benefit by replacing the high-risk zones with a controlled vascular scar.

Knowledge of the spatial distribution of acute coronary thrombosis, however, cannot by itself be translated into an absolute risk of myocardial infarction by coronary segment location. Nor can the spatial maps themselves aid in calculation of the absolute risk reduction provided by potential preventive strategies such as bypass surgery or stenting. In addition to the spatial maps, the patient-based absolute risk of
myocardial infarction must be known to balance the impact and risk of selective bypass or prophylactic stenting. Given the high degree of variance for myocardial infarction risk seen in patients who are treated for obstructive coronary disease, from 0.5% to 1.0% risk per year seen in many published single vessel stent trials44–46 to 8% to 10% risk per year for diabetic patients with 2- or 3-vessel coronary disease referred for complex PTCA or bypass surgery,43 a better understanding of the absolute risk of an myocardial infarction is needed to put the spatial distribution of myocardial infarction risk into practical clinical context.

Combined with demographic and disease-related risks for myocardial infarctions, our spatial model for thrombosis/plaque rupture may sharpen the estimation of coronary thrombosis risk and direct conventional and emerging preventive approaches. Moreover, the clustering of plaque rupture raises the possibility of designing clinical trials of experimental interventions such as standard or modified drug-eluting stents to prevent plaque rupture.

Study Limitations

This is the first application of the quantitative coronary angiography technique developed to measure the distance of acute coronary occlusions along the length of a coronary artery. Further studies are ongoing to validate this technique on a larger data set of patients who present with acute myocardial infarctions. Although we chose angiographic views that were the least foreshortened and measured the coronary segments individually, there was undoubtedly some residual foreshortening. The final limitation of our study is the generalizability of our results. Our cohort was from 1 institution and did not include patients with a prior history of CABG. Nor did we include patients with non-STEMIs and unstable angina who theoretically may have a different spatial distribution of myocardial infarctions. In addition, one would expect a greater number of thromboses within the left main artery than was observed, although an underestimation of left main thromboses might be expected because of the fatality of such thromboses. Nevertheless, the smaller autopsy studies report low incidence of left main thromboses.37,47

References


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