Markers of Inflammation and Rapid Coronary Artery Disease Progression in Patients With Stable Angina Pectoris

Emmanouil Zouridakis, MD*; Pablo Avanzas, MD*; Ramón Arroyo-Espliguero, MD*; Salim Fredericks, PhD; Juan Carlos Kaski, MD, DSc, FRCP, FESC

Background—Both endothelial cell activation and macrophage activation play a significant role in atherogenesis and atheromatous plaque vulnerability and may determine rapid coronary artery disease (CAD) progression. We sought to assess the association between serum inflammatory markers and rapid CAD progression in patients with chronic stable angina pectoris.

Methods and Results—We studied 124 chronic stable angina pectoris patients (84 men; mean age, 61 ± 10 years) who were on a waiting list for coronary angioplasty for a mean time of 4.8 ± 2.4 months. CAD progression was defined as ≥10% diameter reduction of a pre-existing stenosis ≥50%, ≥30% diameter reduction of a stenosis <50%, development of a new stenosis ≥30% in a previously normal segment, or progression of any stenosis to total occlusion. CAD progression occurred in 35 patients (28%). After adjustment with binary logistic regression, neopterin (P < 0.001), high-sensitivity C-reactive protein (P = 0.017), matrix metalloproteinase-9 (P = 0.002), soluble intercellular adhesion molecule 1 (P < 0.001), and previous history of unstable angina (P = 0.01) were independent predictors of rapid CAD progression. The association between rapid disease progression and inflammatory markers remained significant even when presence of complex lesions was introduced into the multivariate model.

Conclusions—Rapid CAD progression in patients with stable angina pectoris is associated with increased C-reactive protein levels and raised concentrations of biochemical markers of endothelial and macrophage activation. (Circulation, 2004;110:1747-1753.)

Key Words: C-reactive protein ■ cell adhesion molecules ■ coronary disease ■ inflammation ■ neopterin

Rapid coronary artery disease (CAD) progression, whether clinically silent or associated with acute coronary events, has been shown to be a powerful predictor of cardiovascular risk.1 Previous studies have found no relation between coronary artery stenosis severity and risk of rapid progression,2 but morphological features of coronary stenoses suggestive of increased plaque vulnerability have been reported to determine CAD progression.2,3 In recent years, it has become apparent that both endothelial cell activation and monocyte/macrophage activation play a significant role in atherogenesis and plaque vulnerability and may determine rapid CAD progression.

Previous angiographic studies from our group have shown that complex coronary stenosis morphology is associated with increased risk of acute coronary events and that complex stenoses are more likely to progress rapidly compared with smooth lesions.2 Of importance, recent intravascular ultrasound studies have confirmed a relationship between vulnerable stenoses and atheromatous plaque disruption.4 The reparative-proliferative response of the vascular wall that follows both clinically manifest and silent plaque disruption has been suggested to be responsible for rapid stenosis progression.5 Markers of systemic inflammation and macrophage activation, ie, serum neopterin and C-reactive protein (CRP) levels, have been found to be associated with the presence of complex stenoses and the development of serious cardiovascular events.6–10 Moreover, CRP has been suggested to be directly involved in atheromatous plaque vulnerability,11,12 and studies using angiographic, angioscopic, and intravascular ultrasound have shown that systemic inflammation is associated with multifocal plaque disruption and the development of acute coronary events.4,13,14 Cellular adhesion molecules (CAMs) and matrix metalloproteinases (MMPs) have also been suggested to represent an important factor in atheromatous plaque disruption and the occurrence of acute coronary syndromes.15,16 The aim of the present study was to investigate whether circulating levels of soluble CAMs, CRP, neopterin, and MMPs (MMP-2 and MMP-9) are associated with rapid angiographic CAD progression in patients with chronic stable angina pectoris (CSA).

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Coronary Stenosis Morphology

Stenosis morphology was assessed in coronary lesions with ≥30% diameter reduction. Complex lesions were defined by the following features: (1) irregular morphology, scalloped borders, or both; (2) overhanging or abrupt edges perpendicular to the vessel wall; (3) ulceration (ie, out-pouchings within the stenosis); and/or (4) the presence of filling defects consistent with intracoronary thrombus.

CRP, Soluble Intercellular Adhesion Molecule-1, Soluble Vascular Cell Adhesion Molecule-1, MMP-2, MMP-9, and Neopterin Measurements

Fasting venous blood samples were obtained in all patients from a large antecubital vein at study entry. Soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) concentrations were measured by quantitative sandwich immunoassay techniques with commercially available kits (R&D Systems). Briefly, a monoclonal antibody specific for sICAM-1 and sVCAM-1 was precoated onto a microplate. Appropriately diluted standards, samples, and controls were pipetted into the wells, together with a monoclonal antibody–specific sICAM-1 and sVCAM-1, respectively, which had been conjugated to horse-radish peroxidase. After removal of unbound conjugated antibody by washing, a substrate was added and color developed. Optical density was determined at 450 nm and corrected at 650 nm (MRX, Dynex Technologies). The concentrations of sICAM-1 and sVCAM-1 in the unknown samples were calculated in relation to the standard curve. With each batch of analyses, quality control material (R&D Systems) was run. The between-batch coefficient of variation was found to be 6.8% at a concentration of 253.9 ng/mL for sICAM-1 and 6.4% at a concentration of 547.3 ng/mL for sVCAM-1. MMP-2 and MMP-9 ELISAs were performed according to the manufacturer’s instructions with commercially available kits (Amersham Pharmacia Biotech). The reproducibility of the MMP-2 assay was <7% and <10% for within and between assays, respectively. According to the kit manufacturer, the expected plasma concentration of MMP-2 from healthy individuals is between 365 and 649 μg/L. The reproducibility of the MMP-9 assay was <6% and <9% for within and between assays, respectively. The expected plasma concentration of MMP-9 in normal control subjects is between 19 and 35 μg/L. The reproducibility of the neopterin assay was <5% and <7% for within and between assays, respectively. The expected plasma concentration of neopterin from healthy individuals is between 3.1 and 7.7 nmol/L. Serum neopterin was analyzed by a commercially available radioimmunoassay (Brahms Diagnostica GmbH). CRP concentrations were measured with a high-sensitivity Immulite ELISA immunoassay (DPC, Gwynedd). The lower detection limit was 0.05 mg/L (0.5 μg/mL); the upper limit was 50 mg/dL. There was no demonstrable cross reactivity with serum amyloid A, human serum albumin, IgG, or transferrin.

Statistical Analysis

Results for normally distributed continuous variables are expressed as mean ± SD; continuous variables with nonnormal distribution are presented as median values and interquartile intervals; categorical data are expressed as percentages. Analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Differences between groups were assessed by unpaired 2-tailed t test and the Mann-Whitney U test for continuous variables, as appropriate. Categorical data and proportions were analyzed by use of χ² or Fisher’s exact test when required. CRP, neopterin, and MMP levels had a nonnormal distribution and were therefore logarithmically transformed before regression analysis to fulfill the conditions required for this type of analysis. Because renal function is an important determinant of neopterin levels in blood, neopterin values were adjusted for creatinine levels. We assessed independent predictors of rapid CAD progression using a binary logistic regression analysis in which we included markers of inflammation, age, gender, cardiovascular risk factors, previous history of unstable angina, treatment with HMG-CoA reductase inhibitors, and glucose and LDL cholesterol levels. We used linear regression analysis to assess...
Patients With and Without Rapid CAD Progression

TABLE 1. Demographic Data and Clinical Characteristics in Patients With and Without Rapid CAD Progression

<table>
<thead>
<tr>
<th></th>
<th>Progressors (n=35)</th>
<th>Nonprogressors (n=89)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±10</td>
<td>60±10</td>
<td>0.44</td>
</tr>
<tr>
<td>Men/women, n</td>
<td>22/13</td>
<td>62/27</td>
<td>0.54</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>148±26</td>
<td>147±23</td>
<td>0.74</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>83±15</td>
<td>81±14</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±4</td>
<td>27±4</td>
<td>0.27</td>
</tr>
<tr>
<td>Cardiovascular risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (17.1)</td>
<td>11 (12.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>20 (57.1)</td>
<td>40 (44.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (42.9)</td>
<td>32 (36)</td>
<td>0.54</td>
</tr>
<tr>
<td>Smoking</td>
<td>23 (65.7)</td>
<td>63 (70.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Family history</td>
<td>21 (60)</td>
<td>45 (50.6)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Previous cardiovascular events, n (%):

- Myocardial infarction: 6 (17.1) vs 21 (23.6), P = 0.48
- Unstable angina: 16 (48.5) vs 16 (18), P = 0.001
- Hemorrhagic stroke: 0 (0) vs 3 (3.4), P = 0.56
- Ischemic stroke: 1 (2.9) vs 6 (6.7), P = 0.67
- Symptomatic PAOD: 0 (0) vs 1 (1.1), P = 0.90

Treatments, n (%):

- Aspirin: 29 (82.9) vs 76 (85.4), P = 0.79
- β-Blockers: 19 (54.3) vs 54 (60.7), P = 0.55
- Nitrates: 22 (62.9) vs 53 (59.6), P = 0.84
- Calcium channel antagonists: 17 (48.6) vs 35 (39.3), P = 0.42
- ACE inhibitors: 6 (17.1) vs 24 (27), P = 0.35
- Diuretics: 8 (23) vs 6 (6.7), P = 0.21
- HMG-CoA reductase inhibitors: 12 (34) vs 26 (29.2), P = 0.66

**BP** indicates blood pressure; **BMI**, body mass index; and **PAOD**, peripheral arterial occlusive disease. Data are expressed as mean±SD when appropriate.

*Hyperlipidemia is total cholesterol >5.4 mmol/L.

the relationship between number of complex coronary artery plaques and markers of inflammation. Backward stepwise selection was used to derive the final model for which significance levels of 0.1 and 0.05 were chosen to exclude and include terms, respectively. Differences were considered statistically significant if the null hypothesis could be rejected with >95% confidence. All probability values are 2 tailed. The SPSS 12.1 statistical software package (SPSS Inc) was used for all calculations.

**Results**

Demographic and clinical data of patients with and those without rapid CAD progression are presented in Table 1. There were no significant differences in cardiovascular risk factors, treatments, or standard biochemical results between groups (Table 2). A history of unstable angina, however, was more frequent in patients with rapid CAD progression (P = 0.001). Treatment remained unchanged, and no patients experienced serious clinical events during their time on the waiting list.

We analyzed a total of 321 lesions (mean, 2.58 per patient): 162 (51%) were located in the left anterior descending coronary artery, 71 (22%) in the circumflex coronary artery, and 88 (27%) in the right coronary artery. During 4.8±2.4 months (range, 3 to 12 months), CAD progression, as diagnosed by pre-established criteria, occurred in 35 of the 124 patients (28%): 18 (51%) had a ≥10% diameter reduction of at least 1 pre-existing stenosis ≥50%, 9 (26%) had a ≥30% diameter reduction of a pre-existing stenosis <50%, and 6 (17%) developed a new lesion ≥30% in a previously normal segment, and 2 (6%) had progression of a lesion to total occlusion at the second angiography. Baseline CAD severity, stenoses location, and time elapsed between the 2 angiograms were not significantly different in progressors compared with nonprogressors (Table 2).

**Inflammatory Markers**

The baseline biochemical results of patients with and those without stenosis progression are presented in Table 2. Neopterin (P = 0.003), high-sensitivity (hs)-CRP (P = 0.007), MMP-9 (P = 0.007), and sICAM-1 (P < 0.001) levels were significantly increased in progressors compared with nonprogressors. MMP-2 (P = 0.69) and sVCAM-1 (P = 0.12) levels, however, did not differ significantly when the 2 patient groups were compared (Figure 1). Figure 2 shows the proportion of patients with rapid angiographic stenosis progression classified according to sICAM-1, CRP, neopterin, and MMP-9 concentrations.

After adjustment using binary logistic regression (Table 3), neopterin (P < 0.001), hs-CRP (P = 0.017), MMP-9 (P = 0.002), sICAM-1 (P < 0.001), and previous history of unstable angina (P = 0.1) were independent predictors of rapid CAD progression. Furthermore, when we calculated ORs using cutoff points for markers of inflammation, patients with neopterin levels ≥7.5 nmol/L (median of total neopterin concentration) had a 5-fold higher risk of developing rapid CAD progression (OR, 5.5; 95% CI, 2.1 to 14.6; P = 0.001). Patients with MMP-9 levels >7.9 μg/L (median of the total MMP-9 concentration) had a 3-fold higher risk of CAD progression (OR, 2.7; 95% CI, 1.2 to 6.4; P = 0.002). Patients with CRP concentrations >3 mg/L had a 3-fold-higher risk of progression (OR, 3.05; 95% CI, 1.2 to 7.6; P = 0.024), and patients with sICAM-1 levels >271.4 ng/mL (mean of the total sICAM-1 concentration) had an ~4-fold higher risk (OR, 3.8; 95% CI, 1.6 to 8.9; P = 0.001) of developing rapid CAD progression.

**Stenosis Morphology**

Coronary stenosis morphology assessment on the first angiogram was feasible in 285 lesions with ≥30% lumen diameter reduction, and we identified 110 complex lesions. Of interest, 88% of coronary stenoses defined as complex corresponded to type C in the ACC/AHA classification. The proportion of patients with at least 1 complex lesion was significantly higher in patients belonging to the group that showed rapid CAD progression (65.7%) than in subjects without coronary stenosis progression (44.9%; P = 0.03).

We found a significant correlation among number of complex coronary lesions and neopterin (P = 0.042), MMP-9 (P = 0.044), and sICAM-1 levels (P < 0.001). Although CRP levels tended to be higher in patients with at least 1 complex lesion, no significant relationship was found between CRP and number of complex plaques (P = 0.15). Because complex lesions differed significantly between progressors and nonprogressors and were associated with the concentrations of...
neopterin, MMP-9, and sICAM-1, we assessed whether these inflammatory markers remained independently related to rapid CAD progression after adjustment for the presence of angiographically complex stenoses. Logistic regression revealed that the association between rapid disease progression, neopterin, MMP-9, and sICAM-1 remained significant after the complex lesion variable was introduced into the multivariate model \( (P=0.003, P=0.02, \text{and } P=0.001 \text{ for neopterin, MMP-9, and sICAM-1 levels, respectively}).

**Discussion**

The present study showed for the first time that increased circulating levels of sICAM-1, MMP-9, CRP, and neopterin are independently associated with rapid angiographic coronary artery stenosis progression in patients with CSA. Our study extends previous observations from our group and others regarding stenosis progression\(^2^5\) and indicates that rapid CAD progression is associated with inflammatory mechanisms and endothelial activation.

**Inflammation-Related Endothelial Cell Activation and Rapid CAD Progression**

The findings in the present study endorse previous suggestions that inflammation is a crucial factor in atherogenesis and CAD progression and that molecules such as CRP, neopterin, and CAMs may not be just markers of inflammation and cardiovascular risk but also are likely to play a pathogenic role in atheromatous plaque vulnerability and rapid coronary stenosis progression.\(^1^1,^2^0\) Indeed, CAMs are preferentially expressed in atheromatous lesions,\(^3^1\) and their expression is upregulated by serum CRP.\(^1^2\) Furthermore, in the Physicians Health Study (PHS), men with raised baseline sICAM-1 levels were shown to be at increased risk of myocardial infarction,\(^1^5\) and in the Atherosclerosis Risk in Communities (ARIC) study, subjects with the highest sICAM-1 values had a 5-fold-increased risk of coronary and carotid artery atherosclerosis than those with the lowest values.\(^2^2\) Similarly, other studies\(^2^3\) have reported that elevated levels of sICAM-1 were associated with the development of symptomatic peripheral arterial disease, suggesting an association between endothelial dysfunction and accelerated atherosclerosis in vascular beds other than the coronary. Regarding CRP and CAD progression, the Global Evaluation of New Events and Restenosis After Stent Implantation (GENERATION) study\(^2^4\) showed a significant association between elevated CRP levels and stenosis progression in nonangioplastied vessels during the first year of follow-up. These findings, which are in agreement with the present study and previous reports from our group,\(^2^5\) support the notion that inflammation-related endothelial cell activation, as reflected by high CRP and increased sICAM-1 levels, is likely to play a significant role in atheromatous plaque vulnerability and rapid stenosis progression.

**Role of Macrophages: MMPs and Neopterin**

Our findings in the present investigation suggest a relation between monocyte/macrophage activation and rapid CAD progression in patients with CSA. Atheromatous plaques associated with rapid CAD progression have well-defined anatomopathological characteristics and are usually referred to as vulnerable or unstable, terms that indicate their propensity to acute disruption and thrombogenicity that may lead to
the development of unstable coronary syndromes. Vulnerable plaques are often the site of intense inflammatory activity in which activated macrophages and lymphocytes play a role in fibrous cap disruption. MMPs produced by activated macrophages are crucial in the process that leads to the disruption of the fibrous cap of atheromatous lesions. MMPs constitute a family of >20 zinc-containing endoproteinases that are involved in the degradation of the collagen that constitutes the extracellular matrix and thus are important for vascular remodeling. Neopterin, a molecule secreted by activated macrophages on stimulation by interferon-γ, has previously been reported to be elevated in the serum of patients with acute coronary syndromes compared with patients with stable forms of CAD and to correlate with the presence of angiographically complex lesions and increased cardiovascular risk. In the present study, we found that MMP-9 and neopterin concentrations were elevated in CSA patients who showed rapid CAD progression. This observation suggests that monocyte/macrophage activation plays a pathogenic role in plaque vulnerability and accelerated stenosis progression and lends further support to previous reports indicating a pathogenic role of activated macrophages in atherosclerosis and the acute coronary syndrome.

Figure 1. Relation between serum CRP, neopterin, MMP-2, MMP-9 (Mann-Whitney U test), sICAM-1, and sVCAM-1 (2-tailed t test) concentrations and rapid CAD progression in 124 patients with CSA awaiting routine coronary angioplasty.
In our study, we did not find a relation between MMP-2 and CAD progression, but this is not surprising in view of the contradictory reports by other investigators regarding MMP-2 levels in patients with stable CAD, findings in previous studies of a positive correlation between circulating MMP-2 and HDL cholesterol, and the finding of increased MMP-2 levels after administration of HMG-CoA reductase inhibitors. The true effects of MMP-2 in patients with stable CAD require further investigation.

Rapid CAD Progression and Angiographically Complex Stenosis

Our observations in the present study regarding complex stenosis morphology confirm and expand previous findings from our group that complex stenoses are more likely to progress rapidly than smooth stenoses. Of importance, the association found in the present investigation between rapid disease progression and increased levels of markers of inflammation remained significant after adjustment for stenosis complexity. This is not surprising because, although stenosis complex morphology is a predictor of CAD progression, angiographic complexity is not a necessary component of stenosis vulnerability and does not necessarily imply the presence of an inflammatory process. Indeed, a sizable proportion of stenoses show inflammatory activity in the absence of complex angiographic features, and, vice versa, complex angiographic stenoses may have a histopathologically stable pattern. In fact, it is the composition—ie, the type of cellular infiltrate, the characteristics of the lipid core, and the presence of proinflammatory molecules and inflammatory cells—rather than the angiographic morphology that determines plaque vulnerability. Furthermore, angiography is just a “lumenogram” and, as such, is unable to provide information regarding plaque composition. Intravascular ultrasound and angioscopy are likely to provide more accurate information regarding atherosclerotic burden and plaque vulnerability.

It is intriguing that no significant relationship was found in the present study between CRP levels and complex plaques in patients with CSA, despite the fact that we and others previously reported a significant association between these variables in the acute coronary syndrome setting. A possible explanation is that complex features at angiography are more likely to represent acute disruption plaques in the acute coronary syndrome setting than in patients with CSA. In CSA patients, ulcerations and irregular/eccentric endoluminal edges may represent the aftermath of plaque disruption or a “partially healed” disruption, not necessarily an acute inflammatory event.

Study Limitations

We measured inflammatory markers at 1 time point only in the study; hence, were unable to ascertain whether dynamic changes in inflammatory marker levels took place during follow-up and whether it was of relevance in this setting. Treatment in our study may not be representative of current management strategies for patients with stable CAD worldwide. Thus, our results may be more important as descriptors of a pathophysiological mechanism rather than of practical clinical relevance. However, our observations may help to explain recent findings that intensive lipid-lowering treatment reduces the progression of coronary atherosclerosis, an effect suggested to be related to a reduction in inflammatory markers. In this context and despite the relatively small sample size, our study has provided evidence that inflammation-related endothelial cell and macrophage activation may predict atheromatous plaque vulnerability and CAD progression.

### Table 3. Multivariate Analysis: Level of Significance of the Association Between CAD Progression and Inflammatory Markers

<table>
<thead>
<tr>
<th>Inflammatory Markers</th>
<th>Adjusted ( \beta )</th>
<th>OR†</th>
<th>95% CI</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin</td>
<td>(&lt;0.001)</td>
<td>5.5</td>
<td>2.1</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.017</td>
<td>3.0</td>
<td>1.2</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>sICAM-1</td>
<td>(&lt;0.001)</td>
<td>3.8</td>
<td>1.6</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>0.65</td>
<td>2.1</td>
<td>0.9</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>MMP-9</td>
<td>0.002</td>
<td>2.7</td>
<td>1.2</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>MMP-2</td>
<td>0.81</td>
<td>0.7</td>
<td>0.4</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, cardiovascular risk factors, history of unstable angina, treatment with HMG-CoA reductase inhibitors, and levels of glucose and LDL cholesterol.
†We calculated OR using as cutoff points for the inflammatory markers the mean of the concentrations for sICAM-1 and sVCAM-1, the median of their concentrations for MMPs and neopterin, and 3 mg/L for hs-CRP.

**Figure 2.** Top, Proportion of patients with rapid angiographic stenosis progression classified according to sICAM-1 and CRP levels (*\( P < 0.001 \)). Bottom, Proportion of patients with rapid angiographic stenosis progression classified according to neopterin and MMP-9 concentrations (*\( P < 0.001 \)).
Conclusions
Baseline serum neopterin, MMP-9, sICAM-1, and CRP concentrations are significantly increased in CSA patients with rapid CAD progression during follow-up compared with those without progression, regardless of plaque morphology. Inflammatory mechanisms involving endothelial and monocyte/macrophage activation appear to play a significant role in atheromatous plaque vulnerability and rapid CAD progression.

Until new imaging techniques and new technology are developed to improve the characterization of atheromatous plaque complexity and vulnerability in clinical practice, biochemical markers of endothelial inflammation and macrophage activation may be useful in identifying the vulnerable patient and may facilitate the identification of systemic therapies that may avoid both CAD progression and the development of coronary acute events.

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