Risk of Myocardial Infarction and Angina in Patients With Severe Peripheral Vascular Disease
Predictive Role of C-Reactive Protein

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Background—Patients undergoing revascularization procedures for peripheral vascular disease (PVD) have a greatly increased risk for coronary artery disease (CAD) that is predicted only partly by clinical data and cardiovascular risk factors. We investigated whether the prognostic assessment in PVD patients could be improved by preoperative measurements of C-reactive protein (CRP).

Methods and Results—We assessed clinical and risk factors profiles, Eagle clinical scores, and preoperative CRP serum levels in 51 patients with PVD at Fontaine-Leriche stages II to IV without severe rest ventricular dysfunction or ischemia. During 24 months of follow-up, 17 patients (34%) had fatal (11) or nonfatal (6) myocardial infarction (MI). With univariate logistic regression analysis, only previous history of CAD, Eagle score, and CRP were independently related to MI. At multivariate logistic regression analysis, only CRP values in the upper tertile (>9 mg/L) were significantly associated with MI (P<0.05) and identified 65% of cases.

Conclusions—The high incidence of MI in patients with PVD severe enough to require revascularization is strongly predicted by preprocedural measurements of serum CRP, independent of previous CAD, Eagle score index, and traditional cardiovascular risk factors. These patients may benefit from therapy modulating the inflammatory response.

Key Words: peripheral vascular disease ▪ inflammation ▪ prognosis
gous reverse saphenous vein bypass grafting in 10 patients. Younger patients with a longer life expectancy had surgical treatment as the first option.

Laboratory Assay
Venous blood samples were collected preoperatively and stored at −20°C before analysis. CRP was measured in the serum using a commercially available high-sensitivity method (Latex/BN II, Dade Behring) that allowed detection of CRP levels as low as 0.02 mg/L. All measurements were done in a single batch at the end of the study, and the laboratory staff was blinded to the clinical data. All patients took antiaggregant therapy (aspirin or ticlopidine). All patients gave their informed consent for the study.

Follow-Up
All patients were followed up for 24 months. At short-term (30 days) and long-term (24 months) follow-up after peripheral revascularization, we examined the occurrence of hard end points: all mortality, cardiac mortality (caused by myocardial infarction [MI]), and MI (increase of at least 2-fold in creatine kinase–MB with typical ECG changes and chest pain), which were defined as major events. We also considered the occurrence of soft end points, including new occurrence of angina pectoris, symptomatic peripheral artery restenosis or obstruction, or leg amputation, which were defined as minor events. All events were documented by hospital records.

Statistical Analysis
CRP levels were abnormally distributed and are reported as median and range. The values were divided and analyzed as tertiles. Data were analyzed by means of nonparametric tests. Univariate logistic regression analysis and multiple logistic regression analysis were performed to assess the independent contribution of the risk factors to major and minor cardiac events. Added to this model were age, sex, smoking habits, history of diabetes mellitus, hypertension, history of previous CAD (previous MI and/or angina), cholesterol >200 mg/L, fibrinogen >400 mg/dL, Fontaine-Leriche clinical stage of the PVD, Eagle clinical score, and CRP serum values. Values of \( P < 0.05 \) were considered statistically significant.

Results

**CRP**
CRP serum values were distributed in tertiles as follows: lower CRP tertile, <4 mg/L; middle tertile, 4 mg/L to 9 mg/L; and upper tertile, >9 mg/L.

**Cardiac Events**
Three patients had cardiac events during the first postoperative months. One died after an MI and 2 developed effort angina. Such events were not correlated with CRP levels or any of the other parameters considered. Epidemiological data of patients and occurrence of cardiac events according to CRP tertiles are reported in Table 1.

At 24 months’ follow-up, 17 of the 50 remaining patients (34%) had experienced major cardiac events (6 nonfatal and 11 fatal MIs), and only 5 (10%) developed effort angina pectoris. Three patients died from other causes (1 neoplasia and 2 diabetes).

Nonfatal and fatal infarction occurred in all 3 patients with high Eagle scores (all of whom also had CAD), in 6 of 22 patients with a history of CAD, and in 11 of 17 patients without a history of CAD and with low or intermediate Eagle scores. In this latter group, CRP identified 6 of 11 patients (54%).

In univariate logistic regression analysis, fatal and nonfatal MIs were associated with Eagle score (\( P < 0.03 \); odds ratio [OR], 9.2; confidence interval [CI], 1.1 to 77) and CRP levels (\( P < 0.01 \); OR, 1.04; CI, 1 to 1.08) and CRP tertiles (\( P < 0.015 \); OR, 2.7; CI, 1.2 to 6.3), but not with history of CAD (Table 2). In a multivariate logistic analysis considering previous CAD, Eagle score index, and CRP, only CRP tertiles were significantly associated with fatal and nonfatal MIs (\( P < 0.05 \); OR, 2.3; CI, 0.9 to 5.7) and with fatal MIs (\( P < 0.04 \); OR, 3.2; CI, 1.03 to 10.02) (Table 3). CRP values in the upper tertile predicted 60% of MIs.

**Vascular Events**
Seven patients had symptomatic arterial restenosis or obstruction and 1 patient had leg amputation during the 24 months of follow-up. None developed stroke. Vascular events were unrelated to clinical data and to CRP levels.

**Discussion**
Our study shows a 34% 2-year incidence of fatal and nonfatal MIs in patients with PVD at Fontaine-Leriche stages II to IV who were undergoing limb revascularization. This incidence seems particularly elevated considering that we excluded patients with poor left ventricular function or evidence of severe myocardial ischemia. The incidence of fatal and nonfatal MI during the 24 months of follow-up also seems particularly high in comparison with the 10% incidence of...
require peripheral vascular intervention. In our patients, CRP of patients with preexisting atherosclerosis severe enough to between inflammation and cardiovascular disease in a group physiological questions, it provides novel information on the link of fatal cardiac events (38% in tertile III versus 7% in tertiles patients in the highest CRP tertile had the highest incidence risk were equally distributed across the CRP tertiles, but cardiac risk. In our study, patients in this intermediate class of examinations are often considered essential to better stratify events in the intermediate class of risk, in which instrumental had a low or intermediate Eagle score and no history of 17 patients who had a fatal or nonfatal MI, 54% of whom patients, inasmuch as values in the upper tertile identified 11 and the absence of stroke.

Angina, the 6% incidence of coronary perioperative events, and the absence of stroke.

CRP level had a high positive predictive value in these patients, inasmuch as values in the upper tertile identified 11 of 17 patients who had a fatal or nonfatal MI, 54% of whom had a low or intermediate Eagle score and no history of previous CAD. In particular, CRP was predictive of cardiac events in the intermediate class of risk, in which instrumental examinations are often considered essential to better stratify cardiac risk. In our study, patients in this intermediate class of risk were equally distributed across the CRP tertiles, but patients in the highest CRP tertile had the highest incidence of fatal cardiac events (38% in tertile III versus 7% in tertiles I and II, *P*<0.05).

Conversely, the negative predictive value of CRP was limited, inasmuch as values in the first 2 tertiles were found in 40% of the cases of MI. This finding is not surprising because, when MI is not preceded by unstable angina, CRP values on admission are below 3 mg/L in >50% of the cases.16

Although this study was not designed to answer pathophysiological questions, it provides novel information on the link between inflammation and cardiovascular disease in a group of patients with preexisting atherosclerosis severe enough to require peripheral vascular intervention. In our patients, CRP levels were not significantly different in Fontaine-Leriche stages III and IV and stage II, suggesting that CRP in this setting does not reflect simply the presence and the severity of obstructive disease or of injured tissues. Furthermore, the median concentration of CRP in the overall population of this study was similar to that found by our group in patients with unstable angina and single-vessel coronary disease, which suggests that CRP is not merely the reflection of the severity of the atherosclerotic process, but rather of a particular type of activity of the disease.16,18 Indeed, in our selected group of patients, only a few developed new stable angina, a sign of progression of the severity of coronary atherosclerotic stenosis. Conversely, the majority of the events were represented by the development of MI, which seems related to the sudden occlusion of an artery without flow limit stenosis in ≈70% of the cases.19 Also, in this group of patients with severe peripheral atherosclerosis and a high incidence of infarction, the positive prognostic value of CRP was unrelated to established risk factors, in agreement with previous studies.13,15

**Clinical Implications**

Our findings suggest that CRP measurements in patients with PVD severe enough to require revascularization procedures may give incremental information on the risk of death and MI

<table>
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<th>TABLE 2. Univariate Logistic Regression Analysis</th>
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<td><strong>All Cardiac Events</strong></td>
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<td><strong>P</strong></td>
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<td>Age</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Smoking</td>
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<td>Diabetes</td>
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<td>Hypertension</td>
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<td>Previous CAD</td>
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<td>Chol &gt;200 mg/L</td>
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<td>Fibr &gt;400 mg/dL</td>
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<td>Eagle score</td>
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<td>CRP single value</td>
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<td>CRP tertiles</td>
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<td>Tertile I</td>
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<td>Tertile III</td>
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Chol indicates cholesterol; Fibr, fibrinogen; and F-L, Fontain-Leriche.

*P*<0.05.

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<tr>
<th>TABLE 3. Multivariate Logistic Regression Analysis</th>
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<td>Eagle score</td>
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<td>CRP tertiles</td>
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*P*<0.05.
above that provided by history of previous CAD, Eagle score index, and traditional cardiovascular risk factors. Thus, these results indicate the need for larger studies to confirm the prognostic value of CRP in the noninvasive risk stratification of patients with PVD who are classified at an intermediate risk on the basis of clinical history and score, and who are currently being assessed by cardiac stress tests. They also suggest that this particular group of patients with a high incidence of MI may be suitable for pilot studies testing the beneficial effect of modulating an enhanced inflammation response and of lowering CRP levels.

Acknowledgment

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References

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