C-Reactive Protein in Offspring Is Associated With the Occurrence of Myocardial Infarction in First-Degree Relatives

Maurizio Margaglione, Giuseppe Cappucci, Donatella Colaizzo, Gennaro Vecchione, Elvira Grandone, Giovanni Di Minno

Abstract—The relevance of elevated levels of C-reactive protein (CRP) in cardiovascular disease is gaining increasing recognition. A family history of coronary artery disease is a major determinant of coronary artery disease in the offspring. In a cohort of 1048 individuals without clinical evidence of atherosclerosis, we investigated the relationships between CRP levels and a family history of myocardial infarction. We measured CRP, fibrinogen, plasminogen activator inhibitor-1, total cholesterol, triglycerides, and some genetic polymorphisms: plasminogen activator inhibitor-1 (4G/5G), fibrinogen (Bβ-chain G→A−455), and angiotensin-converting enzyme insertion/deletion (I/D). Clinical data were collected by a World Health Organization–modified questionnaire for cardiovascular disease. When compared with subjects without first-degree relatives who had suffered a myocardial infarction (n=867), subjects with such first-degree relatives (n=181) were older (P=0.001), more often hypertensive (P<0.001), and homozygous for the 4G allele (4G/4G) of the plasminogen activator inhibitor-1 gene (P=0.003). In addition, they had a higher body mass index (P=0.036), raised plasma fibrinogen (P<0.007) and total cholesterol (P<0.001) concentrations, and CRP levels >0.33 mg/L (P=0.005). In a multiple logistic regression analysis, age (odds ratio [OR] 1.03, 95% confidence interval [95% CI] 1.01 to 1.05), total cholesterol (OR 1.35, 95% CI 1.11 to 1.65), plasminogen activator inhibitor-1 4G/4G (OR 1.72, 95% CI 1.20 to 2.45), and CRP levels >0.33 mg/L (OR 1.75, 95% CI 1.05 to 2.91) were all independently associated with a positive family history of myocardial infarction. We therefore conclude that raised levels of CRP independently identify the offspring of patients with a myocardial infarction. (Arterioscler Thromb Vasc Biol. 2000;20:198-203.)

Key Words: myocardial infarction ■ risk factors ■ thrombosis

In population studies, in addition to a series of environmental factors, a family history of coronary artery disease is a major predictor of coronary artery disease. A parental history of coronary artery disease is associated with an increased risk of myocardial ischemia.1 The presence of coronary artery disease in relatives by itself is considered to be an independent risk factor for developing a myocardial infarction in other family members.1,2 Previous reports have investigated whether dietary fat composition, apo(a) phenotypes, and Lp(a) plasma levels are independently associated with a parental history of myocardial infarction.3–5 Angiotensin-converting enzyme (ACE) gene and lipoprotein lipase gene polymorphisms have been found associated with a history of coronary artery disease in fathers and in second-degree relatives.6–8 We have previously found that the 4G/4G gene variant of the plasminogen activator inhibitor-1 (PAI-1) gene is associated with a history of coronary artery disease in a first-degree relative.9

Raised concentrations of C-reactive protein (CRP) have been found to predict recurrent ischemia, myocardial infarction, and sudden death among patients with multiple risk factors for coronary artery disease and angina pectoris.10–12 In the ECAT study, raised levels of CRP at baseline consistently predicted myocardial infarction or sudden death over the 3 years of follow-up.11 Increased CRP concentrations reflect the inflammatory condition of the vascular wall. Concentrations of CRP have been found to increase with age, body mass index (BMI), and cigarette smoking.13 Overweight and cigarette smoking are associated with a high risk of myocardial infarction.14 The aggregation of myocardial infarction in families1,2 and the observation that dietary or other lifestyle factors are more commonly shared by individuals living in the same household suggest that raised CRP concentrations, as a nonspecific index of inflammation, may explain part of the risk of myocardial infarction associated with a positive family history. No information is available on CRP as related to a familial history of myocardial infarction. An association with a family history of myocardial infarction may indicate the presence of familial transmitted factors. In a cohort of individuals without clinical evidence of atherosclerosis, we
have evaluated the relationships between CRP, risk factors for myocardial infarction, and the occurrence of myocardial infarction in their first-degree relatives.

Methods

Subjects

From January 1995 to October 1996 and after approval of the local Ethics Committee, the study was carried out according to the Principles of the Declaration of Helsinki. Informed consent was obtained from 1192 of the 1319 (90.4%) employees of the “Casa Sollievo della Sofferenza” Hospital, S Giovanni Rotondo, southern Italy. Biochemical and/or clinical data could not be completed in 138 individuals (10.5%). Moreover, all subjects had a history of clinical atherosclerosis (n=6) were excluded from the study. Thus, 1048 employees (22% of the 79.5%) were enrolled. All subjects, none was the offspring of a consanguineous marriage, and all of their parents and grandparents had been born in the same region. The male/female ratio of the sample was 0.77 (men=457, 43.6%; women=591, 56.4%). Blood was collected by venipuncture between 9 and 11 AM after 12 to 15 hours of fasting and abstinence from alcohol ingestion. Platelet-free plasma obtained by centrifugation (2000g x 10 minutes at room temperature) was immediately divided into aliquots of 500 μL each in plastic tubes (Nunc) and frozen at −70°C until assayed (within 12 months). A detailed clinical summary considered 1,247 employees (22% of the 79.5%) were enrolled. All subjects, none was the offspring of a consanguineous marriage, and all of their parents and grandparents had been born in the same region. The male/female ratio of the sample was 0.77 (men=457, 43.6%; women=591, 56.4%). Blood was collected by venipuncture between 9 and 11 AM after 12 to 15 hours of fasting and abstinence from alcohol ingestion. Platelet-free plasma obtained by centrifugation (2000g x 10 minutes at room temperature) was immediately divided into aliquots of 500 μL each in plastic tubes (Nunc) and frozen at −70°C until assayed (within 12 months). A detailed clinical summary, which included the personal and family history of myocardial infarction was obtained from all subjects by a specially trained staff employing a previously validated questionnaire,15 prepared according to the World Health Organization questionnaire for angiographic and cardiovascular disease. In addition to questions about symptoms of ischemic heart disease, peripheral vascular disease, and previous vascular surgery, information concerning stroke history and vascular risk factors, diabetes mellitus, hypertension, drug use, and alcohol and smoking habits was also obtained. Hypertension was defined as a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg in the sitting position after 10 minutes of supine rest on at least 3 different occasions.16 Subjects with a positive personal history of diabetes mellitus or with fasting blood glucose levels >126 mg/dL were considered diabetics.17 Alcohol drinkers and smokers were defined as never/past consumers or current consumers.

Biochemical and Genetic Variables

Serum concentrations of total cholesterol and triglycerides were detected enzymatically by employing commercially available reagents (Roche).15,18 Plasma fibrinogen was assayed by the Clauss clotting method by using reagents and the Coa Data 2000 apparatus from Boehringer-Mannheim. PAI-1 antigen plasma levels were assayed by ELISA method with (Imulysel) from Biopool-Manterini. Reference pooled, normal plasma from 216 apparently healthy male and female volunteers (29 to 70 years old) who had been instructed to avoid any medication for at least 1 week was prepared and stored under the same conditions applied to the study’s subjects’ samples. The intra-assay and interassay coefficients of variation of fibrinogen did not exceed 8% and those of PAI-1 antigen, 4.5%. CRP was assayed by rate nephelometry (N latex CRP Kryptor, Behring Institute) according to the manufacturer’s recommendations. Because of the reduced precision in the low range of the test, and a family history of myocardial infarction and potential interactions. The likelihood-ratio test was applied to determine which variables to remove from the model. Adjusted ORs and 95% CIs were calculated with logistic regression models. Statistical significance was taken at a P value <0.05.

Results

Characteristics of the Study Population

Table 1 shows the demographic characteristics of the study sample analyzed as a whole and stratified according to the presence or absence of a first-degree relative’s history of myocardial infarction. The 2 groups differed with respect to median age (P<0.001), total cholesterol (P<0.001), plasma fibrinogen levels (P=0.007), and BMI (P=0.036). In addition, the group whose first-degree relatives had suffered a myocardial infarction (n=181) had a significantly higher number of subjects who were hypertensive(P<0.001), with CRP levels >0.33 mg/L (P=0.017), and with a 4G/4G PAI-1 genotype (P=0.003). There was no difference between the groups with respect to sex, alcohol consumption, cigarette smoking, triglycerides, PAI-1 antigen, and ACE I/D polymorphism. The genotype frequencies of the fibrinogen Bβ-chain G→A 3455 polymorphism (P=0.080) approximated a statistically significant value. Pearson’s coefficients showed a close correlation between each of the following: plasma fibrinogen, age, BMI, total cholesterol, PAI-1 antigen, and triglycerides (P always <0.001), as well as among subjects with (P always <0.05) and those without (P always <0.02) a family history of myocardial infarction.

Genotype frequencies of the PAI-1 4G/5G, ACE I/D, and fibrinogen Bβ-chain G→A 3455 gene polymorphisms and the allele frequencies calculated were similar to those observed in samples from the same region19,22–24 and in other white samples19,25–27 and did not differ from those predicted by Hardy-Weinberg equilibrium (PAI-1 4G 49.8, 95% CI 47.7 to 51.9; PAI-1 5G 50.2, 95% CI 48.1 to 52.3; ACE D 65.2, 95% CI 63.2 to 67.2; ACE I 35.1, 95% CI 33.1 to 37.1; fibrinogen Bβ-chain 79.5, 95% CI 77.8 to 81.2; and fibrinogen Bβ-chain A 20.5, 95% CI 18.8 to 22.2). When
stratified according to a family history of myocardial infarction, no difference was found as to ACE I/D and fibrinogen stratafied according to a family history of myocardial infarction, no difference was found as to ACE I/D and fibrinogen stratafied according to a family history of myocardial infarction, no difference was found as to ACE I/D and fibrinogen stratafied according to a family history of myocardial infarction, no difference was found as to ACE I/D and fibrinogen

### TABLE 1. Characteristics of the Group as a Whole and Stratified According to Familial History of Myocardial Infarction

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N=1048)</th>
<th>Subjects With a 1° Relative Affected (N=181)</th>
<th>Subjects Without a 1° Relative Affected (N=867)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F, % (n)</td>
<td>43.6 (457)</td>
<td>43.1 (78)</td>
<td>43.7 (379)</td>
<td>NS*</td>
</tr>
<tr>
<td>Age median (range), y</td>
<td>36 (22–66)</td>
<td>40 (22–65)</td>
<td>35 (22–66)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Smokers, % (n)</td>
<td>24.2 (254)</td>
<td>27.1 (49)</td>
<td>23.6 (205)</td>
<td>NS*</td>
</tr>
<tr>
<td>Alcohol drinkers, % (n)</td>
<td>54.4 (570)</td>
<td>58.0 (105)</td>
<td>53.6 (465)</td>
<td>NS*</td>
</tr>
<tr>
<td>Diabetics, % (n)</td>
<td>2.3 (24)</td>
<td>2.8 (5)</td>
<td>2.2 (19)</td>
<td>NS*</td>
</tr>
<tr>
<td>Hypertensives, % (n)</td>
<td>10.2 (107)</td>
<td>17.1 (31)</td>
<td>8.8 (76)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ACE DD, % (n)</td>
<td>43.1 (452)</td>
<td>44.2 (80)</td>
<td>42.9 (372)</td>
<td>NS*</td>
</tr>
<tr>
<td>PAI-1 4G/4G, % (n)</td>
<td>25.6 (268)</td>
<td>34.3 (62)</td>
<td>23.8 (206)</td>
<td>0.003*</td>
</tr>
<tr>
<td>CRP &gt;0.33 mg/L, % (n)</td>
<td>9.2 (96)</td>
<td>13.8 (25)</td>
<td>8.2 (71)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Fibrinogen A 455 carrier, % (n)</td>
<td>36.8 (386)</td>
<td>42.5 (77)</td>
<td>35.6 (309)</td>
<td>0.080*</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>24.04 (1.16)</td>
<td>24.57 (1.16)</td>
<td>23.96 (1.16)</td>
<td>0.036‡</td>
</tr>
<tr>
<td>Cholesterol, mmol/L (SD)</td>
<td>4.84 (1.22)</td>
<td>5.08 (1.21)</td>
<td>4.79 (1.22)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (SD)</td>
<td>1.10 (1.02)</td>
<td>1.12 (1.04)</td>
<td>1.10 (1.02)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Fibrinogen, g/L (SD)</td>
<td>2.88 (0.01)</td>
<td>2.99 (0.01)</td>
<td>2.85 (0.01)</td>
<td>0.007‡</td>
</tr>
<tr>
<td>PAI-1, mg/mL (SD)</td>
<td>12.71 (1.91)</td>
<td>13.32 (1.96)</td>
<td>12.60 (1.92)</td>
<td>NS‡</td>
</tr>
</tbody>
</table>

For continuous variables, means and (SDs) are indicated. Skewed variables (see Methods) were logarithmically transformed, and geometric means and antilog SDs are indicated.

*| †Mann-Whitney U test.
‡Student’s t test.

### TABLE 2. Demographic Characteristics According to CRP >0.33 mg/L

<table>
<thead>
<tr>
<th>Variables</th>
<th>No (n=952)</th>
<th>Yes (n=96)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, % (n)</td>
<td>43.3 (412)</td>
<td>46.9 (45)</td>
<td>NS*</td>
</tr>
<tr>
<td>Age median (range), y</td>
<td>35 (22–66)</td>
<td>40 (22–65)</td>
<td>0.019†</td>
</tr>
<tr>
<td>Alcohol consumers, % (n)</td>
<td>54.6 (520)</td>
<td>52.1 (50)</td>
<td>NS*</td>
</tr>
<tr>
<td>Smokers, % (n)</td>
<td>23.6 (225)</td>
<td>30.2 (29)</td>
<td>NS*</td>
</tr>
<tr>
<td>1° Relative with MI history, % (n)</td>
<td>16.4 (156)</td>
<td>26.0 (23)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Diabetics, % (n)</td>
<td>2.1 (20)</td>
<td>4.2 (4)</td>
<td>NS*</td>
</tr>
<tr>
<td>Hypertensives, % (n)</td>
<td>9.0 (86)</td>
<td>21.9 (21)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BMI, kg/m², (SD)</td>
<td>23.9 (1.2)</td>
<td>25.6 (1.2)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (SD)</td>
<td>4.8 (1.2)</td>
<td>5.1 (1.2)</td>
<td>0.028‡</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (SD)</td>
<td>1.1 (0.0)</td>
<td>1.3 (0.0)</td>
<td>0.008‡</td>
</tr>
<tr>
<td>PAI-1 antigen, ng/mL (SD)</td>
<td>12.6 (1.9)</td>
<td>14.5 (2.0)</td>
<td>0.042‡</td>
</tr>
<tr>
<td>Fibrinogen, g/L (SD)</td>
<td>2.8 (0.0)</td>
<td>3.7 (0.0)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>ACE DD, % (n)</td>
<td>44.1 (420)</td>
<td>33.3 (32)</td>
<td>0.042‡</td>
</tr>
<tr>
<td>PAI-1 4G/4G, % (n)</td>
<td>25.6 (244)</td>
<td>25.0 (24)</td>
<td>NS*</td>
</tr>
<tr>
<td>Fibrinogen A 455 carrier, % (n)</td>
<td>36.6 (348)</td>
<td>39.6 (38)</td>
<td>NS*</td>
</tr>
</tbody>
</table>

Skewed variables (see Methods) were logarithmically transformed; geometric means and (antilog SDs) are indicated.

*| †Mann-Whitney U test.
‡Student’s t test.

CRP Levels and Environmental and Genetic Risk Factors

When the sample was analyzed according to CRP levels (Table 2), subjects whose levels were >0.33 mg/L turned out to be more often older, hypertensive, overweight, hyperlipidemic, and carriers of high plasma levels of fibrinogen and PAI-1 antigen than subjects with CRP levels below this cutoff value. A lower frequency of ACE DD carriers was observed among subjects whose first-degree relatives had suffered a myocardial infarction (Table 2). In addition, the percentage of subjects with first-degree relatives who had suffered a myocardial infarction was 1.5- to 2-fold higher in subjects with CRP levels >0.33 mg/L than in those with lower circulating concentrations of this variable (16.4% and 26.0%, respectively, P=0.017). The latter observation was further analyzed in a multiple regression analysis (Table 3). After adjustment for age (in years), total cholesterol (in millimoles per liter), and PAI-1 4G/4G carrier status (yes/no), the adjusted OR for subjects with CRP levels >0.33 mg/L was 1.75 (95% CI 1.05 to 2.91). The prevalence risk estimates for a 1-mmol/L increase in total cholesterol and for carriers of the PAI-1 4G/4G genotype were 1.35 (95% CI 1.11 to 1.65) and 1.72 (95% CI 1.20 to 2.45), respectively. A significant relationship between first-degree family history of myocardial infarction and age was also observed (OR 1.03, 95% CI 1.01 to 1.05).

Logistic regression models performed with interaction terms excluded any interaction between CRP and age (P=0.862), total cholesterol (P=0.192), and PAI-1 4G/4G
carrier status ($P=0.913$). The effects of CRP and age (or PAI-1 4G/4G carrier status) on the association with a first-degree relative with a history of myocardial infarction was additive. The association was significantly stronger with increasing age, especially in subjects whose CRP levels were >0.33 mg/L (Figure 1). Likewise, the 4G/4G subset exhibited a significantly higher prevalence OR, with a further increase in risk estimate among subjects with CRP levels >0.33 mg/L (Figure 2). When the subjects were stratified according to the median value of total cholesterol (4.87 mmol/L), a significantly increased OR was observed especially in the subset with CRP levels >0.33 mg/L (Figure 3).

Discussion

Twin studies have documented an important genetic component in the pathogenesis of coronary artery disease.26–28 The familial aggregation of risk factors for coronary artery disease suggests that in addition to environmental factors such as lifestyle habits, genetic factors play a significant role in determining their phenotypic expression.30 This implies that the susceptibility to atherothrombosis is largely accounted for by the clustering of several, possibly inherited, risk factors.31 In the present setting, the PAI-1 4G/5G polymorphism— but not the fibrinogen Bβ-chain G→A 455 and ACE I/D polymorphisms—identified the offspring of subjects with a family history of myocardial infarction (crude OR 1.66). This finding is in agreement with a previous report32 but disputes other studies.6,7 These inconsistencies may reflect differences in the genetic background of different ethnic groups. However, the possibility of a play of chance cannot be ruled out by the present data. One should also consider that the calculated ORs only reflect the association between a set of variables and a family history of myocardial infarction. Part of this risk may be mediated by other risk factors that have an important genetic component, eg, high blood pressure and diabetes mellitus.

In addition to genetic factors, the increased risk associated with a family history of myocardial infarction is currently attributed to the environmental factors that are more closely shared by individuals belonging to the same household. CRP levels become raised with age, BMI, and smoking habit.13 In our population, subjects whose CRP levels were >0.33 mg/L but differed for total cholesterol, triglycerides, PAI-1 antigen, and fibrinogen were more frequently hypertensive and had a higher BMI compared with subjects carrying CRP levels <0.33 mg/L (Table 2). The subsets with CRP above or below 0.33 mg/L also differed for median age (Table 2). In the present study, BMI, total cholesterol, triglycerides, plasma fibrinogen, and PAI-1 antigen values increased with increasing age. The age of the relatives may account for the difference between the 2 groups, as older subjects obviously have older relatives. However, age was not the most significant variable associated with a family history of myocardial infarction in our setting (Table 3). Thus, factors other than age are likely to play a role in this relationship. In a multiple regression model, the association between CRP and a positive family history was independent of established risk factors, a significant excess (adjusted OR 1.75) of a family history being present in carriers of CRP levels >0.33 mg/L in the present setting. Moreover, although logistic regression analysis eliminated the association between plasma fibrinogen, hypertension, and positive family history, it had only minor effects on the association between a family history of myo-

![Figure 1](https://www.jto.org/content/42/1/171/F1)

Figure 1. Bar graph of ORs according to CRP levels and quartiles of age as estimated by multiple logistic analysis, adjusted for total cholesterol and PAI-1 4G/4G carrier status. *$P<0.05$, †$P<0.005$.

![Figure 2](https://www.jto.org/content/42/1/171/F2)

Figure 2. Bar graph of ORs according to CRP levels and PAI-1 4G/4G carrier status as estimated by multiple logistic analysis, adjusted for total cholesterol and age. *$P<0.05$. 

### TABLE 3. Factors That Independently Identify Subjects With a Family History of Myocardial Infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>b</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol in mmol/L</td>
<td>0.3030</td>
<td>0.1004</td>
<td>9.1096</td>
<td>1</td>
<td>0.0025</td>
<td>1.35</td>
<td>1.11–1.65</td>
</tr>
<tr>
<td>PAI, 4G/4G vs non-4G/4G</td>
<td>0.5399</td>
<td>0.1820</td>
<td>8.8034</td>
<td>1</td>
<td>0.0030</td>
<td>1.72</td>
<td>1.20–2.45</td>
</tr>
<tr>
<td>Age in years</td>
<td>0.0268</td>
<td>0.0100</td>
<td>7.2285</td>
<td>1</td>
<td>0.0072</td>
<td>1.03</td>
<td>1.01–1.05</td>
</tr>
<tr>
<td>CRP &gt;0.33 mg/L</td>
<td>0.5571</td>
<td>0.2601</td>
<td>4.5887</td>
<td>1</td>
<td>0.0322</td>
<td>1.75</td>
<td>1.05–2.91</td>
</tr>
<tr>
<td>Constant</td>
<td>−3.4029</td>
<td>0.5217</td>
<td>42.5412</td>
<td>1</td>
<td>0.0000</td>
<td>⋮</td>
<td>⋮</td>
</tr>
</tbody>
</table>

b indicates the estimated coefficient. The multivariate logistic regression contained the following nonsignificant covariables: sex, hypertension, diabetes, alcohol consumption, smoking habit, BMI, fibrinogen, PAI-1 antigen, triglycerides, fibrinogen Bβ-chain G→A 455, and ACE I/D polymorphisms.
cardiac infarction and CRP (Table 3). Higher levels of CRP may be a cumulative indicator of the effect of cardiovascular risk factors, ie, hypertension, obesity, and hyperlipidemia.

In the present report, raised CRP concentrations enhanced the prevalence ORs of genetic as much as of environmental variables. Three-dimensional analysis of prevalence rates of family history, CRP, and age revealed a significant prevalence risk estimate for subjects with CRP levels >0.33 mg/L from the second to the fourth quartile of age. Likewise, a nearly 4-fold increase in OR was observed among individuals carrying the PAI-1 4G/4G genotype with CRP >0.33 mg/L compared with non-4G/4G subjects with CRP <0.33 mg/L. When the effect of total cholesterol was considered, a significant association with family history was mainly observed in subjects whose CRP levels were >0.33 mg/L.

A possible limitation of the present investigation was the collection of clinical data by a questionnaire. However, in the Tromsø Heart Study, there was a 78% agreement between a self-reported history of myocardial infarction in first-degree relatives and physician’s records, hospital records, and death certificates. Such agreement was >86% in an Australian Study. In the Tecumseh Community Health Study as well as in the study by Badenhop et al, underreporting of coronary events was more likely to occur than overreporting. In our study, information was collected by a well-trained staff and was limited to definite coronary ischemic events according to the World Health Organization questionnaire. This questionnaire has a specificity and a sensitivity of 91% and 81%, respectively, for angina pectoris; 91% and 87%, respectively, for myocardial infarction; and 90% and 92%, respectively, for intermittent claudication. Any inaccuracy would tend to lower rather than enhance risk estimates of a positive family history.

The mechanisms by which CRP levels are related to coronary artery disease are unclear. Vascular injury is an inflammatory and proliferative event, possibly enhanced by smoking and/or activation of the immune system (infection, immune disorders, etc). Elevated antibody titers against a variety of microorganisms (eg, cytomegalovirus, Chlamydia) have been observed in patients with coronary artery disease. It is conceivable that an elevated CRP level is a nonspecific but very sensitive marker of the inflammatory response to the injury. Similar to fibrinogen and PAI-1, CRP is an acute-phase reactant. Genetic determinants have been shown to be particularly relevant in the regulation of plasma fibrinogen and PAI-1 levels. Such regulation is unlikely to involve the molecular variations so far explored in the genes coding for fibrinogen and PAI-1. This implies that molecular variations of the genes playing a role in the acute-phase reaction (eg, interleukins like interleukin-6 and monokines like tumor necrosis factor-a) should be taken into account, and their clinical impact should be explored with emphasis on the present data. However, within families, it is conceivable that the relatives shared, beyond the genetic array, the same environmental risk factors, BMI and smoking habit, being related to CRP concentrations. Epidemiologists have drawn attention to the importance of social class as an important risk factor in determining health and illness. Differences in socioeconomic status may explain, at least partially, the findings obtained in the present cohort. To fully understand the relative importance of genetic/environmental factors behind this association, it would be necessary to evaluate the risk factors among relatives also. We do not have data on these variables for the relatives at the time of their myocardial infarction. Thus, it was not possible to further address the importance of the relationships we found.

In a large population of first-degree relatives, these results showed an important link between raised levels of CRP and a family history of myocardial infarction. Such an association was independent of the established risk factors for myocardial infarction. The offspring of patients with severe coronary artery disease often exhibits an aggregation of risk factors. Whether an index combining measurements of CRP and risk factor(s) would be a better marker than either variable evaluated alone needs to be evaluated in prospective studies.

References


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