Elevated Serum C-Reactive Protein Levels and Advanced Atherosclerosis in Youth

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Objective—To determine the associations among serum C-reactive protein (CRP) concentration, age, sex, risk factors for coronary heart disease (CHD), and atherosclerosis in young people.

Methods and Results—In 1244 subjects 15 to 34 years of age, we measured gross atherosclerotic lesions in the right coronary artery (RCA) and abdominal aorta (AA) and American Heart Association (AHA) lesion grade in the left anterior descending (LAD) coronary artery; serum CRP, lipoprotein cholesterol, and thiocyanate (for smoking) concentrations; intimal thickness of renal arteries (for hypertension); glycohemoglobin (for hyperglycemia); and body mass index (for obesity). Serum CRP levels increased with age, were higher in women than in men, and were positively related to obesity and hyperglycemia. Serum CRP ≥10 mg/L was associated with more extensive gross raised lesions in the RCA after age 25 and in the AA after age 30. Serum CRP ≥3 was associated with a greater prevalence of AHA grade 5 lesions in the proximal LAD coronary artery after age 25. The associations of CRP with lesions were independent of the traditional CHD risk factors.

Conclusion—Serum CRP level is independently associated with advanced atherosclerosis in young persons. (Arterioscler Thromb Vasc Biol. 2005;25:1237-1243.)

Key Words: atherosclerosis ■ youth ■ risk factors ■ C-reactive protein ■ coronary heart disease

The serum concentration of C-reactive protein (CRP), an acute-phase reactant marker of inflammation, is an independent risk factor for coronary heart disease (CHD),1 but the value of CRP in CHD risk assessment is not firmly established.2 Evidence regarding the association of CRP with preclinical atherosclerosis is limited, and the available results are mixed. However, markers of inflammation are associated with the CHD risk factors in children;3 and elevated CRP levels are associated with surrogate markers of atherosclerosis, such as brachial artery flow-mediated responsiveness, in children.4

In this report, we describe the association of serum CRP levels with the gross and microscopic features of atherosclerosis in young men and women from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study.

Methods

Study Subjects

Study subjects were persons 15 to 34 years of age who died of external causes (accidents, homicides, suicides) within 72 hours after injury and were autopsied within 48 hours after death in a cooperating forensic laboratory. The institutional review board of each participating center approved this study.

CRP Measurements

Serum CRP concentration was measured using a high-sensitivity ELISA method,5 which has a coefficient of variation of ~5%. We grouped CRP levels into 3 categories selected before statistical analysis: low, 0≤CRP<3 mg/L (n=1024; 82.3%); intermediate, 3≤CRP<10 (n=155; 12.5%); and high, CRP≥10 (n=65; 5.2%). Analyses indicated no association of lesions with 1≤CRP<3 mg/L compared with CRP<1 mg/L, and we combined these levels into the 0≤CRP<3 mg/L category.

There was no association between CRP level and time interval between death and autopsy (r=0.018; P=0.5243; mean 20.4 hours; SD 10.9 hours), nor between CRP level and time interval between death and refrigeration of the body (r=0.013; P=0.6775; mean 4.4 hours; SD 5.1 hours).

CHD Risk Factor Measurements

Methods for measuring the CHD risk factors are described in previous publications.6–8 Briefly, we measured total serum cholesterol concentration and high-density lipoprotein (HDL) cholesterol concentration (after precipitation of other lipoproteins) by a cholesterol oxidase method and calculated non-HDL cholesterol by sub-
traction. A non-HDL cholesterol concentration ≥160 mg/dL (4.14 mmol/L) was considered elevated, and an HDL cholesterol concentration <35 mg/dL (0.91 mmol/L) was considered low. A serum thiocyanate level ≥90 μmol/L defined a smoker. Mean blood pressure ≥110 mm Hg, indicated by the intimal thickness of small renal arteries, was identified as hypertension. Body mass index (BMI) ≥30 kg/m² indicated obesity, and red blood cell glycosylated hemoglobin ≥8% indicated hyperglycemia. CRP levels and all risk factor measurements were available for 1244 cases.

Arteries and Lesions
Three pathologists blindly and independently estimated the extent of fatty streaks and raised lesions in the abdominal aorta (AA) and right coronary artery (RCA) as described previously. The average of the 3 independent grades was used as the consensus grade. Gross assessment of lesions was available for 1223 AAs and 1192 RCAs. Two pathologists blindly and independently evaluated left anterior descending (LAD) coronary artery sections using the American Heart Association (AHA) grading system. Differences were resolved by discussion and a consensus grade was determined. Grade 0 designated a normal artery with no intimal lipid and with or without adaptive intimal thickening. Grade 1 and 2 lesions corresponded to gross fatty streaks; grade 1 contained isolated macrophage foam cells, and grade 2 contained numerous macrophage foam cells and fine particles of extracellular lipid but no pools of extracellular lipid. Grade 3 lesions contained numerous macrophage foam cells and ≥1 pools of extracellular lipid, but no well-defined core of lipid, and represented intermediate or transitional lesions. Grade 4 lesions contained numerous macrophage foam cells plus a well-defined core of extracellular lipid covered by normal intima. Grade 5 lesions showed ≥1 cores of extracellular lipid, plus a thickened fibrous cap, vascularization, or calcification. Grade 4 and 5 lesions corresponded to gross raised lesions. Grade 6 lesions were not encountered. AHA grades were available for 884 LAD coronary arteries.

Topographical Maps
The morphometry laboratory digitized the image of each Sudan IV–stained AA and RCA and an outline of raised lesions on a black-and-white print and converted the images to a standard template. Composite images were assembled to indicate prevalence of each type of lesion at each location in the image of the artery.

Statistical Methods
The relation of CRP level to sex, race, age, and the CHD risk factors was analyzed by multiple regression analysis. The distribution of CRP levels was positively skewed, and we analyzed the logarithm of CRP levels. The relation of extent of lesions (percent intimal surface involved) to CRP, with adjustment for sex, race, age, and the CHD risk factors, also was analyzed by multiple regression analysis. A logit transformation, with a small constant added to avoid the logarithm of zero, was applied to the percent surface area involved. Because expected frequencies were low, the StatXact software (3.0.2; Cytel Corp.) was used to calculate the P value. To examine the details of the association using the ordered nature of the AHA grade, the AHA grades were partitioned over a series of incremental cut points with the level of lesions for these data, and we report odds ratios (ORs) appropriate for each cut point. To analyze the association of CRP with AHA grade with adjustment for other variables, we used multivariable logistic regression analysis for the cumulative odds model.

Results
CRP and Sex, Race, and Age
Geometric mean CRP levels by sex, race, and 5-year age group are given in Table 1. CRP levels increased with age and hypertension (BMI ≥30 kg/m² indicated obesity, and red blood cell glycosylated hemoglobin ≥8% indicated hyperglycemia. CRP levels and all risk factor measurements were available for 1244 cases.

CRP and CHD Risk Factors
Geometric mean CRP levels by risk factor groups are given in Table 2. CRP was not associated with non-HDL cholesterol, smoking status, or hypertension. CRP was higher in cases of hyperglycemia (glycohemoglobin <8%) and hypertension (BMI ≥30 kg/m²) compared to normotensive and normoglycemic groups. CRP levels were positively skewed, and we analyzed the logarithm of CRP levels. The relation of extent of lesions (percent intimal surface involved) to CRP, with adjustment for sex, race, age, and the CHD risk factors, also was analyzed by multiple regression analysis. The proportional odds assumption was not valid for these data, and we report odds ratios (ORs) appropriate for each cut point. To analyze the association of CRP with AHA grade with adjustment for other variables, we used multivariable logistic regression analysis for the cumulative odds model.
with low HDL after age 25 (age by HDL interaction $P=0.0244$). CRP was significantly associated with obesity ($P=0.0187$) and with hyperglycemia ($P=0.0001$).

**CRP and Gross Lesions**

The association of extent of gross lesions with CRP levels was similar whether adjusted for CHD risk factors or not adjusted, and only adjusted values are presented. The mean extent involvement with fatty streaks and raised lesions in the AA and RCA by 5-year age group and CRP level, adjusted for sex, race, and risk factors (non-HDL cholesterol, HDL cholesterol, smoking, hypertension, obesity, and hyperglycemia), is given in Figure 1. The associations of CRP with fatty streaks and raised lesions were similar for men and women (sex by CRP interaction $P=0.2792$) and for whites and blacks (race by CRP interaction $P=0.6662$) for both arteries.

The extent of AA fatty streaks was not associated with CRP ($P=0.9788$). In 30- to 34-year-old subjects, the extent involvement with AA raised lesions was greater for those with CRP $10$ compared with 3 in every age group, although these differences were not statistically significant. The increase in RCA fatty streaks observed for cases with CRP $10$ in both 25- to 29-year-old subjects ($P=0.0087$) and 30- to 34-year-old subjects ($P=0.0013$). The extent involvement with RCA raised lesions did not differ significantly between those with 3 $\leq$ CRP $<10$ compared with those with CRP $<3$ ($P=0.5808$).

A total of 106 cases 25 to 34 years old had no CHD risk factors (Non-HDL cholesterol $\leq 160$ mg/dL; HDL cholesterol $\geq 35$ mg/dL; BMI $< 30$ kg/m$^2$; glycohemoglobin $<8$%; normotensive; and nonsmoker). Among these subjects, CRP was not significantly associated with AA fatty streaks, AA raised lesions, or RCA fatty streaks. Involvement with RCA raised lesions was greater for those with CRP $\geq 10$ compared with cases with CRP $<10$ (0.4 $\pm$ 0.1 for CRP $<10$; 1.1 $\pm$ 0.4 for CRP $\geq 10$; $P=0.0092$).

Topographical maps of raised lesion prevalence in the AA and RCA (Figure 2) show that after age 25, cases with 3 $\leq$ CRP $<10$ have slightly greater lesion prevalence, and those with CRP $\geq 10$ have substantially greater prevalence. The increased prevalence associated with CRP levels occurs in areas of the AA and RCA that are prone to raised lesions. Although unadjusted for CHD risk factors, these maps are consistent with the results of adjusted analyses of percent surface area involved with lesions (Figure 1).

**CRP and LAD Lesions**

The prevalence of AHA grade by 10-year age group and CRP level is shown in Table 3.

There was an association of AHA grade and CRP level in 25- to 34-year-olds but not in 15- to 24-year-olds (15 to 24 years: $\chi^2=3.10$, df=10, $P=0.9783$; 25 to 34 years: $\chi^2=16.61$, df=10, $P=0.0815$). Partitioning indicated a significant association of AHA grade with CRP $\geq 3$ compared with CRP $<3$ ($\chi^2=14.517$; df=5; $P=0.0123$) among 25- to 34-year-old persons but not among 15- to 24-year-old persons ($\chi^2=0.986$; df=5; $P=0.9834$). There was no association of AHA grade with CRP $10$ compared with 3 $\leq$ CRP $<10$ in either age group (15 to 24: $\chi^2=2.059$, df=4, $P=0.7517$; 25 to 34:...
χ² = 2.742, df = 5, P = 0.7397). We combined the 3 ≤ CRP < 10 and CRP ≥ 10 categories for subsequent analyses.

To further examine the relation of CRP to AHA grade in individuals 25 to 34 years old, we partitioned the AHA grades into 5 contrasting levels of severity of lesions (Table 4). There was no association of CRP with AHA grades 1 through 5 versus grade 0 (OR, 1.15; P = 0.5796). The association of CRP ≥ 3 with AHA grades 2 through 5 versus 0 and 1 (OR, 1.57; P = 0.0599) was of borderline statistical significance. The ORs for AHA grades 3 through 5 versus grades 0 through 2 (OR, 1.51; P = 0.1514) and grades 4 versus grades 0 through 3 (OR, 1.49; P = 0.2835) were of similar magnitude to the OR for grades 2 through 5 versus 0 and 1, although not statistically significant. The association of CRP ≥ 3 with AHA grade 5 versus 0 through 4 was statistically significant (OR, 3.92; P = 0.0054). The estimated OR of grade 5 versus 0 through 4 was the same whether comparing 3 ≤ CRP < 10 versus CRP < 3 (OR, 3.92; P = 0.0163) or CRP ≥ 10 versus CRP < 3 (OR, 3.92; P = 0.0685).

In cases aged 25 to 34 years, the OR for CRP (CRP ≥ 3 versus CRP < 3) and AHA grade 5 versus 0 through 4 in the LAD coronary artery, with multivariable adjustment for sex, race, age, and CHD risk factors, was 3.07 (95% CI, 1.08 to 8.75). ORs for other lesion comparisons were not statistically significant.

Seventy-seven cases 25 to 34 years old had no CHD risk factors. Three of the 77 cases, all with CRP < 3, had grade 4 lesions, and none of the 77 cases had grade 5 lesions. The ORs for grades 2 through 4 versus grades 0 and 1 (OR, 5.75; 95% CI, 1.71 to 19.38) and grades 3 and 4 versus grades 0 through 2 (OR, 4.67; 95% CI, 1.19 to 18.26) were statistically significant.

To investigate the possibility that an underlying association of smoking with elevated CRP levels was responsible for the association of elevated CRP with greater prevalence of grade 5 lesions, in cases 25 to 34 years old, we examined the association of CRP ≥ 3 with grades 5 versus 0 through 4 by

![Figure 2. Prevalence maps of raised lesions in the AA (top panels) and RCA (bottom panels) by CRP level and 10-year age group. y indicates years.](http://atvb.ahajournals.org/)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AHA Grade</th>
<th>CRP &lt; 3 mg/L</th>
<th>CRP ≥ 10 mg/L</th>
<th>CRP &lt; 3 mg/L</th>
<th>CRP ≥ 10 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>0</td>
<td>248 65.3</td>
<td>35 67.3</td>
<td>9 60.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>62 16.3</td>
<td>9 17.3</td>
<td>3 20.0</td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>53 14.0</td>
<td>5 9.6</td>
<td>3 20.0</td>
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</tr>
<tr>
<td></td>
<td>3</td>
<td>8 2.1</td>
<td>2 3.9</td>
<td>0 0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6 1.6</td>
<td>1 1.9</td>
<td>0 0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3 0.8</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>0</td>
<td>136 38.9</td>
<td>20 34.5</td>
<td>11 37.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
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<td>30 8.6</td>
<td>6 10.3</td>
<td>4 13.8</td>
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<td>2 3.5</td>
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<td>5</td>
<td>10 2.9</td>
<td>6 10.3</td>
<td>3 10.3</td>
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</tbody>
</table>
CRP levels were higher in subjects dying with, but not resulting from, severe coronary atherosclerosis, and were also higher in subjects dying because of recent coronary thrombosis without infarction, than in subjects dying from noncardiovascular causes with minimal coronary atherosclerosis. Immune reactivity to heat shock proteins, but not CRP concentration, was associated with carotid and femoral IMT in young (17 to 18 years) men. Human transgene expression accelerated aortic atherosclerosis in apolipoprotein E–deficient mice.

The AHA classification system is based on a temporal sequence that is deduced from lesions taken from standard locations in many persons of different ages. It is assumed that lesions of a given severity have passed through all lower levels of the lesion at an earlier age. Elevated serum CRP was associated with higher prevalence of grade 5 lesions after age 25. This result indicates that elevated serum CRP is associated with accelerated transition from grade 4 to more advanced grade 5 lesions. Grade 5 lesions have thicker and less orderly fibromuscular caps that have been disrupted by hematomas or thrombotic deposits. Thrombosis is likely to occur with an elevated CRP level, which is also associated with an elevated level of fibrin D-dimer. Whatever the mechanism, progression to a grade 5 lesion is clinically significant because such lesions are more likely to reduce lumen size.

There was a difference between the results based on the gross assessment of raised lesions in the RCA and the microscopic assessment of lesions in the LAD coronary artery. Although AHA grades 4 and 5 correspond to gross raised lesions, these 2 lesion types cannot be separated by gross grading. Grade 5 lesions are more prevalent than grade 4 lesions in the 3 ≤ CRP < 10 and CRP ≥ 10 categories (Table 3). This result suggests that most of the gross raised lesions in the RCA in the elevated CRP categories are likely grade 5. Grade 5 lesions in the LAD coronary artery were associated with CRP ≥ 3, whereas the extent of RCA raised lesions was associated only with CRP > 10. Possible reasons for this different association are that associations vary between different arteries and even between regions within arteries, or

### Summary of Results

Accounting for CHD risk factors, elevated serum CRP was associated with a greater extent of raised lesions in the RCA after age 25 and in the AA after age 30, and with a greater prevalence of grade 5 lesions after age 25. These findings indicate that elevated serum CRP is associated with accelerated progression of atherosclerosis in young adults independently of the traditional CHD risk factors.

### CRP and CHD Risk Factors

The positive association of serum CRP with age and the higher serum CRP concentrations in women are consistent with previous reports. The positive relationships of CRP with obesity and hyperglycemia are also consistent with other reports of an association with the metabolic syndrome and with obesity in adults and children. The lack of an association of CRP with smoking in this study may be attributable to the shorter period of smoking in these young subjects compared with the longer exposure to smoking in middle-aged adults.

### CRP and Atherosclerotic Lesions

Two cross-sectional studies of adults showed no association between CRP levels and carotid intima-media thickness (IMT) measured by ultrasound. Two other studies found no association between serum CRP and coronary artery calcification. The Framingham Study found an association between CRP and internal carotid IMT (but not common carotid IMT) only in women.

### Discussion

#### CRP and CHD Risk Factors

Immune reactivity to heat shock proteins, but not CRP concentration, was associated with carotid and femoral IMT in young (17 to 18 years) men. Human transgene expression accelerated aortic atherosclerosis in apolipoprotein E–deficient mice.

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that microscopic assessments are simply more sensitive than the percent intimal surface involved with gross lesions.

In all of the studies relating CRP to atherosclerosis and CHD, including the present one, the analysis and interpretation of results are complicated by the association of CRP levels with obesity, hyperglycemia, and smoking, all of which are independently associated with atherosclerosis and CHD. Despite these possible sources of confounding, extensive analyses of data from PDAY subjects indicate that the association of CRP with advanced atherosclerosis is independent of the traditional CHD risk factors.

Most reports and reviews indicate that CRP >3 mg/L represents high risk, although some suggest that CRP >10 may be attributable to acute infections and that such values initially should be ignored. The association of CRP may be attributable to acute infections and that such values are independently associated with atherosclerosis and CHD.

Implications for Prevention
Numerous studies have reported that the statin drugs lower CRP levels as well as lower low-density lipoprotein (LDL) cholesterol levels, and statins have been suggested for subjects with high CRP levels as an additional measure to retard the progression of atherosclerosis. However, pharmacological intervention in young persons with high CRP levels may not be necessary because weight loss alone is associated with reduction in CRP levels.

Exercise training and concomitant weight loss reduce CRP, regardless of CRP genotype, and cardiac rehabilitation and exercise training also are associated with substantial reductions in CRP levels independently of weight loss. Although these promising results of exercise and weight loss so far are limited to middle-aged and older adults, they suggest that similar effects likely to lower serum CRP levels.

Conclusion
The results of this study indicate that an elevated serum CRP concentration is independently associated with advanced coronary and abdominal aortic atherosclerosis in young adults. These results provide additional justification for recommending that young persons adopt a healthy lifestyle for the long-range prevention of CHD and related atherosclerotic diseases.

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References


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