High-Sensitivity C-Reactive Protein Is Not Associated With Carotid Intima-Media Progression

The Carotid Atherosclerosis Progression Study

Matthias W. Lorenz, MD; Peter Karbstein; Hugh S. Markus, FRCP, MD; Matthias Sitzer, MD

Background and Purpose—It is unclear whether elevated serum C-reactive protein (CRP) is causal to the initiation and progression of atherosclerosis. We undertook a prospective longitudinal cohort study to address this question.

Methods—In a population-based sample of 3122 subjects, we measured carotid intima media thickness (IMT) at baseline and after 3 years and surveyed clinical events. Associations between baseline high-sensitivity CRP (hs-CRP) and baseline IMT, and IMT progression were determined before and after controlling for vascular risk factors. The relationship between baseline IMT and clinical events during follow up was determined.

Results—All vascular risk factors were significantly associated with hs-CRP (P<0.001). Hs-CRP was significantly associated with baseline IMT in all carotid segments (P<0.001), but this association was no longer significant after controlling for age, gender, and cardiovascular risk factors. Hs-CRP was not related to individual IMT progression. Interactions between hs-CRP and body mass index, HbA1c, or blood pressure showed no association with IMT progression. Baseline hs-CRP was related to the risk of clinical events (myocardial infarction or stroke or death, hazard ratio of 1.22 per mg/L hs-CRP increase, 95% CI: 1.07 to 1.39, P=0.004, adjusted for age and gender), but this association was not significant after controlling for age, gender, and cardiovascular risk factors (1.59, 95% CI: 0.96 to 2.64, P=0.072).

Conclusions—Our results suggest that hs-CRP is not an independent causal factor for the initiation and progression of early atherosclerotic changes of the carotid arteries. Univariate associations between hs-CRP and IMT were largely explained by confounding by age, gender, and cardiovascular risk factors. (Stroke. 2007;38:1774-1779.)

Key Words: atherosclerosis ■ carotid artery ■ C-reactive protein ■ inflammation ■ intima media thickness

Increasing evidence implicates inflammation in the pathogenesis of atherosclerosis and cardiovascular disease, including stroke. This is supported by the association of inflammatory biomarkers with atherosclerosis. Cross-sectional studies have found associations between elevated C-reactive protein (CRP) and both clinical cardiovascular events1-7 and subclinical atherosclerosis.8-11 Carotid intima media thickness (IMT) has been widely used as an indicator of subclinical atherosclerosis, and CRP has been associated with increased IMT in both risk populations12,13 as well as in population-based samples.8-11

Whether CRP itself plays a causal role in the initiation and progression of atherosclerosis remains uncertain. Recent evidence has suggested a possible direct pathogenic role.14 Alternatively, it may merely be an epiphenomena and an indicator of systemic inflammation, which itself is associated with atherosclerosis. A number of conventional cardiovascular risk factors such as smoking, obesity, and the metabolic syndrome may act to increase atherogenesis partly through increasing systemic inflammation. The systemic inflammatory response is heightened in smokers and relates to pack-years of smoking.15 This may relate both to bacterial endotoxin, a potent mediator of inflammation, which has been identified as an active component of cigarette smoke,16 and the increased risk of respiratory tract infection seen in smokers. Adipose tissue has been shown to secrete inflammatory cytokines,17 whereas a number of inflammatory mechanisms have been suggested as mediators between insulin resistance and hyperglycemia and atherosclerosis.18 Therefore, elevated CRP may merely reflect an exaggerated inflammatory response associated with these conventional cardiovascular risk factors.19,20 If CRP plays a causal role, one would expect baseline CRP levels to predict future atherosclerosis progression, ie, patients with elevated CRP at baseline would have more rapid progression of carotid IMT. To date, the information on CRP and progression of atherosclerosis is contradictory.21-23

In the current study, we determined CRP and carotid IMT at baseline in a large community population. We repeated...
IMT measurements at 3 years and determined whether elevated CRP at baseline predicted both IMT progression and clinical cardiovascular events during the follow-up period.

Methods

Subjects
The study sample was taken from participants in the Carotid Atherosclerosis Progression Study, details of which have been published elsewhere. After a mean follow-up period of 38.5 (±4.3) months, a repeat ultrasound investigation was performed in 3422 subjects. Of these, frozen serum samples were available in 3122 subjects. This subsample was chosen for the present study. All IMT measurements were performed using a semiautomated analysis system as described subsequently by readers blind to clinical features, including high-sensitivity CRP (hs-CRP). For the follow-up IMT measurements, the readers were blind to the individual baseline IMT. Details of the risk factor assessment protocol have previously been published. All risk factors were assessed blind to IMT and laboratory results, including hs-CRP.

Intima Media Thickness Measurements
Ultrasound imaging and offline IMT image analysis methods have been described in detail in earlier publications. In brief, ultrasonic examinations were performed with a 7.5-10.0-MHz linear array transducer (P700SE; Phillips Medical System). Using anterooblique insonation, far-wall carotid IMT was visualized bilaterally at 3 sites: the common carotid artery (CCA-IMT, 20 to 60 mm proximally from the flow divider), the carotid bifurcation (BIF-IMT, 0 to 20 mm proximally from the flow divider), and the internal carotid artery bulb (ICA-IMT, 0 to 20 mm distally from the flow divider). The images were digitally captured during the systole of a single heartbeat for offline measurement. For one in every 100 subjects, vertical and horizontal calibration measurements were carried out with an ultrasound quality assurance phantom. Carotid IMT measurements were performed offline using automated imaging processing software as previously reported.

The average intraclass correlation coefficient for interobserver reliability was 0.97 (95% CI: 0.96 to 0.98; P<0.001), and the ±2 SD of the difference between 2 observers varied between 0.03 and 0.06 mm. Furthermore, the intraobserver test–retest reliability testing revealed an intraclass correlation coefficient of 0.93 (95% CI: 0.91 to 0.94; P<0.001), and the ±2 SD of the difference between the first and second examination varied between 0.04 and 0.06 mm.

The change in individual IMT values from every carotid site was determined (follow-up value minus baseline value) and divided by the number of years between baseline and follow up to calculate absolute annual IMT progression. The resulting values were averaged between left and right side of every carotid segment.

Clinical Events
Follow-up events were identified from the primary healthcare scheme records as described in an earlier publication. These data were examined for myocardial infarctions (International Classification of Diseases, 9th Revision [ICD-9]: 410, 411, or 413; ICD-10: I 20 to 24), stroke (ICD-9: 430 to 434 or 436; ICD-10: I 60 to 64) and death. Data management of follow-up data were done blind to all other subject characteristics.

C-reactive Protein Determination
At baseline examination, a blood sample from every participant was drawn and centrifuged within 30 minutes; the serum samples were stored at −80°C. In 2006, the samples were thawed and hs-CRP was determined using an IMMAGE automatic immunoassay system (Beckmann-Coulter). The intrasay variability coefficient lies between 5.0% and 5.0%, the interassay variability coefficient is between 3.8% and 7.5%, and the lower detection limit of the assay is 0.2 mg/L.

Statistical Analyses
For intergroup comparisons, we used the χ² homogeneity test or the Kruskal–Wallis test as appropriate. Associations between continuous variables were determined using Spearman rank correlation. To compare IMT values among hs-CRP quartiles with adjustment to risk factors, we calculated “adjusted IMT values” as follows. Linear models were established with IMT of the respective carotid segment as the dependent variable, including the covariates we wanted to adjust for. Residuals of these linear models were added to the mean of the predicted values and taken as adjusted IMT.

For the analysis of censored data, we used Kaplan–Meier statistics, the log rank test, and Cox regression models. Because hs-CRP was not normally distributed, we categorized into quartiles and compared between these by means of dummy variables. All calculations were done with the SPSS 11.5 software package (SPSS Inc.). In cases with missing values, the relevant case was excluded from that analysis. Numbers of missing cases are specified in the tables and number of cases used in each analysis indicated.

The study was approved by the ethical review committee of the University Hospital of Frankfurt am Main.

Results
Demographic characteristics and cardiovascular risk factor profiles for the subjects are shown in Table 1. Age, gender, and all cardiovascular risk factors (with the exception of statin use) were highly significantly correlated with hs-CRP (all P<0.001).

High-Sensitivity C-reactive Protein and Baseline Intima Media Thickness
The relationship between baseline IMT and hs-CRP is shown in Table 2. For all 3 carotid segments, there was a highly significant (P<0.001) relationship between increasing CRP and increasing IMT. After controlling for age and gender, this association remained highly significant (P=0.002) for CCA-IMT, unlike BIF-IMT and ICA-IMT. The relationship between hs-CRP and IMT in all carotid segments was no longer significant when cardiovascular risk factors (body mass index [BMI], systolic and diastolic blood pressure, antihypertensive treatment, low-density lipoprotein cholesterol, statin treatment, smoking, and Hba1c) were controlled for.

High-Sensitivity C-reactive Protein and Intima Media Thickness Progression
A total of 55.1% of subjects (1720 of 3122) had progression of IMT in the CCA, 65.9% in the BIF (2058 of 3114), and 64.3% in the ICA (2006 of 3112); the others had regression. There was no correlation between baseline hs-CRP and IMT progression in any carotid segment (Spearman rank correlation) and no difference in IMT progression between hs-CRP quartiles on univariate analysis (Kruskal–Wallis test; see Figure 1) or multivariate analysis. Diabetic or hypertensive, overweight, or smoking subsamples did not exhibit any association between hs-CRP and IMT progression, respectively. The interaction terms “hsCRP*systolic blood pressure,” “hsCRP*diastolic blood pressure,” “hsCRP*Hba1c,” and “hs-CRP*BMI” revealed no significant influence on IMT progression. The interaction term “hs-CRP*pack-years” showed a significant negative association with CCA-IMT progression (P=0.012 in a model with age, gender, hs-CRP, pack-years, and the interaction term). This association remained after adjustment for BMI, systolic and diastolic blood
TABLE 1. Subject Characteristics at Baseline by hs-CRP Quartiles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Percent Missing</th>
<th>Total Population (n=3122)</th>
<th>First Quartile* of hs-CRP (n=778)</th>
<th>Second Quartile* of hs-CRP (n=778)</th>
<th>Third Quartile* of hs-CRP (n=778)</th>
<th>Fourth Quartile* of hs-CRP (n=778)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0</td>
<td>51.3±12.3</td>
<td>47.2±12.0</td>
<td>51.4±12.2</td>
<td>54.0±12.6</td>
<td>54.3±13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>0</td>
<td>48.8%</td>
<td>53.4%</td>
<td>58.7%</td>
<td>47.2%</td>
<td>35.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0</td>
<td>26.6±4.0</td>
<td>24.4±3.0</td>
<td>26.2±3.3</td>
<td>27.0±3.6</td>
<td>28.2±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>0</td>
<td>23.3%</td>
<td>14.2%</td>
<td>21.2%</td>
<td>26.6%</td>
<td>31.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.03</td>
<td>127.8±16.7</td>
<td>124.2±14.5</td>
<td>126.9±14.0</td>
<td>130.0±17.4</td>
<td>133.5±18.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.03</td>
<td>77.5±10.0</td>
<td>76.4±9.2</td>
<td>77.1±9.1</td>
<td>78.2±9.9</td>
<td>79.3±10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>0</td>
<td>20.4%</td>
<td>12.1%</td>
<td>17.6%</td>
<td>23.4%</td>
<td>28.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L</td>
<td>37.6</td>
<td>1.50±1.0</td>
<td>1.28±0.97</td>
<td>1.44±1.09</td>
<td>1.59±0.95</td>
<td>1.66±0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>25.0</td>
<td>5.75±1.06</td>
<td>5.79±1.03</td>
<td>5.93±0.95</td>
<td>6.10±1.11</td>
<td>6.03±1.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>0.3</td>
<td>3.37±0.92</td>
<td>3.29±0.85</td>
<td>3.48±0.85</td>
<td>3.61±0.93</td>
<td>3.60±0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>9.3</td>
<td>1.55±0.45</td>
<td>1.67±0.47</td>
<td>1.56±0.43</td>
<td>1.55±0.45</td>
<td>1.50±0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of statins, %</td>
<td>0</td>
<td>0.9%</td>
<td>1.1%</td>
<td>1.0%</td>
<td>0.6%</td>
<td>0.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-years of cigarettes smoked</td>
<td>0</td>
<td>7.9±13.7</td>
<td>6.6±11.0</td>
<td>7.2±11.1</td>
<td>8.2±13.1</td>
<td>9.2±14.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>0</td>
<td>2.5%</td>
<td>1.3%</td>
<td>1.4%</td>
<td>2.7%</td>
<td>4.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hba1c, %</td>
<td>0.2</td>
<td>5.29±0.62</td>
<td>5.19±0.41</td>
<td>5.29±0.55</td>
<td>5.36±0.53</td>
<td>5.46±0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>0</td>
<td>0.248±0.437</td>
<td>0.036±0.012</td>
<td>0.094±0.022</td>
<td>0.203±0.042</td>
<td>0.72±0.870</td>
<td>...</td>
</tr>
</tbody>
</table>

*First quartile: 0.058 mg/L or less, second quartile: 0.058 to 0.136 mg/dL, third quartile: 0.136 to 0.286 mg/L, fourth quartile: more than 0.286 mg/L.
†χ² homogeneity test for proportion; otherwise Kruskal–Wallis test.
NS indicates not significant.

pressure, antihypertensive medication, low-density lipoprotein cholesterol, and Hba1c (P=0.010). The interaction term showed no significant association with BIF- and ICA-IMT progression.

**High-Sensitivity C-reactive Protein and Clinical Events**
During a mean follow-up period of 4.3 (±1.0) years, 147 myocardial infarctions, 57 strokes, and 11 deaths (any cause of death) occurred. The number of combined events (myocardial infarction or stroke or death) was increased in the higher quartiles of hs-CRP (see Figure 2, P<0.001 in the log-rank test). In a Cox regression model, hs-CRP significantly increased the hazard for combined events (hazard ratio of 2.53 for the highest versus the lowest hs-CRP quartile, 95% CI: 1.64 to 3.92, P<0.001). After adjustment for age and gender, the effect decreased (hazard ratio of fourth versus first quartile 1.86, 95% CI: 1.18 to 2.92, P=0.008). When adjusted for age, gender, and other risk factors (as listed previously), the hazard ratio between these hs-CRP quartiles became even smaller and lost statistical significance (hazard ratio of 1.59, 95% CI: 0.96 to 2.64, P=0.072).

**TABLE 2. IMT at Baseline by hs-CRP Quartiles**

<table>
<thead>
<tr>
<th>IMT (mm) in the:</th>
<th>Percent Missing</th>
<th>First Quartile of hs-CRP (n=778)</th>
<th>Second Quartile of hs-CRP (n=778)</th>
<th>Third Quartile of hs-CRP (n=778)</th>
<th>Fourth Quartile of hs-CRP (n=778)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA-IMT</td>
<td>0.1</td>
<td>0.69±0.12</td>
<td>0.74±0.16</td>
<td>0.75±0.16</td>
<td>0.76±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age and gender</td>
<td></td>
<td>0.72±0.10</td>
<td>0.73±0.14</td>
<td>0.74±0.13</td>
<td>0.75±0.13</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjusted for age, gender, and other risk factors†</td>
<td></td>
<td>0.73±0.10</td>
<td>0.74±0.13</td>
<td>0.74±0.13</td>
<td>0.73±0.13</td>
<td>NS</td>
</tr>
<tr>
<td>BIF-IMT</td>
<td>0.1</td>
<td>0.84±0.25</td>
<td>0.94±0.36</td>
<td>0.94±0.36</td>
<td>0.94±0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age and gender</td>
<td></td>
<td>0.89±0.21</td>
<td>0.93±0.33</td>
<td>0.92±0.31</td>
<td>0.93±0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Adjusted for age, gender, and other risk factors†</td>
<td></td>
<td>0.90±0.21</td>
<td>0.93±0.32</td>
<td>0.92±0.31</td>
<td>0.91±0.27</td>
<td>NS</td>
</tr>
<tr>
<td>ICA-IMT</td>
<td>0.1</td>
<td>0.72±0.22</td>
<td>0.77±0.32</td>
<td>0.78±0.31</td>
<td>0.79±0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age and gender</td>
<td></td>
<td>0.75±0.21</td>
<td>0.76±0.29</td>
<td>0.76±0.28</td>
<td>0.79±0.30</td>
<td>NS</td>
</tr>
<tr>
<td>Adjusted for age, gender, and other risk factors†</td>
<td></td>
<td>0.76±0.20</td>
<td>0.77±0.29</td>
<td>0.76±0.28</td>
<td>0.77±0.29</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Kruskal–Wallis test.
†BMI, systolic and diastolic blood pressure, antihypertensive treatment, low-density lipoprotein cholesterol, intake of statins, nicotine consumption, and Hba1c. NS indicates not significant.
models adjusted for age, gender, and the components of the respective interactions, the interaction terms “hsCRP* systolic blood pressure,” “hsCRP* diastolic blood pressure,” “hsCRP* HbA1c,” “hs-CRP* BMI,” and “hs-CRP* pack-years” revealed no significant influence on the combined events.

Discussion

In this large community population, we found a highly significant relationship between baseline CCA-IMT and hs-CRP, but this disappeared after controlling for conventional cardiovascular risk factors. During prospective follow up, baseline hs-CRP levels were related to future cardiovascular events. This relationship was weakened after controlling for age, gender, and cardiovascular risk factors. There was no relationship between hs-CRP at baseline and progression of IMT over a 3-year period. In addition, there were no interactions between CRP and blood pressure, BMI, or HbA1c that were influential on IMT progression or clinical events and no relationships seen in subgroups. The negative association between the interaction “hs-CRP* pack-years” and CCA-IMT progression would mean that the effect of both risk factors on atherosclerosis progression is smaller than the sum of the effects of both individual factors. This would be consistent with the hypothesis that in smoking subjects, hs-CRP is raised as a sequel to smoking rather than being an independent causal factor. However, this association was detectable in association with the clinical end point, although this is statistically less powerful. Overall, our results are consistent with CRP not playing a causal role in increased IMT. Our results suggest the reported associations, and the associations found in our data before controlling for risk factors, are primarily an epiphenomena related to cardiovascular risk factor load. These findings are consistent with an earlier article in which we investigated the association between IMT and baseline in a smaller subsample of this
population with a different CRP assay but did not look at relationships with IMT progression or clinical events.

Considerable epidemiological evidence has linked increased CRP levels with increased risk of cardiovascular events, both cardiac and cerebral. A number of these have suggested this association is independent of conventional risk factors, although others have found it attenuated when conventional risk factors are controlled for. We have found in this population. A number of potential mechanisms by which CRP may play a causal role in atherosclerosis and cardiovascular disease have been implicated, including recruitment of monocytes to the atherosclerotic lesion, intimal growth, and endothelial dysfunction. However, increasing evidence has demonstrated that cardiovascular risk factors, particularly those associated with low-grade inflammation such as obesity, are important determinants of CRP levels. One method of avoiding this confounding by lifelong exposure to environmental risk factors is to use the approach of Mendelian randomization and identify individuals who have a genetic variant associated with lifelong increased CRP levels. A recent study found such variants were not associated with cardiovascular disease arguing against a causal role for CRP.

A number of other groups have investigated the association between hs-CRP and IMT progression. The INVADE study looked at a large community population and found an association between baseline hs-CRP and IMT progression, which disappeared after adjustment for cardiovascular risk factors. However, a significant interaction with HbA1c was found. A series of small studies from Hashimoto et al were in patients with cardiovascular risk factors and hypertension reported positive associations between baseline hs-CRP and progression of plaque number and plaque area. Juonala et al found no association between hs-CRP in childhood (3 to 18 years of age) with IMT 21 years later. There are important differences between these populations, which may account for the differing results. Most of the positive associations have been reported in at-risk populations with more advanced atherosclerosis rather than populations with predominantly early IMT thickening. The INVADE study population was older than the Carotid Atherosclerosis Progression Study population (mean, 70 versus 50 years) and had a higher proportion of diabetic (25% versus 2.4%) and hypertensive (mean systolic blood pressure 140 versus 128 mm Hg) patients. Hashimoto et al’s studies were in patients with advanced disease, although these were in small populations. There are many similarities between our data and those from the other large study INVADE. Both found associations that were markedly reduced after controlling for cardiovascular risks factors. This would be consistent with the unadjusted association with CRP found in both studies being attributable either to confounding or because risk factors act through inflammation and elevation of CRP. INVADE suggested the latter, particularly for glucose intolerance/diabetes. In our data, we found an interaction with smoking suggesting this risk factor may act through increasing inflammation (and therefore CRP). We did not find an interaction with diabetes, but low prevalence of diabetes in the Carotid Atherosclerosis Progression Study compared with INVADE will have reduced our power to detect interactions with glucose intolerance/diabetes.

IMT thickening reflects early atherosclerotic change as well as vessel remodeling. Therefore, studies using this end point can only identify associations with early disease processes. The number of patients with plaques was insufficient to investigate associations with more advanced atherosclerosis in our population. Therefore, it is possible that CRP could play a causal role in the later stages of atherosclerosis such as plaque instability.

The lack of association between hs-CRP and IMT progression in our data may also reflect methodological issues. The rate of progression over a 3-year period is relatively small, and this combined with measurement error reduces the ability to detect an association. Nevertheless, we have identified associations between cardiovascular risk factors and IMT in this population. We have also demonstrated a high degree of interobserver and intraobserver reproducibility in IMT measurement. Although the follow up in our cohort is longer than in previous studies, longer-term follow up will increase the power to detect such associations.

In conclusion, our results suggest that the relationship between hs-CRP and IMT is not causal and explained by conventional cardiovascular risk factors increasing both CRP and cardiovascular risk independently.

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Disclosures
None.

References


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