C-reactive Protein Level and Traditional Vascular Risk Factors in the Prediction of Carotid Stenosis

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Hypothesis: There is no relationship between C-reactive protein (CRP) level and the presence and degree of carotid stenosis (null hypothesis).

Design: Institutional review board–approved cohort study.

Setting: Tertiary care regional medical center.

Patients: Patients (N=146) referred to a vascular surgery clinic for possible carotid stenosis.

Interventions: Baseline serum high-sensitivity CRP level, low-density lipoprotein cholesterol (LDL-C) level, and other traditionally used vascular risk factors were assessed in all patients. All underwent vascular surgery clinical examination, including bilateral duplex ultrasonography of their carotid bifurcations.

Main Outcome Measures: The potential relationship between serum CRP level and the presence and degree of carotid stenosis, as well as the strength of this association with traditionally established demographic, historical, and laboratory risk factors such as age, hypertension, and LDL-C level.

Results: In unadjusted analysis, CRP level, coronary artery disease (CAD), and lower extremity peripheral vascular disease (PVD) positively correlated with carotid stenosis (Pearson product moment correlation r < 0.02 for all). Low-density lipoprotein cholesterol level and other risk factors, including age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, and neurologic history, did not. The mean ± SD CRP level was higher among 72 patients with carotid stenosis compared with that among 74 patients without carotid stenosis (3.7 ± 6.1 vs 1.9 ± 2.1 mg/L [to convert to nanomoles per liter, multiply by 9.524], P = .02), as were the baseline prevalences of CAD (49% vs 29%), PVD (27% vs 11%), and (84% vs 61%) (P = .03 for all). The mean ± SD LDL-C levels were similar between the groups (92.3 ± 28.6 vs 95.8 ± 29.0 mg/dL [to convert to milimoles per liter, multiply by 0.0259], P = .8), and differences in the prevalences of other risk factors were not statistically significant. In multivariate regression analysis adjusting for age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, recent neurologic symptoms (<120 days), CAD, PVD, myocardial infarction, stroke or transient ischemic attack, hypercholesterolemia, aspirin or nonsteroidal anti-inflammatory drug use, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) use, CRP level was independently associated with carotid stenosis (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.1-1.5; P = .04), and LDL-C level was not (OR, 1.0; 95% CI, 0.98-1.01; P = .8). Several risk factors had larger ORs for carotid stenosis than CRP level; however, none were statistically significant. C-reactive protein level and CAD were independently associated with the actual degree of carotid stenosis in multivariate analysis. No corresponding associations for LDL-C level or other risk factors were observed.

Conclusion: C-reactive protein level is a moderate but statistically significant marker of carotid stenosis and may be a useful adjunct to accurate global vascular risk assessment.

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See Invited Critique at end of article
tionship between serum CRP level and the presence and degree of carotid stenosis. We hypothesized that similar inflammatory processes involved in coronary disease might manifest in atherosclerotic carotid arteries, perhaps making CRP level useful in this context as well. Second, we wanted to compare the strength of this association, if any, against that of traditionally established vascular risk factors in an attempt to characterize the additive potential of CRP level to established risk management strategies.

METHODS

DESIGN

This is an institutional review board–approved, Health Insurance Portability and Accountability Act of 1996–compliant prospective cohort study designed (1) to evaluate the potential relationship between serum CRP level and the presence and degree of carotid stenosis and (2) to compare the strength of this association with traditionally established demographic, historical, and laboratory risk factors such as age, hypertension, and LDL-C level. The protocol has 2 arms, a study cohort with carotid stenosis and a control group without disease as defined by bilateral carotid duplex ultrasonography velocity criteria.

PATIENTS

The study was available to any male or female patient 40 years or older who was referred to, or followed up by, the vascular surgery service for possible, known, unilateral, bilateral, symptomatic, or asymptomatic carotid stenosis. Referral patients in general were evaluated in outpatient consultation for a recent stroke, amaurosis fugax, syncope episode, asymptomatic bruit, or transient ischemic attack (TIA). Patients with known disease were offered enrollment at a regularly scheduled surveillance visit or during an evaluation for new symptoms such as recent stroke or TIA. Patients younger than 40 years, pregnant, or with documented active infection, untreated malignant neoplasms, or a chronic autoimmune condition, or those using a corticosteroid were excluded. There were no other exclusions. Of approximately 160 consecutive eligible patients, 149 were interested, enrolled, and studied. Subsequently, 3 patients requested disenrollment or were lost to follow-up before all study procedures were completed, leaving 146 patients available for analysis.

PROCEDURES

All interested eligible patients provided informed consent and were enrolled by the study research nurse. A standardized historical questionnaire was completed, risks and benefits of the study and of evaluation for carotid stenosis were discussed, and scheduled study visits were arranged. Baseline fasting serum high-sensitivity CRP and LDL-C levels were evaluated for all patients. All patients then underwent a vascular clinical examination by a staff vascular surgeon with supervised resident assistance, including a complete medical history and physical examination. Formal bilateral carotid duplex ultrasonography was performed on all patients by a registered vascular technologist at an Intersocietal Commission for the Accreditation of Vascular Laboratories–certified vascular laboratory.

On the basis of duplex velocities, patients were placed in the experimental (disease) study cohort or the control (no disease) group. The experimental cohort included any patient found to have carotid stenosis in 1 or both carotid arteries as defined by bilateral carotid duplex ultrasonography demonstrating internal carotid artery or bulb velocity measurements of 125 cm/s or greater in either artery. A corresponding control group without carotid stenosis demonstrated internal carotid artery or bulb velocity measurements of less than 125 cm/s in both arteries.

STATISTICAL ANALYSIS

Continuous data were compared using independent t tests and categorical proportions using χ² analysis or the Fisher exact test as appropriate. Prevalence data, Pearson product moment r correlations, and odds ratios (ORs) were calculated using the standard equations. Logistic regression analysis was used to examine the independent associations of high-sensitivity CRP level against LDL-C level and various other traditional vascular risk (TVR) factors, with the binary categorical outcome measure being the confirmed presence of 125 cm/s or greater carotid stenosis in either carotid artery by duplex ultrasonography. A corresponding linear regression analysis was performed using the same covariates but with the continuous outcome of actual velocity in centimeters per second to evaluate the relationship of the study variables with the degree of measured carotid stenosis.

Regression equations took the following form: outcome variable = \( b_0 + b_1(TVR_a) + b_2(TVR_b) + b_3(TVR_c) \) (where \( b \) indicates the regression coefficient representing the amount the dependent variable changes when a corresponding independent variable changes 1 U, and the subscript indicates that that coefficient corresponds to that specific variable). The TVR factors studied included age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, recent neurologic symptoms (<120 days), coronary artery disease (CAD), lower extremity PVD, myocardial infarction, stroke or TIA, hypercholesterolemia, and LDL-C level. Potential confounders such as aspirin or nonsteroidal anti-inflammatory drug use or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) use were also included in the models to minimize this potential source of bias because these drugs are known to affect CRP levels. Comparative receiver operating characteristic (ROC) curves were prepared for all study variables with the categorical outcome of carotid stenosis (velocity, ≥125 cm/s). Each area under the ROC curve was calculated and compared against a null line. Statistical significance was set at \( P < .05 \) and reflected 2-tailed distributions in all cases. Statistical analysis was performed using commercially available software (SPSS Windows version 11; SPSS Inc, Chicago, Illinois).

In unadjusted analysis, CRP level, CAD, and lower extremity PVD positively correlated with carotid stenosis (Pearson product moment correlation \( r < 0.02 \) for all). Low-density lipoprotein cholesterol level and other risk factors, including age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, and neurologic history, did not. Among the subset of patients with confirmed carotid stenosis (n = 72), 11 patients (15.3%) endorsed documented ipsilateral neurologic symptoms within 120 days of study enrollment, and the remaining 61 patients (84.7%) were asymptomatic. The mean ± SD CRP level was higher among symptomatic compared with asymptomatic patients with carotid stenosis (3.1 ± 7.1 vs 2.8 ± 3.7 mg/L; [to convert to nanomoles per liter, multiply by 9.524]), but this difference was not statistically significant (\( P = .11 \)). The mean ± SD CRP levels were higher among 72 patients with carotid stenosis compared with those among 74 patients without carotid ste-

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Table 1. High-Sensitivity C-reactive Protein (CRP) Level, Low-density Lipoprotein Cholesterol (LDL-C) Level, and Age Stratified by the Presence or Absence of Confirmed Carotid Stenosis by Duplex Ultrasonography

<table>
<thead>
<tr>
<th>Continuous Study Variable</th>
<th>No Carotid Stenosis (n=74)</th>
<th>Carotid Stenosis (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP level, mg/L</td>
<td>1.9±2.1</td>
<td>3.7±6.1 b</td>
</tr>
<tr>
<td>LDL-C level, mg/dL</td>
<td>95.8±29.0</td>
<td>92.3±28.6</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.7±8.3</td>
<td>71.3±8.3</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; cholesterol to millimoles per liter, multiply by 0.0259.

*a Data are given as mean±SD and are unadjusted comparisons for outcome peak systolic velocity of 125 cm/s or greater using t test.

*b P<.05.

Table 2. Comparative Proportions Stratified by the Presence or Absence of Confirmed Carotid Stenosis by Duplex Ultrasonography

<table>
<thead>
<tr>
<th>Categorical Study Variable</th>
<th>No Carotid Stenosis (n=74)</th>
<th>Carotid Stenosis (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>58</td>
<td>93</td>
</tr>
<tr>
<td>Smoking history</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70</td>
<td>82</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>61</td>
<td>84</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>29</td>
<td>49</td>
</tr>
<tr>
<td>or myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Symptoms</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Lower extremity peripheral vascular disease</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Aspirin or nonsteroidal anti-inflammatory drug use</td>
<td>77</td>
<td>81</td>
</tr>
</tbody>
</table>

*a Data are given as baseline percentages and are unadjusted comparisons for outcome peak systolic velocity of 125 cm/s or greater using χ² test or Fisher exact test as appropriate.

nosis (3.7±6.1 vs 1.9±2.1 mg/dL, P=.02), as were the baseline prevalences of CAD (49% vs 29%), PVD (27% vs 11%), and hypercholesterolemia (84% vs 61%) (P<.03 for all). The mean±SD LDL-C levels were similar between the groups (92.3±28.6 vs 95.8±29.0 mg/dL [to convert to millimoles per liter, multiply by 0.0259], P=.8), and differences in the prevalences of other risk factors were not statistically significant (Table 1 and Table 2).

In multivariate regression analysis adjusting for age, sex, race/ethnicity, smoking history, hypertension, diabetes mellitus, recent neurologic symptoms (<120 days), CAD, PVD, myocardial infarction, stroke or TIA, hypercholesterolemia, aspirin or nonsteroidal anti-inflammatory drug use, and statin use, CRP level was independently associated with carotid stenosis (OR, 1.2; 95% CI, 1.1-1.5; P=.04), and LDL-C level was not (OR, 1.0; 95% CI, 0.98-1.01; P=.8). Several risk factors had larger ORs for carotid stenosis than CRP level; however, none were statistically significant (Table 3).

The first objective of this study was to examine the relationship between CRP level and the presence and degree of carotid stenosis. In this regard, we found that baseline CRP level was prospectively associated with both outcomes in these 146 patients and that this relationship was independent of other statistically significant historical covariates, including CAD, lower extremity PVD, myocardial infarction, and hypercholesterolemia. Second, we wanted to compare the strength of this associa-
tion with that of established risk factors for carotid disease. Herein, we found that the magnitude of independent association of baseline CRP level with carotid stenosis was moderate, with an observed OR of 1.2. Nevertheless, CRP level was the only variable among 15 studied that was statistically significantly associated with both primary outcomes of this study, namely, the presence and degree of carotid stenosis.

Furthermore, CRP level was 1 of only 2 variables with statistically significant areas under the ROC curve, the traditional statistical yardstick against which diagnostic tests are compared against one another. In addition, CRP level generated the second largest area under the ROC curve of any variable studied. These findings are compelling given that included among 14 other variables to which CRP level was compared were several classic, widely used, and well-established risk factors of carotid stenosis (entities such as hypertension, diabetes mellitus, CAD, and LDL-C level). In aggregate, these results suggest that baseline CRP level may be independently contributive, albeit moderately so, to traditional global vascular risk assessment.

Our results reinforce published research linking CRP level with carotid stenosis and with the risk of future stroke.

C-reactive protein level has been demonstrated to be a marker of carotid stenosis, plaque instability, thrombosis, ulceration, and rupture; to relate to the presence of subintimal macrophages and T lymphocytes; and to correlate with the presence of symptoms, the occurrence of future ipsilateral neurologic clinical events, and the risk of death following stroke.13-17 With respect to postneurologic event CRP levels, Canova et al18 demonstrated that the protein elevates in similar quantities regardless of the nature of the neurologic injury incurred. They observed no statistically significant differences in postevent CRP elevations across the spectrum of TIA, completed ischemic stroke without deficit, or hemorrhagic stroke with residual. This observation, along with our present finding that CRP level is independently associated with carotid stenosis even among patients with no prior neurologic history, suggests that an elevated CRP level in these patients is more likely due to smoldering endovascular activity than global postischemic cerebral inflammation.

There are several limitations of this study. First, its sample size is small compared with the large population-based studies that have been published regarding CRP level and CAD. Although the number of patients was adequate to demonstrate several statistically significant differences relevant to our study question, the potential for type I and type II errors is not inconsequential in a project of this size. For example, given the absolute magnitude of difference we observed among the mean±SD CRP levels for symptomatic vs asymptomatic patients with carotid stenosis (5.1±7.1 vs 2.8±3.7 mg/dL, P=.11), it seems possible that this comparison might have achieved statistical significance with a larger sample size and greater statistical power. Indeed, the potential usefulness of CRP level to differentiate symptomatic vs asymptomatic patients with surgically significant carotid disease was well described in a larger study by Rerkasem et al.19 Another potentially confounding issue regarding this patient population is that it may be heterogeneous in that it includes new referrals and follow-up patients. Therefore, any in-
brate differences that might exist in the biology of carotid lesions in these 2 types of vascular clinic patients would theoretically represent unmeasured variance in this study and a potential source of bias.

Second, the definition of carotid stenosis in our study at the low-grade velocity of 125 cm/s has unclear clinical significance in terms of future stroke morbidity. Depending on the context, this velocity might correlate with a degree of luminal carotid stenosis ranging from a mild 15% to a moderate 50%. Factors affecting this interpretation include the ultrasonography equipment used, the local laboratory duplex criteria, the anatomic location of the measurement within the artery, the associated echogenicity and morphologic structure of the plaque, and the presence or absence of spectral broadening and other descriptors. Many of these factors represent unmeasured variance in our study. We selected this velocity because we were interested in evaluating the predictive value of CRP level in part as a possible screening tool, whereby identification of disease at the earliest possible juncture might theoretically be most advantageous for optimal future management. Furthermore, this threshold provided an appropriate early baseline measurement so that we might follow the progression of carotid stenosis, CRP values, and symptoms in these patients longitudinally over time.

Even with the clear association of CRP elevation and carotid stenosis in our patients, how this marker might be used in the future remains uncertain. Future studies will be needed to demonstrate the potential of CRP level to identify asymptomatic patients with occult disease and to differentiate vulnerable plaques from stable lesions in patients with known disease. Population norms would need to be determined that might guide the interpretation of CRP level as an index of disease severity, target for intervention, or therapeutic end point. Finally, management of elevated CRP levels pharmacologically or otherwise must be ultimately demonstrated prospectively to actually prevent future adverse neurologic events. All of these questions remain open at this time.

Our results suggest implications for future therapy. As has been promulgated for CAD, surveillance and management of elevated CRP level with established drugs such as antiplatelets and statins may have a role in carotid stenosis. Aspirin and statin agents have been shown to reduce CRP levels and future stroke incidence. These drugs seem to affect this risk reduction independent of their respective antiplatelet and lipid-lowering effects. Statin agents in particular have numerous anti-inflammatory properties and have recently been shown to reduce interleukin 6 synthesis, inhibit vascular smooth muscle cell proliferation, prevent complement activation, and favorably modulate nitric oxide–derived oxidants. At least for CAD, the magnitude of benefit of antiplatelet and statin therapy correlates quantitatively with the degree of baseline CRP elevation. This suggests that even patients with normal thrombotic risk factors and normal LDL-C levels might benefit from these agents if they demonstrate elevated CRP levels in the context of documented carotid stenosis. Another major area of therapeutic investigation that might someday favorably exploit the inflammatory pathogenesis of carotid stenosis includes emerging anti-inflammatory drug–eluting stent technol-

ogy. The immunosuppressive agent rapamycin, for example, inhibits T-cell proliferation, vascular smooth muscle cell migration, and proliferative changes in the arterial wall, without destroying cells or causing vessel injury. The demonstrated capability of rapamycin–impregnated stents to dramatically reduce carotid restenosis rates in the coronary artery context is compelling and suggests at least the potential for similar future usefulness in carotid disease.

In summary, we performed a prospective comparative cohort study evaluating the potential relationship between serum CRP level and the presence and degree of carotid stenosis in 146 vascular clinic outpatients. We found that CRP level was independently associated with confirmed disease to a moderate degree (OR, 1.2), while LDL-C level and a large group of established demographic and historical risk factors for carotid stenosis were not. Furthermore, CRP level was independently correlated with the actual degree of carotid stenosis and generated a moderate but statistically significant area under the ROC curve for the presence of disease that compared favorably against the other variables. Together, these results suggest that the predictive value of CRP level, while modest, was additive to the traditionally used vascular risk factors currently considered in the management of carotid stenosis. Therefore, CRP level may be a useful adjunct to accurate global vascular risk assessment.

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REFERENCES


