Individual Variation in Susceptibility to Extracranial Carotid Atherosclerosis


Risk factors for coronary disease were assessed and noninvasive methods were used to quantitate the extent of extracranial carotid atherosclerosis in 382 patients free of cerebrovascular symptoms. The ages of the participants ranged from 27 to 80 years. There were 183 men and 199 women, 30 black and 352 white persons. All patients had heart disease symptoms and were hospitalized for coronary angiography. Correlation of risk factors with extent of extracranial carotid atherosclerosis in this series of patients undergoing coronary angiography uncovered individual variability in relationships between risk factors and carotid atherosclerosis that depended on coronary status. Risk factors for carotid atherosclerosis in patients with and without coronary disease differed. Age and hypertension were independently related to carotid atherosclerosis in patients both as those without, coronary disease. However, other risk factors were related to carotid atherosclerosis in only one group or the other. Risk factors correlated strongly with carotid atherosclerosis in patients with coronary disease ($r^2 = 0.41$) but poorly in those with no coronary disease ($r^2 = 0.21$). Certain risk factors (age, pack years of smoking, left ventricular hypertrophy) related differently to the extent of carotid atherosclerosis in patients with, than in those without, coronary disease. Clarification of the role of coronary status in the carotid atherosclerosis response to risk factors may partly explain the results of certain population-based studies that have related race, gender, and other risk factors to carotid atherosclerosis. The increased response to risk factors in patients with coronary disease may be attributable to arterial wall factors in such patients, or, alternatively, to an interaction of measured risk factors. Correlation of risk factors to carotid atherosclerosis patients with other risk factors not measured in this study.

(Arteriosclerosis 8:389–397, July/August 1988)
without coronary disease who were older than or younger than 50 at approximately the same rates. We attempted to schedule noninvasive studies of the carotid arteries for all volunteers, but for logistic reasons, we could only schedule 413 of the 606 patients who met the criteria. Twelve patients with a history of cerebrovascular disease (stroke, transient ischemic attack, or endarterectomy) were excluded, as were 29 patients with aortic valvular disease; the data from the remaining 382 (183 men and 199 women) were analyzed. All subjects were given a standardized questionnaire for evaluation of angina pectoris and other symptoms and risk factors associated with cardiovascular disease. Patients also underwent an abbreviated physical exam (height, weight, blood pressure, and auscultation of the heart for murmurs and of the carotid and femoral arteries for bruits). Blood for assay of glucose, lipid, and lipoprotein concentrations was drawn from fasting patients the morning of catheterization. For this study, diabetes mellitus was coded as present if the patient had ever been told by a physician that he or she had diabetes, if the patient had been treated at the time of hospitalization with oral hypoglycemic agents or insulin, or if the patient's fasting glucose concentration in the hospital exceeded 140 mg/dl; otherwise, it was coded absent. Hypertension was coded as present if the patient had a history of hypertension or if the blood pressure measured in the hospital exceeded 150/95; otherwise, it was coded as absent.

Evaluation of Vascular Status

Extent of carotid atherosclerosis was evaluated by a method previously detailed. Briefly, the left and right carotid arteries of patients were interrogated in the anterior oblique, lateral, and posterior oblique planes using a Biosound compact real-time imager with an 8 MHz mechanical sector scanner probe and digital scan converter. A single carotid artery "score" was computed for each patient by summing maximum axial thickness measurements at four standard sites in the left and right carotid arteries (eight sites total). The correlation coefficient for repeat determinations of this score is 0.88.5

Coronary angiography was performed by the percutaneous technique using either Judkins or multipurpose catheters. Patients were divided into those with coronary stenosis (≥50% stenosis of any artery, n = 229) or those without coronary stenosis (normal coronary anatomy, n = 153). Patients with stenoses that obstructed the lumen by <50% were excluded from the study.

Evaluation of Risk Factor Variables

Fourteen risk factor variables [age, gender, race, history of hypertension, electrocardiographic evidence for left ventricular hypertrophy, history of diabetes, percent ideal body weight, pack years of smoking, and plasma concentrations of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), hemoglobin, and uric acid] were evaluated in all patients by use of standardized questionnaires, electrocardiographic criteria,6,7 and clinical chemistry methods ("Coulter-S + " hematology analyzer, Technicon SMAC).

The plasma concentration of LDL-C was estimated by the Lipid Research Clinics methodology after ultracentrifugation of plasma at d = 1.006 to float VLDL and chylomicrons. LDL-C was calculated as the difference between the total d = 1.006 infranate cholesterol and infranate HDL-C.

Statistical Evaluation

We examined the relation of potential risk factors to the extent of carotid atherosclerosis in patients with or without coronary disease and in the combined group using univariable and multivariable analyses.8 Univariable comparisons were carried out using regression analyses for continuous variables and t tests for dichotomous variables. The log plasma TG concentration, rather than the raw data, was used in analyses because of the skewed distribution of plasma TG concentration. Multivariable stepwise linear regression was used to select from the complete roster of factors those pools of risk factors that contributed independently toward predicting carotid atherosclerosis in the group as a whole, and, separately in patients with and without angiographic evidence for coronary atherosclerosis. Forward selection for the multivariable model was terminated when either all risk factors with p < 0.10 had been added, or all parameters whose partial r² exceeded 0.01 had been included. We attempted to determine, in a uniform manner for each potential risk factor, whether patients with coronary disease differed from those without coronary disease in the relation between the risk factor and extent of atherosclerosis. A series of regression analyses were performed on the combined group of patients to address this question. In each, the pool of risk factors selected from the stepwise regression performed on the combined sample was used to define covariates. For each potential risk factor, we fit regression models that contained all other "risk factors" found in the combined group analysis of Table 3, a term that defined patient group ("cohort"), and a term that was the product of an interaction between patient group and the potential risk factor. For continuous risk factors, the equation defining the relation of potential risk factor to B-mode score allowed us to fit separate regression lines with extent scores for each patient group while controlling for a common set of covariates. For discrete risk factors, this resulted in fitting separate, "covariate-adjusted" mean extent scores for factor levels within the two patient groups. The statistical significance of the interaction term in each regression model on the combined group provided a uniform test for differences in the relationships among patients with and without coronary disease.

Results

Means and standard deviations for continuous variables and distribution of dichotomous variables evaluated in this study, as well as their association with extent of extracranial carotid atherosclerosis, are shown in Table 1 (continuous variables) and Table 2 (dichotomous variables). As expected, a number of risk factor variables (e.g., smoking, TC, LDL-C, HDL-C, log TG, gender, diabetes history) were unequally distributed between patients with or without coronary disease. Based on univariable analyses, the following risk factors were significantly related to
the extent of extracranial carotid atherosclerosis: for the combined group, age, pack years of smoking, TC, low HDL-C, TG, history of hypertension, history of diabetes, left ventricular hypertrophy; for the subgroup with coronary disease, age, pack years of smoking, hemoglobin concentration, history of hypertension, history of diabetes, left ventricular hypertrophy; and for the subgroup without coronary disease, age, TC, log TG, uric acid, and history of hypertension. In Figure 1 the data relating extent of extracranial carotid atherosclerosis and age for men and women are presented to illustrate the constancy of the relationships in men and women and the differences in the relationships for patients with or without coronary disease. For univariable analyses, men and women were grouped together.

Multivariable linear regression analysis with forward selection identified combinations of risk factors that were independently associated with extent of carotid atherosclerosis (partial $r^2$ value >0.01 or $p$ value <0.05) in patients with or without coronary disease and in the combined group (Table 3). For multivariable analysis, all potential risk factor variables including age; gender; pack years of smoking; plasma concentrations of TC, HDL-C, LDL-C, and TG (as its log); plasma hemoglobin and uric acid concentrations; percent ideal body weight; race; high
Figure 1. Relation of B-mode score to age in men and women with or without coronary disease (CAD). The equations of lines relating age to extent of carotid atherosclerosis are given below.

Without CAD
Women: B-mode = (0.14) AGE - 3.6  0.14 < 0.01
Men: B-mode = (0.07) AGE + 0.4  0.35  0.16

With CAD
Women: B-mode = (0.27) AGE - 7.0  0.23 < 0.01
Men: B-mode = (0.35) AGE - 11.8  0.32 < 0.01

blood pressure history; and history of diabetes mellitus and left ventricular hypertrophy were available for selection, irrespective of results obtained on univariable analysis. The coefficient of determination in the group of patients with coronary disease ($r^2 = 0.409$) was higher than that for patients free of coronary disease ($r^2 = 0.212$). For each group, the potential contributions of predictors not selected by the stepwise algorithm were minimal.

The greater $r^2$ value obtained by the stepwise linear regression analysis in the coronary disease group could be explained in a number of ways: 1) since the range of B-mode scores was greater among the coronary disease than among coronary disease-free patients, regression may have had an easier task in predicting B-mode scores in the former group (B-mode scores with a wide range of variation may have been easier to fit to a regression line than scores with a narrower range of variation but with the same trend in relation to risk factors); 2) coronary disease patients might represent a more homogeneous group so that prediction was inherently easier; 3) relationships to

Table 3. Multivariable Analysis: Linear Regression Analysis in Patients with or without Coronary Artery Disease

<table>
<thead>
<tr>
<th>RF</th>
<th>All patients</th>
<th>With CAD</th>
<th>Without CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.201</td>
<td>0.274</td>
<td>0.088</td>
</tr>
<tr>
<td>Cohort</td>
<td>0.092</td>
<td>0.030</td>
<td>0.059</td>
</tr>
<tr>
<td>BP</td>
<td>0.032</td>
<td>0.028</td>
<td>0.037</td>
</tr>
<tr>
<td>SMK</td>
<td>0.018</td>
<td>0.021</td>
<td>0.019</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.016</td>
<td>0.019</td>
<td>0.014</td>
</tr>
<tr>
<td>UA</td>
<td>0.012</td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td>LVH</td>
<td>0.010</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.005</td>
<td>0.08</td>
<td>0.110</td>
</tr>
</tbody>
</table>

Comparison of stepwise regression procedures performed on all patients and separately on CAD and non-CAD patients. Dependent variable is extent of extracranial carotid atherosclerosis.

RF = risk factors selected for multivariable linear regression equation. The other abbreviations are given in the footnotes to Table 1 and Table 2. Cohort = coronary disease or coronary disease-free group.
risk factors might be stronger and better defined among the coronary disease patients.

To investigate the first possibility, we examined residuals from the regression models developed in the stepwise procedures. The model created from the coronary disease patients was fitted to B-mode scores of the coronary disease and coronary disease-free patients, and the positive and negative residuals were examined for selected ranges of predicted B-mode scores. Table 4 lists the results. In general, when individuals with or without coronary artery disease (CAD) were grouped according to similar predicted B-mode scores (<5, 6 to 10, 11+, ), the absolute means of the within-group residuals for the coronary disease patients were similar to those of the coronary disease-free patients. Similarity of mean residuals between patients with or without coronary disease for various B-mode groups suggests that the larger multivariable $r^2$ for CAD patients is not due to reduced variability about the model (less residual variability); i.e., the larger $r^2$ value might not be due to data in the coronary disease group approximating the linear model better than the data in the coronary disease-free group. No comparisons of residuals can be made between patients with coronary disease and those without coronary disease for the group with predicted B-mode score $\geq 11$, since there were no patients free of coronary disease in this range. This analysis also argues against the concept that the coronary disease group was more homogeneous.

On the basis of the regression equations and partial $r^2$ values formed through the stepwise procedures, the association between a number of potential risk factors and extent of carotid atherosclerosis appeared to be stronger among coronary disease patients than among coronary disease-free patients. To determine whether individual risk factors might bear a different relation to the extent of carotid atherosclerosis in patients with coronary disease than in those without coronary disease, we next undertook a formal exploration of differences in the strength and nature of the risk factor relationships between the two groups of patients. We started with the null hypothesis that the risk factor relationships were identical between the two patient groups. On the basis of this hypothesis, the stepwise regression analysis performed on the combined groups of patients was used to identify the appropriate covariates for a series of hypothesis tests of interaction terms between potential risk factors and patient groups as described above (Methods). These tests assessed whether risk factor relationships were inherently different in the two patient groups. Table 5 contains the results of fitting, for each continuous potential risk factor, models that allowed differences in the slopes (between the risk factor and B-mode scores) between the coronary disease and coronary disease-free patient groups, while using as covariates all predictors for the combined group listed in Table 3. For example, the fitted slope of B-mode scores versus age, given the other covariates, was $0.299 \pm 0.029$ for the coronary disease patients and $0.150 \pm 0.037$ for the coronary disease-free patients. This indicated that B-mode scores increased more abruptly with age among the coronary disease patients (based on our cross-sectional data) after control for other covariates. The $p$ value associated with this comparison was 0.001. The relationship between pack years of smoking and B-mode scores also appeared to have a steeper slope among the coronary disease patients ($p=0.05$). No other slopes showed any significant difference between the two groups.

### Table 4. Comparison of Variability of Data Points about Regression Lines (Analysis of Residuals) for Patients with or without Coronary Disease Grouped According to Predicted B-mode Score

<table>
<thead>
<tr>
<th>Predicted B-mode score</th>
<th>With CAD</th>
<th></th>
<th>Without CAD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean resid</td>
<td>Mean resid²</td>
<td>n</td>
</tr>
<tr>
<td>Negative residuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>38</td>
<td>-2.04</td>
<td>5.96</td>
<td>70</td>
</tr>
<tr>
<td>6 to 10</td>
<td>59</td>
<td>-3.65</td>
<td>18.64</td>
<td>16</td>
</tr>
<tr>
<td>≥11</td>
<td>31</td>
<td>-4.18</td>
<td>24.00</td>
<td>0</td>
</tr>
<tr>
<td>Positive residuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>30</td>
<td>3.40</td>
<td>21.14</td>
<td>53</td>
</tr>
<tr>
<td>6 to 10</td>
<td>39</td>
<td>3.43</td>
<td>21.14</td>
<td>14</td>
</tr>
<tr>
<td>≥11</td>
<td>32</td>
<td>5.82</td>
<td>43.31</td>
<td>0</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease.

### Table 5. Continuous Variables: Covariance Adjusted Slopes of Regressions of Risk Factors vs. Extent of Extracranial Carotid Atherosclerosis In Patients with or without Coronary Artery Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>With CAD Slope ± SE</th>
<th>Without CAD Slope ± SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.299 ± 0.029</td>
<td>0.150 ± 0.037</td>
<td>0.001</td>
</tr>
<tr>
<td>SMK</td>
<td>0.037 ± 0.010</td>
<td>-0.004 ± 0.018</td>
<td>0.05</td>
</tr>
<tr>
<td>TC</td>
<td>0.007 ± 0.005</td>
<td>0.014 ± 0.009</td>
<td>0.49</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.012 ± 0.006</td>
<td>0.009 ± 0.010</td>
<td>0.82</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.089 ± 0.034</td>
<td>-0.056 ± 0.030</td>
<td>0.46</td>
</tr>
<tr>
<td>Log TG</td>
<td>0.061 ± 1.164</td>
<td>2.108 ± 1.746</td>
<td>0.29</td>
</tr>
<tr>
<td>Hgb</td>
<td>-0.271 ± 0.218</td>
<td>-0.079 ± 0.288</td>
<td>0.56</td>
</tr>
<tr>
<td>UA</td>
<td>-0.510 ± 0.167</td>
<td>-0.256 ± 0.223</td>
<td>0.35</td>
</tr>
<tr>
<td>%IBW</td>
<td>0.066 ± 0.014</td>
<td>0.021 ± 0.018</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Comparisons of patients with or without coronary artery disease with regard to slopes of regression lines for candidate continuous risk factors for extent of extracranial carotid atherosclerosis vs. B-mode score. The covariates include all risk factors selected from a general stepwise regression performed on the combined groups.

Abbreviations are given in the footnotes to Table 1 and Table 2.
patient groups. Table 6 contains the results of parallel tests for the dichotomous risk factors. The appropriate comparisons were based on mean differences in the coronary disease patients and the coronary disease-free patients. The p values listed in the table assessed whether differences in B-mode scores associated with each risk factor were comparable for the two patient groups. For left ventricular hypertrophy, the pattern of the relationship with B-mode scores appeared to be different in coronary disease patients and coronary disease-free patients after control for other covariates (p = 0.04). Among coronary disease patients, the mean B-mode score was 3.04 units higher when left ventricular hypertrophy was present than when it was absent. Among coronary disease-free patients, B-mode scores appeared not to be related to the presence or absence of left ventricular hypertrophy.

**Discussion**

We previously established that coronary disease is independently related to the extent of extracranial carotid atherosclerosis. This observation led us to inquire whether individual variation in the correlation of carotid atherosclerosis with risk factors might relate to the presence or absence of coronary disease. Individual variation in susceptibility (or resistance) to risk factors has been documented in the Oslo study that related the extent of coronary and cerebral atherosclerosis at autopsy to antemortem serum cholesterol and other risk factors. For individuals with plasma TC between 280 and 320 mg/dl, coronary and cerebral atherosclerosis varied from minimal to extensive. In general, autopsy studies have concluded that, "even after stratifying cases according to race, sex, age, and disease there remains much individual variation in the extent of raised lesions in the aorta and the coronary and cerebral arteries." Considerable variability in the extent of atherosclerosis is also found in nonhuman primates challenged with the same serum cholesterol level for prolonged periods before necropsy. If such "hyper-" and "hyperresponsivity" were related to factors inherent in the arterial wall, then individuals with atherosclerosis of the coronary arteries might be expected to exhibit a more dramatic response to risk factors in other arterial beds than would people with no coronary atherosclerosis. Noninvasive imaging of the extracranial carotid arteries of subgroups of patients in whom the presence or absence of coronary atherosclerosis was established by angiography allowed us to test whether risk factors bore different relationships to (carotid) atherosclerosis in patients with or without CAD.

Univariable analysis of data from this population disclosed certain risk factors that appeared to be related to the extent of carotid atherosclerosis in both subgroups of patients (age, blood pressure), certain that appeared strong only among patients with coronary disease (hemoglobin, pack years of smoking, diabetes, left ventricular hypertrophy), and others that were unique to patients free of coronary disease (TC, TG, and uric acid). Similarities and differences between the subgroups again appeared when we evaluated the independence of associations of risk factors to the extent of extracranial carotid atherosclerosis by multivariable testing. Age and hypertension were independently related to extracranial carotid atherosclerosis extent by multivariable testing in both subgroups, as well as in the combined group. In addition to these risk factors, pack years of smoking, left ventricular hypertrophy, uric acid, low HDL-C, race, and LDL-C were independently related to the carotid atherosclerosis extent in the group with coronary disease and in the combined group, whereas TG and percent ideal body weight were identified as additional independent risk factors only in the coronary disease-free group. Not contributing toward any multivariable model were gender, TC, hemoglobin concentration, or diabetes.

**Risk Factors**

Age and hypertension history are the most important risk factors for symptomatic cerebrovascular disease and have emerged as risk factors for cerebrovascular atherosclerosis in some, but not all, autopsy and angiographic studies of symptomatic populations. Although carotid atherosclerosis is importantly related to events in younger symptomatic populations (<age 50), previous studies have noted a lower correlation in such patients. Thus the relative absence of extracranial carotid atherosclerosis in younger individuals in our asymptomatic population is not surprising.

Cigarette smoking has also been implicated as a risk factor for stroke and cerebrovascular atherosclerosis in some, but not all, previous studies. Smoking has been frequently identified as a risk factor for CAD as
well. In the present study, pack years of smoking entered the multivariable model and was related to extent of carotid atherosclerosis in patients with, but not those without, coronary disease.

Left ventricular hypertrophy has been identified as an independent risk factor for symptomatic heart disease and stroke. This electrocardiographic parameter appears to correlate with hypertension when the episodic variability of blood pressure throughout the day is taken into account, but is relatively independent of blood pressure measured at a single sitting. In this study, left ventricular hypertrophy was related to carotid atherosclerosis in the subgroup of patients with coronary disease, but not in the group free of coronary disease.

To the best of our knowledge, no previous studies have evaluated the role of uric acid in cerebrovascular atherosclerosis; in this study a negative relation that reached statistical significance only for patients with coronary disease was observed.

In this study, HDL-C appeared as an independent risk factor only in patients with coronary disease, whereas plasma TG concentration appeared in the model for coronary disease-free patients. Because plasma HDL-C and TG concentrations are strongly correlated, the appearance of one (HDL-C) in the model for patients with coronary disease and the other (TG) in the model for patients free of coronary disease suggests that one is the "true" risk factor related to disease in both groups and the other is serving a surrogate role in the group in which it surfaces in this study. HDL-C appears to bear a stronger relation than TG to symptomatic coronary disease and coronary atherosclerosis, and has been sometimes, and always, linked to symptomatic cerebrovascular disease and cerebrovascular atherosclerosis, as well. LDL-C related independently to extent of extracranial carotid atherosclerosis in patients with coronary disease only, and there is controversy in the literature about the relation of LDL-C to symptomatic manifestations of cerebrovascular disease. Of interest, LDL-C may be a more important risk factor for coronary disease in men than women, and much of the controversy concerning the relation of LDL-C to cerebral disease is related to the effect in women. The relationship of race to extracranial carotid atherosclerosis was of interest. Univariate analysis indicated that blacks had more extensive extracranial carotid atherosclerosis than whites in either coronary status group; however, whites with coronary disease had more extensive carotid atherosclerosis than blacks who were free of coronary disease. Although these relationships were not significant by univariate analysis, a significant independent relationship could be demonstrated by multivariable analysis between race and extent of carotid atherosclerosis in the combined group and in patients with coronary disease. Previous studies have claimed either less or more extensive carotid atherosclerosis observed in blacks in previous studies might relate to the greater prevalence of coronary disease in them, and might be expected to disappear if patients with and without coronary disease were evaluated separately as in this study. In general, studies of symptomatic populations have found blacks to have less extensive extracranial carotid disease, whereas autopsy studies of presumably previously asymptomatic individuals have led to the observation of equal or greater extracranial disease in blacks. In our study, the selection process may have partly obscured differences in extent of extracranial atherosclerosis between men and women by a design-imposed limitation on the number of men older than 50 with coronary disease. Since the vast majority of men older than 50 hospitalized for coronary angiography have coronary disease, we would likely have observed more extensive carotid atherosclerosis in men had we enrolled them sequentially in our study rather than overselecting men free of coronary disease. TC did not relate to extent of cerebrovascular atherosclerosis in this study; as mentioned above, considerable controversy exists regarding the relation of cholesterol to cerebrovascular symptoms. Diabetes has previously been found to be associated with the extent of extracranial carotid atherosclerosis in univariable analysis, but it has not previously been evaluated in multivariable analysis. The association between hemoglobin and extent of extracranial carotid atherosclerosis has not, to our knowledge, been previously examined.

**Differential Susceptibility to Risk Factors In Patients with and without Coronary Disease**

We were impressed that approximately twice as much of the variability in the extent of carotid atherosclerosis could be "explained" by risk factors in the group of patients with coronary disease compared to those free of coronary disease ($r^2 = 0.409$ vs. $r^2 = 0.212$). While this observation is consistent with the hypothesis that risk factors are more strongly related to atherosclerosis in the former group than in the latter, we could not use formal statistical tests to determine whether this was, in fact, the case. The two groups are not strictly comparable in that the variability in the coronary disease group is much greater than that in the group free of coronary disease. As total variance increases, $r^2$ increases, since:

$$r^2 = 1 - \frac{\text{residual variance}}{\text{total variance}}$$

Although the higher $r^2$ in the coronary disease group implies that the increase in total variance outstripped the increase in residual variance for the coronary disease group compared to the coronary disease-free group, a formal test of residuals showed that residual variance was...
similar for both groups or, if anything, higher for the coronary disease group.

**Interactive Terms**

To examine this issue more closely, we tested individual risk factors for a putative difference in the “dose-response” effect in the two subgroups (patients with and without coronary disease), controlling for all other factors. In this analysis, there was a significantly steeper positive relationship of B-mode score with age, smoking, and left ventricular hypertrophy in the coronary disease subgroup than in the coronary disease-free subgroup.

In our analysis, age was the risk factor that correlated most strongly with cerebrovascular atherosclerosis in both subgroups. Age differed more than any other risk factor in its relation to carotid atherosclerosis for coronary disease patients compared to coronary disease-free patients. This difference reflected a contrast in extent of carotid atherosclerosis between subgroups that was most pronounced in older individuals. It is tempting to speculate that some age-related change in, for example, an arterial wall factor occurs or is more pronounced and leads to accelerated plaque growth in older patients with coronary atherosclerosis more often than in coronary disease-free patients. Studies have shown age-related changes in accumulation of cholesterol in connective tissues with advancing age (there is no accumulation from ages 20 to 40, but there is marked accumulation thereafter) that might reflect changes in connective tissue proteoglycan or other matrix components with age. Similar changes might lead to exaggerated lipid deposition in the arterial wall of older persons. Alternatively, some other risk factor not measured in this study that emerged in older individuals and was associated with coronary disease or interacted with other risk factors to enhance their ability to promote coronary disease might be responsible for the observed differences.

The exaggerated effect of smoking and left ventricular hypertrophy on carotid atherosclerosis in patients with coronary disease is difficult to explain. Apparently coronary disease-free patients are “protected” from the effects of left ventricular hypertrophy and smoking that result in plaque deposition in the carotid arteries in patients with coronary disease. This “protective factor” might be located in the arterial wall, or, alternatively, might be a blood-borne factor not measured in this study and found in coronary disease-free patients.

The relationships of other risk factors (blood pressure, HDL-C, race, uric acid) to extracranial carotid atherosclerosis were similar in both subgroups.

The group-specific nature of the interrelationship of risk factors to extent of carotid atherosclerosis prompts the question: what factor (or factors) is responsible for inconsistencies in the relation between risk factors and carotid atherosclerosis in patients with coronary disease compared to those free of coronary disease? That the difference in the dose-response effect is qualitative, rather than quantitative, is suggested by testing the relationship of risk factors to B-mode scores after accounting for all covariates in the two subgroups of patients. There is a qualitatively different relation between certain risk factors (age, left ventricular hypertrophy, smoking) and carotid atherosclerosis in the two groups. The diversity of these risk factors suggests the arterial wall as a common path whereby patients with coronary disease might differ from those free of coronary disease, but some other unmeasured risk factor that emerged in older individuals may also play a role. Studies focused on patients with coronary disease but not carotid atherosclerosis, or with carotid atherosclerosis but not coronary disease might be particularly illuminating. In addition, the lack of consistency of the relationship of risk factors to carotid atherosclerosis in patients with and without coronary disease may provide insight to interpretation of several previous case-control studies. It is evident that the relative proportion of coronary disease and coronary disease-free patients in either the case or the control group in such studies bears importantly on the observed relationships between risk factors and carotid atherosclerosis.

Ability to distinguish subgroups of patients with and without coronary disease is an obvious advantage of this study as is the asymptomatic nature of the study population; however, there are inherent design-imposed disadvantages as well. Because of the complex nature of the recruitment process, the number of patients studied is not large and numbers of patients with certain characteristics are limited (number of patients with left ventricular hypertrophy = 38; diabetics = 55; blacks = 30). This considerably restricts our ability to draw inferences about the lack of significant differences related to these factors because of low power. Confirmation of the relationships identified in this report through studies with larger numbers of blacks, diabetics, and others will be important.

B-mode studies were obtained in all patients that the ultrasound laboratory could accommodate; however approximately one-third of the patients could not be scheduled for the B-mode because of the brevity of the hospital stay. Although it is possible that the sample is further biased by these logistic factors, we believe this is unlikely. The hospital base of the patient population does lead to bias, as recently noted by Pearson. It is also conceivable that the locale (Southeastern U.S.) from which the sample was drawn might influence the outcome, and this may be reflected in the relatively high mean pack years of smoking in this group of patients. Finally, no comment can be made from these cross-sectional studies as to the relation of risk factors to the progression of disease (this is the subject of an ongoing study). This study does, however, raise important questions concerning the mechanism whereby the presence of coronary disease influences the role of certain factors (age, race, smoking history, hypertension) in the genesis of extracranial carotid atherosclerosis. It is particularly interesting that, in patients with no coronary disease, risk factors are only weakly related to carotid atherosclerosis. Defining determinants of this individual variation in susceptibility to risk factors is a task of considerable biological importance.

**Acknowledgments**

The authors acknowledge the help of Edna Mitchell and Pat Mueller for patient accession. Mike Hines, Robert
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- carotid atherosclerosis
- coronary atherosclerosis
- noninvasive imaging
- risk factors

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doi: 10.1161/01.ATV.8.4.389
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/8/4/389

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