Amount of Smoking Independently Predicts Carotid Artery Atherosclerosis Severity

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Understanding the causes of stroke requires exploration of multiple causal factors under a variety of conditions. Since the 17th century it has been recognized that carotid artery atherosclerosis is an important cause of ischemic stroke.1-3 The causal mechanism relating carotid plaque to ischemic stroke has been thought to be flow restriction,4 embolism,5 or both.6

Because cigarette smoking has been found to be a significant predictor of extracranial carotid atherosclerosis among patients referred for cerebrovascular evaluation,6-8 in representative samples of community populations,9,10 and in pairs of identical twins who are discordant for smoking,11,12 we investigated in this study the independent effect of the level of cigarette use on carotid plaque thickness among smokers after controlling for age, history of hypertension, and history of diabetes.

Subjects and Methods

We studied 790 patients with a history of cigarette smoking who were referred for any reason, including stroke, bruit, transient cerebral ischemia, preoperative evaluation, and screening, to the University of Kentucky Medical Center's Special Diagnostic Laboratory for ultrasound assessment of their carotid arteries during 1988-1989. Patients with a prior carotid endarterectomy and those with cognitive impairment that interfered with information collection were excluded. Otherwise, these subjects represent a continuous sample of all adults with a history of cigarette smoking seen in the vascular laboratory for this procedure. Subjects were 17-94 (mean±SD 61±11.9) years of age. We determined by chart review that nearly one fifth (18.2%) had a history of diabetes, and over two fifths (43.9%) had a history of hypertension. The subjects' sex was not included in the analysis. Cigarette smoking was assessed at the time of the ultrasound examination by asking subjects the number of years and the number of packs per day they had smoked. Multiplication of the responses produced values that ranged from 1 to 210 (mean±SD 51.2±32.2) pack-years of smoking. Thirty-seven percent reported 40 or more pack-years of cigarette use, and 9.2% reported 100 or more pack-years.

Carotid plaque was measured directly by duplex Doppler ultrasound imaging using a Hoffrel 617 machine with 7.5- and 10.0-MHz probes. Maximum plaque thickness in the internal and common carotid arteries on each side was recorded and averaged. This average is the dependent variable in the analysis. The average of the maximum carotid plaque thickness on both sides ranged from 0 mm to 7 mm, with an average of 1.9±1.3 mm (mean±SD). Observables vessel wall thickening due to atherosclerotic plaque was present in 86.9% of these...
Subjects, and 40.5% had an average of 2.5 mm or more of plaque in both sides.

Plaque thickness was correlated with age (r=0.41, p<0.0001), pack-years of cigarette smoking (r=0.21, p<0.0001), history of hypertension (r=0.13, p=0.0003), and history of diabetes (p=0.03). Age was correlated with pack-years of cigarette smoking (r=0.15, p<0.0001) but not with history of diabetes or hypertension. History of diabetes was associated with history of hypertension (r=0.18, p<0.0001), but neither of these was associated with pack-years of smoking. Data were converted to standard scores, and multivariate analysis was performed using a general linear model (GLM) program.

Results

Regression analysis was used to examine the relation between carotid plaque thickness and age. A curvilinear pattern is evident in which each decade of increase in age is associated with smaller increases in plaque thickness. Lower levels of carotid plaque are found in subjects over age 80 than in those who are 1–2 decades younger. A polynomial regression equation in which a quadratic function of age is included indicated that the downward curving pattern in the data is statistically significant (p<0.0001). Similarly, there is a curvilinear relation between carotid plaque thickness and smoking. The polynomial regression of plaque thickness on pack-years of smoking also had a statistically significant negative quadratic predictor (p=0.0003).

Figure 1 shows the age-adjusted carotid plaque thickness by history of diabetes (DM), hypertension (HTN), and pack-years (PY).

Table 1 shows the results of unstandardized and standardized multiple regression analysis of carotid artery plaque thickness. Age, pack-years of smoking, and history of hypertension are positive, independent, statistically significant predictors of carotid plaque thickness among these smokers. The negative quadratic functions indicate that in multiple regression, the curvilinear patterns described above remain statistically significant. History of diabetes is not a statistically significant independent predictor of carotid plaque thickness among these subjects.

All possible two-, three-, and four-way interactions among independent variables were examined and found to be statistically insignificant in the multiple regression model. They are therefore omitted from the analysis. The overall proportion of variance accounted for (R^2) was 21.8%. Stepwise regression was used to examine the incremental contribution of each variable to the explanation of variance in carotid plaque thickness. Figure 2 shows the contribution of each of the independent variables to the explanation of variation in carotid plaque thickness. Age explained 17.7%, followed by pack-years of smoking (which explained 2.6%), and history of hypertension (which explained 1.3%). History of diabetes explained a statistically insignificant 0.2% of the variation in plaque thickness among these subjects. Overall, nearly four fifths (78.2%) of the variation in carotid plaque thickness remains unexplained in this model.

Discussion

Determining the causes of accelerated carotid artery atherosclerosis is important in the understanding of stroke risk factors. Age is generally regarded as the most important risk factor for carotid artery atheroscero-
Unexplained

Explained vs Unexplained

Source of Explained Variation

 explained by each of the variables in the model should not be accepted uncritically. By sampling patients, we have restricted the range of variation in health in our sample to be accepted uncritically. By sampling patients, we have explained by each of the variables in the model should not correct.

The discovery of a negative curvilinear component to the associations between plaque thickness and both age and smoking lends itself to more than one explanation. Initially we believed that it was best explained by a survival selection process. As years of age or pack-years of smoking increase in association with carotid atherosclerosis, the probability of high-plaque patients remaining alive to be referred into such a sample as ours decreases. Examination of the data suggests another explanation, however. The presence of a curvilinear relation between age and plaque thickness is only evident for subjects in the light smoking category (1–30 pack-years). In the higher age groups, these subjects are more likely to be former smokers than are subjects with moderate and heavy levels of tobacco use. If smoking cessation by patients produces the benefit of reducing the rate of atherosclerotic plaque formation (compared with that in patients who continue to smoke), a pattern similar to the one we observed might be expected.16 Ignoring such negative curvilinear aspects of a relation between smoking and plaque progress among patient populations will tend to result in underestimations of its true magnitude. Prospective studies based on representative samples of community-based populations in which current and former smokers can be separated for analysis are needed to determine which explanation is correct.

The magnitude of the proportion of variation explained by each of the variables in the model should not be accepted uncritically. By sampling patients, we have restricted the range of variation in health in our sample compared with community-based populations. By studying only those patients with a history of cigarette smoking, we similarly restrict the range of variation in that variable (by omitting nonsmokers) and underestimates the true magnitude of the effect of tobacco consumption on carotid atherosclerosis.

Measurement factors also influence the explanatory power of variables in the model. Age is measured with much greater reliability than tobacco use (pack-years of cigarette smoking). Unreliability in the measurement of smoking history reduces the amount of variation explained by that factor. The measurement of diabetes and hypertension at only a nominal (categorical) level that neglects duration and severity of those conditions similarly reduces their potential for explaining variation in carotid atherosclerosis.

A recent study showed that duration of cigarette smoking was the most significant predictor of the presence of severe carotid atherosclerosis measured by angiography when analyzed in a multivariate model that included age, hypertension, diabetes, and other factors.7 The results of that report are useful for comparison with our findings. In that study, age of subjects was restricted to 40–69 years (compared with 17–94 years in our study). Further, the investigators studied both smokers and nonsmokers, whereas we studied only subjects with a history of smoking. In that study, patients underwent angiography; therefore, stenosis of the normal carotid artery lumen was measured and used as the dependent variable in the analysis. Unlike ultrasound, angiograms do not give a direct measure of the thickness of the atherosclerotic plaque. Percent stenosis varies not only with plaque thickness but also with the normal (undiseased) carotid lumen diameter. Subjects with 1.9 mm of plaque thickness (the average for our sample) may have a calculated stenosis ranging from 50% (in those with small undiseased vessels) to 25% (in those with large vessels). We have chosen to take advantage of the ability of ultrasound to directly visualize the atherosclerotic plaque.

Although we believe that the ultrasound technique gives a better estimate of carotid atherosclerosis than does angiography, we note that the basic results are similar. Whisnant et al7 emphasize the duration of smoking as a significant risk factor for accelerated carotid artery plaque formation. The present study, on the other hand, focuses on the amount of smoking as a risk factor. An important advantage of duplex ultrasound for these studies in addition to direct visualiza-
tion of the plaque is that the noninvasive nature of duplex ultrasound allows its application to prospective studies based on representative samples of community-based populations.

We conclude that in smokers, the level of cigarette use is associated with an acceleration of the normal age-related development of carotid artery atherosclerosis as measured by thickness of intra-arterial plaques. This effect is independent of age, hypertension, and diabetes. In clinical practice, smoking abatement should be included as a component of stroke prevention strategies. Future studies are needed to determine whether cessation of smoking results in normalization or in deceleration of the normal age-related development of carotid plaque formation.

References

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