Hypertension Status Is the Major Determinant of Carotid Atherosclerosis

A Community-Based Study in Taiwan

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Background and Purpose—Extracranial carotid artery (ECCA) atherosclerosis has been associated with hypertension-related stroke. The present study was aimed at investigating the determinants of ECCA atherosclerosis in patients with hypertension in Taiwan.

Methods—The extent and severity of ECCA atherosclerosis were measured by high-resolution B-mode ultrasonography and expressed as maximal intima-media thickness (IMT) of the common carotid artery, ECCA plaque score, and carotid stenosis ≥50%. From July through December 1996, 263 hypertensive patients (146 with hypertension and 117 with borderline hypertension) and 270 normotensive adults from the Chin-Shan Community Cardiovascular Cohort participated in this study. Risk factors and ECCA atherosclerosis were stratified by the blood pressure status.

Results—A significant dose-response relationship was found between the status of hypertension and the severity of carotid atherosclerosis. Multivariate logistic regression models revealed that hypertension (including borderline), male gender, smoking, and age ≥65 years significantly increased the risk of thicker IMT. The risk of ECCA plaque score ≥6 increased significantly in conjunction with hypertension, age ≥65 years, left ventricular hypertrophy on ECG, and smoking. However, hypertension and smoking were the 2 evident determinants of carotid stenosis ≥50% after adjustment for other covariates. Compared with the normotensive subjects, the ORs (and 95% CIs) for the hypertensive patients to develop carotid atherosclerosis were 5.0 (3.0 to 8.4) indexed by maximal common carotid artery IMT ≥75th percentile, 3.7 (1.8 to 7.9) by ECCA score ≥6, and 4.8 (1.4 to 16.5) by carotid stenosis ≥50%.

Conclusions—Hypertension strongly influence carotid atherosclerosis. Our findings reinforce the hypothesis that hypertension has a major role in the pathogenesis of atherosclerosis. (Stroke. 2001;32:2265-2271.)

Key Words: Atherosclerosis • Carotid arteries • Hypertension • Taiwan

Over the past 2 decades in Taiwan, cerebrovascular and cardiovascular diseases have ranked as the second and the fourth leading causes of death, respectively, and have been the most important causes of morbidity and mortality, especially among the elderly.1 Hypertension is one of the most important risk factors in the development of atherosclerosis, coronary artery diseases (CAD), and cerebrovascular disease (CVD).2–4 Common carotid artery (CCA) intima-media thickness (IMT), extracranial carotid artery (ECCA) atherosclerosis, and maximal carotid stenosis have been proved to have significant association with CAD and CVD.5–8

Bodies of evidence support early detection of atherosclerosis and its associated risk factors in the prevention of atherosclerotic diseases. The measurement of carotid atherosclerosis by ultrasound has been widely used for its simple and reliable detection of early preclinical atherosclerosis9,10 and for the high correlation between measured IMT and the actual pathological change it produces.11 Some studies have documented the association between carotid atherosclerosis and hypertension.12–14 However, the progressive structural changes in extracranial carotid beds in response to blood pressure increment remain unclear. This association was addressed in the present study on the basis of data obtained from a cohort of the Chin-Shan Community Cardiovascular Cohort (CCCC) study in Taiwan.15–18 The other risk factors that are associated with carotid atherosclerosis were also investigated.

Subjects and Methods

Study Subjects

The CCCC study has been established since 1990 as a longitudinal, prospective, community-based surveillance on cardiovascular and cerebrovascular diseases. There were 3602 participants aged ≥35

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2265
years residing in the community of Chin-Shan, 20 miles north of Taipei, Taiwan.\textsuperscript{15–18} Sociodemographics, medical history, and vascular risk factors were evaluated in each subject. Physical examination included general condition, body weight, body height, waist and hip circumferences, and brachial and ankle blood pressures. ECG, echocardiography, and carotid ultrasonography (since 1994) were performed for every subject.

For the carotid atherosclerosis evaluation conducted from July through December 1996, 1802 individuals were randomly selected as study population from the CCCC study cohort and participated in the biennial follow-up evaluation in 1994. Among them, 451 subjects were classified as cases of hypertension or borderline hypertension. These individuals were contacted by telephone and home visit for participation: 146 hypertensives, 117 borderline hypertensives, and 270 normotensive controls received the carotid atherosclerosis evaluation throughout the study. There were no significant differences between participants and nonparticipants in regard to the distribution of age and sex and the prevalence rates of hypertension, diabetes mellitus, and smoking.

**Assessment of Vascular Risk Factors**

Hypertension was defined according to the criteria established by the Fifth Joint National Committee on Detection, Evaluation, and Treatment.\textsuperscript{19} Blood pressure measurements were performed with a mercury sphygmomanometer in a standardized fashion cuff size adjusted to the circumference of the arm. The arm was placed with the cuff at the level of heart. Blood pressure was recorded using the means of 2 measurements taken after 5 minutes of rest in the supine position. Systolic and diastolic blood pressures were defined according to Korotkoff sounds I and V. Diabetes mellitus was defined as fasting serum glucose level of \( \geq 7 \) mmol/L (140 mg/dL) in at least 2 different measurements and/or a history of use of oral hypoglycemic agents or insulin injection. Overweight was defined as a body mass index (BMI) of \( \geq 26.4 \) kg/m\(^2\), which was about 20% overweight, on the basis of recent Health and Nutrition Examination Surveys in Taiwan for Chinese adults.\textsuperscript{20}

Data on alcohol use and smoking were obtained by self-reported questionnaire. Alcohol use was calculated from frequency and amount and was summarized as the average number of alcoholic drinks consumed per week. Evident cardiovascular disease was defined as the presence of history of acute myocardial infarction or angina pectoris verified by coronary angiogram and/or medical records reviewed by at least one cardiologist. CVD was defined as the presence of history of stroke or transient ischemic attack verified by at least one neurologist. Left ventricular hypertrophy (LVH) was diagnosed from ECG according to the criteria of LVH defined in the Physician’s Guide to Marquette Electrocardiographs.\textsuperscript{21}

**ECCA Ultrasonographic Measurement**

Carotid atherosclerosis was assessed by using 3 indexes: the maximal CCA IMT, the ECCA plaque score, and the maximal ECCA stenosis. A Hewlett-Packard SONO 1500 ultrasound system, equipped with a 7.5-MHz real-time B-mode scanner and a 5.6-MHz pulsed-Doppler mode scanner, was used for the evaluation. The examination included the observation of longitudinal and transverse views of the ECCA bilaterally. Trained physicians performed carotid ultrasonography while patient was supine with the neck extended in mild lateral rotation. For future and subsequent off-line analysis, all scans were recorded on super-VHS videotape.

The maximal IMT on the CCA proximal to the carotid bifurcation was obtained bilaterally. The CCA1 and CCA2 are points located 0 to 1 cm and 1 to 2 cm, respectively, on the CCA distal from the carotid bifurcation. The IMT of the posterior wall of the distal CCA was measured as the distance from the leading edge of the first echogenic line (lumen-intima interface) to the leading edge of the second line (media-adventitia interface).\textsuperscript{22} Observers were blinded to subjects’ health status and risk factors. The interobserver correlation coefficients were 0.86 to 0.93, and the intraobserver correlation coefficients were 0.70 to 0.87 for both sides of CCA IMT measurements.\textsuperscript{23} Maximal CCA IMT \( \geq 0.75 \)th percentile was considered thicker IMT.

The plaque scoring quantified method has been mentioned elsewhere.\textsuperscript{24,25} In brief, carotid artery segments, including the proximal CCA (>20 mm proximal to the bulb bifurcation), distal CCA, bulb, internal carotid artery, and external carotid artery were examined bilaterally. A grade was assigned for each chosen segment: grade 0 for normal or no observable plaque, grade 1 for 1 small plaque with diameter stenosis <30%, grade 2 for 1 medium plaque with 30% to 49% diameter stenosis or multiple small plaques, grade 3 for 1 large plaque with 50% to 99% diameter stenosis or multiple plaques with at least 1 medium plaque, and grade 4 for 100% occlusion. The plaque score was computed by summing the plaque grades at each of the segments of the ECCA.

Carotid stenosis was assessed by the velocity criteria and the real-time B-mode images. It was computed from the difference in residual lumen diameter and the original diameter at the site of maximal stenosis in each segment of the arteries and by dividing each difference by the original diameter. Carotid stenosis of \( \geq 50\% \) was also defined in the presence of peak systolic velocity \( \geq 1.25 \) m/s.\textsuperscript{26} Reproducibility of plaque grade scoring showed good agreement, with a \( k \) value of 0.70.\textsuperscript{27} ECCA plaque score >6 or a maximal carotid stenosis \( \geq 50\% \) was defined as significant carotid atherosclerosis.

**Lipid and Lipoprotein Assays**

Serum levels of lipid profiles, including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, were analyzed in a central laboratory, as described previously.\textsuperscript{15–19} Blood samples of 9 to 12 hours overnight fasting for lipid and glucose determination were drawn from the antecubital vein with the patient in a seated position.

**Statistical Analyses**

In the data analysis, clinical features and cardiovascular risk factors of study subjects were first compared by hypertension status, ie, between hypertensives and controls. Continuous variables are expressed as mean±SD. Both \( t \) test and ANOVA were used to make comparisons among these groups. For categorical data, the \( \chi^2 \) test for trend was used to test the significance level among different groups. The average carotid artery IMT measurements at CCA1 and CCA2 on the right side and on the left side were compared separately, also by hypertension status. The frequency of ECCA plaques was compared by hypertension status. Plaque scores were also stratified into 4 levels (0, 1 to 3, 4 to 6, and >6) to evaluate the differences in the percentage distributions of ECCA plaques between hypertensives and controls. Percentages of subjects with stenosis at the 50% level and above were evaluated as well. The strength of associations between carotid atherosclerosis and hypertension and other potential risk factors was measured in terms of ORs in the 95% CIs by using multivariate logistic regression analysis. An IMT at or above the 75th percentile, ECCA score >6, or carotid stenosis at the 50% level and above was considered as an indicator of significant carotid atherosclerosis in performing these analyses. Significant variables identified from the univariate analyses were included as covariate in the multivariate logistic regression models with stepwise procedure to estimate the risks of thicker IMT, significant ECCA plaque score, and significant carotid stenosis.

**Results**

No significant differences in the distributions of sex, average ages, and lifestyles were found among hypertensives patients and normotensive control subjects (Table 1). Normotensives were significantly less likely than hypertensives to have hypertriglyceridemia, diabetes mellitus, CVD, and LVH (on ECG), and they had lower average BMI and waist-to-hip ratio \( (P<0.001) \).
Average CCA IMT measurements at different carotid locations all showed significant trends ($P<0.001$) of IMT progression, as graded by the extent of hypertension (Table 2). The overall average CCA increased from 0.89 ± 0.17 mm for normotensives, 1.00 ± 0.28 mm for borderline hypertensives, and 1.06 ± 0.25 mm for hypertensives.

Table 3 shows significant trends of carotid plaque formations by the status of blood pressure. About 53% of hypertensives were observed to have plaques with an average plaque score of 3.01, while the corresponding values decreased to 41% with 1.88 score for borderline hypertensives, and to 34% with 1.24 score for normotensives. About 17.6% of the hypertensives (the highest prevalence) and 5.2% of the normotensives (the lowest prevalence) had plaque scores.

The prevalence of carotid stenosis at the 50% level and above was observed to be highest in hypertensives as well.

Multivariate logistic regression analyses showed that hypertension, being a male, smoking, and age $\geq 65$ years increased the risk of thicker IMT after adjustment for other associated factors (Table 4). However, the results also noted...
that an inverse relationship was found between subjects with regular alcohol consumption and CCA IMT (OR 0.5; 95% CI 0.2 to 0.9). Hypertension remained consistently a strong risk factor of ECCA atherosclerosis by the other 2 indexes (ECCA score >6 and carotid stenosis $\geq 50\%$). When the subjects with ECCA score $>6$ were evaluated, age $\geq 65$ years, current smoking, and LVH on ECG were also found to be significant covariates. However, if significant carotid stenosis ($\geq 50\%$) was considered, hypertension and current smoking were the 2 evident determinants after adjustment for other covariates. Compared with normotensives, the corresponding ORs (95% CIs) for development of carotid atherosclerosis in hypertensives were 5.0 (3.0 to 8.4) indexed by maximal CCA IMT $\geq$75th percentile, 3.7 (1.8 to 7.9) indexed by significant ECCA score $>6$, and 4.8 (1.4 to 16.5) indexed by carotid stenosis $\geq 50\%$.

**Discussion**

Stroke is prevalent in Taiwan.\textsuperscript{26} The present study is well in line with other findings on the association between IMT and hypertension. Furthermore, we demonstrated that a dose-response relationship exists between them and that hypertension is the most important risk factor for carotid IMT and carotid atherosclerosis. Cross-sectional analysis suggests that age is related to carotid wall thickening in all carotid beds, and carotid wall IMT is greater in men than in women aged 45 to 64 years in the Atherosclerosis Risk in Communities (ARIC) Study.\textsuperscript{27} The Cardiovascular Health Study (CHS) revealed that among the elderly ($\geq 65$ years), women have less carotid atherosclerosis than men, and the prevalence and severity of carotid artery disease continue to increase with age even in the late decades of life. Prevalence of vascular structural adaptation and increased risk factors associated with aging are atherosclerosis related.

A significantly beneficial effect of alcohol consumption on the CCA IMT was observed in this study, although the relationship between alcohol use and carotid atherosclerosis remains controversial. An inverse relationship between

| TABLE 3. Average Plaque Scores and Distributions of ECCA Plaque, ECCA Plaque Score, and Carotid Stenosis $\geq$50%, by Hypertension Status |
|------------------|------------------|------------------|------------------|
|                  | Hypertension ($n=146$) | Hypertension ($n=117$) | Normotension ($n=270$) |
| **ECCA Atherosclerosis** |                  |                  |                  |
| Average plaque score  | 3.01±4.44        | 1.88±3.44        | 1.24±2.41        |
| Presence of plaque   | 78 (53.2)        | 48 (41.0)        | 93 (34.4)        |

Values are n (%), except average plaque score (mean±SD).

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<tr>
<th>TABLE 4. Multivariate Logistic Regression Models for Different Indexes of Carotid Atherosclerosis</th>
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<td><strong>Characteristic</strong></td>
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<td>Smoking, current</td>
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<td>Alcohol, current</td>
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<td>Age $\geq$65 years</td>
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<td>BMI $\geq$26.4 kg/m(^2)</td>
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<td>Cholesterol $\geq$6.21 mmol/L</td>
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<td>HDL-C $&lt;0.91$ mmol/L</td>
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<td>LDL-C $\geq$4.14 mmol/L</td>
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<td>LVH on ECG</td>
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Values are given as OR (95% CI).

*P<0.05; †P<0.01; ‡P<0.005.
alcohol and carotid wall IMT has been noted in some studies. However, alcohol drinking was found to have no relation with carotid wall IMT in the ARIC study. Small to moderate amounts of alcohol drinking may have a protective effect in the very early stages of carotid atherosclerosis; however, the effect may be attenuated by established hypertension. Both the ARIC and CHS studies found that increased exposure to cigarette smoking is significantly related to increased carotid artery IMT and carotid stenosis. Active and passive smoking are also associated with increased carotid wall thickness. Smoking has a detrimental effect, being associated with greater IMT and carotid plaque score, and thereby moderate-to-severe carotid atherosclerosis, in this study. The high prevalence (61.9% of male participants) of smoking was noted with the CCCC study. Cigarette smoking also has been demonstrated to be a more important risk factor for stroke and cerebral infarction than excessive drinking of alcohol in a population study in Taiwan. Thus, the high mortality rate from stroke in Taiwan makes the need for public policy to reduce the smoking rate more urgent.

The Framingham study has shown that in the presence of LVH, the incidence rates of acute myocardial infarction and sudden death increase 6- to 8-fold, irrespective of blood pressure. The CHS further demonstrated that LVH on ECG is a risk factor for maximal CCA and ICA IMT and maximal percent stenosis of carotid arteries. The results of the current study are consistent with these findings: there is moderate but significant increased risk for significant ECCA score > 6 for individuals with LVH on ECG (OR 2.4), which indicates that LVH is an important indicator of end-organ change and is strongly associated with carotid atherosclerosis. Hypertension has been recognized as a strong risk factor for cardiovascular disease, stroke, and peripheral vascular disease. Isolated systolic hypertension and isolated borderline hypertension are associated with a higher risk of cardiovascular disease and subclinical atherosclerotic disease. Mechanisms by which hypertension predisposes to atherosclerosis may include endothelial dysfunction, hyperinsulinemia, hemodynamic stress, and multiple metabolic alterations. Impaired production of endothelium-derived relaxing factors and increased activity of endothelium-derived contractile substances have been demonstrated in hypertensive patients, preceding overt atherosclerotic disease. In addition, enhanced smooth muscle cell proliferation with intimal wall thickening and proteoglycan accumulation accelerates atherosclerosis. Hypertension increases the wall shear stress and barotrauma to the arterial intima. Increased flow velocity and wall shear stress are considered to be the important factors that caused hypertension-induced intima-media hypertrophy and thickness. Hypertension is also associated with insulin resistance and considered a manifestation of metabolic syndrome. A cluster of insulin-resistance syndrome has been noted among the individuals with hypertension in this study cohort, leading to increased risk for atherosclerosis, thrombosis, and other coronary heart disease. Another study conducted in Taiwan shows that hypertension, hypercholesterolemia, and hypertriglyceridemia are pathogenic in carotid atherosclerosis and stroke. The present study links only hypertension as the most prominent risk factor for thicker IMT and clinically for the development of carotid stenosis, and thereby for higher ECCA plaque score. In fact, this is the first study to demonstrate by an apparent dose-response relationship that hypertension is the most important determinant in the development of carotid atherosclerosis.

The thickening of carotid IMT is initiated when hypertension is borderline but does not to a significant degree affect the development of advanced carotid plaques and carotid stenosis (after adjusting for other associated factors). This finding indicates that borderline hypertension (a transition stage to full-blown hypertension) may increase the risk of atherosclerosis, implying that the increase in IMT is an earlier preclinical atherosclerotic change. Possibly, as atherosclerosis progresses to an advanced lesion stage, the status of borderline hypertension changes to evident hypertension. It remains debatable whether to refer to increased IMT as atherosclerosis. It represents end-organ disease of mainly hypertensive medial hypertrophy. Adams et al found only a weak correlation between IMT and severity of CAD; they point out that IMT is approximately 80% media and only 20% intima, whereas atherosclerosis is an intimal process. Furthermore, there is a fundamental conceptual fallacy in the construct: IMT is continuous along the length of the vessel, whereas atherosclerosis is focal. O’Leary et al showed that the R² for prediction of IMT by Framingham risk factors was only 0.15 in the internal carotid artery and 0.18 in the CCAs. Spence et al, on the other hand, showed that Framingham risk factors explain 50% of carotid plaque area. Others have shown a better correlation between IMT and left ventricular mass than with atherosclerosis; 2 studies have shown a better correlation of plaque measurements than IMT with atherosclerotic events. O’Leary et al had demonstrated that IMT predicted events and showed that IMT is a stronger predictor of stroke than myocardial infarction; this is probably because IMT predicts events due to hypertensive small-vessel disease or because of other aspects of physiological aging. Carotid plaque is an even stronger predictor of atherosclerotic events (myocardial infarction) than stroke, which is partly nonatherosclerotic. Our previous work has demonstrated that in patients with ischemic stroke, hypertension is prevalent (49% to 66%) and ECCA atherosclerosis is common. The present study showed hypertension to be the most important risk factor for carotid atherosclerosis among individuals with or without ischemic stroke.

The current study is limited by the cross-sectional design. However, it is reasonable to conclude that carotid atherosclerosis progresses with the transition of normotension to borderline hypertension and then to hypertension. Carotid atherosclerosis evaluation by carotid ultrasound is useful and sensitive in clinical practice, especially for patients with hypertension. Blood pressure measurement...
also should be performed routinely for every adult in clinical practice. The pathogenesis of hypertension in atherosclerosis deserves greater concern and further study. Optimal control of hypertension for the prevention of atherosclerotic disease can never be overestimated, especially in a country such as Taiwan with high prevalence of stroke.

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