Additional Predisposing Risk Factors for Atherothrombotic Cerebrovascular Disease Among Treated Hypertensive Volunteers

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A 7-year prospective study of a cohort of 107 neurologically normal elderly hypertensive volunteers (mean age, 65.8 ± 8.3 years) was undertaken to investigate the predictive validities of additional risk factors for atherothrombotic cerebrovascular disease including stroke, transient ischemic attacks, reversible ischemic neurological deficits, and multi-infarct dementia. This longitudinal study has been in progress now for 7 years with a mean follow-up interval of 50.12 ± 5.76 months. Among 107 formerly symptom-free, normal hypertensive volunteers, 25 (23%) have developed cerebrovascular disease, 7 (6.5%) sustained a stroke, 10 (9.3%) developed multi-infarct dementia, and 18 (16.8%) have transient ischemic attacks. None have suffered intracranial hemorrhage. Mean gray matter cerebral blood flow (CBF) values measured at the initial visit were sensitive predictors of cerebrovascular disease. Eight of 16 hypertensives (50%) with initial CBF values below 60.0 ml/100 g/min now exhibit signs and symptoms of cerebrovascular disease, while 11 of 43 hypertensives (25.6%) with initial CBF values between 60.1 and 69.9 ml/100 g/min and only 6 of 48 (12.5%) with initial CBF levels above 70.0 developed cerebrovascular disease. Incidence of cerebrovascular disease among cigarette smoking hypertensive volunteers (32.5%) was significantly greater than among nonsmokers (17.2%).

HYPERTENSION has been identified as a potent risk factor for cardiovascular and occlusive cerebrovascular disease (CVD) for over 30 years. The Framingham Study reported direct relations between hypertension and increased risk of coronary artery disease and atherothrombotic stroke.1,2 Longitudinal studies confirmed these results.3 Hypertension is also implicated as a risk factor for lacunar infarct, multi-infarct dementia (MID),4,5 and atheromatous occlusion or stenosis of the internal carotid and other major aortocranial arteries,6 particularly among patients complaining of transient ischemic attacks (TIAs).7 Heart disease, cardiac dysrhythmia, and diabetes mellitus are other well established risk factors for stroke. Cigarette smoking, obesity, and elevated serum lipid levels are less well defined as risk factors for atherothrombotic stroke.

As soon as hypertension emerged as the major risk factor predisposing to signs and symptoms of atherothrombotic CVD, emphasis was logically placed on treatment and increased risk of coronary artery disease and atherothrombotic stroke.8 Longitudinal studies confirmed these results.3 Hypertension is also implicated as a risk factor for lacunar infarct, multi-infarct dementia (MID),4,5 and atheromatous occlusion or stenosis of the internal carotid and other major aortocranial arteries,6 particularly among patients complaining of transient ischemic attacks (TIAs).7 Heart disease, cardiac dysrhythmia, and diabetes mellitus are other well established risk factors for stroke. Cigarette smoking, obesity, and elevated serum lipid levels are less well defined as risk factors for atherothrombotic stroke.

To define what, if any, relation the incidence of stroke might bear to serial measurements of cerebral blood flow (CBF) and risk factors for stroke other than hypertension.

Subjects and Methods

A cohort of 107 elderly (mean age, 65.8 ± 8.3; range, 51–89 years) but neurologically normal volunteers with mild to moderate hypertension has now been...
followed for intervals of up to 7 years (average follow-up, 50.12 months; range 2–7 years). To provide a heterogeneous sample of neurologically normal volunteers, subjects were recruited through a variety of sources including local newspaper and magazine advertisements, speaking engagements at communities for healthy elderly individuals, and referrals from physicians and friends in the community. All subjects were right-handed and had at least a high school education. The inception cohort contained 42 men and 65 women.

At the initial visit, all volunteers underwent neurologic examinations, cognitive capacity screening examinations (CCSE), and regional CBF measurements using the xenon-133 inhalation method. Results of all examinations were within normal limits. However, all volunteers gave a history of hypertension that had been present for at least 5 years. Hypertension was defined in this protocol as repeated recordings of blood pressure > 160/90 mm Hg and was confirmed by review of their medical records. The average duration of hypertension was 11.35 years. Ninety-five percent of the subjects were taking their prescribed antihypertensive agents at admission into the study; the remainder had discontinued their medications. In the latter group, repeated blood pressure measurements were required by the design of the study protocol to be above 160/90 mm Hg to be eligible for entry. These subjects were then placed on antihypertensive medications. All subjects had their blood pressures monitored at monthly intervals until controlled at normal levels, and thereafter were monitored at 6-month intervals. The dosage of medications was adjusted when necessary, using diuretics, propranolol, or α-methyldopa.

Criteria for exclusion from the study included 1) signs or symptoms of focal neurologic deficits, 2) history of any cerebrovascular signs or symptoms, 3) abnormal hemoglobin or hematocrit levels, 4) history or signs and symptoms of severe cardiopulmonary disease and/or any other major concurrent medical illness, and 5) CCSE scores of 25 or below, which indicates dementia.

All volunteers were scheduled for return visits at 6-month intervals (or as close as possible to this interval as was convenient) for regular examinations in the laboratory after the initial assessment if the hypertension was properly controlled. All procedures performed during the initial assessment, including complete medical and neurologic examinations, CBF studies, CCSE examinations, Hachinski ischemic score, and blood and urine chemistries, were repeated during each follow-up visit. In volunteers whose blood pressure was above 160/90 mm Hg, the initial assessment was delayed until blood pressure was properly controlled (i.e., remained <150/90 mm Hg on 3 consecutive occasions).

The protocol for this study, regional CBF measurements, and the informed consent forms were approved by institutional review boards of the Veterans Administration Medical Center and Baylor College of Medicine, Houston, Tex.

Regional CBF was measured by the xenon-133 inhalation method. The tracer isotope for measuring CBF was 5–8 mCi per liter of xenon-133 mixed with room air administered by inhalation for 1 minute. During the ensuing 10-minute desaturation interval, the rates of clearance of the isotope from 16 different regions of both cerebral hemispheres were monitored by collimated sodium iodide crystal detectors mounted over the scalp. Gray matter flow values were derived from the fast-clearing compartment by means of a two-compartmental model. Values measured by this noninvasive method correlate well with cerebral gray matter blood flow measured by intracarotid injection of xenon-133. End-tidal curves of xenon-133 recorded from the end-tidal air were used to correct for arterial recirculation.

End-tidal partial pressures of carbon dioxide and oxygen were also monitored from the expired air. There were no statistically significant changes in end-tidal pressures for O2 or CO2 between the series of CBF measurements. Blood pressure was measured before and after each test procedure. Respiration, EEG, and ECG were also monitored by a polygraph during CBF measurements, but none of these recordings showed significant alterations between measurements.

Normative data measured in this laboratory among 250 neurologically normal, age-matched healthy volunteers without hypertension (mean age, 62.39 years; range, 24–98 years) gave mean gray matter CBF values of 71.14 ± 10.66 ml/100 g/min. Earlier reports from this laboratory of test–retest reliability for gray matter CBF measurements indicated a reproducibility coefficient of $r = 0.89$.

During the course of this prospective trial, subjects who developed stroke, TIAs, or MID were compared with those subjects who remained asymptomatic. In addition to the routine screening procedures described, subjects suspected of showing signs and symptoms of CVD were referred for appropriate laboratory testing to confirm the diagnosis. These included computed tomography (CT) with i.v. iodine contrast agents or stable xenon gas contrast by inhalation and/or magnetic resonance imaging (MRI) of the brain. In the majority of individuals who developed signs of occlusive CVD, particularly those with bruits over the neck vessels, cerebral angiography was undertaken in an effort to demonstrate arterial stenosis or occlusion.

The diagnosis of MID was based on the following criteria4,17,18 1) Hachinski ischemic index of ≥ 5, 2) CCSE score of ≤ 21, 3) progressive stepwise mental deterioration, 4) symptoms and signs of focal neurologic abnormalities, and 5) identifiable lesions on CT, contrast CT, or MRI of the brain. Lesions included low-density regions considered to be cerebral infarctions by CT or zones of increased T2 or decreased T1 densities by MRI of the brain. The majority were small subcortical lesions considered to be lacunar infarcts. Many also showed asymmetric evidence of cortical atrophy usually around the Sylvian fissures, considered to be characteristic of MID.

Subjects with TIAs had transient cerebral symptoms...
referable to either the left or right internal carotid or verteobasilar arterial territories persisting for <24 hours’ duration and without residual neurologic deficits. Subjects were defined as having had a stroke if neurologic deficits persisted longer than 3 weeks and if there was evidence of an infarct on CT and/or MRI. Subjects categorized with reversible ischemic neurologic deficits (RINDs) were those developing focal neurologic dysfunction persisting for >24 hours but with more or less complete recovery within 3 weeks.

**Statistical Methods**

Univariate significance of the contributions of premorbid CBF levels, age, cigarette smoking, and presence of multiple risk factors was assessed using $\chi^2$ comparisons of the frequency of atherothrombotic neurologic events. To assess the relations between CBF and the risk of atherothrombotic neurologic symptoms, initial CBF levels were divided into 3 categories (<60.0, 60.0–70.0, and >70.0 ml/100 g/min) on an a priori basis. Analyses of variance (ANOVAs) were used to compare initial CBF levels and ages between the various diagnostic groups. Since several subjects eventually progressed to multiple categories, priority was given to the initial diagnostic classification for these two ANOVAs. Nonorthogonal pairwise comparisons were used. Additionally, both average systolic and average diastolic blood pressures for each subject were compared between asymptomatic and symptomatic subjects using $t$ tests with pooled variance estimates. For symptomatic subjects, only blood pressure prior to the initial onset of symptoms was analyzed. Cholesterol and triglyceride levels between asymptomatic and symptomatic subjects were also contrasted using similar $t$ tests. However, cholesterol and triglyceride levels measured at the time of the CBF measurements were available on only a limited number of subjects in the study (42 asymptomatic and 11 symptomatic patients).

A Cox proportional hazard survival analysis was used to assess the relative influence of CBF, age, presence of additional risk factors, and history of cigarette smoking on the time-to-response survival function. Response was defined as the onset of stroke, TIAs or MID. A multivariate stepwise regression using the maximum partial likelihood ratio method tested the relative significance of the covariants. Effects of multiple risk factors were analyzed by coding the number of risk factors present. To assess the discriminant ability of initial CBF levels, cigarette smoking, age, systolic and diastolic blood pressure, and presence of multiple risk factors, the development of symptoms and signs of CVD during the study formed the discriminant grouping variable. Statistical criteria for entry of prediction variables was based on Wilk’s $\lambda$ statistic. Variables were ordered according to their ability to discriminate between symptomatic and asymptomatic groups.

**Results**

During the course of this prospective study, 25 of the 107 neurologically normal subjects have so far developed symptoms and signs of atherothrombotic CVD. Table 1 displays the incidence according to diagnostic category. The most frequent form of CVD in this cohort has been TIAs (average annual rate, 4.02%), occurring more than twice as often as stroke (1.56% annually) and at almost double the frequency of MID (2.23% annually). Additionally, TIAs occurred at a younger age (mean age, 69.0 years) than either stroke (mean age, 78.7 years, $p<0.02$ by ANOVA) or MID (mean age, 76.7 years, $p<0.05$ by ANOVA). The stroke and MID groups showed no difference in age. Subjects with stroke had lower premorbid CBF levels than subjects with either MID ($p<0.05$) or TIA ($p<0.02$). None of the symptomatic subjects were diagnosed as having RINDs. None of the hypertensive subjects with properly controlled hypertension in this study have suffered intracerebral or subarachnoid hemorrhage, hypertensive encephalopathy, orBinswanger’s subcortical leukoencephalopathy.

To assess the relations between the initial presymptomatic mean bihemispheric CBF values and the risk of atherothrombotic CVD, subjects were classified into 3 categories according to initial CBF levels. Table 2 displays the number of subjects from each CBF group, with the number and percent of subjects who later developed cerebrovascular symptoms. In those with lowest initial CBF levels, 50% later became symptomatic, while 25.6% in the median group became symptomatic, and only 12.5% of those with CBF levels >70.0 ml/100 g/min developed cerebrovascular symptoms. $\chi^2$ comparisons indicate that these distributions were significantly different ($p<0.01$).

Table 3 displays risk of CVD among hypertensive subjects according to age. There is a significant increase in frequency of symptoms of cerebral ischemia with advancing age ($\chi^2; p<0.01$). The incidence ranged from 11.7% in subjects <60, 23.1% in subjects 60–69, and 31.9% for subjects ≥70 years. As displayed in Table 4, the development of symptoms
and signs of CVD among subjects was significantly increased ($\chi^2$; $p<0.01$) among cigarette smokers (32.5%) compared with nonsmokers (17.2%).

Table 5 summarizes the incidence of signs and symptoms of cerebral ischemia among hypertensives according to presence of other established risk factors for stroke, including atherosclerotic heart disease and diabetes mellitus. In hypertensive subjects without additional risk factors, 16.1% became symptomatic, while 35.5% of hypertensives with associated atherosclerotic heart disease and 11.1% with associated diabetes mellitus developed symptoms and signs of occlusive cerebrovascular disease. Of the hypertensive subjects with both heart disease and diabetes mellitus, 3 of 5 (60%) developed symptoms due to cerebral ischemia.

Tests of the differences in systolic and diastolic blood pressures between asymptomatic and symptomatic subjects were not significant. Symptomatic subjects had a mean systolic blood pressure of 140.5 ± 12.6 mm Hg and a mean diastolic blood pressure of 80.6 ± 7.0 mm Hg, while the mean systolic and diastolic blood pressures of the asymptomatic subjects were 140.7 ± 14.8 and 79.4 ± 7.6 mm Hg. There were no significant differences between triglyceride and cholesterol levels of the two groups, although there were some trends for higher lipid levels in the symptomatic group. Mean cholesterol and triglyceride levels were 245.7 ± 45.6 and 263.3 ± 193.4 among symptomatic subjects prior to the onset of symptoms and 217.2 ± 38.8 and 187.6 ± 114.4 among subjects who remained symptom-free.

During the course of the study, 5 deaths were recorded. Two mortalities from myocardial infarction and cardiac arrest occurred among the cohort without any symptoms of CVD, while the other 3 cases (2 myocardial infarctions and 1 complication secondary to stroke) occurred among subjects previously designated as cerebrovascular end-points. In the Cox proportional hazard model, the 3 cases with prior CVD were included as end-points according to the onset of symptoms, while the other 2 were counted as withdrawals at the date of their death.

Results of the stepwise regression using the Cox proportional hazard model are summarized in Table 6. Initial CBF level ($p<0.002$) was the first covariant to enter the equation, followed by multiple risk factors ($p<0.025$), cigarette smoking ($p<0.078$), and age ($p<0.087$). The global significance of the equation with all 4 factors entered was $p<0.0001$.

In the multivariate discriminant function analysis, the first variable to enter the equation was baseline presymptomatic CBF levels (Wilk’s $\lambda = 0.908; p<0.0015$), followed by the presence of multiple risk factors (Wilk’s $\lambda = 0.923; p<0.01$), age (Wilk’s $\lambda = 0.950; p<0.02$), and cigarette smoking (Wilk’s $\lambda = 0.983; p<0.09$). All other variables failed to reach minimum threshold levels. With all prediction

<table>
<thead>
<tr>
<th>Age range</th>
<th>Number with hypertension</th>
<th>Number developing CVD</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>34</td>
<td>4</td>
<td>11.7%</td>
</tr>
<tr>
<td>61-70</td>
<td>26</td>
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<td>23.1%</td>
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<td>≥70</td>
<td>47</td>
<td>15</td>
<td>31.9%*</td>
</tr>
<tr>
<td>TOTALS</td>
<td>107</td>
<td>25</td>
<td>23.3%</td>
</tr>
</tbody>
</table>

CVD, cerebrovascular disease. For the group as a whole, advancing age was associated with greater risk.

Table 3. Risk of Cerebrovascular Disease Among Hypertensive Volunteers According to Age

Table 4. Risk of Cerebrovascular Disease Among Treated Hypertensives Comparing Smokers and Nonsmokers

Table 5. Contribution of Other Risk Factors Combined With Hypertension to Incidence of Cerebrovascular Disease
It has been estimated that occurrence of TIAS increases the risk of stroke 6 or more times compared with rates in normal populations without TIAS. In the Rochester Study, approximately 10% of stroke patients had TIAS prior to the onset of the ictus, and in similar population studies TIAS were present in up to 35% prior to the onset of stroke. In the current study the annual incidence of TIAS has been higher than the incidence of stroke. Of 18 patients who developed TIAS, 3 subsequently had strokes. TIAS also appeared at a younger age (mean, 59.3 years) than strokes (78.7 years).

Though the true incidence of organic dementias in the United States remains to be determined, the prevalence of dementias increases with advancing age, with the most rapid increase occurring between the sixth and eighth decades. The prevalence of dementias of all types in the United States has been estimated to be at least 20% by age 85. Alzheimer’s dementia accounts for 50–60% of all cases of dementia examined at necropsy. MID accounts for another 22% of cases, and both forms coincide in 14%. Results of the present study suggest an annual incidence for MID of 2.23% among chronic hypertensives, with a mean age of 76.7 years at onset of the disease. In a previous longitudinal study the rate of MID among groups of normal volunteers who had one of the major risk factors for stroke (hypertension, hyperlipidemia, heart disease, or diabetes mellitus) was 0.78% new cases per year. This suggests that hypertension is a potent risk factor for MID and that early treatment should reduce its incidence. Previous studies have indicated that hypertension is present in up to 80% of MID cases.

Though cigarette smoking is clearly related to coronary artery disease and myocardial infarction, longitudinal clinical studies have indicated a rather weak relation between cigarette smoking and atherothrombotic stroke. Animal studies indicate that cigarette smoking enhances atherogenesis. Human studies in which CBF was measured as the indicator of cerebral atherosclerosis have demonstrated that cigarette smoking significantly reduces cerebral perfusion as well as cerebrovascular reactivity tested by inhalation of O2 or 5% CO2. Abstinence from cigarette smoking in this population was later shown to improve cerebral perfusion. Results of the present study provide stronger and more significant relations between cigarette smoking and occlusive CVD (including stroke, TIAS, and MID). Possibly cigarette smoking is more closely linked to causation of MID and TIAS than to atherothrombotic stroke. Indeed, results of an earlier longitu-
dinal study indicated that 70% of a group of MID patients had a history of heavy cigarette smoking for at least 20 years.4

Table 5 displays influences of single vs. multiple risk factors in combination on the incidence of CVD. Among these chronic hypertensive subjects, the addition of atherosclerotic heart disease increased the risk of CVD approximately 2.5 times over that seen among those without additional risk factors. All subjects in the current study suffering from heart disease are also under treatment by cardiologists. It is our opinion that the present study reflects a true incidence of CVD among patients who are receiving optimal treatment for both hypertension and cardiac disease. It is difficult to determine, in a cohort of elderly subjects, the precise duration of hypertension and CVD prior to detection and treatment. Without exception, as judged by history, hypertension had been present for at least 5 years prior to admission to the study, with a mean duration for the group of >11 years. It is usually assumed that the occurrence of coronary artery disease among the hypertensive elderly is a manifestation of atherogenesis secondary to hypertension since death and disability from both heart disease and stroke are improved when hypertension is controlled.8,9 Improved screening and earlier detection and treatment of hypertension should also reduce the incidence of heart disease and reduce CVD further since heart disease itself is a risk factor for stroke.

Other studies have demonstrated the additive effects of multiple risk factors and have suggested that multivariate predictive models should allow more logical selection of patients for preventive management.30,31 In the current study, the discriminant function analysis with CBF levels, presence of multiple risk factors, age, and cigarette smoking in the equation indicated 67% correct classification. However, it should be noted that discriminant analyses maximize prediction for the population used in the analyses and that application of the same parameters to another cohort would typically result in a lower percent of correct classification. A cross-validation study would better determine the degree of predictive accuracy of the multivariate model.

During the course of this study, a strong relation was found between initial CBF before cerebrovascular symptoms were present and subsequent risk from CVD. Table 2 shows that among normal elderly hypertensive subjects with CBF levels below the median range (<60.0 ml/100 g/min), atherothrombotic CVD occurred 5 times more frequently compared with hypertensive subjects with CBF levels above 70.0 ml/100 g/min and at almost twice the frequency seen in the 60.0-70.0 ml/100 g/min group. Stepwise discriminant function analysis indicated that presymptomatic CBF level was the most significant and reliable predictor of subsequent onset of cerebrovascular events.

The strong association between CBF levels and the subsequent onset of CVD reflects that reduced CBF indicates subclinical changes in cerebral vasculature including atherogenesis and hypertrophy of the medial muscle of the vessel walls, which have long been associated with hypertension.12 Since autoregulation typically compensates for minor changes in the cerebral vessels, reduced CBF is an early indicator of chronic changes in cerebral vessels that predispose to occlusive CVD.

Cross-sectional studies have demonstrated that CBF levels and vasomotor responsiveness are reduced among normal volunteers at risk from stroke,16,32 and CBF reductions are reversible when risk factors are treated.12 Previous longitudinal studies have indicated that CBF levels are reduced for at least 2 years before atherosclerotic cerebrovascular symptoms appear13 and that patients with MID have lower presymptomatic CBF levels compared with age-matched normal controls who later developed Alzheimer's type dementia.4 The strength of these relations between reduced CBF and later development of CVD suggests that measurement of cerebral perfusion will provide an index of atherogenesis and stenosis of the cerebral arterial vasculature and quantify any predisposition for later development of cerebrovascular symptoms and signs. If this proves to be correct, CBF measurements should be helpful for identifying individuals at high risk and for evaluating effectiveness of therapeutic intervention.

The mean ages in the categories of initial CBF levels in Table 2 were similar, with 4.3 years separating the two extreme groups. It would appear unlikely that such a small difference in age could account for the dramatic increase in risk from 12.5 to 50.0%. ANOVA indicated no statistically significant differences in the ages of the groups. Among patients who developed CVD symptoms, the difference in age increased but was still not significant. Since the multivariate analysis (Table 6) suppresses common variance between CBF and age, results would support the hypotheses that the significant relation between CBF and occurrence of symptomatic end-points was independent of any effects due to age.

In summary: Among asymptomatic subjects with long-standing hypertension, optimal control of blood pressure by antihypertensive medications reduces the risk of stroke, though some risk persists. Reduced cerebral perfusion is a sensitive indicator of subclinical cerebral atherosclerosis. Measurements of cerebral perfusion should prove useful for screening populations and identifying individuals at risk of stroke requiring primary or secondary intervention. Cigarette smoking appears to be another remediable risk factor for stroke among the chronic hypertensive elderly. Of 107 subjects with carefully controlled hypertension followed for a mean of 50 months, none has suffered intracerebral hemorrhage, hypertensive encephalopathy, or Binswanger's disease. Control of hypertension appears to be most effective in preventing brain hemorrhage, hypertensive encephalopathy, and Binswanger's subcortical leukoencephalopathy.

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**KEY WORDS:** risk factors • cerebrovascular disease • hypertension • cigarette smoking • atherothrombotic stroke
Additional predisposing risk factors for atherothrombotic cerebrovascular disease among treated hypertensive volunteers.
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Stroke. 1987;18:335-341
doi: 10.1161/01.STR.18.2.335

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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