Predictors of Carotid Stenosis in Older Adults With and Without Isolated Systolic Hypertension

Kim Sutton-Tyrrell, DrPH; Hope G. Alcorn, MPH; Sidney K. Wolfson Jr., MD; Sheryl F. Kelsey, PhD; and Lewis H. Kuller, MD, DrPH

Background and Purpose: This study was designed to determine the prevalence of carotid stenosis and atherosclerosis in older adults with and without isolated systolic hypertension and to determine risk factors for carotid artery disease in these two groups.

Methods: Duplex scans were performed on 187 participants of the Systolic Hypertension in the Elderly Program and on 187 normotensive control subjects. Doppler measures of blood flow velocity were used to determine the prevalence of internal carotid artery stenosis.

Results: Carotid stenosis was found in 25% of hypertensive participants but in only 7% of normotensive participants ($p < 0.001$). Among hypertensive participants, carotid stenosis was correlated with lower diastolic blood pressure ($p=0.022$). In multivariate analysis, systolic blood pressure of $\geq 160$ mm Hg was the strongest predictor of carotid stenosis. Other variables independently related to stenosis were diastolic blood pressure of $<75$ mm Hg ($p=0.001$), alcohol use ($p=0.005$), heart rate of $\geq 80$ beats per minute ($p=0.013$), smoking ($p=0.034$), high concentration of apoprotein B ($p=0.001$), and low concentration of high density lipoprotein cholesterol (borderline significant, $p=0.069$). Among hypertensive participants, the strongest predictor of carotid stenosis was low diastolic blood pressure. This relation persisted even after taking into account differences in pulse pressure.

Conclusions: Isolated systolic hypertension is strongly correlated with carotid stenosis, and among those with isolated systolic hypertension low diastolic blood pressure is a marker for carotid stenosis. (Stroke 1993;24:355–361)

Key Words • carotid artery diseases • hypertension • elderly

Persons with asymptomatic carotid stenosis are at risk for stroke,1–3 but reported risk varies widely across studies and type and location of the stroke do not always implicate the diseased carotid artery. Persons with carotid stenosis are also at increased risk for ischemic heart disease,4–5 lower-extremity arterial disease,6 and death.1–7 This suggests that carotid stenosis marks the presence of generalized systemic atherosclerosis.

The carotid arteries are easily accessible to noninvasive study using ultrasound techniques, providing researchers with the ability to measure accurately atherosclerosis and associated stenosis in its subclinical stages. By studying carotid stenosis in this manner, risk factors can be identified and patients with early disease can be targeted for treatment and risk factor modification. To this end, we have studied carotid stenosis in older adults with and without isolated systolic hypertension (ISH). This report compares the prevalence of carotid stenosis between these two groups and evaluates risk factors that are associated with carotid artery disease.

Subjects and Methods

As an ancillary study to the Systolic Hypertension in the Elderly Program (SHEP), participants at the University of Pittsburgh Field Center were invited to undergo duplex scanning of the carotid arteries. SHEP was a multicenter randomized clinical trial designed to test the efficacy of treating ISH in adults aged 60 years and older. Screening for the study took place at retirement centers, churches, and other locations where predominantly healthy elderly adults could be found. Qualifications for entry into the study included age of $\geq 60$ years, systolic blood pressure of 160–219 mm Hg, and diastolic blood pressure of $<90$ mm Hg. Exclusions included recent myocardial infarction, stroke with residual paresis, uncontrolled congestive heart failure, peripheral arterial disease with evidence of tissue injury or loss, transient ischemic attacks (TIAs) with associated carotid bruit, and contraindication to study medications. Complete screening techniques and exclusion criteria have been reported.8,9 Of the 222 SHEP participants recruited in Pittsburgh, 16 were lost to follow-up, four died before a scan could be performed, and 15 refused the scan, resulting in 187 hypertensive participants studied.

A group of 187 normotensive participants were recruited from the same locations as the SHEP participants, using the SHEP screening process. All SHEP

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exclusion criteria were applied except that systolic blood pressure was required to be <160 mm Hg. Normotensive participants were recruited immediately following the end of SHEP recruitment. Recruitment of normotensive participants was stratified by age so that comparisons between the hypertensive and normotensive groups could be adequately adjusted for age.

The blood pressure and heart rate values analyzed represent an average of four readings taken during two separate clinic visits. Blood pressures were measured by trained observers using a random-zero manometer according to the SHEP protocol.9 For hypertensive participants, the blood pressures analyzed were taken before randomization to study medication.

Participants underwent duplex scanning at the Peripheral Vascular Diagnostic Laboratory located in Montefiore University Hospital, Pittsburgh, Pa. A Diasonics DRF 400 duplex scanner (Milpitas, Calif.) with a 10-MHz imaging probe and 4.5-MHz Doppler was used. Doppler measurements obtained by duplex scanning have shown good agreement with angiography in the identification of carotid stenosis.10–13 As the lumen of a vessel narrows, the velocity of blood flow at that site increases. The ratio of internal carotid artery (ICA) blood flow velocity to common carotid artery (CCA) blood flow velocity (ICA/CCA ratio) is a measure of stenosis that controls for intersubject variation.10 ICA stenosis was defined as an ICA/CCA ratio of ≥1.4, corresponding to a luminal diameter reduction of ≥50%.14 This definition was used in our previous work6 and is based on studies comparing ICA/CCA ratios in normal patients with ratios in patients with angiographically documented carotid stenosis.10,15 While this cut point does not necessarily represent disease that would cause clinical concern, it represents the lowest level of disease that can be reliably detected by Doppler ultrasonography.

B-mode images were used to assess the extent of carotid plaque. The carotid system was divided into seven segments (Figure 1), and for each segment the degree of plaque was graded as 0, no observable plaque; 1, one small plaque (<30% of vessel diameter); 2, one medium plaque (30–50% of vessel diameter) or multiple small plaques; and 3, one large plaque (>50% of vessel diameter) or multiple plaques with at least one medium plaque. The grades from segments 1–4 of both the right and left carotid arteries were then summed to create the plaque index. Segments 5, 6, and 7 were not included in the plaque index because of the higher prevalence of missing data at these locations.

Duplex scanning requires highly skilled sonographers and readers, and the need for quality control has been documented.16 Both the ICA/CCA ratio and the plaque index were found to be highly reproducible in a sub-study of 30 participants who had duplicate scans performed on the same day. Complete information on the methodology and results of this study have been published.17

Data on smoking and alcohol use were obtained by participant report. Alcohol use was reported by frequency and amount and was summarized as average number of alcoholic drinks consumed per week. A fasting blood sample was drawn for the evaluation of lipids and glucose.

Differences in proportions were determined by a $\chi^2$ test, and differences in means of continuous variables were determined using $t$ tests (if normally distributed) and Wilcoxon rank-sum tests (if not normally distributed). Stepwise logistic regression was used to determine independent predictors of carotid stenosis. The model was developed for the entire study population and then repeated for the hypertensive and normotensive groups separately. In the combined model, systolic blood pressure was dichotomized at 160 mm Hg, but for the separate groups it was analyzed as a continuous variable. Heart rate and diastolic blood pressure were dichotomized because of high colinearity with systolic blood pressure. For all tests, a probability value of ≤0.05 was considered to be significant.

**Results**

Baseline characteristics at the time of study entry were compared for the hypertensive and normotensive groups (Table 1). Hypertensive participants were significantly older, with 28% in the ≥80 years age group compared with 10% of normotensive participants ($p<0.001$). Sex and race distributions for the two groups were comparable, with about 60% female and 99% white. Hypertensive participants were less likely than normotensive participants to have ever smoked (39% versus 54%, $p<0.01$). Participants with ISH had higher diastolic blood pressures ($p<0.001$) as well as higher resting heart rates ($p<0.001$) than normotensive participants (Table 1). With respect to laboratory values, hypertensive participants had higher triglyceride ($p<0.001$), lower high density lipoprotein (HDL) cholesterol ($p=0.007$), lower HDL3 ($p<0.001$), and higher apoprotein B ($p=0.025$) levels (data not shown).

Because many of these baseline variables covary, particularly with age, we used stepwise logistic regression to determine the primary variables that differed between the two groups. Independent associations with ISH were older age ($p<0.001$), no history of smoking ($p=0.023$), greater use of alcohol ($p=0.015$), glucose concentration of ≥140 mg/dl ($p=0.042$), higher total cholesterol concentration ($p=0.009$), and lower HDL3 concentration ($p<0.001$).

Carotid stenosis was found in 25% of hypertensive participants but only 7% of normotensive participants ($p<0.001$). This difference remained significant even when more stringent criteria were used to define steno-
TABLE 1. Comparison of Baseline Characteristics Between Hypertensive and Normotensive Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertensive (n=187)</th>
<th>Normotensive (n=187)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>60–69</td>
<td>44</td>
<td>23.5</td>
<td>78</td>
</tr>
<tr>
<td>70–79</td>
<td>91</td>
<td>48.7</td>
<td>91</td>
</tr>
<tr>
<td>≥80</td>
<td>52</td>
<td>27.8</td>
<td>18</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74</td>
<td>39.6</td>
<td>77</td>
</tr>
<tr>
<td>Female</td>
<td>113</td>
<td>60.4</td>
<td>110</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>186</td>
<td>99.5</td>
<td>184</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>1</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>115</td>
<td>61.5</td>
<td>86</td>
</tr>
<tr>
<td>Former</td>
<td>60</td>
<td>32.1</td>
<td>79</td>
</tr>
<tr>
<td>Current</td>
<td>12</td>
<td>6.4</td>
<td>22</td>
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<tr>
<td>Alcohol use (drinks/wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>143</td>
<td>76.5</td>
<td>136</td>
</tr>
<tr>
<td>1–5</td>
<td>19</td>
<td>10.2</td>
<td>28</td>
</tr>
<tr>
<td>6–10</td>
<td>11</td>
<td>5.9</td>
<td>13</td>
</tr>
<tr>
<td>≥11</td>
<td>14</td>
<td>7.5</td>
<td>10</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>8</td>
<td>4.3</td>
<td>54</td>
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<tr>
<td>65–74</td>
<td>39</td>
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<td>82</td>
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<td>75–84</td>
<td>98</td>
<td>52.4</td>
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<tr>
<td>85–89</td>
<td>42</td>
<td>22.5</td>
<td>6</td>
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<tr>
<td>Heart rate (beats per min)</td>
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<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>14</td>
<td>7.5</td>
<td>26</td>
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<tr>
<td>60–69</td>
<td>58</td>
<td>31.0</td>
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<td>70–79</td>
<td>75</td>
<td>40.1</td>
<td>33</td>
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<tr>
<td>≥80</td>
<td>40</td>
<td>21.4</td>
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</tr>
</tbody>
</table>

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sis. An ICA/CCA ratio of ≥1.8 occurred in 17% of hypertensive and 3% of normotensive (p<0.001) participants, and a ratio of ≥2.0 was found in 15% versus 2% of the hypertensive and normotensive groups, respectively (p<0.001). Participants with ISH were also found to have significantly greater plaque indexes than normotensive participants (p<0.001, Figure 2). As expected, there was a strong positive correlation between carotid stenosis and extent of plaque. The mean plaque index was 8.1 among participants with stenosis and 3.4 among those without (p<0.001, Wilcoxon test).

Other variables were also found to be related to carotid stenosis. For the study population as a whole, carotid stenosis was more prevalent among men than women (21% versus 12%, p=0.013), and among men there was a trend of increasing prevalence with age (Figure 3).

The relations between risk factors and carotid disease were similar for both the hypertensive and normotensive groups, but there was limited power to detect significant relations among normotensive participants because of the low prevalence of carotid stenosis (Table 2).

Among the hypertensive group, carotid stenosis was more prevalent among smokers, ranging from 16.5% in never smokers to 58.3% among current smokers (p<0.001). Stenosis was also more prevalent among those who consumed alcoholic beverages, particularly if ≥11 drinks/wk were consumed (p=0.030).
Surprisingly, carotid stenosis was found to be correlated with lower diastolic blood pressure ($p=0.022$). Hypertensive participants with diastolic blood pressure of $<65$ mm Hg had a 62.5% prevalence of carotid stenosis. Because this observation might reflect a widened pulse pressure (systolic blood pressure minus diastolic blood pressure), the relation between pulse pressure and carotid stenosis was also examined. In both hypertensive and normotensive participants, pulse pressure was found to be positively correlated with stenosis ($p=0.005$ and 0.086 for the hypertensive and normotensive groups, respectively; Table 2). Carotid stenosis was also found to be correlated with higher heart rates ($p=0.006$ for the hypertensive group).

To make the presentation of laboratory values more clinically meaningful, values were dichotomized using clinically relevant thresholds$^{18,19}$ (Table 2). In the hypertensive group, carotid stenosis was significantly associated with triglyceride levels of $\geq 250$ mg/dl ($p=0.010$), cholesterol levels of $\geq 240$ mg/dl ($p=0.021$), HDL cholesterol levels of $<40$ mg/dl ($p=0.001$), and apoprotein B levels of $\geq 100$ mg/dl ($p=0.012$).

Multivariate analysis was performed to determine which factors were independently associated with carotid stenosis. To control for the age difference between groups, age was forced into the model. When the entire study population was tested, a systolic blood pressure of $\geq 160$ mm Hg was the strongest predictor of carotid stenosis (Table 3). Those with ISH had 7.5 times the odds of having carotid stenosis that normotensive participants did after controlling for age, sex, and all other variables related to stenosis. Other variables independently related to stenosis were diastolic blood pressure of $<75$ mm Hg ($p=0.001$), greater alcohol use ($p=0.005$), heart rate of $\geq 80$ beats per minute ($p=0.013$), smoking ($p=0.034$), high apoprotein B level ($p=0.001$), and low HDL cholesterol level (borderline significant, $p=0.069$).

Among the hypertensive group, each 10-mm Hg increment of systolic blood pressure was associated with a 1.79 times greater odds of carotid artery disease. The strongest predictor of carotid stenosis was low diastolic blood pressure. Those with diastolic blood pressure of $<75$ mm Hg had five times the odds of disease that those with diastolic blood pressure of 75–90 mm Hg did. Among normotensive participants, low diastolic blood pressure was associated with a 3.2-fold increase in the odds of stenosis. To determine whether this observation was, in fact, due to pulse pressure rather than to diastolic blood pressure, the model was fit using pulse pressure in place of systolic blood pressure. In this model, the odds ratio for low diastolic blood pressure decreased to 2.24, but the relation remained significant ($p=0.025$).

For normotensive participants, there was a trend for carotid stenosis to be related to increasing age and alcohol use ($p=0.070$ and 0.069, respectively). In general, odds ratios for the normotensive group were of the same sign as those for the hypertensive group, but were lower. Among normotensive participants, those who had smoked at any time did not have increased odds of carotid stenosis. However, if current smokers are compared with never smokers in this same model, the odds of carotid stenosis are 4.61 for hypertensive and 2.08 for normotensive participants.

**Discussion**

The rationale for the initiation of SHEP was based on evidence that ISH is a significant predictor of mortality and cardiovascular disease, especially among older persons.$^{20–23}$ In addition, many authors have noted a positive association between carotid artery disease and elevated blood pressure,$^{24–26}$ including systolic blood pressure specifically.$^{27,28}$ This study supports these findings and indicates that the odds of carotid stenosis continue to rise with each increment of systolic blood pressure over 160 mm Hg.

Independent of systolic blood pressure, low diastolic blood pressure was associated with carotid stenosis. Similar observations have been recently reported by the Cardiovascular Health Study, a population-based study of older adults. These investigators found that carotid intima–media thickness was inversely related to diastolic blood pressure among persons with ISH.$^{29}$ Inferring a causal relation between low diastolic blood pressure and carotid stenosis would be inappropriate. It is likely that among those with ISH, both carotid stenosis and low diastolic blood pressure are markers for generalized atherosclerosis. Decreased arterial compliance due to generalized atherosclerosis would result in a widened pulse pressure, which has been reported to be a strong predictor of carotid atherosclerosis.$^{37}$ However, in our study pulse pressure did not totally account for the relation between low diastolic blood pressure and carotid artery disease. A recent study of the hemodynamics of ISH may explain these findings further.$^{30}$ Both systolic and diastolic blood pressures increase if peripheral vascular resistance increases and arterial stiffness is unchanged.$^{31}$ However, in the case of elderly subjects with ISH, both peripheral vascular resistance and arterial stiffness are increased, resulting in an elevated systolic blood pressure with little or no change in diastolic blood pressure.$^{30,32}$ Finally, an increase in arterial stiffness with no change in peripheral vascular resistance results in a marked decrease in diastolic blood pressure.$^{30}$ This last scenario may represent a more advanced stage of ISH, and this may be the reason for a higher prevalence of carotid stenosis among this group.
The finding that low diastolic blood pressure is related to carotid artery disease is also consistent with other literature on blood pressure. Large population studies have indicated that the relation of blood pressure to morbidity and mortality is not linear, but J shaped, particularly with respect to diastolic blood pressure.33–35 While diastolic blood pressure above 90–95 mm Hg is clearly related to cardiovascular events, these studies also found more events among those with the lowest diastolic blood pressure. The nadir of the curve ranged from 70 to 85 mm Hg, depending on the study. The definition of ISH restricts our study population to those with diastolic blood pressure of <90 mm Hg. Thus, persons with higher diastolic blood pressure associated with increased cardiovascular risk were excluded, leaving patients who fall in the range where lower diastolic blood pressure has been associated with disease.

Other factors related to carotid stenosis were similar between the hypertensive and normotensive groups; however, firm conclusions cannot be made about the normotensive group because of the limited statistical power associated with the low prevalence of carotid artery disease. An ongoing analysis of B-mode score is likely to yield more conclusive results for the normotensive group because the plaque index is sensitive to mild and moderate carotid artery disease.
Our results are unique in demonstrating a strong independent correlation between alcohol use and carotid stenosis. Relatively little research is available on the relation between alcohol use and carotid artery disease, although studies have found heavy drinking to be significantly more common among stroke cases than among control subjects.  

Alcohol use has been shown to be a risk factor for hypertension, and this study has also found higher levels of alcohol use among persons with ISH than among those with normotension. The relation between alcohol use and carotid stenosis may be related to the duration of blood pressure elevation. Participants who have been heavy drinkers over many years may have been hypertensive longer than those drinking lesser amounts, and this may account for the increased prevalence of carotid stenosis in the former.

While this study has provided new information on the relation of blood pressure to carotid stenosis, the results are not generalizable to the older population as a whole. The selection criteria used resulted in a sample of individuals who represent a relatively healthy portion of the older population. In our sample, hypertensive participants were less likely than normotensive subjects to have ever smoked, probably because hypertensive smokers were more likely to have either died before the age of 60 years or to have disease that made them ineligible for SHEP. The selection criteria also may have obscured the relation between age and carotid stenosis.

It is clear that elevated systolic blood pressure is an important risk factor for atherosclerotic disease, including disease of the carotid arteries. Whether or not ISH initially causes this observed excess of atherosclerosis cannot be confirmed by our study. Atherosclerosis may in fact develop first, leading to arterial rigidity and a concomitant rise in systolic blood pressure. However, once present, the widened pulse pressure associated with ISH may be hemodynamically atherogenic, furthering the development of disease. The treatment of ISH has now shown to reduce risk of both stroke and cardiovascular disease. This lowered risk may result from a slowing of atherosclerosis progression with blood pressure control. One might expect the benefit of treatment to be substantially greater in those who have both ISH and carotid stenosis. If this proves to be true, then carotid ultrasound could be used to identify the patients most likely to benefit from antihypertensive therapy.

In conclusion, ISH is strongly correlated with carotid stenosis, and among this group low diastolic blood pressure is a marker for carotid stenosis. Further study may prove carotid ultrasound useful in the identification of patients most likely to benefit from risk factor modification, including antihypertensive therapy.

References

12. Blackshear WM, Lamb SL, Kollipara VSK, Anderson JD, Murtagh FR, Shah CP, Farber MS: Correlation of hemodynamically signifi-

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### Table 3. Independent Predictors of Carotid Stenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive (n=185)</th>
<th>Normotensive (n=181)</th>
<th>Combined (n=366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥160 mm Hg</td>
<td>...</td>
<td>...</td>
<td>7.52 &lt;0.001</td>
</tr>
<tr>
<td>10-mm Hg increments</td>
<td>1.79</td>
<td>0.98</td>
<td>1.12 0.689</td>
</tr>
<tr>
<td>Age (10-year increments)</td>
<td>0.69</td>
<td>2.93</td>
<td>3.69 0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.07</td>
<td>1.69</td>
<td>1.47 0.347</td>
</tr>
<tr>
<td>Diastolic blood pressure &lt;75 mm Hg</td>
<td>5.12</td>
<td>3.16</td>
<td>3.69 0.001</td>
</tr>
<tr>
<td>Alcohol use (7 drinks/wk increments)</td>
<td>1.87</td>
<td>1.68</td>
<td>1.64 0.005</td>
</tr>
<tr>
<td>Heart rate ≥80 beats per min</td>
<td>3.15</td>
<td>4.29</td>
<td>2.76 0.013</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>3.90</td>
<td>0.98</td>
<td>2.12 0.034</td>
</tr>
<tr>
<td>Apoprotein B (25 mg/dl increment)</td>
<td>1.92</td>
<td>1.43</td>
<td>1.73 0.001</td>
</tr>
<tr>
<td>HDL cholesterol (25 mg/dl decrement)</td>
<td>3.19</td>
<td>1.20</td>
<td>2.06 0.069</td>
</tr>
</tbody>
</table>

For combined model, systolic blood pressure was dichotomized at 160 mm Hg. For hypertensive and normotensive models, blood pressure was included as continuous variable and then odds ratios were calculated based on 10-mm Hg increments.
ificant internal carotid stenosis with pulsed Doppler frequency anal-
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