Noninvasive Study of Arterial Hypertension and Carotid Atherosclerosis

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We noninvasively evaluated the prevalence and severity of atherosclerotic lesions of the internal carotid artery in 146 nonobese, nondiabetic hypertensive patients who were free of cardiovascular symptoms. We found internal carotid artery disease in 63 patients (43%), 26 (18%) with unilateral disease and the other 37 (25%) with bilateral disease. Disease severity was correlated with age but not duration of hypertension, cholesterol level, or current smoking habit. We also followed disease progression and clinical outcome with respect to cardiovascular events for 3 years in a subgroup of 95 unselected patients. In 20 of the 93 survivors (21.5%) we noted progression of the atherosclerotic lesions that was predicted by neither risk factors nor initial status of the internal carotid artery. New neurologic symptoms developed in four survivors (4%) and symptoms of cardiac ischemia in six (6%). No survivor who developed new cerebrovascular symptoms showed progression of carotid disease. These data provide useful elements for a rational approach to prevention of the atherosclerotic complications of hypertension. (Stroke 1990;21:410-414)

Experimental, epidemiologic, and clinical evidence shows that arterial hypertension promotes and accelerates atherosclerosis. As a risk factor for atherosclerosis, arterial hypertension affects mainly the cerebral circulation and accounts for an enhanced prevalence of cerebrovascular disease.1-3 Most strokes have an atherothrombotic origin and are frequently associated with involvement of the extracranial carotid arteries at the bifurcation. However, little is known about the prevalence of atherosclerotic lesions at the carotid bifurcation in hypertensive individuals. The only available data have been obtained from selected subgroups of patients studied by angiography4 or necropsy.5-7 Recently, the advent of noninvasive techniques has made it possible to investigate carotid atherosclerosis in vivo, in asymptomatic patients. Among these new techniques, duplex ultrasonography, which combines B-mode real-time imaging and pulsed Doppler spectral analysis, has gained the widest acceptance. This technique permits direct visualization of the entire spectrum of carotid occlusive disease8 to detect relevant anatomic details such as the composition and surface characteristics of plaques with a high degree of accuracy. In recent years, duplex ultrasonography has been used extensively to investigate subjects at risk for atherosclerosis.9-12 However, knowledge concerning hypertensive subjects remains limited.

In a previous study on relatively few stable hypertensive patients,13 we observed that lesions of the internal carotid artery (ICA) occurred more frequently in these patients (28.5%) than in normotensive controls (10%) matched for sex, age, and other major risk factors for cerebrovascular disease. We concluded that arterial hypertension could account for such a difference in the prevalence of ICA lesions independently of other risk factors, and our findings supported the evidence, demonstrated in animal models,14 of arterial hypertension as a true causative factor for atherosclerosis.

The aims of our present study were to estimate the prevalence of carotid atherosclerosis in asymptomatic hypertensive patients and to study the evolution of such lesions with regard to clinical outcome.

Subjects and Methods

We studied 146 stable hypertensive patients with no history of coronary artery disease (angina or myocardial infarction) or cerebrovascular disease (TIA or stroke). The criteria for hypertension were a systolic blood pressure consistently above 160 mm Hg and/or a diastolic blood pressure consistently above 95 mm Hg or a history of arterial hypertension treated with antihypertensive drugs. We recruited consecutive patients from among those referred to the Outpatient Clinic of our institution. Their ages ranged from 40 to 84 (mean ± SD 58 ± 11) years; there were 92 men and 54 women (sex ratio = 1.70). None was obese. Diabetes mellitus was absent from all but...
two patients; one suffered from type II diabetes mellitus and the other had impaired glucose tolerance. The hypertensive status of each patient had been recognized 5.6±2.1 years before and was adequately controlled with various medications (mean±SD systolic and diastolic blood pressure 156±19/94±10 mm Hg). Twenty patients currently smoked >10 cigarettes/day, eight smoked <10 cigarettes/day, 24 were former smokers (36% current or former smokers), and 94 had never smoked. Mean±SD total serum cholesterol concentration was 242±61 mg/dl; 38 patients (26%) had concentrations of >250 mg/dl, 84 (58%) had concentrations of 200–250 mg/dl, and 24 (16%) had concentrations of <200 mg/dl.

After approximately 3 years (mean±SD 37.7±13.3, range 3–63 months), 109 of the 146 patients were invited by letter to a follow-up examination; the other 37 patients were not invited since they lived too far from our center. Of those invited, 95 (87%) accepted and participated in our follow-up study. The demographic and clinical characteristics of this follow-up group were comparable to those of the initial group of 146 hypertensive patients; the mean±SD age was 58.7±8.9 (range 40–83) years, the sex ratio was 1.71, the percentage of current or former smokers was 44%, and mean±SD total serum cholesterol concentration was 244±63 mg/dl. At the follow-up examination, the patients were interviewed about the occurrence of coronary artery disease, cerebrovascular disease, and cardiovascular or vascular surgery.

The ICAs were investigated by duplex ultrasonography with a 5-MHz mechanical probe, using commercially available instrumentation (Mark V with 459 spectrum analyzer, Advanced Technology Laboratories, Bothell, Washington). The images provide visualization of the arterial wall and atherosclerotic lesions, whereas the Doppler signal provides information on blood flow; imaging is essential for correctly locating the sample volume and for measuring the angle from which the Doppler signal is generated. Visual interpretation of the Doppler signal is made possible in real time through fast Fourier transformation spectral analysis.

The right and left carotid bifurcations were visualized in each patient, and the ICAs were identified. The presence of atherosclerotic lesions was determined on the basis of the B-mode images, while the degree of stenosis was determined on the basis of spectral analysis of the pulsed Doppler signal sampled along the ICAs. The lesions were categorized as minimal stenosis (<20% diameter reduction) in the presence of spectral broadening limited to the decelerating phase of systole, moderate stenosis (20–49% diameter reduction) in the presence of spectral broadening throughout systole, and severe stenosis (>50% diameter reduction) in the presence of peak systolic velocity of >135 cm/sec. A lesion was considered to have progressed or regressed if at follow-up the Doppler signal indicated a different disease category. Furthermore, ICA lesions were characterized by means of B-mode imaging in terms of echographic appearance (homogeneous vs. heterogeneous) and surface profile (regular vs. irregular).

All ultrasonic examinations were performed and read by two well-trained investigators. Reproducibility of the method was assessed in terms of interobserver variability by comparing independent observations performed by the same two investigators in 48 different patients randomly selected for this purpose. Overall agreement was 85% for disease category, 74% for echographic appearance, and 88% for surface profile. The adjusted measure of overall agreement (that is, agreement obtained after removing the contribution expected by chance) was calculated using the k statistic13; a value of 1 indicates perfect agreement, whereas a value of 0 indicates agreement due to chance alone. Mean±SEM k was 0.80±0.08 for disease category, 0.47±0.19 for echographic appearance, and 0.72±0.19 for surface profile.

We used Pearson's χ² statistic to compare the prevalence of disease among classes of patients, Student's t test to compare age and total serum cholesterol concentration between the patients who had disease progression and those who did not, and analysis of variance to compare total serum cholesterol concentration among patients in different disease categories.

Results

Of the 292 ICAs investigated in the 146 asymptomatic hypertensive patients, 100 were diseased (44 minimally, 39 moderately, and 17 severely). Thus, the overall prevalence of ICA lesions was 34% (95% confidence interval 29–39%). The frequency distribution of disease categories did not differ significantly between males and females. As for the characteristics of the 100 diseased ICAs, 58 had a homogeneous and 30 a heterogeneous echographic appearance, and 57 had a regular and 28 an irregular surface profile. Twelve lesions could not be classified as to echographic appearance and 15 as to surface profile due to poor-quality images that did not allow any interpretation with a reasonably high degree of certainty.

Eighty-three (57%) of the 146 hypertensive patients had normal ICAs on both sides; 26 (18%) had unilateral and 37 (25%) had bilateral disease. Consequently, the prevalence of disease was 43% (95% confidence interval 35–51%) in terms of patients.

We divided the patients into four age classes (<50, 51–60, 61–70, and >70 years), into three hypertension duration classes (<5, 5–10, and >10 years), into three total serum cholesterol concentration classes (<200, 200–250, and >250 mg/dl), and into two smoking habit classes (nonsmokers or former smokers and current smokers). The frequency distribution of the disease categories was evaluated for each class, disregarding the severity of arterial hypertension since all patients were being treated and considering only the more severely affected ICA for each patient. The prevalence of disease increased significantly with
advancing age (Figure 1; \( \chi^2 = 17.1, p < 0.01 \)) as did the severity of the lesions (\( \chi^2 = 15.3, p < 0.01 \) considering minimal stenosis as the cutpoint, and \( \chi^2 = 13.4, p < 0.01 \) considering severe stenosis as the cutpoint). On the contrary, nonsignificant differences were observed for the prevalence of disease (Table 1) with respect to duration of hypertension (\( \chi^2 = 1.96 \)), total serum cholesterol concentration (\( \chi^2 = 2.35 \)), and current smoking habit (\( \chi^2 = 3.10 \)). Total serum cholesterol concentrations were comparable in patients with no (229±47 mg/dl), minimal (245±35 mg/dl), moderate (225±28 mg/dl), and severe (232±27 mg/dl) disease (\( F = 2.63, \) difference not significant).

Two of the 95 patients invited died (one of stroke and the other of ruptured aortic aneurysm) before the follow-up examination. Body weight and total serum cholesterol concentration remained unchanged in all patients (73.6±12.1 at initial and 73.1±11.6 kg at follow-up examination and 244±63 at initial and 238±47 mg/dl at follow-up examination, respectively); five patients stopped smoking, while two reduced from 238±47 mg/dl at follow-up examination, respectively; total serum cholesterol concentration (233.7±45.9 and 240.1±48.2 mg/dl, respectively), current smoking habit, initial degree of stenosis, and lesion characteristics; in fact, the percentage of patients with severe stenoses or unfavorable lesion characteristics was comparable among those who progressed and those who did not (p>0.05 by the \( \chi^2 \) test).

Two patients, although asymptomatic, underwent unilateral thromboendarterectomy for the presence of severe ICA stenosis; spontaneous evolution of the lesions was therefore evaluated in the remaining 184 ICAs. Eighteen new stenotic lesions appeared, while stenosis progressed in 10 and regressed in five arteries (Table 2). In terms of patients, the cumulative progression rate was 20 of 93, or 21.5%. Of the four patients who developed symptoms of cerebrovascular disease during follow-up, three had minimal and one had severe disease of the corresponding ICA initially, but none showed progression of the disease. Of the six patients who developed symptoms of coronary artery disease during follow-up, none showed progression of the atherosclerotic lesions at the ICA level. Their mean±SD age was comparable to that of those who remained asymptomatic (58.6±12.7 and 58.1±10.4 years, respectively). Disease progression was not predicted by factors such as age (60.1±8.9 years for those who progressed and 58.3±9.0 years for those who did not), total serum cholesterol concentration (233.7±45.9 and 240.1±48.2 mg/dl, respectively), current smoking habit, initial degree of stenosis, and lesion characteristics; in fact, the percentage of patients with severe stenoses or unfavorable lesion characteristics was comparable among those who progressed and those who did not (p>0.05 by the \( \chi^2 \) test).

### Discussion

The relevance of detecting carotid artery disease in asymptomatic individuals, and in hypertensive patients in particular, is double. First, the presence of atherosclerotic lesions at this site is an important factor for the development of stroke. Second, such lesions are good predictors of coronary artery disease as well.16,17 Indeed, there is increasing evidence that carotid atherosclerosis reflects a generalized process ongoing throughout the major vascular districts.18,19

We studied stable hypertensive patients selected only on the basis of the absence of symptoms of cerebrovascular and coronary artery disease. No patient was obese or diabetic, while hypercholesterolemia (total serum cholesterol concentration of >250 mg/dl) was a relatively frequent finding (26% of patients).

In all patients, hypertension was being treated pharmacologically. The importance of studying treated patients can be questioned but it should be noted that, although antihypertensive treatment reduces the risk of stroke, some evidence supports the view that patients with chronic hypertension...
remain at increased risk even after blood pressure is restored to normal levels.\textsuperscript{20}

In our study, 43\% of the hypertensive patients had some degree of atherosclerosis in their ICAs, mostly bilateral. As expected, minimal to moderate stenoses predominated, and lesion severity increased with age; severe stenosis, however, could be found in every age class. This prevalence (43\%) is considerably higher than that previously reported by us (28.5\%).\textsuperscript{13}

A few studies evaluating the prevalence of carotid artery disease in healthy persons or subgroups of persons at risk for atherosclerosis have been reported. These reports are difficult to compare because case selection, methodology, and diagnostic criteria are not uniform. For instance, using duplex ultrasonography, Bucci et al\textsuperscript{21} found a prevalence of 23.9\% among 450 free-living individuals (mean age 60 years). Using ultrasonic arteriography (a pulsed Doppler flow mapping device without imaging), Ramsey et al\textsuperscript{22} found a prevalence of 10.8\% among 102 members of a church congregation >50 years old; the 24 hypertensive members showed a significantly higher prevalence (17\%) than the 78 normotensive members (9\%). Using a high-resolution multigate pulsed Doppler system (without imaging), Van Merode et al\textsuperscript{23} found a prevalence of stenotic ICA lesions (>15\% diameter reduction) of 21\% in 100 free-living individuals; they had no neurologic symptoms, but as many as 23 suffered from coronary artery disease. Using duplex ultrasonography, Sutton et al\textsuperscript{24} found a prevalence of ICA disease of 38\% in 56 asymptomatic elderly adults with isolated systolic hypertension. These data are consistent with our prevalence of 43\%.

We found that during 3 years one patient (1.05\%) died of stroke; of the survivors, four (4.3\%) developed cerebrovascular symptoms and 20 (21.5\%) showed ICA disease progression. These figures compare well with other reported longitudinal studies of asymptomatic patients.\textsuperscript{24,25} Other authors\textsuperscript{26,27} have shown that ICA disease progresses at an annual rate of 10\% in patients with asymptomatic bruits and of 12\% in the ICA contralateral to thromboendarterectomy. In a previous study of 133 subjects (most of whom were asymptomatic) followed for up to 18 months with sequential duplex ultrasonography, we observed a cumulative progression rate of 5.5\%.\textsuperscript{28}

In our present study, disease progression and the onset of symptoms were not associated events since only one of the four patients who became symptomatic had a severe stenosis initially (this was the patient who subsequently developed a stroke), but none of the others showed disease progression. Cardiovascular events (angina and myocardial infarction) were more frequent than cerebrovascular events (6.4\% vs. 4.3\%), supporting the view that carotid artery disease should be considered more as a general indicator of atherosclerosis than as a specific precursor of stroke and allied conditions. ICA disease progression was not predicted by age and other risk factors (current smoking habits, total serum cholesterol concentration) or by initial status of the ICA itself.

The atherosclerotic lesions regressed in five patients; in two patients the degree of stenosis decreased from severe to moderate, in one from moderate to minimal, while in the other two patients minimal lesions were no longer detected at follow-up. Although this apparent regression might be due to uncertainty in classifying patients with borderline stenoses, it must be pointed out that a spontaneous regression of ICA lesions has been described by others.\textsuperscript{29} The consistency of such a phenomenon and its clinical meaning need to be investigated further.

Our follow-up results obviously are not definitive since 3 years can hardly be sufficient to illustrate the natural history of a lifelong disease such as atherosclerosis. Nevertheless, it seems recommendable to study ICAs in hypertensive patients to identify subjects who need closer control of the risk factors for atherosclerosis. Our data provide information that may be useful in the development of a rational approach to preventing the vascular complications of hypertension.

\textbf{References}


\begin{table}[!h]
\centering
\caption{Initial and Follow-up Distributions of Disease in 184 Internal Carotid Arteries in 93 Hypertensive Patients}
\begin{tabular}{|c|c|c|c|c|}
\hline
Disease & At initial examination & None & Minimal (<20\%) & Moderate (20-49\%) & Severe (\geq50\%) \\
\hline
None (normal artery) & 119 & 101 & 13 & 5 & 0 \\
Minimal (<20\%) & 36 & 2 & 27 & 5 & 2 \\
Moderate (20-49\%) & 20 & 0 & 1 & 16 & 3 \\
Severe (\geq50\%) & 9 & 0 & 0 & 2 & 7 \\
Total & 184 & 103 & 41 & 28 & 12 \\
\hline
\end{tabular}
\end{table}

Two arteries submitted to surgery during follow-up were not included. Disease severity as percentage diameter reduction.

Lusiani et al  Hypertension and Carotid Atherosclerosis 413

**KEY WORDS** • hypertension • ultrasonics • carotid artery diseases
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Stroke. 1990;21:410-414
doi: 10.1161/01.STR.21.3.410
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/21/3/410