Cerebral Atherosclerosis as Predictor of Stroke and Mortality in Representative Elderly Population

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Background and Purpose—The aim of this study was to assess the relationship between cardiovascular risk factors, atherosclerotic disease in the carotid bifurcation, and the risk of stroke and mortality in a representative population sample.

Methods—One hundred forty-two men and women participated in a population study at ages 70 and 76 years. At age 78, extracranial and intracranial circulation was examined by means of duplex sonography and transcranial Doppler techniques. Mortality and hospitalization for stroke were analyzed over a 5-year follow-up period up to age 83 years.

Results—Carotid plaques were identified in 82% of the men and 79% of the women. Bilateral plaques were found in 57% of the men and 46% of the women, and stenosis resulting in >50% diameter reduction occurred in 28% of the men and 17% of the women. Carotid stenosis >75% was observed in 7 subjects (0.5%). Bilateral plaques at age 78 were correlated with systolic blood pressure and ischemic heart disease at age 70 years. The pulsatility index was 1.0 to 1.4 in 63% and ≥1.5 in 13% of the study population. The pulsatility index was correlated with systolic and diastolic blood pressure, serum cholesterol, and triglycerides. Men with bilateral carotid plaques at age 78 years had an increased risk of stroke or mortality during the 5-year follow-up period (74% bilateral plaques versus 21% unilateral or no plaques). This was not found in the women (33% versus 26%).

Conclusions—Carotid atherosclerosis was prevalent in a majority of elderly subjects. Bilateral plaques were correlated with systolic blood pressure and ischemic heart disease at age 70 years and predicted the risk of stroke and mortality in men but not in women. (Stroke. 2002;33:224-229.)

Key Words: elderly ■ intracranial atherosclerosis ■ mortality ■ stroke

The risk of stroke increases with age and hospitalization, and the rehabilitation of elderly patients with stroke is associated with extensive costs for society. Earlier studies have indicated that ultrasound evaluation of carotid disease is helpful for the prediction of subsequent cerebrovascular ischemia.1 The association between cardiovascular risk factors and carotid atherosclerosis has been studied in all age groups and has been found to be less distinct in elderly compared with middle-aged subjects.2 A high prevalence of carotid atherosclerosis has been found in elderly populations.3,4 However, it has not been fully clarified to what extent carotid atherosclerosis is related to different cardiovascular risk factors in subjects aged >75 years. Furthermore, because surgical treatment of carotid stenosis may be even more efficient in elderly than in younger patients5 and because controversy exists regarding asymptomatic stenoses, we found it of interest to relate the degree of stenosis and plaque to risk factors, mortality, and stroke morbidity.

The aim of this study was to (1) analyze the degree of atherosclerotic carotid disease in a representative population sample of 78-year-old men and women investigated with duplex sonography (Acuson 128 XP) and transcranial Doppler (Transcan, EME) techniques, (2) study the relationship between extracranial artery disease, pulsatility index (PI) changes, and cardiovascular risk factors measured in subjects from the age of 70 years, and (3) investigate the correlation between atherosclerosis in the carotid arteries and the incidence of stroke, cardiac disease, and mortality measured over a period of 5 years after the examination.

Subjects and Methods

Within the frames of the longitudinal population study of 70-year-old people in Gothenburg, 4 representative population samples of 70-year-old individuals born in 1901 to 1902, 1906 to 1907, 1911 to 1912, and 1922 have been examined and followed longitudinally.6–9 The present study deals with the third population sample. In 1981 to 1982, 25% of the 70-year-old population in Gothenburg (n=800) was invited through random selection. The response rate was 77%, resulting in the enrollment of 302 men and 317 women. Reexaminations were performed at age 72 years (n=504, participation rate 77%) and at age 76 years (n=405, participation rate 77%).
Seventy-one men and 71 women were selected at age 78 years for evaluation of extracranial and intracranial circulation with duplex sonography and transcranial Doppler techniques (Figure 1). To minimize the risk of selection bias, a comparison between the 142 subjects in the study group and the rest of the survivors up to age 78 years was performed. No differences between the groups were found with respect to systolic and diastolic blood pressure, body mass index, smoking habits, serum cholesterol, serum triglycerides, and blood glucose at ages 70 and 76 years. The consumption of hospital care between the ages of 70 and 78 years and during a 5-year follow-up period after the examination was the same in the 2 groups. There was no difference between the 2 groups with respect to mortality up to age 83 years. Subjects who were seriously disabled and living in nursing homes were not invited to participate in the duplex examination. This group constituted of only 4% of the total population at age 78 years.

Clinical Investigations
The investigations at ages 70, 72, and 76 years included a thorough interview regarding social and medical conditions and a medical examination consisting of blood pressure measurements, ECG, and laboratory examinations.

Blood pressure was measured in the right arm of subjects after 5 minutes of rest in the supine position and in the standing position after 1 and 3 minutes. The pressure was read to the nearest 2 mm Hg. Diastolic blood pressure was defined as Korotkoff phase 5. A mercury manometer was used for the registrations.

ECG was recorded and coded according to the Minnesota code,\textsuperscript{10} One investigator was responsible for the coding in subjects at age 70 and then at age 76 years. Angina pectoris was defined according to Rose.\textsuperscript{11} Myocardial infarction was defined as a documented history of cardiac infarction and/or major Q waves (Minnesota code 1.1.1 to 1.2.8). Ischemic heart disease was defined as a history of myocardial infarction, angina pectoris, or signs of ischemia on ECG (major Q waves, left bundle-branch block, ST depression of $\geq$1 mm, or negative or biphasic T waves).

Ultrasound Investigations
The carotid bifurcation was investigated by using 2D color Doppler ultrasound for B-mode imaging (7 MHz) of the vessel walls and simultaneous angle-corrected blood flow velocity measurements with a pulsed 5-MHz Doppler. Usually, we assessed blood flow velocity data at angulations of 60° against the blood stream vector (Acuson 128 XP). However, in tortuous vessels, angulations might have been $<60°$. All scans were performed by the same investigator (M.F.) and stored on S-VHS videotapes and analyzed offline with respect to vessel wall abnormalities and the maximum systolic blood flow velocity ($V_s$) within the stenosis. Wall abnormalities were classified as either none, wall irregularities, or plaque. Plaque was described in terms of regular or irregular, ulcerated or not, homogenous or heterogeneous, and calcified or not calcified. Stenoses were divided into categories hemodynamically significant or not. Wall irregularities with wall thickening in the range of 1 to 2 mm were classified as stenosis with $<20\%$ diameter reduction. Plaque occurrence combined with a $V_s <1.2$ m/s was classified as stenosis $<50\%$. Stenoses of $>50\%$ were functionally quantified by using blood flow velocity data within the stenosis according to Zbornikova,\textsuperscript{12} ie, the combination of plaques and $V_s >1.2$ m/s. The reliability of our earlier ultrasound investigations and statements have previously been tested against selective angiography in 100 consecutive carotid investigations, routinely performed in symptomatic patients with suspected high-grade carotid artery disease.

Transcranial Doppler
The axial blood flow velocities at the middle cerebral artery (MCA) and posterior cerebral artery (PCA) were registered with a pulsed-wave 2-MHz transcranial Doppler instrument (3D-Transcan, EME) by using standard transcranial Doppler techniques for insonation of the arteries within the circle of Willis through temporal windows of each side.\textsuperscript{13} The MCA and PCA were identified by short-lasting compression of the ipsilateral proximal common carotid artery (CCA). The MCA was correctly insonated at a depth of 56 mm, when flow velocities decreased on CCA compression. The proximal PCA (P1) segment was supposed to be correctly insonated when CCA compression resulted in either unchanged or increased flow velocities. In none of the patients was reversed flow in P1 seen. The PI\textsuperscript{14} ($PI=V_{max}-V_s/V_{max}$, where $V_s$ is end-diastolic blood flow velocity, and $V_{max}$ is mean blood flow velocity) of the blood flow velocities within the MCA and PCA was automatically calculated by the software of the 3D-Transcan. For each vessel, PI was expressed as a mean value of 4 different measurements in the MCA at depth $\sim$60 mm and in the PCA at depth $\sim$75 mm. The PI may represent impedance to blood flow distal to the point of sampling and has been reported to be increased when cerebral peripheral resistance is high.\textsuperscript{15}

Follow-Up Data
Mortality data and information about hospital care, including diagnoses, were registered continually. The diagnoses were classified according to the international classification of diseases, ninth revision (ICD-9). Cerebrovascular disease was defined as ICD-9 Nos. 430 to 438, including stroke and transient ischemic attack. Ischemic heart disease was defined as ICD-9 Nos. 410 to 414, including...
myocardial infarction and angina pectoris. Diseases of the circulatory system disease was defined as ICD-9 Nos. 390 to 459, including cerebrovascular disease, cardiac disease, and peripheral vascular disease.

Hospitalization rate was defined as the percentage of the study population admitted to hospital during the 5-year follow-up period.

**Statistical Analyses**

The Fisher exact test and $t$ test were used to test the hypothesis of no difference between the groups. The Pitman permutation test was used to test correlations. A paired permutation $t$ test was used to test the hypothesis of no difference between baseline and follow-up measurements. A value of $P<0.05$ was considered to be statistically significant (2-sided test).

**Results**

Table 1 describes cardiovascular risk factors at ages 70 and 76 years in the study group and in other survivors up to age 78 years. No differences between the 2 groups were found.

Eighty-two percent of the men and 79% of the women had heterogeneous or ulcerated plaques in the carotid arteries. In 97% of the subjects with plaques, the plaques were found in the internal carotid arteries (ICAs). Bilateral plaques were found in 57% of the men and 46% of the women. Stenosis $>50\%$ was found in 28% of the men and 17% of the women. Stenosis $>75\%$ was observed in 7 subjects (0.5%). Only 20% of the 78-year-old subjects had no evidence of carotid artery disease. No differences were found between men and women.

The prevalence of unilateral plaques at age 78 years was not associated with cardiovascular disease or risk factors at age 70 years. Subjects with and without carotid artery disease did not differ in serum cholesterol at ages 70 and 76 years. A significant reduction in serum cholesterol between ages 70 and 76 years was found in all groups ($P<0.001$).

The prevalence of stenosis $>50\%$ was significantly higher in subjects with ischemic heart disease at age 70 years ($P<0.05$).

Subjects with bilateral plaques at age 78 years had significantly more hypertension (39%) or ischemic heart disease (30%) at age 70 years compared with subjects with unilateral or no plaques (Table 2). No difference in diastolic blood pressure was found between subjects with and without bilateral plaques.

$PI$ did not differ between men and women. We found a significant correlation between $PI$ and carotid plaques, stenosis $>50\%$, and hypertension (Table 3). The prevalence of diabetes or ischemic heart disease did not influence $PI$.

The hospitalization rate was measured during 5 years after the evaluation of carotid atherosclerosis. Seventy-seven percent of the men and 58% of the women with bilateral carotid plaques were admitted to hospital during the 5-year period compared with 66% and 55%, respectively, among those with unilateral or no plaques. Men with bilateral plaques differed significantly from other men with respect to hospitalization because of diseases of the circulatory system (56% versus 28%, respectively; $P<0.05$). For women, these figures were 19% and 13%, respectively ($P=NS$). Twenty-three percent of the men with bilateral plaques were hospitalized because of stroke or transient ischemic attack compared with 0% of the men with unilateral or no plaques ($P<0.01$). No significant differences were found between women in the 2 groups (15% for those with bilateral plaques and 13% for those with unilateral or no plaques). Hospitalization due to ischemic heart disease did not differ between the group with bilateral plaques versus the group with unilateral or no plaques (36% versus 17%, respectively, among men; 12% versus 11%, respectively, among women). During the 5-year-follow-up period, the risk of stroke or mortality was 64% in men with bilateral plaques compared with 21% in men with unilateral or no plaques (Figure 2). In women, the risk for stroke or mortality between ages 78 and 83 years was 34% in those with bilateral plaques and 26% in those with unilateral or no plaques.

**Discussion**

A high prevalence of asymptomatic carotid atherosclerosis has been found in the general population, and the number of plaques and the severity of stenosis have been shown to increase with age. Increased intima-media thickness in the CCAs and the ICAs is associated with coronary heart disease and cerebrovascular disease risk factors and has also been found to be associated with asymptomatic myocardial ischemia in older subjects. In middle-aged subjects, an association between structural changes in the carotid arteries and hypertension, serum cholesterol, and cigarette smoking has been found. In the elderly, the association between risk factors and carotid atherosclerosis is less pronounced than in...
younger subjects. Nevertheless, it has been reported that CCA intima-media thickness and plaque occurrence is increased in elderly high-risk hypertensive patients.21 The present study of a representative sample of 78-year-old subjects focused on carotid plaque occurrence because the method of intima-media thickness measurements was not standardized at startup. In our material, we found a high prevalence of atherosclerotic plaques in extracranial carotid arteries in both men and women (82% and 79%, respectively). However, bilateral plaques were correlated with vascular risk factors, but unilateral plaques were not. At this advanced age, atherosclerotic manifestations are also common among healthy individuals. The prevalence of bilateral plaques may indicate a more disseminated atherosclerotic disease, which may explain the correlation with vascular risk factors. The correlation between carotid atherosclerosis and systolic but not diastolic blood pressure is in accordance with other studies.22 Stiffening of the large arteries in the elderly can lead to an increased systolic blood pressure and a low diastolic blood pressure. Increased intima-media thickness has been observed in elderly subjects with high pulse pressures and diastolic blood pressure >70 mm Hg.23

The relationship between serum cholesterol and atherosclerotic plaques in the carotid arteries that has been shown for younger age groups does not seem to exist in subjects aged >75 years.2 This might partly be explained by the fact that in those aged >70 years, serum cholesterol decreases with age, and the most pronounced decline probably affects those with

TABLE 2. SBP, DBP, Heart Rate, Serum Cholesterol, Triglycerides, and Blood Glucose in Men and Women With and Without Bilateral Carotid Plaques

<table>
<thead>
<tr>
<th>Age 70 years</th>
<th>Bilateral Carotid Plaques</th>
<th>Unilateral or No Carotid Plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=39)</td>
<td>Women (n=33)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>165 (157–173)</td>
<td>165 (156–174)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83 (79–86)</td>
<td>83 (79–88)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64 (60–68)</td>
<td>66 (62–69)</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.7 (5.4–6.1)</td>
<td>6.6 (6.2–7.1)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.5 (1.3–1.8)</td>
<td>1.6 (81.3–2.0)</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>5.2 (4.7–5.8)</td>
<td>4.9 (4.4–5.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 76 years</th>
<th>Bilateral Carotid Plaques</th>
<th>Unilateral or No Carotid Plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=151–165)</td>
<td>Women (n=74–84)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>158 (151–165)</td>
<td>167 (157–177)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82 (78–85)</td>
<td>79 (74–84)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64 (60–68)</td>
<td>68 (63–73)</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.2 (4.7–5.8)</td>
<td>6.2 (5.7–6.7)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4 (1.2–1.5)</td>
<td>1.6 (1.3–1.9)</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>5.3 (5.0–6.0)</td>
<td>5.4 (4.9–5.9)</td>
</tr>
</tbody>
</table>

Values are mean (95% CI).

*P<0.05 compared with subjects with unilateral or no plaques.

TABLE 3. PI in the MCA and PCA in Subjects With and Without Carotid Plaques and Stenosis at Age 78 Years

<table>
<thead>
<tr>
<th></th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral or no plaques</td>
</tr>
<tr>
<td></td>
<td>MCA 1.16 (1.06–1.26)</td>
</tr>
<tr>
<td></td>
<td>PCA 1.15 (1.05–1.25)</td>
</tr>
<tr>
<td>Bilateral plaques</td>
<td>MCA 1.15 (1.06–1.24)</td>
</tr>
<tr>
<td></td>
<td>PCA 1.26 (1.16–1.36)</td>
</tr>
<tr>
<td>No stenosis</td>
<td>MCA 1.19 (1.10–1.27)</td>
</tr>
<tr>
<td></td>
<td>PCA 1.21 (1.12–1.30)</td>
</tr>
<tr>
<td>Stenosis ≥50%</td>
<td>MCA 1.07 (1.01–1.12)</td>
</tr>
<tr>
<td></td>
<td>PCA 1.21 (1.12–1.30)</td>
</tr>
</tbody>
</table>

Figures in brackets indicate 95% CIs.
serious diseases with or without malnutrition. The correlation between atherosclerotic manifestations in the carotid arteries, clinical risk factors, and hard end points, such as myocardial infarction, stroke, and death, has been discussed in many studies, and a relationship between prevalent stroke and ICA stenosis and wall thickness has been shown. A large study by O’Leary et al including 4500 subjects aged >65 years without clinical cardiovascular disease has shown an association between intima-media thickness and the risk of myocardial infarction and stroke. However, it is still unclear to what extent atherosclerotic plaques in a normal elderly population predict future excessive mortality and morbidity in cardiac disease and stroke. In the eastern Finnish cohort of the Seven Countries Study, 51% of the men aged 70 to 89 years had nonmineralized atheroma, and 91% had single or multiple mineralizations in any of the arterial segments imaged. Nonmineralized atheromas were associated with cerebral atherosclerosis and ischemic heart disease, but no association was found between carotid mineralization and clinical cardiovascular disease. It is interesting that excessive mortality and morbidity in stroke and cardiac disease were found in men with bilateral plaques but not in women, despite the fact that the prevalence of carotid plaques was the same in both sexes. It is yet to be determined whether there are differences in plaque morphology between men and women and whether the risk for plaque rupture is higher in men. Another explanation might be that the aging process is more pronounced in 78-year-old men compared with women and that the increased risk in men might be associated with this.

The PI of blood flow velocity profiles throughout the cardiac circle is dependent on the volume blood flow (constant MCA during resting conditions), the overall vessel diameter, proximal arterial disease, and some systemic circulatory factors, such as heart frequency and blood pressure pulsatility. If constant hemodynamic conditions during resting are assumed, changes in PI may reflect corresponding changes in downstream peripheral resistance. On the other hand, proximal high-grade ICA stenosis and compensating collateral flows can result in damped blood flow velocity profiles, i.e., a low PI. However, in the present study, we observed a PI increase in patients with carotid artery disease and hypertension. Therefore, this increased PI would indicate structural changes of the peripheral small vessels. We did not establish a correlation with diabetes mellitus and ischemic heart disease. Our investigation of MCA and PCA blood flow patterns indicates that hemodynamically significant stenosis of the proximal intracranial arteries might be a rare condition in this elderly Swedish population, because we did not observe increased maximum systolic blood flow velocities.

The risk of stroke seems to be associated with an extensive atherosclerosis in the carotid arteries, whereas moderate-grade stenosis in this normal population did not show a significant correlation with stroke. Recent studies have shown associations between hypertension, vascular disease, white matter lesions, and dementia in the elderly, but the relationship between cognitive functions and atherosclerosis in the carotid arteries has not been clarified. However, it seems clear that carotid atherosclerosis is an indicator of general atherosclerotic disease in the elderly and that the development of carotid plaques is associated with a high degree of illness and implies a significant increase in hospitalization for vascular disease. The surgery-eligible group is small in an elderly population, and future strategies can be expected to be based on future studies and better knowledge about risk factor interventions and drug treatment programs in the elderly who have an increased risk.

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References


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