As ultrasonographically assessed carotid arteriosclerosis is being used as a surrogate measure for coronary arteriosclerosis, we performed a prospective longitudinal study of the association of our high-resolution ultrasound assessment of extracranial carotid morphology with the risk of acute coronary events in 1,288 eastern Finnish men. The presence of any structural changes in the common carotid arteries or carotid bulbs was associated with a 3.29-fold (95% confidence interval, 1.31–8.29; \( p = 0.0074 \)), intimal–medial thickening with a 2.17-fold (95% confidence interval, 0.70–6.74; \( p = \text{NS} \)), small carotid plaques with a 4.15-fold (95% confidence interval, 1.51–11.47; \( p < 0.01 \)), and large ("stenotic") plaques with a 6.71-fold (95% confidence interval, 1.33–33.91; \( p < 0.01 \)) risk of acute myocardial infarction compared with men free of any structural changes in the carotid artery wall at baseline. These data confirm the close relation between carotid artery wall morphology and coronary heart disease.

Ultrasonographically Assessed Carotid Morphology and the Risk of Coronary Heart Disease

Jukka T. Salonen and Riitta Salonen

As trials for the prevention of coronary heart disease (CHD) events require tens of thousands of subjects and 5–10 years of follow-up, surrogate or intermediate outcomes have been sought (R. Pierce, unpublished observations) and are being used in studies of interventions to prevent atherosclerotic vascular disease. Coronary angiography can be used to assess the progression of coronary arteriosclerosis, but it has the limitation that it can be used only in subjects with severe CHD and even then cannot be repeated several times for ethical reasons. Also, early atherosclerotic lesions cannot be quantitatively assessed with contrast arteriography based on x-rays. High-resolution B-mode ultrasonography has the advantages that it can be performed repetitively, that it can also be used in asymptomatic subjects, that it is inexpensive and safe, and that it can be used to quantitatively measure structural changes in the wall of superficial large arteries. The use of quantitative outcome variables and repetitive measurements over time greatly reduces the sample size necessary for both epidemiological studies and clinical trials. Because of their easy access to ultrasound scanning, extracranial carotid arteries have been used as "windows" to or indicator sites for general and coronary arteriosclerosis. As coronary arteriosclerosis develops, on the average earlier in life than carotid arteriosclerosis,\(^1\) the information about the relation between carotid arteriosclerosis and the risk of CHD events has been considered critically important. (R. Pierce, unpublished observations). For this reason, we investigated the association between structural changes in the extracranial carotid arteries, as assessed ultrasonographically, and the risk of CHD.

Methods

Subjects

The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is a population study whose purpose is to investigate previously unestablished risk factors for CHD and carotid arteriosclerosis\(^2\) in eastern Finnish men, the population with the highest recorded incidence of and mortality from CHD.\(^3\)

Since February 1987, an ultrasonicographic assessment of carotid arteries has been performed as a part of the KIHD by one physician (R.S.). Fifteen participants were examined each study week on Tuesdays, Wednesdays, and Thursdays. Thirty-one men who participated in the KIHD between August 1986 and January 1987 were reinvited for ultrasound examination in the spring of 1987. By the end of 1989, 1,561 eligible men aged 42, 48, 54, or 60 years were invited (a 33% randomly drawn sample of men in these ages residing in the city of Kuopio and six neighboring rural communities in eastern Finland). Two hundred

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seventy-three men either refused or could not be contacted. The participation rate was 82.5%. Complete ultrasonographic assessment of carotid arteries was available for 1,288 men. The numbers of participants in the four age strata were 277, 299, 365, and 347 men, respectively.

Assessment of Arteriosclerosis

The ultrasonographic assessment of carotid arteries was performed while the subject was in the supine position.\(^4\) An ATL UM 4 duplex ultrasound system (Advanced Technology Laboratories Inc., Bothell, Wash.) with a mechanical sector transducer with 10-MHz scanning frequency in B-mode was used.

The KIHD B-mode scanning protocol involved scanning the right and left common carotid artery and the carotid bifurcation–bulb area, the site of predilection for arteriosclerosis development, from three projections: lateral, anterior oblique, and posterior oblique. To simplify the scanning procedure and because of the high location of the carotid bifurcation among eastern Finns, no plaques or intimal–media thickening in either the internal (except the bulb) or the external carotid artery was taken into consideration in the present classification. All scanning, classification, and measurement were performed by one experienced physician (R.S.).

On average, the scanning lasted 30 minutes. The entire scanning procedure was recorded on a videocassette recorder. In all subjects, measurements were made for the intima–media thickness (IMT) of the common carotid arteries. In addition, the sonographer classified the findings during the scanning into four categories: 1) no atherosclerotic lesion, 2) intimal–media thickening, 3) nonstenotic plaque, and 4) large stenotic plaque. The classification was based on the most severely affected site in either the right or left side. Longitudinal “frozen” images chosen to represent the site of the most advanced lesion for each person were reclassified by the same sonographer (R.S.). The video-tapes in a blinded fashion 3 years later. The 1-week reproducibility of the four-category assessment of the IMT was studied by performing a repeated scan 1 week later in a randomly drawn subsample of 49 KIHD participants (of 50 invited) in the spring of 1987. The rescan was performed by the same sonographer (R.S.). The videotapes from the rescan were read, and the IMT measurements were made by another observer (J.T.S.) and the same observer (R.S.). The correlation between the IMT in the first scan and in the rescan was 0.91 for the second reader and 0.97 when the same observer also read the rescanned videotapes in a blinded fashion 3 years later. The 1-week reproducibility of the four-category assessment of carotid arteriosclerosis has been presented earlier.\(^4\) The agreement between the original classifications and reclassifications from the original and the repeated scan was 90%.

Ascertainment of Follow-up Events

A prospective registry for acute myocardial infarction (AMI) was established in the province of Kuopio as part of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project in 1982.\(^6\) This registry collects detailed diagnostic information for all suspected fatal and nonfatal heart attacks in the population, which also includes the present cohort. The events are then classified according to explicitly defined, uniform diagnostic criteria into
definite AMI, possible AMI, no AMI, and insufficient data. This classification was based on autopsy, serial electrocardiographic (ECG) findings, cardiac enzyme levels, symptoms, and history of ischemic heart disease. About half of the fatal cases were autopsied. Serial ECG changes were classified according to the Minnesota code into five categories. Cardiac enzyme levels were routinely determined each day since hospitalization of the patient. Aspartate aminotransferase, lactate dehydrogenase, lactate dehydrogenase 2, creatine kinase, and creatine kinase MB isoenzymes were used, and the determination of enzymes was standardized among several hospitals participating in the AMI registry study in Finland. Enzymes were coded as definite AMI if the highest value of any of the enzymes was twice the upper limit of the normal range and if no other cause for the elevation was apparent. Hospitalized patients were interviewed shortly after admission. In fatal cases, data on symptoms were obtained from medical legal reports and by interviewing the relatives when necessary. Symptoms were coded as typical if the chest pain lasted for at least 20 minutes in the absence of noncardiac nonatherosclerotic causes.

In the present study fatal and nonfatal events in the diagnostic category of definite or possible AMI were regarded as end points. An event was regarded as a definite AMI if any of the following conditions were met: 1) definite ECG changes; 2) symptoms typical, atypical, or inadequately described together with probable ECG and abnormal enzyme levels; 3) symptoms typical and abnormal enzymes; or 4) naked-eye appearance of fresh AMI and/or recent coronary occlusion found at necropsy regardless of other findings. Possible nonfatal AMI was confirmed if there was 1) typical symptoms, together with probable ECG or equivocal enzymes or 2) atypical or inadequately described symptoms, together with probable ECG changes and equivocal enzymes. Possible AMI among fatal cases required exclusion of any other valid evidence for another cause of death. Symptoms were coded as typical if the chest pain lasted for at least 20 minutes in the absence of noncardiac nonatherosclerotic causes.
Relative hazard of a coronary event

<table>
<thead>
<tr>
<th>Carotid morphology</th>
<th>Events</th>
<th>Men at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5</td>
<td>608</td>
</tr>
<tr>
<td>Thickening</td>
<td>6</td>
<td>267</td>
</tr>
<tr>
<td>Plaque</td>
<td>11</td>
<td>396</td>
</tr>
<tr>
<td>Stenosis</td>
<td>2</td>
<td>37</td>
</tr>
</tbody>
</table>

Relative hazard: 6.71

4.15

2.17

2

0

Figure 1. Bar graph showing relative hazard (risk) of a coronary event in men with different structural changes in extracranial carotid arteries.

Discussion

The number of coronary events (24) available for the present analysis was limited because of the short average follow-up time. For this reason it is not yet possible to analyze whether the relation between ultrasonographically assessed carotid morphology and CHD is independent of the major coronary risk factors. We have previously demonstrated that both the qualitative and the quantitative assessment of carotid arteriosclerosis is strongly associated with age, smoking, serum low density lipoprotein cholesterol concentration, and systolic blood pressure. The present data show that ultrasonographically assessed carotid arteriosclerosis predicts CHD events at least equally strong as age, smoking, serum low density lipoprotein cholesterol concentration, and systolic blood pressure. As these risk factors are likely to influence the development of both carotid and coronary atherosclerosis, we did not consider them "confounders" of the association between carotid morphology and CHD.

Possible AMIs, as defined by the MONICA criteria, also included sudden deaths that appeared to be cardiac, even though the diagnosis of an AMI could not be set. These were included because the standard MONICA criteria were used to define AMI. If all outcome events were not true coronary events, then the observed association between carotid morphology and coronary events would be an underestimate of the true relation. A less than perfect sensitivity in detecting all coronary events in the study cohort would also lead to an underestimation of observed relative hazards. Thus, the true relation between ultrasonographically assessed carotid arteriosclerosis and the risk of CHD is likely to be, if anything, stronger than the one observed in this study.

The present data establish the predictive validity of our ultrasonographic classification of extracranial carotid arteriosclerosis with regard to the risk of future coronary events. In addition, our finding confirms the close relation between carotid and coronary arteriosclerosis reported from autopsy studies. The implication of the finding is that an assessment of carotid arteriosclerosis could be used as a proxy measure of coronary arteriosclerosis in epidemiological studies and clinical trials in humans. That even nonfocal intimal-medial thickening in common carotid arteries is associated with some excess risk of CHD during a very short follow-up (mean of about 1 year) suggests that the increase in the IMT, as measured by high-resolution B-mode ultrasonography, is an early form of arteriosclerosis. Because of the importance of this issue, our findings need to be confirmed in further studies of the relation between carotid IMT and carotid plaques and "hard" coronary disease events.

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References

KEY WORDS • atherosclerosis • B-mode ultrasound • coronary heart disease • prospective studies • population studies
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