Ultrasonographically Assessed Carotid Morphology and the Risk of Coronary Heart Disease

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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 = 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. (Arteriosclerosis and Thrombosis 1991;11:1245–1249)

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of thousands of subjects and 5–10 years of follow-up, surrogate or intermediate outcomes have been sought (R. Pierce, unpublished observations) and are being used in studies of interventions to prevent atherosclerotic vascular disease.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 arteriosclerosis2 in eastern Finnish men, the population with the highest recorded incidence of and mortality from CHD.3 Since February 1987, an ultrasonographic 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...
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. An ATL UM 4 duplex ultrasound system (Advanced Technology Laboratories Inc., Bothel, 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 of 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 physician (R.S.) and the same observer (R.S.). The correlation between the IMT in the first scan and in the repeated scan was 90%.

Intimal–medial thickening (category 2) of the arterial wall was defined as a distance of more than 1.0 mm between the intimal–luminal interface and the medial–adventitial interface in the common carotid arteries below the carotid bulb. The atherosclerotic lesion was defined a plaque (category 3) when a distinct area could be identified either with mineralization (bright echo, often producing a typical echogenic shadow) or with focal protrusion into the lumen. A plaque was defined as stenotic (category 4) if it obstructed more than 20% of the luminal diameter in the projection showing the greatest diameter obstruction.

The PCVISION Plus Frame Grabber digitizer board (Imaging Technology Inc., Woburn, Mass.), installed in an IBM PC AT microcomputer, was used to digitize the longitudinal B-scan frames chosen by the reader to represent the greatest IMT. Image-Measure mor-

phometry software (Microscience Inc., Federal Way, Wash.) was used to measure distances to derive IMT measurements.

The IMT was measured from videocassette recordings of the entire scanning procedures by the scanning physician (R.S.). The reader was blinded with regard to the subjects’ identity. The IMT of the posterior (far) wall was measured as the distance from the leading edge of the first echogenic (bright) line to the leading edge of the second echogenic line. The first line represents the intimal–luminal interface, and the second line is produced by the collagen-containing upper layer of the tunica adventitia, close to the medial–adventitial interface. Three measurements of the IMT were made of the far wall of both the right and left common carotid arteries at the site of the greatest IMT in each recording and vessel. The mean of these six IMT measurements was used to derive an estimate of the overall IMT in the common carotid arteries. The measurements were not done at a mineralized (“hard”) plaque because the echogenic shadow resulting from mineralization usually renders the medial–adventitial interface invisible. As the ultrasonographable interfaces are less sharp in the carotid bulb and as the carotid bulb was not accessible for all subjects, the IMT was not measured at the carotid bulb even though the IMT is typically greater there than in the common carotid artery, except for the purpose of four-category classification. However, plaques located in the carotid bulb were taken into consideration in the four-category classification.

The reproducibility (measurement variability) of the measurement 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 rescanned was performed by the same sonographer (R.S.). The videocassette from the rescanned video 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 rescanned was 0.91 for the second reader and 0.97 when the same observer also read the rescanned videos. 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. 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 medicolegal 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 and 1) typical, atypical, or inadequately described symptoms; 2) evidence of chronic coronary occlusion or stenosis, or old myocardial scarring at necropsy without typical, atypical, or inadequately described symptoms; or 3) a valid history of chronic CHD.

The coverage of the registry was checked against the computerized national hospital discharge and death certificate registers. We obtained the diagnostic information and date of all heart attacks in our study cohort by record linkage, based on the uniform Finnish personal identification code (social security number). No personal identification codes were missing in either our study cohort or the AMI registry data. There were no losses to follow-up.

Between September 1986 and June 1990, a definite or possible fatal or nonfatal AMI was registered among 24 subjects of the present study 1 month or more after the baseline (ultrasound) examination. For 13 subjects the event was a definite AMI, and for 11 subjects, a possible AMI. In the case of multiple events, the first one for each subject was considered as the end point in our present analysis. Sixteen subjects died of causes other than CHD. The follow-up period for individual subjects varied between 1 month and 2½ years.

**Statistical Methods**

Three indicator (0,1) variables were constructed that contrasted the three categories of pathological carotid morphology to no arteriosclerosis. These were entered simultaneously in *bmdp* Cox proportional-hazards models. The goodness of fit of the proportional-hazards models was examined by analyzing changes in the proportionality of hazards with time and with carotid morphology categories. The results indicated that the application of the models was appropriate. Partial relative hazards were estimated as antilogarithms of coefficients for indicator (0,1) variables. Their confidence intervals were estimated based on the assumption of the asymptotic normality of estimates. The hypothesis that all regression coefficients were identically zero was tested with the global $\chi^2$ statistic. This test statistic has asymptotic $\chi^2$ distribution with degrees of freedom equal to the number of independent variables in the model. The precision of estimates for categorical independent variables may be limited because of the small number of outcome events in specific strata. However, the number of events is large enough for estimation of the confidence interval and probability value for the impact of the mean maximal IMT on coronary risk. All tests of significance were two sided. Deaths from causes other than CHD were treated as losses to follow-up.

**Results**

Of the 1,288 men examined, 608 (47.2%) had no structural changes, 257 (20.0%) had intimal–medial thickening, 386 (30.0%) had small plaques, and 37 (2.9%) had large stenotic plaques. In these four groups, five (0.8%), six (2.3%), 11 (2.8%), and two (5.4%) men, respectively, experienced an acute coronary event during follow-up. The presence of any structural changes in the common carotid arteries or the carotid bulbs associated with a relative coronary event hazard of 3.29 (95% confidence interval, 1.31–8.29; $\chi^2=7.16$; df=1, $p=0.0074$). In a Cox model including three indicator variables, intimal–medial thickening of common carotid arteries was associated with a 2.17-fold (95% confidence interval, 0.70–6.74; $p=NS$), small plaques in common carotid arteries or the carotid bulbs 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, 3.3–13.9; $p<0.01$) risk of acute coronary events compared with men free of any of these structural changes of the carotid artery wall at baseline (Figure 1). The global $\chi^2$ for the whole model was 11.22 (df=3, $p=0.0106$).

The maximal IMT of common carotid arteries (measured in tenths of millimeters) was signifi-
cantly associated ($\chi^2=4.86, df=1, p=0.0275$) with the risk of an acute coronary event. For each millimeter of IMT, the risk rose 2.14-fold (95% confidence interval, 1.08–4.26).

**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


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