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)

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 in eastern Finnish men, the population with the highest recorded incidence of and mortality from CHD.

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
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–medial 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 in one session to derive an estimate of the overall IMT in the common carotid arteries. The measurements were not done 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 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. 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 insuffi-
cient 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 ac-
gording to the Minnesota code into five categories.
Cardiac enzyme levels were routinely determined
each day since hospitalization of the patient. Aspar-
tate aminotransferase, lactate dehydrogenase, lactate
dehydrogenase 2, creatine kinase, and creatine ki-
nase MB isoenzymes were used, and the determi-
nation 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 medico-
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,
with probable ECG and abnormal enzyme levels; 3)
symptoms typical and abnormal enzymes; or 4) na-
ked-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. Pos-
sible 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 diagno-
sis 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 miss-
ing 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

**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 propor-
tional-hazards models. The goodness of fit of the
proportional-hazards models was examined by ana-
lyzing 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 esti-
mated as antilogarithms of coefficients for indicator
(0,1) variables. Their confidence intervals were esti-
mated based on the assumption of the asymptotic
normality of estimates. The hypothesis that all re-
gression 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
coronal 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 cor-
onary 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,
1.33–33.91; $p<0.01$) 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-
Relative hazard of a coronary event

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

Events
Men at risk 5 608 6 267 11 386 2 37

Carotid morphology
Normal Thickening Plaque Stenosis

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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