Increased Carotid Intimal-Medial Thickness and Coronary Calcification Are Related in Young and Middle-Aged Adults
The Muscatine Study

Patricia H. Davis, MD; Jeffrey D. Dawson, ScD; Larry T. Mahoney, MD; Ronald M. Lauer, MD

Background—Increased carotid intimal-medial thickness (IMT) and coronary artery calcification (CAC) are used as 2 markers of early atherosclerosis. Our objectives were to assess whether increased IMT and CAC are related and to determine the relationship between cardiovascular risk factors and carotid IMT in young adults.

Methods and Results—A sample of 182 men and 136 women aged 33 to 42 years living in Muscatine, Iowa, underwent B-mode carotid ultrasound to determine the mean of 12 measurements of maximal carotid IMT. CAC was defined as calcification in the proximal coronary arteries in ≥3 contiguous pixels with a density of ≥130 HU. The mean IMT was 0.788 mm (SD 0.127) for men and 0.720 mm (SD 0.105) for women. CAC was present in 27% of men and 14% of women and was significantly associated with IMT in men (P<0.025) and women (P<0.005). With multivariate analysis, after adjustment for age, significant risk factors for carotid IMT were LDL cholesterol (P<0.001) and pack-years of smoking (P<0.05) in men and LDL cholesterol (P<0.001) and systolic blood pressure (P<0.01) in women. These risk factors remained significant after CAC was included in the multivariate model.

Conclusions—There is an association between increased carotid IMT and CAC and between cardiovascular risk factors and increased IMT in young adults. Carotid IMT may provide information in addition to CAC that can be used to identify young adults with premature atherosclerosis. (Circulation. 1999;100:838-842.)

Key Words: carotid arteries ▪ ultrasonics ▪ risk factors ▪ arteriosclerosis ▪ coronary disease

M ost epidemiological studies of risk factors for atherosclerosis and clinical trials for the prevention of disease have used the morbidity and mortality that results from coronary artery disease (CAD), stroke, and peripheral vascular disease as measures of the disease process in older adults.1–3 There is a need to identify young subjects at risk for premature cardiovascular disease so that preventive measures may be instituted before occlusive vascular disease occurs. In the present study, we used noninvasive measures of carotid and coronary artery atherosclerosis to evaluate the early process in young asymptomatic adults and to examine the relationship to established cardiovascular risk factors. The noninvasive methods used to evaluate early carotid and coronary atherosclerosis included measurement of carotid intimal-medial thickness (IMT) by B-mode ultrasound and detection of coronary artery calcification (CAC) by electron beam computed tomography (EBCT).

Presence of calcification in the coronary arteries has been correlated with atherosclerotic changes in the coronary arteries found on postmortem examination or coronary angiography.4 CAC has also been shown to be associated with known risk factors for CAD in adults.4 Increased carotid IMT is also associated with known cardiovascular risk factors in older adults,5 as well as with prevalent and incident CAD.6–11 In addition, small case-control studies have shown increased carotid IMT in children with familial hypercholesterolemia.12–14 Since 1971, a cohort of children in Muscatine, Iowa, has been followed up, with risk factors measured in childhood (ages 8 to 18 years) and young adulthood (ages 20 to 33 years). In a prior study of this cohort, Mahoney et al15 demonstrated that in 197 men and 187 women aged 29 to 37 years, CAC was associated with concurrently measured body mass index (BMI), blood pressure, and low HDL cholesterol (HDL-C), as well as with BMI measured in childhood.

Although there have been extensive population-based studies of the distribution of carotid IMT in subjects aged 45 to 65 years16–18 and subjects older than 65,19 our study provides new data concerning the distribution of carotid IMT in a cohort aged 33 to 42 years and the association between increased carotid IMT and CAC.
Methods
Between 1971 and 1981, school children in Muscatine, Iowa, underwent biennial examinations. A total of 14,066 children underwent 32,635 examinations. Between 1981 and 1991, 2,446 participants (67% of those eligible), then aged 20 to 34 years, underwent repeat examination. From 1992 to 1996, a subset of this cohort (769 individuals) had another examination with EBCT to measure CAC. In 1996, we began to reexamine these 769 individuals who had then reached the age of 33 to 42 years. The protocol for the present study was approved by the University of Iowa Institutional Review Board, and informed consent was obtained from all subjects. Subjects were compensated for their participation.

For the study reported herein, the subjects were eligible to be included if they had previously participated in ≥1 childhood survey, 1 young adult survey, and the first CAC study. Participants were contacted by telephone, and an appointment was scheduled for them to come to the Muscatine Coronary Risk Factor Clinic after a 12-hour fast. Height, weight, triceps skin fold, hip circumference, waist circumference, and blood pressure were recorded. Participants completed a medical and personal history questionnaire, which had been pretested to demonstrate adequate interobserver reliability, that contained questions concerning diabetes, smoking, and medications. Each participant had measurements of total cholesterol, HDL-C, LDL cholesterol (LDL-C), triglycerides, lipoprotein(a) (LP[a]), homocysteine, glucose, and insulin. In addition, in women, a pregnancy test was performed.

Participants underwent EBCT as previously described, with 2 separate scans obtained in a single visit. Each scan was read separately at a central reading station by 2 radiologists blinded to the results of the first CAC study and to risk factor status. When the 2 scans obtained during the same session were discordant, the radiologists reviewed both scans again before making a final determination. CAC was defined as a calcified lesion with a density of ≥130 HU present in ≥3 contiguous pixels in the proximal coronary arteries. Many of the duplicate scans were positive for CAC on one and negative for CAC on the other because of different registration and the generally small amounts of calcium in this age group. We defined a positive result as 3 contiguous pixels on either scan.

On the same day, subjects had carotid ultrasound studies performed by a single technician who was unaware of risk factor status and the results of prior CAC determination. The protocol for measuring carotid IMT was the same as that used in the Asymptomatic Carotid Artery Plaque Study (ACAPS). For each subject, the maximum carotid IMT was imaged for the near and far wall of each common carotid artery (CCA), carotid bifurcation (BIF), and internal carotid artery (ICA). Scans were read at a central reading center (AUTREC, Inc in Winston-Salem, NC), which had demonstrated high interreader reliability during the ACAPS trial. A 10% random sample underwent repeat carotid ultrasound studies during a second visit within 3 months of the first study to assess intraobserver reliability.

Statistical analysis used the mean of the maximum carotid IMT measured at the 12 locations (3 sites×2 sides×2 walls) as the primary outcome of interest. Separate analyses were planned for each sex.

For each sex, the risk factors and outcomes were described with percentages for dichotomous variables and means and SDs for continuous variables). Men and women were compared with respect to these variables by a χ² test or a rank sum test as appropriate. With stratification by sex, the data were analyzed to determine whether CAC or cardiovascular risk factors predicted carotid IMT. The mean carotid IMT in subjects with and without CAC was compared by the 2-sample Wilcoxon rank sum statistic, and the relationship between the tertile of IMT and the presence of CAC was examined by the Cochran-Armitage trend test. The associations between carotid IMT and individual risk factors were tested with Spearman rank correlation coefficients. These correlations were based on age-standardized z scores for all risk factors except smoking and age. All risk factors were then included in a robust stepwise regression procedure, with age forced into the model. The multiple linear regression model identified by the stepwise procedure was also modified by including CAC as an additional predictor in the model.

Results
There were 182 men and 136 women aged 33 to 42 years included in the analyses. This included 318 (85.7%) of 371 of those targeted for the study. Risk factors at the last childhood examination of these 318 participants were compared with the results (standardized by age, sex, and year of examination) for the 53 eligible subjects who did not participate, and there were no significant differences. The order of selection for participation in the study was as follows: the oldest men (39 to 42 years), the youngest men (33 to 36 years), the oldest women (39 to 42 years), and the youngest women (33 to 36 years). Studies of the remainder of the cohort (aged 36 to 39 years) are in progress. The means of the 12 maximum carotid IMT measurements for men and women were 0.788 mm (SD 0.127) and 0.720 mm (SD 0.105), respectively. For men and women, respectively, 87.3% and 90.5% had ≥10 walls measured, and 6.1% and 3.0% had ≥6 walls missing. The completeness of the data measured according to site was as follows: near ICA 77.2%, far ICA 89.2%, near BIF 93.7%, far BIF 92.3%, near CCA 99.2%, and far CCA 99.5%. In those with missing data, all available IMT measurements were included to calculate the mean IMT. For the 10% sample of subjects who were randomly remeasured, the within-subject reliability was 87%, with a mean absolute value of the within-subject deviation of 0.043 mm and a median of 0.034 mm.

Among the men, 27% had CAC on ≥1 scan in the proximal coronary arteries, whereas 14% of the women had CAC. For men, the mean carotid IMT was 0.825 mm (SD 0.138) with CAC and 0.774 mm (SD 0.120) without CAC (P<0.025). For women, the mean carotid IMT was 0.790 mm (SD 0.104) with CAC and 0.709 mm (SD 0.102) without CAC (P<0.005). In the Figure, the prevalence of CAC is shown for each tertile of carotid IMT and including sex and age of the subjects. There was a strong relationship between IMT tertile and the presence of CAC adjusted for age and sex (P<0.005 on the stratified Cochran-Armitage trend test). In men, the prevalence of CAC was greater among those...
TABLE 1. Current Risk Factors, Carotid IMT, and CAC by Sex

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men (n=182)</th>
<th>Women (n=136)</th>
<th>Difference (P*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;38 y, %)</td>
<td>Mean (SD</td>
<td>Mean (SD</td>
<td>0.36</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>56.5</td>
<td>51.5</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>0.6</td>
<td>5.9</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>116.8 (11.9)</td>
<td>111.7 (11.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77.3 (8.8)</td>
<td>69.9 (9.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3 (4.8)</td>
<td>28.1 (6.8)</td>
<td>0.102</td>
</tr>
<tr>
<td>Triceps skin fold, mm</td>
<td>18.4 (8.3)</td>
<td>31.2 (9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.91 (0.07)</td>
<td>0.78 (0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.81 (0.89)</td>
<td>4.64 (0.83)</td>
<td>0.051</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.94 (0.77)</td>
<td>2.74 (0.77)</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.16 (0.37)</td>
<td>1.29 (0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.55 (1.00)</td>
<td>1.45 (1.94)</td>
<td>0.004</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.46 (1.15)</td>
<td>5.19 (1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>14.1 (10.2)</td>
<td>13.2 (12.2)</td>
<td>0.054</td>
</tr>
<tr>
<td>Pack-years smoking</td>
<td>8.2 (10.7)</td>
<td>5.6 (8.4)</td>
<td>0.073</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>9.9 (2.9)</td>
<td>8.4 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp(a), μg/mL</td>
<td>17.8 (21.3)</td>
<td>17.0 (23.6)</td>
<td>0.982</td>
</tr>
<tr>
<td>Carotid IMT, mm</td>
<td>0.788 (0.127)</td>
<td>0.720 (0.105)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAC, %</td>
<td>27</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The first 3 risk factors and CAC were compared across sexes by χ² test; the rest used the rank sum test.

Discussion

Autopsy studies have demonstrated that the atherosclerotic process begins during adolescence with the appearance of fatty streaks and fibrous plaques in the aorta, coronary arteries, and cervical carotid arteries. These early changes are correlated with cardiovascular risk factors in young adults, and the severity of the atherosclerosis increases with the number of risk factors present. Several methods can detect these early, subclinical atherosclerotic changes noninvasively. Measurement of carotid IMT, which can be performed reproducibly, has now gained acceptance as a marker of the atherosclerotic process. Studies in older adults show that increased carotid IMT correlates with known cardiovascular risk factors and that progression of carotid IMT decreases with the use of lipid-lowering agents.

Risk Factors for Increased Carotid IMT

We found an increase in carotid IMT with age and male sex, as noted in the subjects aged >45 years. In the study reported herein, current risk factors based on univariate analysis included age, waist-hip ratio, total cholesterol, LDL-C, diastolic blood pressure (DBP), and pack-years of smoking in men and age, BMI, waist-hip ratio, total cholesterol, and LDL-C were significant in women. These results demonstrate that the association between CAC and carotid IMT cannot be explained by shared risk factors.

TABLE 3. Multivariate Risk Factor Models for Carotid IMT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men (R²=0.166), Estimate* (SE)</th>
<th>Women (R²=0.184), Estimate (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0061† (0.0030)</td>
<td>0.0074† (0.0028)</td>
</tr>
<tr>
<td>SBP</td>
<td>NS</td>
<td>0.00024† (0.007)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.0013§ (0.003)</td>
<td>0.0011§ (0.003)</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0.0018† (0.0009)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Change in mean carotid IMT per SD change in risk factor except for age, which is per year.
†P<0.05, ‡P<0.01, §P<0.001.
terol, LDL-C, SBP, DBP, and triglycerides in women. There are limited data available concerning risk factors in young adults that show increased carotid IMT in subjects with hypertension (mean age 24 years), familial hypercholesterolemia, type 1 diabetes mellitus (mean age 27.5 years) compared with controls in small case series. The magnitude of our correlation coefficients is similar to those obtained in a study of women aged 44 to 50 years. Data about cardiovascular risk factors and carotid IMT in older subjects show an association with SBP, DBP, LDL-C, apolipoprotein B, diabetes, fasting glucose and insulin, reduced insulin sensitivity, active and passive smoking, and BMI and an inverse association with HDL-C. The relationships to serum triglycerides, Lp(a), plasma homocysteine, pulse pressure, and apolipoprotein A are less definite.

With multivariate analysis, our data showed that LDL-C was significant for both men and women, whereas SBP was included for women only and pack-years of smoking for men only. In the present study, the association of carotid IMT with risk factors was affected by sex. Pack-years of smoking was significant only in men, and this may be explained in part by less lifetime smoking exposure among women than men, although this difference was not significant. Two studies comparing risk factors for increased carotid IMT according to sex also showed that pack-years of smoking was not a risk factor for women, whereas 2 studies that included only women did find smoking to be a risk factor. In the present study, SBP was a risk factor only in women, despite a lower mean SBP in women than men. In the Edinburgh Artery Study, SBP was a significant risk factor only for women, but more women were hypertensive. Other studies have found SBP to be a significant risk factor in men. Because carotid IMT is less thick in women than in men, the lesions may be at an earlier stage in the atherosclerotic process, and this could explain sex differences in risk factors.

Relationship of Carotid IMT and CAC
Carotid IMT may also be used as a surrogate measure of coronary artery atherosclerosis. Carotid IMT was linked to prevalent and incident cardiovascular disease in studies from Finland, Holland, and the United States. In the Atherosclerosis Risk in Communities study, there was an association of incident myocardial infarction and carotid IMT in adults aged 45 to 64 years. In the Cardiovascular Health Study, the relative risk of myocardial infarction and stroke in asymptomatic subjects aged 65 years or older increased for each quintile of increase in carotid IMT, and the association remained significant even after adjustment for traditional risk factors. Carotid IMT was as powerful a predictor of cardiovascular events as traditional risk factors. Longer-term follow-up in a clinical trial showed that measurement of carotid IMT also predicted coronary events.

Detection of the presence of CAC by EBCT can noninvasively detect the early atherosclerotic process in asymptomatic individuals. CAC predicts future coronary events in asymptomatic patients, but the data are less definitive for asymptomatic patients. The presence of CAC has also been associated with known CAD risk factors. In a previous study, we showed that the presence of CAC was associated with concurrently measured high BMI, high blood pressure, and low HDL-C.

Because both carotid IMT and the presence of CAC are associated with the early atherosclerotic process and the presence of CAD, it would be expected that increased carotid IMT and CAC would also be correlated. Our study did show an association between carotid IMT and CAC in a sample of asymptomatic young to middle-aged adults. In a study of older adults (mean age 78 years), the coronary calcification score was correlated with carotid IMT. After adjustment for cardiovascular risk factors, carotid IMT was no longer independently associated with the coronary calcium score. However, in a study of 111 asymptomatic middle-aged men with hypercholesterolemia, the presence of CAC was significantly associated with atherosclerosis in the aorta and femoral arteries but not the carotid arteries. Megnien et al evaluated 94 asymptomatic men with multiple cardiovascular risk factors and found that carotid IMT measured in the far wall of the right common carotid artery correlated with the presence of CAC, but this association did not persist after adjustment for age.

In the present study, the association of risk factors with carotid IMT remained significant in young adults even after CAC was included in the multivariate model. This would suggest that the association of carotid IMT and CAC was not solely due to shared risk factors and that measurement of carotid IMT, in addition to CAC, may provide information that may be used to identify young adults with premature atherosclerosis.

Summary
Cardiovascular risk factors are associated with increased carotid IMT in adults aged 33 to 42 years. We demonstrated an association between carotid IMT and CAC that supports the use of carotid ultrasound to identify young adults at risk for premature atherosclerosis not only in the carotid arteries but also in the coronary arteries. Identification of atherosclerosis at an early age could lead to the development of interventions to ameliorate the process before the development of symptomatic disease.

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References


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