Carotid Plaque and Intima-Media Thickness Assessed by B-Mode Ultrasonography in Subjects Ranging From Young Adults to Centenarians

Satoki Homma, MD; Nobuyoshi Hirose, MD; Hiroyuki Ishida, MD; Toshiharu Ishii, MD; Goro Araki, MD

Background and Purpose—To investigate relationships among plaque formation, increasing intima-media thickness, and age, we examined ultrasonographically carotid arteries of subjects who had no major atherosclerotic risk factors and who ranged in age from young adults to centenarians.

Methods—We studied 319 healthy subjects (154 men, 165 women; age range, 21 to 105 years) with no history of hypertension, diabetes mellitus, or atherosclerotic disease. Mean intima-media wall thickness (IMT) of common carotid arteries at plaque-free sites and prevalence of plaques were evaluated by B-mode ultrasound.

Results—Mean common carotid IMT increased in a linear manner with age for all decades of life, including centenarians [IMT = (0.009 × Age) + 0.116 (r = 0.83)]. In centenarians (n = 30), intima-media complexes were diffusely thickened (mean IMT, 1.01 mm). Plaque prevalence increased up to the tenth decade of life (83.3%, n = 30) but decreased in centenarians (60.0%). IMT and plaque prevalence were closely associated in the seventh and eighth decades of life but not at older ages.

Conclusions—The present study indicates that increased IMT is a physiological effect of aging that corresponds to diffuse intimal thickening, especially in very elderly persons, and that IMT is distinct from pathological plaque formation. (Stroke. 2001;32:830-835.)

Key Words: aging ♦ atherosclerosis ♦ plaque ♦ thickness, intima-media ♦ ultrasonography

In recent years, the numbers of elderly people have increased in developed countries, particularly in Japan. Atherosclerotic diseases are considered to be the most important factor compromising physical and mental activity in the oldest individuals. Age has been found to be the chief determinant of atherosclerotic progression. However, to the best of our knowledge, progression of atherosclerosis in the oldest age class has not been explored.

High-resolution ultrasound imaging of arteries, a convenient noninvasive method for evaluating carotid arterial walls, depicts 2 relevant findings: increased intima-media thickness (IMT) and plaque formation. Both changes are related to aging and are accelerated by hypertension and other risk factors. However, studies have suggested that those findings were affected by different risk factors independent of each other, and plaque measurement showed a better correlation with atherosclerotic events than IMT. Thus, plaque formations may have much more significance for atherosclerotic progression than increase in IMT. With regard to relation to aging, some previous studies indicated that progression of IMT accelerated exponentially with age up to the eighth decade of life, whereas plaque accrual may slow in the ninth decade of life.

In the present study, we investigated whether IMT and plaque formation continued to increase up through the eldest age class and whether IMT increases and plaque occurrence were independent of each other. We therefore sonographically examined carotid arteries in subjects from young adults to centenarians with no history of hypertension, diabetes mellitus, atherosclerotic complications, or other diagnosed physical illnesses.

Subjects and Methods

Subjects

Subjects apart from centenarians (n = 289, age 21 to 98 years) were recruited from 1995 to 1999 to balance subject numbers in decade classes (4 to 10). All subjects resided in Tokyo, Japan, and consulted Kugayama Hospital or the Hospital of the School of Medicine, Keio University, for routine health evaluation. Evaluations included phys-

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ical examination, measurement of body weight and height, blood chemistry analyses, ECG, chest roentgenography, and carotid arterial ultrasonography. Blood samples were obtained from subjects who were in the fasting state. Blood chemistry analysis included screening for liver and renal dysfunction as well as inflammatory processes. Serum concentrations of total cholesterol (TC), triglyceride (TG), HDL cholesterol (HDL-C), and fasting blood sugar (FBS) were measured. Concentration of LDL cholesterol (LDL-C) was calculated by Friedewald’s formula.17

By multiple regression analysis of IMT and carotid plaques in all potential subjects (n=423), including those with hypertension, diabetes, or a history of atherosclerotic disease, IMT was associated significantly with age (P<0.0001), hypertension (P<0.0001), diabetes mellitus (P<0.0001), and male sex (P<0.0005) but not serum lipid status or smoking. Plaque occurrence was affected by age (P=0.0001) and hypertension (P=0.0004). Therefore, 122 subjects <100 years old with a history of hypertension, diabetes mellitus, or atherosclerotic disease were excluded. Twelve other subjects were excluded because of familial hypercholesterolemia, liver or renal disease, inflammatory disease, or neoplasm. The remaining subjects (n=289; 146 men and 143 women) were investigated as noncentenarians. Oral informed consent was obtained from all participants.

Thirty-four centenarians living in 6 wards in central Tokyo consented to be investigated at Kugayama Hospital or at their home between 1993 and 1997. The centenarian population in this area was about 150 persons in 1994.18 Four centenarians were excluded from the present study because of hypertension or atherosclerotic disease (arteriosclerosis obliterans in a lower limb). The remainder (n=30) who were investigated as centenarian subjects had no known diabetes or liver or renal disease. Among these subjects, 26 lived at home and 4 lived in nursing homes. As for activities of daily living, 10 subjects (33%) were bedridden, a rate equal to that in the general centenarian population of the Tokyo metropolitan area.19 The health evaluation included physical examination, measurement of body weight and height, blood chemistry analyses as previously described for younger subjects, ECG, and carotid ultrasonography. The present study was approved by each institutional review committee.

### Ultrasound Protocol

Ultrasonograms were performed by use of duplex equipment with a 7.5-MHz scanning frequency in B mode (SSD-2000, Aloka, and SSA-220A, Toshiba). Subjects were examined in the supine position. Images were obtained bilaterally from 40 mm proximal to 30 mm distal to the common carotid artery (CCA) bifurcation, including internal and external carotid arteries. Investigators, who were kept unaware of clinical data, scanned the vessel in multiple longitudinal and transverse planes to determine the best view perpendicular to the vessel wall for measuring IMT in each segment, according to the method of Pignoli et al.5 As in several previous studies,9,20 we defined a plaque as a focal raised lesion rather than using an IMT cutoff value. IMT was measured bilaterally at 3 defined points 10, 20, and 30 mm proximal to the bifurcation at the far wall of the CCA, provided that these points were free of plaque. Mean CCA IMT was determined to be mean value of IMT only at the defined sites that were plaque free. Plaque occurrence was quantified as percentage of subjects per decade who demonstrated plaque in internal or external carotid or CCA on either side. Plaques were present unilaterally or bilaterally in the CCA in 28 subjects: in those individuals, CCA IMT was calculated as the mean of 3 to 5 plaque-free points.

To evaluate differences in IMT measurement by the 2 ultrasonography machines used, 1 investigator (S.H.) repeated the scans in each machine <1 month apart in a randomly chosen subsample (n=12). Mean absolute difference ± SE was 0.03±0.02 mm.

### Statistical Analysis

Regression lines and associated correlation coefficients were computed by use of the least-squares method to extract factors contributing to IMT and plaque occurrence. Stepwise multivariate analysis was performed on several variables determined to be significant (F=4.0) by univariate analysis. For comparisons of mean carotid arterial IMT between plaque-free subjects and others with plaques, Student’s t test was performed. Significance of differences in occurrence of plaques was calculated by χ² test. Probability value <0.05 was considered to indicate significance.

### Results

#### Subject Profile

Table 1 depicts sex distribution, prevalence of smoking, and mean values and standard deviations for age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum concentration of TC, TG, HDL-C, and FBS by decade. In subjects in the tenth decade of life and in centenarians, distribution was skewed forward at relatively young ages within the decade and in females, similar to that observed in the general population.1,19 SBP tended to increase with age, except for in subjects in the tenth decade of life. Mean values for DBP, TC, TG, HDL-C, and FBS increased with age until the seventh or eighth decade of life but began to decrease in more elderly subjects. These findings are in accord with past studies of the general population.21 Mean TC concentration in our subjects in the fourth to eighth decades of life was similar to that in the general population as measured in a recent nationwide Japanese clinical survey.21 However, mean SBP and DBP in our subjects were 10 to

<table>
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<th>Age category, y</th>
<th>≤39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>80–89</th>
<th>90–99</th>
<th>≥100</th>
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<tr>
<td>No.</td>
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<td>39</td>
<td>56</td>
<td>63</td>
<td>45</td>
<td>34</td>
<td>30</td>
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<td>Age, y</td>
<td>34.5 (4.7)</td>
<td>45.0 (2.6)</td>
<td>55.0 (2.9)</td>
<td>63.9 (2.6)</td>
<td>73.7 (2.8)</td>
<td>84.4 (3.3)</td>
<td>92.5 (2.5)</td>
<td>101.4 (1.4)</td>
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<td>Men/women, n</td>
<td>13/9</td>
<td>22/17</td>
<td>33/23</td>
<td>28/35</td>
<td>25/20</td>
<td>16/18</td>
<td>8/22</td>
<td>8/22</td>
</tr>
<tr>
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<td>16/23</td>
<td>18/38</td>
<td>22/41</td>
<td>12/33</td>
<td>5/29</td>
<td>2/28</td>
<td>2/28</td>
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<tr>
<td>BMI</td>
<td>22.7 (2.6)</td>
<td>23.4 (3.2)</td>
<td>23.4 (2.4)</td>
<td>22.8 (2.5)</td>
<td>22.7 (3.1)</td>
<td>20.8 (3.4)</td>
<td>19.2 (3.6)</td>
<td>18.5 (3.2)</td>
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<tr>
<td>SBP, mm Hg</td>
<td>115.0 (19.7)</td>
<td>114.6 (16.5)</td>
<td>117.1 (17.5)</td>
<td>122.7 (19.1)</td>
<td>129.6 (17.9)</td>
<td>133.2 (18.3)</td>
<td>126.6 (14.6)</td>
<td>135.3 (21.1)</td>
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<tr>
<td>DBP, mm Hg</td>
<td>71.3 (10.6)</td>
<td>73.0 (11.5)</td>
<td>74.0 (8.2)</td>
<td>73.0 (9.0)</td>
<td>75.1 (12.6)</td>
<td>72.4 (10.1)</td>
<td>69.3 (9.9)</td>
<td>68.0 (18.5)</td>
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<td>TC, mmol/L</td>
<td>4.74 (0.76)</td>
<td>5.38 (0.82)</td>
<td>5.64 (0.83)</td>
<td>5.79 (0.90)</td>
<td>5.58 (0.86)</td>
<td>5.08 (1.11)</td>
<td>4.70 (0.99)</td>
<td>4.35 (1.01)</td>
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<td>TG, mmol/L</td>
<td>1.16 (0.79)</td>
<td>1.48 (1.08)</td>
<td>1.46 (0.78)</td>
<td>1.52 (1.01)</td>
<td>1.21 (0.48)</td>
<td>1.01 (0.42)</td>
<td>0.99 (0.35)</td>
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<td>HDL-C, mmol/L</td>
<td>1.53 (0.40)</td>
<td>1.41 (0.32)</td>
<td>1.44 (0.33)</td>
<td>1.60 (0.43)</td>
<td>1.60 (0.39)</td>
<td>1.50 (0.43)</td>
<td>1.32 (0.39)</td>
<td>1.21 (0.28)</td>
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<tr>
<td>FBS, mmol/L</td>
<td>5.18 (0.48)</td>
<td>5.18 (0.47)</td>
<td>5.21 (0.51)</td>
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<td>5.28 (0.56)</td>
<td>5.21 (0.54)</td>
<td>5.38 (0.61)</td>
<td>4.96 (0.37)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
20 mm Hg lower than for subjects in that nationwide study. Mean HDL-C concentration was 0.13 to 0.26 mmol/L (5 to 10 mg/dL) greater in our subjects than in the general population.

CCA IMT, Plaque Occurrence, and Risk Factors
Table 2 presents results of stepwise multiple regression analyses among age, sex, smoking, SBP, DBP, BMI, and serum concentrations of TC, TG, HDL-C, LDL-C, and FBS with respect to CCA IMT and plaque occurrence. Plaque occurrence was not analyzed in subjects <50 years of age because plaques were absent at those ages. Age was the only factor independently related to mean CCA IMT in subjects overall. In the subjects <50 years of age (including women in the late premenopausal period), serum LDL-C and sex differences were more significant for IMT than age. However, in subjects >50 years old, only age was independently related to increased IMT. This also was true when analysis was limited to subjects in the sixth and seventh decades of life (data not shown). Furthermore, the appearance of plaque was associated with age alone. Therefore, subjects in the present study were considered appropriate for evaluation of aging effects on IMT and plaque. We did not distinguish between male and female subjects in the statistical analysis, especially among elderly subjects, given that aging was the focus of the study.

CCA IMT and Occurrence of Plaques With Aging
Figures 1 and 2A indicate a linear increase in mean CCA IMT with age for all decades, including centenarians. Intima-media complexes in most centenarians characteristically showed diffuse thickening: average CCA IMT was >1 mm.

Figure 2B indicates that occurrence of plaques also increased progressively up to the tenth decade of life. However, plaques were less prevalent in centenarians than in subjects in the tenth decade of life ($P<0.05$), with a prevalence similar to that in subjects in the ninth decade of life.

Relationship Between IMT and Occurrence of Plaque
Figure 3 compares mean CCA IMT in subjects with and without plaques by decade. Subjects <60 years of age are not shown, because subjects with plaques in decades preceding the seventh were few or none, precluding statistical analysis. For the seventh and eighth decades, mean IMT in subjects with plaques was significantly greater than that in subjects free of plaques. However, after the ninth decade of life, this association was not significant.

![Figure 1. Correlation between mean IMT and age.](http://stroke.ahajournals.org/Downloadedfrom)
Discussion

Our study excluded subjects with hypertension, diabetes, and atherosclerotic disease. Mean extent of atherosclerotic lesions in hospitalized patients not dying of hypertension, diabetes, or atherosclerotic disease was found to be similar to lesion extent by age in forensic autopsies, which represent the general (nonhospital) population. Mean HDL-C in our subjects was greater than in the general population. Our subjects were considered to be a basal group of the population with respect to the effects of risk factors and representative of healthy individuals (of similar age).

Although we found a linear correlation between mean CCA IMT and age, some previous studies indicated that the relationship was nonlinear, with accelerating IMT progression. However, IMT assessment in these studies included IMT at plaque sites. An autopsy study revealed that mean aortic intimal thickness increased with age, particularly in the sixth decade of life, during which advanced raised lesions such as preatheromas and atheromas began to appear. The increase in IMT reflects predominantly intimal thickening. When sites with plaques are used to measure IMT, progression of IMT will show acceleration in the elderly. In contrast, mean IMT in plaque-free sites correlates linearly with age from young adults to centenarians.

Investigation of centenarians discloses extremes of biological change induced by aging. Linear progression of CCA IMT at the plaque-free sites for individuals aged >100 years suggests that this change may be a physiological aging effect. Such an homogeneous increase in IMT may correspond to the histologic change of diffuse intimal thickening, which has been considered physiological. Our ultrasonographic findings support this view.

On the other hand, investigation of centenarians, a sort of elite among the long-lived, may reflect unique attributes. Plaque occurrence increased up to the tenth decade of life but then decreased. Some reports suggested that clinical cardiovascular disease is associated with plaque status but is not or is less significantly associated with an increase in IMT. In autopsies, raised lesions that would be defined sonographically as plaques have been related to clinical atherosclerotic disease. Therefore, plaques imply an advance to a potentially symptomatic stage of atherosclerosis. A cross-sectional study found declining plaque prevalence as early as the ninth decade. However, because that study included hypertensive patients, healthy participants in the ninth decade of life were considered to be overrepresented.

A relatively low plaque prevalence in centenarians suggests that at least some centenarians may possess unknown genetic or acquired characteristics conferring resistance to plaque progression. An ultrasonographic study of carotid arteries found more plaques among subjects with a family history of ischemic heart disease than in those without, whereas IMT did not differ between groups after adjustment for classical cardiovascular risk factors. Thus, factors other than age have a greater effect on plaque formation compared with IMT.

Most reports have demonstrated an association between IMT progression and plaque formation. Although our results for subjects in the seventh and eighth decades of life agree, no association was found for the oldest subjects. These results imply that diffuse intima-media thickening not accompanied by plaque formation is frequent at the most advanced ages.

In conclusion, clinical significance of increased IMT differs from that of plaque formation. Increasing IMT at plaque-free sites does not indicate atherosclerotic changes and reflects diffuse physiological aging processes as diffuse intimal thickening, especially in very elderly persons, whereas plaque formations are more clearly pathological. Although a diffuse increase in IMT is a predictive factor for plaque formation, genetic or acquired factors other than age are considered to mediate this progression, which reflects the relationship between diffuse intimal thickening and atheromatous lesions.

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Many investigators, myself included, have regarded intimal and medial thickening as a precursor lesion of atherosclerosis, ultimately to be manifested by plaque development. Both findings become increasingly common with age. Most of us have believed that the thickening of the vessel wall may predispose it to lipid accumulation and plaque formation and/or that lipid penetration may induce thickening before it accumulates into recognizable plaque.

The interesting article by Homma et al contributes an important new perspective in the assessment and understanding of these processes by studying a unique series of subjects that included healthy centenarians. They have studied the carotid bifurcation by ultrasond in 319 healthy subjects aged 21 to 105 years, measuring the combined thickness of the intima-media complex at predetermined locations at and below the carotid bifurcation, excluding

References


those measurements at the site of plaque, and the prevalence of plaque elsewhere in the image. They excluded subjects with diabetes, hypertension, familial hyperlipidemia, and clinical atherosclerotic disease. Thus, there was purposeful selection bias in favor of health.

The significant finding is that while intima-media thickness became higher with age through the whole series, plaque prevalence, increasing to the tenth decade, was decreased among centenarians, comparable to that found among those aged 80 to 90 years. It is important to realize that there was only one observation per subject, not serial measurements over time within subjects. Thus, there was selection for healthy (surviving) subjects.

Their conclusion, evident in the data, is that intima-media thickening alone is an age-related, probably physiological phenomenon, whereas plaque formation, while more common among old people than young, is pathological and is less frequent when disease is absent. The authors observe that people surviving beyond age 100 must have unique health factors permitting such survival, incidentally reflected in a lessened frequency of plaque.

This is an important observation, and if confirmed by complementary studies based on histology, clinical outcome, and within subject serial measurements, will help clarify our thinking about the morphogenesis of atherosclerotic lesions.

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