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Distribution and Cross-Sectional Age-Related Increases of Carotid Artery Intima-Media Thickness in Young Adults

The Bogalusa Heart Study

James H. Stein, MD; Pamela S. Douglas, MD; Sathanur R. Srinivasan, PhD; M. Gene Bond, PhD; Rong Tang, MD, MS; Shengxu Li, MD, PhD; Wei Chen, MD, PhD; Gerald S. Berenson, MD

Background and Purpose
Reference values and age-related changes of carotid intima-media thickness (CIMT) have not been described in a community-based sample of young asymptomatic adults. CIMT measurements from the Bogalusa Heart Study, a study of the natural history of atherosclerosis in young adults and children, were used to characterize age-, race-, and sex-specific CIMT distributions and yearly rates of change.

Methods
Age-, sex-, and race-specific CIMT percentile values and cross-sectional changes with age were estimated using B-mode carotid ultrasound images from 519 young adults (mean age 32 years, 61% female, 29% black). Nomograms of CIMT percentiles between the ages of 25 and 40 years are provided in 5-year increments.

Results
CIMT was thickest in the carotid bulb and increased linearly with age, most rapidly in the bulb. With age, composite CIMT increased most slowly in white females and most rapidly in white males. Sample size estimates projected that 268 to 462 subjects are needed to detect CIMT changes ≥0.010 mm/year.

Conclusions
These estimated CIMT distributions and percentiles can serve as reference values for assessment of subclinical atherosclerosis in young adults. The observed age-related differences in CIMT can be used to plan epidemiological and clinical trials investigating atherosclerosis and anti-atherosclerotic interventions. (Stroke. 2004;35:2782-2787.)

Key Words: aging ■ atherosclerosis ■ cardiovascular diseases ■ carotid arteries

Ultrasound measurement of carotid intima-media thickness (CIMT) provides a direct, noninvasive assessment of subclinical atherosclerosis. CIMT is associated with prevalent and incident cardiovascular disease and provides incremental predictive information for traditional risk assessment. As a research and clinical tool, CIMT measurements are used to evaluate cardiovascular risk and to assess the effects of interventions on the degree of subclinical atherosclerosis. Nomograms for CIMT values and age-related changes have been reported for middle-aged (45 to 64 years) and older adults (65 years or older); however, these values have not been described in detail in a large, community-based sample of asymptomatic young adults. The purpose of this study was to characterize age-, race-, and sex-specific CIMT distributions and yearly rates of change in young adults.

Materials and Methods

Subjects and Study Design
The institutional review board at Tulane University Health Sciences Center approved this study. All participants provided informed consent. The Bogalusa Heart Study is a longitudinal epidemiological study of the natural history of early atherosclerosis in children and young adults from Bogalusa, Louisiana. Detailed descriptions of study methods have been described previously. In brief, a subgroup of 519 subjects who were 20 to 38 years old (mean [standard deviation] 32 [3] years, 29% black, 39% men) underwent B-mode ultrasonography of the carotid arteries during the 1995 to 1996 survey (Table 1). Subjects in the ultrasound subset were randomly selected from age-, race-, and sex-specific groups. They were similar to the total population (n=1420) in regard to race (P=0.92), sex (P=0.72), body mass index (P=0.92), systolic blood pressure (P=0.20), and lipid values, but on average were 4 years younger (P<0.001). One subject (a white male) had experienced a myocardial infarction that was identified at the time of this survey.

Study Procedures
Study-related protocols have been described previously. Images of the right and left common carotid (CCA), carotid bulb, and internal carotid (ICA) arterial segments were acquired using a Toshiba Sonolayer SS1 160A (Toshiba Medical) ultrasound system and a 7.5-MHz linear array transducer. Carotid arterial segments were imaged and measured following previously described protocols developed for the Atherosclerosis Risk in Communities studies (ARIC). A single certified reader conducted measurements using a semi-automated program. Fifty-four subjects underwent repeat
CIMT examination within 10 to 12 days to determine repeatability. The mean absolute value of the difference of repeated measures was 0.06 [0.05] mm (median 0.04) for the mean CIMT of all 6 segments. There was a mean difference of <0.01 mm between replicate scans, indicating an absence of bias in repeat measurements.

Data Analysis
Analyses were performed using the SAS software package (SAS Systems). CIMT distributions for white males, white females, black males, and black females were described by means (standard deviations) and compared using the general linear model, after adjustments for height and weight. For each segment, the average of the right- and left-sided far wall measurements was used to define segmental CIMT. Composite CIMT was defined as the average of the segmental CIMT measurements. Missing data were handled conservatively by list-wise deletion, such that both right- and left-sided measurements were required to determine CCA, bulb, and ICA values.

Race- and sex-specific distributions of CIMT values for each segment were estimated using ordinary least-squares (OLS) regression for the 5th, 10th, 25th, 75th, 90th, and 95th percentiles across subject aged 25 to 40 years in 5-year increments. Age-specific percentiles were obtained using Ave Xp(n+1), which gives the common value of the median. The 100th percentile was computed as Zp=(1-g)X[k1]+gX[k2], where k1 equals the integer part of p(n+1), k2=k1+1, g is the fractional part of p(n+1), and X[k] is the kth observation when the data are sorted from lowest to highest. Linear and nonlinear (quadratic, CIMT2, . . . K patient ages per race and sex, with y being the known age-specific percentile, and y being the regression estimated percentile. Biases for all composite CIMT percentiles in each race–sex group were <1.4%, except for the 75th, 90th, and 95th percentiles in black males, for which biases were 2.6% to 5.3%. Biases for all CCA CIMT percentiles in each race–sex group were <0.9%. For bulb CIMT, biases in all race–sex groups were <1.2%, except for the 90th and 95th percentile in black males (biases <6.1%). In the ICA, all biases were <1.6%, except black males (biases 2.6 to 5.0%). Therefore, both assessments indicated little benefit for modeling percentile line curvature, so only linear percentiles are reported.

Yearly changes in CIMT were estimated from cross-sectional data using linear and nonlinear OLS regression models as a function of age. Age-related changes of CIMT were determined from the slope (B). Assuming that the residual values were normally distributed, tests of hypotheses about the rates of CIMT changes (determined from the slopes) were constructed. Specifically, an F-ratio was used to test the hypothesis that the yearly rate of CIMT change=0 versus the alternative hypothesis that the rate=B (B not 0). When the slope is zero, there is no linear relationship between CIMT and patient age. Because the values of each of the parameters α, β, σ2(y), N, σ2(x), and the slope (B) can be determined from the others, β error and, subsequently, power (1-β) were derived.10

Results

CIMT Distributions
CIMT in the bulb (0.861 [0.180] mm) was greater than in the CCA (0.665 [0.089] mm, padj=0.001) and ICA (0.683 [0.136] mm, padj<0.001). CIMT in the CCA was greater than the ICA (padj=0.017).

CIMT values are presented in Table 2. In general, CIMT values in white females were lower than in white males, black males, and black females. CCA CIMT in white males was less than in black males (P=0.034). Estimates of segmental and composite CIMT and percentiles by age, sex, and race are presented in Table 3. Composite CIMT values are displayed graphically in Figure 1. In general, linear increases in composite CIMT were seen with aging; however, negative slopes in the 5th, 10th, and 25th percentiles for black males were seen because of small numbers. In general, linear increases in segmental CIMT also were seen with aging; however, negative slopes in the 5th and 10th percentiles for the bulb and at the 5th, 75th, 90th, and 95th percentiles for the ICA (data not shown). Other negative slopes for segmental CIMT were seen in white males at the 25th percentile for ICA, for white females at the 90th and 95th percentiles for ICA, and for black females at the 5th percentile for bulb and ICA (data not shown).

Age-Related CIMT Changes
Cross-sectional age-related differences in CIMT are presented in Table 4. Significant age-related differences in CIMT between males and females were not observed; however,
among males the yearly change in the CCA was faster in white than black subjects \( (P=0.030) \). Among females, significant differences were not seen between races. Significant differences between black and white subjects were not observed; however, among white subjects the yearly difference in composite CIMT tended to be greater among males than females \( (P=0.082) \). Among black subjects, differences were not seen between sexes.

Cross-sectional age-related differences in CIMT were greater in the CCA than the ICA for white females \( (P=0.047) \). With age, yearly CIMT changes tended to be greater in the bulb than in the ICA for white males \( (P=0.010) \), white females \( (P=0.089) \), and black males \( (P=0.090) \). Age-related CIMT changes in the bulb were greater than in the ICA for white males \( (P=0.045) \) and white females \( (P=0.005) \). Between sex–race combinations, composite CIMT age-related changes were smaller in white females than black males \( (P=0.043) \), and tended to be greater in white males than white females \( (P=0.082) \) and black females \( (P=0.073) \). White males had greater estimated CIMT changes in the CCA than black males \( (P=0.030) \) and tended to have greater changes in the CCA than black females \( (P=0.070) \). White females had greater estimated CIMT changes in the CCA \( (P<0.002) \) than black males.

### Power Analyses

Power curves to detect composite CIMT changes of 0.010 mm/year (80% power) are in Figure 2. Sample size estimates to detect this difference in composite CIMT ranged from 268 white female to 462 white male subjects. In the CCA, sample size estimates ranged from 220 white female to 292 black female subjects (data not shown).

### Discussion

To our knowledge, this is the first detailed description of CIMT distributions and cross-sectional age-related CIMT changes in a large group of young adults. In young adults, as in middle-aged adults, CIMT in the bulb was greater than in the CCA and ICA. \(^5\) CIMT in the CCA also was greater than in the ICA, although less ICA segments were visualized and variability was greater. In general, white females had the thinnest CIMT. Composite CIMT increased with aging in all segments except in the lowest quartile of black males, a relatively small number of subjects.

Cross-sectional age-related changes in CIMT were not significantly different between sexes and races; however, comparison of group combinations of sex and race demonstrated some important differences. With age, composite CIMT increased most slowly in white females and most rapidly in white males. Bulb CIMT increased faster than CCA and ICA CIMT, and in white females age-related increases in CCA were greater than ICA CIMT. Compared with the middle-aged subjects, aging-related cross-sectional rates of CIMT change were quite similar, with differences in mean segmental CIMT change rate estimates that were \( <0.0033 \) mm/year for white males (except ICA), white females (except ICA), black males (except CCA), and black females. \(^5\) Mean differences of \( \geq 0.010 \) mm/year were observed for white male ICA and black male CCA estimates. The sample size estimates provided in this data set represent reasonable targets for recruitment into epidemiological and clinical trials investigating atherosclerosis and interventions.

### Limitations

Although this study was one of the largest cross-sectional studies of CIMT in young adults to date, the number of subjects was relatively small given the number of age–race–sex combinations analyzed. The relatively small number of black males and the relatively increased number of ICA segments that were not visualized or measurable led to small cell sizes in certain race–sex–segment percentiles, which may have been sensitive to outlier values. This was manifested by increased variability at extreme percentiles of some segments and some of the negative slopes for CIMT distribution percentiles. The relatively low number of black male and females subjects led to nearly identical regression lines for the 5th and 10th percentiles and 90th and 95th percentiles for composite CIMT in both groups.

<table>
<thead>
<tr>
<th>TABLE 2. CIMT Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
</tr>
<tr>
<td>CCA, no.</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Bulb, no.</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>ICA, no.</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Composite, no.</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
</tbody>
</table>

* \( P<0.034 \) vs black males.  
† \( P<0.001 \) vs black males, black females.  
‡ \( P=0.055 \) vs white males.  
§ \( P<0.008 \) vs white males, black females.  
¶ \( P=0.011 \) vs black males.  
\( P=0.029 \) vs white males.  
** \( P=0.005 \) vs white males, black males, black females.  
SD indicates standard deviation.
In young adults, CIMT was thickest in the carotid bulb, where it increased linearly and most rapidly. Estimates of CIMT and increased variability; however, the biases in the models and composite CIMT values may have decreased cell sizes and increased variability; however, the biases in the models remained small. Although only far-wall CIMT was measured, far-wall CIMT predicts prevalent and incident cardiovascular disease.2,3 Because this study was cross-sectional, the accuracy of the predicted age-related changes in CIMT need to be validated longitudinally. Also, because of the very small number of cardiovascular events in the Bogalusa Heart Study, the ability of CIMT values to predict events is not yet known.

Conclusions
In young adults, CIMT was thickest in the carotid bulb, where it increased linearly and most rapidly. Estimates of CIMT
percentiles and age-related changes in CIMT for black males were limited by small numbers, emphasizing the importance of longitudinal studies. These estimated CIMT distributions and percentiles can serve as reference values for assessing subclinical atherosclerosis in young adults. The observed age-related differences in CIMT can be used to plan epidemiological and clinical trials investigating atherosclerosis and interventions.

**Acknowledgments**

The authors express appreciation to the subjects in this study, whose participation made these observations possible. This study was funded in part by the National Center for Research Resources (RR-1617601), the National Heart, Lung, and Blood Institute (HL-38844), the National Institute on Aging (AG-16592), the National Institute of Child Health and Human Development (HD-043820), and the American Heart Association (0160261B).

**TABLE 4. Estimated Age-Related CIMT Changes (mm/year)**

<table>
<thead>
<tr>
<th>Site</th>
<th>White Males</th>
<th>White Females</th>
<th>Black Males</th>
<th>Black Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid</td>
<td>0.0094*‡</td>
<td>0.0055§</td>
<td>−0.0010</td>
<td>0.0062</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0043–0.0145</td>
<td>0.0022–0.0088</td>
<td>−0.0069–0.0067</td>
<td>−0.0003–0.0128</td>
</tr>
<tr>
<td>Carotid bulb</td>
<td>0.0204</td>
<td>0.0113</td>
<td>0.0145</td>
<td>0.0119</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0075–0.0334</td>
<td>0.0053–0.0173</td>
<td>−0.0024–0.0314</td>
<td>−0.0008–0.0246</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>0.0045</td>
<td>−0.0015</td>
<td>0.0067</td>
<td>0.0055</td>
</tr>
<tr>
<td>95% CI</td>
<td>−0.0041–0.0131</td>
<td>−0.0081–0.0050</td>
<td>−0.0037–0.0171</td>
<td>−0.0035–0.0146</td>
</tr>
<tr>
<td>Composite</td>
<td>0.0116†‡</td>
<td>0.0045*</td>
<td>0.0060</td>
<td>0.0081</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0040–0.0191</td>
<td>0.0003–0.0087</td>
<td>−0.0047–0.0166</td>
<td>0.0009–0.0154</td>
</tr>
</tbody>
</table>

*P<0.050 vs black males.
†P<0.090 vs white females.
‡P<0.080 vs black males.
§P<0.002 vs black females.
CI indicates confidence interval.
References


In the December issue of *Stroke*, the article entitled, “Distribution and Cross-Sectional Age-Related Increases of Carotid Artery Intima-Media Thickness in Young Adults: The Bogalusa Heart Study” by Stein et al. included incorrect age values in Table 1. The corrected values are in the table below. The author regrets the error.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>White Males</th>
<th>White Females</th>
<th>Black Males</th>
<th>Black Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32 (3)</td>
<td>32 (3)</td>
<td>33 (3)</td>
<td>32 (3)</td>
</tr>
</tbody>
</table>

*All values mean (standard deviation).*