Ultrasound in Med. & Biol., Vol. 36, No. 4, pp. 560–565, 2010

0301-5629/10/$–see front matter

ELSEVIER

doi:10.1016/j.ultrasmedbio.2010.01.002

● *Original Contribution*

# MEASUREMENT OF AORTIC INTIMAL-MEDIAL THICKNESS IN ADOLESCENTS AND YOUNG ADULTS

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(*Received* 6 *May* 2009; *revised* 21 *December* 2009; *in final form* 13 *January* 2010)

**Abstract—Atherosclerosis begins in childhood in the distal abdominal aorta and later involves the carotid arteries. Noninvasive screening to detect these lesions may allow early intervention. Ultrasound images of the distal 10 mm of the aorta were obtained after an 8-h fast and were analyzed by an automated program to determine the mean far wall intimal-medial thickness (IMT). The results were compared with the mean carotid IMT obtained concurrently. The mean age of the 313 males and 322 females imaged was 20.4 years (SD 5.6) and 61 participants had a second study to assess reproducibility. The mean aortic IMT was 0.63 mm (SD 0.14) for males and 0.61 mm (SD 0.13) for females while the mean carotid IMT was 0.50 (SD 0.04) mm and 0.49 (SD 0.04) mm, respectively. Images were analyzed in 95% of participants. Intra-subject reproducibility for the mean aortic IMT had a coefficient of variation of 18% with a mean absolute difference of 0.12 mm (SD 0.10). For carotid IMT, the results were 3% and 0.02 mm (SD 0.01), respectively. Aortic IMT can be measured in normal adolescents and young adults with low rates of missing data and reasonable reproducibility. Aortic IMT increased with age at a greater rate than carotid IMT. (E-mail: pat-davis@uiowa.edu)  © 2010 World Federation for Ultrasound in Medicine & Biology.**

*Key Words:* **Carotid arteries, Aorta, Ultrasound, Atherosclerosis.**

## INTRODUCTION

Recent attention has focused on preventive measures for atherosclerosis beginning during childhood to reduce the risk of heart disease, stroke and peripheral vascular disease later in life (McGill Jr. et al. 2008; Daniels et al. 2008). Data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study demonstrated that 20% of 15- to 19-year-olds have raised fatty streaks in the abdominal aorta on autopsy and the presence of these lesions is related to cardiovascular risk factors (CRF) (McGill Jr. et al. 2000). The earliest lesions affect the dorsolateral aorta just before the bifurcation into the iliac arteries (McGill Jr. et al. 2000). Involvement of the coronary and carotid arteries occurs later in life (McGill Jr. et al. 2000; Guzman et al. 1968). Ultrasound studies using measurement of intimal-medial thickness (IMT) have been used to detect the atherosclerotic process before the development of vessel stenosis. Most studies have been performed on the carotid arteries since they are close to the surface, can be reliably imaged and may correlate with changes in the coronary arteries which are not accessible to noninvasive ultrasound studies although the amount of correlation has varied across studies (Bauer et al. 2009, Davis et al. 1999). In older adults, carotid IMT (cIMT) is predictive of subsequent cardiovascular events (Lorenz et al. 2007). However, the association of CRF in normal adolescents with cIMT is less well-established (Jourdan et al. 2005; Sass et al. 1998). If prevention is to begin early in life, it would be useful to have a noninvasive method to detect premature atherosclerosis so that interventions could be targeted at those at the highest risk (Slyper 2004). Our objective was to determine if we can reliably measure IMT in the distal abdominal aorta (aIMT) in a cohort of healthy adolescents and young adults living in Muscatine, Iowa, and compare the results with concurrently obtained cIMT.

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## METHODS

The members of the cohort were the offspring of the Muscatine Study Longitudinal Adult Cohort who had previously participated in studies relating childhood risk factors to adult cIMT performed between 1996 and 2001 (Davis et al. 2001). We invited offspring of ages 11 years or older to participate, with priority given to participants in the age range of 11 to 20 years. We have data on 635 of these offspring. A random sample of 61 out of 635 participants returned for a second visit within 3.5 months (mean of 38 days) to enable us to examine reproducibility. This study was approved by the Institutional Review Board of the University of Iowa and all participants signed informed consent forms. All participants responded to a health questionnaire and had an anthropometric evaluation.

A Biosound Technos/MPX ultrasound system (Indianapolis, IN, USA) along with a linear and a convex array transducer with multi frequency ranges was used to obtain the images. For aIMT, the depth of the aorta determined the type and frequency of the transducer that was used to obtain the images. If the aorta was visualized at 4, 5 or 6 cm, the linear array transducer was used with a frequency of 5.5 MHz. If the aorta was visualized at 7, 8 or 9 cm, the convex array transducer was used, with a desired frequency of 4.0 or 3.5 MHz. If the location of the aorta was more that 9 cm deep, no IMT images were obtained. For obtaining cIMT, the linear transducer was used with a target frequency of 8.0 MHz (range 5.0–10.0 MHz), regardless of the depth of visualization.

Fasting for 8 h before the examination was necessary to facilitate sufficient visualization of the aorta. The quality of images was optimal if the study was done within 2 h after awakening because there was less abdominal gas. The abdominal aorta was first identified in the upper abdomen and scanning continued distally to the aortic bifurcation, where the transducer was turned to the longitudinal view, to locate the distal 10 mm of the abdominal aorta just above the aortic bifurcation (flow divider). Two images of the far wall IMT were optimized and saved. A loop of approximately 20 sequential frames was also saved. After capturing the individual images and the loop of sequential frames, the data were electronically transferred to a central database and then read by a single technician using a computerized reading program. The mean time to complete imaging of the abdominal aorta was approximately 12 min.

To measure the extent and severity of atherosclerosis in the carotid arteries, we imaged left and right carotid arteries at 12 locations positioned at the near and far wall of three arterial segments on each side. The near and far wall of the proximal 10 mm of the internal carotid artery, the near and far wall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal and the near and far wall of the arterial segment extending 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery were successively imaged using the same ultrasound machine and the same probes as described above. Specified interrogation angles of 180, 135 and 90 degrees on the right side and 180, 225 and 270 degrees on the left side were maintained for 5 s using a Plexiglas neck collar to accurately measure the angle (Stein et al. 2008). All of these images were electronically transferred to a central database in DICOM format and then read by a single reader using a computerized reading program. The mean time to complete carotid imaging was approximately 20 min.

### *Measuring IMT values*

Aortic and carotid wall borders were identified from ultrasound B-mode image data using globally optimal graph search border detection approach within the Carotid Analyzer 5 software package (Medical Imaging Applications, LLC, Coralville, IA, USA) (Mancini et al. 2004). Two sets of borders were identified. First, the media-adventitia (or M-line) borders were determined and approved by the operator. If necessary, their locations could be semiautomatically modified by mouse-clicking to a desired location and instructing the software to redetect. Once M-line borders were approved, the lumen-intima boundaries (I-lines) were automatically detected using the M-lines for guidance (Fig. 1). Individual frames were used whenever the quality of the image was adequate to allow valid measurements. For the looped sequences of aIMT, the best quality images were selected for reading, which resulted in approximately 75% of the images being analyzed. On average, it required approximately 10 min to read an aortic study and 20 min to read a carotid study. We assessed intra-reader reliability by the reader analyzing the same 20 aortic studies on two separate occasions.

### *Statistical methods*

Descriptive statistics were calculated for aortic and carotid IMT values. Mixed effects regression analysis was used to quantify how age was related to aIMT and cIMT, and how aIMT and cIMT related to each other, accommodating within-family clustering. The correlations that come from this mixed effects model are scaled and interpreted in the same manner as the Pearson correlation (Lipsitz et al. 2001).

The age effect was also examined by categorizing age into five groups (11–14 years, 15–17 years, 18–21 years, 22–25 years and 26–34 years) and then using simultaneous quantile regression models with bootstrapped error (Gould 1997). Exact logistic regression analysis

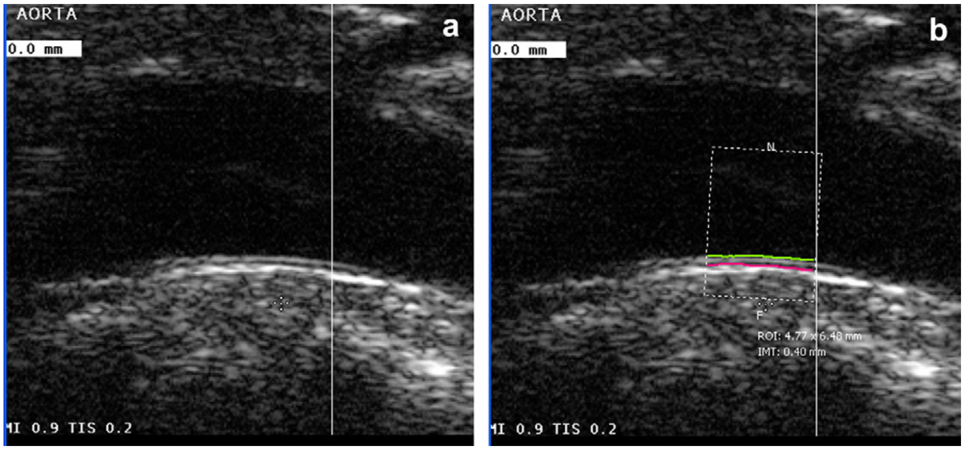


Fig. 1. (a) The left panel shows the distal abdominal aorta of an 11-year-old child with the bifurcation into the iliac artery marked by the vertical line. The far wall of the aorta is well-visualized. (b) In the right panel, the media-adventitia and lumen-intima borders in the same image is detected using the Carotid Analyzer 5 software package (Medical Imaging Applications LLC, Coralville, IA, USA) and are shown in red and green, respectively. The program displays the mean intimal-medial thickness of 0.40 mm.

was used to determine whether age and/or body size were related to the ability to obtain aIMT values.

For the reproducibility data, the mean and standard deviation of the absolute value of the differences between the measures from the first and second visit were calculated. Linear regression analysis was used to see if these differences were affected by age and/or body size.

Coefficients of variation (CV) were calculated using the log transformation method (Bland and Altman 1996), specifically,

$$CV = \exp\sqrt{\left(\frac{\sum_{i=1}^{n}[\log(Y_{1i}) - \log(Y_{2i})]^2}{2n}\right)} - 1,$$

where $i$ indexes the $n$ subjects with two visits. This method of estimating the underlying coefficient of variation is preferable to using the average of subject-level coefficients of variation, as that method is known to underestimate the true parameter (Chow and Tse 1990).

## RESULTS

Data were obtained from 313 males and 322 females. The average (SD) age was 20.4 (5.6), with a range from 11 to 35 years, and with 228 participants (36%) less than 18 years of age. Nearly all of the participants (98.5%) were Caucasian, corresponding to the racial composition of the Muscatine Cohort. Means (SDs) for aIMT were 0.63 (0.14) mm and 0.61 (0.13) mm for males and females, respectively. For cIMT, the mean (SD) was 0.50 (0.04) mm for males and 0.49 (0.04) mm for females. The unadjusted correlation of aIMT with cIMT was 0.35 while the correlation was 0.16 after adjusting for age. Both carotid and aIMT increased with age (Figs. 2 and 3). Using these cross-sectional data and a linear regression model, the mean increase in aIMT with age was 0.10 mm/decade compared with 0.04 mm/decade for cIMT. This steeper age effect for aIMT compared with cIMT can also be seen in Figure 4, which displays the estimated age-group-specific 10th, 25th, 50th, 75th and 90$^{th}$ percentiles of aIMT and cIMT for males. The patterns for females (not shown) were very similar, but shifted slightly lower.

Of the 635 offspring, 606 (95.4%) had ultrasound images adequate to measure aIMT. For the remaining 29 participants (4.6%), aortic images were not acquired and measured, generally because the sonographer deemed them of insufficient quality. This rate of missing aortic data varied according to age, with 5.2% missing in those at least 18 years of age and 3.5% missing in those under 18 years ($p$ = 0.044 for trend test). Missing data also

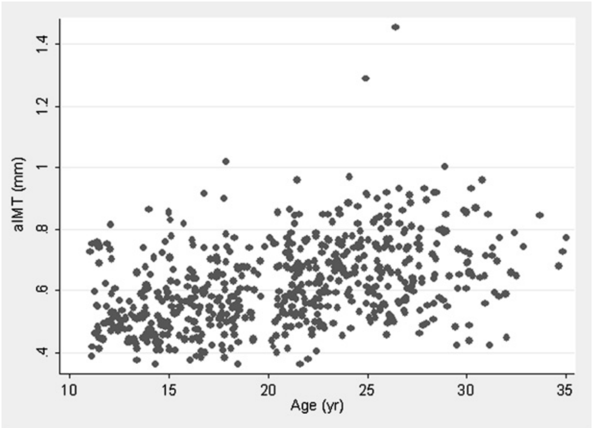


Fig. 2. Scatterplot showing age trend of aortic intimal-medial thickness (aIMT) (both genders). Note the residual variability and the slight positive skewness of the aIMT values.

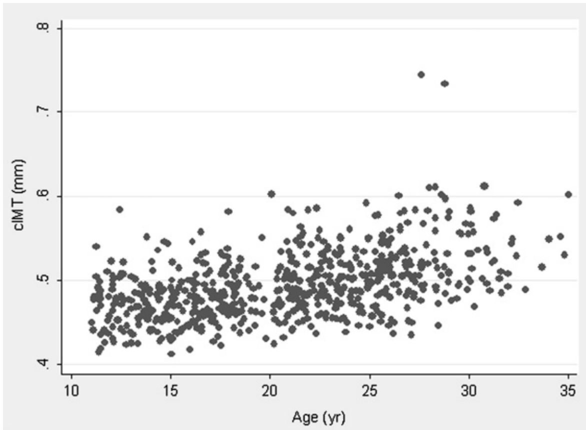


Fig. 3. Scatterplot showing age trend of carotid intimal-medial thickness (cIMT) (both genders). Note the residual variability and the slight positive skewness of the cIMT values.

varied with body mass index (BMI) in adolescents as well as young adults (Table 1). In exact logistic regression models with age and BMI as simultaneous predictors, only BMI was a significant predictor of missing aIMT. Looped sequence data were obtained for 550 (86.6%) of the participants, with an average of 14 analyzed frames per loop. As in the case of missing individual-frame aortic data, loops were not acquired when the sequences were deemed of insufficient quality. Carotid IMT was measurable in all participants, with 95.3% of participants having at least 10 walls measurable (average of 11.5 walls per participant).

Intra-reader as well as the intra-subject reliability was assessed for aIMT. The intra-reader correlation was 0.78 with a mean absolute difference of 0.027 mm. For the intra-subject reliability, 58 of 61 participants provided aortic images at both visits, with 47 of those providing aortic loops where more than two frames could be measured. Among those 47, the mean absolute difference for two aortic images was 0.12 mm (SD 0.11), with a coefficient of variation (CV) of 18%. Reliability seemed to be better in those younger than 18 years vs. those 18 and older, both in terms of mean absolute difference (0.065 mm (SD 0.058 mm) vs. 0.154 mm (SD 0.117 mm), $p = 0.004$) and CV (12% vs. 21%, $p = 0.005$). See Table 2 for more details. The reliability of these two images was then compared with a single digital image and a loop of approximately 14 images. In the older age group, these three methods had fairly similar mean absolute differences and CVs, while in the younger age group, there was a slight gain in reliability using the loop of images. Note that the reliability of these aIMT measures is lower than that of cIMT.

## DISCUSSION

In this study, we have shown that both aIMT and cIMT can be reproducibly measured in adolescents and young adults with low rates of missing data. Measurement of abdominal aIMT has previously been reported in studies of neonates with a between-subject coefficient of variation of 4% and a mean aIMT in term babies of 0.385 mm (SD

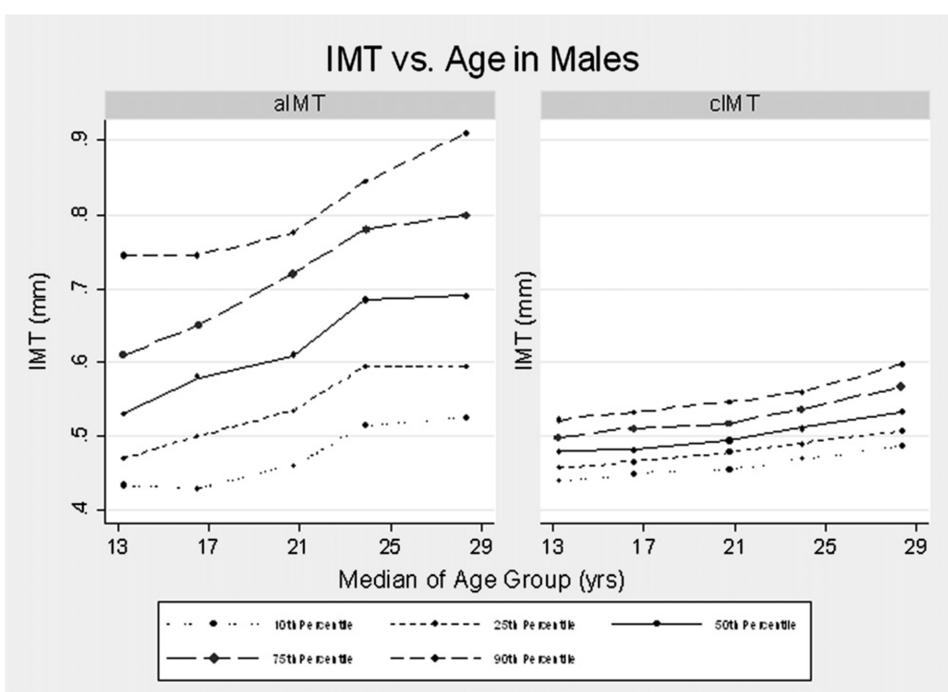


Fig. 4. The percentiles of aortic intimal-medial thickness (aIMT) and carotid intimal-medial thickness (cIMT) according to age in males. Female trends were similar but slightly lower (0.03 mm less for aIMT and 0.02 less for cIMT).

Table 1. Percent of participants missing aortic intimal-medial thickness, as a function of age and body mass index (BMI)

| | | | |
|---|---|---|---|
| Age < 18 years | BMI < 85th percentile* (*n*)<br>0% (151) | BMI ≥ 85th but <95th percentile (*n*)<br>3.0% (33) | BMI ≥ 95th percentile (*n*)<br>15.9% (44) |
| Age ≥ 18 years | BMI < 25 (*n*)<br>1.6% (187) | BMI ≥ 25 but <30 (*n*)<br>2.5% (121) | BMI ≥ 30 (*n*)<br>15.2% (99) |

* Based on the BMI for age 2000 growth charts from the Centers for Disease Control and Prevention (Kuczmarski et al. 2002).

0.019) to 0.534 mm (SD 0.058) (Gunes et al. 2007; Koklu et al. 2007; Skilton et al. 2005). A case-control study of children with a mean age of 11 years demonstrated a between-subject mean absolute difference of 0.041 mm with a CV of 5% (Jarvisalo et al. 2001). The mean aIMT in the control group was 0.46 mm (SD 0.05) (Jarvisalo et al. 2001). The mean aIMT among 50 middle-aged adults was 0.63 mm (SD 0.14) with a CV of 11% (Astrand et al. 2003). In the current study, the mean aIMT was 0.63 (SD 0.14) mm and 0.61 (SD 0.13) mm for males and females, respectively, with a CV of 18% and a mean absolute difference of 0.12 mm (SD 0.11). This compared with a CV of 3% for cIMT and absolute mean difference of 0.03 (SD 0.02). There are several reasons why aIMT measurements may be less reproducible than cIMT. The cIMT was an average of 36 measurements at 12 sites and the measurement was made at different angles at each site. The measurement of aIMT was made at one site and the angle was not standardized so that reproducibility could have been affected if the wall thickness was asymmetric. The ultrasound image may also be sharper in carotids vs. aortas due to less tissue between the probe and the arteries, with this difference being more pronounced with increased age. Measurement of aIMT was not made only in end-diastole as was done in other studies (Jarvisalo et al. 2001). It seems unlikely that the absence of cardiac gating explains the observed variability since the CV did not improve significantly when we analyzed multi-frame aortic loops. However, we did find an improvement in reproducibility in those less than 18 years of age when we used a loop. The contribution of intra-reader variability appears to be small in this study as has been previously shown for cIMT (Espeland et al. 1996). The reproducibility for cIMT in the current study is superior to the recommended intrasonographer variability (SD of the mean absolute difference) of less than 0.04 mm for children and 0.2 mm for adults (de Groot et al. 2008). To our knowledge, the current study is the largest study of measurement of aIMT reproducibility and the cohort was selected from the general population, rather than from high-risk populations as in prior studies (Astrand et al. 2003; Jarvisalo et al. 2001). The amount of missing data in this study was low at 5%. In a study of 54 middle-aged adults, four could not be imaged (7%) (Astrand et al. 2003). We found that there was more missing data in older participants, which was primarily associated with increased body size. Even though the amount of missing data was greater with increasing BMI, we were still able to obtain images in 86% of obese adults and 84% of overweight adolescents. (Table 2)

The procedure was well-tolerated by adolescents with a high rate of participation. The study could be performed and analyzed more rapidly than cIMT. A disadvantage to measuring aIMT is that the participant must be fasting and the study is optimal if it is done within 2 h of awakening.

A case-control study of high-risk children with familial hyperlipidemia or diabetes found that aIMT showed a greater increase than cIMT in high-risk children (Jarvisalo et al. 2001). Another study found an association with aIMT but not cIMT in children with seropositivity to *C pneumoniae* (Volanen et al. 2006). We have previously shown that both aortic and carotid IMT are related to CRF in adolescents but aortic IMT provides additional information to that obtained from carotid IMT alone (Dawson et al. 2009). Our cross-sectional results predict that the thickness of aIMT increases at a greater rate with age than cIMT among adolescents. It remains to be demonstrated whether progression of aIMT can be reliably detected in adolescents and young adults to assess the effects of interventions to slow the atherosclerotic process. It would also require a longitudinal study to determine the optimal length of time required between measurements to accurately detect progression of aIMT.

Table 2. Reproducibility of aortic and carotid intimal-medial thickness measurements

| | Mean (SD) absolute difference (mm) | | Coefficient of variation (%) | |
|---|---|---|---|---|
| Site (average number of analyzed images) | Age < 18 yrs (*n* = 19) | Age ≥ 18 yrs (*n* = 28) | Age < 18 yrs (*n* = 19) | Age ≥ 18 yrs (*n* = 28) |
| Aortic (1) | 0.071 (0.060) | 0.156 (0.110) | 12.1 | 20.8 |
| Aortic (2) | 0.065 (0.058) | 0.154 (0.117) | 12.1 | 20.8 |
| Aortic loop (14) | 0.053 (0.042) | 0.150 (0.130) | 9.0 | 21.6 |
| Carotid (36) | 0.011 (0.011) | 0.015 (0.014) | 2.3 | 2.8 |

The current study demonstrates that aIMT can be measured with greater reproducibility and less missing data in younger than older participants, which is the group where this evaluation is likely to be the most useful. In evaluating individuals 18 years or older, cIMT may be the preferred method of imaging subclinical atherosclerosis.

In summary, we have demonstrated that it is feasible to measure aIMT in a large cohort of adolescents and young adults selected from the general population with acceptable reproducibility and a low rate of missing data. The short time required for data acquisition and analysis would allow this test to be practical as a screening tool. In those less than 18 years of age, the test has the best reproducibility and a low rate of missing data and this is the age group in which a noninvasive test to screen for premature atherosclerosis would be the most useful (Daniels et al. 2008).

*Acknowledgements*—This work was supported by NIH Award HL54730. The authors would like to thank the entire Muscatine Study research team for their contributions towards this study. The authors are especially indebted to the Muscatine Study participants. All authors received salary offset support from the above-listed NIH Award. Dr. Milan Sonka has financial interest in the Carotid Analyzer 5 software (co-founder of Medical Imaging Applications, LLC, Coralville, IA, USA).

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