Carotid Artery Intima-Media Thickness Measurements in the Youth: Reproducibility and Technical Considerations

Elif Seda Selamet Tierney, MD, Kimberlee Gauvreau, ScD, Michael R. Jaff, DO, Dana Gal, BA, Susan E. Nourse, BS, Shari Trevey, RDCS, Stephen O'Neill, JD, RDCS, Annette Baker, MSN, PNP, Jane W. Newburger, MD, MPH, and Steven D. Colan, MD, *Boston, Massachusetts; and Palo Alto, California*

Background: Carotid artery intima-media thickness (CIMT), a marker of atherosclerosis, is increased in youth at risk for future cardiovascular disease. Some pediatric studies have used CIMT as a primary outcome in clinical trials, yet data are limited on the standardization of methodology in children. The goal of this study was to evaluate reproducibility of CIMT measurements using two different measurement techniques.

Methods: Carotid artery ultrasound studies of children and adolescents obtained as a component of a research study in Kawasaki syndrome were retrospectively analyzed. The CIMTs of both common carotid arteries (CCAs) were measured by one of two sonographers at the time in the cardiac cycle when resolution subjectively was determined to be optimal (Opt-CIMT). These sonographers blindly remeasured a random sample of studies of their own and each other's, using the same method. Another observer made CIMT measurements using exclusively frames on the R wave (R-CIMT). A fourth observer independently measured a random sample of studies twice with the R-CIMT method.

Results: Carotid artery images from 184 subjects (mean age, 14.7 ± 2.2 years) were analyzed. The intraclass correlation coefficient for interobserver variability was 0.86 (95% confidence interval [CI], 0.69–0.94) compared with 0.85 (95% CI, 0.65–0.93) for the right and 0.86 (95% CI, 0.67–0.94) versus 0.95 (95% CI, 0.87–0.98) for the left CCA for Opt-CIMT and R-CIMT, respectively. R-CIMT was significantly thicker than Opt-CIMT (right CCA, 0.439 ± 0.030 vs 0.428 ± 0.024 mm, $P < .001$; left CCA, 0.446 ± 0.030 vs 0.434 ± 0.025 mm, $P < .001$).

Conclusion: Pediatric CIMT measurements have excellent reproducibility when the same methodology is applied but vary significantly throughout the cardiac cycle. This report highlights the need to standardize CIMT measurements in the youth and supports the use of electrocardiographic timing, as recommended in adults, in pediatric longitudinal studies. (J Am Soc Echocardiogr 2014;■:■-■.)

Keywords: Carotid artery IMT, Youth, Reproducibility, Variability, Carotid artery ultrasound, Atherosclerosis

Carotid artery intima-media thickness (CIMT) has been used as a noninvasive modality to evaluate the presence of atherosclerosis since the early 1990s. In adults, increased CIMT is associated with coronary artery disease and is predictive of future cardiovascular events, including stroke and myocardial infarction.[1,2] CIMT is robust and reproducible in the evaluation of changes over time to serve as an end point in clinical trials assessing the impact of antihypertensive and lipid-lowering medications on cardiovascular risk in adults.[3-5] To evaluate early, subclinical disease, assessment of CIMT also has been used in children and young adults with known risk factors for cardiovascular disease, including hypercholesterolemia, hypertension, obesity, and type 1 diabetes mellitus.[6-16] Some pediatric clinical trials have also used CIMT as a primary outcome measure.[17,18] Despite the clear value of this tool in the assessment of cardiovascular risk in high-risk children and adolescents, its application has been restricted by a number of factors, including variable protocols for data acquisition and analysis and limited data on reproducibility. Different methods used for research purposes limit the ability to make comparisons and generalizations of reported findings. Furthermore, the magnitude of the difference in CIMT during the cardiac cycle can affect risk stratification in asymptomatic individuals because of a mismatch between acquisition protocol and CIMT normative data, as shown in a recent adult study.[19,20] Another important aspect in the pediatric population is image resolution,

From the Department of Cardiology, Children's Hospital Boston, Boston, Massachusetts (E.S.S.T., K.G., D.G., S.T., S.O., A.B., J.W.N., S.D.C.); the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts (E.S.S.T., K.G., D.G., S.T., S.O., A.B., J.W.N., S.D.C.); the Division of Pediatric Cardiology, Department of Pediatrics, Stanford University, Palo Alto, California (E.S.S.T., S.E.N.); and the Department of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (M.R.J.).

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Reprint requests: Elif Seda Selamet Tierney, MD, Stanford University, Pediatric Heart Center, 750 Welch Road, Suite 350, Mail Code 5731, Palo Alto, CA 94304 (E-mail: *tierneys@stanford.edu*).

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Abbreviations
CCA = Common carotid artery
CIMT = Carotid artery intima-media thickness
ICC = Intraclass correlation coefficient

because the CIMT values are lower overall.[21] More recent guidelines recommend measurement of CIMT on the R wave for standardization purposes.[22,23]

The aim of this study was to evaluate the reproducibility and the impact of the timing of measurement within the cardiac cycle on CIMT values in the pediatric population. Precise and reliable noninvasive testing for atherosclerosis in youth will improve the ability to examine cardiovascular risk.

METHODS

Subjects

The present study was a retrospective review of data gathered from a subgroup of children and young subjects (ages 11–29 years) who were enrolled in a prospective Kawasaki disease research study conducted between 2007 and 2011 at Boston Children's Hospital. Subjects either had history of Kawasaki disease or were healthy volunteers. All subjects underwent carotid artery ultrasound performed by one of the two sonographers trained for the study as part of the study protocol designed in 2006 and 2007.[24] Subjects were included in the present retrospective study if they were in the pediatric group (11–19 years of age) at the time of carotid artery ultrasound testing.

Clinical Variables

Height and weight; systolic, diastolic, and mean blood pressure; and fasting lipid profile, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, were also obtained as part of the study protocol.[24] Body mass index and body surface area were calculated. Blood pressure *Z* scores (Boston Children's Hospital normative database)[25] and body mass index *Z* scores (Centers for Disease Control and Prevention) were calculated.[26] This study was approved by the institutional review board of Boston Children's Hospital.

Carotid Artery Ultrasound and Measurements

A linear array probe (L11-3 MHz, iE33 Ultrasound System; Philips Medical Systems, Andover, MA) was used to obtain three 10-sec loops taken at the anterior, posterior, and lateral angles on the right and left common carotid arteries (CCAs). We did not use a Meijer's arc, which is a tool used to standardize angles of insonation for carotid ultrasound studies,[27] and therefore referred to these angles as anterior, posterior, and lateral angulations. However, these angles would corroborate to approximately 60°, 105°, and 150° for the right and 300°, 255°, and 210° for the left CCA on the arc. The images were stored as Digital Imaging and Communications in Medicine loops. The resolution was 1,024 × 768 pixels/cm. In general, gain and compress adjustments were made on default vascular settings (P mode, no harmonics) to optimize the images. The frame rate was kept at >50 frames/sec and persistence at low. The CIMT of the far wall of the CCA was measured online by one of the two sonographers (S.T. or S.O.) using a frame from each of the loops with anterior, posterior, and lateral angulations over the length of a 1 cm segment located at the distal aspect of the right and left CCA just proximal to the bifurcation into the internal and external carotid arteries, using commercially available, semiautomated edge detection software (QLAB; Philips Medical Systems).[28] The sonographer made the CIMT measurements on the frame in which he or she subjectively noted the resolution to be optimal, regardless of the timing within the cardiac cycle (Figure 1A). The measurements were accepted only if the edge detection software was able to automatically measure 95% of the 1-cm segment. As per original prospective study protocol, after 3 to 9 months of study acquisition and online measurements, the sonographers were blinded to their original CIMT measurements and frame choice for the measurements and asked to remeasure CIMT in a random subset of their original studies and the other sonographer's studies, offline, using the same "optimal resolution" method they had previously used (QLAB) for intra- and interobserver variability (Table 1).

The purpose of the present retrospective study was to evaluate the impact of standardizing the timing of measurement of CIMT within the cardiac cycle, and therefore a separate observer (D.G.) made offline CIMT measurements on the studies of the included subjects using the same software and images but exclusively using the frames coincident with the R wave on the electrocardiogram (Figure 1B.) This observer was blinded to the measurements originally taken by the sonographers. A fourth observer (E.S.S.T.) independently measured a random subset of the studies measured by D.G. offline, using the same method D.G. used, to determine interobserver variability. Six months later, the same observer (E.S.S.T.) remeasured a subset of the studies measured by E.S.S.T. offline, using the same method, for intraobserver variability (Table 1). The original sonographers were not asked to do offline R-wave measurements, so that no measurement bias was introduced in the ongoing prospective study.

Statistical Analysis

For both the right and left carotid arteries, up to three measurements of CIMT were averaged for the analysis. The intraclass correlation coefficient (ICC) was used as a measure of reproducibility, and ICCs are reported with 95% confidence intervals. Agreement was also estimated by percentage error measurement, defined as 100 times the absolute value of the difference in the two measurements divided by the mean of the two measurements. Bland-Altman plots were used for comparison and reproducibility of the "optimal resolution" and R-wave measurements; statistical significance was assessed with a paired *t* test. Pearson or Spearman correlation coefficients were used to explore the relationships of CIMT values, age, biometrics, blood pressure, and lipid profile with the CIMT value and percentage error, and an unpaired *t* test was used for the binary variables gender and case or control status. Differences in intraobserver variability among the observers were assessed by analysis of variance using the Welch modification for unequal variances, and the Games-Howell post-hoc test was used to evaluate the significance of differences between groups. A two-sided P value $< .05$ was used to indicate statistical significance. Analyses were performed with SPSS version 20 (SPSS, Inc, Chicago, IL).

RESULTS

Carotid artery ultrasound images of 184 children and adolescents (149 cases, 35 controls; mean age, 14.7 ± 2.2 years [range, 11.3–19.0 years]; 116 male [63%]) were included in the study (Tables 2 and 3). In 97.8%