

# Reproducibility of Carotid Intima-Media Thickness Measurements in Young Adults<sup>1</sup>

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## Purpose:

To prospectively compare the reproducibility of carotid intima-media thickness (CIMT) measurements obtained from the right and left carotid arteries in young adults by using ultrasonographic (US) images acquired at the maximum dimension, minimum dimension, and electrocardiographically (ECG)-triggered cardiac end diastole.

## Materials and Methods:

This study was HIPAA compliant and approved by the institutional review board; all participants provided informed consent. Medical history, anthropometric measurements, and blood pressure (BP) values were obtained from 50 men and 50 women aged 18–25 years. Images of the common carotid arteries were acquired from three independent complete cardiac cycles by using a 15L8-MHz US transducer. CIMT was measured on the images of each cycle that depicted the narrowest and widest vessel diameters, and at the R wave of the ECG. Measurements from the right and left carotid arteries were analyzed by using paired *t* tests; possible sex differences, by using unpaired *t* tests. Reproducibility was determined by using coefficients of variation and intraclass correlations (ICCs). Pearson correlations and multiple regression analyses were used to compare CIMT, body mass index (BMI), and BP.

## Results:

CIMT values were 7.2% and 7% greater in frames showing the narrowest lumen diameter and in R-wave ECG-triggered frames, respectively, than in those with the widest diameter. CIMT measurements were 2.2%–3.1% greater in the right carotid artery than in the left ( $P < .001$ ) and were significantly related to BMI ( $r = 0.40$ ,  $P < .001$ ) and systolic BP ( $r = 0.34$ ,  $P < .001$ ). ICCs were stronger when assessments were obtained in three different cardiac cycles (0.92–0.98), rather than in one (0.79–0.91).

## Conclusion:

In healthy young adults, reproducibility of CIMT measurements is greatest when combining values from both carotid arteries and/or from the maximal and minimal arterial diameters.

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The ability to detect subtle anatomic evidence of atherogenesis by using ultrasonography (US) has revolutionized the assessment of the risk of cardiovascular disease in adult populations. Measurements of carotid intima-media thickness (CIMT) have been strongly related to the presence of atherosclerotic lesions in the aorta and the coronary, cerebral, and peripheral arteries (1,2) and increased CIMT has been associated with myocardial infarction, stroke, and cardiovascular death (3–6). Increased CIMT is also associated with known cardiovascular risk factors in middle-aged and older adults (7–10) and in pediatric populations at risk for cardiovascular disease, such as children with hypertension, diabetes, morbid obesity, and familial hyperlipidemia (11–20). The capacity for CIMT measurements to help predict arterial disease noninvasively has justified their use as a surrogate outcome for risk of vascular events in intervention trials for lipid- (21,22) and blood pressure (BP)-reducing (23,24) therapies. The greater sensitivity of CIMT measurements for helping detect early atherosclerosis is an additional advantage over angiography for tracking the progression or regression of subclinical disease over time.

Short-term reproducibility of CIMT measurements, key for determining the length of and the number of participants in a trial, is influenced by a multitude of factors, including the operator, equipment, and population studied. Even when these factors are controlled, CIMT measurements vary greatly with methods

of analysis. Intimal thickness changes throughout the cardiac cycle because of concomitant changes in arterial cross-sectional area (25). Available data also indicate substantial differences between measurements in the common and internal carotid arteries, as well as between the right and left carotid arteries (26,27). In an attempt to standardize measurements, investigators currently analyze frames depicting the widest and/or the narrowest arterial lumen or use a continuously recording electrocardiograph (ECG) to trigger the frame to be analyzed, usually incident with the R wave corresponding to end diastole (28–31).

The purpose of our study was to prospectively compare the reproducibility of CIMT measurements obtained from the right and left carotid arteries in young adults, by using frames acquired at the maximum dimension, minimum dimension, and ECG-triggered cardiac end-diastole.

## Materials and Methods

### Study Participants and Characterization of Cardiovascular Risk Factors

The study participants were healthy young adults, aged 18–25 years (50 men, 50 women), who were recruited from schools, sports clubs, and universities in Los Angeles County, California. The investigation protocol for our study was Health Insurance Portability and Accountability Act compliant and ap-

proved by our institutional review board for clinical investigations, and informed consent was provided by all participants. Siemens Medical Solutions (Mountain View, Calif) provided the edge-detection software to measure CIMT; however, all authors had complete control of the data and the information submitted for publication.

Possible candidates were asked about their age and medical history; those who had been diagnosed with hypertension or a familial lipid disorder were excluded. Candidates were further excluded if their parent(s) had a history of cardiovascular disease or if the students had ever been diagnosed with a chronic illness or had been taking any medications (including hormone preparations), or had a history of major medical illness.

Participants were dressed in an examination gown and asked to remove their shoes and hair clips. Weight was measured by using a digital electronic scale accurate to 0.1 kg and the mean of two measurements was recorded and used for analysis. Standing height was obtained by using a wall-mounted, digital stadiometer accurate to the nearest 0.1 cm and the mean of three measurements was used for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Participants whose BMI was above 30 kg/m<sup>2</sup> were excluded from fur-

## Advances in Knowledge

- Reproducibility of carotid intima-media thickness (CIMT) measurements is greatest when those of the right and left carotid arteries are combined.
- Reproducibility of CIMT measurements is similar in the left and right carotid arteries.
- CIMT is related to weight, body mass index (BMI), and systolic blood pressure (BP) in young adults.

## Implications for Patient Care

- Our results may aid in the understanding of the number of participants needed for clinical trials when using CIMT as an outcome measure to monitor disease risk in its early stages.
- Our results indicate that in healthy, nonhypertensive, non-obese young adults, CIMT measurements are related to BMI and to BP—a suggestion that disease risk may be more of a continuous measure than an arbitrary threshold value.

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## Abbreviations:

BMI = body mass index  
 BP = blood pressure  
 CIMT = carotid intima-media thickness  
 CV = coefficient of variation  
 ECG = electrocardiograph

## Author contributions:

Guarantors of integrity of entire study, J.G., V.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.G., V.G.; clinical studies, J.G., J.C.W., V.G.; statistical analysis, J.G., F.J.D., T.A.L.W., V.G.; and manuscript editing, J.G., V.G.

See Materials and Methods for pertinent disclosures.

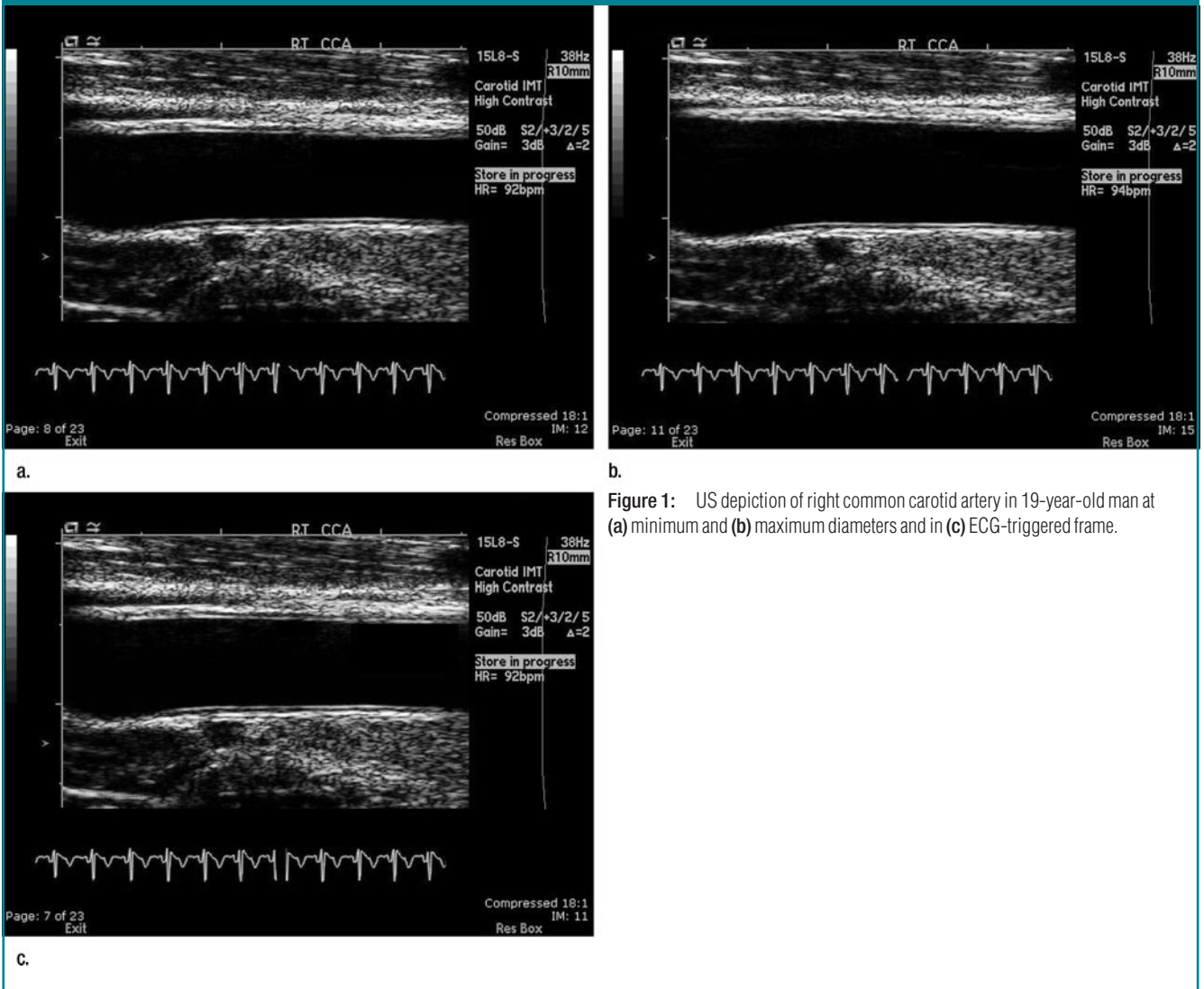
their evaluation. Readings of BP were taken after a 10-minute rest immediately prior to, and immediately following, the US examination by using a standard mercury sphygmomanometer (Critikon Dura-cuf; GE Healthcare, Wis). The participant was as relaxed as possible and was instructed not to talk during the procedure. BP was measured in a supine position from the right and left brachial arteries below the level of the right atrium and the average of all these readings was used for analysis. Participants whose BP was outside the mean age-adjusted normal values were excluded from further evaluation (32).

**Carotid US**

All studies were acquired by the same-technologist (a nonauthor, with 15 years US experience) by using a US scanner (Acuson Sequoia 512; Siemens Medical Solutions) and a high-frequency 15L8-MHz linear-array transducer by following a predetermined standardized scanning protocol. The participants were studied in the supine position with the head turned slightly away from the side that was examined. Images of the arterial wall were obtained from the posterior walls of both common carotid arteries 1 cm below the carotid bulb (bifurcation) during three complete and independent cardiac cycles.

An automated computerized edge-detection software package (version 1.0, 2002; Siemens Medical Solutions) was used to determine CIMT values in the frames of each cycle that depicted the narrowest and widest vessel diameters. Additional measurements were obtained from both common carotid arteries in the frames concordant with the R wave of the ECG (Fig 1). All examinations were digitally stored and analyzed by the same researcher (J.G.), who selected the frames that depicted the largest and smallest arterial vessel diameter, but who had no previous expertise in US measurements.

**Figure 1**



**Figure 1:** US depiction of right common carotid artery in 19-year-old man at (a) minimum and (b) maximum diameters and in (c) ECG-triggered frame.

### Statistical Analysis

Statistical analyses were carried out by using software (Stata for Windows, version 9, 2005; Stata, College Station, Tex). Values for age, anthropometric measurements, BP, and CIMT (for the first cycle and for an average of three independent cycles) are expressed as the mean  $\pm$  standard deviation. To assess the relations and differences in CIMT measurements between the left and right carotid arteries, and in CIMT measurements obtained with the various techniques in the same artery, Pearson correlations and paired *t* tests were used. Unpaired *t* tests were used to assess sex differences in CIMT values. Co-

efficients of variation (CVs) were calculated to determine the within-subject variability, and intraclass correlations (ICCs) to examine the reliability and reproducibility of measurements, for each analysis technique (33). Simple and multiple linear regression analyses were used to examine the relationships between CIMT values and risk factors for cardiovascular disease that are known to be associated with CIMT in high-risk children (BMI, weight, and systolic BP). For the latter, the average CIMT of the minimum and maximum diameters of both carotid arteries was assigned as the dependent variable, while BMI and BP were assigned as the independent

variables. For all statistical analyses, a *P* value of less than .05 was considered to indicate a significant difference.

### Results

Values for weight, height, BMI, and systolic BP were greater in men than in women ( $P < .01$ ) (Table 1). There were no sex differences in CIMT measurements, regardless of the analytical technique used (Table 2).

There were no differences between CIMT measurements obtained from three different cardiac cycles or from one cycle only. However, CIMT values were significantly different at the maximum and minimum carotid diameters; this was true for the right and left arteries independently and when both arteries were considered together ( $P < .001$ ). When both sides were analyzed together in all participants, mean CIMTs in the frames that showed the narrowest lumen diameter were 7.1% greater than CIMTs at the widest arterial lumen (393 vs 367;  $P < .001$ )—the numerator indicates the thickest CIMT and the denominator indicates the narrowest CIMT. Similarly, measurements in the ECG-triggered frames were 6.8% (392 of 367) thicker than those as-

**Table 1**

#### Age, Anthropometric Measures, and BP Values

Characteristic	Women	Men	Women and Men Combined
Age (y)	19.8 $\pm$ 1.7 (17.9–24.9)	19.7 $\pm$ 1.2 (17.9–23.1)	19.8 $\pm$ 1.5 (17.9–24.9)
Height (cm)	162.4 $\pm$ 5.6 (154–176)	174.3 $\pm$ 8.4 (157.5–194)	168.3 $\pm$ 9.3 (154–194)
Weight (kg)	61.7 $\pm$ 10.6 (45.5–91.7)	70.5 $\pm$ 10.4 (52.6–108.4)	66.1 $\pm$ 11.3 (45.5–108.4)
BMI (kg/m <sup>2</sup> )	23.4 $\pm$ 3.4 (17.4–29.9)	23.2 $\pm$ 2.9 (16.7–29.9)	23.3 $\pm$ 3.2 (16.7–29.9)
Systolic BP (mm Hg)	106.3 $\pm$ 7.6 (91.5–131.5)	114.5 $\pm$ 11.3 (84.0–134)	110.4 $\pm$ 10.3 (84–134)
Diastolic BP (mm Hg)	60.6 $\pm$ 6.9 (48.5–76.5)	58.1 $\pm$ 5.5 (47.5–69.0)	59.3 $\pm$ 6.3 (47.5–76.5)

Note.—Data are the mean  $\pm$  standard deviation. Data in parentheses are the range.

**Table 2**

#### CIMT Values

Location and Technique	Women (n = 50)		Men (n = 50)		Women and Men Combined	
	Single	Multiple	Single	Multiple	Single	Multiple
<b>Right carotid artery</b>						
Minimum arterial diameter	394 $\pm$ 49	399 $\pm$ 51	399 $\pm$ 55	399 $\pm$ 56	396 $\pm$ 52	399 $\pm$ 53
Maximum arterial diameter*	373 $\pm$ 46	372 $\pm$ 41	371 $\pm$ 52	370 $\pm$ 50	372 $\pm$ 49	371 $\pm$ 46
Average arterial diameter	384 $\pm$ 44	385 $\pm$ 44	385 $\pm$ 51	384 $\pm$ 51	384 $\pm$ 47	385 $\pm$ 48
ECG triggering	393 $\pm$ 49	394 $\pm$ 46	399 $\pm$ 61	396 $\pm$ 53	396 $\pm$ 55	395 $\pm$ 49
<b>Left carotid artery</b>						
Minimum arterial diameter	384 $\pm$ 47	386 $\pm$ 46	393 $\pm$ 63	388 $\pm$ 58	388 $\pm$ 56	387 $\pm$ 52
Maximum arterial diameter*	364 $\pm$ 50	360 $\pm$ 45	365 $\pm$ 57	365 $\pm$ 53	364 $\pm$ 53	363 $\pm$ 49
Average arterial diameter	374 $\pm$ 45	373 $\pm$ 44	379 $\pm$ 59	376 $\pm$ 55	376 $\pm$ 52	375 $\pm$ 49
ECG triggering	381 $\pm$ 50	386 $\pm$ 47	395 $\pm$ 61	394 $\pm$ 57	388 $\pm$ 56	390 $\pm$ 52
<b>Both carotid arteries</b>						
Minimum arterial diameter	389 $\pm$ 42	392 $\pm$ 44	396 $\pm$ 55	393 $\pm$ 52	392 $\pm$ 49	393 $\pm$ 48
Maximum arterial diameter*	368 $\pm$ 40	366 $\pm$ 39	368 $\pm$ 50	367 $\pm$ 48	368 $\pm$ 45	367 $\pm$ 43
Average arterial diameter	379 $\pm$ 39	379 $\pm$ 40	382 $\pm$ 51	380 $\pm$ 49	380 $\pm$ 45	380 $\pm$ 45
ECG triggering	387 $\pm$ 45	390 $\pm$ 43	397 $\pm$ 55	395 $\pm$ 49	392 $\pm$ 50	392 $\pm$ 46

Note.—All values were measured in micrometers and are the mean  $\pm$  standard deviation. CIMT values were measured in single or multiple cardiac cycles.

\*  $P = .01$  when compared with measures obtained at minimum diameter or by using ECG, regardless of sex or carotid site.

essed at the widest diameter ( $P < .001$ ) (Table 2). Significantly greater CIMT values were also observed at the maximum and minimum arterial diameters for the right carotid artery when compared with the left—on average, 2.2% (371 of 363) and 3.1% (399 of 387) greater, respectively (both  $P < .05$ ).

Pearson correlations between the CIMT measurements obtained from the same artery by using different techniques were stronger ( $r = 0.83$ – $0.97$ , all  $P < .001$ ) than those obtained between carotid arteries by using the same technique ( $r = 0.62$ – $0.68$ , all  $P < .001$ ).

Regardless of technique, reproducibility was similar for the left and right arteries. However, as expected, ICCs were stronger when assessments were obtained from three independent cardiac cycles rather than one, and when both carotid arteries were analyzed together. Similarly, CV was strongest when the average of the right and left arteries at both the minimum and maximum diameters were obtained (2.3%), and weakest when only the ECG-triggered frames were analyzed on one side (4.6%) (Table 3).

CIMT measurements correlated moderately with those of BMI, weight, and systolic BP (Fig 2); neither age nor height was associated with CIMT measurements ( $r = 0.08$  and  $0.15$  and  $P = .14$  and  $.45$ , respectively). When all participants were considered together, results of multiple regression analysis confirmed an independent effect of BMI ( $\beta = 3.33$ ,  $P = .01$ ) and systolic BP ( $\beta = 1.01$ ,  $P = .03$ ) on CIMT measurements ( $r^2 = 0.17$ ).

**Discussion**

Our study was designed to determine the variability and reproducibility of CIMT measurements by using different US methods in healthy young adults. Our results revealed significant differences between measurements of carotid wall thickness obtained at the maximum and minimum carotid artery diameters, and in ECG-triggered single frames. On average, CIMT values measured in the frames depicting the narrowest lumen

**Table 3**

**ICC and Coefficient of Variation for CIMT Measurements**

Sex and Technique	Right Carotid Artery			Left Carotid Artery			Both Carotid Arteries		
	Single ICC	Multiple ICCs	CV	Single ICC	Multiple ICCs	CV	Single ICC	Multiple ICCs	CV
<b>Women</b>									
Minimum arterial diameter	.86	.95	4.3	.84	.94	4.4	.89	.96	3.3
Maximum arterial diameter	.79	.92	4.5	.81	.93	4.5	.86	.95	3.4
Average arterial diameter	.90	.96	3.3	.88	.96	3.4	.93	.98	2.5
ECG triggering	.83	.94	4.5	.83	.94	4.3	.90	.96	3.2
<b>Men</b>									
Minimum arterial diameter	.86	.95	4.5	.88	.96	4.3	.92	.97	3.2
Maximum arterial diameter	.84	.94	4.3	.89	.96	4.1	.93	.98	2.9
Average arterial diameter	.92	.97	3.3	.93	.98	3.1	.96	.98	2.2
ECG triggering	.85	.94	4.8	.87	.95	4.6	.91	.97	3.3
<b>Women and men combined</b>									
Minimum arterial diameter	.86	.95	4.4	.87	.95	4.4	.91	.97	3.2
Maximum arterial diameter	.82	.93	4.4	.85	.95	4.3	.90	.96	3.1
Average arterial diameter	.91	.97	3.3	.91	.97	3.3	.94	.98	2.3
ECG triggering	.84	.94	4.6	.85	.95	4.4	.90	.97	3.3

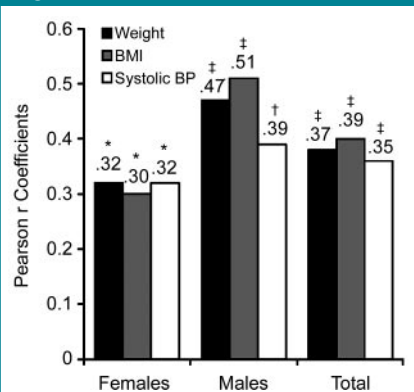
Note.—ICCs are given for single and multiple measurements.

diameter and those triggered by the R wave were on average 7.1% greater than at peak arterial dilation. Regardless of the technique used, we also found consistently greater CIMT measurements in the right carotid artery than in the left, on average, by 2.2%–3.1%. The large differences in CIMT values among the various techniques, as well as between the right and left carotid arteries, are likely to account for, at least in part, the discrepant results of previous studies (25–27).

The results of our study also indicate that CIMT measurements are greatly dependent on the method used for analysis, even after accounting for operator, equipment, and population. Values for ICCs and CV for assessments in the left or right carotid artery by using the maximum diameter, minimum diameter, and ECG-triggered frames were comparable. As expected, reproducibility was greatest when both carotid arteries were combined, and when assessments were obtained from multiple independent cardiac cycles (26).

It should be noted that several elements were considered in the design of our study to enhance reproducibility. All participants were examined by following a predetermined standardized scanning protocol performed by the same

**Figure 2**



**Figure 2:** Correlation coefficients for CIMT measurements and weight, BMI, and systolic BP in 50 males and 50 females. \* =  $P < .05$ , † =  $P < .01$ , ‡ =  $P < .001$ .

US technologist, and all analyses were performed by the same researcher. Because available data indicate better reproducibility for measurements in the common carotid arteries than in the internal carotid arteries, only the former were examined (34). To optimize image detail, high-frequency/low-penetration focused transducers were used for the acquisition of images. The thinner skin and subcutaneous fat layers in the necks

of healthy young adults, when compared with those of obese and/or elderly subjects, minimized the errors associated with soft-tissue attenuation, allowing the use of high-frequency transducers to improve resolution (theoretically twice that of most previous investigations). Additionally, to account for the substantial temporal variability in wall thickness during systole and diastole and among cardiac cycles, we employed multiple methods for analysis in three separate cardiac cycles by using semiautomated software. In contrast, prior studies were frequently performed on the basis of the analysis of single frames triggered by a set point in the ECG during the cardiac cycle (28–31).

Researchers in previous studies found that pediatric populations at high risk for cardiovascular disease have greater measurements of CIMT (11–20); few, however, have examined the associations between cardiovascular disease risk factors and CIMT values in healthy young adults, with varying results (12,30,31,35–39). Several investigators reported that CIMT was associated with BP and BMI or with age and height (31,35–37), while others reported no such relations (12,30,38,39). In our study, while neither age nor height influenced CIMT values, we found these measurements to be significantly related to weight, BMI, and systolic BP in nonhypertensive, nonobese young adults, regardless of sex.

There were limitations in this study. The population studied was composed solely of healthy young adults, and the acquisition and analysis of the data were greatly optimized by using a sophisticated method. Hence, our results may not be applicable to other populations or age groups, or studies that use different technology. Indeed, CIMT values in youth have better reproducibility than in the elderly, since measurement variability increases proportionally with the degree of arterial wall thickening (40). Additionally, the clinical implications of CIMT measurements in healthy young adults are difficult to determine owing to the lack of a measurable negative health outcome. Longitudinal studies are needed to establish the degree to

which CIMT measurements in young adults are tracked throughout life and are related to cardiovascular events.

In conclusion, the findings of our study indicate that reproducibility of US measurements of CIMT in young adults is greatest when combining values from both carotid arteries and/or from the maximal and minimal arterial diameters. This knowledge should aid in the understanding of the number of participants needed in clinical trials when using CIMT as an outcome measure to noninvasively monitor cardiovascular disease risk in its early stages.

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