Published in final edited form as:

J Am Soc Echocardiogr. 2012 September ; 25(9): 1023–1028. doi:10.1016/j.echo.2012.05.007.

Variations in Common Carotid Artery Intima-Media Thickness (cIMT) during the Cardiac Cycle: Implications for Cardiovascular Risk Assessment

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Abstract

Introduction—Common carotid artery (CCA) intima-media thickness (cIMT), a measure of atherosclerosis, varies between peak-systole (PS) and end-diastole (ED). This difference might affect cardiovascular risk assessment.

Materials and methods—IMT measurements of the right and left CCA were synchronized with an electrocardiogram: R-wave for ED and T-wave for PS. IMT was measured in 2930 members of the Framingham Offspring Study. Multivariable regression models were generated with ED-IMT, PS-IMT and change in IMT as dependent variables and Framingham risk factors as independent variables. ED-IMT estimates were compared to the upper quartile of IMT based on normative data obtained at PS.

Results—The average age of our population was 57.9 years. Average difference in IMT during the cardiac cycle was 0.037 mm (95% CI: 0.035–0.038 mm). ED-IMT and PS-IMT had similar associations with Framingham risk factors (total R²= 0.292 versus 0.275) and were significantly associated with all risk factors. In a fully adjusted multivariable model, a thinner IMT at peak-systole was associated with pulse pressure ($p < 0.0001$), LDL-cholesterol ($p = 0.0064$), age ($p = 0.046$), and no other risk factors. Performing ED-IMT measurements while using upper quartile

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Disclosures

MJ Pencina is a consultant on a Data Safety Monitoring Board for Abbott Laboratories

Data access and responsibility:

JFP, AM, MJP, PAW, and RBD had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

PS-IMT normative data lead to inappropriately increasing by 42.1% the number of individuals in the fourth IMT quartile (high cardiovascular risk category).

Conclusion—The difference in IMT between peak-systole and end-diastole is associated with pulse pressure, LDL-cholesterol, and age. In our study, mean IMT difference during the cardiac cycle lead to an overestimation by 42.1% of individuals at high risk for cardiovascular disease.

Keywords

Ultrasonics; Risk Factors; Carotid Arteries; Blood Pressure; systole; diastole

Introduction

Common carotid artery intima-media thickness (cIMT) is an ultrasound marker of incident cardiovascular disease¹⁻⁴. Carotid IMT measurements are most often done on ultrasound images of the carotid artery acquired at end-diastole.

Small studies have shown that IMT changes during the cardiac cycle⁵⁻⁷, with IMT decreasing as the artery diameter increases during systole.

Current strategies recommending the use of carotid IMT for cardiovascular risk assessment⁸ indicate that individuals be classified at high risk if their IMT is above the 75% percentile^{8,9} at end-diastole. A review of recommended normative data¹⁰ shows inconsistent synchronization of IMT measurements with the cardiac cycle. In addition, reference is often made to normative data derived from the Atherosclerosis Risk In Communities (ARIC) study where IMT was measured in 12,629 of 15,800 participants in whom it was attempted¹¹. The ARIC common carotid artery IMT measurements, although often refereed to as the best source for IMT normative data, were acquired at peak-systole¹².

We hypothesize that IMT measurements made at peak-systole and end-diastole have similar associations with Framingham risk factors and study this hypothesis in members of the Framingham Offspring cohort that are free of prevalent cardiovascular disease. We also hypothesize that IMT measured at end-diastole may over-classify individuals into a high cardiovascular disease risk category when referenced against normative IMT data acquired at peak-systole.

Materials and Methods

Subject Population and Measurement of Risk Factors

The Framingham Offspring Study (FOS) cohort was constituted in 1970 and included 2483 men and 2641 women, selected by virtue of being the offsprings and spouses of the original Framingham Heart Study participants¹³. At incept, ages ranged from 5 to 70 years. Examination cycle 1 was conducted between 1971 and 1975, cycle 2 from 1979 to 1983, cycle 3 from 1983 to 1987, cycle 4 from 1987 to 1991, cycle 5 from 1991 to 1995, and cycle 6 from 1995 to September 1998. The total number of individuals seen during the cycle 6 clinic visit was 3532 of which 1657 were men and 1875 were women. Carotid ultrasound data were acquired on 1593 men and 1784 women, i.e. corresponding to 95.6% of participants (3377 / 3532) seen at examination cycle 6. We further restricted our analyses to individuals free of prevalent cardiovascular disease (according the the Framingham Heart study definition¹⁴) and with complete risk factor data as well as both peak-systolic and end-diastolic carotid IMT measurements (2930 of 3377 individuals with a carotid ultrasound examination; 86.8%) All participants provided informed consent, and the Institutional Review Board of the Boston Medical Center approved the study protocol.

During the clinic visit, a medical history was obtained and a physical examination was performed. The cardiovascular risk factors relevant to this study were the components of the Framingham risk score (systolic blood pressure, cigarette smoking status, total serum cholesterol, high density lipoprotein (HDL) cholesterol, diabetes to which was added diastolic pressure in order to calculate pulse-pressure. Treatment for hypertension was determined from the medical history.

Blood pressure was determined from the average of two resting readings taken by a physician using a 14 cm blood pressure cuff on the right arm. Smoking status was based on a self-reported history of cigarette smoking. All lipid analyses were performed at the Framingham Heart Study laboratory according to the Standardization Program of the Centers for Disease Control (CDC) and the National Heart Lung and Blood Institute Lipid Research Clinics^{15, 16}. The presence of diabetes was based on a history of diabetes, either current/previous fasting glucose ≥ 126 mg/dL or current/previous use of anti-hyperglycemic medication.

Ultrasound studies

Ultrasound studies were acquired (Toshiba SSH-140A; Toshiba Medical Systems, Tustin, CA) according to a standard protocol using a high-resolution linear array 7.5 MHz transducer at the level of the common carotid artery, and at a frame rate of 32 Hz. The images were acquired with the participant's head rotated 45 degrees opposite to the side being imaged with the transducer held 45 degrees from the vertical. Images were centered below the common carotid artery bulb, the edge of the bulb to the left of the image, in an area free of plaque. Image scale was set at 140 pixels/cm. A continuous series of images lasting 3 seconds were first acquired and stored in the memory of the ultrasound device and on a Hi-video tape (EV C-100; Sony Corp, Park Ridge, NJ). The acquired series of images were then slowly replayed on the ultrasound device playback mode and reviewed. A frame counter highlighted the position of the stored image with respect to the synchronously acquired electrocardiogram. The first image to be acquired was centered on the T-wave. The sonographer was allowed to select the image with the largest systolic expansion if located within 2 frames of the T-wave. The image was directly digitized into a Macintosh IIfx (Apple Corp, Cupertino CA) with a PixelBuffer digitizing board (Perceptics Corp, Knoxville TN) and stored on a WORM (Write Once Read Many) drive (Pioneer Electronics, Long Beach, CA) using customized software. The process was then repeated, this time with the sonographer selecting an image with the frame marker on the R-wave of the electrocardiographic tracing and with the sonographer confirming that this corresponded to the smallest diameter. The selected images were also recorded on videotape in addition to the dynamic video sequence. A certified reader reviewed all images and performed IMT measurements using an offline and blinded process where the reader made continuous tracings of the key arterial wall interfaces (lumen to intima and media to adventitia). The images were analyzed at least one week after their acquisition. Custom designed software displayed the images from the optical disks through the MacIntosh computer onto a 19" screen. The reader activated a series of tools that permitted review the images, their grading as to quality, and the drawing of lines at the key wall interfaces (lumen-intima and media-adventitia). An automated algorithm then determined the mean IMT values¹⁷ by processing the position of these lines. Image quality was scored on a Likert scale from 1 to 5, 5 being the best quality image possible with all key interfaces visualized and traceable and 1 being non-interpretable (visualization of 1 interface or less). Based on the availability of ultrasound device and sonographer, carotid ultrasound studies were acquired on 3377 individuals (1593 men and 1784 women). Final numbers reflect availability of Framingham risk factor data, absence of prevalent disease and IMT measurements at both end-diastole and peak-systole (n = 2930). Reproducibility was assessed by replicate (inter-reader)

measurements as part of the certification process in 37 randomly selected participants. The inter-reader Pearson correlation coefficients between replicate readings for mean CCA end-diastolic IMT was 0.94 whereas it was 0.93 for the mean CCA IMT at peak-systole.

The videotaped study was replayed at the time of image analysis to help identify key anatomical landmarks. The videotape record had to be used to redigitize the images in 16 (of 2930) participants due to poor quality of the images stored on the optical disks.

Statistical Analysis

The mean (and standard deviation) values of continuous variables, Framingham risk factors, peak-systolic IMT, end-diastolic IMT and change in IMT between diastole and systole (end-diastolic IMT-peak-systolic IMT) are presented. Dichotomous variables are presented as percentages.

Multivariable regression models were fitted for peak-systolic IMT and end-diastolic IMT as dependent variables with age, gender, smoking, diabetes, LDL cholesterol, HDL cholesterol and pulse pressure.

We generated a parsimonious model using multivariable linear regression with the difference in IMT between diastole and systole as the outcome, forcing age and gender into the model.

The cumulative distribution of IMT measurements made at peak-systole was used as normative data. This was done since peak-systole was used to measure IMT in the ARIC study¹². Inter-quartile ranges of IMT were calculated. The IMT values obtained at end-diastole were matched against these normative values. The percentage over estimation of individuals at increased risk (upper quartile of normative IMT values) was calculated as the percentage increase of individuals within the upper quartile.

All analyses were run using SAS version 9.1 (Cary, NC) and p-values below 0.05 were considered statistically significant (two-sided).

Results

The mean age of our population was 57.9 years, with 55.3% women (Table 1). Mean end-diastolic IMT was 0.595 ± 0.131 mm and mean peak-systolic IMT was 0.558 ± 0.123 mm. The mean difference was 0.037 ± 0.053 mm indicating a thinner wall thickness at peak-systole when the artery is maximally dilated.

For the right common carotid artery, mean image quality scores of end-diastolic images was 4.12 ± 0.71 (mean $\pm$ sd) as compared to 4.13 ± 0.70 for peak-systolic images. On the left, mean scores were 4.02 ± 0.74 for end-diastolic images and 4.04 ± 0.75 for peak-systolic images.

Multivariable adjusted associations between end-diastolic and end-systolic IMT and all Framingham risk factors were similar (Table 2) with all risk factors being significantly associated with the respective IMT values. The overall model for predicting IMT from Framingham risk factors explained 29.2% of the variability for ED-IMT and 27.5% for PS-IMT. The overall predicted variability for the models did not change after pulse pressure was substituted for systolic and diastolic pressure (Table 3).

Pulse-pressure, LDL-cholesterol and age were significant predictors of the difference in IMT between systole and diastole after adjustment for gender (Table 4).

Inter-quartile ranges of IMT were greater for end-diastole than for peak-systole. For end-diastole, the IMT values were 0.343, 0.508 mm; 0.510, 0.570 mm; 0.572, 0.650 mm and 0.650 mm whereas they were 0.288, 0.478 mm; 0.478, 0.535 mm; 0.535, 0.608 mm; and 0.610 mm for peak-systole. When the upper quartile IMT cut-point of 0.601 mm based on peak-systole normative data (as was done in ARIC) was used and the IMT was measured at end-diastole, 1046 individuals were placed in the upper quartile high-risk category instead of the 736 who were actually in this quartile. This corresponds to an over-estimation of individuals at high risk since the upper quartile increases by 310 as compared to the original 736 thereby inflating by 42.1% the number of individuals estimated to be in the high risk group.

Discussion

We have found an average difference of 0.037 mm in carotid IMT between the peak-systolic and end-diastolic phases of the cardiac cycle. In essence, the intima-media complex of the artery wall is the thinnest during systole at the point of maximal arterial expansion and the thickest at end-diastole when the artery diameter is the smallest. The variables associated with this difference were pulse pressure, LDL-cholesterol, and age. Associations between Framingham risk factors and either end-diastolic or peak-systolic IMT were similar. We identified a significant (42.1%) overestimation of individuals categorized as being at high risk for cardiovascular disease simply by noting a mismatch between published normative data (peak-systole) and current recommendations for IMT measurements (end-diastole).

Prior ultrasound studies of the common carotid artery have shown that IMT is thinner at end-systole than at end-diastole by an average of 5.3% in 48 arteries imaged with B-mode ultrasound⁶. However, Baldassarre et al studied a small sample of 14 subjects and did not detect any systematic difference in IMT during the cardiac cycle¹⁸. In children, QRS IMT measured within 2 frames of the QRS complex of an electrocardiogram are thinner than those measured further away from the QRS complex¹⁹.

We confirm the original observations of Seltzer et al.⁶ that IMT varies during the cardiac cycle and estimate the magnitude of this change at a mean of 0.037 mm. We also show for the first time that this change in IMT is associated with pulse pressure, LDL-cholesterol, and age. The association with pulse pressure is likely based on simple physiology with a larger pulse pressure causing more arterial distension and an accompanying thinning of the wall. The positive association of the difference in IMT during the cardiac cycle with age and LDL-cholesterol are more difficult to explain. A plausible explanation is based on the positive association of IMT with age and LDL-cholesterol. Larger IMTs are more easily measured because of the limited spatial resolution of ultrasound. Since IMT is positively associated with age and LDL-cholesterol, these variables might enter in the model as confounders. Another possibility is that age and exposure to LDL-cholesterol alter the characteristics of the artery wall and make the artery more likely to distend in the radial direction thereby increasing overall thinning of the wall during systole. This seems unlikely since age is also associated with increased artery stiffness. These possibilities are purely speculative and would require in vitro observations to either confirm or reject either hypothesis.

We observe that image quality for end-systolic and peak-systolic images are similar based on a semi-quantitative score. This would suggest that measurements made at peak-systole might be as reliable as measurements made at end-diastole. Interestingly, images from the left side of the neck show a slightly lower image quality than on the right. This suggests that if common carotid artery measurements are to be used for risk assessment then the right side should be favored.

Previous IMT studies have either underestimated the role of the cardiac cycle²⁰, used the R-wave to gate the IMT measurement to end-diastole²¹ or made a visual evaluation of the smallest diameter to identify end-diastole²². These studies indicate a large variation on how carotid IMT is acquired and how this can potentially affect the derivation of normative values for IMT. Even the eight referenced sources of normative IMT data¹⁰ show wide variations in whether or not acquisitions were synchronized to the cardiac cycle. For example, the phase of the cardiac cycle was not controlled for in the Cardiovascular Health Study (CHS)(Polak, 2012 Personal Communication), the Multi-Ethnic Study of Atherosclerosis (MESA)(Polak, 2012 Personal Communication), the Edinburgh study²³, and the Malmo study²⁴. One study did the acquisitions at end-diastole, the AXA study²⁵. Two studies clearly indicate acquisition at peak-systole: the Atherosclerosis Risk In Communities (ARIC) study²⁶ and the Carotid Atherosclerosis Progression Study (CAPS)²⁷. In one study, the Bogalusa Heart study²⁸, reference is made to the methods used in the ARIC study where measurements were made at peak-systole.

The most often quoted source of common carotid artery IMT normative data is the ARIC study since it is one of the first epidemiologic studies addressing IMT measurements of the carotid arteries and has the largest number of participants. Their IMT data were acquired at peak-systole. Recommendations for risk cardiovascular risk assessment are to take the 75% cut-point from a population distribution and use this as a demarcation for risk stratification⁸. Since we are an epidemiologic study as well, we used the 75% percentile of our peak-systolic values as a reference. We then determined the number of individuals in our cohort who would have been inappropriately classified as being at high risk when end-diastolic measurements are used. This approach has its limitations since we are not using published values but data generated from our own measurements. However, this seems appropriate given the strong associations of our IMT measurements with risk factors¹⁷ and outcomes²⁹.

ARIC has averaged three views of the common carotid artery whereas we have one view only²⁶ and included plaque in their measurement whereas we did not. Areas of plaque deposition are known to have different biomechanical characteristics and wall dynamics during the cardiac cycle³⁰. We therefore believe that our measurements better reflect the dynamics of the arterial wall despite the fact that we acquired images from one projection. On average, measurements of common carotid IMT have been shown not to be dependent on angular projection³¹ when plaque is not included in the measurement.

Given the magnitude of the change in carotid IMT during the cardiac cycle, careful attention should be given to the portion of the cardiac cycle used to perform IMT measurements. For example, carotid IMT is known to increase at a rate of 0.008 mm/year in epidemiological studies and up to 0.0147 mm in intervention trials³². As such, a change of 0.037 mm would correspond to a change in the equivalent of 3 to 5 years of age. In Framingham, IMT increases with age at a rate of 0.007 mm/year¹⁷. A difference of 0.037 mm would correspond to a difference of 5 years in age.

The 75% percentile is proposed as the IMT cut-point for identifying asymptomatic individuals at high risk for cardiovascular disease^{8, 9}. A panel of the American Heart Association and American College of Cardiology Foundation on cardiovascular risk in asymptomatic individuals gave a Class IIa recommendation for the use of carotid IMT for cardiovascular risk assessment⁸ and referenced a source of normative data^{10, 11}. However, IMT was measured at peak-systole in ARIC¹². Based on our data, adoption of normative IMT data acquired at peak-systole might inappropriately classify individuals as being at high risk and therefore increase their likelihood of undergoing further investigation or treatment. We recognize that the magnitude of this effect is small given the inherent variability of IMT measurements but the effect is a quantifiable one nonetheless. If we compare the lowest 75th

percentile to the highest 25th percentile rather than quartiles, we essentially get the same results since we are focusing on the additional cost of inappropriately classifying individuals into the upper 25th percentile. The original costs of treatments and investigations are focused on the upper 25th percentile and these would therefore be inflated by 42%. As such, the potential costs of lipid lowering interventions or investigations would still be 42% higher for individuals stratified based on acquired end-diastolic IMT as compared to normative peak-systolic IMT values.

Conclusion

We conclude that IMT values obtained at peak-systole and end-diastole have similar associations with Framingham risk factors. IMT is slightly larger during end-diastole than it is during end-systole and the difference is associated with pulse pressure, LDL-cholesterol and age. Use of published normative data based on peak-systole can lead to significant over-classification of individuals as being at high risk for cardiovascular disease.

Acknowledgments

Funding:

From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195). Dr. Polak was partly supported by NHLBI R01 HL069003 and HL081352.

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Figure 1.

The cumulative distribution of IMT values using normative data based on peak-systolic IMT as done in ARIC is shown as the curve to the left. When an IMT measurement is made at end-diastole, the 75% percentile cut-point for IMT values is shifted downwards, increasing the number of individuals classified as high risk (shaded area). Individuals in the shaded area are inappropriately classified as being in a high-risk category. In this case, the original upper quartile is inflated by 42%.

Table 1

Basic demographics of study participants with measurements of Intima-Media Thickness (IMT) performed at end-diastole and peak-systole.

Variable	Values
Age in years (SD)	57.9 (9.6)
Male/female	44.7% / 55.3% (1310/1620)
LDL Cholesterol in mg/dL (SD)	127.8 (33.3)
HDL Cholesterol in mg/dL (SD)	52.0 (16.0)
Systolic Pressure in mmHg (SD)	127.8 (18.7)
Diastolic Pressure in mmHg (SD)	75.6 (9.4)
Pulse Pressure in mmHg (SD)	52.2 (15.4)
Treated blood pressure (Yes/No)	24.4% / 75.6% (714 / 2216)
Smoker (Yes/No)	14.8% / 85.2% (433 / 2497)
Diabetes (Yes/No)	8.4% / 91.6% (246 / 2684)
CCA IMT diastole in mm (SD)	0.595 (0.131)
CCA IMT systole in mm (SD)	0.558 (0.123)
Difference in IMT in mm (SD)	0.037 (0.053)

SD : standard deviation. Total sample size: 2930. CCA: common carotid artery; IMT: Intima-Media Thickness

Table 2

Associations of end-diastolic (ED) and peak-systolic (PS) Intima-Media Thickness (IMT) with Framingham risk factors in multivariable adjusted models.

Variable	Beta Coefficient (PS-IMT)	p-value (PS-IMT)	Beta Coefficient (ED-IMT)	p-value (ED-IMT)
Sex (female)	−0.044	<0.0001	−0.043	<0.0001
Age (years)	0.0042	<0.0001	0.0045	<0.0001
LDL-Cholesterol (mg/dL)	0.00019	0.0018	0.00027	<0.0001
HDL-cholesterol (mg/dL)	−0.00065	<0.0001	−0.00067	<0.0001
Systolic Pressure (mmHg)	0.0013	<0.0001	0.0016	<0.0001
Diastolic Pressure (mmHg)	−0.0012	<0.0001	−0.0017	<0.0001
Diabetes (Yes)	0.023	0.0016	0.022	0.0036
Smoker (Yes)	0.029	<0.0001	0.032	<0.0001
Blood Pressure Treatment (Yes)	0.012	0.013	0.015	0.0042

Total R² for model with common carotid artery peak-systolic IMT as outcome: 0.275

Total R² for model with common carotid artery end-diastolic IMT as outcome: 0.292

Table 3

Associations of end-diastolic (ED) and peak-systolic (PS) IMT with Framingham risk factors in multivariable adjusted models. Pulse pressure is substituted for systolic and diastolic pressures.

Variable	Beta Coefficient (PS-IMT)	p-value (PS-IMT)	Beta Coefficient (ED-IMT)	p-value (ED-IMT)
Sex (female)	−0.045	<.0001	−0.043	<.0001
Age (years)	0.0042	<.0001	0.0045	<.0001
LDL-Cholesterol (mg/dL)	0.00019	0.0014	0.00027	<.0001
HDL-cholesterol (mg/dL)	−0.00065	<.0001	−0.00067	<.0001
Pulse pressure (mmHG)	0.0013	<.0001	0.0016	<.0001
Diabetes (Yes)	0.023	0.0016	0.023	0.0036
Smoker (Yes)	0.029	<.0001	0.032	<.0001
Blood Pressure Treatment (Yes)	0.013	0.010	0.015	0.0037

Total R2 for model with CCA peak-systolic IMT as outcome: 0.275

Total R2 for model with CCA end-diastolic IMT as outcome: 0.292

Table 4

Result of multivariable regression model with Framingham risk factors selected using stepwise procedure and the difference between end-diastolic and peak-systolic Intima-Media Thickness (IMT) as outcome (age and sex forced into the model).

Variable	Beta	p-value
Sex (female)	0.00087	0.66
Age (years)	0.00024	0.046
LDL-Cholesterol (mg/dL)	0.000079	0.0064
Pulse pressure (mmHg)	0.00033	<.0001