Associations of Edge-Detected and Manual-Traced Common Carotid Intima-Media Thickness Measurements With Framingham Risk Factors

The Multi-Ethnic Study of Atherosclerosis

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Background and Purpose—Carotid intima-media thickness (IMT) is a marker of cardiovascular disease derived from ultrasound images of the carotid artery. In most outcome studies, human readers identify and trace the key IMT interfaces. We evaluate an alternate approach using automated edge detection.

Methods—We studied a subset of 5640 participants with an average age 61.7 years (48% men) of the Multi-Ethnic Study of Atherosclerosis composed of whites, Chinese, Hispanic, and blacks that are part of the Multi-Ethnic Study of Atherosclerosis IMT progression study. Manual tracing IMT (mt-IMT) and edge-detected IMT (ed-IMT) measurements of the far wall of the common carotid artery served as outcome variables for multivariable linear regression models using Framingham cardiovascular risk factors and ethnicity as independent predictors.

Results—Measurements of mt-IMT were obtainable in 99.9% (5633/5640) and measurements of ed-IMT were obtainable in 98.9% (5579/5640) of individuals. Average ed-IMT was 0.19 mm larger than mt-IMT. Inter-reader systematic differences (bias) in IMT measurements were apparent for mt-IMT but not ed-IMT. Based on complete data for 5538 individuals, associations of IMT with risk factors were stronger (P<0.0001) for mt-IMT (model $r^2$, 19.5%) than for ed-IMT (model $r^2$, 18.5%).

Conclusions—We conclude that this edge-detection process generates IMT values equivalent to manually traced ones because it preserves key associations with cardiovascular risk factors. It also decreases inter-reader bias, potentially making it applicable for use in cardiovascular risk assessment. (Stroke. 2011;42:00-00.)

Key Words: atherosclerosis ■ carotid artery ■ carotid intimal medial thickness ■ imaging ■ methodology ■ risk factors

Carotid intima-media thickness (IMT) is a marker of cardiovascular disease,$^1$–$^3$ with measurements performed mostly by readers who either place calipers at selected points$^4$ or trace continuous lines along the lumen-intima and media-adventitia interfaces of the artery wall.$^5$ The distance between these the lumen-intima and media-adventitia interfaces defines IMT. An alternate approach is to use automated edge detectors to identify these interfaces.$^6$–$^{11}$

Two consensus groups have proposed the use of edge detection for IMT measurements.$^{12,13}$ IMT measurements derived from manual tracings and from edge detectors and their associations with risk factors have not been compared in any large population study. We have designed one that uses cost-functions for gradients and echo density$^{11}$ and applied it to ultrasound images acquired on a subset of a large multi-ethnic cohort, the Multi-Ethnic Study of Atherosclerosis.

We compared edge-detected IMT (ed-IMT) measurements to manual-traced IMT (mt-IMT) measurements in the Multi-Ethnic Study of Atherosclerosis IMT progression study, their respective associations with cardiovascular risk factors, and the effect on inter-reader differences.

Materials and Methods

Population

Multi-Ethnic Study of Atherosclerosis recruited and examined a multi-ethnic population of 6814 men and women aged 45 to 84 with no history of clinical cardiovascular disease$^{14}$ between July 2000 and August 2002. The Multi-Ethnic Study of Atherosclerosis cohort is a multi-ethnic cohort including white, black, Hispanic, and Chinese participants. Participants were excluded if they had physician-diagnosed heart attack, stroke, transient ischemic attack, heart failure, angina, atrial fibrillation, history of any cardiovascular...
procedure, weight >300 lb, pregnancy, or any medical conditions that would prevent long-term participation. Multi-Ethnic Study of Atherosclerosis protocols and all studies described herein have been approved by the Institutional Review Boards of all collaborating institutions. The participants studied underwent carotid artery imaging at the baseline visit.

Risk Factors and Anthropomorphic Variables
The risk factors used in this article are derived from the updated Framingham Risk Score as presented by D'Agostino et al. Age, gender, smoking and diabetes status, systolic blood pressure, and total and high-density lipoprotein cholesterol to which treatment of hypertension has been added.

Age, gender, ethnicity, and medical history were self-reported. Current smoking was defined as self-report of a cigarette in the past 30 days. Resting blood pressure was measured 3 times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). The average of the last 2 measurements in analyses was used.

Lipid levels were measured after a 12-hour fast. Diabetes mellitus was based on self-reported physician diagnosis, use of insulin and/or oral hypoglycemic agent, or fasting glucose ≥126 mg/dL. Total cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics) and high-density lipoprotein after precipitation of non-high-density lipoprotein cholesterol with magnesium/dextran.

Carotid Artery Measures
Participants were examined supine with the head rotated 45 degrees toward the left side. Imaging was performed in the plane parallel to the neck with the jugular vein lying immediately above the common carotid artery (or at 45 degrees from the vertical if the internal jugular vein is not present). Images of the right common carotid artery were centered 10 to 15 mm below (caudad to) the right common carotid artery bulb. A matrix array probe (M12L; General Electric) was used, with the frequency set at 13 MHz, 2 focal zones, and with the frame rate set at 32 frames per second. A super-VHS videotape recording was then made for 20 seconds. Images were digitized at 30 frames per second and end-diastolic images (smallest diameter of the artery) were captured. Although the theoretical resolution of the ultrasound at 13 MHz is 0.07 mm, it might be as low as 0.24 mm, taking into consideration the number of cycles in the transmitted ultrasound pulses.

IMT was measured over a length of ~10 mm, starting 5 mm to 10 mm below (caudad to) the right common carotid artery bulb and excluding any carotid artery plaque. Trained readers traced the key 2 interfaces to obtain manual tracings on 19-in monitors in a low-light environment. The readers activated the edge detector after completing their tracings (http://stroke.ahajournals.org). The edge detector did not use the location of the manually traced interfaces but operated on the same arterial segment. The edge detection algorithm weighed gradients between pixels and pixel density values through a dynamic programming process that minimizes cost functions. The readers had the option of modifying the cost-function coefficients if the edge detector failed to track an interface. The readers were not given the option of tracing any start points or editing the line tracings. Manual-traced and edge-detected line tracings were processed by the same algorithm to obtain mt-IMT and ed-IMT measurements.

Reproducibility was assessed by blinded replicate re-reads by 2 readers of a set of 114 studies (66 for one reader and 48 for a second reader) and both were compared to a third reader. The third reader had intrareader evaluation of reproducibility in a set of 18 individuals. The readers performed the measurements after blindly selecting images from the 20-second video loop.

Statistical Analyses
The mean (and standard deviation) values of continuous variables, mt-IMT and ed-IMT, are presented. The distribution of dichotomous variables is also shown as percentage in each group.

Results
There were 5633 individuals with mt-IMT values (mean, 0.678 ± 0.190 mm) as compared to 5579 with ed-IMT values (mean, 0.867 ± 0.226 mm). We were able to obtain paired IMT values in 5574 individuals. Restricting the analyses to all individuals with complete risk factor data, there were 5538 individuals with a mean age of 61.9 years. Demographics are shown in Table 1. The mean difference between measurements was −0.191 ± 0.15 mm, with ed-IMT values being larger, as shown on a Bland-Altman plot (Figure 1).

Results of paired replicate studies (Table 2) show that the standard deviations of paired measurements between readers (variance) are lower for mt-IMT measurements than for ed-IMT measurements. Measurements made by different readers were similar when the edge detector was used, whereas differences between readers were apparent when manual tracings were used. These findings are displayed graphically in Figure 2A and 2B. Intrareader measurements showed a similar effect (Table 2).
Table 3 summarizes the strength of the associations between risk factors and the carotid IMT measurements made by both methods. Risk factors account for slightly more (P<0.0001) of the variability of mt-IMT (19.5%) than for ed-IMT (18.5%).

Based on the partial correlations, associations of mt-IMT with age, gender, total cholesterol, and smoking were qualitatively stronger than for ed-IMT. Diabetes and high-density lipoprotein cholesterol had qualitatively stronger associations with ed-IMT than mt-IMT.

Discussion

The ed-IMT measurements of the common carotid artery far wall can be consistently obtained in a large cross-sectional sample of the population. The ed-IMT measurements have strong associations with cardiovascular risk factors that are similar but slightly weaker than mt-IMT measurements. Contrary to previous publications, we have not found that ed-IMT measurements are more reproducible than manual measurements, although we show that they decrease inter-reader differences.

Carotid IMT measurements have been proposed as a measure of cardiovascular risk and a means of possibly identifying individuals in need of pharmacotherapy or lifestyle interventions. Edge detection offers the advantage of obtaining IMT measurements in a standardized fashion so that they can be compared against normative or calibrated values.

We show that IMT measurements made with an edge detector preserve key associations with cardiovascular risk factors (Table 3) while decreasing reader bias (Table 2). As such, they could be substituted for manual-traced measurements generating normative data for IMT risk assessment.

We used an algorithm based on dynamic programming that resembles one developed by Wendelhag et al. This algorithm processes data based on pixel intensity and gradients and is different than edge detector algorithms based on polynomial fitting of intensity curves perpendicular to interfaces or to algorithms using template matching. The results presented in this article are specific to our implementation of a specific edge detector and do not apply to other edge detectors.

We were able to obtain automated IMT measurements in 99% (5574) of the 5633 individuals with mt-IMT values. Wendelhag et al reported that readers manually identified a new start point for their edge detection process in 17% of cases. Our readers had the option to slightly alter the weighting factors used for edge detection. Preselected values

Table 3. Reproducibility of Intima-Media Thickness Measurements Based on the Difference Between Replicate Readings Between Readers Using Either Manual-Traced Interfaces or Edge-Detected Interfaces

<table>
<thead>
<tr>
<th>Readers</th>
<th>Manual-Traced IMT</th>
<th>Edge-Detected IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Difference</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td></td>
<td>(mm)</td>
<td>of Difference (mm)</td>
</tr>
<tr>
<td>1 vs 3</td>
<td>66</td>
<td>-0.139*</td>
</tr>
<tr>
<td>2 vs 3</td>
<td>48</td>
<td>-0.087*</td>
</tr>
<tr>
<td>3 vs 3</td>
<td>18</td>
<td>0.044†</td>
</tr>
</tbody>
</table>

IMT indicates intima-media thickness; SD, standard deviation. *P<0.0001 and †P=0.049 by 2-sided t test. Differences between readers are not significant with edge-detected readings (P=0.62 and P=0.97, respectively) and for intra-reader readings (P=0.64).
were used in 93% of cases for the media-adventitia interface and in 83% of cases for the lumen-intima interface (http://stroke.ahajournals.org). Despite these adjustments, Figure 1 shows outliers in individuals with low IMT values and when the algorithm failed (63 cases or 1.1% of individuals). We believe that this algorithm failure depends on the thickness of the media layer because the algorithm requires a minimum number of pixels between the lumen-intima and media-adventitia interfaces. Increasing image size (scaling in pixels/mm) could circumvent this limitation. We have included these 63 cases because they did not substantially alter our findings. By protocol, the same image was measured to reduce the variability inherent in image selection. This might bias our results in favor of manual tracings because selecting a different image might have improved edge detection, reduced variability, and increased the predictive value of risk factors.

Whereas edge detectors have been used in clinical trials, associations between risk factors and IMT measurements have not been studied. In our review of the literature, we have found studies with small groups of subjects in which the reproducibility of edge detector data were evaluated or in which ed-IMT values were compared to mt-IMT tracings. The mathematical location of these edges tends to be different than the line perceived by the human eye. For example, a human reader would tend to trace a line on the lumen-intima interface, whereas the edge detector would place the edge above this line and cause an overestimation of 0.056 to 0.11 mm (1 to 2 pixels at an image scale of 180 pixels/cm). The weighing function in our algorithm would also tend to “pull” the estimated interface toward the denser pixels in the adventitia, thereby further increasing the estimated IMT. The IMT differences between readers (Table 2) are 0.09 to 0.14 mm, which are lower than the difference between mt-IMT and ed-IMT values (0.19 mm). Mean ed-IMT values show lack of inter-reader differences (Figure 2A, B). Contrary to previous studies, the variability of ed-IMT was slightly higher than for manual tracing. This may represent an image quality issue because we accepted images from 6 centers rather than from 1 laboratory. Our observations apply to this ultrasound device with its presets for image texture and scale. This may limit the general applicability of our observations.

Conclusions
We conclude that ed-IMT measurements can be substituted for mt-IMT measurements in cross-sectional IMT studies. As implemented, this specific edge detector gives IMT measurements comparable to mt-IMT measurements in a large multi-ethnic patient population. The ed-IMT values might be better-suited for cardiovascular risk assessment because they...
do not seem to have the significant inter-reader differences seen with mt-IMT measurements.

Acknowledgments
The authors thank the investigators, the staff, and the participants of the Multi-Ethnic Study of Atherosclerosis study for their valuable contributions.

Sources of Funding
This research was supported by NIH contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95167, as well as R01 HL069003 and R01 HL081352. A full list of participating Multi-Ethnic Study of Atherosclerosis investigators and institutions can be found at http://www.mesa-nhlbi.org.

Disclosures

References

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Stroke. published online May 5, 2011;

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Description of Edge Detection process and Intima-Media Thickness Measurement Process
Supplemental Methods

The edge detection process consists of the following steps:
1. Defining a region-of-interest within the image,
2. Generating a gradient image for this region-of-interest,
3. Determining a cost function for the lumen-intima interface and tracing this interface,
4. Determining a cost function for the media-adventitia interface and tracing this interface,
5. Optional modification of weight functions used to generate the cost functions and
6. Final processing of the distance between interfaces to calculate IMT

General approach to processing by the edge detector:
A region of interest defined by the reader is then sent to the edge detector algorithm. The reader can only verify whether or not the edge detector is following the appropriate edges. The reader has the option of modifying the parameters used in the edge detection algorithm. Information on the manually traced interfaces is not sent to the edge detector algorithm. The algorithm resembles the one published by Wendelhag et al.1

1. Definition of a region-of-interest:
A reader defines a rectangular region of interest where the upper boundary is located 1/3 to 1/2 of the artery diameter above the far wall of the artery. The bottom of this region of interest is located approximately the same distance below the far wall lumen-intima interface. The reader then performs manual tracings of the lumen-intima and media-adventitia interfaces.

2. Generation of a gradient image:
The gradient image is derived by calculating the change in pixel intensity (change in pixel intensity for every pixel along the Y-axis) from the top to the bottom of the region of interest. This is repeated for every X-axis coordinate. The locations of the lumen-intima and media-adventitia interfaces are estimated by examining the gradient image. The algorithm selection rule is that the first large gradient corresponds to the lumen-intima interface and the average pixel values above this interface have low values (dark on the image). The second and larger gradient corresponds to the media-adventitia interface with the additional constraint that the contiguous pixels below the interface have large values (white on the image). For ease of discussion, interface 4 corresponds to the lumen-intima interface and interface 5 corresponds to the media-adventitia interface.

Description of mathematical process:

3. **Lumen-adventitia**: The location of interface 5 (lumen-adventitia) is determined first. The process starts one point short of the left boundary of the region of interest. Three parameters are used to define the cost function used for dynamic programming: \(w_{5,1}\), \(w_{5,2}\) and \(w_{5,3}\). Because of the constraints of dynamic programming, their sum must equal 1. The parameter \(w_{5,1}\) is multiplied by a value derived form the average gray scale value of a predefined number of pixels below the point being evaluated. The parameter
w5,2 is multiplied by a value derived from the gradient along the Y-axis at the point being evaluated. The value of w5,3 is multiplied by the square of the difference between the current point and the point immediately to the left of the image. The three expressions are evaluated for different values along the Y-axis and the point with the lowest value is selected as the most likely to represent the media-adventitia interface. The process is then repeated for the next point to the right until the right boundary is reached.

4. Media-adventitia: The location of interface 4 (media-adventitia) is determined in a similar fashion. The parameter w4,1 is multiplied by a value derived from the average the gray scale value for a predefined number of pixels above the point being evaluated. The parameter w4,2 is multiplied by a value derived from the gradient along the Y-axis at the point being evaluated. The value of w5,3 is multiplied by a composite variable derived from the difference between the current point and the point immediately to the left of the image as well as a corresponding set of points on interface 5. The dynamic algorithm then searches for the point above interface 5 that minimizes the cost-function for different Y-axis values.

5. Processing of both lines and optional modification of cost-function weights: The final interface lines are chosen so that each line minimizes a cost function that incorporates three attributes: (1) distinguishing between interfaces 4 and 5, (2) following the gradient peaks, and (3) smoothing the effects of speckle and noise in the image. Increasing w4,1 and w5,1 tends to distinguish lines 4 and 5 more reliably, increasing w4,2 and w5,2 tends to follow the gradient peaks more closely at the expense of smoothing, and increasing w4,3 and w5,3 produces smoother lines that follow the gradient peaks more loosely. The weights are determined through a training procedure that makes the algorithm lines 4 and 5 look similar to a training set of reader lines 4 and 5.

Default weights for cost functions: The default weights are listed below. The number of times they were used is indicated between brackets:

w4,1 = 0.3, w4,2 = 0.5 and w4,3 = 0.2  (used in 83% of cases)
w5,1 = 0.5, w5,2 = 0.3 and w5,3 = 0.2 (used in 93% of cases)

Alternates for interface 4 include:
W4,1 = 0.1, w4,2 = 0.7 and w4,3 = 0.2 (<1%)
W4,1 = 0.3, w4,2 = 0.6 and w4,3 = 0.1 (<1%)
W4,1 = 0.5, w4,2 = 0.3 and w4,3 = 0.2 (6%)
W4,1 = 0.6, w4,2 = 0.2 and w4,3 = 0.2 (6%)
W4,1 = 0.7, w4,2 = 0.1 and w4,3 = 0.2 (3%)

Alternates for interface 5 include:
W5,1 = 0.1, w5,2 = 0.7 and w4,3 = 0.2 (1.5%)
W5,1 = 0.3, w5,2 = 0.5 and w4,3 = 0.2 (2.2%)
W5,1 = 0.4, w5,2 = 0.4 and w4,3 = 0.2 (<1%)
W5,1 = 0.6, w5,2 = 0.2 and w4,3 = 0.2 (<1%)
6. IMT measurement by processing the lumen-intima and media-adventitia lines:

The same algorithm\textsuperscript{2} is used for lines determined by manual tracing or edge detection.

Mean intima-media thickness (IMT) measurement of the far wall of the common carotid artery is performed according to a heuristic algorithm. The algorithm requires that the line corresponding to interface 5 be longer, both to the left and right, than the one for interface 4. It also assumes that line 5 is a straight line.

The algorithm then searches for the perpendicular to lines 4 and 5 at the edges and discards portions of line 5 on the right and left. The algorithm then sequentially searches for the minima between the two lines using the media-adventitia interface as an anchor line. The sets of minima are then used to calculate the mean IMT (averaged over the number of minima obtained). The implicit assumption is that the media-adventitia interface is a straight line. This assumption would not hold in the carotid artery bulb for example.