Common Carotid Intima-Media Thickness Measurement
A Method to Improve Accuracy and Precision

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Background and Purpose High-resolution ultrasonographic imaging is a noninvasive method that allows estimation of the thickness of the intima-media complex in human carotid arteries. The determination of intima-media thickness involves several steps, each of which may introduce an error that influences the reproducibility of the method. In the present study, apart from the general reproducibility of the determination of intima-media thickness, the error introduced by each step was evaluated.

Methods B-mode scans were performed on 14 randomly selected patients. The common carotid arteries were examined in anterior, lateral, and posterior planes, with a standard methodology and by a new method, making use of external reference points.

Results The error in general reproducibility in determination of the subject’s mean intima-media thickness was 5.9%. This parameter was also evaluated in a paired manner after dividing the whole artery into sectors; with this protocol, the percent error in general reproducibility was 15%. The main source of variability in the evaluation of common carotid intima-media thickness was found to lie in the operator’s subjectivity in the choice of the carotid sector to be processed (percent error, 10.27%). A method was therefore designed that used external reference points, resulting in reduction of this error by 38.2%.

Conclusions While the mean intima-media thickness might be considered a reproducible parameter to evaluate differences between populations exposed to diverse risk factors, evolutionary or therapy-induced changes in the individual may be better monitored on defined carotid sectors. This may be achieved with a high reproducibility by use of the proposed method based on external reference points.

Key Words • carotid arteries • diagnostic imaging • ultrasonics

In recent years B-mode ultrasound echography has allowed direct visualization of both the lumen and vessel wall of superficial arteries.1 By use of this technique it is possible to identify on the common carotid artery wall two echogenic lines separated by a relatively anechoic space. These lines were previously shown to be generated by the blood-intima and media-adventitia interfaces, respectively.1,2 The distance between these two lines was defined as the intima-media thickness (IMT).

It was proposed that increased IMT of extracranial carotid arteries may represent an expression of carotid and possibly also of coronary atherosclerosis.1,3,4 Although the atherosclerosis-IMT relation is not conclusively validated, an important atherosclerosis risk factor, hypercholesterolemia, was clearly associated with increased IMT.5-7 Likewise, IMT shows a direct association with age, blood pressure, cigarette-years of smoking, and diabetes, all risk factors of atherosclerosis.6,8 In a recent report, carried out on a nonselected eastern Finnish male population, carotid IMT showed a mean increase of 0.12 mm during the 2 years of study.9

Specific risk factors may have a strong influence on the rate of progression of atherosclerosis.9,10 Other disorders of the arterial wall, such as myointimal hyperplasia and/or hypertrophy, subsequent to carotid wall shear stress and/or mural tensile stress alterations may induce a compensatory and/or pathological increase in the IMT.11-15 Finally, myointimal hyperplasia consequent to surgical injury may account for the IMT increase.16

In an attempt to define the progression/regression of atherosclerosis, several clinical trials using pharmacological or dietary approaches are ongoing. These studies include the near and far wall B-mode ultrasound visualization of three specific segments of both extracranial carotid arteries. The sectors visualized are the proximal segment of the internal carotid artery, the carotid bifurcation, and the last distal centimeter of the common carotid artery.17,18 According to several studies that show an association between common carotid IMT (CC-IMT) and atherosclerosis risk factors,7,14 the importance of analyzing all visible tracts of the common carotid arteries other than the bifurcation is clearly evident. In the common carotid arteries the lack of clear anatomic reference points such as that available in the carotid bifurcation (ie, the flow divider) and methodological errors of estimation may limit the sensitivity of the approach, thus masking or underscoring either spontaneous evolution or changes induced by treatment.

In the present study the reproducibility of the method for CC-IMT determination was evaluated and quanti-
Subjects and Methods

Fourteen patients (age range, 48 to 64 years) attending the E. Grossi Foaletti Center for Metabolic Diseases were enrolled in the study. Oral informed consent was obtained from all patients. No specific selection criteria were used except that patients who presented with hard or mixed plaques at the level of the common carotid arteries were not considered. IMT in the far wall of the common carotid arteries of the patients ranged between 0.33 and 2.48 mm.

B-mode scans were performed with a Biosound 2000 II with a linear probe that generates a wide-band ultrasound pulse with a midfrequency of 8 MHz. The axial resolution of the system in B mode is at least 0.3 mm. In view of the difficulty in estimating near wall thickness because of artifacts, only the far walls of the right and left common carotid arteries were examined in the anterior, lateral, and posterior planes. Each common carotid artery was analyzed from distal to proximal, starting from the crest of the bifurcation.

To visualize the common carotid artery in its full length, without overlapping, two methodological approaches were used. In the first, to determine the thickness of common carotid arteries a standardized scanning technique was developed. Scanning of extracranial carotid arteries in the neck was performed in three different projections (anterior and posterior [patient lying on his/her back with the head in axis] and lateral [head turned 45° contralateral to the carotid artery under examination]). For each projection the carotid was identified at the level of the bifurcation and scanned in a cranio-caudal direction. Maximal care was taken to obtain a complete visualization of each common carotid artery. Since the instrument visualizes anatomic structures in a field approximately 2 cm long, for each projection two to four images were usually produced during the complete scan of the common carotid artery. To avoid overlapping the probe was placed along the common carotid artery, with anatomic internal points of reference displayed on the monitor (ie, echogenic structure present in the muscles).

To improve reproducibility in the choice of the carotid sector, the second methodological approach was used. With this method external references projected on the neck were used to place the probe on each carotid sector.

Specifically, a slide projector was assembled on a system that allows three axial movements. The patient is in the supine position, with the head extended and slightly rotated, with the projector displaying a grid (Fig 1, left panel) on the neck and face (Fig 1, right panel). Vertical and horizontal lines on the grid are labeled with numbers and letters, respectively. To define the location of the patient’s head as well as the carotid sector to be measured, the following procedures are followed. (1) The height of the slide projector is positioned to achieve a 1-cm distance between the lines displayed on the neck; the monitor is divided into three sectors with two horizontal lines, and only the middle third of the image is considered. The 1-cm distance between the lines displayed on the neck corresponds to the entire middle third of the carotid image. (2) The head of the patient is gently rotated to a position opposite the scanning site, setting point X (Fig 1, right panel) of the grid on the tip of the eye and extending the head until the diagonal line ZV (or for contralateral screening, UT) passes through the lower edge of the nose (point Y; Fig 1, right panel). (3) Specific markers of this line are then recorded.

During the first scanning, each common carotid sector chosen by the operator was designated by its corresponding grid lines. This parameter guided the operator in the search for the same carotid sector during the second scanning. In all conditions each identified sector was labeled with consecutive numbers. The complete procedure is generally carried out in approximately 30 minutes.

Measurements

Measurements were obtained by freezing videotape images on a television monitor. Selected frames were printed through a video copy processor (Mitsubishi, model P70B). The area between the two echogenic lines, corresponding to intima and adventitia, was manually traced on the printouts to define the image sector under study (Fig 2). To reduce image distortion, only the middle third of the carotid image displayed on the monitor was evaluated.

Area was measured on each print with a computer-assisted technique. The area of the carotid sector was manually traced with the pencil of a graphic tablet equipped with GRAPHICS TABLETS software. The precise length of each segment was determined with the same device. These measurements were performed by two operators, one performing the manual tracing of each carotid sector, the other recording the measurements. In this way the former was blinded regarding the results of each measurement. To reduce measurement error, areas and lengths were determined six times each.
The individual subject's mean CC-IMT values were calculated as the ratio between sum of the areas (A) of different sectors and sum of the lengths (L):

$$
\frac{(A_1 + A_2 + A_3 + \ldots + A_n)}{(L_1 + L_2 + L_3 + \ldots + L_n)}
$$

**Reproducibility of IMT Values Corresponding to Each Carotid Sector**

Reproducibility of IMT values corresponding to each carotid sector was determined using the two methods (with and without external reference guides).

For the paired analysis, the IMT of each sector was calculated as the ratio between area and length. The reproducibility of IMT values corresponding to defined carotid sectors (anterior 1 versus anterior 1, anterior 2 versus anterior 2, \ldots) was also evaluated. Percent error between paired data corresponding to IMT determinations was calculated as follows:

$$\frac{[(\text{Higher Estimate} - \text{Lower Estimate})]}{\text{Lower Estimate}} \times 100.$$

**Statistical Analysis**

The mean percent error was used when data had a normal distribution. If data had a skewed distribution, the median percent error and ranges were used. Precision in the evaluation of the same image was calculated by the percent coefficient of variation.

Accuracy was determined by comparing observed versus known values (2 mm) of a quadrangular image displayed on the video. Differences between percent error, obtained using the method of anatomic internal references and the method of external references, were compared using the Mann-Whitney U test.

**Results**

We evaluated intraobserver and interobserver variability in the quantification of the IMT in 14 subjects. B-mode examinations were performed twice by three sonographers on 2 different days, with at least a 2-week interval between the first and the second scan. Each operator selected and processed 10 images from each scan performed by himself. Intraoperator and interoperator percent errors in the evaluation of mean IMT were 2.5% (range, 0% to 4.54%) and 5.9% (range, 0% to 8.31%), respectively. When IMT values of specific carotid sectors (anterior 1 versus anterior 1, anterior 2 versus anterior 2, \ldots) were compared, intraoperator and interoperator percent errors rose to 11.6% (range, 0.84% to 24.42%) and 15.0% (range, 0% to 33.33%), respectively. Since a mean IMT progression of approximately 10% in 2 years can be estimated, this error must be considered unacceptably high. A series of studies was performed to identify major factors contributing to the generation of the error.

The first approach consisted of measuring the IMT of the common carotid artery using the conventional technique (see "Subjects and Methods"). To define accuracy of image determination each operator measured 10 times with the graphic system a rectangular image of known size displayed on the video, and area and length were defined. With this kind of image, percent error (accuracy) was 2.5% (range, 0% to 4.5%), and percent coefficient of variation (precision) was 1.3%.

Because the irregularity of the vessel wall profile can influence the reproducibility of image processing, determinations of IMT were performed on images showing irregularities in the far wall profile. Therefore, for each operator, 10 printouts from three particularly irregular IMT images were processed. In this case percent coefficient of variation rose to 4.3%. Thus, irregularity of the vessel wall profile yielded an increase in error of 3%.

To evaluate the influence of cardiac cycle changes on CC-IMT determination, several frames from 10 patients, corresponding to the maximum and minimum luminal diameters of the common carotid arteries, were chosen to compare systolic and diastolic IMTs. No significant difference was found between systolic and diastolic IMT determinations. The median percent variation was 2.73% (range, 0% to 11.53%). Moreover, we did not find any constant trend in changes in CC-IMT determined in systole and diastole.

We also evaluated the intraoperator and interoperator precision of intima-media complex tracings on printouts of frozen carotid images. Three operators, using 10 printouts each of a single carotid image, repeatedly traced the same area on the common carotid artery. All traced images were measured by a single operator. Intraoperator and interoperator coefficients of variation were 4.7% and 4.9%, respectively. On 10 previously traced printouts with different anatomic characteristics,
we also determined the intraoperator and interoperator precision of IMT measurements. Each operator measured these images six times on 2 different days. Intraoperator and interoperator mean percent errors were 1.8% (range, 0% to 8.33%) and 1.5% (range, 0% to 6.25%), respectively. Therefore, the error attributable to the manual tracing of the perimeter was greater than that consequent to image measurement.

The operator’s subjectivity in the choice of the carotid sector for IMT measurement was also evaluated. To this end, two sonographers examined 10 patients and labeled each common carotid sector by a progressive number. Corresponding IMT images were processed by a third operator to isolate the variable analyzed in this step. Interpersonal comparisons corresponding to determination of each carotid sector were performed. Median percent error was 10.27% (range, 0% to 42.36%). Since the selection of the image was the step with the major variability in the evaluation of CC-IMT, to reduce this error a reference guide for patient and probe positioning was tested, as described in “Subjects and Methods.” This step was repeated on the same 10 patients by using the reference guide. To this end the height of the projector was defined and the head of the patient rotated in the appropriate position (see “Subjects and Methods”). With this system, overlapping and subjectivity in the selection of images were avoided. In this case, interpersonal comparison corresponding to each carotid sector yielded a median percent error of 6.35% (range, 0% to 27.4%). Thus, significantly smaller errors were obtained when the reference line system was used to locate the same carotid sector repeatedly (10.27% versus 6.35%; P<.05).

Discussion

The individual IMT may be considered a descriptive general index of the presence or absence of atherosclerosis in the carotid arteries.1-3-4 Previous studies have evaluated reproducibility in the estimation of mean IMT. An absolute difference in blinded replicate measurements of mean IMT of less than 0.2 mm was reported by Insull et al.10 In this study changes in IMT of more than 0.35 mm were rated as “progression” or “regression” of atherosclerosis.

The same parameter was evaluated by Riley et al19 in the multicenter Asymptomatic Carotid Artery Plaque Study (ACAPS). In this study the investigators evaluated the effect of the performance of the sonographer/reader on two different end points. The primary end point was measurement of the extent and severity of atherosclerosis in the carotid artery, assessed as the mean of 12 measurements of maximal IMT. Mean absolute differences in blinded replicate measurements of mean IMT of 0.1 mm (intrapersonal) and 0.11 mm (interpersonal) were reported. When the same parameter was evaluated on the primary end point (single maximum IMT of the 12 measurements), the mean absolute differences were 0.31 mm (intrapersonal) and 0.36 mm (interpersonal), which were three to four times larger than those for the primary end point.

In a single-center study of carotid atherosclerosis, using IMT measurements obtained only from the common carotid artery, Touboul et al20 reported correlations of 0.61 and 0.58 (intraobserver and interobserver, respectively) with a standard echographic investigation; when using a computer-assisted method for recognizing echographic sections, the same authors instead reported correlations of 0.77 and 0.71 (intraobserver and interobserver, respectively). A better correlation was found in the reproducibility study performed by Salonen et al,21 in which the intraobserver correlation was approximately 0.9. In a previous study carried out by our group an average difference between duplicate thickness determinations of 4.6% was found.7

Therefore, the reproducibility of CC-IMT evaluation depends on the performance of the sonographer/reader and also on the technique used for image processing. In the present study the influence of each variable on the reproducibility of our image processing method was analyzed, evaluating one variable at a time and keeping the others constant. Our results show that images can be measured with the image processing system used in this study with a high degree of accuracy. Neither irregularity of processed images nor the moment of the cardiac cycle when images are obtained significantly influences reproducibility.

The observed lack of influence of cardiac cycle changes on CC-IMT determination is in contrast with the findings by Devereux et al.22 These authors, using M-mode ultrasonography, found a 5.3% decrease in arterial wall thickness from end-diastole to the time of peak arterial pressure. This could be due to either the different ultrasonographic technique or the fact that the 5% difference is within the range of the intrinsic error of the method. Tracings and measurement of the intima-media complex did not introduce a substantial error.

The definition of the carotid sector appears to be the more important determinant that influences reproducibility (median percent error, 10.27%). This finding is in agreement with Salonen et al,21 who recently reported a 10.5% interobserver precision in the evaluation of the point of maximal IMT on the common carotid arteries, and is also in agreement with Riley et al.19 In fact, although the methods used to acquire the atherosclerosis end points in ACAPS are quite different compared with our scanning/reading protocol, in the latter study mean absolute differences for the secondary end point (analogous to our “sector-to-sector” paired analysis) are three to four times larger than those for the primary end point (analogous to our standard IMT analysis).

Thus, earlier and present data suggest that reproducibility in the estimation of the mean IMT might be considered adequate (approximately 5% error) to allow evaluation of long-term evolutional changes and influence of specific risk factors. However, spontaneous or therapy-induced changes of irregular IMT might not be uniform. Furthermore, a localized change in the IMT of the common carotid artery might be underestimated by the subject’s mean IMT value. This prompted us to analyze data in a paired manner, considering specific carotid sectors. Paired analyses showed intrapersonal and interpersonal percent errors of 11.58% and 15.02%, respectively. Thus, this error might mask small local changes that take place in a relatively short-term study of progression or regression of atherosclerotic lesions. Moreover, by using a system that allows one to follow over time single lesions with high reproducibility, the analysis of multiple images might be avoided, with a significant saving in time and costs.
With the use of the proposed method based on external reference points, the major factor influencing reproducibility, ie, the error in the definition of the common carotid sector (10.27%), was reduced by almost 40%, thus obtaining a reproducibility error (6.35%) comparable to that achieved when evaluating the subject's mean IMT.7

The described method represents an inexpensive and relatively time-saving approach to optimize the reproducibility of IMT evaluation for clinical trials with CC-IMT evaluation as the primary end point. The main difficulty with the proposed technique is that the exact head position has to be continuously monitored during examination. Small changes in the head position might significantly impair reproducibility. The proposed method was validated only in the common carotid arteries because the carotid bifurcation offers a clear anatomic reference point, the flow divider, which allows us to study this structure with good reproducibility.10,19-21

While the mean CC-IMT may be considered an appropriate parameter to evaluate differences in the IMT between populations with different risk factors, evolution or therapy-induced changes in the individual should be better monitored on well-defined common carotid sectors. The proposed method based on external reference points may achieve the necessary reproducibility.

References
Common carotid intima-media thickness measurement. A method to improve accuracy and precision.
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