Noninvasive Quantification of Atherosclerotic Lesions

Reproducibility of Ultrasonographic Measurement of Arterial Wall Thickness and Plaque Size

Jerker Persson, Lars Stavenow, John Wikstrand, Bo Israelsson, Johan Formgren, and Göran Berglund

A noninvasive method based on high-resolution B-mode ultrasonography and a computerized image-analyzing system were used for the quantification of early (thickening of the intima-media complex) and late (plaque) atherosclerosis in the carotid and the femoral artery. The difference between repeated measurements was assessed to estimate intraobserver and interobserver differences. The results were satisfactory, with a coefficient of variation for measurement of lumen diameter in the common carotid artery of 3.8±4.1% (r=0.91) and for the femoral artery of 4.8±4.1% (r=0.93). Corresponding figures for intima-media thickness in the common carotid artery and the femoral artery were 10.0±8.5% (r=0.86) and 16.2±12.6% (r=0.91), respectively. The coefficient of variation for measurements of maximal intima-media thickness at the site of the plaque was 14.6±10.5% (r=0.88); for plaque base, 13.1±9.0% (r=0.91); and for plaque area, 16.3±12.6% (r=0.90). The method seems promising for the detection and quantification of early and late atherosclerotic lesions in the carotid and femoral arteries.

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It has been possible to study the extent of atherosclerosis mainly by identifying clinical symptoms or by analyzing morbidity and mortality caused by vascular events. Symptoms and vascular events are, however, signs of advanced vascular disease and, as such, are not useful for studies of the asymptomatic phase of atherosclerosis.

In the clinical situation, the extent of atherosclerosis has been evaluated by angiography, but for ethical reasons, this method cannot be used for serial investigations of atherosclerotic lesions in an asymptomatic population. Furthermore, results from other studies suggest that so long as the atherosclerotic process occupies less than 40% of the cross-sectional area inside the internal elastic layer, the artery may dilate to keep its lumen diameter intact, at least in the coronary arteries.1,2 This phenomenon further diminishes the usefulness of angiography for detection of early atherosclerotic lesions, as this method only visualizes the lumen of the vessel.

During the past few years, several groups have attempted to develop noninvasive (ultrasonographic) methods to measure the thickness of the arterial wall.3-7 Duplex-scanning estimations of the degree of stenosis have been correlated to those on angiograms and to findings in specimens obtained at thrombendarterectomy.8 Studies of intima-media thickness, as determined by high-resolution B-mode ultrasonography and light microscopy, have been done on autopsy material3 and in animal models,7 and these show good correlation. The usefulness of this method is substantiated by findings that show that patients with hypercholesterolemia have a thicker intima-media layer than those with normal serum cholesterol levels.9 The change in intima-media thickness has also been found to be associated with other risk factors for atherosclerosis.10 Reproducibility concerning the methods for quantification of late-stage lesions such as plaque size are, however, not yet available.

An ultrasound-based method with a computerized image-analyzing system for the quantification of early (thickening of the intima-media complex) and late (plaque) atherosclerosis in the carotid and femoral arteries has been used in clinical studies of the...
progression and regression of atherosclerosis. The aim of the present study was to describe the examination procedure of the ultrasound investigation and to determine the reproducibility of measurements of lumen diameter, intima–media thickness, and plaque size with this method.

Methods

Subjects who attended the Section of Preventive Medicine or the Hypertension Unit at the Department of Medicine at Malmö General Hospital because they had risk factors for cardiovascular disease were invited to undergo an ultrasound examination of the carotid and femoral arteries. The subjects had no symptoms of atherosclerotic disease in the investigated vessel area. Age ranged from 45 to 70 years, and the approximate male to female ratio was 3:2. They were examined by two independent, well-trained, and experienced sonographers and were reexamined by the same sonographers within 2 weeks (minimum, 1 week). The sonographers were technicians who had been educated in basic ultrasound technology and human anatomy. In addition, they had received 6 months of training, including use of the ultrasound system, reading procedures, and quality control programs. On no occasion did the observer have knowledge of the results of previous measurements. The results were compared, and intraobserver (same sonographer at the same occasion) and interobserver (different sonographers at the same occasion) differences were calculated as the mean difference (percent) of the paired observation:

Percent difference = (highest value - lowest value)/lowest value

As a general measurement of the laboratory’s ability to perform reproducible investigations, total difference was calculated as the average of intraobserver and interobserver differences.

Examination Procedure

An Acuson 128 Computed Sonography System (Acuson, Mountain View, Calif.) with a 5-MHz linear transducer was used. Patients were examined in the supine position and, during examination of the carotid artery, with the head turned 45° contralaterally with the help of a cushion that had been specially designed for this purpose. When needed, Doppler ultrasound was used to identify the different arteries. The bifurcation region of the arteries was thoroughly scanned for the occurrence of plaques from a distance 3 cm proximal to 1 cm distal to the flow divider. They were examined in both the longitudinal (in the carotid artery, with the transducer placed in front of and behind the sternocleidomastoid muscle) and the transverse view. If a plaque (defined as a discernable focal thickening of the artery wall confirmed on a high-quality recording) was present, it was visualized in both the longitudinal and transverse views to determine the transducer projection from which to record three “frozen” end-diastolic (electrocardiographic R-triggering) images in the longitudinal view on videotape for off-line analysis. To avoid misinterpretation of plaque proportions when recording the images, we always attempted to align the ultrasound beam (transducer projection) so that it crossed the axis (center) of the vessel. Frozen end-diastolic images showing the intima–media complex along at least 1 cm of the artery proximal to the bifurcation were recorded. Also for these recordings, we attempted to align the ultrasound projection so that it crossed the axis of the vessel to guarantee true proportions of lumen diameter and intima–media thickness. Only in this projection are the inner echoes of both the near and far walls clearly visible. All repeated examinations were performed without knowledge of the results of previous examinations. The purpose was to detect and quantify all atherosclerotic lesions within a predefined window 3 cm proximal and 1 cm distal to the flow divider in the carotid and femoral arteries and to determine the intima–media thickness proximal to the bifurcation. Within this defined vessel area, the extent of atherosclerosis was quantified as maximal intima–media thickness at the site of the plaque, plaque base, and area.

Image Analysis

Images were analyzed off-line by the sonographer according to a strict protocol and with the use of a computerized image-analyzing system. The identities of the subjects were coded and thus were unknown to the observers during analysis to minimize the possibility of their remembering results from previous measurements. Edges of echoes, intima–media thickness at the site of the plaque, plaque base, and plaque contour were outlined on the frozen video image by use of a digitizer. Intima–media thickness and lumen diameter were calculated by the computer as the mean thickness and diameter along a 1-cm
portion of the vessel (Figure 1). The distance between the leading edges of the inner echoes of the artery walls represents lumen diameter, and intima-media thickness is the distance between the leading edges of the inner and outer echoes of the far wall. Results of plaque analysis were calculated as mean values of the results of three frozen images recorded on videotape (Figure 2). The lumen-intima and the media-adventitia interfaces were traced to the points where no thickening of the intima-media complex could be seen. Lines connecting these points were then drawn so that the computer could calculate plaque area. At several places, the intima-lumen interface did not give rise to any echo because the sound waves were not transmitted perpendicularly to the anatomic surface. On the screen, the line was extrapolated across these minor irregularities. Plaque base was marked as a straight line and was used to define the maximal length of the plaque in the longitudinal section, but the line in itself did not correspond to any acoustical interface. In this study of reproducibility, plaques were located in the far wall of the femoral artery proximal to the beginning of the profund femoral artery and in the far wall of the carotid artery bifurcation at an approximate ratio of 1:1.

Results

Measurements of Intima-Media Thickness and Lumen Diameter

The mean intima-media thickness in the common carotid artery was 0.88±0.20 mm (n=43) and in the femoral artery, 0.87±0.42 mm (n=17). Lumen diameter measurements averaged 6.33±0.71 mm (n=43) in the common carotid artery and 8.07±1.04 mm (n=17) in the femoral artery. Values for intraobserver and interobserver differences are listed in Table 1. Results are given in absolute (millimeters) and relative (percent) terms. Correlations between repeated measurements are presented in Figure 3, separately for intima-media thickness (panel A) and lumen diameter (panel B) determinations in the common carotid artery and the femoral artery (panels C and D). A small variation was achieved for lumen diameter measurements irrespective of vessel type (3.5-5.6%) as well as for intima-media thickness determinations in the carotid artery (9.7-11.0%). In the femoral artery, intima-media thickness determinations varied somewhat more (13.8-18.5%). Whether the examinations were performed by the same or different observers did not signifi-

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<th>TABLE 1. Absolute and Relative Differences Between Repeated Measurements of Intima-Media Thickness and Lumen Diameter</th>
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Absolute (millimeters) and relative (percent) differences were measured in the common carotid (CCA) and femoral arteries. Intraobserver difference, same observer at different occasions; Interobserver difference, different observers at the same occasion. Total is the average of intraobserver and interobserver differences. Values are given as mean±SD.
FIGURE 3. Scatterplots showing reproducibility of intima-media thickness (mm) (panel A) and lumen diameter (panel B) measurements in the common carotid artery and corresponding measurements in the femoral artery (panels C and D). Intraobserver (o) and interobserver (x) differences are given separately. For panel A, n=65, r=0.89 and n=69, r=0.84 for intraobserver and interobserver differences, respectively. The corresponding values for panel B are n=65, r=0.90 and n=69, r=0.92; for panel C, n=32, r=0.93 and n=34, r=0.92; for panel D, n=32, r=0.93 and n=34, r=0.93. p<0.001 for all panels.

Determination of Plaque Size

Intraobserver and interobserver differences have been assessed with regard to intima-media thickness at the site of the plaque, plaque base, and plaque area. Results are listed in relative terms in Table 2. Correlations between repeated measurements of these variables are presented in Figure 4. Intraobserver and interobserver differences between repeated measurements of the three variables ranged from 11.9 to 17.3%. Figure 4 describes the correlation between repeated examinations of plaques of very different sizes.

Discussion

Image analysis is prone to observer bias. Therefore, we developed a special off-line image-analyzing system, based on an inexpensive personal computer, to minimize this bias. The good reproducibility obtained for quantitative measurements of both intima-media thickness and plaques indicates that the strict protocol applied to our examination procedure and to image analysis is valuable. Because the purpose of this study was to determine the reproducibility of the method, the sonographers and the analyzers were the...
same persons. In future studies of atherosclerosis progression and regression, however, the risk for bias would probably be lower if these tasks were separated. Our experience, however, indicates that to achieve reliable results, all technicians involved should have training in both the investigation and reading procedures.

Our technicians have been trained and checked repeatedly during the 2 years of the study. If interobserver difference equals that of the difference between repeated measurements performed by one skilled observer at different occasions, this indicates that the training program is adequate and that the results of serial investigations is not dependent on one specific observer.

The method described was found to be highly reproducible for measurements of intima-media thickness in the carotid artery and of lumen diameter in the carotid and femoral arteries. The reason for this and the advantage of this method are mainly that an average of a large number of intima-media thicknesses along 1 cm of artery is calculated by the computer. The reproducibility for measuring intima-media thickness in the femoral artery, however, was less satisfactory. The total difference was 16.2%, even though the investigations were carried out by trained and experienced sonographers. Moreover, in many cases it was difficult to visualize the intima-media complex in the femoral artery. This is probably because of the curvature of this artery in the area of investigation. Because the transition between blood and intima is not perpendicular to the ultrasound waves, it does not give rise to an echo strong enough to be discriminated from surrounding artifacts. The few extreme values of intima-media thickness (>1.2 mm; Figure 3C) could be expressions of early soft plaques. The results of lumen diameter measurements were obtained, although the small blood pressure variation between two examinations was not taken into consideration.

The analysis of a two-dimensional representation of a three-dimensional object demands practical and theoretical considerations. First, there is the desire to return to exactly the same probe projection during serial investigations. To our knowledge, there are no technical instruments or generally accepted methods to guarantee the same investigation plane repeatedly. However, if the vessel is carefully investigated in the transverse view also, the observer can more easily see in which projection the plaque obstructs the vessel lumen the most, and from this, the observer can visualize a representative two-dimensional

**Figure 4.** Scatterplots showing reproducibility of measurements of intima-media thickness at the site of the plaque (panel A), the plaque base (panel B), and plaque area (panel C). The plaques were located in the carotid and femoral arteries. Intraobserver (○) and interobserver (×) differences are given separately. For panel A, n=13, r=0.90 and n=20, r=0.86 for intraobserver and interobserver differences, respectively. The corresponding values for panel B are n=13, r=0.94 and n=20, r=0.90; for panel C, n=13, r=0.92 and n=20, r=0.92. p<0.001 for all panels.
image of the (three-dimensional) plaque through the axis of the artery. Second, there is the question of high image resolution combined with the ability to visualize deeper-lying structures. The use of a 7-MHz transducer to improve reproducibility is presently under evaluation.

As a complement to the described quantitative method to evaluate plaques, the extent of atherosclerosis in a defined vessel area may also be improved by estimation according to a semiquantitative scale. The reason for this is that the quantitative method is unable to distinguish between two arteries with plaques of similar size, but where one of the arteries contains more than one plaque (the analyzed plaque). Furthermore, the sensitivity and specificity of prospective studies of atherosclerotic progression and regression may improve if a description of plaque composition is added.11 Some groups have tried to determine the presence or absence of plaque ulceration with ultrasonography.12,13 Other studies have attempted to correlate ultrasound appearance of plaques (hypoechoigenicity, ulceration, or calcification) with clinical manifestations of atherosclerotic disease.14-16 The validity of these applications of ultrasound technology, however, needs to be further confirmed.

We conclude that this noninvasive method seems promising for serial investigations of early and late atherosclerosis. Reproducibility was high for measurements of intima-media thickness and lumen diameter in the carotid artery. The results from repeated measurements of plaque size showed good correlation. Hence, the method seems sensitive enough to be applied in clinical studies of the progression and regression of atherosclerosis. The value of surrogate variables for hard end points such as myocardial infarction and total mortality in epidemiological studies and clinical trials has been discussed elsewhere.18

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References


Key Words • atherosclerosis • intima-media thickness • plaque • reproducibility • ultrasound imaging
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