From the Society for Vascular Surgery

Carotid plaque morphometric assessment with three-dimensional ultrasound imaging

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Objective: **As investigations into nonsurgical treatment for atherosclerosis expand, the measurement of plaque regression and progression has become an important end point to evaluate. Measurements of three-dimensional (3D) plaque volume are more reliable and sensitive to change than are traditional estimates of stenosis severity or cross-sectional area. 3D ultrasound (3D US) imaging may allow monitoring of plaque volume changes but has not been used routinely due to the cumbersome motorized units required to drive transducers. We investigated the variability, reliability, and the least amount of change detectable by 1D plaque measures, as well as 2D and 3D measures of plaque morphometry, that can be applied in a clinical environment.**

Methods: **3D US imaging was obtained in 10 patients with carotid stenosis. The lumen and outer wall boundaries were outlined in serial cross-sectional images 1 mm apart. Three observers manually segmented vessel wall volumes (VWVs), and the segmentation was repeated again 4 weeks later. This allowed measurement of interobserver and intraobserver variability of 6 pairs of observations. We measured Bland-Altman statistics, intraclass correlation coefficients, coefficient of variability, and the minimum detectable plaque change for each morphometric measure.**

Results: **The mean VWV of carotid lesions in the study was 1276.8 mm^3 (range, 620.6-1956.3 mm^3). Bland-Altman plots demonstrated low interobserver and intraobserver variability. The interobserver variability of volume measurements as a function of mean volume was 14.8% and interobserver variability was 8.9%. Reliability was 87% as quantified by the interclass correlation and was 95% by the intraclass correlation. The least detectable change in VWV was 12.9% for interobserver variability and 4.5% for intraobserver variability for the three observers.**

Conclusions: **Carotid plaque diameter measurements from B-mode images have high variability. Plaque burden, as estimated by VWV, can be measured reliably with a 3D US technique using a clinical scanner. The volumetric change, with 95% confidence, that must be observed to establish that a plaque has undergone growth or regression is ~12.9% for different observers and 4.5% for the same observer performing the follow-up study. (J Vasc Surg 2015;61:690-7.)**

Traditional methods of assessing the severity of carotid atherosclerosis use a Doppler velocity-based classification of stenosis categories in broad ranges. However, these ranges of stenoses are insensitive to small changes in the plaque burden. An alternative is direct measurement of diameter reduction by B-mode imaging. However, plaques progress along the length of an artery 2.4 times faster than they thicken.[1] Therefore, methods that capture longitudinal and circumferential growth (ie, area and volume) are inherently more sensitive to a change in plaque burden (change in size of the plaque) than methods limited to thickness measurements (ie, diameter-reducing stenosis). These measures are important in clinical practice as emphasis increases for pharmacologic management of asymptomatic carotid atherosclerosis. The ability to accurately detect and quantify plaque change will become a critical determinant of treatment success or failure, which may predict a reduced or increased risk for stroke.[2,3]

Only three-dimensional (3D) plaque imaging can capture all critical dimensions of a plaque. Although computed tomography (CT) or magnetic resonance imaging (MRI) offer 3D imaging capabilities, they are expensive, often associated with nephrotoxic contrast agents (CT and MRI) and radiation exposure (CT), and are less suitable for longitudinal life-long surveillance of carotid plaques. Imaging with 3D ultrasound (US) can reduce the operator variability inherent in traditional US imaging and is economical and safe for serial testing. However, previously reported 3D US methods for carotid plaque imaging have involved cumbersome and specialized motorized units that move the transducer across the neck, required significant postprocessing time and experience, and have not received widespread clinical acceptance.[4]

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In this study, we tested the reliability of 3D plaque imaging using a new commercially available 3D US transducer. We measured operator variability, reliability, and the least amount of change detectable by traditional 1D plaque measures, as well as nontraditional 2D and 3D measures of plaque morphometry. Our study forms the first comprehensive assessment of the same carotid plaques for 1D (diameter), 2D (longitudinal and cross-sectional area), and 3D (volume) measures. We also provide one of the first evaluations of the reliability of atherosclerotic carotid vessel wall volume (VWV) measurements as a measure of total plaque burden using a clinical 3D US transducer.

METHODS

The University of Maryland School of Medicine Institutional Review Board and the VA Medical Center Research and Development Committee, in Baltimore, Md, approved the protocol for this study.

Patients. The study enrolled 10 consecutive patients with ≥50% asymptomatic carotid stenosis. Patients with an occlusion in the target artery were excluded. Demographics and risk factors recorded prospectively were ethnicity, diabetes mellitus, coronary artery disease, hypertension, hypercholesterolemia, smoking, and peripheral arterial occlusive disease. The patients were recruited from the Veteran Affairs Medical Center in Baltimore, Md, and provided informed consent.

Clinical duplex US examination. Patients first underwent a standard carotid duplex US examination according to recommendations of the Inter-societal Accreditation Commission using a Sonix MDP system (Ultrasonix, Richmond, BC, Canada) and an L9-4/38 linear probe. The degree of stenosis in the carotid artery was estimated using Doppler velocities with appropriate angle correction according to standard techniques used by our group[5-7] (Fig 1, *A*). We used consensus velocity criteria to define the degree of stenosis for the purposes of inclusion into the study.[8]

2D US imaging protocol. Standard clinical B-mode imaging techniques were used to define the least luminal diameter (LLD) and plaque area in longitudinal and cross-sectional views as reported previously by our group.[6,9] As in clinical testing protocols, the sonographer was free to select the optimal insonation angle to obtain the best image of the plaque. A longitudinal image (Fig 1, *B*) was obtained first, and the transducer was then swept from the base of the neck to the angle of the mandible to identify and record the cross-sectional image where the tightest stenosis was visualized (Fig 1, *C*). The images were digitally recorded and analyzed off-line with a computer-assisted image-analysis program by independent observers blinded to clinical findings. The entire US examination was recorded on digital video for subsequent interpretation.

3D US imaging protocol. A standardized imaging protocol described by our group previously[10] was used to obtain 3D images of the carotid artery with a 4DL14-5/38 transducer (Fig 1, *D*). This 3D probe consists of a motorized linear array transducer that moves within a housing to capture a sequence of 2D image frames at different elevation angles, which can then be reconstructed into a 3D volume (Fig 1, *E*). The operator's hand and the patient were held still to reduce movement artifacts. A complete volume was acquired in <1 second, which minimized movement artifact from cardiac and respiratory movements.

Image analysis protocols. The acquired volumes consisted of raw unprocessed US data after envelope detection. The volumes were reconstructed using custom software developed using MATLAB (The MathWorks Inc, Natick, Mass). Brightness levels were adjusted using an automatic adaptive histogram-equalization method with a Rayleigh distribution[11] to enhance visualization of the vessel boundary. After postprocessing, three observers analyzed the images from the 10 patients. Stradwin (Cambridge, United Kingdom) image analysis software was used for manually outlining the plaque in reconstructed 2D sagittal (cross-sectional) images.[12]

Each observer was blinded to measurements performed by the other individuals. The three observers repeated the segmentation on all 10 patients after an interval of at least 4 weeks between the two segmentations to minimize recall bias. This approach allowed calculation of interobserver and intraobserver variability of the protocol. Intrascan analysis was performed by scanning the same patient (for the initial volume), then resting the patient, and performing the scan again. A single observer performed the intrascan segmentation on three patient data sets.

Analysis of 3D images. Each individual cross-sectional image was segmented commencing from where the plaque started until where it ended, with an interslice distance of 1 mm. The plaque in most of the cohort became visible in the common carotid artery proximal to the carotid bulb and ended in the proximal or middle internal carotid artery. Two boundaries were manually traced: first, the lumen-intima boundary (LIB), which defined the plaque surface; and second, the outer wall boundary (OWB), the outer edge of the adventitia layer, which defined the outer surface of the plaque.

For all situations, including those where the boundaries in cross-sectional slices were ill defined due to shadowing or echolucent plaques, the cross-sectional outlining was guided by longitudinal sectional slices of the volume to identify the relative location of the boundaries in that slice. Additional views obtained in color-flow and grayscale modes, as well as video of the 2D US examination, were also used as a guide to identify the boundaries.

The region between these two boundaries was the VWV and is the most complete estimation of atherosclerosis within the carotid artery. Previous segmentation methods identified plaque as the region between the LIB and media adventitia boundary (MAB).[13] However, MAB is often poorly visualized in US images, and the OWB, including the adventitial layer, is easier to visualize. We therefore used OWB to determine VWV rather than MAB. At the end of segmentation, the program