Three-Dimensional Ultrasound of Carotid Plaque

J. David Spence, MD, FRCPa,*, Grace Parraga, PhDb

KEYWORDS
• Carotid arteries • Atherosclerosis • Plaque • Measurement

KEY POINTS
• Carotid plaque burden can be measured by two-dimensional or 3D ultrasound.
• Measurements of carotid plaque burden are useful in risk assessment, genetic research, and evaluation of new therapies.
• Three-dimensional ultrasound of carotid plaque volume is useful for risk stratification, for evaluating effects of therapy on atherosclerosis, and for managing patients at risk of cardiovascular events, by a strategy that has been called “treating arteries instead of risk factors.”

HISTORY OF THE DEVELOPMENT OF THREE-DIMENSIONAL CAROTID PLAQUE ULTRASOUND

Early applications of ultrasound in the carotid arteries focused on using the Doppler shift to evaluate blood velocity and flow disturbances; our group used implanted ultrasound probes in the carotid arteries to assess effects of antihypertensive drugs on blood velocity and pulsatility, using spectral analysis to evaluate flow patterns.1 The primary clinical use was for diagnosing carotid stenosis2,3; we used a primitive device, the Dopscan, to evaluate effects of antihypertensive drugs on turbulence at sites of stenosis.4 When the author JDS obtained a duplex scanner because it provided spectral analysis to evaluate drug effects on flow disturbances,5,6 he realized that it was possible to image and begin to quantify carotid plaque burden. It was Maria DiCicco RVT, in the author’s laboratory, who told JDS that there was software in the scanner that could measure plaque area, and first measured carotid total plaque area (TPA), in 1990. After JDS told Jon Wikstrand about it, Wikstrand’s group published a method in 1992.7 Then in 1997, TPA was used to study effects of mental stress on atherosclerosis8; Fig. 1 is reproduced from that paper.

In 1994, around the time that Delcker and Diener9 published their early work on three-dimensional (3D) ultrasound estimation of plaque volume, Dr Aaron Fenster visited JDS at Victoria Hospital in London, Ontario to ask if he would be interested in using the 3D ultrasound system that Fenster had developed for other purposes10,11 to measure 3D carotid plaque volume. JDS visited his laboratory soon after. Fig. 2 shows perhaps the first measurement of plaque volume, in his right carotid artery in 1994 on Fenster’s prototype machine. In 1995 JDS moved to University Hospital and the Robarts Research Institute to collaborate with Dr Fenster, and then later Dr Grace...
Parraga, to develop 3D ultrasound of carotid plaque.

Topics discussed in this article include measurement of plaque burden, ulceration, echolucentcy, and plaque texture.

**MEASUREMENT OF PLAQUE BURDEN AND ITS PROGRESSION/REGRESSION**

Measurement of carotid intima-media thickness (IMT) had begun around 1985, first in monkeys\(^1\) and then in human subjects.\(^13,14\) Having been taught atherosclerosis by Dr Daria Haust (for many years the Editor of *Atherosclerosis*, and a Professor of Pathology at University of Western Ontario), JDS understood early on that IMT did not truly represent atherosclerosis,\(^15–18\) and decided to focus on quantification of plaque burden.

In 2002 his group reported\(^19\) that TPA was a strong predictor of cardiovascular risk among patients attending cardiovascular prevention clinics. After adjusting for age, sex, blood pressure, cholesterol, smoking, diabetes, homocysteine, and treatment of blood pressure and cholesterol, patients in the top quartile of TPA had a 3.4 times higher 5-year risk of stroke, death, or myocardial infarction. By quartile of TPA, the 5-year risks were approximately 5%, 10%, 15%, and 20%. Thus TPA was much stronger than a Framingham risk profile in predicting risk. During the first year of follow-up, approximately half the patients had plaque progression, a quarter had regression, and a quarter was stable. Those with plaque progression had twice the risk of events, after adjustment for the panel of risk factors listed previously. Our findings were borne out in the Tromsø study, a population-based study in Northern Norway of more than 6000 participants who were healthy at baseline. That study showed that TPA, but not IMT in the distal common carotid, predicted myocardial infarction\(^20\) and stroke.\(^21\) Added to risk calculation using scores based on risk factors, TPA significantly improves risk prediction.\(^22\) Subsequently it has...
become apparent in meta-analyses that IMT is only a weak predictor of cardiovascular events, adding little to a Framingham risk score,23,24 and that progression of IMT does not predict events.25 Brook and colleagues26 found that TPA significantly changed risk prediction and was more predictive of coronary stenosis than IMT, coronary calcium score, or C-reactive protein.27 Sillesen and colleagues28 found that carotid plaque burden (an estimated plaque volume assessed by moving the probe along the carotid) was much more closely correlated with coronary calcium score than IMT.

**Measurement of Three-Dimensional Plaque Volume**

Perhaps the first description of estimation of plaque volume was in a study by Hennerici and Steinke in 1987.29 Initial measurements of carotid plaque volume were laborious; the method, called disk segmentation, required acquisition of a series of two-dimensional cross-sectional slices captured by translating the ultrasound probe along the carotid artery with a mechanical device, tracing of the plaque area in serial cross-sections of the artery, stepping through the plaque at intervals of 1 to 2 mm, and summing the slices to obtain plaque volume (Fig. 3). Early work specified the reproducibility, reliability, interslice distance, and other technical issues.30–34 Ludwig and colleagues35 in 2008 and papers in 2014 and 201536,37 reported good reproducibility, similar to results previously reported by Fenster’s group, and also found that reproducibility was better for large plaques than for small ones.

The disk segmentation method was not only laborious; it required 2 to 3 months of training and practice to learn to do it reliably and achieve certification in its use, and some candidates (approximately a third) were not able to perform it reliably: it seemed that perfectionists struggled too much with deciding where to demarcate boundaries, and others were too careless. These issues were the impetus for development of semi-automated and automated methods that would be less operator-dependent, less laborious, and perhaps more reproducible and reliable.

Early semiautomated methods38,39 reduced the number of slices of the plaque that required manual input to set the proximal and distal ends of each

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**Fig. 3.** Procedure for determining plaque volumes from 3D ultrasound (US) images. (A) An approximate axis of the vessel is selected in a longitudinal view (purple line) and the internal elastic lamina and lumen boundary are outlined (yellow). (B) Using the surfaces generated by the vessel contours and the 3D US image, the position of the bifurcation (BF; yellow arrow) is determined and marked. The axis of the vessel is selected based on the bifurcation point, and marked along the branch as far as the plaque can be measured (purple line). This axis is used as a reference for distance measurements. (C) All plaques within the measurable distance are outlined, different colors being used for each separate plaque to aid in identification. (D) Volumes are calculated for each plaque, and surfaces of the vessel wall and plaques are generated to better visualize the plaques in relation to the carotid arteries. *(From Ainsworth CD, Blake CC, Tamayo A, et al. 3D ultrasound measurement of change in carotid plaque volume: a tool for rapid evaluation of new therapies. Stroke 2005;36(9):1906; with permission.)*
plaque, and tracing the contour of slices at the midpoint, and 25% and 75% of the length of the plaque, with automated interpolation of the surface of the remainder of the plaque assuming uniform plaque geometry, adjustable by the operator (Fig. 4).

In 2013 an automated method was developed using mechanical movement of the probe along the artery that provided good agreement with manual segmentation by experts (Fig. 5). However, the machine used to translate the ultrasound probe is large and clumsy, and difficult to use in patients with obesity or short necks. A mechanical sweep, obtained by holding the probe in one location and having the angle changed mechanically (Fig. 6), is faster and more convenient. Recently Graebe and colleagues, using the Philips system used by Sillesen and colleagues in the High-Risk Plaque Bioimage Study, showed that the mechanical sweep gave improved reproducibility of plaque volume quantification compared with manual translation of the probe along the artery (Fig. 7).

Progression of Carotid Plaque Volume and Cardiovascular Risk

Progression of TPA was shown to strongly predict the 5-year risk of stroke, myocardial infarction, and death after adjustment for risk factors. Carotid plaques grow along the artery 2.4 times faster than they thicken, so measuring plaque area is more sensitive than measuring thickness alone. Plaques also grow and regress circumferentially, so measuring 3D plaque volume is even more sensitive than measuring area. Carotid 3D plaque volume is also more sensitive to effects of therapy than coronary intravascular ultrasound (IVUS); whereas carotid plaques are focal and can change in three dimensions, coronary plaques are present along the entire length and entire circumference of the artery, so change is reduced to a change in average thickness (i.e., a one-dimensional change). In a meta-analysis, Noyes and Thompson concluded that using IMT or IVUS, 2 years would be required to study effects of statins on plaque progression/regression; however, change in TPA or total plaque volume can be done in 3 months.

Progression of plaque volume predicted cardiovascular events in a small sample of prevention clinic patients who had plaque at baseline (N = 323), whereas progression of IMT or TPA did not significantly predict events. Regression of carotid plaque area was reported in a quarter of patients in 2002; by 2010 it was observed in half of patients being followed in the same clinic, probably caused by more intensive medical therapy. In 2005, Ainsworth and colleagues reported that by measuring carotid plaque volume, significant plaque regression with high-dose atorvastatin in patients with carotid stenosis could be shown in only 3 months, in a study comparing only 21 patients randomized to placebo with 17 randomized to atorvastatin. This reduced

Fig. 4. User input for semiautomated total plaque volume measurement. In the longitudinal view (and with assistance from the axial view, not shown) the user identifies the maximum and minimum z-values representing the end points of the plaque (Min Z and Max Z). The user identifies the midpoint of the plaque (C1) and finally C2 and C3 are identified and generated in the axial view. Uniform plaque geometry between C2 and C3 is assumed and a final volume is generated. (From Buchanan D, Gyacskov I, Ukwatta E, et al. Semi-automated segmentation of carotid artery plaque volume from three-dimensional ultrasound carotid imaging. Proc SPIE 2012;8317:831701–4; with permission.)
by two orders of magnitude the sample size and duration of studies to assess new therapies for atherosclerosis compared with IMT. Carotid plaque volume is also significantly more sensitive than IVUS, as reported by Noyes and Thompson\textsuperscript{42} in a meta-analysis indicating that patients in studies of antiatherosclerotic therapies should be followed for 2 years to detect effects of therapy. An issue that is little understood is that because carotid plaques are focal, whereas coronary plaques extend throughout the length of the pullback, measuring progression of carotid plaque is more sensitive to effects of therapy than coronary IVUS.\textsuperscript{41}

**VESSEL WALL VOLUME**

Not all patients have carotid plaque at the time they are studied. Table 1 shows, from data in 7591 patients attending our vascular prevention clinics, the percentage with measurable plaque increased from 26.6\% at age less than 35, to 50\% at age 35 to 39, and 98.5\% at age 70 to 74 (see Table 1). An issue that requires discussion is the definition of carotid plaque. The Mannheim consensus\textsuperscript{47} defined plaque as an IMT greater than 1.5 mm. In the High Risk Plaque Study, among participants with a mean age of 68, 78\% had measurable plaque. In that study, plaque was defined as local thickening of the carotid IMT of greater than 50\% compared with the surrounding vessel wall, an IMT greater than 1.5 mm, or local thickening greater than 0.5 mm. However, our studies and the Tromsø study (ie, the studies that showed that TPA predicted cardiovascular events\textsuperscript{19–21}) used a definition of a focal thickening of the intima-media complex greater than 1 mm. It is therefore suggested that the validated definition is the latter.

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**Fig. 5.** Automated measurement of plaque volume. Sample results of algorithm and manual segmentations for three patients (one subject in each column). The panels in the rows were obtained at distances of 0, 1, and 2 mm from the carotid bifurcation. Yellow solid contours, algorithm results; red dashed contours, results of expert 1; green dashed contours, results of expert 2. (From Cheng J, Li H, Xiao F, et al. Fully automatic plaque segmentation in 3-D carotid ultrasound images. Ultrasound Med Biol 2013;39:2440; with permission.)
For children and healthy study participants who have no measurable plaque, it has been common to measure IMT. However, a strong alternative is measurement of vessel wall volume (VWV; the volume of the artery minus the volume of the lumen) (Fig. 8).48 That measurement, which is conceptually equivalent to a 3D IMT, has significant advantages over IMT. Like plaque volume,49 it has a much greater dynamic range. VWV also markedly reduces sample size and duration of therapy compared with IMT and IVUS. Atorvastatin significantly reduced VWV in 3 months50 in the same images in which total plaque volume was measured in the study discussed previously.51 Dietary weight loss, probably through reduction of blood pressure, significantly reduced VWV in 2 years.52

ULCERATION

Besides quantifying plaque burden, 3D ultrasound is being developed to identify patients with vulnerable plaque. Methods for identifying high-risk asymptomatic carotid stenosis include MR imaging characterization of plaque composition, PET/computed tomography imaging of inflammation, assessment of neovascularization in plaque, detection of microemboli by transcranial Doppler, and ultrasound imaging of echolucency and ulceration.53,54

Ulceration was shown in the North American Symptomatic Carotid Endarterectomy Trial to be associated with a tripling of risk55; however, the detection of ulceration by angiography (which provides an image of the lumen, not the wall of the artery) was unreliable.56 Although reproducibility of ulcer detection is poor with two-dimensional ultrasound,57 reliable detection of ulceration was shown with 3D ultrasound by Schminke and colleagues.58

In 2011, Madani and colleagues59 found in patients with asymptomatic carotid stenosis that the presence of three or more ulcers in either carotid artery identified patients with 3-year risk of stroke or death of 18%, similar to the 20% risk of patients
with microemboli on transcranial Doppler, versus a 2% risk with neither ulceration nor microemboli. Importantly, and perhaps surprisingly, ulceration and microemboli identified different high-risk patients, increasing the proportion that could benefit from endarterectomy from 5% to 10%.

In 2014, Kuk and colleagues found that measurement of carotid plaque volume was useful in identifying high-risk patients among a population attending vascular prevention clinics (Fig. 9). Patients with a total ulcer volume greater than or equal to 5 mm$^3$ had a significantly higher risk of “stroke, transient ischemic attack, or death (P = .009) and of developing stroke/transient ischemic attack/death/myocardial infarction/revascularization (P = .017).”

**ECHOLUCENCY AND PLAQUE TEXTURE: APPROACHING PLAQUE COMPOSITION**

It has long been thought that echoluent plaque represented “soft plaque” that was more likely to rupture and embolize. Several studies have shown that echolucency predicted higher risk of cardiovascular events. Nicolaides and colleagues discussed echolucency and “black juxtaluminal plaque,” which may represent soft plaque or perhaps thrombus, as a predictor of high risk. Echolucency was shown to improve the prediction of stroke among patients in the Asymptomatic Carotid Emboli Study. A combination of

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**Table 1**

<table>
<thead>
<tr>
<th>Age Group (y)</th>
<th>Number of Cases</th>
<th>Mean Total Plaque Area (mm$^2$)</th>
<th>Standard Deviation</th>
<th>Percent with Plaque</th>
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<tbody>
<tr>
<td>&lt;35</td>
<td>290</td>
<td>7.37</td>
<td>29.25</td>
<td>26.6</td>
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<tr>
<td>35–39</td>
<td>218</td>
<td>13.48</td>
<td>27.16</td>
<td>50.0</td>
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<tr>
<td>40–44</td>
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<td>71.1</td>
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<td>45–49</td>
<td>594</td>
<td>44.07</td>
<td>65.27</td>
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<tr>
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<td>766</td>
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<td>101.78</td>
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<td>100.97</td>
<td>120.44</td>
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<td>133.46</td>
<td>138.75</td>
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<td>65–69</td>
<td>910</td>
<td>153.20</td>
<td>150.87</td>
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<td>70–74</td>
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<td>80+</td>
<td>945</td>
<td>198.24</td>
<td>135.50</td>
<td>99.5</td>
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</tbody>
</table>

Data are from 7591 patients attending the Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, London, Canada.
microemboli and echolucency identified a subgroup with a 10-fold increase in the risk of ipsilateral stroke, which remained significant after adjustment for risk factors.

More recently, radiofrequency analysis (as opposed to gray-scale analysis) has been used to study plaque “texture,” a way of assessing plaque composition. Inhomogeneity of plaque texture and some other features of plaque texture have been shown to identify patients at higher risk of events. In 2014, van Engelen and colleagues found that 2 of the 64 mathematical algorithms, Law’s spot-spot ripple and Law’s edge-edge ripple (Fig. 10), were particularly useful, and showed that a combination of change in plaque texture and change in plaque volume were more predictive than either parameter alone.

A problem for clinicians is relating to mathematical abstractions; this is apparent from the appearance of the texture analysis images shown in Fig. 10. Our group has recently made some progress in comparing features of plaque texture from carotid images obtained before endarterectomy with histologic features of plaque. Fig. 11 shows

Fig. 8. Vessel wall volume segmentation. (A) The transverse view of the common carotid artery shows the vessel boundary outlined in red and the lumen boundary outlined in yellow. (B) The three-dimensional ultrasound image volume is sliced longitudinally to reveal the vessel and lumen boundaries in the common, internal, and external carotid branches. The internal carotid artery vessel and lumen boundaries are shown in blue and pink, respectively. (From Egger M, Spence JD, Fenster A, et al. Validation of 3d ultrasound vessel wall volume: an imaging phenotype of carotid atherosclerosis. Ultrasound Med Biol 2007;33:908; with permission.)

Fig. 9. Measurement of ulcer volume and ulcer depth. Contours of ulcers were traced and depth of ulcers measured in cross-sectional views. Each slice had a thickness of 1 mm; ulcer volume was computed from the sum of the volumes of all slices in which ulceration was traced. (From Kuk M, Wannarong T, Beletsky V, et al. Volume of carotid artery ulceration as a predictor of cardiovascular events. Stroke 2014;45:1438; with permission.)
Fig. 10. Plaque texture. Texture for two plaques in the same vessel with a different appearance. In a total of 50 runs of sparse Cox regression (5 × 10-fold cross-validation) on changes in texture, Law’s edge-edge ripple (EER) was selected in the model 49 times, and Law’s spot-spot ripple (SSR) 48 times. (From van Engelen A, Wannarong T, Parraga G, et al. Three-dimensional carotid ultrasound plaque texture predicts vascular events. Stroke 2014;45:2698; with permission.)

Fig. 11. Plaque texture and histology. A hematoxylin and eosin stained cross-section of a carotid endarterectomy is shown on the left, with calcification outlined in dark blue. The upper right panel shows the corresponding 3D ultrasound slice of the plaque, with the arrow pointing to the area of calcification, which is very echodense. The lower right panel shows the appearance of one of the plaque texture features, Entropy_1. (Courtesy of Dr Rob Hammond, Neuropathologist at University Hospital, and Lucy Chung, a medical student at the Schulich School of Medicine and Dentistry, London, Canada, who carried out a project funded by the Canadian Institutes of Health Summer Research Training Program.)
the relationship of one of the plaque texture algorithms to plaque calcification.

SUMMARY

3D ultrasound of carotid plaque volume is useful for risk stratification, for evaluating effects of therapy on atherosclerosis, and for managing patients at risk of cardiovascular events, by a strategy called “treating arteries instead of risk factors.” It will also be useful for genetic research and evaluation of new risk factors, such as metabolic products of the intestinal microbiome. Ulceration and other features of plaque vulnerability, such as plaque texture and surface plaque roughness, will probably also be useful in risk stratification, and in identifying among patients with asymptomatic carotid stenosis the small proportion that might benefit from revascularization.

REFERENCES

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