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Vulnerable Atherosclerotic Carotid Plaque Evaluation by Ultrasound, Computed Tomography Angiography, and Magnetic Resonance Imaging: An Overview

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Abstract

Ischemic syndromes associated with carotid atherosclerotic disease are often related to plaque rupture. The benefit of endarterectomy for high-grade carotid stenosis in symptomatic patients has been established. However, in asymptomatic patients, the benefit of endarterectomy remains equivocal. Current research seeks to risk stratify asymptomatic patients by characterizing vulnerable, rupture-prone atherosclerotic plaques. Plaque composition, biology, and biomechanics are studied by noninvasive imaging techniques such as magnetic resonance imaging, computed tomography, ultrasound, and ultrasound elastography. These techniques are at a developmental stage and have yet to be used in clinical practice. This review will describe noninvasive techniques in ultrasound, magnetic resonance imaging, and computed tomography imaging modalities used to characterize atherosclerotic plaque, and will discuss their potential clinical applications, benefits, and drawbacks.

Résumé

Les syndromes ischémiques associés à l'athérosclérose de la carotide sont souvent liés à la rupture d'une plaque. Le bénéfice de l'endartériectomie carotidienne chez les patients symptomatiques qui présentent un fort degré de sténose a été établi, mais demeure équivoque chez les patients asymptomatiques. La recherche vise actuellement à stratifier le risque chez ces patients asymptomatiques en procédant à la caractérisation de plaques d'athérosclérose vulnérables et susceptibles de se rompre. Ces plaques sont étudiées au regard de la composition, de la biologie et de la biomécanique, à l'aide de techniques d'imagerie non effractives telles que l'imagerie par résonance magnétique, la tomodensitométrie, l'échographie et l'élastographie ultrasonore. Encore à l'étape de mise au point, ces techniques ne sont pas utilisées dans un contexte de pratique clinique jusqu'à maintenant. Cette étude décrit les techniques non effractives, notamment l'échographie, l'imagerie par résonance magnétique et la tomodensitométrie, utilisées pour caractériser les plaques d'athérosclérose, puis analyse leurs éventuelles applications cliniques, de même que leurs avantages et leurs inconvénients.

Key Words: Carotid artery plaque; Atherosclerotic plaque; Vulnerable plaque; Ultrasound; Noninvasive vascular elastography; Multidetector computed tomography angiography; Magnetic resonance imaging

Stroke ranks third among all causes of death in Western countries [1]. Of all strokes, 87% are ischemic [2], and an estimated 20% are caused by carotid atherosclerotic disease [3]. Symptomatic extracranial internal carotid artery occlusive disease is currently managed by carotid endarterectomy (CEA) by using internal carotid artery luminal stenosis severity as an indication, based on the North American Symptomatic Carotid Endarterectomy Trial [4] and the European Carotid Surgery Trial [5]. Under medical therapy, symptomatic patients had a 22% risk of stroke at 5 years and 26% risk at 2 years, with 50%-69% and 70%-99% carotid stenosis, respectively [4].

In asymptomatic patients, however, indications for CEA remain controversial. Stenosis severity is a poor predictor of fatal or nonfatal stroke in asymptomatic patients, with only

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a 2% annual risk with >60% stenosis (17.9% at 10 years) [6,7]. Despite improved medical therapy over the past 20 years, CEA offered a small but significant risk reduction at 5 and 10 years [7], but in a controlled clinical trial setting with very low perioperative risks unlikely to reflect common practice. Therefore, choosing the most appropriate treatment to prevent stroke in asymptomatic patients continues to pose a significant challenge for physicians; further risk stratification is required. Coronary artery literature [8] and, more recently, results of carotid atherosclerosis studies [9] suggest examining pathology of atherosclerosis noninvasively to help determine which patients would benefit from early intervention. Imaging could be performed to characterize carotid plaque, to risk stratify asymptomatic patients, and to provide appropriate preventative therapy.

Plaque imaging is becoming increasingly used in clinical studies and trials; therefore, radiologists involved in the management of cerebrovascular diseases need to be aware of the pathophysiology of atherosclerotic carotid disease and the development of noninvasive imaging techniques that can characterize atherosclerotic plaques. This review will provide a basic understanding of atherosclerosis pathology and vulnerable plaque (VP) definition, and will describe noninvasive imaging techniques in ultrasound (US), computed tomography angiography (CTA), and magnetic resonance imaging (MRI) used to characterize carotid atherosclerotic plaque. The potential clinical applications, benefits, and drawbacks of each technique will be discussed; this will offer readers a better outlook on developments to come.

Pathophysiology of Atherosclerosis

Atherosclerosis is a chronic systemic inflammatory disease characterized by thickening of the arterial wall due to an accumulation of lipids and fibrous elements [10]. Atherosclerosis lesion formation is complex and involves shear stress, endothelial dysfunction, inflammation, neovascularization, and thrombosis. The modified American Heart Association classification summarizes the natural history of atherosclerosis (Table 1) [11].

Endothelial Dysfunction and Leukocyte Recruitment

Under physiological conditions, the endothelium functions as a selective barrier between blood and tissues, and inhibits adhesion of leukocytes to the endothelium [13]. In areas of low shear stress and flow turbulence (curved and bifurcating arteries), the endothelium is more permeable to large molecules such as low-density lipoprotein (LDL), which accumulates in the intima. Atheromas preferably form in those areas, and their growth is enhanced with elevated serum LDL levels [14]. Endothelial dysfunction, an imbalance of physiological activities, leads to increased oxidation of LDL in the intima and increased production of chemotactic factors (interleukins), surface adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1] intercellular adhesion molecule-1 [ICAM-1] and selectins) and growth factors (macrophage colony-stimulating factor). Monocytes and T-lymphocytes from the circulation bind to VCAM-1 [13] and enter the arterial wall by diapedesis. Monocyte-derived macrophages phagocytose oxidized LDL and become foam cells [10]. Foam cells accumulate in layers to form an intimal xanthoma (“fatty streak”). Macrophages further release cytokines and growth factors that induce smooth-muscle cell migration, proliferation, and production of extracellular matrix.

Atheroma Formation

The confluence of extracellular lipid pools, degenerating foam cells, and necrosis result in the formation of a lipid-rich necrotic core. Smooth-muscle cells proliferate and produce extracellular matrix (collagen and proteoglycans), which covers the lipid core and forms the fibrous cap. With progression, angiogenesis originating from the vasa vasorum occurs to supply oxygen to the growing plaque.

VP: From Asymptomatic Atheroma to Culprit Plaque

The term vulnerable plaque emerged more than 20 years ago to describe an atherosclerotic plaque that is susceptible to rupture, thrombose, and subsequently cause a cardiac ischemic event [15]. Culprit coronary plaques that cause acute coronary syndromes were retrospectively identified in pathology studies with features similar to histopathology of carotid plaques [9]: plaque rupture (65%-70%), surface erosion (25%-30%), and superficial calcium nodule (2%-5%) [11]. The definition of VP is based on the assumption of plaque features that precede those of culprit plaques. Criteria defining VP were proposed (Table 2, Figure 1) [8]. Commonly, a VP has a ruptured fibrous cap, a large lipid core with a thin fibrous cap, or intraplaque hemorrhage (IPH).

As the atheroma increases in size, neovessels leak (IPH), and macrophages within the fibrous cap secrete matrix-degrading enzymes (matrix metalloproteinases). Eventually, it becomes structurally fragile: the fibrous cap thins and ruptures, the thrombogenic lipid core is exposed, and thrombosis at the plaque surface occurs. A thin fibrous cap is defined as less than 200-μm thick [16], and a large lipid core

Table 1
Modified American Heart Association classification[a]

Lesion type	Description
I	Initial lesion with foam cells (intimal xanthoma or fatty streak)
II	Fatty streak with multiple foam cell layers
III	Preatheroma with extracellular lipid pools
IV	Atheroma with a confluent extracellular lipid core
V	Fibroatheroma
VI	Complex plaque with possible surface defect and/or hemorrhage and/or thrombus
VII	Calcified plaque
VIII	Fibrotic plaque without lipid core

[a] Data from Refs. 11,12.

Table 2
Criteria defining vulnerable atherosclerotic plaque[a,b]

Major criteria
Active inflammation
Thin cap with large lipid core
Endothelial denudation with superficial platelet aggregation
Fissured plaque
Stenosis >90%
Minor criteria
Superficial calcified nodule
Glistening yellow (seen on angioscopy)
Intraplaque hemorrhage
Endothelial dysfunction (measurement of flow-dependent coronary artery dilatation and other emerging techniques)
Outward (positive) remodelling

[a] The presence of at least 1 major criterion qualifies a plaque as vulnerable.
[b] From data published in Ref. 8.

is defined as a cross-sectional plaque area of at least 25% [9]. There is no single imaging modality that can characterize all plaque features (morphologic, molecular, and biomechanical), thus, the best technique to identify VP is yet to be established.

US, CTA, and MRI Features of Plaque Vulnerability

Currently, carotid atherosclerosis burden is assessed by measuring luminal stenosis, but this measure remains insufficient to risk stratify asymptomatic patients. Multiple imaging techniques have been developed to identify the key features of vulnerable atherosclerotic plaque. Some techniques (B-mode US, MRI, CTA) have been studied to a greater extent, whereas others, such as targeted contrast agents and noninvasive US elastography, are under investigation.

US

US is a well-known method of atherosclerotic carotid disease evaluation; it is clinically used to assess the presence of plaque, the degree of carotid stenosis with blood-flow velocity profiles, and the carotid intima-media thickness. US is reliable and reproducible, and is often the only diagnostic imaging modality used for the assessment of carotid arteries before CEA. It is also a low-cost, low-risk, and accessible imaging modality that is well tolerated by patients. The following section will focus on the US evaluation of carotid plaque vulnerability by using morphology and echo texture analysis.

Two-Dimensional B-mode US Imaging

Stable carotid plaques are associated with fibrocalcified content and uniform architecture, which render their appearance more echogenic and homogeneous (Figure 2A). Unstable symptomatic plaques are associated with fibrofatty and hemorrhagic content, with an echolucent appearance (Figure 2B) [17]. In addition, symptomatic plaques may have an irregular surface or ulcerations [18], which is detected with colour-Doppler US by demonstrating eddy flow within an anechoic area of the plaque. Nevertheless, conflicting study results exist about the appearance of symptomatic plaques; the Asymptomatic Carotid Stenosis Trial showed no association between ipsilateral stroke and echogenicity [7]. This could be explained by limited reproducibility of subjective characterization of plaque echogenicity by B-mode US. Hence, an objective measure of echogenicity was introduced. Grey-scale median (GSM) scores measure plaque echogenicity by assessing overall plaque brightness from the frequency distribution (histogram) of grey-level pixels within the plaque. The technique involves standardization of B-mode images and adjustment with the signals from blood (GSM, 0) and adventitia (GSM, 190) [19]. Studies demonstrated associations between low GSM scores and both symptomatic plaques [19–21] and greater necrotic core areas [20].

B-mode US has limitations. First, GSM measures can be affected by settings such as time-gain compensation and log

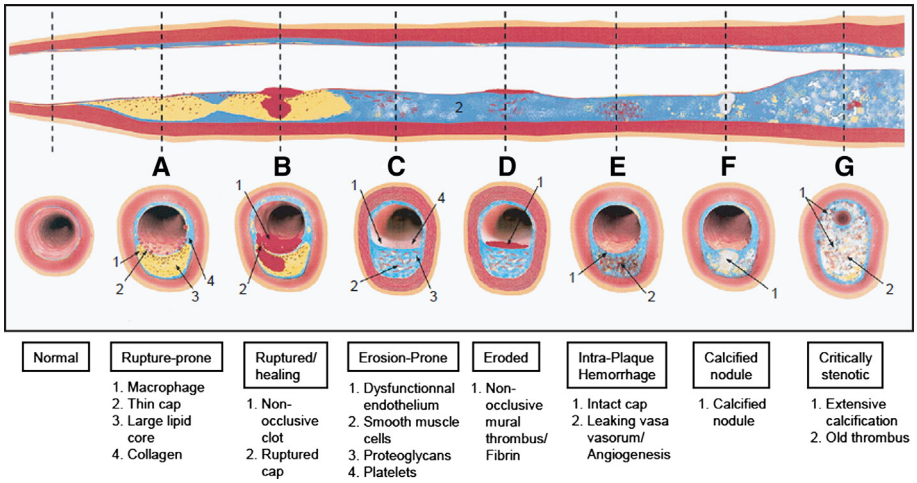

Figure 1. Different types of vulnerable plaque. (A) Rupture-prone plaque with a large lipid core, a thin fibrous cap, and macrophages. (B) Ruptured plaque with a subocclusive thrombus and ruptured cap. (C) Erosion-prone smooth-muscle cell-rich plaque with a proteoglycan matrix. (D) Eroded plaque with a subocclusive thrombus. (E) Intraplaque hemorrhage from the vasa vasorum. (F) Calcified nodule protruding into the vessel lumen. (G) Chronic critically stenotic plaque with extensive calcification and an old thrombus. Adapted from Naghavi et al [8] with permission from the Society for Heart Attack Prevention & Eradication (SHAPE). This figure is available in colour online at http://carjonline.org/.

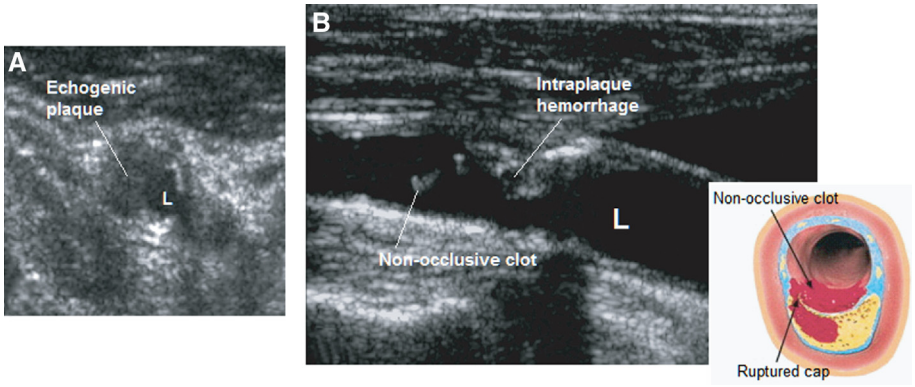

Figure 2. B-mode ultrasound of carotid arteries. (A) Cross-sectional view of the left internal carotid artery in a 46-year-old woman with hypercholesterolemia, showing significant stenosis from an echogenic homogeneous plaque that narrows the vessel lumen. (B) A longitudinal view of the left carotid artery of an 82-year-old man with left-sided amaurosis fugax and transient middle cerebral artery territory ischemia, showing a heterogeneous plaque, ruptured with a nonocclusive clot. The echolucent zone may reflect hemorrhage or a lipid core. The schematic inset reflects the plaque features seen on ultrasound in this case. This patient underwent endarterectomy, which demonstrated a ruptured atheroma with a surface thrombus intraoperatively. L = lumen. Schematic inset was adapted and modified from Naghavi et al [8] with permission from the Society for Heart Attack Prevention & Eradication (SHAPE). This figure is available in colour online at http://carjonline.org/.

compression. Ideally, tissue echogenicity should be analysed by an appropriate processing of the raw radiofrequency data, such as integrated backscatter [22] or pixel distribution analysis. Second, GSM does not take into account plaque heterogeneity. Echo-texture analysis, a computer-aided system that can characterize both echogenicity and heterogeneity, can detect focal hypoechoic areas and showed associations with neurologic events [23]. However, heavy calcifications impair echo-texture analysis. Finally, 2-dimensional imaging limits visualization of regions of interest.

Three-Dimensional B-mode US Imaging

Three-dimensional (3D) US of carotid arteries has been developed and validated to measure plaque volume and vessel wall volume changes over time [24]. This technique uses a conventional transducer that produces 2-dimensional (2D) images in the composite imaging (SonoCT) mode [25]. Composite imaging is a US mode that acquires several images based on transmitted US waves, which results in a single composite image. This mode helps reduce speckle artifact and sharpens tissue boundaries. The probe, attached to a mechanical motorized mover, is displaced along the neck at a constant speed of 3 mm/s, whereas 2D image frames are acquired at regularly spaced intervals. Image reconstruction and multiplanar reformatting provide 3D images that can be segmented manually or automatically, one cross-sectional slice at a time. To determine plaque volume, each slice area is computed, summed with all other slice areas, and multiplied by interslice distance [26]. A semiautomated segmentation algorithm was developed and validated to measure vessel wall volume and considerably reduced operator time [27]. The effect of pharmacologic agents on plaque volume assessed by 3D US was demonstrated over short periods of time (3-6 months): even with small sample sizes of fewer than 40 patients, there was a significant decrease in plaque volume in comparison with placebo groups [26,28], which makes 3D US plaque volume assessment more effective than intima-media thickness in detecting size differences over time. Finally, 3D US was more effective than 2D US in detecting plaque ulcers [29]. Additional studies with 3D US are warranted to validate its ability to assess plaque composition, surface morphology, and VP before use in large clinical studies.

Contrast-Enhanced US

Microbubble contrast agents are strictly intravascular: they help to better outline lumen contours and can penetrate microvasculature. Contrast-enhanced US (CEUS) imaging depicted unsuspected wall irregularities and ulceration [30], but this is not yet validated with histology. Significant correlations were found between the degree of intraplaque contrast-enhancement on US and the amount of neovascularization on histopathology (Figure 3) [31], symptomatic carotid plaques [32], and echolucent plaques [33].

Molecular imaging can also be achieved with CEUS by designing microbubbles with monoclonal antibodies in their lipid shell. Antibodies targeted to VCAM-1, ICAM-1, selectins, and CD81 expressed by endothelial cells provided an in vivo assessment of endothelial dysfunction in animals and humans [34,35]. Late-phase CEUS and microbubbles targeted to CD31 (angiogenesis marker) and CD68 (macrophage inflammation marker) showed significant correlations with immunohistologic staining [36]. More studies on CEUS molecular imaging are required to determine if the detected endothelial dysfunction or neovascularization can predict cerebral ischemic events. Drawbacks of CEUS include rare and minor adverse effects such as headache and injection-site bruising and pain [37]. There also is a theoretical risk of potentiating plaque instability, because a small number of microbubbles destroyed during US scanning can potentially damage neovessels and lead to IPH [38].

Noninvasive Vascular Elastography by US

Elastography is a map of deformations of a biologic tissue in response to a mechanical stress. Elastography techniques

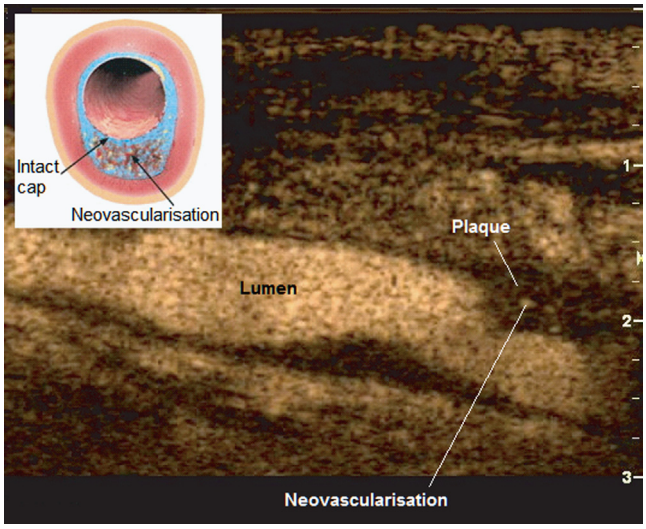

Figure 3. Carotid artery contrast-enhanced ultrasound. Hyperechoic foci within the plaque represent neovessels. SonoVue is an aqueous suspension of stabilized sulfur hexafluoride (SF_6) microbubbles (precontrast image currently unavailable for pre- and postcontrast comparison). Courtesy of Christian Greis, Bracco Diagnostics Inc (Monroe Township, NY). The colour image is a schematic representation of vulnerable plaque with a normal cap and neovessels. Schematic inset was adapted from Naghavi et al [8] with permission from the Society for Heart Attack Prevention & Eradication (SHAPE). This figure is available in colour online at http://carjonline.org/.

function in 3 steps: application of a stress (force) on the tissue, measurement of tissue displacement (strain) in response to the applied stress, and estimation of tissue elasticity (rigidity). For the same applied stress, rigid tissues will have smaller displacements than supple tissues. The applied force could either be external (compression or dynamic vibration) or internal (natural arterial pulsation or shear wave propagation from an acoustic radiation force). There are 2 types of elastography: static (or quasi-static) and dynamic. Static elastography consists in measuring the strain gradient between 2 different levels of stress application. It cannot provide an estimation of the tissue elasticity because the absolute stress force is unknown; instead it displays a map of tissue strain called an ''elastogram.'' In contrast, dynamic elastography estimates tissue elasticity (Young's tensile modulus) by measuring both strain and the absolute force applied to the tissue.

US noninvasive vascular elastography (NIVE) is a quasi-static elastography technique that measures the elastic deformation of the arterial wall. When compressed and relaxed by the natural pulsation of the artery, the displacement between pairs of pre- and postcompression radiofrequency lines is estimated, and a strain profile (elastogram) is determined by computing the gradient of the displacement field. The presence of inhomogeneous strain distribution in a carotid plaque may hypothetically lead to biomechanical instability and VP. A feasibility study showed that the maximal strain concentration was located close to the vessel lumen and at the interface between hard and soft materials (Figure 4) [39]. Currently, researchers who study plaque deformations hypothesize that deformations can potentially distinguish symptomatic from asymptomatic plaques and lipid-rich from calcium-rich plaques. Results of a recent clinical study found significant correlations between lipid content and axial strain [40]. Another study, of 16 patients, compared 2 strain parameters, relative lateral shift and accumulated axial strain, with US-identified calcified and noncalcified plaque areas; there was a greater variability and higher strain values in noncalcified echolucent areas [41]. Presently, methodology of US NIVE (choice of region of interest and strain parameter) differs among researchers; therefore, results cannot be readily compared among studies. Further studies are needed to validate US NIVE, notably to improve plaque segmentation as well as determine associations between strain, plaque composition, and clinical symptoms.

Few dynamic elastography techniques are used for carotid plaque analysis, partly because of their relatively recent technical developments. Acoustic radiation force imaging consists in the generation of an acoustic radiation force of very short duration (<300 μsec) to small volumes of tissue, followed by mapping of tissue displacements (<10 μm), which resulted from shear-wave propagation. Limitations of acoustic radiation force imaging include the inability to compare absolute values of displacement and elasticity among patients [42], and low temporal resolution, which may lead to nonrepresentative strain values in arteries because strain varies with the cardiac cycle. Supersonic shear-wave imaging is another dynamic elastography technique that also uses a radiation force but with a much higher temporal resolution than acoustic radiation force imaging (5000 image frames per second). Instead of measuring tissue displacements, shear-wave propagation speed is measured; this provides a more accurate estimation of tissue stiffness and ability for comparison among patients. There are no studies yet of supersonic shear-wave imaging in patients with carotid atherosclerotic plaques, but an in vivo study of the common carotid artery of a healthy subject showed an elevation of the shear modulus (stiffness) at the onset of systole in every cardiac cycle [43].

Multidetector CTA

With the advent of multislice helical CT, improved resolution resulted in better accuracy of plaque composition assessment (Figure 5). The minimal fibrous cap thickness of plaque can be measured on multidetector CTA (MDCTA) (R^2 = 0.77; P < .001) [44]. Ulcerations can also be more accurately detected than by US echo colour-Doppler (93% sensitive and 98% specific; κ = 0.855) [45]. MDCTA could quantify calcifications and fibrous tissue with good histologic correlation (R^2 > 0.73; P < .001) but could not quantify the lipid core except in mildly calcified plaques [46]. With cutoff attenuation values to identify calcium (>130 HU), fibrous tissue (60-130 HU), and lipid or hemorrhage (<60 HU), there was a good interobserver variability in plaque and component volume measurements (interclass correlation coefficient [ICC], 0.76-0.99) [47].

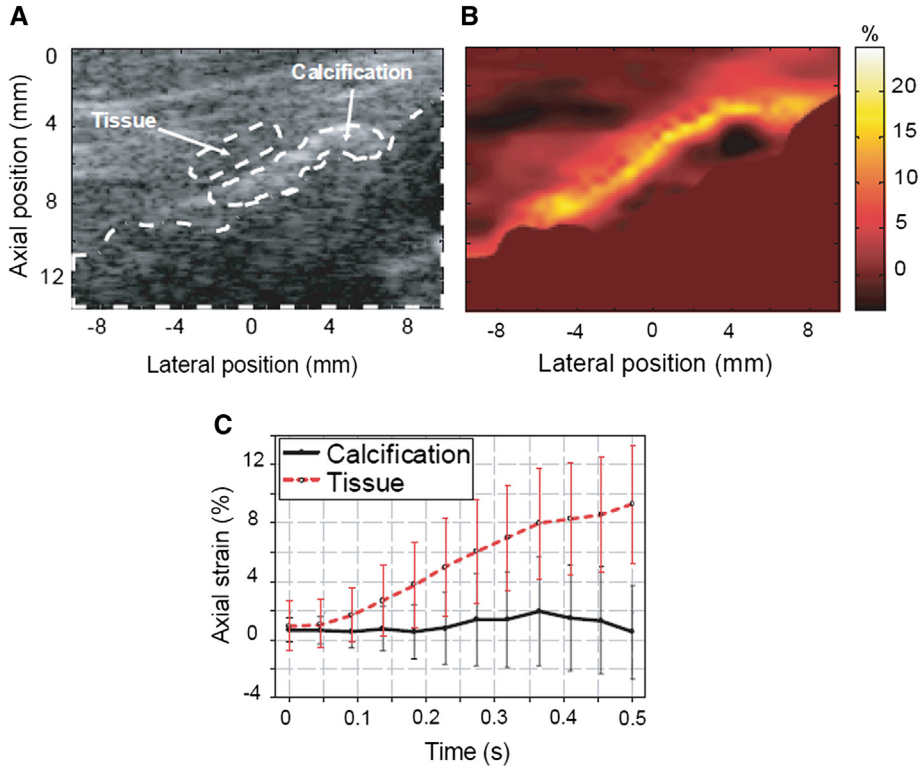

Figure 4. (A) B-mode image of a carotid plaque from reconstructed raw radiofrequency signals used for vascular elastography. (B) For the same B-mode image, strain values can be displayed by colour code (elastogram). Dark zones represent calcifications with low strain values. (C) Strain profile of segmented areas in (A). Rigid structures, such as calcifications, have stable cumulative strain values, whereas soft plaque areas have increasing cumulative strain values. Adapted from Schmitt et al [39] with permission from Elsevier. This figure is available in colour online at http://carjonline.org/.

Another classification of plaque into fatty (<50 HU), mixed (50-119 HU), or calcified (>120 HU) also showed good interobserver agreements [48] and sensitivities of 85%, 89%, and 100%, respectively [49]. Similarly, a study of 31 patients demonstrated that plaque density analysis could detect hemorrhage with 100% sensitivity and 64.7% specificity but only in plaques that have a median density below 31 HU [50]. Carotid plaques are characterized according to the America Heart Association classification system adapted for MDCTA (Table 3) [44]. MDCTA can accurately evaluate plaque composition but could not differentiate lipid cores from hemorrhage except for large plaques that are mainly fatty or hemorrhagic [44].

The major advantages of MDCTA lie in its availability, rapidity, relatively low cost, ability to measure absolute tissue density, and ability to identify and quantify calcifications with great accuracy. The role of MDCTA in plaque component characterization shows promise but still lacks specificity to identify lipid core and IPH. Beam-hardening artifacts associated with calcification alter Hounsfield values and contribute to inaccurate plaque characterization. Also, plaque enhancement after contrast injection is highly variable because it depends on blood flow and time delay of image acquisition. Therefore, conflicting results were found pertaining to associations between circumferential plaque enhancement, neovascularization, and symptomatic fatty plaques [51–55]. Other drawbacks of MDCTA include exposure to ionizing radiation and nephrotoxic iodine-based contrast agents.

Macrophage-Designed Nanoparticle Contrast Agents

To overcome the variability of density measures observed with conventional contrast injection, researchers developed N1177, an iodinated nanoparticle contrast agent selectively phagocytosed by macrophages. In rabbits, 2 hours after intravenous N1177 administration, the intensity of N1177 enhancement correlated significantly with increased glucose uptake on positron-emission tomography and macrophage density on histology [56]. Another team found that N1177 nanoparticles were only present in macrophage-rich areas of ruptured plaques but not in those of nonruptured plaques, which suggests specificity for identifying ruptured atherosclerotic plaques [57]. This technique has not yet been experimented on humans because an optimal dosage of N1177 has not been determined; the required pre- and postinjection image acquisition protocol doubles the radiation dose compared with MDCTA with conventional contrast agents.

High-Resolution MRI

Studies with histologic validation determined that multicontrast high-resolution MRI can characterize carotid plaque morphology [58], identify and measure plaque components such as lipid-rich necrotic core, fibrous cap thickness, IPH,

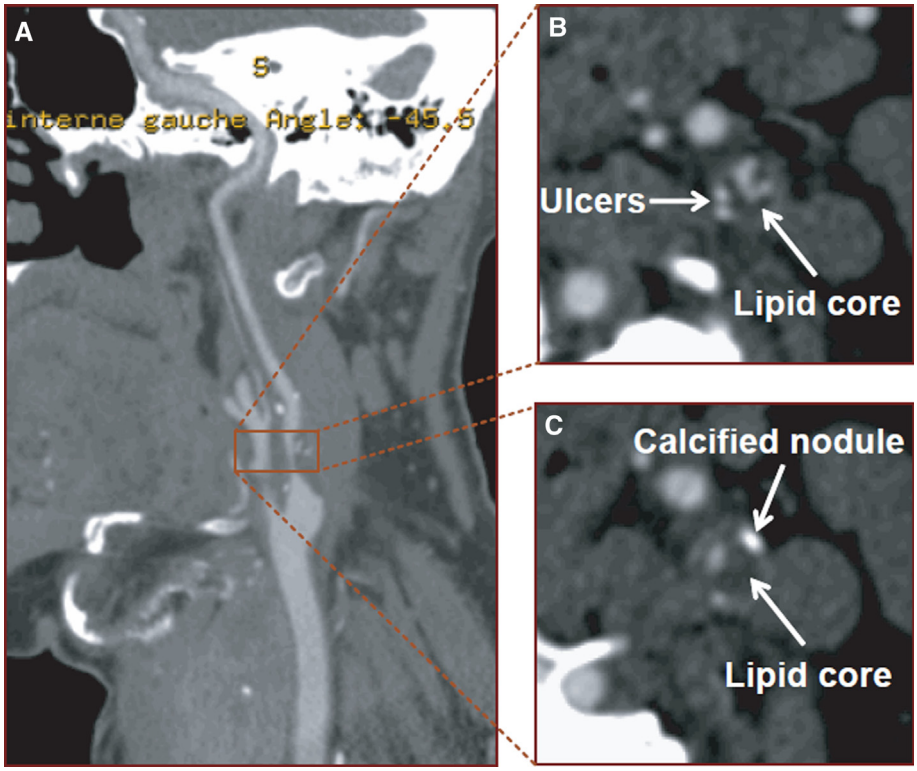

Figure 5. Multidetector computed tomography angiography of the neck of a patient with left-sided amaurosis fugax. (A) Sagittal reconstruction of the carotid artery lumen, showing severe left internal carotid artery stenosis and ulcerations. Cross-sectional images from the superior (B) and inferior (C) cuts of the region of interest in (A). (B) The plaque contains a lipid core (hypodense posterior vessel wall) and is ulcerated because contrast has extravasated posteromedially (arrow pointing to "ulcers"). (C) Inferiorly, the lipid core is larger, and there is a calcified nodule in the anterior vessel wall. This figure is available in colour online at http://carjonline.org/.

Table 3
Modified AHA classification for MDCTA[a] and MRI[b]

MDCTA description	
Lesion type	
I-II	Thin plaque with no calcification
III	Plaque with small lipid cores and no calcification
IV-V	Plaque with a large lipid core, covered by a fibrous cap, possible small calcifications
VI	Ulcerations and/or wide hemorrhage and/or thrombosis
VII	Plaque with a lipid core or fibrotic tissue, with large calcifications
VIII	Plaque with fibrous tissue, no lipid core, possible calcifications
High-resolution MRI description	
Lesion type	
I-II	Near-normal wall thickness, no calcification
III	Diffuse intimal thickening or small eccentric plaque with no calcification
IV-V	Plaque with a lipid or necrotic core, surrounded by fibrous tissue with possible calcification
VI	Complex plaque with possible surface defect, hemorrhage or thrombus
VII	Calcified plaque
VIII	Fibrotic plaque without lipid core and with possible small calcifications

AHA = American Heart Association; MDCTA = multidetector computed tomography angiography; MRI = magnetic resonance imaging.
[a] From Ref. 44.
[b] From Ref. 60.

and calcifications [59], and characterize atherosclerotic lesions as defined by the modified version of the American Heart Association criteria for MRI (Table 3) [60] and VP definition by Naghavi et al [8].

Multicontrast MRI (T1, T2, proton density, and 3D time-of-flight) had 81% sensitivity and 90% specificity for identifying a thin or ruptured cap [61]. Fibrous cap thickness on T1-weighted (T1W) imaging both pre- and postgadolinium injection also has a good correlation with histology [62]. A retrospective study showed that a ruptured fibrous cap by MRI was associated with recent history of stroke or transient ischemic attack [63], and a prospective study found an increased risk of development of symptoms in patients with a previously detected ruptured fibrous cap by MRI [64].

IPH was accurately identified by multicontrast MRI as a hyperintense signal on T1W turbo spin echo images with 93% sensitivity and 96% specificity [65] and on T1W 3D gradient echo images (direct thrombus MRI) with 84% sensitivity and specificity [66]. Retrospective [67] and prospective [68] studies demonstrated a strong association between IPH and cerebral ischemic symptoms. IPH detected in asymptomatic patients was associated with significant plaque progression over 18 months [69]. Moreover, a retrospective study found that type VI plaque was significantly more frequent in patients with ipsilateral ischemic stroke or transient ischemic attack [70] and

Table 4
Relative signal intensity of plaque components on MRI[a]

	MRI weighting				
Plaque components	3D TOF	T1W	T1W postcontrast	T2W	Proton density
Lipid-rich necrotic core	+/−	+/− to +	+/−	−	+/− to +
Fibrous tissue					
Dense matrix	+/−	+/−	+/− to +	+/−	+/−
Loose matrix	+/−	+/−	+/− to +	+	+
Fibrous cap					
Intact thick	Hypointense dark band	+/−; smooth	+/− to +	+	+/−
Intact thin	Absent dark band	Not visible	Not visible	Not visible	Not visible
Ruptured	Hyperintense signal at plaque-lumen interface	Irregular plaque surface	Irregular plaque surface	Irregular plaque surface	Irregular plaque surface
Intraplaque hemorrhage	+	+	+	+ to +/−	+ to +/−
Calcification	−	−	−	−	−

MRI = magnetic resonance imaging; 3D = 3-dimensional; TOF = time-of-flight; T1W = T1-weighted; T2W = T2-weighted; +/− = isointense; + = hyperintense; − = hypointense.
[a] Based on pooled data from Refs. 58-60,63,72.

a cross-sectional study found that preoperative VP morphology was more frequent in symptomatic than asymptomatic patients [71]. The MRI signal intensity criteria for identifying plaque components are listed in Table 4. High-resolution MRI of carotid plaques is presented in Figures 6 and 7.

MRI Technique and Reproducibility

Pulse sequences for carotid plaque include black-blood and bright-blood imaging. Black-blood imaging is a technique that suppresses the signal from flowing blood by using double or quadruple inversion recovery in T1, T2, and proton density sequences. The lumen appears black, and the vessel wall and plaque components can be more accurately delineated. Bright-blood is a technique used for magnetic resonance angiography (the lumen appears hyperintense); it uses gradient-recalled echo sequences (eg, 3D time-of-flight). This type of sequence is useful to improve visualization of the fibrous cap and superficial calcifications. The current recommendation for carotid plaque imaging and interpretation requires multiple contrast image sequences: T1, T2, proton density, 3D time-of-flight, and postcontrast T1 sequences. Gadolinium shortens T1 and improves contrast resolution and signal-to-noise ratio (SNR). It results in better delineation of the fibrous cap and lipid core, and increased intensity of fibrous tissue, and

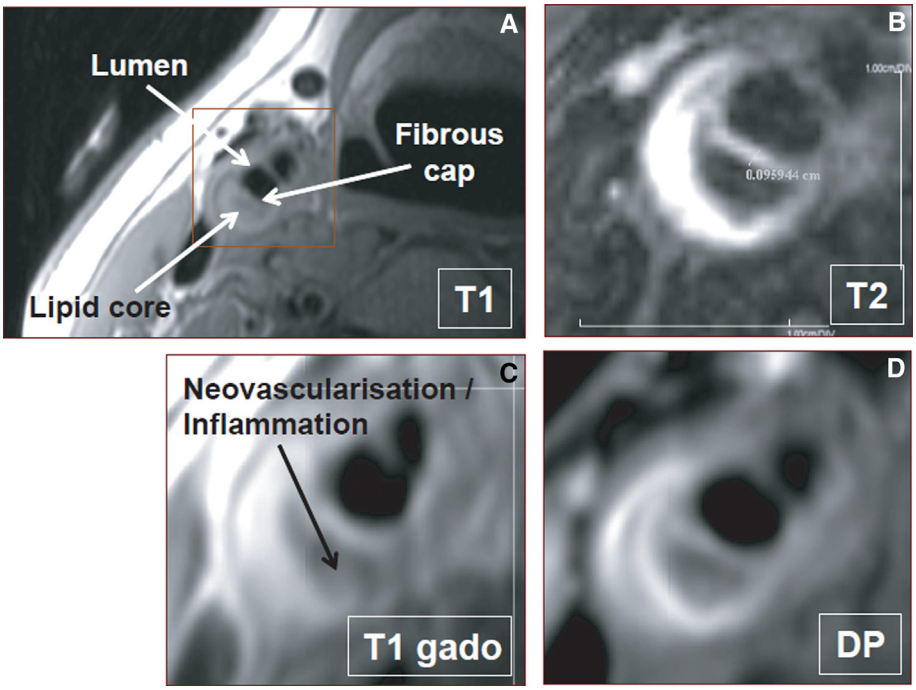

Figure 6. High-resolution magnetic resonance imaging of an asymptomatic patient's right internal carotid artery plaque, cross-sectional views. This patient has a 50% stenosis. (A) T1-weighted image, showing a thick fibrous cap and large lipid core, easier to depict on (C) the corresponding postgadolinium injection T1-weighted image (T1 gado). (D) Proton density image (DP), showing an isointense core. (B) A drop in relative signal intensity on the T2-weighted image (compared with other sequences) confirms the presence of a lipid-rich necrotic core. The fibrous cap measures more than 900 μm in its centre. (C) After gadolinium injection, plaque enhancement is observed in the posteromedial aspect of the plaque, which suggests neovascularization or inflammation (T1 gado). This figure is available in colour online at http://carjonline.org/.

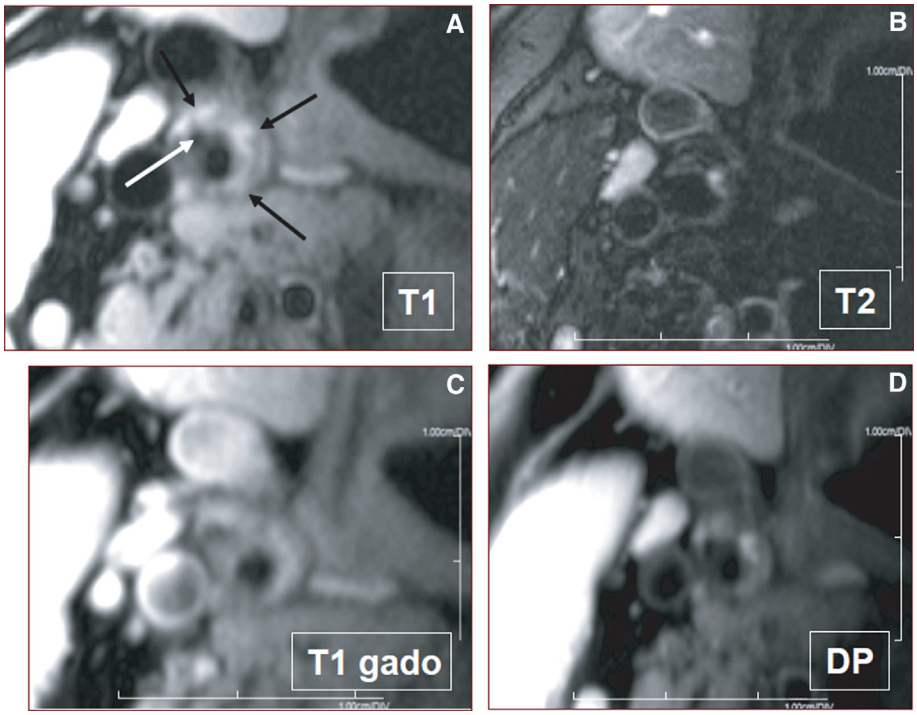

Figure 7. High-resolution cross-sectional magnetic resonance imaging of the right carotid bifurcation of an asymptomatic patient. (A) On T1-weighted acquisition of right internal carotid artery stenosis, the plaque appears heterogeneous. The external carotid artery lumen is observed (white arrow), and both vessel walls consist of heterogeneous signals, which reflect fibrocalcific tissue (black arrows). (B-D) T2-weighted and proton density (DP) images, showing a hyperintense area in the medial internal carotid artery wall, not clearly apparent on T1 pre- and postcontrast (T1 gado) images, which likely represents loose matrix fibrous tissue. There is no significant plaque enhancement after gadolinium injection, which suggests the absence of neovascularization or inflammation. This figure is available in colour online at http://carjonline.org/.

correlates with neovascularization and macrophage infiltration [72]. All MRI sequences are fat-suppressed and cardiac triggered to minimize motion artifacts. Total scanning time can be up to 40 minutes.

To visualize atherosclerotic plaque components, high spatial resolution (0.5 × 0.5 mm in-plane and 2-3 mm thick) with excellent contrast between plaque components is essential. To optimize SNR, a dedicated phased-array surface coil with at least 2 elements on each side of the neck is required. In a study that compared 8-channel to 4-channel phased array coils at 3T, an 8-channel coil improved both SNR and contrast-to-noise ratio compared with a 4-channel coil [73]. Moreover, 3T showed a significant improvement over 1.5T in SNR and contrast-to-noise ratio [74], stronger inter- and intraobserver reproducibility for measuring vessel wall contours (Pearson $r > 0.9$) [75], and better repeated scan reliability to quantify plaque components and vessel wall thickness (ICC > 0.87 vs > 0.38) [76,77]. Nevertheless, interreader reproducibility studies for plaque morphology are lacking; 1 study found moderate reproducibility for plaque component discrimination [78], and another found good reproducibility for fibrous cap measurement (ICC $= 0.71$) [79].

Molecular MRI

Nanoparticles, such as ultra-small superparamagnetic iron oxide (USPIO), are phagocytosed by macrophages and help identify plaque inflammation. Symptomatic patients had greater areas of signal drop from phagocytosed USPIO [80], and aggressive lipid-lowering therapy over 3 months significantly decreased USPIO-identified inflammation [81]. Recently, the contrast agent P947 was found to detect matrix metalloproteinases, angiotensin-converting enzyme, and aminopeptidase N activity in VPs ex vivo and in a rabbit model in vivo [82]. More developments on molecular imaging of plaques with targeted contrast agents in MRI are expected for the future.

Clinical and Future Perspectives

Multicontrast high-resolution MRI of carotid plaque has shown significant promise to detect VP, which is why it is currently used in numerous clinical studies. Compared with other imaging techniques, it has very good sensitivity and specificity to identify and measure plaque components. However, significant drawbacks prevent high-resolution MRI from being easily introduced into clinical practice. It is an expensive examination with frequent contraindications, limited availability, and lengthy examination duration, thus not suitable for screening purposes. It is also susceptible to poor image quality, reaching at times more than 30% of patient examinations, mainly due to motion artifacts [83].

So far, technical improvements such as parallel imaging techniques [84] and a new T1W sequence, Rapid Acquisition Gradient Echo, resulted in shorter scanning times, and better

diagnostic capability to detect IPH [85]. The current area of research is also focusing on prospective studies to measure plaque progression [83]; assessing predictive value of VP [86]; determining clinical factors associated with VP [87]; increasing the use of 3T magnetic field and measuring reader reproducibility.

Conclusion

The best noninvasive imaging modality to study the natural history of atherosclerosis for stroke prevention is yet to come. By describing how US, MDCTA, and MRI are used to characterize atherosclerotic carotid disease, this review has helped explore different avenues for noninvasive carotid plaque imaging. Newer developments in US elastography, targeted contrast agents, and MRI technical optimization are emerging. Prospective studies of plaque progression are the next step.

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Letter to the Editor / Lettre à la rédaction

Ultrasound Training for Nonradiologists

I enjoyed the editorial on ultrasound training for nonradiologists [1]. In addition to the points made, it seems to me important to make a clear distinction between ultrasound used as part of a clinical examination, which attracts no billing fee, and ultrasound performed at the request of a referring physician, which does attract a professional fee and requires a requisition, documented and stored images, and a written report, and that is subject to audit and peer review.

Ultrasound with small portable equipment is now so good, that its use during clinical examination of a patient should be routine and should be taught in all medical schools as part of the basic clinical skills program, not significantly different to the skills required in using a stethoscope, an ophthalmoscope, a tongue depressor, or a proctoscope. It is inconceivable to me that a modern young physician would speculate on whether the spleen feels enlarged, whether there is an effusion in a knee or a hip, whether there are gallstones present, and whether that lump in the neck is the thyroid. Look at it with ultrasound and then ask, when necessary, for further imaging to clarify or seek for further explanations.

It is more than 20 years since we put 2 small portable ultrasound units in the anatomy laboratory at McMaster with the hope that in due course all graduating medical students would be able to make a basic examination of the abdomen and of the heart, and be able to declare either that all appears normal or that there is a problem here that needs further evaluation. The anatomy laboratory now offers solid training for medical students in abdominal examination with ultrasound. Technology has improved, and more ultrasound is being used in medical schools, but it is far from being accepted as a basic clinical skill for all physicians.

I agree that radiologists should have a major role in setting standards and regulations for imaging studies but also suggest that we should encourage and promote the use of ultrasound, this wonderfully safe window into the body, by all our young physicians in training.

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