Contemporary carotid imaging: from degree of stenosis to plaque vulnerability

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Carotid artery stenosis is a well-established risk factor of ischemic stroke, contributing to up to 10%–20% of strokes or transient ischemic attacks. Many clinical trials over the last 20 years have used measurements of carotid artery stenosis as a means to risk stratify patients. However, with improvements in vascular imaging techniques such as CT angiography and MR angiography, ultrasonography, and PET/CT, it is now possible to risk stratify patients, not just on the degree of carotid artery stenosis but also on how vulnerable the plaque is to rupture, resulting in ischemic stroke. These imaging techniques are ushering in an emerging paradigm shift that allows for risk stratifications based on the presence of imaging features such as intraplaque hemorrhage (IPH), plaque ulceration, plaque neovasculature, fibrous cap thickness, and presence of a lipid-rich necrotic core (LRNC). It is important for the neurosurgeon to be aware of these new imaging techniques that allow for improved patient risk stratification and outcomes. For example, a patient with a low-grade stenosis but an ulcerated plaque may benefit more from a revascularization procedure than a patient with a stable 70% asymptomatic stenosis with a thick fibrous cap.

This review summarizes the current state-of-the-art advances in carotid plaque imaging. Currently, MRI is the gold standard in carotid plaque imaging, with its high resolution and high sensitivity for identifying IPH, ulceration, LRNC, and inflammation. However, MRI is limited due to time constraints. CT also allows for high-resolution imaging and can accurately detect ulceration and calcification, but cannot reliably differentiate LRNC from IPH. PET/CT is an effective technique to identify active inflammation within the plaque, but it does not allow for assessment of anatomy, ulceration, IPH, or LRNC. Ultrasonography, with the aid of contrast enhancement, is a cost-effective technique to assess plaque morphology and characteristics, but it is limited in sensitivity and specificity for detecting LRNC, plaque hemorrhage, and ulceration compared with MRI.

Also summarized is how these advanced imaging techniques are being used in clinical practice to risk stratify patients with low- and high-grade carotid artery stenosis. For example, identification of IPH on MRI in patients with low-grade carotid artery stenosis is a risk factor for failure of medical therapy, and studies have shown that such patients may fair better with carotid endarterectomy (CEA). MR plaque imaging has also been found to be useful in identifying revascularization candidates who would be better candidates for CEA than carotid artery stenting (CAS), as high intraplaque signal on time of flight imaging is associated with vulnerable plaque and increased rates of adverse events in patients undergoing CAS but not CEA.

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KEY WORDS carotid artery; MRI; ultrasound; risk; vascular disorders

ABBREVIATIONS AHA = American Heart Association; CAS = carotid artery stenting; CEA = carotid endarterectomy; CEUS = contrast-enhanced ultrasonography; CTA = CT angiography; DCE = dynamic contrast-enhanced; DSCT = dual-source CT; FDG = fluorodeoxyglucose; FSE = fast spin echo; Gd = gadolinium; HU = Hounsfield units; IPH = intraplaque hemorrhage; LRNC = lipid-rich necrotic core; MDCT = multidetector-row CT; MDCTA = MDCT angiography; MES = microembolic signal; MMP-9 = matrix metalloproteinase–9; MRA = MR angiography; PDW = proton density–weighted; SUV = standardized uptake value; SUVmax = maximal SUV; TBR = target-to-background ratio; TCD = transcranial Doppler ultrasonography; TIA = transient ischemic attack; TOF = time of flight; USPIO = ultrasmall superparamagnetic iron oxide.


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DISCLOSURE Dr. Lanzino reports being a consultant for Covidien.
Carotid artery stenosis is a well-established risk factor for ischemic stroke, contributing to 10%–20% of strokes or transient ischemic attacks (TIAs). Randomized clinical trials comparing medical therapy with surgical intervention have primarily selected patients by degree of stenosis. Because current guidelines have established degree of stenosis as the primary surrogate for stroke risk and indication of intervention, much research has been dedicated to determining sensitive, specific, and cost-effective techniques to accurately measure degree of stenosis. It has been known for many years that plaque stability and vulnerability are more important than degree of stenosis in determining the risk of acute coronary syndrome. It has been often said that the situation is different in the carotid arteries because they have much larger diameter and different hemodynamic conditions. Also, coronary arteries typically cause symptoms because of plaque rupture leading to thrombotic luminal occlusion, whereas carotid arteries characteristically cause symptoms by embolization without local vessel closure. However, as we will discuss, there is increasing evidence that active, unstable plaques in the carotid arteries are more prone to embolization, regardless of the degree of stenosis.

The inadequacy of limiting the assessment of carotid atherosclerosis to the degree of stenosis is also highlighted by clinical experience. Cryptogenic stroke, stroke with no definite cause despite extensive workup, occurs in up to 30% of patients with ischemic stroke. One-third of patients with cryptogenic stroke have nonstenotic (or producing mild or minimal stenosis) carotid atherosclerotic plaques ipsilateral to the stroke. On MRI, these plaques often demonstrate variable characteristics of vulnerable plaque, such as intraplaque hemorrhage (IPH), plaque rupture, and luminal thrombus. Thus, it is likely that a high proportion of these strokes are due to rupture or erosion of nonstenotic, high-risk plaques. Furthermore, many patients with a high degree of stenosis have stable plaques that are thought to be at low risk of rupture. Because of such findings, over the last decade there has been a paradigm shift on the imaging-based risk stratification of carotid disease from static measurements of carotid artery stenosis to characterization of the dynamic biological processes occurring within carotid plaques. It is important for neurosurgeons to be aware of this paradigm shift as it allows for improved risk stratification of patients with both high- and low-degree carotid artery stenosis.

In this review article, we summarize current developments in imaging-based assessment of carotid plaques. We first discuss current paradigms in plaque biology and discuss, there is increasing evidence that active, unstable plaques in the carotid arteries are more prone to embolization, regardless of the degree of stenosis.

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In this review article, we summarize current developments in imaging-based assessment of carotid plaques. We first discuss current paradigms in plaque biology and then review how various imaging modalities (CT, MRI, ultrasonography, and PET) can be used to characterize the pathological characteristics of plaques. We also discuss how these advanced imaging techniques are being used to monitor the effects of medical treatment and to identify ideal candidates for surgical and medical therapies.

Plaque Histopathology

Carotid plaque imaging hinges on the understanding of the histopathological characteristics of advanced atherosclerotic disease. The American Heart Association (AHA) developed a well-validated criterion for histological classification of atherosclerotic plaque in 1995. The early process of atherosclerotic plaque formation involves isolated deposition of macrophages and foam cells (Type I), followed by a fatty streak lesion with mainly intracellular lipid accumulation (Type II) and then deposition of extracellular lipids within the plaque (Type III). This process occurs over the course of the first 3 decades of life and is clinically silent. The Type IV lesion, also known as an atheroma, is the first manifestation of advanced atheromatous disease and is characterized by dense accumulation of extracellular lipid within the intima, known as a lipid core. At this stage in the disease, there is no fibrous tissue formation along the plaque nor are there surface defects or thrombosis. Macrophages, smooth muscle cells, and inflammatory cells (lymphocytes and mast cells) can be seen on the intimal border of the lipid core, whereas microvessels, macrophages, foam cells, and lymphocytes can be seen on the luminal surface of the plaque. Type IV lesions are considered clinically significant as the luminal surface of the plaque lacks a fibrous covering, leaving proteoglycans and foam cells at the luminal surface. The abundance of macrophages at the luminal surface renders the plaque prone to fissuring and rapid progression to a Type VI lesion, as described below.

Type V lesions are characterized by development of a fibrous cap overlying the lipid core. Fibroatheroma (Type Va) is characterized by a lipid core with a fibrous cap. Type Vb is characterized by partial calcification of the lipid core and other parts of the plaque, and lipid-poor plaques are classified as Type Vc. It is at this stage that arterial narrowing occurs. Histologically, Type V lesions demonstrate increased capillary proliferation around the lipid core and the presence of lymphocytes, macrophages, plasma cells, and microhemorrhages. Inflammation is also seen in the vasa vasorum of the artery wall. These plaques are considered clinically relevant because they are prone to fissuring, hematoma development, and thrombus and thus progression to Type VI lesions.

Arterial ischemic stroke secondary to extracranial carotid artery disease is thought to be due to progression of Type IV and V plaques to Type VI plaques. Type VI plaques are characterized by fissuring of the luminal surface of the plaque, hemorrhage, and thrombotic deposits. Disruption of the plaque due to inflammatory and hemodynamic factors leads to ulceration and fissuring. Ulceration and fissuring of the plaque result in loss of the normal endothelium and luminal exposure of the necrotic lipid core. IPH also occurs due to disruption of some newly formed vasa vasorum proliferation within the plaque. This process is extremely prothrombotic and puts the patient at risk for ischemic events. These fissured and ulcerated plaques can reseal around the thrombi and hemorrhage, resulting in intraplaque hematomas and intraplaque thrombus. As this process recurs, the plaque can rapidly expand, resulting in rapid progression of stenosis, as well as increased incidence of distal thromboembolic events. A summary of the histopathological grading of atheromatous plaques is provided in Table 1.
The above findings are well validated in histopathological studies of carotid plaques. Histopathological studies of symptomatic plaques have demonstrated high concentrations of inflammatory cells, such as macrophages and lymphocytes, with associated focal areas of loss of the fibrous cap. Symptomatic carotid plaques have also been demonstrated to have higher rates of IPH and increased presence of lipid-rich necrotic cores (LRNCs), neovascularization, thin fibrous plaque, and plaque thrombus on histological studies.

In contrast, stable carotid plaques are characterized by a thick fibrotic cap without a lipid-rich core. The goal of plaque imaging is to distinguish plaques based on these features.

### Magnetic Resonance Imaging

#### Imaging Techniques

MRI is the most well-established imaging modality for plaque characterization. There is a wide variety of pulse sequences available for plaque characterization with MRI. Fast spin echo (FSE) is a commonly used technique, which allows for T1-, T2-, and proton density–weighted (PDW) imaging. FSE sequences allow for an extremely high spatial resolution and signal-to-noise ratio, especially with the use of a surface or phased-array coil, but suffer from prolonged scanning times, leading to potentially higher rates of motion artifact. However, many techniques are available to reduce scan time. Gradient echo imaging with or without an inversion recovery preparatory pulse is another technique that allows for rapid image acquisition and can be used with high reliability to detect IPH and LRNC on T1-weighted images.

Another popular technique for plaque imaging is the black-blood technique. This method uses an FSE sequence with double inversion recovery preparatory pulses, which results in high contrast between the dark lumen and the vessel wall. The high signal-to-noise ratio comes at the cost of long examination times. However, techniques are being developed to decrease image acquisition time while preserving the high signal-to-noise ratio provided by the black-blood technique, to allow for a simple and quick assessment of IPH on T1-weighted images.

Fat suppression is essential for proper characterization of plaque morphology. This method is used in all sequences to suppress the signal of subcutaneous fat, thus resulting in improved contrast between various plaque components as well as between the carotid wall and surrounding tissues. Furthermore, fat-suppressed T1-weighted images are helpful in distinguishing between the high T1 signal of intraplaque lipid and that of IPH.

Contrast-enhanced images are essential in differentiating between various plaque components. Gadolinium (Gd)–based contrast imaging can be used to evaluate plaque neovascularity, as well as differentiate necrotic core from fibrous tissue on T1-weighted images. The LRNC and IPH do not enhance since these components are avascular, whereas the fibrous cap component of the plaque does. Increased enhancement with Gd is also associated with neovascularity and plaque inflammation. Ultrasound superparamagnetic iron oxide (USPIO) particles are another contrast agent used in plaque evaluation. These particles result in magnetic susceptibility on T2*-weighted images.

#### Characteristics of Unstable Plaques on MRI

Studies comparing MRI findings with histopathology have demonstrated that MRI can accurately distinguish between plaque calcification (Fig. 1), fibrous cap, IPH (Fig. 2), and LRNC (Fig. 3). MRI is excellent at detecting and differentiating between LRNC and IPH. IPH is often diffusely located within the plaque and located in the LRNC. Given the high T1 signal of the lipid-rich core and IPH, several studies have devised techniques to distinguish between the two. Multisequence protocols are essential to differentiate these 2 entities. When combining T1-weighted with time of flight (TOF) MR images, IPH is often hyperintense on both sequences, whereas LRNC is hyperintense only on T1-weighted and isointense on TOF MR images. The addition of T2-weighted and PDW sequences helps to further identify IPH. Fresh IPH is hyperintense on T1 and hypointense/isointense on T2 and PDW images. Recent IPH (1–6 weeks) is hyperintense on all contrast weightings, and old (> 6 weeks) IPH is hypointense on all contrast weightings. Fat-saturated black-blood FSE images can be used to saturate the fat in the LRNC to help further identify hemorrhage. The correlation between MRI and histopathological findings of LRNC and IPH is extremely strong. Sensitivity and specificity for detection of these 2 entities are very strong, and interobserver agreement for their detection and differentiation is excellent.

Plaque enhancement on postcontrast T1-weighted MR

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**TABLE 1. Summary of histopathological features of atheromatosus plaques**

<table>
<thead>
<tr>
<th>AHA Plaque Type</th>
<th>Histopathological Findings</th>
<th>Symptomatic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Isolated deposition of macrophages &amp; foam cells.</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Type II</td>
<td>Fatty streak lesion w/ mainly intracellular lipid accumulation.</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Type III</td>
<td>Deposition of intracellular lipids w/in the plaque.</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Type IV</td>
<td>Dense accumulation of extracellular lipid (i.e., lipid core). Inflammatory cell infiltration. No fibrous tissue formation, no surface defects or thrombosis.</td>
<td>Possibly symptomatic</td>
</tr>
<tr>
<td>Type V</td>
<td>Fibrous cap overlying necrotic lipid core. Inflammation w/in plaque &amp; in the vasa vasorum of the artery wall. Prone to hematoma, thrombus formation, &amp; fissuring.</td>
<td>Possibly symptomatic</td>
</tr>
<tr>
<td>Type VI</td>
<td>Fissuring &amp; ulceration of plaque. Necrotic lipid core. Intraplaque hemorrhage &amp; thrombus. Inflammation w/in the plaque.</td>
<td>Probably symptomatic</td>
</tr>
</tbody>
</table>
images is associated with plaque vulnerability, neovascularization, and macrophage infiltration. Prior studies have used dynamic contrast-enhanced (DCE) MRI to quantify plaque enhancement and thus neovascularity and inflammation. Adventitial $K_{\text{trans}}$ (volume transfer coefficient) as calculated by DCE MRI has a strong correlation with plaque neovascularity and inflammation.49 This technique has been shown to be highly reproducible and reliable.33 Millon et al. demonstrated that neovascularity is seen in up to 97% of areas with Gd enhancement on postcontrast images, whereas macrophage infiltration is seen in 87% of regions of Gd enhancement.64 This technique has been shown to be highly reproducible and reliable.33

MRI is extremely sensitive in detecting plaque ulceration (Fig. 4). In MR angiography (MRA), the fibrous cap appears as a dark band between the bright lumen and the gray plaque. The absence of the thin, dark band signals plaque ulceration. The best technique for detection of plaque ulceration is contrast-enhanced MRA.28 Interobserver agreement for detection of plaque ulceration is good, with kappa values ranging from 0.74 to 0.85.22 Plaque calcification is detected by MRI with both high sensitivity and specificity.22,81 Calcifications are usually hypointense on all contrast-weighted sequences.

Plaque characterization with MRI has been shown to be a valuable tool in predicting subsequent ischemic events. In a systematic review of 9 studies involving 779 subjects, Gupta et al. found that IPH, LRNC, and thinning/rupture of the fibrous cap were associated with hazard ratios of 4.59, 3.00, and 5.93, respectively, for subsequent TIA or stroke.36 In fact, MRI plaque characteristics have been found to have a stronger association with patient symptomatic status than degree of stenosis. One large cross-sectional study of 97 patients with 50%–99% stenosis found that the presence of a LRNC and thin or ruptured fibrous cap was associated with symptomatic events, whereas the degree of stenosis was not. The size of LRNC and presence of ulceration have been found to be independent predictors of symptomatic events in one study.17
IPH has also been found to have a very strong association with symptomatic events independent of degree of stenosis. Studies of both asymptomatic and symptomatic patients with moderate (< 70%) carotid stenosis have found that MRI findings of IPH are associated with a higher hazard ratio of future ipsilateral ischemic events.\(^3,6\) One meta-analysis of 8 studies found that IPH was associated with stroke at a rate of 17.7% per year of follow-up.\(^8\)

Plaque enhancement, a marker of plaque neovascularization and inflammation, is also strongly associated with symptomatic events. Prior studies have demonstrated that plaque enhancement on DCE MRI is significantly associated with ipsilateral ischemic events, independent of degree of stenosis.\(^64,74\) These studies are in accord with previous reports demonstrating the increased expression of the angiogenic pathway in unstable plaques, thus underscoring the seminal role of plaque neovascularization in plaque vulnerability. A summary of imaging characteristics of vulnerable plaques on MRI is provided in Table 2.

**Medical and Surgical Therapy**

In vivo MRI has been used to evaluate the efficacy of pharmacological therapy in improving plaque stability. In fact, one randomized trial comparing efficacy of statin versus niacin plus statin used MRI to characterize carotid plaque regression and found that both treatment regimens resulted in similar, but significant, reductions in plaque volume.\(^93\) Another trial used MR plaque imaging to demonstrate that intensive lipid therapy with atorvastatin resulted in significant reductions in the carotid plaque LRNC volume.\(^128\) Serial MRI studies have also demonstrated that high-dose rosuvastatin is associated with marked (60%) reduction in LRNC volume.\(^112\)

MR plaque imaging has also been used to identify surgical candidates. Yoshida et al. found that patients with low-grade carotid stenosis with IPH on MRI had high rates of ischemic events even when placed on antithrombotics and statins. Because these patients with IPH were refractory to medical therapy, they elected to proceed with endarterectomy and found that surgery was associated with marked reductions in subsequent ischemic events.\(^124\) MR plaque imaging has also been found to be useful in identifying revascularization candidates that would be...
better candidates for carotid endarterectomy (CEA) than carotid artery stenting (CAS), as high intraplaque signal on TOF imaging has been shown to be associated with vulnerable plaque and increased rates of adverse events in patients undergoing CAS but not CEA.125,126

Computed Tomography

Imaging Techniques

The 2 principal CT techniques for plaque characterization are multidetector-row CT (MDCT) and dual-source CT (DSCT). MDCT allows for multiplanar reconstructions in the axial, sagittal, and coronal planes, as well as high spatial and contrast resolution. Similar to MRI, CT allows for high, submillimeter spatial resolution. Plaques are imaged using a bolus tracking CT angiography (CTA) technique. Plaque calcification, fibrous plaque thickness, IPH, and LRNCs can be characterized on MDCT based on voxel Hounsfield units (HUs). The high resolution of MDCT allows for accurate identification of plaque ulcerations as small as 1 mm (Fig. 5). Plaque enhancement following contrast injection is also an extremely valuable imaging parameter. The main limitations to MDCT include beam hardening artifact from densely calcified plaques, need for iodinated contrast, and radiation exposure.

DSCT uses 2 different x-ray sources at 2 different x-ray energies to achieve different HUs in the same tissue. This allows for better tissue differentiation and advanced postprocessing techniques. DSCT also has high spatial and temporal resolution and can be combined with bone-removal algorithms, thus offering better visualization of vasculature, with high spatial resolution and the capability to perform multiplanar reformats. Advantages of DSCT compared with standard MDCT include the ability to differentiate calcified plaque from iodinated contrast, thus allowing for accurate assessment of calcified plaque volume and easy bone subtraction. No studies to date have been performed comparing the sensitivity and specificity of DSCT and MDCT for plaque characterization.

Characteristics of Unstable Plaques on CT

Prior studies characterizing components of unstable plaques have demonstrated that CT Hounsfield density can be used to distinguish between LRNC, connective tissue, IPH, and calcifications. Calcifications are easily identified by their high density (mean approximately 250 HU). However, there is considerable overlap between the CT densities of LRNC, connective tissue, and IPH (approximate means 30, 45, and 100 HU). For this reason, reliability is reduced when assessing plaque components on a pixel-by-pixel basis. However, macroscopic changes, such as large hemorrhage and large low-density lipid cores, can be easily recognized on MDCT with high interobserver agreement. As a general rule, the lower the density of the plaque, the more likely it is to be vulnerable. Examples of low-density vulnerable plaques are provided in Figs. 6 and 7.

MDCT is also very effective at detecting plaque ulcerations and plaque neovascularity, with sensitivities and specificities well over 90%, especially with multiplanar imaging. Interobserver agreement for detection of
plaque ulcerations and plaque enhancement is very high. Plaque contrast enhancement has been shown to be strongly associated with both plaque ulceration and neovascularity.\(^{86,89}\) However, sensitivity and specificity of blood-pool contrast-enhanced MRA exceeds that of MDCT angiography (MDCTA).\(^4\)

MDCTA findings are strongly correlated with patient symptomatology as well. In a study of 97 patients, Saba and Mallarini found that symptomatic plaques had a significantly higher degree of plaque enhancement following contrast administration than asymptomatic plaques; a threshold of 15 HU had a specificity of 83\% and a sensitivity of 76\%.\(^87\) Delayed phase images have also been demonstrated to have a strong correlation with symptomatology, as patients with stable plaques have progressive enhancement of the plaque on delayed images while symptomatic plaques tend to have more washout. This is likely related to the presence of neovascularization within unstable plaques leading to increase washout of contrast on delayed images.\(^42\) Other MDCTA findings associated with symptomatology include a fissured fibrous cap and LRNC.\(^{88,120}\) A summary of CT characteristics of stable and vulnerable plaques is provided in Table 2.

**CT Plaque Imaging in Medical Management**

Few studies have investigated the utility of MDCTA for monitoring response to medical therapy. In a study of 109 patients with history of TIA or ischemic stroke, van Gils et al.\(^{113}\) performed serial MDCTA of the carotid arteries over 5 years. This study demonstrated that MDCTA is a reliable method for monitoring plaque progression and response to therapy, with high rates of intraobserver and interobserver agreement. Furthermore, this study demonstrated that approximately one-third of patients who were on statin therapy following stroke had decreased plaque volume over time.\(^{113}\) No studies to date have used MDCTA plaque imaging to select candidates for revascularization therapy.

**Ultrasonography and Carotid Plaque Imaging Imaging Techniques**

B-mode ultrasonography and contrast-enhanced ultrasonography (CEUS) are the 2 most widely used techniques in evaluation of carotid plaque. B-mode examination is typically performed with a 4- to 7-MHz linear array transducer. Images are typically obtained in longitudinal section to maximize visualization of the atherosclerotic plaque. Color and power Doppler can be used to further delineate the plaque border. B-mode ultrasonic images are used primarily in assessing the echogenicity of plaques. One of the limitations of B-mode characterization of carotid plaques is the lack of consistent inter- and intraobserver agreement, as well as poor signal-to-noise ratio.\(^5\) By applying a technique called real-time compounding, in which scan information from multiple angles is combined,

**FIG. 5.** MDCTA scans obtained in 3 separate patients with ulcerated plaques. A: Plaque found in a 53-year-old symptomatic male, resulting in a 50\% stenosis. The surface is markedly ulcerated and demonstrates multiple areas of decreased density suggestive of LRNC. B: Plaque found in a symptomatic 64-year-old female with a 40\% stenosis. Ulcerations are shown along the plaque surface. C: Plaque found in a 75-year-old male showing multiple areas of decreased density, as well as surface irregularity. The plaque resulted in a high-grade stenosis and was symptomatic. The white borders indicate the surface of the plaque.

**FIG. 6.** Case of a 25-year-old female with sudden-onset, right-sided hemiparesis. A and B: High-resolution CTA of the left ICA showing a low-grade stenosis with a low-density plaque at the carotid bifurcation (curved arrows). Findings are suggestive of a vulnerable plaque. C: Diffusion-weighted axial MR image showing a large left middle cerebral artery territory infarction.
signal-to-noise ratio and interobserver agreement can be improved. In addition, image processing techniques should be applied to best assess plaque echogenicity. However, many studies use the echogenicity of the overlying sternocleidomastoid muscle as a reference for plaque echogenicity. Operator variability is also a major limitation of B-mode plaque characterization.

Most recent developments in carotid plaque characterization with ultrasound have come in the field of CEUS. CEUS uses an intravenous microbubble contrast agent. These bubbles do not diffuse into surrounding tissues like other contrast agents; consequently, all signals from CEUS examinations are intravascular, which allows for accurate assessment of vessel lumen and neovascularity within the carotid plaque. In the setting of carotid stenosis, CEUS can be used to distinguish between total carotid occlusion and high-grade stenosis, identify plaque ulceration, and evaluate carotid plaque neovascularization. Specific, commercially available pulse sequences are needed to suppress signal from tissue within the image and accentuate signal from the intravascular bubbles. Quantitative methods have been established to improve reproducibility of measurements of contrast enhancement. There are, however, limitations to use of CEUS. Contraindications to microbubbles include allergy, acute heart failure, endocarditis, right to left shunts, and unstable angina. This technique is highly operator dependent and prone to high interobserver variability. Also, CEUS is prone to an artifact known as pseudoenhancement, in which ultrasound waves are propagated through the contrast agent leading to increased signal in the vessel wall furthest from the probe, thus leading to overinterpretation of vessel wall enhancement.

**Plaque Characterization With B-Mode and CEUS**

**B-Mode**

A strong correlation has been demonstrated between sonographic and histopathological features of carotid plaques using B-mode ultrasound. B-mode carotid ultrasonography has high specificity but only moderate sensitivity in identifying ulceration of the plaque surface. Absent, thin, or ruptured echogenic caps are established risk factors for acute ischemic stroke. Large plaque ulcerations are easily identified as obvious craters within the plaque, with reversed or stagnated flow (Fig. 8). There is wide variability in the prevalence of ulceration in symptomatic plaques on B-mode ultrasonography ranging from 5% to 40%. Ultrasonography lacks sensitivity for the detection of plaque ulceration compared with CT, MRI, and histopathological studies. Sensitivity is especially poor in examining patients with moderate stenosis, in whom determining the presence of ulceration is important due to the potential for changing the therapeutic approach. Some authors have suggested that this poor sensitivity can be improved by changing the diagnostic criteria for plaque ulceration. Conventional criteria require the size of the concavity to be greater than 2×2 mm and the presence of a color Doppler flow signal within the concavity. However, Muraki et al. argue that considering any concavity with an echogenic line at the plaque base as diagnostic of plaque ulceration is significantly more sensitive and specific.

Plaque echolucency is another strong marker of plaque vulnerability (Figs. 9 and 10). This is the sonographic equivalent of a LRNC. Plaque echolucency is seen in up to 50% of recently symptomatic plaques compared with less than 5% of asymptomatic plaques. Furthermore, the risk of stroke among patients with echolucent plaques, regardless of degree of stenosis, is up to 13%, which is higher than the risk of stroke among patients with high-grade stenosis. In addition, the size of the juxtaluminal hypoechoic area of the carotid plaque is strongly associated with stroke risk.

**CEUS**

CEUS is used primarily to identify neovascularization within carotid plaques. Histological examinations have demonstrated that plaque enhancement is strongly associated with plaque neovascularity and inflammation. A number of inflammatory markers including matrix metalloproteinase–9 (MMP-9) are highly expressed in enhancing plaques. Studies comparing plaque enhancement in asymptomatic and symptomatic plaques have demonstrated that plaque enhancement is markedly increased in patients with symptomatic plaque and is associated with a higher rate of cardiovascular events in general. Retention of microbubbles on the plaque surface on delayed images has been shown to correlate with plaque disruption and inflammation as macrophages are known to...
plagocytose this contrast agent.\textsuperscript{56} When combined with B-mode ultrasonography, CEUS provides further details in plaque characterization. More than 90\% of echolucent plaques demonstrate contrast enhancement.\textsuperscript{18,43} Contrast bubble agents are also used in characterizing the plaque surface. Disruptions in the plaque-lumen border are easily characterized using CEUS. Compared with B-mode and color-Doppler ultrasonography, CEUS has higher interobserver agreement, sensitivity, specificity, and accuracy in identifying plaque ulceration.\textsuperscript{109} A summary of plaque characteristics on ultrasonography evaluation is provided in Table 1.

Ultrasound Plaque Imaging in Medical and Surgical Management

Carotid ultrasonography is emerging as an effective tool to monitor response to lipid-lowering therapy. One study found that 80 mg/day of atorvastatin resulted in decreased echolucency of carotid artery plaques within just 30 days of treatment.\textsuperscript{21} Others have found that patients with moderate carotid stenosis on an aggressive atorvastatin regimen demonstrate increased plaque echogenicity after 12 months of treatment.\textsuperscript{47} Plaque neovascularization on CEUS is also known to decrease following statin therapy. These findings highlight the role that detailed carotid ultrasonography can play in monitoring response to therapy.\textsuperscript{23}

Plaque imaging on ultrasonography has also been effectively used in selecting carotid revascularization candidates. Ballotta et al.\textsuperscript{6} used CEUS to select patients with symptomatic carotid plaques with < 50\% stenosis. In this study, the authors selected patients with enhancing and echolucent or heterogeneous plaques with surface irregularities, ulcer, or rupture for surgical treatment and found stroke-free survival rates of 98\% at 1 year using these criteria.\textsuperscript{6} Further studies are needed to determine whether plaque characteristics on CEUS and B-mode ultrasonography can be reliably used to select surgical candidates with low-grade stenosis.

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography (TCD) is a portable and noninvasive technique used to image the intracranial vasculature. Generally, imaging is performed with a low-frequency (2 MHz) sector-array transducer to allow penetration of signal through the calvaria. Transtemporal, transfornaminal, and transorbital acoustic windows can be used for imaging.\textsuperscript{51} One potential side effect of TCD is thermal injury, especially when using the transorbital window, but this is only a concern when higher frequencies are employed.

The principle role of TCD in carotid imaging is the evaluation of cerebral microembolic signals (MESs).\textsuperscript{57,98} The middle cerebral artery is the preferred artery to monitor. A number of studies have suggested that MESs detected in patients with carotid artery disease are due to unstable plaque. This is further supported by the fact that MESs rapidly diminish following CEA.\textsuperscript{114}

Role in Risk Stratification

MESs are a strong marker of unstable plaque. In a systematic review of the literature, Ritter et al.\textsuperscript{77} found that 43\% of patients with symptomatic carotid stenosis had MESs on TCD compared with just 10\% of asymptomatic patients. Furthermore, presence of just 1 MES was associated with 7.5 times higher odds of future symptomatic event in asymptomatic patients and 13.4 times higher odds of embolic event in asymptomatic patients.\textsuperscript{77} Conversely, absence of MESs is associated with a very low risk of future symptoms in patients with asymptomatic carotid plaques.\textsuperscript{97} TCD is especially helpful when combined with other imaging modalities. Topakian et al. found that the combination of plaque echolucency on B-mode ultrasonography and MESs on TCD was associated with a 10 times higher risk of stroke in patients with asymptomatic carotid stenosis. These patients had an annual stroke risk of 8\% compared with < 1\% in the low-risk cohort.\textsuperscript{110} The
The main molecular imaging technique used to evaluate carotid plaques is \(^{18}\)F-fluorodeoxyglucose (FDG) PET/CT. FDG is partially metabolized through glycolysis within the atherosclerotic plaque and serves as a marker of plaque inflammation and hypoxia. \(^{31}\) FDG is injected intravenously, and image acquisition is performed after 60–180 minutes. Imaging is typically performed on a dedicated PET/CT scanner, and images are reconstructed into coronal, transverse, and sagittal planes. Corrections are applied for attenuation, scatter, random coincidences, and scanner dead time. Low-dose CT imaging is typically performed for both anatomical localization and attenuation correction.\(^{92}\)

There are a number of variables that need special attention when characterizing plaques with FDG-PET/CT. First, following injection of FDG, the concentration of FDG in the blood pool can result in poor contrast resolution when evaluating a small area such as a carotid plaque. For this reason, there is much debate regarding the ideal timing for imaging following FDG administration. Typically, when performing imaging for malignancy staging, images are obtained 1 hour following intravenous administration of FDG. However, imaging this early may result in low contrast resolution. Over time, blood activity declines and contrast resolution improves. In a study of patients undergoing imaging for carotid plaques, Blomberg et al.\(^ {10}\) found that imaging at 180 minutes resulted in improved quantification of atherosclerotic plaque inflammation compared with imaging at 90 minutes, as target-to-background ratios (TBRs) were highest at this point. Furthermore, carotid maximal standardized uptake value (SUVmax) at 180 minutes was more strongly associated with 10-year risk for fatal cardiovascular disease compared with imaging at 90 minutes.\(^ {10}\)

Another important variable is carotid plaque metabolism. The 2 principle quantitative methods for evaluating this variable are TBR and standardized uptake value (SUV). Furthermore, these values can be broken down into maximum and mean TBR and SUV values. Blomberg et al. suggested that the SUVmax of the carotid plaque is the most reliable surrogate for plaque vulnerability.\(^ {10}\) However, Niccoli-Asabella et al. argued that TBR maximal and mean values are more reliable than SUV in identifying inflamed plaques.\(^ {71}\) One advantage of FDG-PET imaging of carotid plaques is the high reproducibility of measurement techniques. Numerous studies have found that inter- and intraobserver agreement for plaque characterization is excellent (interclass correlation values greater than 0.90).\(^ {79,80}\)

**Plaque Characterization With Molecular Imaging**

A number of studies have been performed correlating findings from FDG-PET/CT and histopathological examination. Masteling et al. found that high FDG activity in carotid plaques was localized to areas with macrophage infiltration.\(^ {59}\) In a study of 21 patients undergoing CEA following FDG-PET/CTA, SUVmax was associated with increased concentration of CD68, a marker of macrophage activity.\(^ {61}\) In a small study, Tawakol et al. also found that CD68 staining was higher in high SUV plaques than in low SUV plaques.\(^ {106}\) Other studies have correlated FDG-PET findings with MR plaque imaging and have found that FDG uptake is higher in lipid-rich plaques compared with collagen-rich plaques.\(^ {94}\) Although FDG uptake is strongly associated with inflammation, the relationship between FDG uptake and plaque neovascularization is considered weak at best.\(^ {113}\) Thus, this imaging modality may not be the ideal choice to assess plaque vulnerability and progression.

Several studies have demonstrated that increased FDG uptake in carotid plaques is associated with clinical symptoms as FDG-avid plaques are significantly more likely to be found in symptomatic patients and are known to be associated with future ischemic events.\(^ {83,84,66}\) FDG imaging of carotid plaques shows the most promise when used as an adjunct to other imaging modalities, especially MRI. A number of investigators have examined the value of the combination of FDG-PET to detect active inflammation and MRI to identify worrisome morphological features for the optimization of risk stratification. In a study of 49 combination of plaque neovascularization on CEUS and MESs on TCD is also emerging as a strong risk factor for acute ischemic stroke.\(^ {78,129}\)

**Combining CEUS and TCD for Stroke Risk Assessment**

The combination of plaque neovascularization on CEUS and MESs on TCD is also emerging as a strong risk factor for acute ischemic stroke.\(^ {78,129}\)

**Molecular Imaging Techniques**

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patients, Truijman et al. found only a weak correlation between plaque inflammation on PET and neovascularization detected by DCE MRI. This suggests that these 2 techniques are complementary. Calcagno et al. found a weak inverse relationship between neovascularization on DCE MRI and plaque inflammation on PET. Similarly, FDG uptake did not strongly correlate with IPH seen on MRI. Further studies are needed to develop models that integrate findings from FDG-PET and MRI in risk stratification of carotid atherosclerotic disease. A summary of FDG-PET/CT characteristics of stable and vulnerable plaques is provided in Table 2. A summary of the advantages and disadvantages of carotid imaging techniques is provided in Table 3.

**FDG-PET and Medical Therapy**

FDG-PET of carotid plaques has been used as a tool to monitor response to medical therapy in patients with carotid stenosis. In a study of 43 patients randomized to simvastatin versus no simvastatin, Tahara et al. found that statin therapy resulted in a significant reduction of SUVmax in carotid plaques. Tawakol et al. found that intensive statin therapy produced significant dose-dependent reductions in FDG uptake after just 4 weeks of therapy. Mizoguchi et al. found that pioglitazone attenuated FDG uptake and thus inflammation in diabetic patients with carotid atherosclerotic disease. Thus, FDG-PET is emerging as a promising tool to measure response to therapy in patients with carotid atherosclerosis. To date, no large studies have been performed using FDG-PET to identify candidates for carotid revascularization.

**Other Molecular Markers**

A number of other molecular markers have been applied to plaque imaging. 18F-sodium fluoride (NaF) is another tracer that targets active microcalcifications in atherosclerotic plaques. Microscopic deposits of calcium are thought to signal plaque progression, rupture, and inflammation. Joshi et al. found that 18F-NaF PET/CT was more reliable than FDG-PET in identifying vulnerable coronary plaques. In carotid artery specimens, these authors found that 18F-NaF uptake occurred at the site of all carotid plaque ruptures and was strongly associated with active calcification, macrophage infiltration, apoptosis, and necrosis. A number of imaging agents targeting molecules that are highly expressed within vulnerable plaques have been proposed as well. For example, 18F-galacto-RGD has been shown to target αvβ3, an integrin highly expressed in angiogenic cells and macrophages. 18F-folate has been shown to target folate receptors highly expressed in macrophages. Imaging of matrix metalloproteinases, proteases associated with plaque rupture, has also shown promise in early preclinical studies. None of these radiotracers have been validated in large clinical studies as of yet.

**Future Directions and Conclusions**

Advanced imaging for characterization of carotid plaque vulnerability is useful for the identification of stroke risk. Our current reliance on degree of stenosis has clear limitations that can be overcome by the use of imaging for plaque characterization. Good clinical examples are the estimation of stroke risk in asymptomatic patients with high-grade carotid stenosis and in symptomatic patients with moderate or mild stenosis ipsilateral to the symptomatic territory. In these instances, advanced imaging for plaque characterization can help refine risk stratification and allow for individualization of care.

Future studies comparing different modalities of plaque imaging can be useful, but it is likely that a strategy combining more than one technique will prove most valuable, as some techniques offer complementary information. Cost-effectiveness studies will also need to be conducted. Several small clinical studies have used advanced imaging for plaque characterization to guide therapy (selecting candidates for medical treatment or revascularization, moni-
toring patients on medical therapy), but large multicenter trials are needed to determine whether plaque imaging can be superior to using only degree of stenosis for selecting candidates for invasive therapy.

References


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