Advances in Carotid Artery Imaging: Beyond Luminal Stenosis

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ABSTRACT: Ischemic stroke secondary to thromboembolic event from extracranial carotid artery disease remains an important cause of morbidity and mortality in the United States. Previous landmark trials have shown correlation of degree of carotid stenosis and future cerebrovascular events. Numerous imaging modalities including ultrasound, magnetic resonance angiography, computed tomography angiography, and digital subtraction angiography have been traditionally utilized in order to assess the severity of carotid artery stenosis and identify patients appropriate for carotid artery revascularization. However, there is a growing interest in assessing carotid artery plaque morphology and composition in order to identify patients with vulnerable plaque. With rapid advances in imaging technology, characterizing plaque with novel modalities may help to understand natural progression of carotid artery disease and identify lesions at risk for stroke beyond the severity of stenosis.

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Cerebrovascular disease remains one of the leading causes of morbidity and mortality in the United States.1 Stroke is still the third leading cause of death in the United States, and imposes an enormous economic burden on the society.2 Extracranial internal carotid artery disease is an important cause of ischemic stroke, and significant advances have been made in treatment of carotid artery disease. Early trials including ECST (European Carotid Surgery Trial) and NASCET (North American Symptomatic Carotid Endarterectomy Trial) demonstrated the association of severe carotid artery stenosis with ischemic stroke and the long-term benefit of carotid endarterectomy (CEA) in improving outcomes in patients with significant carotid artery disease.3,4 Despite evidence from randomized trials demonstrating the benefit of CEA and results from a recent landmark trial demonstrating efficacy/safety of carotid artery stenting (CAS) to CEA, there remains controversy over patient selection for carotid artery revascularization, especially in asymptomatic patients.5,6 Therefore, early identification of patients with carotid artery disease with plaque features associated with high risk for cerebrovascular events remains a critical component of vascular medicine. In this review, we discuss the various imaging modalities in the modern era of vascular medicine as well as future directions in vascular imaging.

PATHOPHYSIOLOGY OF CAROTID ATHEROSCLEROTIC DISEASE AND ISCHEMIC STROKE

Numerous studies have demonstrated that ischemic stroke frequently arises from thromboembolic sources, with the internal carotid artery (ICA) as one of the frequent sources.7 Previous studies of coronary atherosclerosis demonstrated plaque vulnerability and/or stability as a marker for occurrence of acute coronary syndrome. Similarly, histology of carotid atheroma after ischemic stroke demonstrates features suggestive of plaque rupture including thin fibrous cap and infiltration by macrophages and T cells.8 Inflammation involving macrophages, mast cells, and T cells with resulting foam cells have shown to result in large lipid-core plaque, sometimes associated with intraplaque hemorrhage.9,10 Prior studies have shown the role of intraplaque hemorrhage in plaque vulnerability, and plaque hemorrhage has been shown to be a marker of thromboembolic activity in patients with symptomatic carotid disease.12-14 Despite numerous landmark trials showing the association of ischemic stroke with degree of carotid artery stenosis, recent studies have shown that moderate plaque with high-risk features is frequently observed in patients with cryptogenic stroke.15 Recent studies suggest that there may be a correlation between the degree of stenosis and amount of inflammation. High-grade carotid stenosis is frequently associated with plaque destabilization with infiltrates of macrophages and T cells, potentially providing explanations for the findings in the earlier trials.16 With better understanding of carotid artery atherosclerosis and its pathophysiology, progress has been made in carotid artery imaging modalities in order to provide means to identify patients at risk.

Carotid ultrasound. Numerous studies have demonstrated a lack of sensitivity and specificity of carotid bruit on physical exam in identifying patients with significant carotid artery disease.17 However, there is no clear consensus for screening asymptomatic patients as various societies have varying recommendations.18,19 The United States Preventive Services Task Force recommends against screening the general population for asymptomatic carotid artery disease.
ipsilateral stroke beyond luminal stenosis. In fact, patients with carotid artery disease who underwent ultrasound studies. However, several factors can affect the Doppler velocity and can accurately assess the degree of carotid disease. Using grayscale and Doppler ultrasound, carotid ultrasound has shown to be an effective initial tool to assess carotid artery disease in numerous studies. However, several factors can affect the Doppler velocity, including arterial tortuosity, contralateral disease, and gender. In addition, anatomical features including high bifurcation and obesity can diminish accuracy of the studies. Quality of carotid ultrasound is highly dependent on the technicians, and all ultrasound laboratories need to validate and confirm the accuracy of their studies. Therefore, the Intersocietal Accreditation Commission (IAC) has established accreditation standards for vascular testing facilities.

Recently, there is growing interest in utilizing carotid ultrasound to identify carotid artery features suggestive of high risk for embolization (Figure 1). Initial studies demonstrated correlation of ultrasound densitometric analysis and carotid plaque composition. The echolucency of plaque has been shown to be associated with large amount of lipid-rich necrotic core as well as intraplaque hemorrhage. A recent meta-analysis of asymptomatic patients with carotid artery disease who underwent ultrasound demonstrated that carotid plaque echolucency is predictive of ipsilateral stroke beyond luminal stenosis. In fact, patients with predominantly echolucent plaque had an approximately 2.6-fold increased risk of ipsilateral stroke in a subgroup of patients with 50% or greater stenosis. Furthermore, carotid plaque echolucency was shown to be associated with increased risk of stroke in carotid stenting, demonstrating its potential use in identifying patients at risk of post-revascularization complication as well.

Numerous studies have suggested that ultrasound can successfully identify some of the other features of high-risk plaque, including plaque ulceration and stenosis progression. Recent studies have shown promise in using contrast sonogram to detect intraplaque neovascularization in order to identify some of the features associated with vulnerable plaque. However, these techniques and analyses are not yet widely available in the majority of vascular laboratories in the United States. With advances in ultrasound technology and standardization of sonogram laboratories, future modalities will provide risk assessment for ischemic stroke beyond measurement of luminal stenosis by allowing enhanced assessment of carotid plaque composition.

**Magnetic resonance imaging/Magnetic resonance angiography.** Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) has been widely used to assess the degree of stenosis as defined by the NASCET criteria. As a non-invasive test without radiation and iodinated contrast, MRI/MRA has an appeal as an effective tool to assess extracranial carotid vessels as well as intracranial circulation. In addition to limited utility in patients with ferromagnetic devices and claustrophobia, the possibility of overestimation with MRA needs to be taken into account when MRA is used as the only tool to make decisions regarding carotid artery revascularization. In particular, MRA sometimes can pose problems in discriminating occluded versus subtotally occluded carotid vessels, which can drastically alter the revascularization strategy. That being said, comparison with digital subtraction angiography (DSA) has shown specificity of 92.5% and sensitivity of 97.1% in previous studies. Caution must be taken in patients with preexisting renal dysfunction, as gadolinium exposure in this group of patients has been associated with nephrogenic systemic fibrosis.

Recent studies focused on the high spatial resolution of MRI to detect and analyze plaque morphology, such as intraplaque hemorrhage, plaque rupture, and luminal thrombosis. High-resolution, contrast-enhanced MRI has been used to visualize and measure fibrous cap thickness as well as quantify lipid-rich necrotic core size, and advances in MRI technology have improved the correlation of plaque morphology to histopathology. There is growing interest in identifying predictors of plaque disruption with MR imaging. In fact, a meta-analysis of 8 studies demonstrated a 6-fold increased risk of cerebrovascular events in patients with intraplaque hemorrhage, while another study showed lipid-rich necrotic core and thin fibrous cap were predictors as well (hazard ratio, 3.00 and 5.93, respectively). Furthermore, a recent study performed a quantitative analysis of plaque characterization using MRI black-blood imaging, which demonstrated that high signal intensity of plaques compared with the adjacent stenomeidastoid muscle was able to predict higher risk of embolic stroke after CAS (Figure 2). These findings indicate that MRI can offer findings beyond measurement of luminal stenosis, which can better identify patients at risk of future cerebrovascular events.

**Computed tomography angiography.** Computed tomography angiography (CTA) provides another option to directly assess the extracranial and intracranial lumen stenosis, with excellent specificity for high-grade stenosis (96%). CTA offers high-resolution images with short scan time and compares favorably to...
which may have implications in the plaque composition and risk of embolization. Recent studies suggest that soft plaque with low HU is associated with vulnerable plaque.\textsuperscript{43} Future studies are necessary to further examine the utilization of CTA beyond assessment of lumen stenosis.

**Digital subtraction angiography.** Conventional catheter-based digital subtraction angiography (DSA) is the gold standard against which other imaging modalities are compared in terms of assessing severity of luminal stenosis. Given the invasive nature, DSA is used mostly when there are conflicting results with non-invasive testing, when MRA or CTA is not feasible, or when CAS is being considered. Severity of stenosis is measured using the method utilized in the NASCET. Limitation of DSA is mostly due to cost and risks of the procedure. Neurologic complication rates resulting from DSA range from 0.4% to 12.2% for transient events and 0% to 5.4% for permanent deficits.\textsuperscript{44} However, the rates of neurological complications are usually $<1\%$ when performed by experienced operators.\textsuperscript{45} Therefore, DSA should be performed by experienced operators only when there is a clear indication. Other invasive methods of carotid artery imaging include intravascular ultrasound (IVUS) and optical coherence tomography (OCT), but the roles of these imaging modalities are limited given the invasive nature and the potential complications (Figure 3).\textsuperscript{46}

**Positron emission tomography.** Positron emission tomography (PET)/CT utilizes 18F-fluorodeoxyglucose (FDG), which is metabolized within the atherosclerotic plaque as a marker of inflammation and hypoxia.\textsuperscript{47} Although PET/CT has limited utility in assessing degree of stenosis, studies have shown that 18F-FDG uptake is higher in unstable plaque and potentially can predict future cerebrovascular events. High 18F-FDG activity has been associated with macrophage infiltration.\textsuperscript{48} Furthermore, symptomatic patients were found more likely to have high 18F-FDG activity in the carotid plaque, suggesting that 18F-FDG uptake may be associated with vulnerable plaque.\textsuperscript{49} A recent study demonstrated that 18F-FDG PET can identify patients with inflammatory activity in the carotid artery plaque. Therefore, 18F-FDG PET has been studied as a potential tool to monitor antiinflammatory response to medical therapy in patients with carotid artery disease. Studies have shown that intense statin therapy is associated with a reduction in 18F-FDG activity.\textsuperscript{50} Other molecular markers have been studied with PET/CT. 18F-sodium fluoride (NaF) has been shown to detect microcalcification, which is accumulated by apoptosis.\textsuperscript{51} There is growing interest in potentially combining PET scan with other imaging modalities, such as MRI, to better delineate plaque morphology.\textsuperscript{51}

**IMAGING AFTER CAROTID THERAPY**

CEA has been the gold-standard therapy for severe carotid artery stenosis and one of the most frequently performed vascular surgeries in North America. Numerous studies have validated the long-term patency rates after CEA with relatively low risk of restenosis after revascularization.\textsuperscript{52-55} Recent studies have suggested that routine follow-up studies may not be necessary if the initial ultrasound post CEA is negative.\textsuperscript{56} Similar to CEA,
landmark randomized trials demonstrated excellent long-term patency after CAS. However, given the relative novelty of the procedure, there are limited data to suggest recommendations for follow-up studies after revascularization. Currently, the guidelines suggest that evaluation of the extracranial carotid arteries is reasonable at 1 month, 6 months, and annually after carotid artery revascularization. Furthermore, it is recommended that surveillance at extended intervals may be appropriate once stability has been established.

**FUTURE DIRECTIONS**

Advances in various imaging modalities are changing the landscape of carotid artery disease management and may have a huge impact in how clinicians manage this challenging group of patients. In patients with asymptomatic carotid artery disease, we now have ample data to suggest that degree of stenosis alone is not sufficient to guide revascularization strategy. Identification of vulnerable plaque by the above modalities can potentially help distinguish which patients are better served with early invasive strategy, while patients with stable plaque can be conservatively managed. Furthermore, advances in PET/CT scan technology can potentially allow physicians to follow responses of aggressive medical therapy by monitoring the inflammatory responses in the carotid plaque. It is likely that this risk stratification will involve a combination of various markers of stroke risk including degree of stenosis as well as other plaque features described above.

Figure 3. Lipid-rich plaques demonstrated by intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Representative images of a lipid-rich plaque of the patient with symptomatic right internal carotid artery stenosis prior to carotid artery stenting are shown. (A) OCT demonstrated a large lipid pool (asterisk) as a homogenous, diffusely bordered, signal-poor region with an overlying signal-rich band corresponding to a fibrous cap. (B) IVUS depicted the plaque as heterogeneous with an echolucent core (asterisk). (C) IVUS-virtual histology (VH) revealed a large lipid core (asterisk) colored by light green. (D) A T1-weighted image of black-blood magnetic resonance imaging showed higher intensity in the carotid artery plaque (white arrow) compared with sternocleidomastoid muscle (arrowhead), indicating lipid-rich component.

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CONCLUSION

Currently, non-invasive modalities including ultrasound, CTA, and MRI/MRA are frequently used to assess degree of stenosis, which in turn guide decisions for carotid revascularization. Recent studies suggest degree of stenosis alone may not be sufficient to accurately assess risk of cerebrovascular events in patients with carotid artery disease. There is a growing interest in imaging and characterizing plaque with novel modalities, which may help to understand natural progression of disease and identify lesions at risk beyond the severity of stenosis.

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