Diagnostic and Therapeutic Approach of Carotid and Cerebrovascular Plaque on the Basis of Vessel Imaging

Dong Hyun Lee, Jong-Ho Park
Department of Stroke Neurology, Seonam University Myongji Hospital, Goyang-si, Korea

Atherosclerosis, characterized by chronic systemic inflammation with plaque formation, is one of the major causes of cerebrovascular disease. Recent advances in imaging technologies can help further understand the overall process and biology of plaque formation and rupture. Thus, these imaging techniques could aid clinicians to make better decision for risk stratification, therapeutic planning, and prediction of future cerebrovascular event. Ultrasonography, magnetic resonance imaging, and positron emission tomography are the rapidly-evolving imaging modalities dealing with assessment of atherosclerotic plaque. By advances in imaging technology for evaluating plaque, we can characterize the vulnerability of plaque in-vivo, understand the composition and activity of plaque, assess therapeutic response to treatment, and ultimately predict the overall risk of future cerebrovascular episodes. In this review, we will introduce current understanding of various advanced imaging modalities and clinical application of these imaging technologies. (J Lipid Atheroscler 2017 June;6(1):15-21)

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these imaging technologies.

**PLAQUE IMAGING IN THE CAROTID ARTERY**

Carotid artery, superficially located and easily palpated, has a bifurcating region, which bears significant amount of shear stress, and is susceptible to early atherosclerotic changes. Therefore, carotid bifurcation is suitable for imaging evaluation and generally a good surrogate for other systemic vascular beds.

1. **Assessment of carotid plaque burden using ultrasonography**

   Measurement of the plaque severity to accurately quantify the plaque burden in the carotid arteries have been tried before, because the predictive power for clinical outcome is limited in the assessment of the luminal stenosis in the carotid arteries. The assessment of plaque burden in the carotid arteries using ultrasonography had begun from measuring carotid intima-media thickness (IMT) around 1985. Since then, unfortunately IMT did accurately reflect neither atherosclerosis nor prediction of clinical events. To improve the predictive power of plaque screening for cardio-cerebrovascular events beyond IMT, quantifying the carotid plaque burden has been developed as a good alternative to IMT measurement. Carotid plaques grow along the artery 2.4 times faster than they thicken, thus we can easily deduce that two-dimensional measurement of total plaque area reflects the actual plaque burden more accurately. Actually, measurement of total plaque area had more predictive power in future risk of stroke, death, or myocardial infarction than measurement of carotid IMT, and also improved the accuracy of risk scoring system. Carotid plaques also progress circumferentially, thus quantification of plaque volume instead of plaque area can reflect the actual plaque burden more sensitively. Recent study compared progression of IMT, total plaque area, and total plaque volume in the same patients. The study demonstrated that progression of total plaque volume strongly predicted stroke, death or transient ischemic attack (Kaplan-Meier log rank \( p=0.001 \)), stroke/death/myocardial infarction (\( p=0.008 \)). Annual changes in total plaque area and total plaque volume reach around 10 mm²/year and 50 to 100 mm³/year respectively. It is thus more advantageous and sensitive to monitor treatment effect on carotid arteries during statin therapy in patients with vascular risk factors for measuring total plaque volume than total plaque area. The previous methodology of measuring the plaque volume goes beyond the scope of this review, and summarized well elsewhere. Among semi- or fully automated methods, mechanical sweep using Philips system recently has shown the excellent reproducibility and feasibility in the plaque volume quantification.

Atherosclerotic stenosis in the carotid arteries is one of the major risk factor of ischemic cerebrovascular diseases. Besides degree of the luminal narrowing or quantification of plaque volume, both the composition and the morphological characteristics of the plaques are related to future cerebrovascular ischemic episodes. Histopathologically, it is known that a vulnerable plaque is covered with a thin fibrous cap, and contains a large necrotic lipid core. A recent meta-analysis demonstrated that plaques with complex features such as intra-plaque echolucency, neovascularization, ulceration, and intra-plaque motion were significantly associated with cerebral ischemic symptoms. Intra-plaque echolucency represents intra-plaque hemorrhage and lipid-rich necrotic core histologically. Ultrasonography is more sensitive to detect the size and location of echolucency within the plaque than computed tomography (CT) or magnetic resonance imaging (MRI). Large-sized echolucency adjacent to lumen, especially, is associated with increased risk of stroke episodes. Although ultrasonography is generally inferior to CT or MRI for detecting ulceration, three dimensional ultrasonography can reliably
Table 1. Typical MRI signal characteristics of carotid plaque composition

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<tr>
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<th>T1W</th>
<th>T2W</th>
<th>PDW</th>
<th>3D TOF</th>
<th>T1GD</th>
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<tr>
<td>Fibrous cap</td>
<td>Isointensity</td>
<td>Mixed intensity</td>
<td>Mixed intensity</td>
<td>Hypointensity</td>
<td>Isointensity</td>
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<tr>
<td>Lipid-rich necrotic core</td>
<td>Iso/hyperintensity</td>
<td>Mixed intensity</td>
<td>Hypointensity</td>
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<td>Intra-plaque hemorrhage</td>
<td>Hyperintensity</td>
<td>Mixed intensity</td>
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<td>Calcification</td>
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T1W: T1-weighted image, T2W: T2-weighted image, PDW: proton density weighted image, 3D TOF: three dimensional time-of-flight image, T1GD: T1 gadolinium enhancement image

detect the ulceration, and characterize the surface morphology of plaques.15

- **Intravascular Ultrasound (IVUS)**

  As IVUS gets a three dimensional image from inner vascular lumen, the characteristics of vessel wall and atherosclerotic plaques can be analyzed with excellent resolution compared to routine ultrasonographic study.16 IVUS has gained clinical usefulness from several studies dealing with coronary artery diseases. In carotid artery diseases, IVUS is used as a complementary tool during carotid artery stenting. IVUS can accurately detect plaque characteristics such as calcification, necrosis, lipid-rich core, and measure a degree of stenosis in eccentric lesion the digital subtraction angiography cannot detect.17

2. Intravascular near-infrared spectroscopy

Intravascular near-infrared spectroscopy (NIRS) is an emerging imaging modality, which can detect a lipid core inside the unstable atherosclerotic plaque.18,19 Briefly, NIRS emits near-infrared light to specified tissue of interest, and measures the proportion of reflected light determined by scattering and absorption according to different biochemical compositions of the specified tissue. Thus, NIRS easily distinguish cholesterol from other constituents.18 A small experimental study tried to show safety and feasibility of application of NIRS to detect and analyze the lipid-rich plaque into patients with carotid stenosis combined with IVUS.19

3. Assessment of carotid plaque burden using MRI

High resolution carotid MRI has a good spatial, temporal, contrast resolution, and can evaluate accurately both the carotid stenosis and plaque characterization.20,21 MRI can visualize the carotid wall, and quantify the vascular burden by three dimensional volumetric measurement.22,23 Detailed advanced technique of high resolution MRI sequence is well described in recent article.24 Changes of plaque burden after therapeutic interventions can be monitored by MRI. A small study comparing high resolution MRI with ultrasonography, however, showed inferiority of MRI in detecting small-size plaque (<2.5 mm).22 Several key features of vulnerable plaque can also be visualized by high resolution MRI. These features include positive remodeling in the vessel wall, lipid-rich necrotic core, intra-plaque hemorrhage, and presence of thin/ruptured fibrous cap.20,23,25-27 Typical characteristic features of plaque in the variable MRI sequence were shown in the Table 1. Recent cross sectional study in the stroke-free population from Rotterdam study investigated determining factors of carotid plaque burden in about 1500 subjects. This study measured vessel wall volume and lumen volume as a plaque burden by using high resolution MRI. The study showed that intra-plaque hemorrhage is strongly associated with luminal stenosis independent of plaque burden.28 In the substudy of Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health
Outcomes (AIM-HIGH) trial, 214 patients receiving intensive medical therapy with established atherosclerotic diseases underwent high resolution MRI and ultrasonography in the carotid arteries, and was prospectively followed for about 3 years. The study demonstrated that plaque characteristics suggestive of vulnerability rather than clinical vascular risk factor and plaque burden was strongly associated with clinical outcomes such as myocardial infarction, ischemic stroke, etc.\(^{23}\) In the study, subjects with thin/ruptured fibrous cap and lipid-rich necrotic core volume had a 4-fold and 1.5-fold risk of future vascular events respectively. None of the plaque burden measurement (maximum wall thickness, maximum percent wall area, and percent wall volume) were significantly associated with clinical outcomes describe above. Therefore, markers of carotid plaque vulnerability may serve as novel surrogate markers for systemic atherothrombotic risk, and overcome the limited predictive power of plaque burden and luminal stenosis.

4. Assessment of carotid plaque burden using molecular imaging

Progression of atherosclerosis and plaque rupture are mostly determined by extent of the inflammatory reaction within the vessel wall triggered by vascular risk factors. Macrophage among immune cells is a key player in the pro-inflammatory signaling cascade within vulnerable plaques. Thus, macrophage is an attractive molecular imaging target to track vascular inflammation.\(^{26}\)

- \(^{18}\)F-fluorodeoxyglucose (FDG) PET

FDG is a radio-labeled glucose analogue used commonly in PET imaging. In atherosclerosis, vascular \(^{18}\)F-FDG uptake seems to be highest during early foam cell formation, and at late time points (>2 hours) reflects increased activity of macrophages.\(^{26}\) Several studies in vascular inflammation by using \(^{18}\)F-FDG PET demonstrated good correlation to macrophage density within carotid plaque and high-risk plaque morphology.\(^{27,29}\) However, as \(^{18}\)F-FDG is taken up by all cells with active glucose metabolism, it provides a nonspecific marker of inflammation in atherosclerosis. Vascular \(^{18}\)F-FDG uptake is also influenced by plaque hypoxia and the efficiency of tracer delivery by the microcirculation.\(^{26}\) Due to these limitations, specialized molecular PET tracers are actively investigated for atherosclerotic imaging including \(^{64}\)Cu-DOTATATE (macrophages), \(^{18}\)F-galacto-RGD (angiogenesis), \(^{18}\)F-sodium fluoride (calcification), and \(^{64}\)Cu-ATSM (hypoxia).\(^{27,30}\) As previously mentioned, high resolution MRI well visualizes vessel wall and plaque, whereas PET has poor resolution with high sensitivity for visualizing specific molecular targets. Recently, hybrid PET/MR imaging for carotid plaque can provide morphological (plaque characteristics) and functional (macrophage activity) information of atherosclerotic plaques simultaneously. One study reported high frequency of active unstable plaques found by the hybrid PET/MR imaging in patients with cryptogenic ischemic stroke. The study showed high prevalence of vulnerable plaques in the ipsilateral carotid artery in patients with ischemic stroke.\(^{31}\) Therefore, hybrid PET/MR imaging may have a potential benefit of early detection of carotid atherosclerosis.

PLAQUE IMAGING IN THE INTRACRANIAL ATHEROSCLEROTIC DISEASE

1. Intracranial atherosclerotic plaque

Intracranial atherosclerotic disease is the main cause of ischemic stroke in Asian population including South Korea.\(^{32}\) Like atherosclerosis in other vascular beds, those in the intracranial vessels also start to grow outward direction from the center of lumen then enlarge the size of vessel (positive remodeling) before reaching up to detectable stenosis.\(^{33,34}\) Traditional vascular imaging mainly focuses on the lumen, thus frequently misses non-stenotic lesions or underestimates the atherosclerotic
burden caused by positive remodeling. Recent autopsy studies from ischemic stroke show that the degree of stenosis cannot fully be responsible for intracranial atherosclerotic burden. The burden, characteristics, and morphology of atherosclerotic plaques in the intracranial vessels are essential in assessing the vulnerability of the plaque similar to those in the extracranial arteries. In this regard, it is an important field of research to investigate the intracranial vascular burden by using vessel wall imaging.

2. Assessment of plaque burden in the intracranial atherosclerotic disease vessel wall MRI

High resolution, black-blood MRI with fast spin echo sequence is the typical imaging modality to directly evaluate and visualize intracranial vascular morphology. This imaging modality can acquire the accurate structure of the arterial wall by selective signal suppression from the arterial lumen. Compared to extracranial vessel wall imaging, intracranial vessel wall imaging is technically limited due to sensitivity to motion artifact, small caliber and tortuous course of the intracranial arteries, and requires high-resolution and superior signal-to-noise ratio. Notwithstanding this limitation, advanced MR imaging techniques make us improve in understanding the pathomechanism of intracranial atherosclerosis.

The frequent locations of atherosclerotic plaques are distal internal carotid artery (ICA), intracranial ICA bifurcation, and the M1 segment of the middle cerebral artery (MCA). The plaque characteristics shown in the vessel wall imaging may be one of important predictors of future stroke episodes, and correlate well with pathological findings. Positive remodeling, the degree of stenosis, and ratio of wall thickening to lumen is associated with symptomatic plaque. Size of the lipid-rich necrotic core, which is isointense on T1 and hypointense on T2, correlates with risk of plaque rupture. Presence of plaque eccentricity can help differentiate intracranial atherosclerosis from other etiologies. Eccentric wall thickening seems to be associated with frequent cerebrovascular episodes. Histology-verified in vitro study on intracranial atherosclerotic diseases showed the trend that eccentric plaques were associated with higher risk of cerebrovascular episodes compared with concentric plaques (30.77% vs. 17.39%, p=0.241). Retrospective high resolution MR study including non-significant stenosis in the intracranial vessel demonstrated that eccentricity was more higher in the symptomatic plaque than in the asymptomatic plaque (p=0.028). Another study including symptomatic significant MCA stenosis showed that plaques with non-significant luminal narrowing was associated with eccentricity (p<0.05). Therefore, the analysis of the plaque component and characteristics as well as the wall remodeling pattern in the vessel wall imaging can further reinforce the current therapeutic strategy toward ischemic cerebrovascular diseases primarily limited to the stenosis in the luminal imaging.

CONCLUSION

With remarkable advances in imaging technologies during last decades, we can evaluate not only the presence or burden of atherosclerosis but the composition, activity, and vulnerability of the plaques in vivo. As we have further understood the molecular biological process of atherosclerosis by the help of multimodal imaging, we are narrowing the gap little by little between the area of basic research and the routine clinical practice. By these advanced imaging modalities, we can assess more accurately the therapeutic response to anti-atherosclerosis treatment. In the future, we will reach up to the extent which we precisely tailor and predict the risk of forthcoming clinical vascular episodes individually.
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