Various methods including MRI plaque imaging have been used to evaluate carotid artery plaques, but ultrasonography, which can be performed readily and non-invasively at the bedside, is excellent for follow-up examination and rapid diagnosis in emergency situations. Conventionally, ultrasound examination of carotid artery plaques has focused on vascular stenosis due to plaques and emphasized quantitative aspects such as the degree of stenosis. Clinically, however, some plaques resist treatment and repeatedly cause ischemic events despite a relatively low degree of stenosis. In such cases, qualitative diagnosis based on the evaluation of plaque vulnerability is important. In addition to the items that have been conventionally evaluated, such as the plaque echogenicity, ulceration, and mobility, evaluation of diverse aspects of plaques has become possible due to the advent of new ultrasound techniques. Plaque neovascularization can be evaluated by contrast-enhanced ultrasound (CEUS), visualization of slow blood flows has become possible without the use of a contrast agent by superb micro-vascular imaging (SMI), and detailed morphology and volume can now be examined using a 3D probe. Moreover, because of the excellent portability of ultrasound devices, the evaluation of plaque properties is occasionally useful for the planning of the therapeutic strategy in the acute phase of cerebral infarction. Thus, ultrasonography can provide a wide range of diagnostic information.

Keywords ▶ carotid artery ultrasonography, plaque, vulnerable plaque, contrast agent, atherosclerosis

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Ultrasound Diagnosis of Carotid Plaques

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Various methods including MRI plaque imaging have been used to evaluate carotid artery plaques, but ultrasonography, which can be performed readily and non-invasively at the bedside, is excellent for follow-up examination and rapid diagnosis in emergency situations. Conventionally, ultrasound examination of carotid artery plaques has focused on vascular stenosis due to plaques and emphasized quantitative aspects such as the degree of stenosis. Clinically, however, some plaques resist treatment and repeatedly cause ischemic events despite a relatively low degree of stenosis. In such cases, qualitative diagnosis based on the evaluation of plaque vulnerability is important. In addition to the items that have been conventionally evaluated, such as the plaque echogenicity, ulceration, and mobility, evaluation of diverse aspects of plaques has become possible due to the advent of new ultrasound techniques. Plaque neovascularization can be evaluated by contrast-enhanced ultrasound (CEUS), visualization of slow blood flows has become possible without the use of a contrast agent by superb micro-vascular imaging (SMI), and detailed morphology and volume can now be examined using a 3D probe. Moreover, because of the excellent portability of ultrasound devices, the evaluation of plaque properties is occasionally useful for the planning of the therapeutic strategy in the acute phase of cerebral infarction. Thus, ultrasonography can provide a wide range of diagnostic information.

Introduction

Various imaging modalities including MRI plaque imaging are used for the evaluation of carotid artery plaques, but ultrasonography, which can be performed readily and non-invasively at the bedside, is convenient for follow-up examination and rapid diagnosis in emergency situations. Conventionally, ultrasound examination of carotid artery plaques has focused on narrowing the blood vessels due to plaques and emphasized quantitative aspects such as the degree of stenosis. Indeed, much evidence that has been reported concerning the risk of cerebral infarction has been based on the evaluation of the degree of stenosis. Clinically, however, we often encounter refractory plaques that repeatedly cause ischemic events and resist treatment despite a relatively low degree of stenosis. With the use of carotid artery ultrasound for screening examinations of cerebrovascular disorders, opportunities to detect asymptomatic plaques and asymptomatic stenosis caused by them have increased, and the necessity of qualitative evaluation of plaques in question to assess the risk of the future occurrence of stroke is considered to be increasing. This report, therefore, focuses on the qualitative ultrasound diagnosis of carotid artery plaques.

Quantitative Evaluation of the Degree of Stenosis

The degree of stenosis is evaluated by ultrasonography according to the area ratio and vascular diameter ratio (the
the degree of stenosis has progressed compared with the previous examination (Fig. 2).

### Qualitative Evaluation of Plaques (Evaluation of Plaque Vulnerability)

#### Plaque echogenicity

The qualitative evaluation of plaques by ultrasound has long been made according to the echogenicity. Hypoechoic plaques are called soft plaques and have been pathologically demonstrated to suggest intraplaque hemorrhage with a necrotic core (Fig. 3). Patients with hypoechoic plaques showing an echo level close to that of the vascular lumen are known to suffer ischemic events more frequently than those with isoechoic plaques. The echogenicity of plaques is evaluated by comparison with the echogenicity of the surrounding intima-media complex (IMC), but plaques with an echo level similar to that of the vascular lumen may be overlooked by B-mode ultrasonography, and caution is needed. There are some plaques so hypoechoic that they can be recognized only as defects by color Doppler imaging (Fig. 3). Turbulent flows may occur at the bifurcation of the carotid artery and interfere with adequate
A case of progressive asymptomatic stenosis that led to cerebral infarction. Asymptomatic stenosis at the origin of the internal carotid artery periodically followed up with medical treatment. ECST: European Carotid Surgery Trial; PSV: peak systolic velocity.

Color representation and be mistaken for plaques, so careful examination is necessary. Particularly, a severe stenotic lesion is easy to recognize as a source of emboli, but whether mild stenosis is the responsible lesion or not is often difficult to judge. However, as there are mild stenotic lesions that cause repeated recurrence, careful examination not to overlook hypoechoic lesions, in particular, is necessary (Fig. 4). Also, whether the echogenicity of the plaque is homogeneous or not is another point of examination. The echogenicity of plaques may be heterogeneous and partially hypoechoic or contain discrete white areas (DWAs), which are not accompanied by an acoustic shadow and are recognized as white hyperechoic areas. There have been reports that the presence of DWAs was related to the risk of the occurrence of events, that inflammation and hemosiderin deposits were demonstrated by pathological examination in DWAs, and that DWAs suggest plaque vulnerability.

In clinical situations, the echogenicity is evaluated qualitatively by comparison with IMC, but techniques to quantify the echogenicity including gray scale median (GSM) and integrated backscatter (IBS) have been developed. By GSM, B-mode images are input into a computer, and the echogenicity of the plaque is calculated by correction for the echogenicity of the intima/media and the vascular lumen, and this can be performed using commercial image processing software. In carotid artery stenting, the risk of ischemic events has been shown to be high when a hypoechoic plaque with a GSM value of ≤25 is noted. On the other hand, IBS is calculated by integrating the intensity of raw signals, and use of raw signals characterizes the less differences of image quality among the devices. Using this index, quantitative evaluation by comparison with pathological findings of plaques and therapeutic effect of statin have been reported. These quantification methods may lead to more objective evaluation of echogenicity and a decrease in inter-rater variation.
However, internal properties of calcified plaques cannot be evaluated sufficiently by ultrasound due to acoustic shadows. Usually, the event risk of calcified lesions is not considered high, but studies using CT and MRI have suggested that some plaques surrounded by a wide calcified area may exhibit signals suggestive of intraplaque hemorrhage and that such plaques need attention as they may have a high risk of ischemic events.\(^\text{12,13}\)

**Ulceration**

Ulceration is the state in which plaque has ruptured, and the atheroma inside is exposed in the vascular lumen. It may cause thrombus attachment and increases the risk of embolism if it, along with the exposed atheroma, scatters into the intracranial arteries. In addition, recurrence is known to be more frequent in patients with symptomatic stenotic lesions accompanied by ulcerated lesions,\(^\text{14}\) so ulceration is an important item to be evaluated. By ultrasound, ulcerated lesions are characterized as blood flow signals inside the plaque. Formerly, depressions 2 mm or greater in depth were diagnosed as ulcers, but, with improvements in ultrasound devices, those with clear unevenness on the plaque surface are currently diagnosed as ulcers regardless of the depth. Since some lesions are misdiagnosed as ulcers by B-mode ultrasonography due to apparent unevenness of the plaque surface, which is caused by the similarity of the echo level of hypoechoic components to that of the vascular lumen, the blood flow inside the lesion must be checked simultaneously by color Doppler imaging. However, the identification of ulcers is often difficult if color signals are not obtained sufficiently due to turbulence or attachment of thrombus inside the plaques. Moreover, ulcers have been reported to be often overlooked if the stenosis is severe.\(^\text{15}\) With improvements in the resolution of the ultrasound device, it has also been reported that the clarity of the image of the plaque surface has increased and that rupture of structures corresponding to relatively hyperechoic fibrous cap on the surface has become observable, permitting the diagnosis of rupture of the fibrous cap.\(^\text{16}\) In addition, as discussed below, the ability to visualize ulcers has been improved with technological

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**Fig. 3** A case of symptomatic stenosis that had the onset with transient amaurosis and recurrence with a transient ischemic attack. On carotid artery ultrasonography, the plaque at the origin of the internal carotid artery was hypoechoic and was visualized by color Doppler imaging as a defect of color signal (A) B-mode long-axis view, (B) color Doppler long-axis view. Angiography also showed marked stenosis due to a plaque at the same site (C) lateral view (arrow). On MR plaque imaging (D) MPRAGE image, the plaque was hyperintense, suggesting intraplaque hemorrhage. The histopathological sample obtained by endarterectomy (E) Masson trichrome stain showed a wide area of hemorrhage inside the plaque (asterisk). ECA: external carotid artery; ICA: internal carotid artery; MPRAGE: magnetization-prepared rapid acquisition with gradient echo; MR: magnetic resonance
Evaluation of plaque mobility
By MRI and CT, the morphology of plaques can be evaluated if they are protruded, but their mobility is usually difficult to evaluate. Ultrasonography, on the other hand, is excellent in real-time evaluation of the plaque mobility. Mobile plaques have been reported pathologically to often contain a necrotic core with thrombus. Mobile lesions have a high risk of embolism, and, as symptomatic mobile lesions are related to the risk of recurrence, close follow-up is needed. Video recording is recommended if they are detected. Also, if the plaque is not clearly protruded, jellyfish sign, or wobbling of part of the plaque with pulses like a jellyfish, is occasionally observed. Intraplaque hemorrhage is observed at the site of jellyfish sign, and this sign is known to be a risk factor for events since it suggests rupture of the fibrous cap and is frequently associated with recurrence. While evaluation of individual patients is necessary, surgical treatment is an option when the lesion is considered a source of emboli, particularly, if it is symptomatic and recurrent. As mentioned above, ultrasonography is advantageous for serial evaluations, and follow-up at short intervals should be considered, particularly, when the plaque is symptomatic and is accompanied by a mobile lesion, as its morphology may change within a few days.

Fig. 4  A case of recurrent cerebral infarction despite mild stenosis at the origin of the internal carotid artery. The patient had the onset with right hemiplegia and was found to have a focus of infarction in the left MCA territory (A) diffusion-weighted MRI. Carotid artery ultrasonography showed a hypoechoic plaque from the bifurcation to the origin of the carotid artery (D). At this site, stenosis was mild on carotid artery MRA with a NASCET of 22% (C), but the signal intensity was high on MR images (MPRAGE) (B). On CEUS images, many linear traces of microbubbles into the plaque were observed (E), suggesting neovascularization. Since the grade of stenosis was mild, the patient was observed with internal treatment but had recurrence of cerebral infarction of the left MCA territory with mild right-sided paralysis after 1 year (F). Although the lesion was also a hypoechoic plaque on color-Doppler imaging (G), CEUS demonstrated ulcers that could not be identified by color Doppler imaging (H). CEUS: contrast-enhanced ultrasound; MCA: middle cerebral artery; MPRAGE: magnetization-prepared rapid acquisition with gradient echo; NASCET: the North American Symptomatic Carotid Endarterectomy Trial.
have become available in B-mode, color Doppler, and Doppler imaging on the daily practice level with improvements in the ultrasound device. In B-mode ultrasonography, evaluation of small mobile lesions and the properties of the plaque surface suggestive of rupture of the fibrous cap, which was mentioned above, has become possible with improvement in resolution. Non-contrast imaging of slow blood flow in ulcer and neovessels of plaques has also become possible, and further improvements are expected for the future. In Doppler blood flow imaging, the continuous-wave Doppler method using a linear probe has become available, and the evaluation of faster blood flows and more accurate blood flow evaluation have been made possible. Further improvements are also expected in this field.

**Diagnosis of plaque vulnerability by contrast-enhanced ultrasonography**

Ultrasound contrast agents, such as Sonazoid, produce consistent contrast-enhancing effects using microbubbles made of insoluble gas with shells. In addition, as a contrast-enhancing effect can be obtained at a fixed low acoustic pressure without destroying the bubbles, movements of bubbles along the blood flow can be observed continuously. This has made visualization of not only vascular lumens with a slow minute blood flow but also newly formed vessels inside the plaque possible. Neovessels in the plaque, which are vulnerable and likely to rupture, may cause intraplaque hemorrhage and are a factor of plaque vulnerability. A correlation between contrast-enhancement and plaque neovascularization has been pathologically demonstrated, and they are also reported to be related to symptoms.²⁰ (Figs. 4E and 5).

Small ulcers that emit no blood flow signals in non-contrast imaging are also visualized clearly by the use of an ultrasound contrast agent²¹ (Fig. 4H). Since contrast-enhanced ultrasonography is advantageous for visualization of slow blood flows, it clearly delineates even pseudo-occlusion that appears to be occluded on non-contrast
Fig. 6 A case of symptomatic stenosis at the origin of the internal carotid artery in which CEUS suggested a thrombus attaching to the plaque. The plaque morphology could not be clearly visualized by non-contrast carotid artery ultrasound (A) color Doppler long-axis view partly due to turbulence caused by severe stenosis, but CEUS (B) clearly visualized the plaque as a filling defect and suggested the presence of a thrombus at the distal end (B: arrow). At the same site, carotid artery CTA showed similar morphology and also suggested a thrombus at the distal end of the plaque (C: arrow). CEUS: contrast-enhanced ultrasound

imaging due to marked stenosis and the consequent lack of blood flow signals on the distal side (Fig. 5). Moreover, by contrast-enhanced ultrasonography, the morphology of plaques which cannot be evaluated by color Doppler imaging due to turbulence caused by their complex shape can also be visualized, and thrombi that attach to the plaque can be clearly delineated as filling defects (Fig. 6). Thus, contrast-enhanced ultrasonography may provide necessary and important detailed information on the routine clinical level. Since ultrasound contrast agents have few adverse effects and do not affect the renal function, they can also be used safely in patients who do not tolerate iodine-based contrast media. However, as their use is presently restricted to the liver and breast lesions, and their application to the brain and carotid arteries is not covered by insurance in Japan, their clinical availability is limited.

Superb micro-vascular imaging

Non-contrast imaging techniques that permit detection of even slower blood flows than those detectable by conventional color Doppler or power Doppler methods at a high frame rate by suppression of motion artifact have begun to be provided. Using superb micro-vascular imaging (SMI), lesions that are used to be impossible to identify by conventional color Doppler imaging such as pseudo-oclusions and minute ulcers (Fig. 7) and, occasionally, intraplaque new vessels (Fig. 8) have become identifiable. Using such techniques, images similar to those by contrast-enhanced imaging may become available without using a contrast agent for the future. They may be useful in situations where a contrast agent is not usable, and further development of the technology is awaited.

Plaque evaluation by 3D ultrasonography

The evaluation of the morphology of ulcerated lesions and protruding plaques is facilitated by 3D rather than 2D observation. The evaluation of the shape of ulcers and plaques has become possible by collecting 3D data of the carotid artery simply using a linear type 3D probe and reconstructing the data (Fig. 9). There is also the technique to create 3D images by collecting ultrasound images simultaneously with positional information using a 2D probe to which a
position sensor is attached and reconstructing the data. The use of this technique makes it possible not only to clarify 3D morphology but also to calculate the volume of the plaque. Since the plaque mass can be evaluated more accurately than by calculation using 2D data, changes in the plaque volume with time can be captured more sensitively, leading to reports that the plaque volume was correlated with cardiovascular events\(^{22}\) and that changes in plaque volume were used for the evaluation of the effectiveness of medical treatment.\(^{23}\) If the measurement of the plaque volume is facilitated further, the application range of this technique is expected to be expanded.

Fig. 7 Ulcerated lesion of the origin of the internal carotid artery. SMI (B) long-axis view, (C) short-axis view; arrows showed an ulcer which could not be detected with color Doppler imaging (A) color Doppler image, long-axis view. SMI: superb micro-vascular imaging.

Fig. 8 Neovessels observed in the plaque. In the areas that could not be identified by color Doppler imaging (A) short-axis view but were visualized as linear images by SMI (B) short-axis view; arrows, linear influx of microbubbles were also observed on CEUS (C) short-axis view (arrows), suggesting neovascularization. CEUS: contrast-enhanced ultrasound; SMI: superb micro-vascular imaging.
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...stensosis, and the properties of the interior of the plaque such as the presence of a calcified area can also be evaluated (Fig. 10). While the definitive diagnosis is impossible by ultrasonography alone, if such information can be obtained readily in an early stage of examination, we can plan the therapeutic strategy for revascularization quickly.

Limitations of Plaque Diagnosis by Ultrasonography

Ultrasonography is highly portable and can be performed readily at the bedside, but the accuracy of the diagnosis depends on the skill of the examiner, and the possibility of inadequate diagnosis and poor reproducibility is undeniable. In addition, in lesions accompanied by marked calcification, examination of the interior is impossible due to the acoustic shadows derived from the characteristics of ultrasound. Also, in patients with the bifurcation of the internal carotid artery at a high position, which is observed frequently in Japanese, the plaque of the internal carotid...
artery is located at a high position, and its detailed evaluation may be prevented by the mandible.

The primary theme of this paper is the qualitative diagnosis of carotid artery plaques. With the development of technology, indices that can be evaluated by ultrasonography have increased recently, and ultrasonography is expected to contribute more to the evaluation of indications of treatments including endovascular treatment and examinations before and after the treatment.

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Disclosure Statement

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