Characteristics of Unstable Carotid Plaques – New Image Modalities

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Ischemic stroke is a socially significant health problem due to high mortality and disability. One of the leading causes for cerebrovascular accidents is the carotid atherosclerosis. The mechanism of its formation presents not only lipid accumulation in the arterial wall but a complex inflammatory disease. The aims of this review are to point the new methods and approaches for diagnostic of the unstable and high-risk carotid plaques. The old plaque imaging modalities emphasized mainly to the degrees of luminal stenosis. The new possibilities reveal plaque morphology so detailed even compared to histological verification. Recent techniques as Shear wave elastography, optical coherence tomography, Superb microvascular imaging, USPIO MRI give information about the pathological mechanisms of carotid atherosclerosis. The efforts are directed to predict the atherosclerotic burden, plaque instability and the occurrence of cerebrovascular events for each patient and to optimize personal management.

INTRODUCTION

Atherosclerosis is a slowly progressive systemic disease affecting mainly medium and large size arteries. It is a major cause for cardiovascular and cerebrovascular diseases. About 20% of ischemic strokes originate from macroangiopathy, mainly from the atherosclerosis affecting the carotid arteries. Artery to artery embolism, hypoperfusion and the combination of the two are the stroke mechanisms in patients with extracranial atherosclerosis.

Previous studies (NASCET 1999, ESCT 1998) used the degree of stenosis to predict stroke risk and also for selecting patients for surgical removal of plaque. Now it is evident that patient with similar risk factors, including the degree of the stenosis have different cerebrovascular risk score. The stratified approach uses new image modalities or modified old ones trying to detect the features of unstable carotid plaques and their changes after treatment options.

IMAGING CAROTID PLAQUES MODALITIES (TABLE 1)

Carotid ultrasonography is the easiest and non-invasive method for observation of atherosclerotic plaques. It can reveal the morphology, the shape of the plaque, the plaque surface and ulcerations, the plaque echogenicity and to estimate the degree of the luminal stenosis. Ultrasound measurements with controversial prognostic value are intima media thickness (IMT) index and arterial stiffness. Intima media thickness presents the thickness of tunica intima and tunica media of the wall of the artery. Although IMT has some predictive value for future accidents some researches dispute it significance. However, there are still no convinced evidences for their clinical significance and usefulness.

Morphological ultrasound characteristic of the carotid plaque gives the Modified Gray-Weale / Gerolacus ultrasound classification. It divides the plaque in five subgroups: type 1-uniformly echolucent, type 2-predominantly echolucent, type 3-predominantly echogenic, type 4-uniformly echogenic, type 5-unclassified plaques. Echolucent carotid artery plaques (rich in lipids and/or intraplaque hemorrhage) are associated with increased risk of stroke,
Measuring the unstable and vulnerable to rupture plaque can be done by Plaque risk score and the following ultrasound plaque characteristics: echolucent, heterogeneity, plaque irregularity, plaque neovascularization. In their meta analysis Brinjikji W and al. described that echolucent, neovascularization, ulceration and intraplaque motion are the characteristics of symptomatic carotid plaques. Computerised evaluation of plaque echogenicity can be done with grey-scale median (GSM). It is B-mode method that measures the echogenicity according the frequency distribution of the grey values within the plaque image. The echogenicity of the plaque can be measured using grey-scale median (GSM) method. This method is based on the distribution of grey values within the plaque image and is used to quantify the echogenicity of the plaque components. The advantages and limitations of the different image modalities of carotid plaques are summarized in Table 1.

Table 1. Advantages and limitations of the different image modalities of carotid plaques

| Carotid plaques image modalities | Advantages | Limitations/Disadvantages |
|----------------------------------|------------|---------------------------|
| Ultrasound                       |            |                           |
| -visual analysis                 | noninvasive, easily accomplished, real-time measuring | limitations connected with the patients, with the pathology and the equipment |
| -computer-aided analysis         | segmentation of the lumen and patient-specific 3D models | accessible only in some laboratories, no official algorithm for daily use |
| grey-scale median                | measuring the echogenicity of the plaques components | limited measurements |
| Shear wave elastography          | quantifying fibrous cup elasticity | limited measurements |
| CT angiography                   | measuring moderate and severe stenosis, distinguish calcification and plaque ulceration | ionizing radiation, not useful for mild stenosis, not presenting plaque morphology |
| MRI                              |            |                           |
| -visual analysis                 | non-invasive, no ionizing radiation, highly reproducible, present artery wall, distinguish moderate and severe stenosis, present plaque | limitations connected with the equipment, contraindications in some patients, time consuming |
| -computer-aided analysis         | morphology, segmentation of the lumen and patient-specific 3D models |                           |
| Optical coherence tomography     | can directly visualize and quantify thin-cap fibroatheroma, intraluminal thrombus, calcified nodules, and vascular inflammation | poor tissue penetration, limited measurements |
| Contrast enhanced ultrasound     | detects the new vessel formations, improves visualization of vessel wall irregularities and provides direct visualization of intraplaque neovascularization | not detecting microvessels, limited measurements |
| Superb microvascular imaging     | visualization of low microvascular flow, high-resolution image of the minute vessels and low-velocity flows | not detecting plaque morphology, limited measurements |
| Positron emission tomography     | can assess the plaque inflammatory agents and metabolically active cells | ionizing radiation, no information about stenosis and plaque morphology |

independent of the degree of artery stenosis. Measuring the unstable and vulnerable to rupture plaque can be done by Plaque risk score and the following ultrasound plaque characteristics: echolucent, heterogeneity, plaque irregularity, plaque neovascularization. In their meta analysis Brinjikji W and al. described that echoluency, neovascularization, ulceration and intraplaque motion are the characteristics of symptomatic carotid plaques. Computerised evaluation of plaque echogenicity can be done with grey-scale median (GSM). It is B-mode method that measures the echogenicity according the frequency distribution of the grey values within the plaque image. The echogenicity of the
plaque is divided in three groups. The high GSM values have good correlation with the fibrous tissue and calcium, the low GSM values show good correlation with the lipid core and haemorrhage. Some researches prove that plaques with low GSM values carry greater risk for new strokes. Disadvantage of the method is low sensitivity.

Atherosclerotic burden is a personal predictive risk factor for future vascular accidents. Information about it can be obtained by the total plaque surface on ultrasound or magnetic resonance images. Three-dimensional ultrasound plaque volume measurement allows semianatomical quantification. The advantages of the method is quick (mean time, 14 minutes), accurate, repeatable, and implementable in a clinical environment and in longitudinal studies. Studies reported good intra- and inter-observer reproducibility ranging from 2.8-6.0% to 4.2-7.6%, respectively. Still the results are not compared with the standard modalities and there are no criteria for unstable plaques.

A novel ultrasound technique for quantifying tissue elasticity is Shear wave elastography (SWE). Elasticity is quantified by using Young’s Modulus (YM) within the plaque and within the vessel wall. Some authors suggest that SWE can predict the rupture of the fibrous cap. For getting more information it can be joined with other ultrasound techniques as Grey-scale median and Gray-Weale classification.

According American Heart Association (AHA) the process of plaque formation is divided in the following stages (Table 2).

Carotid magnetic resonance images (MRI) gives new possibilities to indentify High-risk plaques. It is one of the most promising modalities for visualizing the carotid atherosclerotic plaque. A modified American Heart Association classification (Table 3) based on the magnetic resonance appearance of plaque components is shown to have good correlation between MRI image and histology of the plaque.

Histopathological studies of carotid plaques have identified key features of high-risk plaques: a thin and ulcerating fibrous cap, lipid-rich necrotic core, inflammation, neovascularization, intraplaque hemorrhage, microcalcifications and cholesterol crystals. Several markers of plaque vulnerability can be identified by MRI: large lipid-rich necrotic core, intra-plaque hemorrhage, surface disruption, inflammation, surface calcified nodules.

High-resolution magnetic resonance imaging allows direct visualization of the diseased vessel wall, of the plaque morphology and can monitor the progression of the disease. MR imaging is non-invasive, does not involve ionizing radiation, and is highly reproducible.

Well-established Magnetic resonance (MR) modality for plaque characterization is 1.5T multi-contrast MRI. Three basic contrast weightings (T1, PD, T2) in addition to contrast enhancement (CE) of carotid atherosclerosis can give a high-resolution image of the vessel walls and plaque components. Some studies prove that Contrast-enhanced MR plays an important role for the identification of the lipid-rich necrotic core and the structure of the fibrous cap.

As local inflammation is very important for the vulnerable carotid plaques there is a MR modality that can observe it. Dynamic contrast-enhanced MRI is a modality that can measure the activity of inflammatory biomarkers in arterial plaques suggested by the increased vascular supply and the disturbed endothelial permeability.

3T MR carotid image shows significant advantages compared to 1.5T (Fig. 1): improvement in the signal-to-noise ratio, contrast-to-noise ratio, image quality, its ability to reduce scan time and increase spatial resolution. Some studies validate the 3T MR findings to histological proven 1.5T carotid image criteria and find prospective correlations.

One of the new possibilities of magnetic resonance imaging is the use of USPIO (ultra small iron particles) contrast agents. As it accumulates in activated macrophages this method is used for experimental studies for identification of the inflamed carotid plaques. The USPIO MR imaging can also be used for observing the pathological mechanisms of the stroke.

In the last years several efforts have been made to obtain better characteristics of the structures of carotid wall and plaques. Visual analysis is the most basic but not enough detailed approach to determine the morphology of the atherosclerotic plaque. Computer-aided methods have been developed for better identification of the carotid lumen and atherosclerotic components. Automatic segmentation of the lumen of the carotid artery is done in ultrasound B-mode images and in magnetic resonance images. Patient-specific 3D luminal surface reconstruction and computer fluid stimulation gives better understanding of the hemodynamic parameters in the place of the plaque. Image-based computational studies of the carotid plaque gives a noninvasive approach for subject-specific flow analysis.
Computed tomography (CT) angiography (Fig. 2) is used for detecting arterial stenosis. It can present moderate and severe stenosis, calcification and plaque ulceration. This image method is quick and easily applicable for carotid stenosis but it includes radiation exposure.

Optical coherence tomography (OCT) is a new intravascular modality using near-infrared light (1,300 nm). It provides the highest imaging resolution (10 to 15 μm) of the vascular pathology. With this method it is possible the identification of plaque components such as lipid, calcium, and fibrous tissue. In addition, with OCT it can directly visualize and quantify thin-cap fibroatheroma (TCFA), intraluminal thrombus, calcified nodules, and vascular inflammation. Limitation of the method is poor tissue penetration.

Neovascularization inside the carotid plaque is consider to be one of the risk factors for plaque hemorrhage and rupture leading to new cerebrovascular accident. These vessels have low-velocity blood flow that makes different to observe with the conventional methods.

Contrast enhanced ultrasound (CEUS) is one of the possibility to detect the new vessel formations. The ultrasound contrast agents contain microbubbles (1-8 μm) that resonate when exposed to ultrasound waves. It improves visualization of vessel wall irregularities and provides direct visualization of intraplaque neovascularization. But still it is a challenge for microvessels.

Superb microvascular imaging (SMI) is a technology that provides visualization of low microvascular flow never seen before with ultrasound. With smart algorithm it analyzes the small clutter motions and thus result in better and high-resolution image of the minute vessels and low-velocity flows.

For researches there is an investigation that can give information on molecular level. The Positron emission tomography (PET) can assess the plaque inflammatory agents and metabolically active cells. It is measured by the increased 2-deoxy-2-[18F] fluoro-D-glucose (18F-FDG) uptake. Some studies show correlations with the inflammation, with plaque instability, with the risk of new ischemic events, risk of early stroke recurrence and with poor patient outcome after an incident.

All this new imaging modalities are promising not only for studying the characteristics of the unstable carotid plaque but also to observe the changes of the plaque after medical treatment.

**CONCLUSIONS**

As carotid atherosclerosis is one of the leading causes for cerebrovascular accidents it is very important to study the mechanisms of its formation and the stages of its transformation and destabilization. The new plaque imaging modalities can identify the
**Figure 1.** Severe stenosis of right ICA shown on ultrasound, TOF and T1 black blood MRI (black arrow).

**Figure 2.** Stenosis and calcification of ICA shown on ultrasound and CT angiography.
high-risk patients and to contribute to the stratified medicine where the patient get the right treatment at the right time.

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Ишемический инсульт является социально значимой проблемой здравоохранения из-за высокой смертности и травм, которые он вызывает. Одной из основных причин цереброваскулярных осложнений является атеросклероз каротидных артерий. Механизм его образования заключается не только в накоплении липидов в стенке артерии, но и в комплексном воспалительном заболевании. Целями данного обзора являются выявление новых методов и подходов для диагностики нестабильных и опасных бляшек каротидных артерий. Старые методы визуализации бляшек делают акцент в основном на уровнях люменального стеноза. Новые возможности раскрывают морфологию бляшки в таких деталях, которые даже сопоставимы с гистологическим исследованием. Современные методы, такие как эластография сдвиговой волны, оптическая когерентная томография, превосходная микрососудистая томография и контрастная МРТ с применением лимфотропных наночастиц (USPIO MRI), предоставляют информацию о патологических механизмах атеросклероза каротидных артерий. Усилия направлены на прогнозирование атеросклеротического бремени, нестабильности бляшек и проявления цереброваскулярных событий для каждого пациента и оптимизацию персонального проведения лечения.