Atherosclerotic Carotid Vulnerable Plaque and Subsequent Stroke: A High-Resolution MRI Study

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Key Words

Atherosclerosis • Carotid arteries • Stroke • Magnetic resonance imaging

Abstract

Background: High-resolution contrast-enhanced magnetic resonance imaging (CEMRI) has been proven to be an effective tool for the identification of carotid atherosclerotic vulnerable plaque, such as a large lipid core and thin fibrous cap. The aim of this study was to evaluate the relationship between carotid plaque characteristics and the types of stroke in patients who had carotid artery (CA) stenosis $\geq 50\%$. **Methods:** 102 consecutive subjects (mean age 67.2 ± 10.2 years; 73 males) who initially had ischemic stroke or asymptomatic CA stenosis from 50 to 100% diagnosed by ultrasound were included in this study. Carotid CEMRI, brain MRI and magnetic resonance angiography were performed to understand the infarct patterns and to exclude intracranial artery stenosis. The modified American Heart Association (AHA) plaque classification was used in our study. **Results:** Our study demonstrated that 45 patients had CA stroke, and 55 patients had lacunar and asymptomatic lesions. The majority of patients had AHA classification type IV–V and VI which presented as vulnerable plaques. Of 63 patients with mild to moderate stenosis ($\leq 70\%$), 44 (69.8%) had type IV–V

vulnerable plaques, which was significantly higher than those of patients with severe stenosis ($>70\%$; $p < 0.001$). In CA stroke, the number of patients with a thin or ruptured fibrous cap was twice that of those with a thick and intact fibrous cap. **Conclusions:** CEMRI may have important applications in clinical risk evaluations in CA atherosclerosis. Physicians ought to recognize that different types of stroke should be identified by brain MRI detection before invasive therapies.

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According to the reports of the WHO MONICA study, acute ischemic cerebrovascular disease of atherosclerosis remains the primary cause of morbidity and mortality in China [1]. Carotid atherosclerosis is closely correlated with subsequent stroke. About 23% of ischemic stroke originates from carotid atherosclerosis and stenosis [2].

Nowadays, we generally recognize that predicting carotid artery (CA) vulnerable lesions is not possible by relying on stenosis alone. The low-grade disease of an atherosclerotic carotid can also result in cerebrovascular ischemic events [3]. We are becoming aware of the structure of the CA wall, including the composition, remodeling and inflammation of plaques. Rupture of the plaque

surface and subsequent luminal thrombus formation are probably the most important mechanisms underlying acute ischemic stroke [4].

High-resolution contrast-enhanced MRI (CEMRI) is an optimal noninvasive imaging technique that allows the discrimination of large lipid cores with macrophage infiltration, thin and fragile fibrous caps, calcific nodules and adventitia in human atheromatous vulnerable plaques both in vivo and ex vivo [5]. This technique also characterizes intraplaque hemorrhage and acute thrombosis which fulfill the criteria for vulnerable plaque progression, stabilization and rupture [6].

Using a multiple CEMRI protocol, we matched the images of CA and the subsequent histological sections from specimens to verify the accuracy of MRI. Furthermore, we evaluated the relationship between carotid plaque characteristics and the different types of stroke in patients who had CA stenosis $\geq 50\%$.

Subjects and Methods

Study Population

A single-center, prospective trial was conducted in the neurological department of Beijing Anzhen Hospital, Capital Medical University, from January 2007 to March 2008. We screened 102 hospitalized patients, 45 with acute ischemic stroke, including transient ischemic attacks (TIAs), who were subsequently proven to have 50–100% carotid stenosis by ultrasound, and 57 with lacunar and asymptomatic carotid stenosis, who sought medical treatment for their CA diseases. All patients underwent a detailed history assessment and a physical examination at baseline that included routine blood biochemistry tests, electrocardiography, chest radiography, ultrasound cardiography, transcranial Doppler sonography, carotid CEMRI, computed tomography, MRI and magnetic resonance angiography of the brain. Carotid and cerebral vascular digital subtraction angiography was performed once the patients' condition permitted the procedure.

We excluded patients who had (1) atrial fibrillation or a probable cardiac source of embolism, (2) Takayasu's arteritis, (3) intracranial artery stenosis proven by transcranial Doppler sonography and brain magnetic resonance angiography, and (4) any contraindication for MRI.

This study was approved by the Medical Ethical Committees of Beijing Tiantan Hospital, and written informed consent was obtained from each patient. The investigation conformed to the principles outlined in the Declaration of Helsinki.

All CA imaging and brain scans were reviewed collectively. Baseline brain MRI scans were evaluated to detect the types of brain infarction which corresponded to the territory of the index internal carotid artery (ICA).

The patients were divided into four categories according to the degree of stenosis measured by ultrasound: 50%, 51–69%, 70–89% and 90–100%. In addition, the patients were assigned to 1 of 3 groups according to their results of brain MRI: (1) symptomatic group, lesion originated from the ICA, including watershed

infarction (superficial-deep arterial and cortical border zone), mono- or multiembolic infarctions and TIA; (2) lacunar stroke, and (3) asymptomatic group.

TIA was defined as an onset focal neurological deficit lasting <24 h with normal brain MRI. Lacunar strokes were defined by a combination of symptoms or signs and radiological criteria: presentation with deep white-matter lesions or basal-ganglion lesions <15 mm in diameter [7]. An asymptomatic lesion was defined as producing no ipsilateral symptoms or signs caused by cerebral or retinal ischemia with normal brain MRI [8].

MRI Protocol and Review

All patients were imaged at the Beijing Anzhen Hospital in a 3.0T MRI Scanner (GE Signa, Excite, Waukesha, Wisc., USA), using an 8-channel phased-array CA coil. A standardized protocol was used to obtain 4 different contrast-weighted images – time of flight, T_1 -weighted, proton density-weighted and T_2 -weighted – of the CAs centered at the common carotid bifurcation on the index side [9]. MRI parameters were: T_1 -weighted, double inversion recovery, black blood, 2-dimensional fast spin echo, repetition time/effective echo time = 800/11 ms, echo train length = 12; proton density-weighted and T_2 -weighted, fast-spin echo, cardiac gated, repetition time = 3 or 4 cardiac R–R intervals, effective echo time = 15 ms for proton density-weighted and 65 ms for T_2 -weighted, echo train length = 12, and 3-dimensional time of flight, repetition time/effective echo time 21/3.8 ms, flip angle 15° . Images were obtained with a field of view of 14 cm, matrix size of 256, slice thickness of 2 mm.

Image quality was rated per artery for each contrast-weighted image on a 5-point scale (1 = poor, 5 = excellent), and cases in which image quality was ≤ 2 were excluded from the study. One experienced reviewer (W.Y.) who was blinded to clinical outcomes reviewed all magnetic resonance images for plaque features.

The tissue components including lipid-rich/necrotic core, calcification and hemorrhage were obtained by using a custom-designed Computer-Assisted System for Cardiovascular Disease Evaluation software [10]. The carotid bifurcation was used as a landmark for matching the 4 different contrast-weighted images at each slice location. The variety of tissue components was identified by using the criteria that had previously been proven in accordance with histology [11].

Fibrous cap status was categorized as either 'thick' versus 'thin or ruptured' based upon the previously published, histologically validated criteria [12]. The age of hemorrhage was classified as previously described [13].

Histology Processing and Criteria

Patients in the Department of Vascular Surgery underwent carotid endarterectomy (CEA) because of their atherosclerotic CA diseases. The excised intact specimens were fixed in 4% polyoxymethylene, decalcified and embedded in paraffin. Sections were cut (5 μ m thick) in every 1.0 mm in the common CA and in every 0.5 mm in the bifurcation throughout the length of the specimen and stained (hematoxylin-eosin and Masson trichrome). Histological classification of specimens was made using the criteria of the modified American Heart Association (AHA) classification [14]. The slides were independently evaluated by a reviewer (X.F.H) who was unaware of the imaging results.

Fig. 1. Multicontrast weighted images (T_1W , TOF, PDW and T_2W) of vulnerable plaque were obtained in vivo (**A–C**) and ex vivo (**D–G**). Asterisks indicate the lumen. Lumens show moderate eccentric stenoses. Tissue components of the wall: the thin fibrous cap above the large lipid core was enhanced; an old intraplaque hemorrhage adjacent to the lumen (arrows) produced hypointensity on MRI. Masson-trichrome- and hematoxylin-eosin-stained matching histology sections showed good consistency of in vivo with ex vivo MRI. T_1W = T_1 -weighted; TOF = time of flight; PD + T_2W = proton density- and T_2 -weighted.

Criteria for defining vulnerable plaque was a thin or ruptured cap with a large lipid core, superficial platelet aggregation and lumen thrombosis, plaque surface ulceration and fissuration, intraplaque hemorrhage and a superficial calcified nodule [15].

Statistical Analysis

All data were expressed as means $\pm$ SD. The Student unpaired *t* test was used for comparison of enumeration data between 2 groups, and the Fisher exact probability test was used for comparison between categorical variables.

All calculations were made with SPSS 12.0 for Windows. Statistical significance was defined as a value of $p < 0.05$.

Results

Carotid MRI and Specimen Validation Study

The gross and histological morphology features came from 2 patients with CEA. The initial in vivo CEMRI and subsequent ex vivo imaging of specimens, including tissue components of lipid-rich/necrotic core, intraplaque

hemorrhage and calcification, showed favorable consistency with histological findings. Histology and MRI matching images are shown in figures 1 and 2.

Patient Characteristics

Of 102 consecutive patients (102 arteries) with atherosclerotic ICA disease, 100 patients (73 men and 27 women) met the criteria for an image quality rating of ≥ 3 . The mean age of the participants was 67.2 ± 10.2 years. The study demonstrated that 45 patients had CA stroke and 55 patients lacunar and asymptomatic infarction. Of 63 patients with stenosis $<70\%$, 29 had stroke originating from the ICA. Of 37 with stenosis $\geq 70\%$, 16 had ICA stroke. Patients with stenosis $<70\%$ were more frequently seen with asymptomatic and lacunar stroke, but no significant differences between ICA and asymptomatic/lacunar stroke in mild and moderate-severe CA stenosis ($p = 0.787$) were found. The baseline clinical characteristics and baseline MRI findings are presented in table 1.

Fig. 2. CA bifurcation vulnerable plaque of in vivo and ex vivo samples as seen on MRI (T_1W , TOF, PDW and T_2W) along with the corresponding matched hematoxylin-eosin-stained (HE) histological cross-section. The external CA was seen just above and to the right of the ICA. The external CA was occluded with a large lipid necrotic core (LNC). Areas of dense calcification (Ca) appeared as a dark region from the 1- to 5-o'clock position on MRI and the histological cross-section of the ICA. The hematoxylin-eosin-stained matching histology section confirmed the presence of a superficial calcified nodule. T_1W = T_1 -weighted; TOF = time of flight; PDW = proton density-weighted; T_2W = T_2 -weighted.

Table 1. Baseline clinical characteristics (n = 100 patients)

	Watershed/ embolism/TIAs (n = 45)	Asymptomatic/ lacunar stroke (n = 55)	p value
Age, year	66.13 ± 11.29	68.00 ± 9.30	0.367
Males	33 (73.3)	40 (72.7)	1.000
Smoking	29 (64.4)	31 (56.4)	0.539
Hypertension	29 (64.4)	41 (74.5)	0.284
Diabetes	13 (28.9)	20 (36.4)	0.523
Stenosis <70%	29 (64.4)	34 (61.9)	0.787
Stenosis ≥70%	16 (35.6)	21 (38.2)	
TC, mmol/l	4.63 ± 0.98	5.07 ± 1.34	0.068
HDL-C, mmol/l	1.20 ± 1.03	1.11 ± 0.80	0.253
LDL-C, mmol/l	3.13 ± 0.94	3.28 ± 1.22	0.253
BG, mmol/l	6.09 ± 1.97	6.89 ± 3.51	0.174
hs-CRP, mg/l	13.40 ± 27.76	4.82 ± 8.36	0.057

TC = Total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; BG = blood glucose; hs-CRP = hypersensitivity C-reactive protein. Figures in parentheses indicate percentages.

Vulnerable Plaques: MRI-Based Atherosclerotic Lesion Type Classification

A total of 100 subjects were included by using the modified AHA classification: 4 cases of type III, which were equal to invulnerable plaques, which was defined as a diffuse intimal thickening or small eccentric plaque without calcification; 50 cases of type IV–V, which were similar to vulnerable plaques, which was described as plaque with a lipid or necrotic core surrounded by fibrous tissue with possible calcification; 43 cases of type VI represented complex vulnerable plaques with a possible surface defect, hemorrhage or thrombus; and 3 cases of type VII indicated calcified plaques. The majority of patients had AHA classification type IV–V and VI which presented as vulnerable plaques. There were no differences of plaque types among any category of patients.

ICA Stenosis Degree and Types of Plaques

Of 63 patients with mild to moderate stenosis ($\leq 70\%$), 44 (69.8%) had type IV–V vulnerable plaques; this number was significantly higher than that of patients with severe stenosis ($>70\%$; $p < 0.001$). Type VI was seen in most of the patients with severe stenosis. The relationship

Fig. 3. Patient, male, 72 years. **A** Digital subtraction angiography (DSA) appearance of the left ICA with stenoses of 60%. **B** Cervical B ultrasound showed 76% left ICA stenoses with superficial ulceration. **C** Brain MRI: diffusion-weighted imaging indicated an infarction of the left corona radiata. **D** Contrast-enhanced magnetic resonance angiography (CEMRA) appearance of the left ICA with stenoses of 70%. Plaque type with ruptured fibrous cap and intraplaque hemorrhage, delineation of ICA adventitia (green contour), lipid/necrotic core (yellow contour), intraplaque hemorrhage (pink contour) and lumen (red contour) shown in T₁-weighted (T₁W), contrast-enhanced T₁W (CE T₁W), proton density-weighted (PDW) and T₂-weighted (T₂W) images.

of different stenoses and types of plaques is shown in table 2.

Fibrous Cap Status and Intraplaque Hemorrhage

Twenty-eight patients were observed to have a thick and intact (type I) superficial fibrous cap of the lumen. Thin or ruptured fibrous caps (type II) were observed in 72 subjects of whom 1 patient had luminal thrombosis. In CA stroke, the number of patients with thin or ruptured fibrous caps was twice that of those with thick and intact fibrous caps (30/15). Forty-six patients had intraplaque hemorrhage which was adjacent to the luminal surface. No differences of fibrous cap status and intraplaque hemorrhage were found in all groups. Figure 3 demonstrates serial imaging of one subcortical infarction patient with ICA vulnerable plaque.

Table 2. Relationship of different ICA stenoses and types of plaque

Stenosis	Type				total
	III	IV–V	VI	VII	
50%	3	27*	2	1	33
51–69%		17*	11	2	30
70–89%		6	12	0	18
90–100%	1	0	18	0	19
Total	4	50	43	3	100

* $p < 0.001$.

Discussion

Results of the North American Symptomatic Carotid Endarterectomy Trial indicate that the benefit of CEA in stroke patients with symptomatic stenosis is >69% [16]. However, patients who have vulnerable lesions, such as those with low-grade stenosis, may also experience cerebrovascular events. Pathological studies suggest that the atherosclerotic plaque composition may represent an independent risk factor for ischemic stroke.

Rupture-prone lesions or vulnerable plaques consist of a large atheromatous core, which is separated from the lumen by a thin fibrous cap. Inflammatory cells such as macrophages and T lymphocytes are located in the 'shoulder' region of the fibrous cap which lacks smooth muscle cells and collagen [17].

As the focus of CA studies has been shifted from stenosis to composition, imaging modalities that can distinguish plaque components are coming to the forefront. A series of experiments involving *ex vivo* imaging of endarterectomy specimens were carried out, and tissue components including lipid-rich necrotic core, hemorrhage and calcification were detected with a sensitivity and specificity ranging from 84 to 100%. Translation of these findings to *in vivo* imaging showed that soft plaques (necrotic core or hemorrhage) could be identified with a sensitivity of 85% and a specificity of 92% [18].

Histological findings from this study further demonstrated that CEMRI permitted depiction of the vessel adventitial boundary and that it was also capable of identifying different components of vulnerable plaques. Carotid plaques excised from CEA patients presented the typical pathological characteristics of more advanced atherosclerotic vessel lesions. However, the amount of carotid plaque sections was limited, it was not enough to verify the accuracy of CEMRI. In a further study, we intend to find more CA specimens for MRI detection, and interrater and intrarater reliability assessments will be performed.

The vulnerable plaque plays an important role in critical events of stroke pathogenesis. Morphological data from autopsies as well as clinical MRI studies indicate the presence of surface irregularities, which has been proven highly associated with a recent history of TIA and stroke [19, 20].

After excluding patients with probable cardiac origin embolism and intracranial artery stenosis detected by ultrasound cardiography, transcranial Doppler sonography and brain magnetic resonance angiography, we subsequently enrolled the majority of patients (63%) with

mild to moderate stenosis (<70%). The asymptomatic and lacunar stroke cases (34%) were mostly seen in this group. Different categories of stroke, especially the topographic patterns of infarction associated with ICA stenosis, have been widely described in previous studies [21, 22]. Former studies indicated that in patients with symptomatic and asymptomatic stenosis, approximately 20–40% of subsequent ipsilateral strokes were attributable to lacunes and cardioembolism separately [23]. Our study agreed with this conclusion. As the result, the decisions about whether to recommend CEA for such patients must be taken into account. Not all future strokes will originate from the stenosed ICA.

However, the degree of stenosis does not always accurately point out those patients who will eventually develop vulnerable lesions, because low-grade stenosis with vulnerable lesions may also result in cerebrovascular events [24]. In the present study, the association between baseline CA plaque features and stenosis showed that in moderate and severe ICA stenosis ($\geq 70\%$), the number of patients with advanced plaques of AHA classification type VI was higher than that of patients with stenosis <70%, and plaque type IV–V was frequently seen in patients with stenosis <70%.

Virmani et al. [24] indicated that thin cap fibroatheroma, which was equal to AHA classification type IV–V, was a vulnerable plaque characterized by a necrotic core with an overlying thin fibrous cap (<65 μm). The thin cap fibroatheroma usually occurred in lesions showing <50% diameter stenosis; it had been postulated to be the precursor lesion of plaque ruptures and was more frequently observed in stroke patients [25]. The complicated type VI was a ruptured plaque with surface defects, hemorrhage and thrombosis. This kind of lesions in severe CA stenosis was subject to higher blood flow of the carotid bifurcation region. The high shear stress promoted the rupture of the thin fibrous cap. The high pressure in the lumen also induced rupture of the intraplaque vasa vasorum and intraplaque hemorrhage, and the atheromatous plaque might quickly develop into a fissure. Furthermore, rupture of the fibrous cap, with the resultant exposure of thrombogenic subendothelial plaque constituents, was believed to be the critical event that leads to thromboembolic complications [26].

CA plaque AHA classification types IV–V and VI, which were equal to vulnerable plaque, frequently occurred in all kinds of patients. No distinction was found in ICA and asymptomatic/ lacunar stroke. The focus of studies on symptomatic high-grade stenosis lesions and asymptomatic autopsy specimens without high-grade

CA stenosis showed that high-grade carotid stenotic plaques were associated with a significantly higher incidence of complicated plaques compared with nonstenotic asymptomatic plaques. Nevertheless, complicated plaques were also present in moderate stenosis, and they did not distinguish between symptomatic endarterectomy and asymptomatic autopsy lesions [27]. Most of our patients had mild stenosis (63%). There were no distinct morphological differences between asymptomatic and symptomatic carotid lesions.

We here investigated the superficial fibrous cap morphology of CA and its relationship with different kinds of stroke. In CA stroke, the number of patients with a thin or ruptured fibrous cap was twice that of patients with a thick and intact fibrous cap. It is well known that a thin or ruptured fibrous cap is an important morphological feature of the vulnerable atherosclerotic plaque. Patients with thin and ruptured fibrous caps were more likely to have a recent TIA or stroke [19].

In our study, thin and ruptured fibrous caps were also found in patients with asymptomatic and lacunar strokes. Morphological studies of coronary arteries suggested that plaque progression beyond 50% cross-sectional luminal narrowing occurred secondary to repeated ruptures, which might be clinically silent. The sites of healed plaque ruptures could be recognized by a necrotic core with a discontinuous fibrous cap [28].

As the causes and risk of stroke in patients with carotid vulnerable plaques are complicated, we must take into account that not all future strokes will originate from the vulnerable ICA. In our study, vulnerable plaques (type IV–V and VI) frequently occurred in all kinds of stroke patients; thin and ruptured fibrous caps were also

found in patients with asymptomatic and lacunar lesions. This indicated that such patients might have arteriosclerosis of the intracranial circle of Willis and even arterio-sclerosis combined with CA disease. CA stroke that arises from a rupture or fissure (small rupture) of a vulnerable plaque may contribute to the natural history of plaque progression and ultimately luminal stenosis; the plaque tissue components became more complicated (type IV–V and VI) in which a lipid-rich necrotic core, hemorrhage and calcification could be detected. In general, a vulnerable atherosclerotic plaque of the stenotic CA is the underlying cause of the majority of ischemic strokes, and specific plaque characteristics have been associated with ischemic brain injury.

In conclusion, this prospective study indicates that high-resolution CEMRI may provide a useful tool for risk stratification and selection of candidates for invasive therapies. The alternative therapeutic agents which can initiate actual plaque regression have created a need to attempt to image the plaque itself, with the CA being an achievable target [29]. Atherosclerosis of the ICA is an important cause for stroke. Stroke patterns in ICA disease are complicated and include large-artery and lacunar stroke which is of small-artery origin. Physicians ought to recognize that the causes of stroke should be identified by brain MRI before invasive therapies.

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