Atherosclerotic Carotid Plaques: Multimodality Imaging with Contrast-enhanced Ultrasound, Computed Tomography, and Magnetic Resonance Imaging

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Abstract

Introduction: The imaging of carotid plaques has undergone a paradigm shift increasing importance being given to plaque characterization. Patients with “vulnerable” plaques are more prone to develop future neurovascular events. **Purpose:** The purpose of this study is to analyze the role of multimodality imaging techniques in the assessment of carotid atherosclerotic plaques. **Materials and Methods:** Twenty-six patients were prospectively enrolled in the study. Patients underwent multidetector computed tomography (CT) angiography, ultrasound, contrast-enhanced ultrasound, and high-resolution magnetic resonance imaging (MRI) of the carotid arteries with special emphasis on the carotid bifurcation. **Results:** The mean age of patients was 65.41 years. Twenty-one were males. Plaque neovascularization was seen in 10 of the 18 plaques studied (55.56%). Based on the predominant components of the plaque, plaques were characterized as lipid (3), lipid with recent hemorrhage (1), fibrous (7), fibrofatty (4), fibrofatty with some hemorrhagic components (3), and recent hemorrhage (2). **Conclusions:** Together, contrast-enhanced ultrasound, CT, and MRI provide complete information about the plaque characteristics.

Keywords: Computed tomography, contrast-enhanced ultrasound, magnetic resonance imaging, neovascularization, vulnerable carotid plaque

Introduction

Stroke is one of the most important causes of death and the greatest cause of disability all over the world. Approximately 20% to 30% of the strokes can be related to carotid artery stenosis.[1] While previously only the degree of carotid stenosis was used to determine treatment options in patients with carotid plaques,[2] now there is a paradigm shift with increasing importance being given to plaque characterization (based on composition and surface characteristics on ultrasound, computed tomography [CT], and magnetic resonance imaging [MRI])[3] to determine which patients would benefit from surgical treatment. Patients with “vulnerable” plaques are more prone to develop future neurovascular events.[4] Neovascularization is an important factor contributing to vulnerability of atherosclerotic plaque.[3] This can be evaluated with multimodality imaging.[5-7]

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We hypothesized that certain morphologic characteristics of atherosclerotic plaque could serve as an adjunct to grade of stenosis.

The purpose of this study is to analyze the role of multimodality imaging techniques in the assessment of carotid atherosclerotic plaques.

Materials and Methods

This study was performed at our institute which is a tertiary referral center in South India with a “comprehensive stroke

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care" unit. It was performed over a period of 20 months from November 2010 to June 2012.

This multimodality observational study compared various imaging modalities for carotid atherosclerotic plaque characterization.

Patient recruitment

Twenty-six patients were prospectively enrolled in the study. Patients who had ischemic cerebral events including amaurosis fugax or focal cerebral ischemia (transient ischemic attack [TIA] and minor ischemic stroke) were recruited from the neurology department's stroke outpatient clinic or stroke unit. Carotid Doppler was also performed to study the arteries of asymptomatic patients who underwent cardiac interventions for coronary artery disease, aortic interventions, and lower leg artery surgery and for patients with diabetes who were older than 50 years.

Patients underwent multidetector CT angiography (CTA), ultrasound, contrast-enhanced ultrasound, and high-resolution MRI of the carotid arteries with special emphasis on the carotid bifurcation. The study protocol was approved by the Technical Advisory Committee and the Institutional Review Board (Independent Ethics Committee approval 324). All patients gave written informed consent. The study was an institute-funded project. The funding body did not pay any role in study design, data collection, analysis, or reporting of this study.

Selection criteria

Inclusion criteria

Patients with an ultrasound examination that showed a stenosis (50%–99% stenosis according to the NASCET criteria[2]) were explained about the study. Patients were included if they were willing to provide consent to participate in this study, age >40 years, renal function was normal (serum creatinine <1.2 mg/dl), and they had >50% stenosis on B-mode ultrasound according to the NASCET criteria. The risk factor details and history of TIA and stroke were obtained from the case files.

Exclusion criteria

A known allergy to the iodinated contrast material, elevated renal function test results, and cardiac failure excluded the patients from undergoing CTA. Patients were questioned regarding their history of drug allergy, asthma, chronic lung disease, and right-to-left cardiac shunt, which are contraindications to the administration of the ultrasound contrast agent (UCA).[3] Patients with plaque calcification involving >30% of plaque area were also excluded from the study (as calcification would preclude assessment of contrast enhancement on ultrasound). General contraindications to MRI examinations included pacemakers, metallic implants, and claustrophobia. Patients who were not interested in participation/did not give informed consent or those who clinically required emergent surgery (endarterectomy) were also excluded from this study.

Imaging technique

B-mode ultrasound

Ultrasound carotid duplex scanning was performed with a Philips iU22, with standard vascular presets, and equipped with multipulse nonharmonic imaging software contrast pulse sequence (CPS). Linear phased array probes (7 and 12 MHz) with standard presettings were used to assess carotid plaques. The same machine presets were maintained for all the patients.

The plaque morphology was evaluated both in longitudinal as well as in transverse axes, and the stenosis was calculated based on the pulsed-wave Doppler evaluation of blood flow velocities.

Contrast-enhanced ultrasound

Contrast reconstitution

The contents of the glass syringe prefilled with 0.9% w/v NaCl were transferred to the vial containing 25 mg of dry, lyophilized powder in an atmosphere of sulfur hexafluoride using the MiniSpike transfer system. The vial was shaken vigorously for 20 s to mix contents. On reconstitution, 1 ml of the resulting dispersion contained 8 µl sulfur hexafluoride in the microbubbles.

Contrast ultrasound investigations were performed after a short (1.5 ml) bolus injection into an antecubital vein (20-gauge Venflon) of Sonovue (Bracco Altana Pharma, Konstanz, Germany), being promptly followed by a 5 ml saline flush. The 15 MHz linear array probe, with a mechanical index varying from 0.4 to 1.4, with CPS continuous real-time recording software, was used to achieve the best visualization of the plaque morphology and vascularization. After the study, the patients were monitored for 30 min to look for any adverse events.

Computed tomography angiography

Multidetector CT angiography (MDCTA) was performed using a 256 slice iCT scanner. Nonionic iodinated contrast iohexol (Omnipaque, GE Healthcare, Shanghai, China) was injected through an 18-gauge antecubital venous access (Venflon). Fifty milliliters of 350 mg/ml contrast was injected at a rate of 5 ml/s followed by 40 ml of normal saline bolus chaser at the same rate. A real-time bolus-tracking technique was used to synchronize the acquisition with passage of contrast. Data acquisition was started after a postthreshold delay of 4.5 s. MDCTA acquisition parameters were as given in Table 1.

Magnetic resonance imaging plaque imaging

MRI was performed on a 1.5T clinical magnetic resonance (MR) scanner (Magnetom Avanto; Siemens, Erlangen, Germany).

Patient preparation before the MRI study, the carotid bifurcation on the affected was marked using B-mode ultrasound. Appropriate positioning was performed with a head holder, and coils were positioned at the level of carotid bifurcation marking.

Dedicated phased array surface coils (carotid coils, Machnet, Eelde, the Netherlands; http://www.machnet.nl/) were used to increase the signal-to-noise ratio. Oblique scout view (three-dimensional phase-contrast, two-dimensional time-of-flight [TOF], 1 min) was obtained. The carotid bifurcation was used as an internal landmark to reproducibly prescribe slice locations for serial studies. Acquisition time was about 14 min.

Parameters used for the various sequences are given in Table 2.

Image analysis

Ultrasound classification of plaques

Based on the B-mode echogenicity, plaques were characterized as hypoechogenic, hyperechoic, and hyperechoic with shadowing.

Contrast-enhanced ultrasound (CEUS) studies primarily focused on three areas of clinical importance:

1. Enhancement of the carotid lumen and plaque morphology
2. Identification of atherosclerotic-related neovascular changes within the adventitial vasa vasorum and plaques
3. Identification of ulcerations/irregularities on the surface of the plaque.

UCA microbubbles seen moving within the plaque on dynamic scan were considered to indicate neovascularization.

Computed tomography angiography

Window level and window center were generally set at 700 and 200 HU, respectively, for optimum visualization of the vascular structures. After evaluating the axial source images, several reformatting techniques were utilized for assessing the carotid arteries: maximum intensity projection, multiplanar reconstruction, curved planar reconstruction, and volume rendering. The degree of stenosis, location of plaque, surface irregularity/ulceration, calcification, and attenuation of the plaque were studied.

Measurements to quantify the degree of stenosis were made by selection of a plane perpendicular to the lumen centerline using the NASCET criteria.

Plaque surface morphology was classified as smooth, irregular, or ulcerated. Plaque ulceration was considered as an outpouching of contrast material adjacent to or within the carotid wall, larger than 1 mm in width, exposing the necrotic core of the atheromatous plaque as described by Sitzer *et al*.[4] Ulcerated plaques were categorized according to the shape of the ulcer as Type 1-4 as described by Lovett and Rothwell.[5]

The plaque density was calculated by drawing elliptical regions of interest in the predominant area of the plaque. Based on the density, carotid plaques were classified into three different groups:[6] fatty (soft) plaques defined as a plaque with a density value <50 HU; mixed (intermediate) plaque defined as a plaque with a density value between 50 and 119 HU; and calcified plaque defined as a plaque with a density value >120 HU. For each patient, the average value of three sample measurements in three contiguous axial was calculated for categorizing the patient.

Table 1: Multidetector computed tomography angiography acquisition criteria

Parameter	Value
Section thickness (mm)	0.9
Increment (mm)	0.45
Pitch	0.993
Rotation time (s)	0.5
kV	120
mAs/slice	400
Collimation	128×0.625
FOV (mm)	220
Matrix	512

FOV = Field of view

Table 2: Parameters used for magnetic resonance imaging plaque imaging

Sequence	fse PD Fat saturated, dark blood	fse T2 Fat saturated, dark blood	fse T1 Fat saturated, dark blood	3D TOF
Slices	16	16	16	48 in 1 slab
Slice thickness (mm)	2.9	2.9	3	1
Distance factor	0	0	0	−20.83
Phase encoding	A >>P	A >>P	A >>P	R >>L
pH oversampling	80	60	70	60
FOV read (mm)	80	80	80	114
FOV phase (%)	100	100	100	75
TR (ms)	2750	2870	1110	29
TE (ms)	12	60	8.7	7.27
Flip angle degree	120	180	180	25
Resolution	192×100	192×100	192×100	320×75
Time (min)	4.3	5.27	4.31	3.59

PD = Proton density, FOV = Field of view, 3D TOF = Three-dimensional time-of-flight, TR = Time to repeat, TE = Time to Echo, FS = Fat saturated

Magnetic resonance imaging plaque imaging

We visually evaluated the signal of the carotid plaque and defined the main plaque component as the plaque feature that had the largest area among plaque range. The signal intensity of the main plaque component was compared to the signal intensity of the ipsilateral sternocleidomastoid muscle for each image sequence.

The various components of the plaques were classified as follows [Table 3].[7]

Statistical analysis

Statistical analysis was performed using Stata IC/Ver. 11.2, Stata Corps, College Station, Texas, USA. Descriptive variables were described as mean and standard deviation (SD). Plaques were dichotomized based on the presence or absence of neovascularization on CEUS and presence or absence of surface ulceration on CEUS, CTA, and MRI. Agreements and kappa correlation coefficients between the various modalities were calculated. Z-test was used to calculate statistical significance. Two-sample t-test with unequal variances was used to calculate

Table 3: Plaque characterization based on components

Plaque component	T1	PD	T2	TOF
Lipid-rich necrotic core	High	High	Variable (loss of signal as compared with PD)	Moderate
Fibrous tissue	Moderate	High	Variable (no loss of signal as compared with PD)	Moderate to low
Recent hemorrhage	High to moderate	Variable	Variable	High
Calcification	Low	Low	Low	Low

PD = Proton density, TOF = Time-of-flight

the difference between mean CTA attenuation in various groups. $P < 0.05$ was considered to be statistically significant.

Results

Twenty-six patients were recruited. Examinations of two patients were excluded because of poor quality. Two patients (serial number 18 and 24) had bilateral bifurcation plaque studies done. Thus, we studied 26 carotid bifurcation plaques in 24 patients. The mean age of patients was 65.41 ± 10.43 years with an age range of 45–80 years. Twenty-one (87.5%) of our patients were males and three were females.

Four plaques caused moderate carotid stenosis (50%–70%) and 23 had severe stenosis (70%–99%). The mean stenosis (±SD) by the NASCET criteria was 75.85 ± 14.7 with a range of 50%–99%.

Baseline characteristics of the study population are given in Table 4.

Table 4: Baseline characteristics of the study population

Characteristics	Number
Total number of patients studied	24
Total number of plaques studied (*n*)	26
Age, years (mean±SD)	65.13±10.56
Symptomatic artery (%)	
Right	8 (30.8)
Left	13 (50)
Bilateral	1 (7.6)
Asymptomatic patients	2 (8.3)
Bilateral plaques	9 (37.5)
Cerebrovascular symptoms	
TIA (%)	15 (62.5)
Number of TIAs (mean, median)	1->10 (3.3; 1)
Stroke (%)	14 (58.3)
Risk factors (%)	
Smoking	2 current; 5 reformed (8.3, 20.8)
Hypertension	15 (62.5)
Diabetes	14 (58.3)
Hypercholesterolemia	3 (12.5)
Cardiac disease (coronary artery disease)	6 (25)

TIAs = Transient ischemic attacks, SD = Standard deviation

B-mode ultrasound (gray scale) evaluation

All 26 plaques in 24 patients were evaluated with B-mode ultrasound. The echogenicity of the plaques was studied. Of 26 plaques, 12 (46.15%) were hypoechoic, 10 were hyperechoic, and 4 were hyperechoic with shadowing. Fourteen (53.85%) plaques had hyperechoic components. Surface ulceration was seen in 2 of the 24 plaques.

Contrast-enhanced ultrasound

Contrast-enhanced ultrasound was performed in 18 plaques (16 patients). When using a reduced mechanical index for imaging, the plaques and corresponding intima-media complex appeared hypoechoic, whereas the adventitial layer was observed as echogenic. UCA microbubbles were visualized few seconds after the bolus injection as a hyperechoic dynamic flow in the carotid vessel lumen, providing an enhanced visualization of the carotid intima-media complex and a better identification of the plaque surface and the degree of stenosis.

Few seconds after the contrast agent detection in the carotid lumen, the dynamic distribution of the UCA inside the plaque allowed the visualization of the plaque vascularization.

Plaque neovascularization was seen in 10 of the 18 plaques studied (55.56%). Representative case is demonstrated in a video (supplementary material). Of the 10 plaques with neovascularization, only 1 was asymptomatic while 2 of the 8 patients without neovascularization were asymptomatic. Vascularization was detected at the shoulder of the plaque in the adventitial layers and in the iso-hyperechoic fibrous and fibrofatty tissue. It was represented by little echogenic spots rapidly moving within the atheromatous lesion, easily identifiable in the real-time motion, and depicting the small microvessels. The diffusion of the contrast agent appeared to be in an "outside-in" direction.

After administration of ultrasound contrast, ulceration of the surface was detected in 4 out of 18 plaques (22.22%). Three out of four ulcerations were associated with neovascularization. All four ulcerated plaques were symptomatic.

The examination was well tolerated in all patients with no adverse events.

Computed tomography angiogram

CTA was performed in 18 patients. Nineteen (73.08%) plaques were studied. The attenuation of plaques (excluding the calcified components) ranged from 4.8 to 79 HU with a mean of 49.82 ± 19.66 HU. Fifteen out of 19 (78.95%) plaques had calcification. Eight surface ulcerations were seen in 7 out of 19 (42.11%) plaques. One of the 19 plaques had 2 ulcerations, of which 1 was Type 3. One more plaque had a Type 3 ulcer. All the remaining ulcers were Type 1.

Magnetic resonance imaging plaque imaging

Nineteen patients underwent MRI plaque imaging of 20 (76.92%) carotid bifurcations. Based on the predominant components of the plaque, plaques were characterized as lipid (3), lipid with recent hemorrhage (1), fibrous (7), fibrofatty (4), fibrofatty with some hemorrhagic components (3), and recent hemorrhage (2). This is further described in Table 5.

An intact fibrous cap was visualized in nine patients. Surface ulceration was visualized in ten patients. In one patient, the fibrous cap was not visualized. The surface ulceration also could not be seen.

Comparison of B-mode ultrasound and contrast-enhanced ultrasound

Of the18 plaques evaluated with CEUS, neovascularization was seen in 10. Of these, 7 were hyperechoic and 3 were hypoechoic. Of the 8 plaques without neovascularization, 4 were hypoechoic.

Comparison of plaque composition by magnetic resonance imaging and ultrasound B-mode echogenicity

Twenty plaques in 19 patients had undergone both MRI and B-mode ultrasound evaluation. Observed agreement between these tests was 75% and expected agreement was 59% with a kappa value of 0.39 (fair agreement) with a significant $P = 0.03$.

Comparison of magnetic resonance imaging and contrast-enhanced ultrasound

Eleven patients underwent both MRI and CEUS of 12 plaques. Five plaques did not show any enhancement. Of the 7 plaques that did show enhancement, 2 were fibrous, 1 was fibrofatty, 2 were fibrofatty with some hemorrhage, and 2 were hemorrhagic. None of the plaques with predominantly lipid content shows neovascularization.

Ulceration was seen both on MRI and CEUS in 2 plaques, only on CEUS but not on MRI in 2 plaques, and only on MRI but not on CEUS in 4 plaques. Ulceration was seen neither on CEUS or MRI in 4 plaques.

Comparison of plaque composition by computed tomography angiography attenuation and ultrasound B-mode echogenicity

Nineteen plaques were evaluated by both CTA and B-mode ultrasound. There were 52.63% observed agreement and 49.86% expected agreement between the tests with a kappa value of 0.05 (slight) with $P = 0.4$ (not significant) [Figure 1].

Comparison of magnetic resonance imaging and computed tomography angiography

Thirteen patients (14 plaques) had both MRI and CTA imaging available.

Of these, three patients had predominantly lipid or fibrofatty core with a density range of 28.9–66.1 HU and a mean density of 44.53 HU.

Three patients had a predominantly fibrous core with a density range of 56.9–73.3 HU and a mean density of 64 HU.

One patient had a predominantly hemorrhagic core with a density of 52.9 HU. One patient had an intraluminal thrombus with a density of 50.9 HU.

Table 5: Plaque characterization of various plaques on magnetic resonance imaging

PD	T2	T1	TOF	Composition	Fibrous cap	Ulcer
Isointense	Hypointense	Mildly hyperintense	Isointense	Lipid	Yes	No
Isointense	Hypointense	Hyperintense	Hyperintense	Lipid with recent hemorrhage	No	Yes
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrous	Yes	No
Hyperintense	Hyperintense	Hyperintense	Isointense	Blood thrombus	No	No
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrous	Yes	No
Isointense	Hypointense with small hyperintense component	Small hyperintense component	Isointense	Fibrofatty with small hemorrhagic	No	Yes
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrous	No	No
Isointense	Hypointense	Mildly hyperintense	Isointense	Lipid	No	No
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrous	No	Yes
Hyperintense	Hyperintense	Mildly hyperintense	Hyperintense	Hemorrhagic	No	Yes
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrous with little lipid	Yes	Yes
Isointense	Hypointense	Mildly hyperintense	Isointense	Fibrofatty	Yes	Yes
Hyperintense	Hyperintense	Hyperintense	Hyperintense	Hemorrhagic	No	Yes
Isointense	Isointense	Isointense	Isointense	Fibrous	Yes	No
Isointense	Hyperintense	Hyperintense	Hyperintense	Fibrofatty with hemorrhagic	Yes	No
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrous	Yes	No
Isointense	Isointense	Mildly hyperintense	Isointense	Fibrofatty	Yes	Yes
Isointense	Hypointense	Mildly hyperintense	Isointense	Lipid	Yes	Yes
Isointense	Hypointense with small hyperintense component	Small hyperintense component	Isointense	Fibrofatty with small hemorrhagic	No	Yes
Isointense	Hypointense	Isointense	Isointense	Fibrofatty	Yes	No

PD = Proton density, TOF = Time-of-flight

The observed agreement between MRI composition and CT attenuation (<50 vs. 50–119 HU) was 78.57% and expected agreement was 54.08% with a kappa value of 0.53 (moderate correlation), $P = 0.01$.

The mean attenuation of plaque with predominantly lipid content was 38 HU and other plaques (fibrous/fibrofatty/hemorrhagic) was 58 HU, P value was statistically significant ($P = 0.0001$) [Figure 2].

Comparison of contrast-enhanced ultrasound and computed tomography angiography

Eleven patients (13 plaques) had both CEUS and CTA imaging available.

Of these, 8 plaques had neovascularization seen on CEUS. The average attenuation of these plaques was 52.14 ± 16.74 HU (range: 37.6–56.9 HU). Of the 5 plaques without neovascularization on CEUS, the average attenuation was 40.26 ± 22.87 HU (range 4.8–74 HU), $P = 0.35$ [Figure 3].

Comparison of evaluation of plaque surface by various modalities

The observed agreement between detection of ulceration by MRI and CEUS was 50% and expected agreement was 37.5% with a kappa value of 0.2 (slight agreement), $P = 0.12$.

The observed agreement between detection of ulceration by MRI and CTA was 92.86% and expected agreement was 52.04% with a kappa value of 0.85 (almost perfect agreement), $P = 0.0006$.

The observed agreement between detection of ulceration by CEUS and CTA was 61.54% and expected agreement was 52.07% with a kappa value of 0.2 (slight agreement), $P = 0.20$.

Representative images of a few selected cases have been described in Figures 4 and 5.

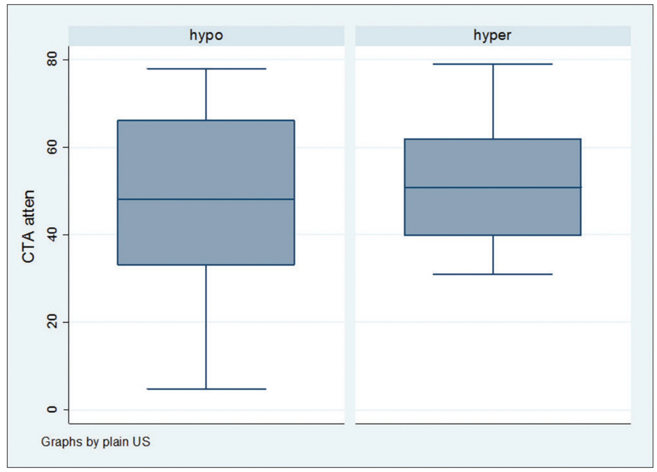

Figure 1: Box-and-whisker plot of computed tomography angiography attenuation of hypoechoic and hyperechoic plaques on B-mode ultrasound

Figure 2: Box-and-whisker plot of computed tomography angiography attenuation of plaques by composition on magnetic resonance imaging

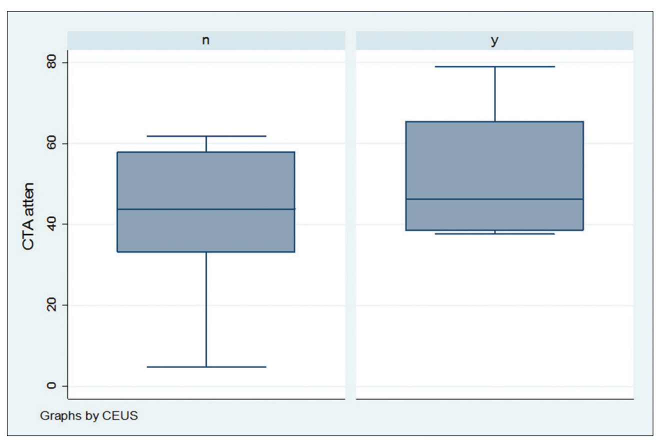

Figure 3: Box-and-whisker plot of computed tomography angiography attenuation of plaques with (y) and without (n) neovascularization

Discussion

Majority of ischemic strokes appear to result from embolization from an atherosclerotic plaque or acute occlusion of the carotid artery and propagation of the thrombus distally.[8] The frequency of embolization on transcranial Doppler is greater in patients with recent symptoms such as TIA compared with patients with similarly severe asymptomatic disease.[9]

Atherosclerotic plaques with a large lipid core, hemorrhage within the core, or thin/ulcerated fibrous cap are prone to the development of local thrombosis/occlusion or distal embolism with related ischemic consequences.[7] Thus, assessment of plaque constituents and surface characteristics may help to predict "vulnerability" of plaques and occurrence of future neurological thromboembolic events.[10] According to the concept of "vulnerable" carotid plaques described by Golledge *et al*.,[11] carotid artery disease, which is not necessarily stenotic, may sometimes be unstable and at high risk of producing symptomatic embolization or carotid occlusion.[11] As atherosclerosis progresses, the ongoing deposit of plasma components appears to further reduce vessel wall oxygen diffusion, triggering continued growth of angiogenesis.[12] Ultimately, the plaque is enveloped in luxurious adventitial

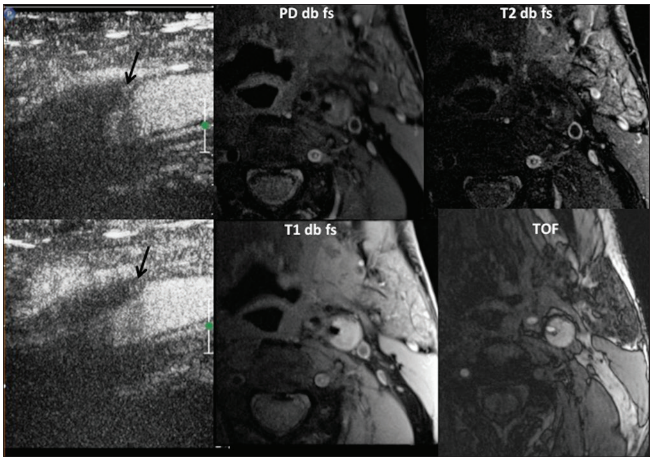

Figure 4: A 71-year-old male with left middle cerebral artery stroke. Left internal carotid artery 80% stenosis. On contrast-enhanced ultrasound, moving microbubbles are seen on the shoulder of the plaque. On magnetic resonance imaging plaque imaging, it appears isointense on proton density, hypointense on T2-weighted with small hyperintense component, and hyperintense on T1-weighted and time-of-flight s/o fibrofatty plaque with a small hemorrhagic component. Surface ulceration is present

vasa vasorum and intraplaque neovascularization, a hallmark of symptomatic atherosclerosis.[13]

Several pathological studies have shown that an extensive plaque neovascularization is associated with features of plaque vulnerability and with clinically symptomatic disease.[14-16] Besides MDCTA and digital subtraction angiography (DSA), MR angiography has been used for the assessment of atherosclerotic carotid plaque surface morphology. Randoux *et al*.[17] compared these techniques and concluded that luminal surface irregularities were most frequently recognized by CTA and that CTA and MR angiography recognized ulcerations more frequently than DSA.

Saba *et al*.[14] have recently demonstrated that ultrasound has a high specificity (93%) but a low sensitivity (38%) for the detection of carotid ulceration. Similarly, in our study, we found almost perfect agreement for detection of ulceration by CTA and MRI, slight agreement between CEUS and CTA and CEUS and MRI. Ultrasound is conventionally the first line of investigation for evaluation of the carotid bifurcation. Echogenicity on ultrasound has been shown to predict ipsilateral ischemic stroke; patients with echolucent plaques are at increased risk compared to those with echorich plaques.[15,16] However, hazard ratios for the development of stroke that are associated with differing echogenicity scores are not sufficiently great to warrant translation into clinical practice.

Various studies have attempted to correlate the enhancement seen on CEUS with number of microvessels on histopathologic evaluation[3,18,19] and symptoms.[20,21] The constituents of plaque have been differentiated on MRI in both *ex vivo* and *in vivo*[7,22,23] studies. MR measurements of the lipid necrotic core did not differ significantly from findings on histologic specimens (23.7% vs. 20.3%; $P < 0.1$), and a strong correlation was demonstrated between MR and histologic area measurements ($r = 0.75$; $P < 0.001$).[23]

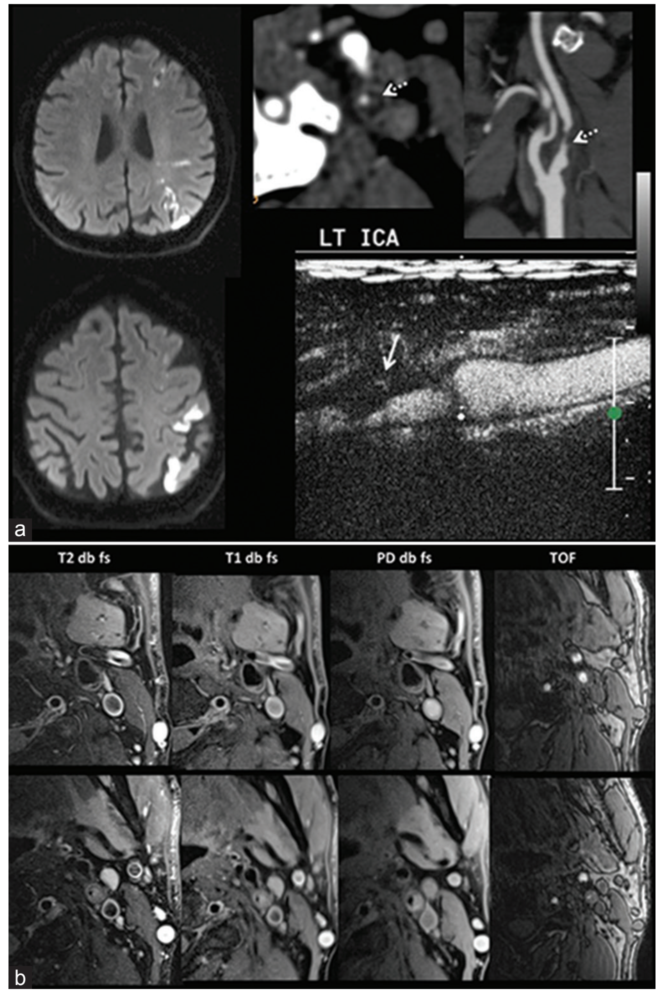

Figure 5: A 67-year-old male with left middle cerebral artery and middle cerebral artery-anterior cerebral artery watershed territory stroke. On computed tomography angiography (a), left internal carotid artery 80% stenosis. Plaque has attenuation of 37.6 HU. A Type 3 ulceration is present (dotted white arrows). On contrast-enhanced ultrasound, plaque neovascularization is seen with surface irregularity. On magnetic resonance imaging plaque imaging (b), plaque appears isointense on proton density and hypointense to isointense on T2-weighted. It is mildly hyperintense on T1-weighted and isointense on time-of-flight images s/o fibrofatty plaque. Surface ulceration is present

To the best of our knowledge, no studies have compared the assessment of plaque composition by multiple techniques. In our study, we observed good agreement between MRI and ultrasound and MRI and CT characteristics. We feel that the identification of the plaque characteristics with multimodality imaging will have implication in the decision-making in patients with moderate stenosis. These methods need to be considered in any patient with stroke/TIA in the corresponding territory, where a screening method – either ultrasound or CTA – has demonstrated some change in the carotid bifurcation wall characteristics.

Limitations

These techniques, especially contrast-enhanced ultrasound and MRI, are limited to small portions of the vascular tree, and it may be difficulty to evaluate the entire vascular tree in a single study. Hence, these studies need to be focused on the affected portion if screening techniques reveal focal narrowing.

We realize that it is a limitation of our study that we do not have a gold standard (e.g., histological specimens). Unfortunately, correlation with histological results is troublesome because only patients with severe stenosis (NASCET >70% stenosis) are eligible for intervention (surgery) and have specimen available for analysis. Histopathological analysis requires special stains and immunohistochemical markers. Matching the histopathological and imaging sections is also difficult.

We did not correlate the plaque composition with patients' symptoms because of the limited sample size. As our institute is a tertiary referral center for patients with stroke, most of the patients were symptomatic. Quantitative analysis of the various components of the plaque on MRI and CTA was also not performed due to lack of availability of software.

Conclusions

We have performed a prospective study on the evaluation of carotid plaques beyond the degree of stenosis. Different modalities of imaging provide supplementary information for the characterization of carotid plaques. The echogenicity of plaques on B-mode ultrasound is the basic technique for characterizing plaques. Contrast-enhanced ultrasound, apart from better characterization of the stenosis and surface characteristics, can also depict the plaque neovascularization. Since CEUS agents are safe and commercially available, they can be used in the clinical setting to help in risk stratification of carotid atherosclerotic disease. CTA is a noninvasive technique for the evaluation of luminal stenosis which is not operator dependent, unlike ultrasound. It can also provide information about the composition of plaque based on attenuation and also the surface ulceration. It is the "gold standard" for detecting calcification of plaques. Plaque composition and thus vulnerability can also be studied by MRI. Together, all these techniques provide complete information about the plaque characteristics and may be considered in planning further management of patients with carotid atherosclerotic plaques.

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Conflicts of interest

There are no conflicts of interest.

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