

Evaluation of Fibrous Cap Rupture of Atherosclerotic Carotid Plaque with Thin-Slice Source Images of Time-of-Flight MR Angiography

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Objective: To investigate the ability of source image of time-of-flight magnetic resonance angiography (TOF-MRA) in the detection of fibrous cap rupture of atherosclerotic carotid plaques.

Materials and Methods: From the database of radiological information in our hospital, 35 patients who underwent carotid MR imaging and subsequent carotid endarterectomy within 2 weeks were included in this retrospective study. MR imaging included thin-slice time-of-flight MR angiography, black-blood T1- and T2-weighted imaging. Sensitivity, specificity and accuracy were calculated for the detection of fibrous cap rupture with source image of TOF-MRA. The Cohen k coefficient was also calculated to quantify the degree of concordance of source image of TOF-MRA with histopathological data.

Results: Sensitivity, specificity and accuracy in the detection of fibrous cap rupture were 90% (95%CI: 81–98), 69% (95%CI: 56–82) and 79% (95%CI: 71–87) with a k value of 0.59. The false positives (n = 15) were caused by partial-volume averaging between fibrous cap and lumen at the shoulder of carotid plaque. The false negatives (n = 5) were underestimated as partial thinning of fibrous cap.

Conclusion: Source image of TOF-MRA can be useful in the detection of fibrous cap rupture with high sensitivity, but further technical improvement should be necessary to overcome shortcomings causing image degradation.

Keywords: atherosclerotic plaque, carotid artery, MR imaging, fibrous cap, time of flight MR angiography

Introduction

The most common source of emboli in cerebral ischemia such as transient ischemic attacks and embolic stroke originates from atherosclerotic carotid plaque.^{1–3)} It is important to detect unstable plaque for the purpose of preventing future cardiovascular events. There have been reported to be several key factors in advanced plaque that are likely to lead

to cerebral ischemic disease: condition of the fibrous cap, size of necrotic core and hemorrhage, and extent of inflammatory activity within atherosclerotic carotid plaque.^{4–6)} Progressive thinning of fibrous cap of carotid plaque can lead to plaque fissuring and ulceration. Acute thrombosis might occur and cause an occlusion of the arterial lumen prompted by the release of thrombogenic materials from the plaque.⁷⁾

Plaque rupture has been shown to occur regardless of the degree of luminal stenosis, and it is difficult to predict ischemic events with only the degree of narrowing of the carotid artery lumen.^{8,9)} Thick fibrous caps are more likely to withstand pulsatile mechanical forces. In contrast, thin fibrous caps are vulnerable to fissuring or ulceration.^{10,11)} Fibrous cap rupture is considered to be a predisposing factor to

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cause ischemic cerebral disease. Soft plaque components such as intraplaque hemorrhage and necrotic lipid core could worsen the degree of symptoms by massive ingredient outflows.⁷⁾

High-resolution magnetic resonance (MR) imaging has emerged as a potential technique for atherosclerotic plaque imaging.^{3,6,7,12-14)} MR imaging provides tremendous information in evaluating plaque surface morphology such as ulceration and fibrous cap disruption as well as in measuring total plaque volume and identifying plaque components.^{3-7,10,13,15-18)}

The purpose of this article is to investigate the ability of source image of time-of-flight MR angiography (TOF-MRA) in the detection of fibrous cap rupture of atherosclerotic carotid plaques.

Materials and Methods

Patient population

From the database of radiological information in our hospital, 44 symptomatic patients who underwent MR imaging of carotid arteries and subsequent carotid endarterectomy within 2 weeks between June 2006 and April 2010 were nominated in this retrospective study. Excluded were 9 patients because of severe damage of the surgical specimen ($n = 4$) and motion artifact in TOF-MRA ($n = 5$). Thus, this retrospective study included 35 patients. The written informed consent from the patients was waived owing to the retrospective design of this study.

MR imaging

MR imaging was performed on a 1.5 Tesla superconductive magnet system (Gyrosan ACS-Intera; Philips Medical systems, Best, the Netherlands). Each patient was positioned supine on the patient table. A pair of commercially available 8-cm circular surface coil was placed on each side of a patient's neck centered over carotid bifurcation. After initial T1-weighted localizing images were obtained in sagittal, coronal and transaxial direction, MR angiography of carotid arteries was performed with fat-suppressed three-dimensional (3D) TOF sequence (TR/TE/FA: 40/1.8/20) in the transaxial direction. Other parameters included a 512×512 matrix, 1.4 mm section thickness, 0.7 mm section overlap, and 150 mm field of view yielding a voxel size of $0.29 \times 0.29 \times 0.7$ mm³. A number of data sampling was two and the scan time was about 3 minutes 50 seconds.

In the characterization of carotid plaque, 3 transverse images with a section thickness of 3 mm were obtained using black-blood TSE sequences with a double inversion recovery technique.¹⁹⁾ The parameters used are: fat-suppressed (FS) T1-(TR/TE: 750-1000/12), FS T2-weighted TSE (TR/TE: 1500-2000/80) images with ECG-triggering. Other imaging parameters were a 256×256 matrix, 3 mm section thickness, 150 mm field of view, yielding a voxel size of $0.6 \times 0.6 \times 3$ mm³.

Histological evaluation

For each patient, a plaque resected on surgery served as the reference standard. A whole piece of carotid plaque was marked laterally and ventrally in the longitudinal direction and then fixed with formalin. It was then divided into 2-mm transverse contiguous slices, processed, embedded in paraffin, and those slices were subjected to hematoxylin-eosin, Masson-trichrome and Elastica-von-Gieson staining. The histologic slices were examined microscopically. Rupture of fibrous cap was determined by using Masson-trichrome and Elastica-von-Gieson staining. Major components such as lipid core, intraplaque hemorrhage, fibrous tissue and calcification were also identified by the pathologists.

Assessment of plaque

Three imaging sections of TOF MRA source images matched with each section of FST1- and FST2-black blood images were selected in each patient and analyzed by two radiologists who jointly assessed all the sequences and expressed a consensus opinion on fibrous cap rupture as well as major plaque components.

Assuming that the fibrous cap is arranged in layers, it appears as a hypointense band of varying thickness in the TOF-MRA sequences. Fibrous cap covering carotid plaque was classified as thick, thin, disruption and unassessable. Lack of the hypointense band indicates that the cap has ruptured.

TOF-MRA imaging sections were then compared with the corresponding histological sections.

Data analysis

Histopathology was the standard of reference in the diagnosis of fibrous cap rupture. Sensitivity, specificity and accuracy were calculated for the detection of fibrous cap rupture with source image of

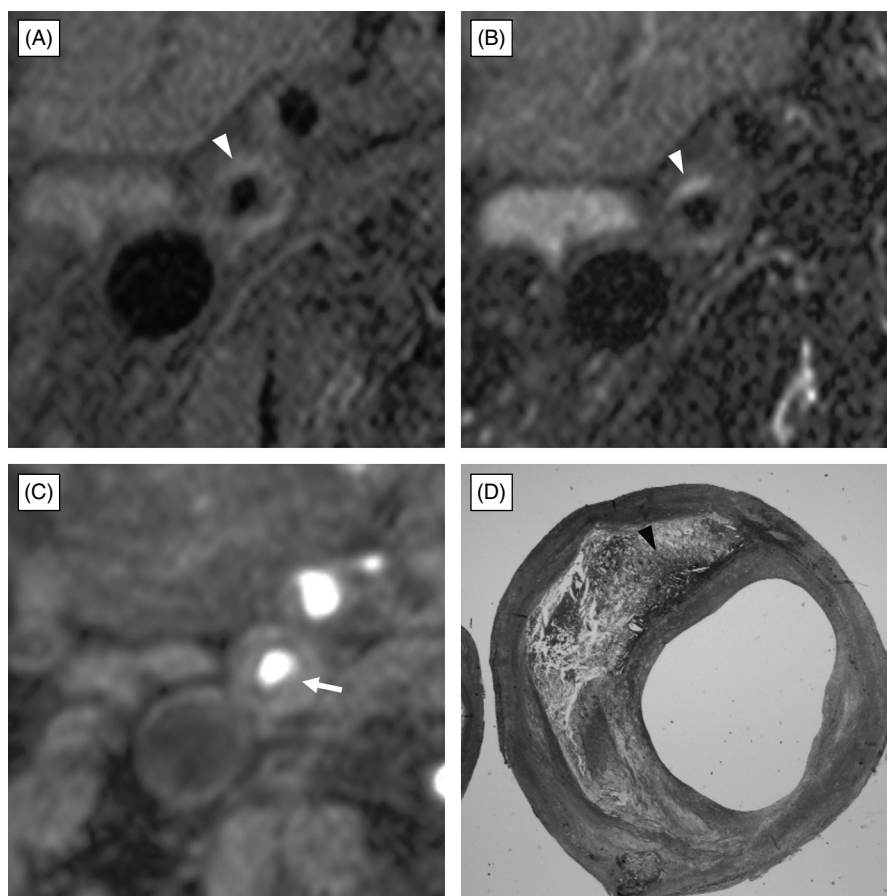


Fig. 1 Atherosclerotic plaque composed of fibrous tissue and small amount of intraplaque hemorrhage with no fibrous cap rupture. **(A)** black-blood fat-suppressed T1-weighted image, **(B)** black-blood fat-suppressed T2-weighted image, **(C)** source image of time-of-flight magnetic resonance (TOF MR) angiogram, **(D)** histological section with Masson-Trichrome staining. Black-blood fat-suppressed T1-weighted image **(A)** and T2-weighted image **(B)** demonstrates carotid plaque composed of a large isointensity portion and small crescent-shape high intensity (arrowhead) relative to the submandibular gland. Source image of TOF MR angiography **(C)** shows moderate stenosis of the right carotid artery with thin hypointensity band of fibrous cap covering the plaque completely. Note partial thinning (arrow) on the fibrous plaque. Histological section with Masson-Trichrome staining **(D)** demonstrates fibrous cap covering the fibrous plaque with intraplaque hemorrhage (arrowhead), and no disruption is found.

TOF-MRA. The Cohen k coefficient was also calculated to quantify the degree of concordance of source image of TOF-MRA with the histopathological data. A k value >0.75 indicates good concordance; k between 0.40 and 0.75 indicates moderate concordance.²⁰⁾

Results

Among the 105 sections of TOF-MRA source images in all the 35 patients, 8 sections proved not to be assessable because of complete occlusion ($n = 3$) and

inappropriate slice direction ($n = 5$). Thus, 97 sections were assessed and compared with histopathology findings.

Out of the 97 sections, source image of TOF-MRA showed true positive and negative findings of disruption of fibrous cap in 44 and 33 sections, respectively (Figs. 1–3). The number of sections with false positive and negative results was 15 and 5, respectively. Sensitivity, specificity and accuracy in the detection of fibrous cap rupture were 90% (95%CI: 81–98), 69% (95%CI: 56–82) and 79% (95%CI: 71–87) with a k value of 0.59 (Table 1).

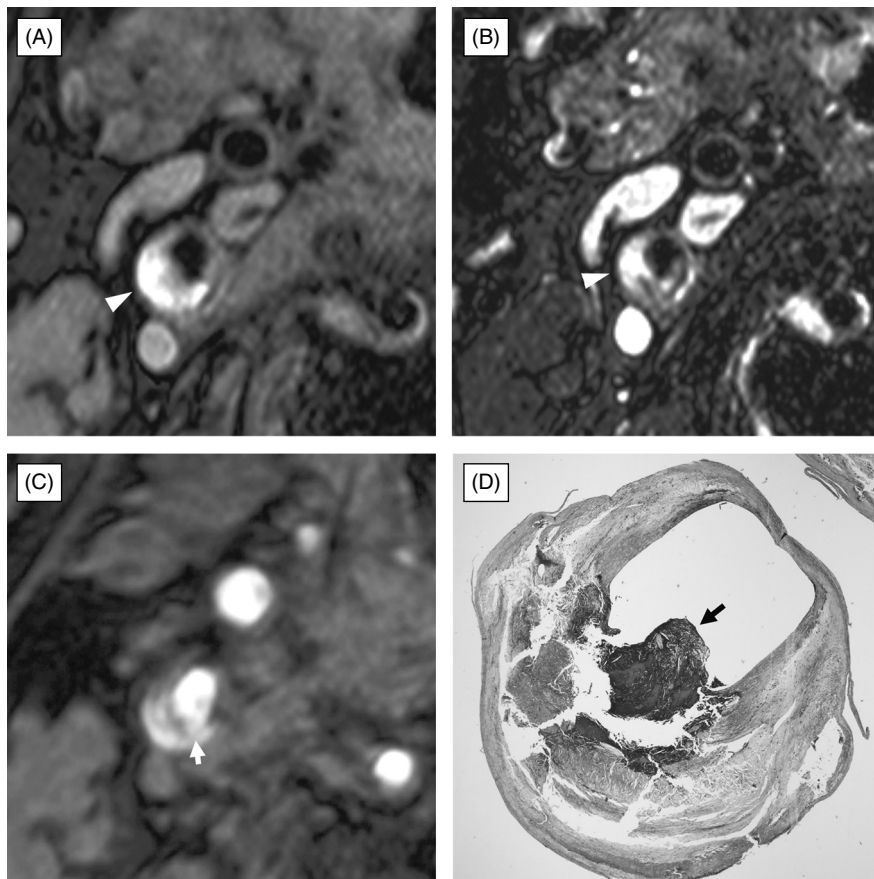


Fig. 2 Rupture of thick fibrous cap covering atherosclerotic plaque composed of intraplaque hemorrhage. **(A)** black-blood fat-suppressed T1-weighted image, **(B)** black-blood fat-suppressed T2-weighted image, **(C)** source image of time-of-flight magnetic resonance (TOF MR) angiogram, **(D)** histological section with Masson-Trichrome staining. The atherosclerotic carotid plaque consists of a large portion of high signal intensity on black-blood fat-suppressed T1-weighted image **(A)** and mixed high and intermediate signal intensity on black-blood fat-suppressed T2-weighted image **(B)**. Fibrous cap cannot be identified on the black-blood MR imaging. Source image of TOF MRA **(C)** demonstrates rupture of thick fibrous cap (arrow) lying on the hyperintense carotid plaque. Histopathological examination with Masson-Trichrome staining **(D)** clearly reveals disruption of fibrous cap (arrow) covering a large portion of intraplaque hemorrhage.

The false positives of source image of TOF-MRA ($n = 15$) were caused by partial-volume averaging between fibrous cap and lumen at the shoulder of carotid plaque. The false negatives ($n = 5$) were underestimated as partial thinning of fibrous cap.

Discussion

Fibrous cap was first reported as hypointense band or rim surrounding bright lumen on source image of three-dimensional (3D) TOF MR angiography by Hatsukami, et al.,²¹⁾ and it was also demonstrated

that high-resolution MRI with a 3D TOF protocol was capable of distinguishing an intact thick fibrous cap from an intact thin and/or ruptured fibrous cap.^{10,11,21)} Hatsukami, et al.²¹⁾ reported high sensitivity and specificity for the detection of fibrous cap rupture with source image of TOF-MRA. Our study also showed high sensitivity with a kappa value of 0.59, indicating moderate concordance between source image of TOF-MRA and histopathology findings in the evaluation of fibrous cap rupture.

However, there was considerable number of cases that could not be assessed for the condition of

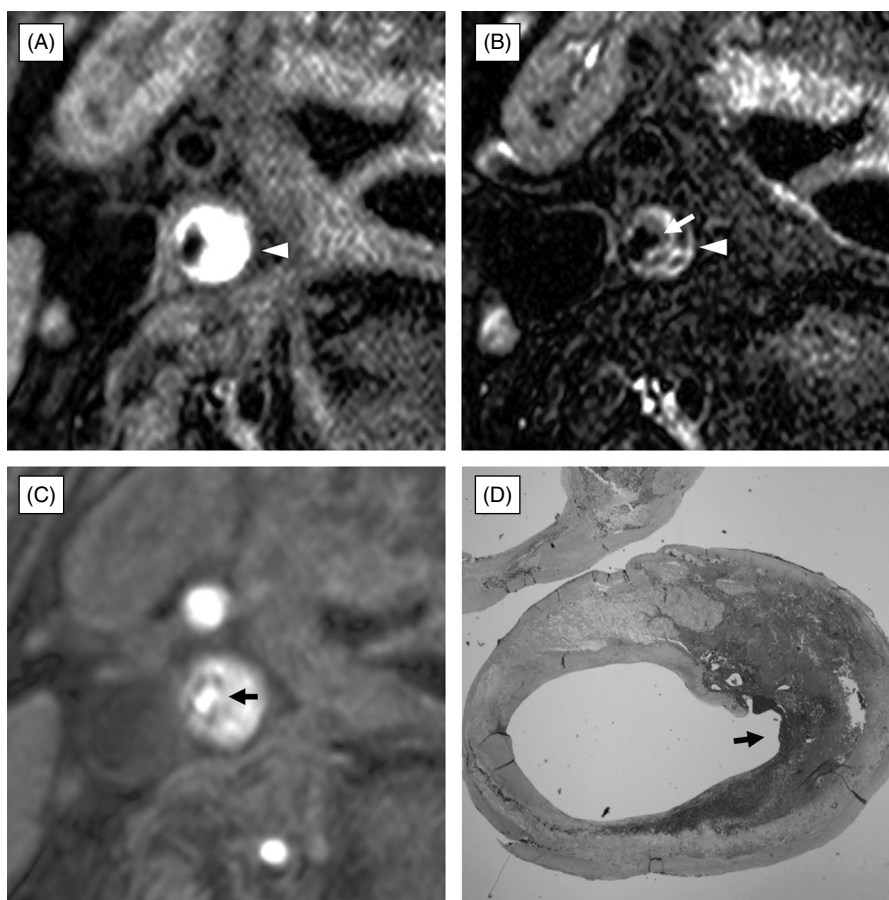


Fig. 3 Ulcerated atherosclerotic plaque composed of lipid core and intraplaque hemorrhage with rupture of fibrous cap. **(A)** black-blood fat-suppressed T1-weighted image, **(B)** black-blood fat-suppressed T2-weighted image, **(C)** source image of time-of-flight magnetic resonance (TOF MR) angiogram, **(D)** histological section with Masson-Trichrome staining. The atherosclerotic carotid plaque demonstrates a large portion of high signal intensity on black-blood fat-suppressed T1-weighted image **(A)** and mixed high and intermediate signal intensity on black-blood fat-suppressed T2-weighted image **(B)**. Source image of TOF MRA **(C)** shows disruption of thick fibrous cap (arrow) covering the hyperintense carotid plaque. Histopathological examination with Masson-Trichrome staining **(D)** clearly reveals that a plaque composed of lipid core and intraplaque hemorrhage has small ulceration with disruption of fibrous cap (arrow). Note protruded lumen (arrow) into hyperintense plaque on black-blood fat-suppressed T2-weighted image **(B)**.

fibrous cap. As Pappin²²⁾ and Touze²³⁾ reported, a major problem can be low assessability of source image of TOF-MRA for the identification of fibrous cap. In our study, a major cause of failure in the identification of fibrous cap lying on the carotid plaque was image degradation due to motion artifact in obtaining TOF-MRA. Even respiratory and pulsatile movement could spoil image quality. Another is inappropriate slice direction resulting in partial volume averaging between hypointensity of fibrous cap and hyperintensity of lumen, which makes hypointensity band obscure. To overcome these disadvantages,

TOF-MRA should be taken by using ECG-gating in multiangle transaxial directions against long axis of carotid arteries.

The specificity of 69% obtained in this study was relatively low, and most of false positives were found at the shoulder of carotid plaque. The section thickness of 1.4 mm used in this study might not be enough to avoid partial volume averaging between lumen and carotid plaque at the shoulder. The section thickness should be much thinner to minimize this unfavorable effect, though it may need longer acquisition time which lead to increase of motion

Table 1 Sensitivity, specificity and accuracy of source image of Time-of-flight MR angiography in the detection of fibrous cap rupture of carotid plaque

	Sensitivity % (95%CI)	Specificity % (95%CI)	Accuracy % (95%CI)	k value
TOF-MRA	90 (81–98)	69 (56–82)	79 (71–87)	0.59

TOF-MRA: time-of-flight magnetic resonance angiography

artifact. False positives were also found with thin fibrous cap. The spatial resolution of this method was 290 μ m, which might give false positive results to thin fibrous cap.

Fibrous cap was reported to show hyperintensity in comparison to the underlying lipid-rich necrotic core on T2-weighted images by Trivedi, et al.^{10,24} However, intraplaque hemorrhage within lipid-rich necrotic core increases signal intensity and may obscure the boundary between fibrous cap and the underlying lipid-rich necrotic core on T2-weighted images.⁷ In our study, T2-weighted image could not identify the condition of fibrous cap, which seems that T2-weighted imaging may not be appropriate in the evaluation of fibrous cap rupture.

Plaque surface morphology on carotid angiography could be a sensitive marker of plaque instability.²⁵ An appearance of ulceration, when found at carotid stenosis in a symptomatic patient, is a strong independent predictor of stroke.^{25,26} TOF-MR angiography can allow for accurate evaluation of plaque surface morphology at carotid stenosis by observing luminal stenosis from multi-direction view points. However, when carotid plaques including lipid core and/or intraplaque hemorrhage appears as hyperintensity on TOF-MRA, source image of TOF-MRA may be difficult to distinguish hyperintense plaque from protruded lumen. In such a case, black-blood T1- and T2-weighted imaging could be good to determine the presence or absence of plaque ulceration as shown in Fig. 3. This may suggest that simultaneous interpretation of source image of TOF-MRA with black-blood MR images can facilitate to evaluate the overall risk factors including plaque ulceration, fibrous cap rupture, underlying plaque components of lipid core and intraplaque hemorrhage, etc.⁷ Therefore, information concerning the condition of fibrous cap as well as the plaque composition should be included in the determination of treatment plan; carotid endarterectomy, carotid artery stenting, and medical treatment with lipid-lowering therapy.^{5,7,12,27–30}

In conclusion, the condition of fibrous cap can be assessed in source image of TOF-MRA with high sensitivity, but further technical improvement should be necessary in obtaining source image of TOF-MRA to overcome problems causing image degradation.

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Disclosure Statement

The authors have no conflict of interest.

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