Table 2: Clinical characteristics for symptomatic and asymptomatic carotid stenosis

Variable	Symptomatic[a] (n = 13)	Asymptomatic[a] (n = 77)	P Value[b]
Age (yr)	68.7 ± 10.9	71.4 ± 8.3	.311
Male sex (%)	53.8 (7/13)	58.4 (45/77)	.757
Hyperlipidemia (%)	69.2 (9/13)	70.1 (54/77)	.948
Hypertension (%)	61.5 (8/13)	71.4 (55/77)	.472
History of coronary artery disease (%)	30.8 (4/13)	41.6 (32/77)	.463
History of peripheral vascular disease (%)	30.8 (4/13)	36.4 (28/77)	.697
History of diabetes mellitus (%)	30.8 (4/13)	19.5 (15/77)	.361
Current statin use (%)	76.9 (10/13)	81.8 (63/77)	.677
Current smoker (%)	69.2 (9/13)	83.1 (64/77)	.258

[a] Mean ± SD. Other values represent percentages; numbers in parentheses are used to calculate the percentages.
[b] P values by unpaired t test for age and by χ^2 test or Fisher exact test for the other variables.

Table 3: Relationship between in vivo 3T carotid plaque components and recent ipsilateral thromboembolic symptoms for 50 patients with mild/moderate carotid stenosis measured by contrast-enhanced MR angiography

Variable	Symptomatic (n = 6)	Asymptomatic (n = 44)	OR (95% CI)	P Value	AUC
Plaque burden					
% wall volume	61.0 ± 5.8	56.1 ± 9.2	1.93 (0.70–5.31)[a]	.204	0.689
% stenosis on MRA	50.8 ± 6.9	55.5 ± 9.7	0.61 (0.25–1.46)[a]	.265	0.339
Ulceration on MRA	50%	36%	1.75 (0.32–9.72)	.661	0.568
Prevalence plaque components					
Fibrous cap thin/ruptured	100%	39%	n/a (2.13-infinity)[b]	.006[c]	0.807
Lipid-rich necrotic core	100%	43%	n/a (1.77-infinity)[b]	.022[c]	0.784
Hemorrhage	67%	25%	6.00 (0.96–37.4)	.055	0.708
Calcifications	67%	84%	0.38 (0.06–2.48)	.311	0.413
% Volume of plaque components					
Lipid-rich necrotic core	18.5 ± 12.2	6.6 ± 11.3	1.90 (1.03–3.51)[a]	.040	0.837
Hemorrhage	6.9 ± 6.6	1.9 ± 5.0	3.22 (0.97–10.71)[a]	.056	0.750
Calcifications	2.9 ± 3.7	4.7 ± 5.9	0.44 (0.05–4.02)[a]	.470	0.405

[a] OR and 95% CI for a 10% increase.
[b] Lower limit CI estimated by exact logistic regression analysis. "n/a" was used because OR cannot be calculated in the presence of zero cells in a 2 × 2 table.
[c] Fisher exact test.

values. All analyses were performed with the Statistical Package for the Social Sciences, Version 16 (SPSS, Chicago, Illinois), except for the exact models, which were performed by using SAS, Version 9.1 (SAS Institute, Cary, North Carolina). $P < .05$ was used to designate statistical significance.

Accuracy to classify symptom status for each statistically significant metric selected in the logistic regression analysis was assessed with ROC, and the AUC was evaluated.

Results

Among the 97 patients (97 arteries), 90 (92.8%) arteries had sufficient image quality for plaque interpretation. None of the symptomatic subjects were excluded. Accordingly, 77 asymptomatic and 13 symptomatic arteries were analyzed. The 90 arteries yielded 1451 sections available for image review. Seventy-eight (5.4%) of 1451 interpreted sections required mutual discussion for consensus agreement. The presence of clinical cardiovascular risk factors did not correlate with symptom status (Table 2). Although all patients in this study had 50%–99% stenosis of the index carotid artery as detected by entry duplex sonography or CT angiography, the high-resolution research carotid CE-MRA revealed a wider range of stenoses. On the basis of the high-resolution research CE-MRA, 50 patients were classified as having mild/moderate carotid stenosis (Table 3). In these 50 patients with mild/moderate carotid stenosis, 6 were symptomatic with a mean percentage stenosis of 50.8 ± 6.9 and a range of 42%–62% as measured on the research high-resolution CE-MRA. There were 44 asymptomatic patients with mild/moderate stenosis with a mean percentage stenosis of 55.5 ± 9.7 and a range of 30%–69%. On the basis of high-resolution research CE-MRA, 40 patients were classified as having severe carotid stenosis (Table 4). Of the 40 patients with severe stenosis, 7 were symptomatic with a mean percentage stenosis of 86.3 ± 6.5 and a range of 79%–95% as measured on the research high-resolution CE-MRA. There were 33 severely stenotic asymptomatic patients with a mean percentage stenosis of 81.7 ± 6.9 and a range of 71%–99%.

Mild/Moderate Carotid Stenosis

In 50 patients with mild/moderate stenosis as identified on the high-resolution carotid CE-MRA, the prevalence of each plaque and luminal surface characteristic was the following, respectively, in symptomatic and asymptomatic patients: 100% versus 39% ($P = .006$) for a thin/ruptured fibrous cap, 100% versus 43% ($P = .022$) for lipid-rich necrotic core, 67% versus 25% ($P = .055$) for hemorrhage, 67% versus 84% ($P = .311$) for calcification, and 50% versus 36% ($P = .661$) for the prevalence of MRA ulceration. All symptomatic patients had a lipid-rich necrotic core and a thin/ruptured cap (Table 3 and Figs 1 and 2). Univariate logistic regression models demonstrated that the presence of a thin/ruptured fibrous cap, the presence of a lipid-rich necrotic core, and the percentage volume of lipid-rich necrotic core were significantly associated with recent symptoms (Table 3). The presence and the per-

Table 4: Relationship between in vivo 3T carotid plaque components and recent ipsilateral thromboembolic symptoms for 40 patients with severe carotid stenosis measured by contrast-enhanced MR angiography

Variable	Symptomatic (n = 7)	Asymptomatic (n = 33)	OR (95% CI)	P Value	AUC
Plaque burden					
% wall volume	63.7 ± 7.6	60.7 ± 8.8	1.52 (0.58–4.02)[a]	.395	0.602
% stenosis on MRA	86.3 ± 6.5	81.7 ± 6.9	2.72 (0.77–9.65)[a]	.121	0.669
Ulceration on MRA	86%	36%	10.50 (1.13–97.91)	.039	0.747
Prevalence of plaque components					
Fibrous cap thin/ruptured	57%	52%	1.26 (0.24–6.50)	.787	0.528
Lipid-rich necrotic core	57%	64%	0.76 (0.15–3.99)	.748	0.481
Hemorrhage	43%	36%	1.31 (0.25–6.88)	.748	0.532
Calcifications	86%	73%	2.25 (0.24–21.38)	.480	0.565
Volume of plaque components					
Lipid-rich necrotic core	9.7 ± 11.8	10.6 ± 13.4	0.94 (0.49–1.82)[a]	.863	0.481
Hemorrhage	2.8 ± 3.7	4.1 ± 7.4	0.73 (0.18–2.96)[a]	0.661	0.519
Calcifications	6.6 ± 5.5	5.0 ± 6.1	1.51 (0.43–5.31)[a]	0.525	0.608

[a] ORs for a 10% increase.

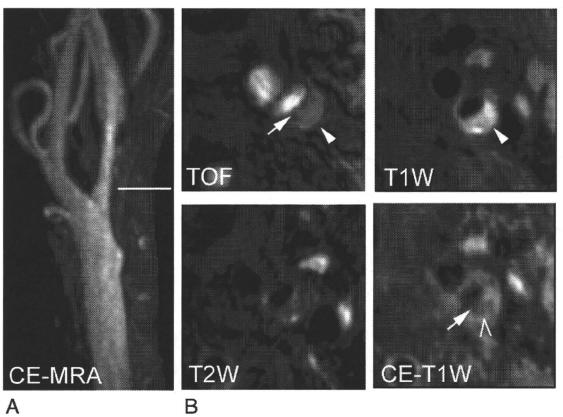

Fig 1. Coronally acquired MRA and transverse images of a complicated carotid plaque of the left carotid artery from a 75-year-old man with right-sided weakness. *A*, Maximum intensity projection of CE-MRA demonstrates a 55% smooth stenosis at the left internal carotid artery. The horizontal line indicates the level of the transverse carotid plaque images (shown in *B*). *B*, Disrupted dark band (*arrow*) on the TOF angiogram and discontinuation of the high-intensity band on CE-T1WI indicate a thin fibrous cap. High intensity on TOF and precontrast T1WI indicate regions of hemorrhage (*arrowhead*). The low-intensity area on the CE-T1WI indicates a lipid-rich necrotic core area occupying 31% of the wall area (*chevron*). Notice that the hemorrhage seen on TOF and T1WI almost completely fills the lipid-rich necrotic core as seen on the CE-T1WI. Symptomatic plaques tend to have a hemorrhagic lipid-rich necrotic core with a thin or ruptured fibrous cap.

centage volume of intraplaque hemorrhage were marginally significantly associated with symptom status (Table 3). Accuracy to classify the symptom status of these 5 plaque components by using ROC demonstrated the largest AUC for the percentage volume increase of the lipid-rich necrotic core, followed by the presence of a thin or ruptured fibrous cap (Table 3 and Fig 3). All the other carotid plaque characteristics, CE-MRA stenosis as well as clinical variables, were not significantly associated with symptom status.

Severe Carotid Stenosis

In 40 patients with severe carotid stenosis, the prevalence of MRA ulceration was 86% for symptomatic patients and 36% (P = .039) for asymptomatic patients. The prevalence of thin/ruptured fibrous cap (57% versus 52%, P = .787), the prevalence of lipid-rich necrotic core (57% versus 64%, P = .748), the prevalence of hemorrhage (43% versus 36%, P = .748), and the prevalence of calcifications (86% versus 73%, P = .480) were similar in symptomatic versus asymptomatic patients with severe stenosis. Univariate logistic regression indicated that the presence of an ulcer detected by CE-MRA (OR, 10.5; 95% CI, 1.1–97.9, P = .039) was significantly associated with recent symptoms (Table 4). There were no other statistically significant findings between the other plaque characteristics and symptom status or between clinical risk factors and symptom status (Table 4).

Discussion

This study demonstrates a correlation of in vivo 3T MR plaque and lumen findings with recent symptoms in patients with

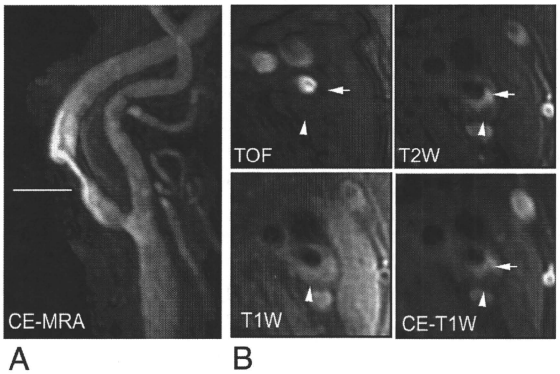

Fig 2. Transverse carotid plaque images and coronally acquired CE-MRA of the left carotid artery from an asymptomatic 61-year-old woman. *A*, Maximum intensity projection of the CE-MRA demonstrates a 74% stenosis at the left internal carotid artery. The horizontal line indicates the level of the transverse carotid plaque images (shown in *B*). *B*, Transverse image of a TOF angiogram demonstrates a smooth luminal surface and a dark juxtaluminal band indicating an intact thick fibrous cap. The thick fibrous cap is easier to appreciate as a high-intensity band (*arrow*) on the CE-T1WI and the T2WI. An isointense area on TOF images and T1WI, an iso- to low-intensity area on the T2WI, and a low-intensity area on the CE-T1WI image indicate a lipid-rich necrotic core without hemorrhage occupying 29% of the wall area (*arrowhead*). Notice that the lipid-rich necrotic core is easiest to appreciate on the CE-T1WI. Asymptomatic plaques tend to have a smaller lipid-rich necrotic core without hemorrhage as well as a thick fibrous cap.

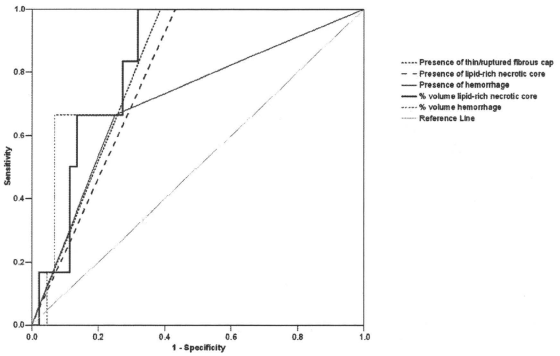

Fig 3. Strength of the association ROC between carotid plaque features and ipsilateral symptoms for 50 patients with mild/moderate carotid stenosis measured by CE-MRA.

mild/moderate versus severe carotid stenosis. The ability to noninvasively characterize carotid plaque on 3T MR imaging extends our knowledge of which distinctive wall features are associated with symptoms to include a patient population that does not meet established criteria for surgical resection. The preliminary results from this study suggest that there may be specific wall features that discriminate symptomatic from asymptomatic plaque in the cohort of people with mild/moderate stenosis as measured by CE-MRA, including: the presence of a thin or ruptured fibrous cap as well as the presence and size of a lipid-rich necrotic core. The presence and size of plaque hemorrhage demonstrate a tendency to be associated with recent symptoms. The quantitative analysis of the size of percentage volume lipid-rich necrotic core demonstrates the highest AUC in the ROC of the strength of association of plaque findings with recent ipsilateral carotid symptoms. These preliminary findings need to be confirmed in larger studies before the results can be applied to larger populations. If confirmed, in vivo 3T MR carotid plaque imaging may identify patients with mild/moderate stenosis who are at a higher risk of stroke or TIA from unstable plaque.

Previous studies have shown that MR imaging can distinguish thick, thin, and ruptured caps of carotid plaque with good sensitivity and specificity in vivo.[23,28] Yuan et al[13] demonstrated that patients with thin and ruptured fibrous caps were more likely to have had a recent TIA or stroke (OR, 10 and 23, respectively) compared with plaques with thick caps identified by carotid plaque MR imaging. Our study may extend these conclusions to patients with less severe atherosclerotic disease who do not require carotid endarterectomy by

demonstrating that all symptomatic patients with mild/moderate stenosis had a thin or ruptured fibrous cap. Our study also corroborates a prior 1.5T MR imaging study of patients with moderate carotid stenosis that demonstrated a significant correlation of thin or ruptured fibrous cap and ipsilateral subsequent carotid stroke.[11]

There are limitations in spatial resolution with our current implementation of in vivo 3T carotid MR imaging. Using an in-plane resolution of 550–625 μm, we were able to demonstrate a significant association between the presence of a thin or ruptured fibrous cap in patients with mild/moderate stenosis and a history of recent ipsilateral carotid thromboembolic symptoms. Recent work has suggested that the minimal fibrous cap thickness associated with plaque rupture in the carotid artery is much larger than that in the coronary artery, perhaps due to differences in the caliber of the internal carotid artery and the coronary artery.[29] In a recent histologic review of 526 carotid plaques removed from symptomatic patients with severe carotid stenosis, Redgrave et al[29] concluded that a representative cap thickness of 500 μm or a minimum cap thickness $<$200 μm should be used as specific cut-points for discriminating ruptured and nonruptured plaques. The former criteria are within the resolution capabilities of current in vivo carotid MR imaging. In the future, it may be possible to use the higher signal intensity–to-noise ratio of 3T MR scanning to achieve higher spatial resolution to allow depiction of the minimal fibrous cap thickness.

Histopathologic studies have demonstrated that plaque that has the potential to rupture is characterized by a large thrombogenic lipid core with thinning or rupture of the overlying fibrous cap.[30] Takaya et al[11] demonstrated that the development of new stroke or TIA was associated with larger lipid-rich necrotic core size in a prospective longitudinal study of 154 asymptomatic patients with 50%–79% carotid stenosis. Our study results are in agreement with those of Takaya et al in that the size of the lipid-rich necrotic core is associated with ipsilateral carotid symptoms in patients with moderate stenosis. Our study also demonstrated a significant correlation of recent symptoms with the presence of a lipid-rich necrotic core in patients with mild/moderate stenosis. Combined with the results from Takaya et al, our study would suggest that as the lipid-rich necrotic core increases in size, the plaque may become more unstable in patients with mild/moderate carotid stenosis.

An important gap in the histologic literature exists because carotid specimens are not available for asymptomatic patients with $<$70% stenosis. The use of in vivo carotid plaque MR imaging to evaluate patients with moderate stenosis has been reported. Several MR imaging studies have demonstrated associations of intraplaque hemorrhage with neurologic symptoms in patients with moderate stenosis. In prospective studies of patients with 50%–79% carotid stenosis, hemorrhage as seen on multicontrast MR plaque imaging was related to subsequent ipsilateral carotid cerebrovascular events during follow-up.[11] Multiple studies using inversion recovery T1WI magnetization-prepared rapid acquisition of gradient echo have demonstrated that recent or recurrent symptoms were associated with intraplaque hemorrhage on the baseline MR plaque imaging studies for patients with symptomatic moderate and high-grade carotid stenoses.[8,31,32] Our current work supports these earlier studies by demonstrating a tendency for plaque hemorrhage to correlate with recent ipsilateral carotid symptoms in patients with mild/moderate carotid stenosis.

Although the size of the current study does not support a multivariate analysis, the strength of associated ROC comparing the correlation of recent symptoms with plaque characteristics indicates that the AUC is largest for the percentage volume lipid-rich necrotic core followed by the presence of a thin or ruptured fibrous cap. These plaque components may be the most indicative of a "vulnerable" plaque.

In this study, neither the lipid-rich necrotic core nor intraplaque hemorrhage was significantly associated with symptoms in patients with severe stenosis. This finding is consistent with the large number of histologic studies that have compared carotid plaques removed from symptomatic and asymptomatic patients in an attempt to understand the mechanisms underlying plaque "activation." In recent summaries of the literature by Golledge et al[6] and Gao et al,[7] most of these histologic studies were unable to demonstrate a correlation between the depiction of a lipid-rich necrotic core or intraplaque hemorrhage and ipsilateral carotid symptoms in patients with carotid stenosis severe enough to warrant CEA. Despite the lack of correlation between histologic studies and symptoms, it is also possible that larger and more numerous in vivo MR imaging carotid plaque studies may consistently depict a correlation of symptoms with necrotic core or intraplaque hemorrhage in patients with severe carotid stenosis. For instance, Yamada et al[32] did find an association of plaque hemorrhage and recent symptoms in patients with severe stenosis that just did reach significance (Fisher exact test, P = .0498).

One potential feature associated with symptoms in patients with severe carotid stenosis is the presence of MRA-determined ulceration. The same histologic review study cited above by Golledge et al[6] also reported that surface ulceration and plaque rupture were associated with ipsilateral carotid symptoms in patients with stenosis severe enough to warrant CEA. In our study, ulceration correlated with recent symptoms in patients with severe stenosis. This finding is also in agreement with previous results from the NASCET trial, which identified an increased risk of stroke in patients with the 70%–99% stenosis when an ulcer was present compared with the same degree of stenosis without an ulcer.[33] The risk of ipsilateral stroke at 24 months for medically treated patients with ulcerated plaques increased incrementally from 26.3% to 73.2% as the degree of stenosis increased from 75% to 95%. For patients with no ulcer, the risk of stroke remained constant at 21.3% for all degrees of stenosis.[33] Our results are also in agreement with an observational subgroup analysis of the NASCET data that demonstrated a smaller risk of stroke in medically treated patients with near occlusion of the internal carotid artery who had a low incidence of ulceration compared with patients with 90%–94% stenosis who had a higher incidence of ulceration.[34]

There are 2 limitations to this study. First, this cross-sectional study is a retrospective comparison of in vivo 3T MR carotid plaque imaging characteristics of patients with recent ipsilateral thromboembolic symptoms. A larger prospective study is needed to evaluate whether carotid plaque characteristics that are associated with subsequent symptoms vary be-

tween mild/moderate and severe stenoses. Second, the number of symptomatic patients was too small to support extrapolation of these preliminary findings to larger patient populations or support a multivariate analysis. However, the multiple carotid plaque characteristics that were individually observed to be significantly associated with recent symptoms in patients with mild/moderate carotid stenosis suggest that future prospective studies correlating vessel wall MR imaging with the development of thromboembolic events should include the ability to identify the presence and size of the lipid-rich necrotic core, the presence of a thin or ruptured fibrous cap, and the presence and size of intraplaque hemorrhage.

Conclusions

This in vivo 3T MR imaging of patients demonstrates several plaque components that are correlated with recent ipsilateral carotid thromboembolic symptoms. These preliminary results also suggest that the associations between plaque characteristics and symptoms may vary by degree of stenosis. If confirmed in larger studies, carotid MR imaging may distinguish stable from unstable lesions, particularly in individuals with mild/moderate carotid stenosis in whom the role of surgical intervention is currently unclear.

Acknowledgments

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An Optimized 3D Spoiled Gradient Recalled Echo Pulse Sequence for Hemorrhage Assessment Using Inversion Recovery and Multiple Echoes (3D SHINE) for Carotid Plaque Imaging

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Intraplaque hemorrhage into the carotid atherosclerotic plaque has been shown to create instability and progression. We have developed an optimized 3D Spoiled Gradient recalled echo pulse sequence for Hemorrhage assessment using INversion recovery and multiple Echoes (3D SHINE) for carotid plaque imaging. The sequence was developed by incorporating multiecho acquisition to its clinically validated optimized single-echo counterpart 3D inversion recovery prepared fast spoiled gradient recalled sequence. With similar scan time (4 min), 3D spoiled gradient recalled echo pulse sequence for hemorrhage assessment using inversion recovery and multiple echoes maintained comparable high-resolution volumetric coverage, black-blood effect, contrast, signal-to-noise and contrast-to-noise ratios, and similar sensitivity and specificity in detecting whether intraplaque hemorrhage was present on an artery. The multiple echoes acquired with 3D SHINE allowed the estimation of intraplaque hemorrhage T_2^* and then the subsequent characterization of intraplaque hemorrhage (T_2^* for type I < 14 msec, and for type II > 14 msec). The type I intraplaque hemorrhage size estimated by 3D SHINE was significantly and positively correlated with the size estimated manually by an expert reviewer using the histology-validated multicontrast MRI technique ($r = 0.836 \pm 0.080$, $p < 0.001$). With only one fast sequence, 3D SHINE can detect and characterize intraplaque hemorrhage that has previously required a multicontrast approach using a combination of black-blood T_1-weighted, black-blood T_2-weighted, and time-of-flight imaging techniques. Magn Reson Med 64:1341–1351, 2010. ©2010 Wiley-Liss, Inc.

Key words: carotid plaque imaging; hemorrhage; MPRAGE; IR FSPGR

In an effort to find clinically relevant markers of plaque vulnerability that increases the risk of stroke, a number of noninvasive imaging strategies have been investigated. MRI shows to be promising for imaging the carotid artery lumen and at the same time provides detailed artery wall information (1). Recent pathophysiological studies have centered on the identification and understanding of "vulnerable plaque" that poses an increased risk for thromboembolic events causing ischemia (2). Based on the previous histopathological studies of carotid endarterectomy specimens, intraplaque hemorrhage (IPH) into the carotid atherosclerotic plaque has been shown to create instability and progression as well as an association with current symptoms (3,4). An MRI technique that can successfully detect and characterize IPH is important. Such noninvasive evaluation of the in vivo appearance of carotid plaque would permit evaluation of the prospective importance of IPH to predict new ipsilateral carotid thromboembolic disease.

Previous experience at 1.5-T MR demonstrates that T_1-weighted black-blood images and 3D time-of-flight (TOF) MR angiogram (MRA) can detect IPH with good sensitivity and moderate specificity (5). The in vivo appearance of carotid IPH could be further characterized as type I or type II based on their appearance on T_2-weighted images (5,6). The classification of hemorrhage type was shown to correlate with a history of recent ipsilateral carotid thromboembolic disease (7,8). Specifically, type I hemorrhage that was characterized by decreased signal intensity compared with muscle on T_2-weighted images due to relatively short T_2 values was associated with recent symptoms. Moody et al. developed a 3D T_1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence to detect the hemorrhagic carotid plaque at 1.5 T with good sensitivity and specificity (9).

We sought to extend in vivo carotid plaque imaging from 1.5 to 3 T because recent work demonstrated the improved signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and image quality at 3 T compared to 1.5 T for multicontrast carotid plaque imaging (10). As a part of this project to begin 3-T carotid plaque imaging, we developed a 3D inversion recovery prepared fast spoiled gradient recalled sequence (3D IR FSPGR) optimized for the detection of carotid IPH. The 3D IR FSPGR sequence was similar to the MPRAGE sequence described by Moody et al. for 1.5-T MR plaque hemorrhage imaging but optimized for 3 T. With the 3D IR FSPGR sequence we achieved a good level of success in detecting hemorrhage (11), also with improved time efficiency over the product sequence to allow high-resolution imaging of both carotid bifurcations under 5 min. Because of the short T_1 values of IPH and the T_1-weighted nature of the sequence, the 3D IR FSPGR or its equivalent counterpart 3D MPRAGE has demonstrated with improved hemorrhage CNR versus surrounding regions at 3 T comparing to 2D T_1-weighted fast

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spin echo (FSE) and 3D TOF sequences, which are typically used in hemorrhage detection, and thus have led to improved sensitivity and specificity (12). Therefore, an optimized 3D IR FSPGR sequence can potentially be used to replace the more traditional precontrast 2D T_1-weighted FSE technique in the detection of IPH and can offer additional benefits of high-resolution volumetric visualization with 3D rendering.

With the success of the optimized 3D IR FSPGR sequence in carotid plaque detection, we further developed a sequence called 3D Spoiled Gradient recalled echo pulse sequence for Hemorrhage assessment using INversion recovery and multiple Echoes (3D SHINE) by incorporating multiple gradient echoes. This sequence includes a short echo time similar to the original 3D IR FSPGR sequence for optimal depiction of hemorrhage as well as longer echo times, which could be used to estimate the T_2^* of the hemorrhage. We hypothesized that 3D SHINE would allow us to identify IPH and further characterize the hemorrhage into types I and II based on the T_2^* value estimated from the multiple echoes.

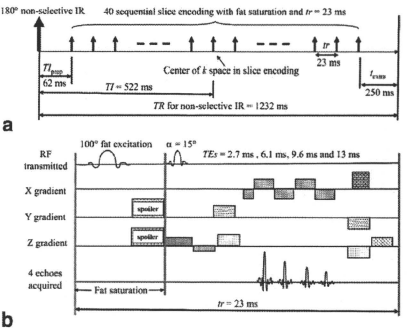

FIG. 1. The optimized 3D SHINE sequence is shown with parameters indicated, including (a) the overall timing diagram and (b) the detailed information at each slice phase encoding step.

MATERIALS AND METHODS

Pulse Sequence Development and Optimization

The 3D SHINE sequence (Fig. 1) was further developed by modifying the optimized single-echo 3D IR FSPGR that we developed on a 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) (11). Our goal was to provide the additional feature of T_2^* mapping of IPH without extra scan time while maintaining the same coverage, the ability in IPH detection, high-resolution volumetric acquisition, and similar level of black-blood effect. As discussed in Ref. 11, the single-echo sequence includes the following important components: a 180° nonselective Silver-Hoult adiabatic inversion recovery (IR) preparation radiofrequency (RF) pulse, an inclusion of an off-resonance fat signal saturation pulse on every encoding step and a sequential phase encoding strategy in the slice encoding direction. These components were maintained in the 3D SHINE technique. The nonselective Silver-Hoult adiabatic inversion RF pulse provides a uniform inversion of spins even in the presence of a nonuniform B_1 field and inverts spins within the entire sensitive volume of the transmit coil (13). Several fat suppression techniques were considered in this study. Spectral inversion fat nulling (a.k.a. SPECIAL, SPIR, SPAIR) technique where IR pulse is applied intermittently every few slice phase encoding steps is more time efficient than the off-resonance fat saturation technique. However, centric phase encoding is often employed to achieve optimal fat suppression, but which is in conflict with the black-blood IR pulse in combination with the sequential phase encoding strategy implemented in this work. A spatial–spectral pulse for selectively water excitation is another choice of fat signal reduction. However, spatial–spectral pulses are relatively long and thus limit the ability to shorten the echo time for the first echo. A short echo time is advantageous in IPH detection, especially in the presence of field inhomogeneity. Therefore, off-resonance fat saturation was chosen. By properly selecting the time of inversion (TI), the time of repetition (TR) with respect to the nonselective IR pulse, the data acquisition flip angle, the time of repetition in data acquisition, and the time between the RF excitation of the last slice phase encoding step and the application of the nonselective IR pulse (t_{extra}), based on the T_1 of the blood, the signal from the blood in the lumen can be minimized to reach the maximum contrast between the carotid vessel lumen and vessel wall. As TI is equal to the time from the middle of the non-selective IR pulse to acquisition of the center of k-space in the slice direction, by properly selecting the number of slice phase encoding steps, the "dead" time TI_{prep} (the time from the middle of the nonselective IR pulse to the middle of the RF pulse for the first encoding step) can be minimized.

We started the pulse sequence optimization with computer simulations using the same procedure as in our single-echo 3D IR FSPGR sequence (11) according to the basic design of the pulse sequence (Fig. 1a). In this simulation, five hypothetical tissue types with T_1 values of 500, 1000, 1500, 2000, and 2500 msec were compared. Demonstrated in Fig. 2 is the result with the parameters of TR = 23 msec, TI_{prep} = 62 msec, t_{extra} = 250 msec, flip angle = 15°, and number of slice encoding steps = 40 as indicated in Fig. 1. Stanisz et al. reported T_1 values of 1932 ± 85 msec for blood, 1412 ± 13 msec for skeletal muscle, and 1471 ± 31 msec for heart at 3 T (14). Noeske et al. reported T_1 values of 1550 ± 85 msec for blood and 1115 ± 10 msec for myocardium at 3 T (15). It is reasonable to estimate that the T_1 of blood is within the range of 1500–2000 msec, and the T_1 of vessel wall is within the range of 1000–1500 msec at 3 T. Based on these numbers, the proposed parameters should provide reasonable levels of black-blood effect. The other even

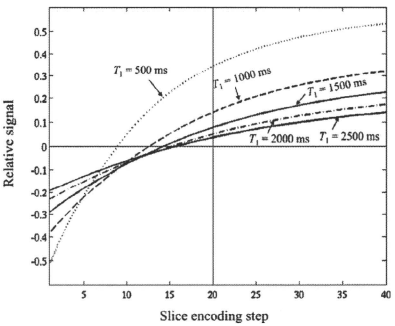

FIG. 2. Computer simulation with the scan timing parameters in Fig. 1.

more important consideration is that this technique needs to be highly sensitive to hemorrhage detection. T_1-shortening is one characteristic of hemorrhage both in the intracellular and extracellular methemoglobin state (16,17). A hypothetical T_1 of 500 msec has been used in this simulation. The simulation also shows that a range of scanning parameters can be used to provide imaging result that is sensitive to detect hemorrhage and to visualize the vessel wall. The simulations provided a guide for our protocol optimization and evaluation, but they did not provide the final parameters. Because of the relative uncertainty of the tissue T_1 values at the carotid region, the more optimized scanning parameters were achieved via studies on healthy volunteers and then confirmed on patients, as demonstrated in the Result section.

With the inclusion of multiple echo acquisitions in 3D SHINE, T_2^* values can be calculated. The T_2^* was calculated with least-square estimation based on the semi-log linear regression (18) of the voxel signal values from all echoes and their corresponding times of echo according to the following linear relationship:

$$\frac{1}{T_2^*} = -\frac{\ln S_n - \ln S_m}{\mathrm{TE}_n - \mathrm{TE}_m} \quad [1]$$

where S_n and S_m are voxel signal intensity values at echo time values of TE_n and TE_m.

The weighted-averaged images of m echoes can be obtained by

$$S_{\mathrm{ave}} = \sum_{i=1}^{m} \left(S_i \times \left(\frac{S_i}{\sum_{j=1}^{m} S_j} \right) \right) \quad [2]$$

where S_i is the signal at TE_i.

The weighted averaging is expected to increase the SNR when compared with individual echo as well as emphasizing the signal at the first echo so that the ability of hemorrhage detection is maintained.

Subjects

Three healthy subjects (Ages 31, 33, and 41, one female) participated in this study for the purpose of protocol optimization. Twenty-two patients referred by vascular surgeons or stroke neurologists with carotid stenosis between 50 and 99% measured by duplex ultrasound participated in this study. Of these patients, there were 10 patients (12 arteries) with probable carotid hemorrhagic plaque based on the single echo 3D IR FSPGR technique. We reviewed data of all the patients. However, for the detailed evaluation and demonstration of the 3D SHINE sequence, only patients with probable carotid IPH were used for data analysis (mean age ± standard deviation (SD) = 70.4 ± 8.7 years; mean weight ± SD = 87 ± 15 kg). All subjects signed consent forms approved by the Michigan State University institutional review board.

Data Acquisition

The data were collected on a 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) using a dedicated four-channel carotid bilateral-phased array coils (Pathway MRI, Seattle, WA). Single-echo 3D IR FSPGR image data were collected along with 3D SHINE image data for comparison. The 3D SHINE protocol was optimized by varying the t_{extra} with a minimal $\mathrm{TI}_{\mathrm{prep}}$, a sufficient coverage around bifurcation to include the range of carotid plaque typically found (11), a receiver bandwidth (rBW) without much sacrifice of SNR to allow the visualization of the bifurcation. The finalized 3D SHINE and the single-echo 3D IR FSPGR parameters used in patient data collection are listed on Table 1. More traditional quadruple inversion-recovery T_1-weighted (19), multisection double inversion-recovery T_2-weighted (20) and 3D TOF images were also collected to detect the hemorrhagic regions, and to allow independent characterization of the hemorrhage type. These procedures of hemorrhage detection and characterization have previously been validated with carotid endarterectomy specimens (5,7). The pulse sequence parameters are listed on Table 2. All data were acquired in the axial plane for image comparison. The frequency encoding was set at right–left direction to minimize the motion artifacts from swallowing, and to eliminate the potential flow artifacts introduced from the carotid artery at the other side of the neck.

Phantom Verification

The accuracy of the our finalized 3D SHINE protocol was evaluated with a phantom consisting of superparamagnetic magnetite (Fe*REX*™) (BioPhysics Assay Laboratory, Inc., Worcester, MA) water solution with the concentrations of 0.003 to 0.035 mg Fe/ml against an eight-echo 3D FSPGR sequence without RF inversion with the following parameters: TEs = 2.6, 6.1, 9.5, 13.0, 16.4, 19.9, 23.3, and 26.8 msec, time of repetition = 30.6 msec, flip angle = 15°, field of view = 16 cm, number of slices = 40, slice thickness = 1 mm, matrix size = 256 × 256, and rBW = ± 41.7 kHz. Then the data was acquired again with another eight-echo 3D FSPGR sequence by modifying the rBW to ± 62.5 kHz, echo times to 2.2, 4.6, 7, 9.4, 11.8, 14.3, 16.7, and 19.1

Table 1
Imaging Parameters for IR FSPGR and 3D SHINE

Parameter	Single-echo IR FSPGR	Four-echo 3D SHINE
Acquisition plane	Axial	Axial
1st TE (msec)	3.2	2.7
2nd TE (msec)	None	6.1
3rd TE (msec)	None	9.6
4th TE (msec)	None	13
Flip angle	15°	15°
Receiver bandwidth (kHz)	±31.25	±41.7
tr (msec)	13.7	23
TI_{prep} (msec)	45	62
Effective TI (msec)	318	522
t_{extra} (extra rest time) (msec)	0	250
TR (msec)	591	1232
Off-resonance fat saturation	Apply on every tr	Apply on every tr
Field of view	16 × 16 cm^2	16 × 16 cm^2
Matrix size	256 × 192	256 × 192
Number of slice encoding steps	40	40
Slice thickness (mm)	1	1
Slab size (mm)	36	36
Number of excitation	2	1
Scan time	3 min 50 sec	3 min 54 sec

tr, time of repetition for each phase encoding step; TI_{prep}, the time from the middle of the nonselective IR pulse to the middle of the RF pulse for the first encoding step; TR, the time of repetition with respect to the nonselective inversion; t_{extra} (extra rest time), the extra rest time after the sequence of slice phase encoding steps.

msec, and time of repetition to 22.4 msec. If the T_2^* is at the middle of the echo time range, the T_2^* estimation is expected to be most accurate. At higher T_2^* values, the first 3D FSPGR protocol is expected to provide more accurate estimation. At lower T_2^* values, the second 3D FSPGR protocol is expected to provide more accurate estimation. Data were acquired twice with each sequence. Regions of interest (ROIs) were drawn at multiple slice locations at the central slices from both acquisitions. The T_2^* values were calculated based on Eq. 1.

Patient Data Analysis

The presence and location of hemorrhage within the carotid plaque were identified by reviewing bright-blood T_1-weighted images, specifically TOF, black-blood T_1-weighted images, black-blood T_2-weighted images (5), and 3D IR FSPGR images (11,12) according to previously described techniques verified by histology. Two radiologists who were well-trained in carotid plaque detection and characterization and who were blinded to the results of the 3D SHINE reviewed all the 22 patients and reached consensus reading in all cases. Besides identifying the hemorrhage they further characterized hemorrhagic ROIs as types I and II based on T_2-weighted images based on the criteria that type I hemorrhage tends to be hypointense and type II hemorrhage tends to be isointense or hyperintense (5,7). These ROIs of types I and II were drawn at the similar anatomical locations on both the 3D IR FSPGR and 3D SHINE images. Voxel T_2^* values from these drawn ROIs were estimated from 3D SHINE images. The T_2^* values at the voxels of the types I and II ROIs from all subjects were pooled together to calculate their distributions and to test whether the T_2^* values for types I and II were statistically different from each other. To test the reliability of the 3D SHINE technique in hemorrhage characterization, a cut-off T_2^* value yielding the maximum overall accuracy was indentified from the T_2^* distributions. With this cut-off T_2^* value, the areas of type I hemorrhage were extracted from overall hemorrhagic regions on a slice-by-slice basis. Pearson's correlation analysis (standard error estimated by bootstrapping to accommodate the use of multiple slices per artery) was applied to compare type I hemorrhage areas identified based on 3D SHINE T_2^* values and those identified based on expert drawing according to T_2-weighted images. To evaluate the equivalency on hemorrhage

Table 2
Parameters for Carotid Imaging Sequences

Parameter	T_1-weighted	T_2-weighted	Time-of-flight MRA
Acquisition mode	2D	2D	3D
Acquisition sequence	Fast spin echo	Fast spin echo	Spoiled gradient and flow compensation
Blood suppression technique	Quadruple Inversion Recovery	Multisection double inversion recovery	Saturation-veins
TE (msec)	10.8	52	3.9
TR (msec)	800	4800	23
TI (msec)	520	290	N/A
Echo train length	10	12	N/A
Excitation flip angle (degrees)	90	90	20
Receiver bandwidth (±kHz)	20.83	31.25	15.63
No. of repetition	1	1	1
Field of view	160 × 160 mm^2	160 × 160 mm^2	160 × 160 mm^2
Matrix size	256 × 256	256 × 256	288 × 256
No. of slices	18	18	48
Slice thickness (mm)	2	2	1
Coverage (mm)	36	36	44
Imaging time (min:sec)	6:47	3:41	4:46

detection in sensitivity and specificity, the two radiologists also recorded and reached consensus on the presence/absence of hemorrhage based on the images of 3D IR FSPGR and then independently on the images of the first echo of 3D SHINE, without prior knowledge of whether these two sets of images belonged to a same subject or which subject they belonged to.

Image quality of the 3D SHINE data was assessed by comparing the 3D IR FSPGR images based on ROI analysis. At all the arteries with probable hemorrhages, ROIs at multiple slice locations of the 3D IR FSPGR images were drawn at the hemorrhagic region, the vessel wall outside the hemorrhagic region, the vessel lumen, the adjacent scalenus muscle, and adjacent artifact-free air region. Then the ROIs with similar sizes and locations were drawn at the first-echo of 3D SHINE. The contrast, SNR, and CNR were calculated based on an established procedure (10,21). Specifically, noise measurements were estimated from the ROI at the air region and this ROI was regarded as the noise ROI. SNR was calculated as $\text{SNR} = 0.695 \times (S_m^2 - S_n^2)^{1/2}/\sigma$, where S_m is the signal magnitude for the tissue of interest, S_n is the signal magnitude in a noise ROI, σ is the measured standard deviation of the noise, and 0.695 is the correction factor for a four-array coil design. CNR was defined as the difference between SNRs of two tissue types. The contrast of IPH versus another tissue region was calculated as $[(S_{IPH} - S_{other})/S_{other}] \times 100\%$, where S_{IPH} = signal at IPH and S_{other} = signal at other tissue. Paired t tests and correlation analyses were performed between the first-echo of 3D SHINE, the weighted average of 3D SHINE and the 3D IR FSPGR.

RESULTS

Protocol Optimization

About 36 mm (40 1-mm slices with four discarded) of coverage was needed to cover the carotid bifurcation (11). We started with ±31.25 kHz rBW (corresponding to a time of repetition of 27 msec), but a long extra recovery time (t_{extra}) would be needed to achieve a good level of black-blood effect. With the increase of rBW, we qualitatively inspected the decrease of SNRs of the first echo and weighted-average images to make sure that the image quality was qualitatively sufficient in visualizing the bifurcation. We finalized the receiver bandwidth to ±41.7 kHz (corresponding to a time of repetition of 23 msec), and then collected 3D SHINE images with various t_{extra} to quantify the black-blood effect on the three healthy volunteers. The effect of blood suppression was assessed based on the signal ratio between vessel lumen and vessel wall. With spline interpolation, an optimized t_{extra} was found at ~250 msec to maximize the lumen-wall contrast. With t_{extra} = 250 msec, the lumen/wall signal ratio at the first echo of 3D SHINE was estimated to be of 37.3%, which is lower than the 45.4 ± 9.2% from the 3D IR FSPGR protocol we have applied in our previous research (11,12).

Phantom Verification

Table 3 shows the T_2^* comparison between the eight-echo 3D FSPGR sequences (used as the standard) and the four-echo 3D SHINE sequence. T_2^* measurements from 3D SHINE varied less than 1 msec from the eight-echo 3D FSPGR sequences for T_2^* below 25 msec and less than 2 msec for T_2^* between 25 and 50 msec. However, the variation increased rapidly at high T_2^* values (>50 msec) due to the relatively lower range of echo time from 2.7 to 13 msec. However, the variation of the T_2^* measurement at high T_2^* values would not lead to misclassification of the hemorrhage type because the T_2^* threshold discriminating types I and II was found at 14 msec as discussed later.

Hemorrhage Detection and Characterization

The 3D SHINE protocol listed in the "Data Acquisition" section was the result of the optimization and was applied to patient imaging. Of the 22 patients imaged, 10 patients (12 carotid arteries) demonstrated regions of IPH based on histology-validated multicontrast MR imaging techniques, including bright-blood TOF, black-blood T_1-weighted imaging, black-blood T_2-weighted imaging, and black-blood 3D IR FSPGR. Table 4 shows the SNRs at the hemorrhagic region, the vessel wall, and the adjacent scalenus muscle region, the contrasts and CNRs of the hemorrhagic region versus lumen, wall, and muscle, as well as vessel wall versus lumen, for both 3D SHINE and its single-echo counterpart 3D IR FSPGR. For 3D SHINE, the weighted image averaging significantly improves the SNR at the hemorrhagic region, the vessel wall, and surrounding muscle. CNR of hemorrhagic region versus lumen, wall, and muscle, and the CNR of wall versus lumen were also improved with the weighted averaging strategy. Although the first echo of 3D SHINE has lower SNR and CNR when compared with 3D IR FSPGR, the weighted average of the four echoes became comparable with 3D IR FSPGR. For the first echo of 3D SHINE, the contrast of hemorrhage versus surrounding regions were comparable with 3D IR FSPGR, but it was significantly higher than the weighted average of the 3D SHINE images.

Based on the 22 patients we studied, the 3D IR FSPGR and 3D SHINE images demonstrated the same results regarding whether IPH existed on an artery. Specifically, the same 12 arteries showed probable IPH with these two imaging techniques when the reviewers evaluated both sequences in a blinded fashion. Thus, these two techniques had the same sensitivity and specificity in hemorrhage detection on an artery basis. The two sequences yielded similar IPH locations, sizes, and shapes as demonstrated by the case in Fig. 3. The two sequences show the similar nonhemorrhagic region of the plaque as well. Because of the high-resolution nature of the 3D imaging, both techniques provide the flexibility of reformatting to locate and view the IPH in various orientations.

Table 5 lists the T_2^* distribution of the types I and II regions estimated by 3D SHINE for the 10 patients participating in this study on artery basis. When reviewing all ROIs, the T_2^* values of type II hemorrhage in two (Arteries 4 and 11 in Table 5) of the 12 arteries appeared clearly as outliers. Moderate to large calcifications (10 to 40 mm^2 in area) were seen in both cases and were immediately adjacent to the type II hemorrhage ROIs.

Table 3
Phantom Comparison of T^*_2 value with Different Sequences

Fe*REX*™ concentration (mg Fe/ml)	T^*_2 (msec) from 3D SHINE, four echoes, ±41.67 kHz rBW	T^*_2 (msec) from FSPGR, eight echoes, ±41.67 kHz rBW	T^*_2 (msec) from FSPGR, eight echoes, ±62.5 kHz rBW
0.003	69.6 ± 43.8	66.3 ± 1.8	67.3 ± 3.5
0.004	47.4 ± 9.4	48.7 ± 0.7	49.1 ± 1.6
0.005	36.6 ± 4.3	35.8 ± 0.6	35.8 ± 1.0
0.006	33.5 ± 2.8	31.7 ± 0.5	31.8 ± 0.6
0.007	28.6 ± 2.8	28.9 ± 0.4	29.1 ± 0.4
0.008	23.8 ± 2.0	23.2 ± 0.3	23.4 ± 0.6
0.009	19.7 ± 1.5	20.0 ± 0.3	20.1 ± 0.4
0.01	14.9 ± 0.9	14.4 ± 0.2	14.4 ± 0.2
0.0125	13.7 ± 0.4	13.5 ± 0.2	13.6 ± 0.1
0.015	9.0 ± 0.4	9.4 ± 0.2	9.0 ± 0.1
0.0175	8.8 ± 0.3	8.9 ± 0.2	8.7 ± 0.1
0.02	7.4 ± 0.2	8.0 ± 0.1	8.1 ± 0.2
0.03	5.3 ± 0.2	8.2 ± 0.1	5.9 ± 0.1
0.035	4.8 ± 0.1	8.4 ± 0.1	5.9 ± 0.1

rBW, receiver bandwidth.

Calcification can lead to magnetic field inhomogeneity and thus result in an underestimation of T^*_2. While there were many other examples of calcifications in the other 10 hemorrhagic carotid plaques, no additional cases of calcifications with size = 10 mm^2 were noted immediately adjacent to any other type I or II ROIs. Therefore, these two arteries with hemorrhage ROIs adjacent to moderate or large calcifications were excluded from further analysis. On a voxel-by-voxel basis, T^*_2 were 11.5 ± 3.7 msec for type I hemorrhage and 19.7 ± 9.1 msec for type II hemorrhage (statistically different at $p < 0.001$) (Fig. 4). A T^*_2 value of 14 msec (sensitivity 81.7% and specificity 70.8%) was found to discriminate most hemorrhage types. For 60 slices compared, the areas of type I hemorrhage calculated based on 3D SHINE T^*_2 values ($T^*_2 < 14$ msec) was significantly correlated with the areas of type I identified based on expert drawing according to T_2-weighted images ($r = 0.836 \pm 0.080$, $p < 0.001$) (Fig. 5).

The application of 3D SHINE is demonstrated with a carotid plaque containing both types I and II IPH, characterized by the traditional 3D TOF, the single-echo 3D IR FSPGR, T_1 and T_2-weighted FSE images. These results were found to be closely corresponding with the T^*_2 maps generated from 3D SHINE (Fig. 6). At the hemorrhage, if the T_2-weighted FSE image signal is hypointense to muscle, suggesting a type I hemorrhage, the T^*_2 value tends to be 14 msec or lower (Fig. 6b). On the other hand, if the T_2-weighted FSE image signal is iso-intense or hyperintense to muscle, suggesting a type II hemorrhage, the T^*_2 value tends to be higher than 14 msec (Fig. 6c). The 3D dataset can be reformatted to visualize the plaque from any orientation (Fig. 6a). Figure 7 shows the four echoes from 3D SHINE at TEs of 2.7, 6.1, 9.6, and 13 msec. The SNR and CNR appear to be improved through weighted averaging of the four echoes, and become comparable to those of the single-echo 3D IR FSPGR image.

DISCUSSION

The role of IPH as a potential marker for symptomatic carotid plaque had been suggested as early as 1982 by Lusby et al. (4). Their retrospective study of carotid endarterectomy specimens identified a significantly higher association of IPH in symptomatic patients when compared to asymptomatic patients. With the advancement of *in vivo* MR plaque imaging, it is now possible to prospectively evaluate IPH. One such study involved a total of 154 patients who were followed for a mean of three years after the initial in vivo carotid plaque study. In that study, IPH was shown to be statistically significantly associated with the development of new ipsilateral carotid stroke or transient ischemic attack in a prospective evaluation of asymptomatic patients with moderate carotid stenosis (22). Multiple studies using inversion-recovery T_1-weighted MPRAGE have demonstrated that recent or recurrent symptoms were associated with IPH in patients with symptomatic moderate and high-grade carotid stenosis (23–25). Patients with IPH demonstrated a more rapid increase in the size of the carotid plaques compared to those patients without hemorrhage when followed by longitudinal MRI studies (26). The potential significance of type I hemorrhage to be associated with recent symptoms was highlighted by Saam et al. (7). In that study, no significant difference was found between symptomatic and asymptomatic plaques when considering the prevalence of all types of hemorrhage. However, type I hemorrhage was found significantly more often in patients with symptomatic plaques. Conversely, the prevalence of type II hemorrhage was comparable in patients with symptomatic and those with asymptomatic plaques. This suggests the importance of identifying type I hemorrhage. This importance was also demonstrated more recently by Sadat et al. (8).

We have published a 3D IR FSPGR pulse sequence similar to the original 3D MPRAGE sequence proposed by Moody et al., but optimized for 3 T (11). When our optimized 3D IR FSPGR sequence is combined with dedicated carotid coil imaging at 3 T, it is possible to achieve high spatial resolution (~0.7 mm in-plane resolution) with sufficient coverage to visualize both carotid bifurcations in ~4 min. This high-resolution dataset supports multiplanar reformation to visualize the anatomical

Table 4
Image Quality Comparison Among 3D IR FSPGR, Preprocessed and Postprocessed 3D SHINE Images

	3D IR FSPGR	3D SHINE 1st echo	3D *SHINE* weighted average of four echoes	Paired *t* test of 3D SHINE weighted average > 1st echo	Paired *t* test of 3D SHINE weighted average < 1st echo	Correlation between 3D IR FSPGR and 1st Echo of 3D SHINE	Correlation between 3D IR FSPGR and weighted average of 3D SHINE
Hemo SNR	43.4 ± 6.5	32.0 ± 4.1	43.7 ± 5.0	$P < 0.001$			0.897 ($P < 0.001$)
Wall SNR	14.3 ± 2.1	10.9 ± 1.3	14.8 ± 1.6	$P < 0.001$			0.860 ($P < 0.001$)
Muscle SNR	11.5 ± 6.0	8.5 ± 3.8	12.7 ± 5.3	$P < 0.001$			0.816 ($P = 0.001$)
(Hemo-lumen)/lumen × 100%	625.6 ± 332.7	644.9 ± 304.2	464.4 ± 239.3		$P < 0.001$	0.969 ($P < 0.001$)	
(Hemo-wall)/wall × 100%	208.1 ± 101.6	201.4 ± 111.4	191.0 ± 103.3		$P = 0.0495$	0.929 ($P < 0.001$)	
(Hemo-muscle)/muscle × 100%	269.5 ± 91.5	264.6 ± 92.3	223.5 ± 79.6		$P < 0.001$	0.910 ($P < 0.001$)	
CNR: Hemo vs. lumen	37.5 ± 18.9	28.5 ± 13.4	37.4 ± 16.6	$P < 0.001$			0.889 ($P < 0.001$)
CNR: Hemo vs. wall	29.1 ± 4.9	21.1 ± 3.3	28.8 ± 4.2	$P < 0.001$			0.904 ($P < 0.001$)
CNR: Hemo vs. muscle	31.9 ± 5.0	23.5 ± 3.1	30.9 ± 3.8	$P < 0.001$			0.91 ($P < 0.001$)
CNR: Wall vs. lumen	8.4 ± 3.4	7.3 ± 3.4	8.6 ± 4.0	$P = 0.08$			0.641 ($P < 0.025$)

Hemo, hemorrhage region.

FIG. 3. The 3D IR FSPGR images (**a**) and the 3D SHINE weighted-average images (**b**) yield the similar locations, sizes, and shapes of the intraplaque hemorrhage (IPH) and the nonhemorrhagic region of the plaque (NHP). Because of the high-resolution nature of 3D acquisition, both techniques provide the flexibility of reformatting to locate and view the IPH in various orientations. The reformatted axial (ax), saggital (sag), and coronal (cor) views are shown.

relationship of hemorrhage with the carotid stenosis. The optimized 3D IR FSPGR highlights IPH by providing higher contrast and CNR compared with the more traditional 2D T_1-weighted FSE and 3D TOF MRA (11). The optimized 3D IR FSPGR sequence demonstrated higher

Table 5
Summary of Intraplaque Hemorrhage T^*_2 value in Patients

Patient #	Artery #	T^*_2 for type I (msec)	T^*_2 for type II (msec)
1	1	11.0 ± 3.4	19.1 ± 5.9
2	2	11.5 ± 2.4	18.5 ± 9.2
3	3		23.9 ± 7.8
4	4		6.9 ± 2.8[a]
5	5	11.2 ± 5.4	16.3 ± 11.5
5	6	8.8 ± 1.6	10.6 ± 6.1
6	7	14.4 ± 7.0	17.6 ± 6.2
7	8		23.8 ± 9.6
8	9		15.5 ± 8.1
9	10	11.1 ± 5.1	14.8 ± 4.5
9	11		8.4 ± 2.1[a]
10	12	12.8 ± 2.4	

[a]Heavy calcification was found adjacent to the hemorrhagic region.

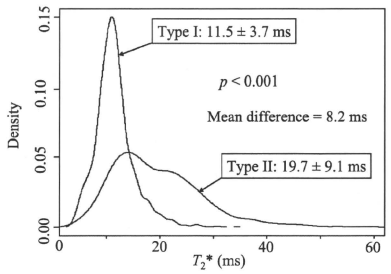

FIG. 4. Voxel-basis type I and type II T^*_2 distribution from hemorrhagic ROIs from 10 arteries in 10 patients with probable intraplaque hemorrhage.

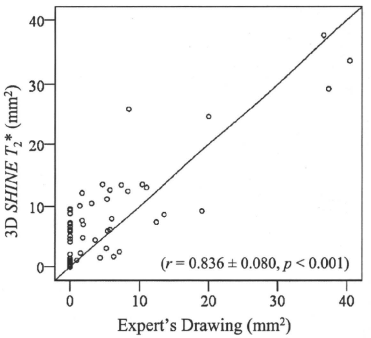

FIG. 5. On a slice-by-slice basis with a total of 60 slices, the areas of type I hemorrhage calculated based on 3D SHINE T^*_2 values ($T^*_2 < 14$ msec) were significantly correlated with the areas of type I estimated manually by an expert reviewer based on the signal intensity of the T_2-weighted images.

diagnostic capability for the detection and quantification of IPH compared with 2D T_1-weighted FSE and 3D TOF MRA based on histological evaluation of the carotid endarterectomy specimen (12). The 3D SHINE sequence presented in this work has been able to maintain the contrast, CNR of the 3D IR FSPGR single-echo counterpart within approximately the same scan time. Judging on whether IPH is present or absent on an artery, the sensitivity and specificity for the detection of IPH were the same comparing 3D SHINE with the previously

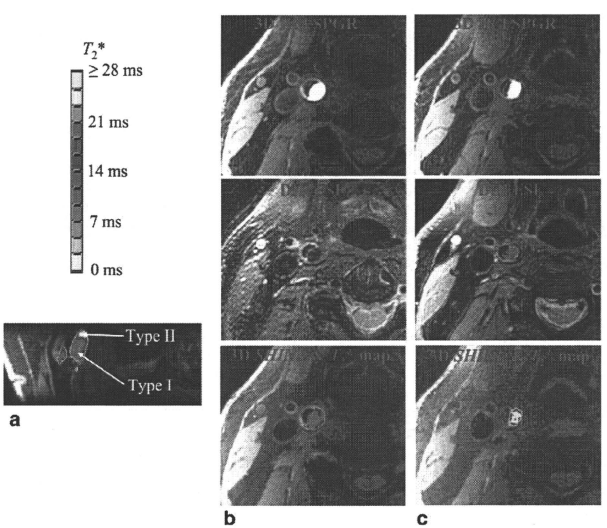

FIG. 6. An intraplaque hemorrhage with both type I and type II hemorrhagic regions is shown. The high-contrast hemorrhagic region is clearly depicted by 3D IR FSPGR or 3D SHINE. The T^*_2 value is color coded with the bar at the upper-left corner. The type I hemorrhage tends to have a T^*_2 value below 14 msec, and type II hemorrhage tends to have a T^*_2 value above 14 msec. The two hemorrhage types are shown clearly in the reformatted coronal view (**a**). Consistent with the results from 3D SHINE, (**b**) type I hemorrhage (shown are axial slices at predominately type I region) appears to be hypointense in DIR FSE, and (**c**) type II hemorrhage (shown are axial slices at predominately type II region) appears to be iso-intense in DIR FSE.

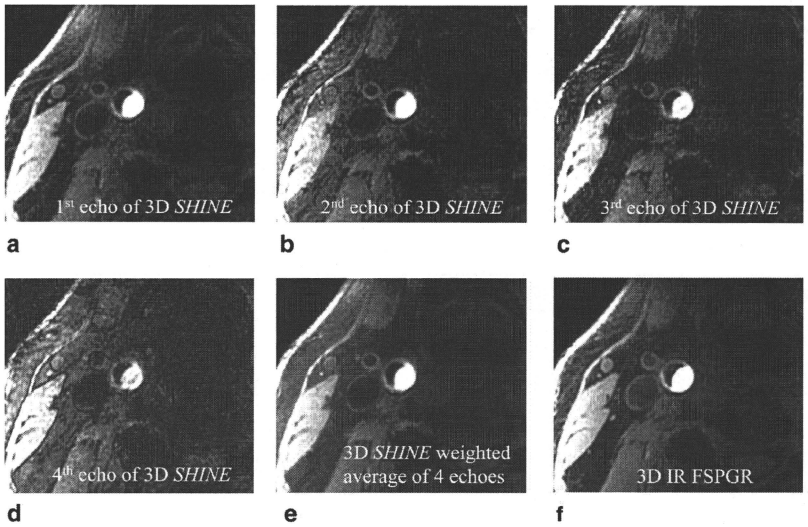

FIG. 7. The four images at the echoes with TEs of (**a**) 2.7 msec, (**b**) 6.1 msec, (**c**) 9.6 msec, and (**d**) 13 msec from 3D SHINE are shown. **e**: The SNR is improved with the weighted average of the four echoes and appears comparable to the SNR of the single-echo 3D IR FSPGR image (**f**).

histology-validated 3D IR FSPGR sequence. Their equivalence is also demonstrated by the case study shown in Fig. 3. The 3D SHINE technique will be able to replace the 3D IR FSPGR single-echo technique. In addition, the 3D SHINE sequence provides the valuable addition of T_2^* mapping, which in-turn can characterize the hemorrhage type with approximately the same imaging time compared with its 3D IR FSPGR single-echo counterpart. Our data suggest that a T_2^* threshold of 14 msec provides the best overall accuracy in hemorrhage characterization. Based on this threshold, the type I size characterized by 3D SHINE T_2^* maps was significantly and positively correlated with the size estimated manually by an expert reviewer. We must add the caveat that the size of the dataset was limited. The type I hemorrhage size estimation and T_2^* threshold identification were based on a same dataset. However, small variation of the T_2^* threshold, which leads to the change of the hemorrhage size estimation in the same direction, should not change the trend of the type I hemorrhage size estimated by 3D SHINE and its positive correlation with the size estimated manually by an expert reviewer. This correlation validated the reliability of the 3D SHINE technique in hemorrhage characterization. Although a binary method based on a single threshold is easy to be adopted in clinical practice, it is not ideal because IPH types differ in a continuous manner. With enough data, the correlation between symptom and T_2^* distribution within IPH can be established, and thus a statistical prognosis can potentially be established.

Our four-echo 3D SHINE protocol was optimized to identify type I hemorrhage, the type of hemorrhage that has been shown to be associated with thromboembolic events (7), by applying the range of echo time values from 2.7 to 13 msec. The estimation of the T_2^* values outside this echo time range tends to be less accurate. Based on our phantom study, the inaccuracy was limited to less than 1 msec for T_2^* below 25 msec when comparing the results from our 3D SHINE sequence with the eight-echo FSPGR sequence. Also, the standard deviation of the T_2^* measurement estimated by the 3D SHINE were about 6% between T_2^* of 13 and 24 msec, and less than 5% for $T_2^* < 13$ msec. The disagreement in T_2^* estimated by 3D SHINE compared with the eight-echo FSPGR sequence and the SD of the T_2^* measurement by 3D SHINE increased rapidly at T_2^* value over 50 msec. These inaccuracy and variation would not lead to the misclassification of the hemorrhage types as the cutoff between types I and II was found to be ~14 msec, unless the T_2^* happened to be in the range of 13 to 14 msec. Phantom study on Table 3 shows that a higher number of echoes can reduce the variation of estimation for T_2^* of less than 40 msec, the range of the IPH T_2^* distribution found in our work (Fig. 4). Assuming the receiver bandwidth and the data acquisition scheme are maintained, the increase in the number of echo would lead to the increase of

required extra recovery time (t_{extra}) to achieve a similar level of black-blood effect, and thus the increase of scan time. As T_2^* estimation was quite accurate and precise for T_2^* below 25 msec (Table 3) and the threshold T_2^* for discriminating the IPH types was around 14 msec, adding more echoes might not improve IPH characterization, but at the expense of longer scan time. Validation of the 3D SHINE sequence in detecting and quantifying the volumes of types I and II hemorrhage with histological analysis of carotid endarterectomy specimens is still ongoing.

One limitation of the 3D SHINE technique is that it is prone to the effect of magnetic field inhomogeneity in hemorrhage characterization. This happens when there is calcification within or right next to the hemorrhagic region. Basically, the T_2^* is shortened due to magnetic field inhomogeneity at or near the calcification, and thus type II hemorrhage can be mis-classified as type I. In this study, moderate or large calcifications (10–40 mm^2) were noted immediately adjacent to the hemorrhage in two arteries. With the 14 msec T_2^* threshold we found, the probable type II hemorrhage in these two arteries would have been mis-classified as type I hemorrhage. While the calcifications were the main sources affecting T_2^* estimation at IPH based on our data, any field inhomogeneity, such as poor shimming, can affect T_2^* estimation and thus lead the mis-classification of type II hemorrhage to type I hemorrhage. High-order shimming (27), although having not been used in the data acquired in this work, will be useful in reducing the static field inhomogeneity. As type I but not type II hemorrhage is significantly associated with recent symptoms (7), the misclassification of type II to type I will inherently make the 3D SHINE technique more conservative. However, its ability of hemorrhage detection is comparable to 3D IR FSPGR due to the short echo time of its first echo. Histological correlation has demonstrated that heavy calcification in some rare cases can lead to the failure of hemorrhage detection for 3D IR FSPGR (12). This failure would likely occur with 3D SHINE as well. An even shorter first echo time, through an excitation RF pulse with a shorter duration (A 0.36-msec short RF pulse was already applied in 3D SHINE.) and/or the shift of the center of k_x space, can be beneficial in this aspect. The effect of calcification on the characterization of IPH into type I and type II using 3D SHINE has not been fully quantified and further research with histological correlation is on-going. T_2-weighted FSE images, which are less affected by the magnetic field inhomogeneity, should also be acquired as a complementary to 3D SHINE. When there is inconsistency found between 3D SHINE images and T_2-weighted FSE images, the IPH characterization based on T_2-weighted FSE images should be used.

The 3D SHINE technique was developed for IPH detection and characterization at the carotid artery. It can be used to visualize the stenosis. However, it is still necessary to use other standard sequences (black-blood T_1-weighted precontrast and postcontrast, black-blood T_2-weighted, and bright-blood 3D TOF) to extract other plaque components, such as fibrous cap and lipid-rich necrotic core. It may be possible to reduce the overall scan time by deleting the precontrast black-blood T_1-weighted sequence and using the information from the first echo of the 3D SHINE sequence instead. The 3D SHINE technique is directly applicable to other anatomical sites where motion artifacts are not issues, such as the femoral arteries. For sites suffering image motion artifacts, such as the coronary arteries, the 3D SHINE sequence needs to be implemented with a motion-correction technique such as the application of a navigator echo.

As discussed earlier, the 3D SHINE sequence was optimized with the 3D IR FSPGR single-echo sequence as a reference. We did not attempt a global optimization of parameters. The choice of number of echo has been discussed earlier. A few other parameters are further discussed following with respect to optimization. A 180° flip angle was chosen for the non-selective IR in the 3D SHINE protocol. If a non-180° flip angle is used, the null point for the blood signal would occur at an earlier slice phase encoding step (Fig. 2). As a slice sequential phase encoding scheme is applied, a longer extra recovery time (t_{extra}) would be needed. Thus a 180° flip angle is the best choice in terms of scan time efficiency. The TI_{prep} has already been set at the minimum limited by the RF and gradient pulse widths. The scan time efficiency (setting t_{extra} to zero) has been considered by dividing the slice phase encoding steps to two or more nonselective IR applications while still with the blood signal nulled. However, simulation shows a proportional drop of the relative signal (drop to ~50% of the relative signal generated with the protocol shown in Fig. 2 if two IR applications are used), and thus the drop of image SNR. A longer t_{extra} provides extra time for signal recovery and thus higher SNR. Similarly, the rBW was chosen based on conflicting benefits of image SNR and scan time efficiency. The decrease of rBW increases the SNR, but a longer t_{extra} (and thus a longer scan time) would be needed to set the blood signal null point at the center of the k space. The increase of rBW leads to a shorter t_{extra} (and thus a shorter scan time) to achieve similar black-blood effect, but the image SNR would drop. As our single-echo 3D IR FSPGR sequence has been validated in previous studies (11,12), its rBW became the reference for the manipulation of the rBW for 3D SHINE. As demonstrated in the results, the 3D SHINE weighted-average images achieved similar SNRs with its single-echo 3D IR FSPGR counterpart. Therefore, we relied on the manipulation of the t_{extra} to qualitatively maximize the contrast between the lumen and wall. Lastly, 3D SHINE images were acquired in axial plane for easy image comparison in this work. The black-blood effect allows data acquisition at a coronal plane without flow artifacts from the artery at the other side of the neck, and potentially with a larger coverage of the carotid arteries.

In summary, the optimized 3D SHINE technique can detect and characterize carotid IPH. The 3D SHINE images can also provide high-quality visualization at any direction through multiplanar reformation to localize the abnormal regions. This sequence satisfies multiple functions in carotid plaque imaging with one 4-min scan. The 3D SHINE technique also eliminates the issue of image misregistration when comparing images from multiple sequences. The relatively short examination time,

high sensitivity in hemorrhage detection, the ability to characterize type I and type II hemorrhage, as well as the possibility of inherent high-quality multiplanar reformations due to the 3D volumetric acquisition with submillimeter resolution should greatly facilitate the acceptance of the 3D SHINE technique in a busy clinical practice. With the advantages of the 3D SHINE technique, a semiautomated quantification of IPH is currently under development to systematically quantify and characterize the progression of the hemorrhage. This further development can potentially be used as an objective tool in multi-site clinical trials as well as longitudinal carotid plaque studies.

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Localized Measurement of Atherosclerotic Plaque Inflammatory Burden With Dynamic Contrast–Enhanced MRI

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Inflammation plays an important role in progression and rupture of atherosclerotic plaque. Dynamic contrast–enhanced MRI has been proposed as a tool to evaluate inflammation in vivo by measuring the transfer constant and partial plasma volume, which are influenced by inflammation. This study sought to demonstrate the ability of dynamic contrast–enhanced MRI to provide localized measurements of transfer constant and partial plasma volume within plaque regions of different compositions. In order to do that, a highly automatic procedure for localized measurement of dynamic contrast–enhanced MRI parameters was developed. In 47 subjects, the average transfer constant and partial plasma volume were highest in loose matrix and fibrous tissue and substantially lower in intraplaque hemorrhage, lipid rich/necrotic core, and calcification. In addition, except for hemorrhage and calcification, statistically significant differences of transfer constant and partial plasma volume were observed for any pair of these components. This suggests that transfer constant and partial plasma volume could be helpful to differentiate different plaque components and that dynamic contrast–enhanced MRI has the potential to assess inflammatory burden in specific regions. Magn Reson Med 64:567–573, 2010. © 2010 Wiley-Liss, Inc.

Key words: dynamic contrast–enhanced MRI; atherosclerosis; carotid artery; kinetic model; inflammation

Inflammation is important in both the pathogenesis and outcome of atherosclerosis and is associated with fibrous cap rupture (1,2). Plaque inflammation may have multiple effects that weaken plaque structural integrity, including inhibition of new collagen production and dissolution of existing fibrous matrix by matrix metalloproteinases (3). Thus, noninvasive methods to quantify plaque inflammation in atherosclerosis plaque could be valuable for identifying plaques at increased risk for rupture.

Recently, ^{18}F-fluorodeoxyglucose, which is a glucose analog that is taken up by cells in proportion to their metabolic activity (4), has been used to detect atherosclerotic plaque inflammation with positron emission tomography. Elevated ^{18}F-fluorodeoxyglucose positron emission tomography signal shows increased glucose metabolism associated with macrophages, a key inflammatory marker.

High resolution MRI with injection of gadolinium contrast agents offers another approach for evaluating inflammation in vivo. The degree of enhancement of fibrous regions has been found to relate to the amount of neovasculature (5), which is a key pathway for inflammatory cell infiltration. Furthermore, dynamic contrast–enhanced MRI (DCE-MRI) has been shown to be sensitive to inflammatory content within plaque (6). Model-based estimates of transfer constant (K^{trans}) and the fractional plasma volume (v_p) produced from kinetic analysis of DCE-MRI quantify the increased vascular supply and permeability that support macrophage metabolism. Thus, DCE-MRI has a similar interpretation to ^{18}F-fluorodeoxyglucose positron emission tomography regarding macrophage metabolism. In fact, Calcagno et al. (7) showed that the DCE-MRI and ^{18}F-fluorodeoxyglucose positron emission tomography parameters both have positive correlation with neovessel count in a rabbit model of atherosclerotic plaque.

A potential advantage of DCE-MRI is that it provides relatively high (<1 mm) spatial resolution, which may allow DCE-MRI to generate measurements of inflammatory burden localized to key regions within the plaque. In previous studies, however, only the mean measurements of the whole plaque were investigated. Mean values are less sensitive to noise and partial-volume artifacts caused by technical limitations of DCE-MRI, but mean values fail to provide critical location information. For instance, inflammation in the plaque shoulders may be more destabilizing than inflammation deep within the plaque. The question of whether the current spatial resolution and image quality of DCE-MRI are high enough to evaluate localized characteristics is unknown.

In this study, we sought to demonstrate the ability of DCE-MRI to provide localized measurements by comparing K^{trans} and v_p of contrast agent uptake across plaque regions with different compositions. We hypothesized that different plaque components would be associated with different values of K^{trans} and v_p, reflecting the varying vascularities and permeabilities of each region. A highly automatic procedure to generate the colorized vasa vasorum image (V-V image), presenting K^{trans} and v_p with green and red, was established. To map components contours from standard weightings to DCE-MRI

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Table 1
Summary of the Relevant Imaging Parameters in MRI Acquisition Protocol

	DCE	T_1-weighted, contrast-enhanced T_1-weighted	Time of flight	Proton density–weighted	T_2-weighted
TR (ms)	100	800	29	Variable*	Variable*
TE (ms)	6.2	8.8	2.1	13.1	56.9
Slice thickness (mm)	2	2	2	2	2
Gap between slices (mm)	0	0	0	0	0
Matrix	256 × 192	256 × 256	256 × 256	256 × 256	256 × 256
Field of view (mm)	140 × 112	140 × 112	140 × 112	140 × 112	140 × 112

*Proton density–weighted and T_2-weighted: pulse repetition time = three or four cardiac R-R intervals.

images, two steps of registration algorithms were also developed to deal with the mismatch between them automatically.

MATERIALS AND METHODS

Study Population

A total of 55 subjects (age: 66.36 ± 11.99) were randomly selected after informed consent was obtained. The inclusion criterion was more than 50% stenosis by duplex ultrasound examination. The study procedures and consent forms were reviewed and approved by the institutional review board. There were 48 male subjects and seven female subjects.

MRI Protocol

Images were acquired from all subjects on a 3-T MR scanner (Signa; General Electric Healthcare, Milwaukee, WI). A custom-built, phased-array carotid coil was used to improve signal-to-noise performance. The examination included a DCE-MRI sequence consisting of axial two-dimensional spoiled gradient recalled echo imaging without cardiac gating. Data were simultaneously acquired at six contiguous 2mm-thick locations, centered on the bifurcation of the index carotid artery, and at 12 time points separated by a repetition interval of 19 sec. Index side was assigned as the symptomatic side for the symptomatic patients and the artery with greater stenosis for each asymptomatic patient. Symptomatic status was obtained from the clinical history of the patient and was defined as amaurosis fugax, transient ischemic attacks, or overt stroke. Coincident with the second image in the sequence, 0.1 mmol/kg of a gadolinium-based contrast agent (Omniscan; General Electric Healthcare Canada, Mississauga, Ontario, Canada) was injected at a rate of 2 mL/sec by a power injector. The use of a spoiled gradient recalled echo sequence produced a T_1-dependent signal within the imaging slice. To impose a T_1-dependent signal on inflowing blood, spatial saturation bands with width of 80mm were used and resulted in dark blood on images prior to contrast bolus arrival. The saturation bands were arranged at the proximal and distal ends of the acquisition slab, with gaps of 5 mm.

Before and after the injection of contrast agent, an axial T_1-weighted fast spin echo sequence with a quadruple inversion recovery black-blood preparation (8) was applied to obtain precontrast T_1-weighted and contrast-enhanced T_1-weighted images. Other contrast weightings acquired with a standard protocol (9) included time-of-flight, T_2-weighted, and proton density–weighted images. The imaging sequences were as follows: time of flight: fast gradient echo; T_2-weighted and proton density–weighted: double echo, cardiac-gated. Relevant imaging parameters are summarized in Table 1.

Image Analysis

Lumen/Wall and Components Identification

Based on a standard review protocol of multicontrast MRI validated with histology (10), one expert reader (X.Z.) blinded to DCE results reviewed all the images of standard weightings. Then all the cases were randomly distributed among the other three readers (H.U., H.O., M.O.) to be peer reviewed. If the peer reviewer had different opinions, the final decision was made by consensus of the two reviewers. Analyses were performed using the semiautomatic analysis software CASCADE (11), wherein the readers identified the lumen and outer wall boundaries of the carotid artery and lipid rich/necrotic core (NC), calcification (CA), hemorrhage (Hem), and loose matrix (LM) regions within the plaque. Unclassified regions within the plaque wall were considered to be fibrous tissue (FIB). The lumen and wall boundaries were represented by B-splines and the components were manually drawn.

Initial Registration of DCE-MRI and Other Weightings

After the compositional analysis, parametric images of K^{trans} and v_p were automatically generated from the DCE-MRI results. To automatically extract the arterial input function (AIF) and define the analysis region of interest for generation of these images, an initial three-dimensional registration of the DCE-MRI series and standard contrast weightings is required, in order. An automated registration algorithm was devised that searches for the optimal z-direction shift (*sz*), in-plane shift (*sx*, *sy*) and contour scaling to maximize the function

$$\sum_{i=1}^{3} Energy(C_i) \qquad [1]$$

where C_i is the sets of points making up the lumen contour in slice i ($i = 1$, the contours of slice before bifurcation; $i = 2$, the bifurcation slice; and $i = 3$, the slice after bifurcation). The energy function is given by

$$Energy(C) = \oint_{(x,y)\in C_a} \left|\vec{G}_{z+sz}(x - sx, y - sy) \times \vec{C}_a(x,y)\right| * E_{z+sz}(x,y) \quad [2]$$

where $\vec{G}_z$ (x, y) is the intensity gradient vector of the DCE-MRI image at *zth* slice. Contour C_a is the scaled C with scaling factor a ($a = -0.5$, shrink 0.5 mm; $a = 0$, original contour; $a = 0.5$, expand 0.5 mm). $\vec{C}_a$ (x, y) is the unit vector function representing the direction of tangent at point (x, y) of contour C_a. E_z (x, y) is the edge energy function of the DCE-MRI image at *zth* slice. To generate the edge energy function, edges were produced by Canny Edge detector and then blurred by two-dimensional gaussian filter. The calculated location shift was automatically applied, and the in-plane shift is stored and will be used as the initial shift for mapping boundaries.

Generation of Parametric Image From DCE-MRI

After initial registration, the method described by Kerwin et al. (12) was used to automatically generate parametric images of K^{trans} and v_p. This approach uses a two-compartment kinetic model to characterize contrast agent concentration according to the differential equation

$$\dot{C}_t(t) = v_p\dot{C}_p(t) + K^{trans}C_p(t) \quad [3]$$

where $C_t(t)$ and $C_p(t)$ are the contrast agent concentration functions in the tissue and blood plasma, respectively. These two functions are approximated by the change in signal intensity of DCE-MRI due to contrast agent in the tissue and artery over time and used to solve for K^{trans} and v_p.

A critical component of the model is the AIF $C_p(t)$, which must either be determined from the DCE-MRI results directly or from a population model. In this study, both approaches were used and compared to understand the influence of the AIF on the results. First, a single AIF was automatically extracted for each subject from all slices in a small region around the center of the blood vessel, using a clustering algorithm (12). This approach minimizes the influence of partial-volume artifacts and flow artifacts by selecting only those pixels with high and rapid enhancement and then averages their intensity curves to obtain the AIF.

One drawback of this approach is that signal enhancement generally underestimates concentration in the blood due to factors such as T_2^* shortening affecting the spoiled gradient recalled echo acquisition, thereby leading to an inaccurate AIF (13). This effect is particularly problematic at bolus arrival when the peak concentration occurs. To address this concern, we also performed the kinetic analysis a second time with a model-based universal AIF for the whole population. This population-derived AIF is assumed to have a biexponential decay:

$$C_p(t) = \begin{cases} 0, & t < t_0 \\ D(a_1\exp(-m_1(t - t_0)) + a_2\exp(-m_2(t - t_0))), & t \geq t_0 \end{cases} \quad [4]$$

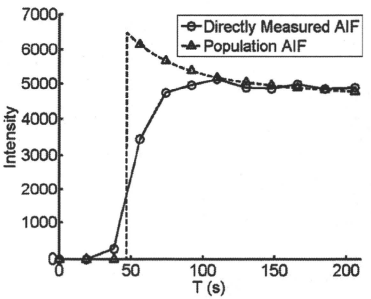

FIG. 1. The directly measured AIF and the corresponding population-derived AIF used for the case shown in Fig. 2.

where $a_1 = 3.51866$ *kg/L*, $a_2 = 13.0023$ *kg/L*, $m_1 = 1.7746$ min^{-1}, and $m_2 = 0.0267735$ min^{-1} (14). The bolus arrival time t_0 is aligned to the arrival time of the directly measured AIF. Finally, the population-derived AIF is scaled by setting the value of D such that the difference between the last five points of the population curve and the measured AIF is minimized, under the assumption that at later times, the nonlinearities of the enhancement versus concentration relationship are less problematic. Figure 1 shows an example of the directly measured AIF and the corresponding scaled population-derived AIF.

After $C_p(t)$ is extracted, K^{trans} and v_p are computed for every pixel in a 4-cm × 4-cm region of interest centered on the carotid artery, and the results are displayed in a colorized image, with v_p in the red channel and K^{trans} in the green channel. Thus, regions with blood, such as the carotid artery lumen, appear red and regions with rapid transfer appear green (Fig. 2f,g). We refer to this colorized image as a V-V image.

Mapping Boundaries and Computing Average K^{trans} and v_p of Components

After computing the V-V images, the slice correspondence between the V-V images and the other contrast weightings was visually verified and adjusted up or down as necessary. Then, the boundaries of the lumen, outer wall, and components drawn on the corresponding other weightings were automatically mapped to the V-V image by refining the in-plane registration. The lumen boundary was first mapped to the V-V image, with the in-plane shift determined during the initial location registration. To account for small remaining misregistration, the algorithm searched over a small region to maximize the function

$$\int\int_{(x,y)\in L} v_p(x + dx, y + dy) \quad [5]$$

where L is the region inside the lumen boundary, and dx and dy are the in-plane shifts to be found. The outer wall and components boundary were then mapped to

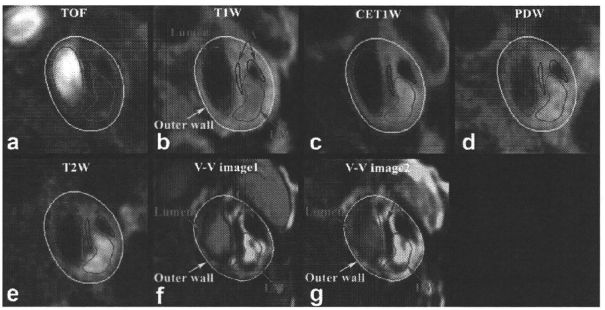

FIG. 2. One example of mapping contours of lumen, outer wall, and plaque components (arrows) from other weightings onto produced V-V image. **a:** Time of flight, **(b)** T_1-weighted, **(c)** contrast-enhanced T_1-weighted, **(d)** proton density–weighted, **(e)** T_2-weighted, **(f)** produced V-V image using directly measured AIF, **(g)** produced V-V image using population-derived AIF.

and displayed on the V-V image, using the same shift obtained by the lumen registration. Further manual shifting was then allowed in case of registration failure. Small manual adjustments in the lumen and outer wall contours were also allowed by manipulating the node points of the B-spline when the vessel shape in the V-V image was not well matched to the standard weightings. The component contours were not adjusted. An example of the contour mapping is shown in Fig. 2.

Once all the contours have been mapped, the average values of K^{trans} and v_p inside all the components for each DCE-MRI slice, such as NC, CA, Hem, LM, and FIB, are reported.

Data Analysis

The analysis procedure was applied to the index carotid artery of each subject, using both AIF approaches. For each component, the mean values and 95% confidence intervals of K^{trans} and v_p are compared. To eliminate any potential overlap between NC and Hem, which generally occurs within the NC, the NC analysis was limited to regions that did not contain Hem. The nonparametric comparison (Mann-Whitney U test) was used to compare the significance of differences between components in K^{trans} and v_p, with P values below 0.05 considered significant.

RESULTS

Of the original 55 subjects, eight subjects were excluded because the DCE imaging location missed the bifurcation of the index artery. For the remaining 47 subjects, 227 matched slices were available with DCE-MRI results and at least one plaque component drawn within the wall.

For performance of the automated registration algorithms, the correct longitudinal correspondence of slices was identified in 76.6% of 47 cases. The in-plane refinement of the lumen, wall, and component mapping was successful in 72.7% of slices, with the remainder requiring additional manual in-plane shift adjustment.

For the results using the directly measured AIF, the mean K^{trans} and v_p values for each component are

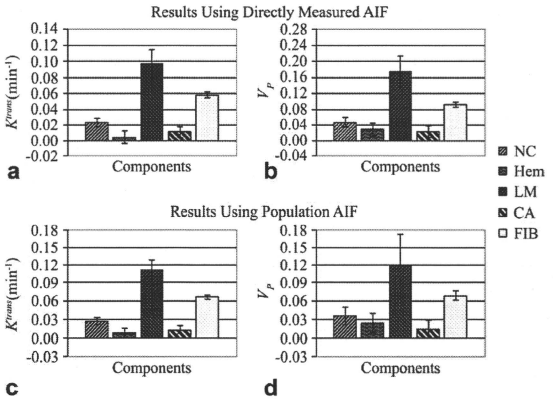

FIG. 3. Comparison of mean K^{trans} (**a**) and v_p (**b**) (columns) using directly measured AIF and their 95% confidence interval (bars) across different components. **c,d:** The comparison results using population-derived AIF.