Spatio-temporal texture (SpTeT) for distinguishing vulnerable from stable atherosclerotic plaque on dynamic contrast enhancement (DCE) MRI in a rabbit model

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Purpose: To develop a new spatio-temporal texture (SpTeT) based method for distinguishing vulnerable versus stable atherosclerotic plaques on DCE-MRI using a rabbit model of atherothrombosis.

Methods: Aortic atherosclerosis was induced in 20 New Zealand White rabbits by cholesterol diet and endothelial denudation. MRI was performed before (pretrigger) and after (posttrigger) inducing plaque disruption with Russell's viper venom and histamine. Of the 30 vascular targets (segments) under histology analysis, 16 contained thrombus (vulnerable) and 14 did not (stable). A total of 352 voxel-wise computerized SpTeT features, including 192 Gabor, 36 Kirsch, 12 Sobel, 52 Haralick, and 60 first-order textural features, were extracted on DCE-MRI to capture subtle texture changes in the plaques over the course of contrast uptake. Different combinations of SpTeT feature sets, in which the features were ranked by a minimum-redundancy-maximum-relevance feature selection technique, were evaluated via a random forest classifier. A 500 iterative 2-fold cross validation was performed for discriminating the vulnerable atherosclerotic plaque and stable atherosclerotic plaque on per voxel basis. Four quantitative metrics were utilized to measure the classification results in separating between vulnerable and stable plaques.

Results: The quantitative results show that the combination of five classes of SpTeT features can distinguish between vulnerable (disrupted plaques with an overlying thrombus) and stable plaques with the best AUC values of 0.9631 ± 0.0088 , accuracy of $89.98\% \pm 0.57\%$, sensitivity of $83.71\% \pm 1.71\%$, and specificity of $94.55\% \pm 0.48\%$.

Conclusions: Vulnerable and stable plaque can be distinguished by SpTeT based features. The SpTeT features, following validation on larger datasets, could be established as effective and reliable imaging biomarkers for noninvasively assessing atherosclerotic risk. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4867861>]

Key words: spatio-temporal texture, atherosclerotic plaque, rabbit model, DCE-MRI

1. INTRODUCTION

Cardiovascular disease (CVD) and its subsequent ischemic complications remain the most common cause of morbidity and mortality in the United States.¹ The acute event of atherosclerotic plaque rupture and subsequent thrombus formation can cause severe complications, such as stroke, or myocardial infarction.^{2,3} Therefore, early diagnosis of atherosclerosis before the additional and potentially irreversible damage due to plaque rupture is an increasingly important diagnostic priority.

Atherosclerotic plaques have been characterized as stable and vulnerable. Compared to stable atherosclerotic plaques

(SAP), vulnerable atherosclerotic plaques (VAP) that disrupt and form a luminal thrombus generally do not produce rate-limiting stenosis, in advance of a fatal or debilitating event. Due to the asymptomatic nature of VAP, identification of a culprit lesion before it ruptures remains a challenging task.⁴

With the development and progress of imaging techniques, plaque imaging has a significant role to play in the evolution of diagnosis and therapy. Intravascular ultrasound (IVUS) is most commonly performed clinically to determine both plaque volume within the wall of the artery or the degree of stenosis of the artery lumen.⁵ IVUS is a highly invasive procedure and adds significant additional examination time and increased risk to the patient by the use of the IVUS catheter.⁶

As a nonionizing radiation imaging modality with the capability to distinguish tissue characteristics, magnetic resonance imaging (MRI) is an optimal method to characterize the morphology and composition of atherosclerotic carotid plaques.⁷⁻¹⁰ For instance, Sun *et al.*¹¹ employed a Fuzzy C-means clustering algorithm and a priori knowledge of each constituent's T2 distribution on multicontrast MR images (PD-, T1-, and T2-weighted MRI) to automatically differentiate plaque constituents, such as calcification, adipose fat, media, necrotic tissue, and fibrocellular. In contrast to Sun's method, the SpTeT-based method focuses on identification of spatio-temporal texture features for distinguishing VAP from SAP using DCE-MRI. Morphologically, a typical VAP is characterized by a thin fibrous cap, large lipid-rich necrotic core, increased plaque inflammation and vasa-vasorum neovascularization, and intraplaque hemorrhage.^{12,13} Multiple centers have showed that MRI can reliably identify fibrous cap status,¹⁴ plaque composition,^{15,16} neovascularity and vascular wall inflammation¹⁷ to identify vulnerable plaque. Further, researchers have developed various techniques for automatic characterization and detection plaque vulnerability using MRI.^{18,19}

Dynamic contrast enhancement (DCE) MRI has become a noninvasive imaging tool to study the extent of plaque neovascularization in animals and patients with atherosclerosis.²⁰ Work by a number of investigators have demonstrated different enhancement of carotid plaque tissue using DCE-MRI.²¹ They found that strong enhancement generally suggests the presence of a highly permeable vascular supply within the plaque (neovascularity) and loose extracellular matrix for contrast agent uptake, which are both associated with plaque inflammation. Further, contrast enhancement of the vessel wall has been quantitatively analyzed and was found to be an effective marker of the vascular wall inflammation as evaluated by histological analysis of plaque composition and inflammation.^{22,23} Therefore, DCE-MRI is a useful tool for quantifying the extent of plaque neovascularization in atherosclerosis and improving the discrimination of different plaque components, such as lipid-rich necrotic core and the fibrous cap, which is critical to distinguish VAP from SAP.

In this work, various image filters were applied to vessel wall area to compute static texture features. The computerized textures include: (1) The first order spatial intensity variations/statistics²⁴ within small neighborhoods allow for capture of local, spatially proximal textural changes (i.e., microchanges). These may be subtle, local changes that are differential between the types of pathologies present in VAP and SAP. (2) Sobel²⁵ and Kirsch²⁶ are gradient/edge filters, which are similar to the first order statistics, but specifically capture changes in specific directions - predominantly along the X, Y, and diagonal directions. The assumption here is that there might be an orientedness of microtextures in the more acute versus less acute pathologies. We anticipate a further deterioration in microarchitecture with increasing vulnerability and acuteness of the pathology, which would be captured by the Sobel and Kirsch filters. (3) Steerable Gabor features²⁷ have been modeled on the pattern-

ing of the human visual cortex and have been found to be particularly appropriate for texture representation and discrimination in image analysis.²⁸ (4) Haralick features,²⁹ calculated via second order co-occurrence features, reflect regional heterogeneity in the plaque. Unlike the Sobel and Kirsch filters, these features are global measures and not limited to specific orientations. Additionally unlike the first order statistical filters, these features reflect the total disorder or chaos throughout the entire pathology of interest rather than specific local neighborhoods. Thus, the microarchitectural morphologic differences between the types of pathologies in VAP and SAP would be reflected through the Haralick features.

Our new approach is different from previous work of estimating parameters on time-intensity curve or using DCE-MRI pharmacokinetic (PK) analysis. For instance, Chen *et al.*³⁰ computed enhancement kinetic features, such as uptake rate, time to peak, washout rate, etc. from a characteristic time course curve to distinguish benign and malignant breast masses. These methods attempted to correlate imaging markers with physiologic and pathophysiologic parameters in human or animal models.^{31,32} We utilize a comprehensive set of spatio-temporal texture (SpTeT) features to characterize the pathophysiologic changes in various aspects of tumor vascular structure and functionality in atherosclerosis. SpTeT features have been used in diagnosing and predicting aggressiveness of breast cancer and reported as reliable imaging markers for discriminating subtypes of breast lesions.^{24,33}

However, our SpTeT based features are different from the work published by Shen *et al.*,³⁴ in which the spatiotemporal enhancement pattern (STEP) features were computed through two static texture descriptors applied to the generated temporal enhancement maps. In the implementation of SpTeT, texture features are calculated per voxel at each time point in the time series. Each texture feature is plotted as a function of time and polynomial fitting is applied to fit the curve to constitute a vector of coefficients that describe the textural kinetics of the plaque reflecting heterogeneity of contrast uptake between subtypes of vascular lesions.

The remainder of this paper is organized as follows. The overview of the SpTeT method and major contributions of this work are described in Sec. 2. The materials and detailed methods are presented in Sec. 3. The detailed experimental design is presented in Sec. 4. In Sec. 5.D, we present experimental results with accompanying discussion. Finally, Sec. 6 presents concluding remarks.

2. OVERVIEW OF THE SpTeT BASED METHOD AND NOVEL CONTRIBUTIONS

We present a new SpTeT based method to distinguish vulnerable from stable plaque using DCE-MRI in a rabbit model. The methodology consists of three modules as illustrated in the flowchart shown in Fig. 1. Module 1 involves two different steps. Step 1 is to align DCE-MRI and T1-weighted black blood (T1wBB) sequences via a 3D volume registration method. Black blood (BB) imaging is routinely used to visualize atherosclerotic plaque morphology, which is capable of

FIG. 1. The flowchart shows the main components of the new framework. Module 1 shows the preprocessing procedure to register and segment DCE-MRI and T1wBB. Module 2 extracts five different SpTeT feature classes, including Gabor, Kirsch, Sobel, Haralick, and first-order textural. In Module 3, quantitative evaluation of the five feature classes in distinguishing VAP from SAP on MRI was done via a random forests classifier.

delineating luminal boundaries of arteries. The contour of the lumen was identified on T1wBB sequence. Due to the fact that the commonly used double inversion BB imaging technique limits spatial resolution, especially in a through plane axis, the outer wall of artery is segmented on DCE-MRI. In Step 2, the lumen and outer wall segmentation is performed via a semiautomatic segmentation algorithm, named distance regularized level set evolution (DRLSE) based method.³⁵ Module 2 exemplifies SpTeT features within vessel wall area to characterize spatio-temporal changes in plaque texture before and during the contrast injection. Module 3 focuses on the evaluation of capability of computerized SpTeT features in discriminating between VAP and SAP using a minimal-redundancy-maximal-relevance (mRMR) feature selection method³⁶ in conjunction with a random forest classifier.³⁷ Results of both qualitative and quantitative evaluation are presented.

This paper attempts to make two major contributions: (1) A comprehensive set of SpTeT features are computed for discriminating between stable and vulnerable plaque on aortic DCE-MRI by quantifying the spatiotemporal patterns of plaque texture during the contrast enhancement time series. Compared to PK modeling and parameter estimation approaches on time-intensity curves, the computerized SpTeT

features are able to capture both local and global spatial variations through image texture features (e.g., first order statistics, Sobel, Kirsch, Gabor, and Haralick) along with temporal enhancement patterns. (2) Although spatiotemporal properties of DEC-MRI have been studied in distinguishing between benign and malignant breast lesions, our new approach characterizes the microchanges of contrast uptake through a polynomial fitting on various textural kinetic curves generated from DCE-MRI time series, thus providing reliable image descriptors particularly for DCE-MRI sequences. In addition, this work, to our best knowledge, is the first attempt to employ the SpTeT features to capture enhancement characteristics of atherosclerotic plaque in order to differentiate between vulnerable and stable plaques.

3. MATERIALS AND METHODS

3.A. Data description

3.A.1. Rabbit animal model

Atherosclerosis was induced in 20 New Zealand White rabbits (Charles River Laboratories, MA) by feeding a 1% cholesterol diet for 2 weeks before and 6 weeks after balloon injury of the abdominal aorta, followed by 4 weeks of

normal chow diet. Two pharmacological triggerings with 24 h apart of thrombosis was induced with Russell's viper venom (0.15 mg/kg IP; Enzyme Research, IN), followed by histamine (0.02 mg/kg IV; Sigma-Aldrich, MO) in rabbits. The rabbits were sacrificed with a bolus injection of sodium pentobarbital (>120 mg/kg IV). In total, 16 vulnerable (plaques with a luminal thrombus attached) and 14 stable plaques were confirmed through a histological analysis. Animal studies were performed in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Boston University.

3.A.2. In vivo MRI

In vivo MRI acquisition was performed on supine rabbits using a 3T Philips Intera Scanner (Philips Medical Systems, OH) with a six-channel synergy knee coil. The aorta of atherosclerotic rabbits, between the left renal branch to the iliac bifurcation, was imaged before (pretrigger) and 48 h after (posttrigger) inducing plaque disruption. Several MRI protocols were collected, including two image modalities of 2D axial T1wBB images and DCE-MRI. 2D axial T1wBB images were acquired with a double inversion recovery, turbo spin echo sequence and cardiac gating. DCE-MRIs were acquired before and every 2–3 min after injection of the contrast agent (Magnevist 0.01 mmol/kg, IV) for additional seven time points. The detailed MRI acquisition parameters are listed in Table I.

3.B. General notation used

We denote $\mathcal{C} = (C, f^t)$ as a 2D section of a 3D MRI volume, where C is a set of pixels $c \in C$, and f^t is the associated intensity function at every pixel c and at each time point $t \in \{0, 1, \dots, T-1\}$ in the DCE-MRI time series. $\mathcal{C} = (C, f^0)$ refers to the precontrast image.

For each rabbit subject, the vulnerable and stable plaques were confirmed by the histopathology analysis and defined in a target G , where $G = [C_1, \dots, C_M]$ is a subvolume of DCE-

MRI. Hence, we define a dataset $\mathcal{Z} = \{G_1, G_2, \dots, G_N\}$ of N targets in total. Each G_i , $i \in \{1, 2, \dots, N\}$ is associated with a feature set $\mathcal{F}(G_i)$, and a class label $\mathcal{L}(G_i) \in \{1, 2\}$, where $\mathcal{L}(G_i) = 1$ represents VAP, and $\mathcal{L}(G_i) = 2$ represents SAP. The segmentation performed by the DRLSE-based method defines the region of the vessel wall W (the region between vessel outer wall and lumen area), where $W \in G$. The voxels $c_q \in W$, $q \in \{1, 2, \dots, Q\}$ (Q is the total number of voxels), were used to form a 3D vessel wall dataset $\mathcal{W} = \{W_1, W_2, \dots, W_N\}$.

3.C. Methods

3.C.1. Module 1: Data preprocessing

Step 1: 3D volume registration

A 9-parameter 3D affine transformation (including three translation, three rotations, and three scales) was adopted to register a pair of DCE-MRI and T1wBB volumes. Let V_d and V_t define DCE-MRI (fixed) and T1wBB (moving) image volumes, respectively. The V_t can be aligned to V_d via

$$\mathbf{x}'_t = \mathbf{b} + \mathbf{s} \cdot \mathbf{R} \cdot \mathbf{x}_t, \quad \mathbf{x}_t \in V_t, \quad (1)$$

where $\mathbf{x}'_t$ and $\mathbf{x}_t$ are the position vectors of the same point in transformed and moving coordinate system, and $\mathbf{b}$, $\mathbf{s}$, and $\mathbf{R}$ denote the translation vector, scale factor, and rotation matrix, respectively. The interpolation method, which is used to calculate intensities on the deformed moving image, is linear interpolation. Mutual information (MI) was utilized as a similarity measure to drive transformation optimization.³⁸ It is assumed that the global MI maximum will occur at the point of precise registration, when maximal uncertainty about V_d is explained by V_t .³⁹

Step 2: Vessel wall segmentation

After registration between DCE-MRI and T1wBB, an edge-based active contour model, i.e., the DRLSE based method,³⁵ was utilized to perform segmentation on DCE-MRI and T1wBB to segment vessel outer wall and lumen region from the image background. In the segmentation model, a general variational level set formulation with a distance regularization term and an external energy term drives the motion of the zero level contour toward desired locations. The energy function $\mathcal{E}(\phi)$ was defined by³⁵

$$\mathcal{E}(\phi) = \mu \mathcal{R}_p(\phi) + \lambda \mathcal{L}_g(\phi) + \alpha \mathcal{A}_g(\phi), \quad (2)$$

where ϕ is a level set function. $\mathcal{R}_p(\phi)$ is the level set regularization term, and $\mu > 0$ is a constant. $\lambda > 0$ and α are the coefficients of the edge-based energy functions $\mathcal{L}_g(\phi)$ and $\mathcal{A}_g(\phi)$, which are defined as external energy functions to ensure that the zero level contour of ϕ is located at the object boundaries. This allows for speeding up of the motion of the zero level contour in the level set evolution process. The DRLSE based segmentation is a semiautomatic approach as it requires an initialization of zero level set function. This is undesired for handling large datasets. The segmentation task can also be performed in a fully automated fashion. For instance, Xu *et al.*⁴⁰ introduced an automatic segmentation method using a spatially constrained Markov random walk approach to

TABLE I. Summary of MRI acquisition parameters.

MRI parameter	2D axial T1wBB	DCE-MRI
Slice thickness (mm)	4	4
TE (ms)	5.4	4.1
TR (ms)	2 heartbeats	10.1
Flip angle (deg)	90	10
Echo train length	–	50
Black-blood pulse thickness (mm)	4	–
Delay (ms)	350	–
Field of view (mm)	120 × 85	50 × 30
Flow velocity (cm/s)	–	150
Matrix	384 × 270	208 × 158
Acquired resolution (mm)	0.31 × 0.31	0.24 × 0.18
Reconstructed resolution (mm)	0.23 × 0.23	–
Inplane resolution (mm)	–	0.22 × 0.24
No. of averages	2	6
Slices	23–28	23–28

accurately estimate inner and outer airway wall surface of lung on CT scans.

3.C.2. Module 2: SpTeT feature extraction

A series of 352 voxel-wise spatio-temporal texture features, including 192 Gabor,²⁷ 36 Kirsch,²⁶ 12 Sobel,²⁵ 52 Haralick,²⁹ and 60 first-order textural²⁴ based SpTeT features, were calculated to describe the characteristics of the kinetic changes in plaques on DCE-MRI. Plaque textures can be characterized quantitatively by assessing the enhancement curve obtained by plotting the texture feature values of each voxels within plaques over time point before and after contrast injection. The shape of enhancement curve E represents important texture kinetic features.

For each voxel $c_q \in W_i$, where $W_i \in \mathcal{W}$, $q \in \{1, 2, \dots, Q\}$, $i \in \{1, 2, \dots, N\}$, we compute five types of static texture features, including Gabor, Kirsch, Sobel filters, Haralick, and first-order textural features on each time point of DEC-MRI image slice. Table II summarizes all the textural features considered in this work. The feature value $F_{q,k}$, $k \in \{1, 2, \dots, K\}$ (K denotes the total number of features) at each time point t forms a kinetic vector $\hat{F}_k = [F_{q,k}^0, F_{q,k}^1, \dots, F_{q,k}^{T-1}]$. A third-order polynomial is fitted to kinetic curve E to characterize its shape via a set of model coefficients $[\rho_{q,3}, \rho_{q,2}, \rho_{q,1}, \rho_{q,0}]$, which is obtained by minimizing the root mean squared difference error between E and approximate model $\tilde{E}$:

$$\tilde{E} = \rho_{q,3}x^3 + \rho_{q,2}x^2 + \rho_{q,1}x + \rho_{q,0}. \quad (3)$$

The spatio-temporal texture feature set $\mathcal{F}(c_q)$, $q \in \{1, 2, \dots, Q\}$ contains the model coefficients of the third-order polynomial for all the voxels that are extracted from the vulnerable and stable plaques. The quality of fitting relies on the order of

polynomials and the number of sampling points extracted on the curve. The failure (bad fitting) might appear in the cases of using high order of polynomials and/or insufficient sampling points although the fit is mathematically possible. In addition, the fit might not be good due to the unbounded nature of polynomials.⁴¹ We utilize a low order ($n = 3$) polynomial fitting to quantify spatiotemporal patterns of the textural feature curves during the contrast enhancement time series. When a polynomial function does not produce a satisfactory model of data, a linear model with nonpolynomial terms is added to the original fitting function to provide a good approximation to the data. The confidence bounds are computed to measure the degree of certainty of the fit.

3.C.3. Module 3: Voxel level classification

The computerized SpTeT features $\mathcal{F}(c_q)$, $q \in \{1, 2, \dots, Q\}$, were selected and ranked by the mRMR method,³⁶ and then evaluated by a random forest classifier.³⁷ Before performing feature selection, we rescaled the range of features in order to make the features independent to each other. The SpTeT features were rescaled to the range of $[-1, 1]$ due to the nature of the textural features that had positive and negative values. The mRMR method is employed to select features by minimizing redundancy and maximizing statistical dependency based on MI. The theoretical analysis³⁶ revealed that mRMR is equivalent to Max-Dependency for first-order feature selection with higher efficiency. The SpTeT features are ranked through scoring of the most relevant features based on mRMR criterion. The optimal subset of features $\mathcal{F}_o(c_q)$ was generated by adding the best features with the highest ranking scores, which is known as the stepwise regression method.⁴²

Random forest (RF) classifiers are a combination of tree predictors that operate by constructing a multitude of decision trees at training time and outputting the class that is the mode of the classes output by individual trees. For the h th tree, a random vector $\mathbf{p}_h$ is generated, independent of the past random vector $[\mathbf{p}_1, \dots, \mathbf{p}_{h-1}]$, but with the same distribution. A new tree is grown using the training set and $\mathbf{p}_h$, resulting in a classifier $\varphi(\mathbf{x}, \mathbf{p}_h)$, where $\mathbf{x}$ is an input vector. For instance, in bagging the random vector $\mathbf{p}$ is generated as the counts in N boxes resulting from N darts thrown at random at the boxes, where N is number of examples in the training set. In random split selection, $\mathbf{p}$ consists of a number of independent random integers between 1 and H (H is the number of variables in the classifier φ). After a predefined number of trees is constructed using above criteria, the trees vote for the most popular class at input $\mathbf{x}$. This procedure is iterated over all trees in the ensemble, and the mode vote of all trees is aggregated as the random forest prediction.

4. EXPERIMENTAL DESIGN

4.A. Parameter setting

To evaluate the discrimination capability of the extracted SpTeT features for distinguishing VAP from SAP, each type of texture features, including Gabor, Kirsch, Sobel, Haralick,

TABLE II. Summary of all textural features considered in this work with associated parameters.

Textural feature class	Individual feature	Parameters
Gabor filters	6 scales	$\Lambda \in \{\frac{\pi}{2\sqrt{2}}, \frac{\pi}{4}, \dots, \frac{\pi}{16}\}$
	8 orientations	$\theta \in \{0, \frac{\pi}{8}, \dots, \frac{7\pi}{8}\}$
Kirsch filters	Maximum gradient in the 8 directions	Window size, $w = 3$
	8 orientations	$\theta \in \{0, \frac{2\pi}{8}, \dots, \frac{14\pi}{8}\}$
Sobel filters	X-direction, Y-direction, XY-diagonal	Window size, $w = 3$
Haralick	Contrast inverse moment	Window size, $w = 3$
	Contrast energy, average	
	Contrast variance, entropy	
	Intensity average, variance	
	Intensity entropy	
	Entropy, energy	
	Correlation	
	Info. measure of correlation 1	
First-order textural	Mean, median, range	Window size, $w \in \{3, 5, 7\}$
	Standard deviation, average deviation	

First-order textural, was used to train a RF classifier and tested via a 2-fold cross-validation method. The classification task was performed on a voxel basis. The default parameters setting reported in Ref. 37 was adopted in the RF classifier for separating between vulnerable and stable plaques.

A collection of $N = 30$ plaques from 20 rabbit subjects were acquired in the work. A number of 8419 and 11 841 voxels were extracted from 16 vulnerable plaques and 14 stable plaques, respectively. A voxel-based classification directly utilized voxels as training and testing data. To avoid a biased evaluation, we ensured that there were no voxels from the same plaque in the training and testing sets simultaneously. In the experiments, the 16 vulnerable and 14 stable plaques were randomly separated into two sets for training and testing. Thus, the training set $\mathcal{Z}_{tra}$ contained voxels from eight vulnerable and seven stable plaques, and the testing set $\mathcal{Z}_{tes}$ contained voxels from the rest of eight vulnerable and seven stable plaques. The cross-validation process is then repeated 500 trials to reduce random errors.

4.B. Performance measures

4.B.1. Qualitative evaluation of SpTeT features via graph embedding

Graph embedding (GE) is a nonlinear dimensionality reduction scheme that is used to transform the high-dimensional set of image features into a low-dimensional embedding while preserving relative distances between images in the original feature space.⁴³ Embedding plots of the data reduced to three dimensions were used to visualize the discriminability of each feature to cluster the plaques into distinct categories. Given $\mathcal{Z}$ containing N samples, we denote feature matrix $\mathcal{F} = [F_1, F_2, \dots, F_N]$, $F_i \in \mathbb{R}^K$, $i \in \{1, \dots, N\}$. Let $G = \{\mathcal{F}, \mathcal{A}\}$ be a graph with vertex set $\mathcal{F}$ and the similarity matrix $\mathcal{A} \in \mathbb{R}^{N \times N}$. The diagonal matrix $\mathcal{D}$ and the Laplacian matrix $\mathcal{B}$ of the graph G are defined as $\mathcal{B} = \mathcal{D} - \mathcal{A}$, and $\mathcal{D}_{ii} = \sum_{j \neq i} \mathcal{A}_{ij}$, $\forall i$. Let $\mathcal{F}' = [F'_1, F'_2, \dots, F'_N]$ denote the low-dimensional representation of $\mathcal{F}$, $F'_i \in \mathbb{R}^{K'}$ ($K' \ll K$). For each voxel $c_q \in \mathcal{Z}$, a high-dimensional feature $F(c_q)$ will be transformed into a low-dimensional representation $F'(c_q)$ with $K' = 3$.

4.B.2. Quantitative evaluation of voxel level classification

The extracted SpTeT features were evaluated via an iterative cross-validation process, and the resulting mean μ_{AC} and standard deviation σ_{AC} of the classification accuracy (AC) were computed. Additionally, two commonly used measures, i.e., sensitivity (SN) and specificity (SP), were computed for each type of feature.

A receiver operating characteristics (ROC) analysis was utilized to evaluate the performance of the RF classifier. A ROC curve was created by plotting SN versus 1-SP at various discrimination threshold settings. The area under the curve (AUC) was computed to quantitatively measure each feature's ability in distinguishing VAP from SAP.

5. RESULTS AND DISCUSSION

5.A. Qualitative results

Figure 2 shows the embedding plots for four SpTeT features, including mean, median, intensity entropy, and 6th-scale 8th-orientation Gabor filter, that enable separation of the vulnerable from stable plaques using voxel-wise features. For a better visualization, only partial voxels, including 100 vulnerable samples and 100 stable samples, were used for visualization. Figure 2 reveals that these four SpTeT features performed reasonably well for separating the data into vulnerable and stable plaque categories.

Figure 3 illustrates two representative MR images within predefined targets for a vulnerable plaque and a stable plaque. The vessel outer wall and lumen contour were delineated by the DRLSE based segmentation method after 3D volume registration between DCE-MRI and T1wBB. Each row shows the precontrast image [Figs. 3(a) and 3(e)], the postcontrast image corresponding to the peak lesion enhancement [Figs. 3(b) and 3(f)], the segmentation result [Figs. 3(c) and 3(g)], and the texture image [Figs. 3(d) and 3(h)] using spatio-temporal first-order textural mean feature in which the feature values were encoded in colors.

5.B. Quantitative results

The classification was quantitatively evaluated through measures of sensitivity, specificity, accuracy, and AUC. Table III lists the classification results associated with μ and σ of these four metrics by increasing the number of mRMR selected features as inputs in the classification. For example, feature number 5 means that the top five features selected by the mRMR method were used to perform the classification task. In addition, the number of features from each feature class is listed in Table III. Moreover, Fig. 4 illustrates a histogram plot of classification accuracy on a plaque target basis using the top selected 20 features.

Figure 5(a) shows the corresponding ROC curves of each feature set tabulated in Table III. For a good visualization, only the number of features between 5 and 35 were plotted in the ROC curves. The trend of AUC curve shown in Fig. 5(b) illustrates improved classification performance for the SpTeT based method as the number of selected feature was increased till the peak performance was obtained at feature number 20.

5.C. Computation analysis

The computational complexity with respect to 3D volume registration, vessel wall segmentation, SpTeT feature extraction, and voxel level classification was measured using the Matlab code on an Intel Core2 2.67GHz machines with a 4GB RAM. Since the plaque targets used in the experiments contain different sizes of vessels and different numbers of 2D image sections, the computational times reported here are the average values by using one image section of DCE-MRI.

The running time for registering a pair of DCE-MRI and T1wBB sequences is 0.32 s. The inner and outer vessel segmentation performed on registered DCE-MRI and T1wBB

FIG. 2. Four examples of 3D graph embedding (GE) plots for (a): first-order textural feature (mean); (b) first-order textural feature (median); (c) Haralick (intensity entropy); and (d) Gabor filter (6th scale and 8th orientation). GE is a nonlinear dimensionality reduction scheme to transform high-dimensional data into low-dimensional embedding representations. 3D GE plotting for specific feature was utilized to visualize the discriminability of feature to cluster the plaques into distinct categories. The figures demonstrated that the SpTeT features are effective imaging based descriptors for differentiating vulnerable and stable plaques.

take 0.67 s and 0.39 s, respectively. For one section of DCE-MRI containing eight time points, the process of feature extraction takes 1.82 s. For a classification task using 20 selected features, the average computational time is 0.41 s for one iterative cross validation.

5.D. Result discussion

The qualitative results of 3D plots of classification boundaries shown in Fig. 2 suggested that the SpTeT features are robust and effective descriptors for differentiating VAP

FIG. 3. Two examples of the contrast enhancement patterns associated with a stable plaque (first row) and a vulnerable plaque (second row). (a) and (e) Precontrast images. (b) and (f) Postcontrast images at peak enhancement. (c) and (g) The vessel and lumen segmentation overlaid on (a) and (e), respectively. The outer contour indicates vessel outer wall, and the inner contour indicates lumen area. (d) and (h) The texture images using the first-order texture (mean) feature corresponding to (b) and (f), respectively. The color encoded texture images suggested a higher heterogeneity in lesion enhancement patterns for the vulnerable plaques compared to the stable plaques.

TABLE III. The RF classification performance using different number of mRMR selected features was measured by classification accuracy (AC), sensitivity (SN), specificity (SP), and AUC values. The number of features from each feature class that were selected by mRMR is given in brackets. A combination of 20 features yielded the highest AC, SP, AUC, and second highest SN values.

No. of features	Feature name	AC ($\mu_{AC} \pm \sigma_{AC}$)	SN ($\mu_{SN} \pm \sigma_{SN}$)	SP ($\mu_{SP} \pm \sigma_{SP}$)	AUC ($\mu_{AUC} \pm \sigma_{AUC}$)
5	Kirsch(1), Haralick(2), First-order textural(2)	83.29% $\pm$ 0.43%	74.36% $\pm$ 1.20%	89.17% $\pm$ 0.82%	0.9057 $\pm$ 0.0216
10	Kirsch(3), Haralick(2), First-order textural(5)	86.62% $\pm$ 0.16%	79.33% $\pm$ 0.70%	91.80% $\pm$ 0.37%	0.9357 $\pm$ 0.0114
15	Kirsch(4), Haralick(4), Sobel(1), First-order textural(6)	89.90% $\pm$ 0.27%	83.71% $\pm$ 1.71%	94.31% $\pm$ 0.41%	0.9417 $\pm$ 0.0103
20	Kirsch(5), Haralick(5), Sobel(2), First-order textural(7), Gabor(1)	89.98% $\pm$ 0.57%	83.54% $\pm$ 1.02%	94.55% $\pm$ 0.48%	0.9631 $\pm$ 0.0088
25	Kirsch(7), Haralick(6), Sobel(2), First-order textural(8), Gabor(2)	89.76% $\pm$ 0.29%	82.85% $\pm$ 0.54%	94.67% $\pm$ 0.45%	0.9594 $\pm$ 0.0074
30	Kirsch(10), Haralick(7), Sobel(2), First-order textural(9), Gabor(2)	89.61% $\pm$ 0.29%	82.16% $\pm$ 0.78%	94.91% $\pm$ 0.19%	0.9580 $\pm$ 0.0067
35	Kirsch(10), Haralick(7), Sobel(2), First-order textural(12), Gabor(3)	89.34% $\pm$ 0.19%	82.06% $\pm$ 0.65%	94.52% $\pm$ 0.41%	0.9548 $\pm$ 0.0054
40	Kirsch(11), Haralick(8), Sobel(2), First-order textural(16), Gabor(3)	88.57% $\pm$ 0.33%	80.86% $\pm$ 1.08%	94.05% $\pm$ 0.34%	0.9534 $\pm$ 0.0073
45	Kirsch(11), Haralick(8), Sobel(2), First-order textural(21), Gabor(3)	88.72% $\pm$ 0.37%	80.35% $\pm$ 1.67%	94.67% $\pm$ 0.58%	0.9509 $\pm$ 0.0069
50	Kirsch(11), Haralick(8), Sobel(2), First-order textural(26), Gabor(3)	88.41% $\pm$ 0.37%	80.02% $\pm$ 1.19%	94.38% $\pm$ 0.21%	0.9485 $\pm$ 0.0084
55	Kirsch(11), Haralick(9), Sobel(2), First-order textural(29), Gabor(3)	88.28% $\pm$ 0.36%	79.89% $\pm$ 0.77%	94.25% $\pm$ 0.15%	0.9433 $\pm$ 0.0092

from SAP. Moreover, the color encoded texture images using the first-order texture (mean) feature shown in Fig. 3 reveal that the VAP appears more heterogeneous compared to the SAP, suggesting a higher heterogeneity in lesion enhancement patterns.

The quantitative results tabulated in Table III showed that the first-order textural, Kirsch, and Haralick features were the top three feature classes to be selected by the mRMR method. The AUC curve [Fig. 5(b)] illustrates that the AUC measure starts to decrease after reaching its peak (number of feature is 20), even more features were utilized to perform the classification. This is due to the fact that high-dimensional input data may overfit the training samples, thus leading to poor predictive performance in the classification. This is also referred to as the curse of dimensionality.⁴⁴ Further, from

Table III, these top 20 selected features included 7 first-order textural, 5 Haralick, 5 Kirsch, 2 Sobel, and 1 Gabor filter features, suggesting that a combination of all five SpTeT feature class could provide a complete and effective set of image markers, thus leading to a superior classification performance in distinguishing VAP from SAP. Although the classification accuracy was measured on the voxel basis, the histogram plot shown in Fig. 4 suggests that the SpTeT features can more accurately identify SAP than VAP, which is consistent with the SN and SP measures in Table III.

In this work, DCE-MRI was the only MRI protocol used for feature extraction and subsequent classification. The prior work⁴⁵ illustrates that intelligent integration of parameters from multiparametric MRI data may allow for capture of even more disease pertinent information. This could

FIG. 4. A histogram plot shows the classification accuracy (AC) for each plaque target using the top 20 selected features. The results suggested that the SpTeT features can more accurately identify SAP compared to VAP.

FIG. 5. (a) The ROC curves use different number of mRMR selected features. (b) The AUC curve by varying number of selected features. A combination of 20 features yielded the highest AUC values.

potentially allow for an improvement in disease detection, diagnosis, and prognosis. Other image protocols, such as T1wBB, coronal 3D phase contrast MR angiograms, can be included in the MRI exam. Moreover, a combination of MRI and positron emission tomography (PET) has been studied and showed capability in assessing inflammation in atherosclerotic plaques.⁴⁶ Both anatomical and functional information extracted on these image modalities, along with SpTeT features, would form a complimentary set of imaging attributes for better characterization of pathologies in subtypes of vascular lesions. Although SpTeT features have shown good classification results in distinguishing VAP from SAP, we believe that a combination of SpTeT features from DCE-MRI and imaging attributes from other image protocols can further improve the discrimination results.

In addition, the work presented here was evaluated on rabbit aortic data using DCE-MRI. Recent studies have revealed the histological similarities between rabbit and human plaques, including six well-characterized stages of human plaques, and many histological characteristics in rabbit disrupted plaques, such as thin fibrous cap, dense lipid-core, increased inflammatory infiltrate, etc., which are features of plaque vulnerability in humans.^{3,47} Also *in vivo* MRI measurements have been proved to be effective to identify plaques with a high risk for sudden disruption.⁴⁸ Although thrombosis in rabbit shares several well-established histological features of plaque vulnerability as those described in humans, no animal model is expected to exhibit all features of human atherosclerosis and plaque rupture.³ In real-world clinical practice, the SpTeT features need to be further tested using human subjects.

6. CONCLUDING REMARKS

In this paper, we presented a spatio-temporal texture based method to discriminate between stable and vulnerable aortic plaques by DCE-MRI using a rabbit model. Unlike previous work focusing on PK model or kinetic parameters calculated on time-intensity curve, we studied a complimentary set of spatio-temporal texture features to quantitatively mea-

sure the local and global imaging changes within the plaque over the course of contrast injection. The SpTeT features reflected the heterogeneity of contrast uptake between the subtypes of pathologies of vulnerable and stable plaques through kinetic texture descriptors. The computerized SpTeT features were evaluated in a voxel-based classification. The quantitative results showed that a combination of all five SpTeT feature classes, yielded the highest AUC values of 0.9631, which was consistent with the best AC, SP, and second best SN values in the RF classification. The extracted spatio-temporal texture attributes can serve as effective imaging biomarkers to establish noninvasive imaging-based test for distinguishing vulnerable from stable plaque.

Future work will entail an intelligent combination of imaging attributes from individual image protocols in order to develop powerful meta-classifiers. While the qualitative and quantitative results are promising, the computerized SpTeT features need to be further evaluated on a larger cohort of data.

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¹V. L. Roger *et al.*, "Heart disease and stroke statistics 2012 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation* **125**, 2–220 (2012).

²A. V. Finn, M. Nakano, J. Narula, F. D. Kolodgie, and R. Virmani, "Concept of vulnerable/unstable plaque," *Arterioscler., Thromb., Vasc. Biol.* **30**, 1282–1292 (2010).

- ³A. Phinikaridou, N. Hua, T. Pham, and J. A. Hamilton, "Regions of low endothelial shear stress co-localize with positive vascular remodeling and atherosclerotic plaque disruption: An *in vivo* MRI study," *Circ.: Cardio-vasc. Imaging* **6**(2), 302–310 (2013).
- ⁴T. Thom *et al.*, "Heart disease and stroke statistics 2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation* **113**, e85–e151 (2006).
- ⁵V. Jasti, E. Ivan, V. Yalamanchili, N. Wongpraparut, and M. A. Leeser, "Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis," *Circulation* **110**(18), 2831–2836 (2004).
- ⁶S. E. Nissen and P. Yock, "Intravascular ultrasound: Novel pathophysiological insights and current clinical applications," *Circulation* **103**(4), 604–616 (2001).
- ⁷J. Sanz and Z. A. Fayad, "Imaging of atherosclerotic cardiovascular disease," *Nature* **451**, 953–957 (2008).
- ⁸B. Chu, M. S. Ferguson, H. Chen, D. S. Hippe, W. S. Kerwin, G. Canton, C. Yuan, and T. S. Hatsukami, "MRI features of the disruption-prone and the disrupted carotid plaque: A pictorial essay," *JACC Cardiovasc. Imaging* **2**(7), 883–896 (2009).
- ⁹W. Kerwin, D. Xu, F. Liu, T. Saam, H. Underhill, N. Takaya, B. Chu, T. Hatsukami, and C. Yuan, "Magnetic resonance imaging of carotid atherosclerosis: plaque analysis," *Top Magn. Reson. Imaging* **18**(5), 371–378 (2007).
- ¹⁰W. M. Suh, A. H. Seto, R. J. Margey, I. Cruz-Gonzalez, and I. K. Jang, "Intravascular detection of the vulnerable plaque," *Circ. Cardiovasc. Imaging* **4**(2), 169–178 (2011).
- ¹¹B. Sun *et al.*, "Automatic plaque characterization employing quantitative and multicontrast MRI," *Magn. Reson. Med.* **59**(1), 174–180 (2008).
- ¹²L. G. Spagnoli, A. Mauriello, G. Sangiorgi, S. Fratoni, E. Bonanno, R. S. Schwartz, D. G. Piepgras, R. Pistolese, A. Ippoliti, and D. R. Holmes, "Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke," *J Am. Med. Assoc.* **292**(15), 1845–1852 (2004).
- ¹³P. R. Moreno, "Vulnerable plaque: Definition, diagnosis, and treatment," *Cardiol. Clinics* **28**(1), 1–30 (2010).
- ¹⁴J. Cai, T. S. Hatsukami, M. S. Ferguson, W. S. Kerwin, T. Saam, B. Chu, N. Takaya, N. L. Polissar, and C. Yuan, "In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology," *Circulation* **112**(22), 3437–3444 (2005).
- ¹⁵H. C. Groen, F. J. Gijzen, A. van der Lugt, M. S. Ferguson, T. S. Hatsukami, A. F. van der Steen, C. Yuan, and J. J. Wentzel, "Plaque rupture in the carotid artery is localized at the high shear stress region: A case report," *Stroke* **38**(8), 2379–2381 (2007).
- ¹⁶L. Biasioli, A. C. Lindsay, J. T. Chai, R. P. Choudhury, and M. D. Robson, "In vivo quantitative T2 mapping of carotid arteries in atherosclerotic patients: segmentation and T2 measurement of plaque components," *J. Cardiovasc. Magn. Reson.* **15**, 69 (2013) (accessed 16 August 2013).
- ¹⁷P. G. Camici, O. E. Rimoldi, O. Gaemperli, and P. Libby, "Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque," *Eur. Heart J.* **33**(11), 1309–1317 (2012).
- ¹⁸I. Adame, R. van der Geest, B. Wasserman, M. Mohamed, J. Reiber, and B. Lelieveldt, "Automatic segmentation and plaque characterization in atherosclerotic carotid artery MR images," *Magn. Reson. Mater. Phys., Biol. Med.* **16**(5), 227–234 (2004).
- ¹⁹R. van't Klooster *et al.*, "Automated versus manual *in vivo* segmentation of carotid plaque MRI," *NJNR Am. J. Neuroradiol.* **33**(8), 1621–1627 (2012).
- ²⁰C. Calcagno, V. Mani, S. Ramachandran, and Z. A. Fayad, "Dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) of atherosclerotic plaque angiogenesis," *Angiogenesis* **13**(2), 87–99 (2010).
- ²¹T. S. Hatsukami and C. Yuan, "MRI in the early identification and classification of high-risk atherosclerotic carotid plaque," *Imaging Med.* **2**(1), 63–75 (2010).
- ²²H. Chen, J. Ricks, M. Rosenfeld, and W. S. Kerwin, "Progression of experimental lesions of atherosclerosis: assessment by kinetic modeling of black-blood dynamic contrast-enhanced MRI," *Magn. Reson. Med.* **69**(6), 1712–1720 (2013).
- ²³M. E. Gaens *et al.*, "Dynamic contrast-enhanced MR imaging of carotid atherosclerotic plaque: model selection, reproducibility, and validation," *Radiology* **266**(1), 271–279 (2013).
- ²⁴S. C. Agner, S. Soman, E. Libfeld, M. McDonald, K. Thomas, S. Englander, M. A. Rosen, D. Chin, J. Noshier, and A. Madabhushi, "Textural kinetics: A novel dynamic contrast-enhanced (DCE)-MRI feature for breast lesion classification," *J. Digital Imaging* **24**, 446–463 (2011).
- ²⁵K. Engel, M. Hadwiger, J. Kniss, C. Rezk-Salama, and D. Weiskopf, *Real-Time Volumen Graphics* (Eurographics Association, Natick, MA, 2008).
- ²⁶R. Kirsch, "Computer determination of the constituent structure of biological images," *Comput. Biomed. Res.* **4**(3), 315–328 (1971).
- ²⁷S. E. Grigorescu, N. Petkov, and P. Kruijzinga, "Comparison of texture features based on Gabor filters," *IEEE Trans. Image Process.* **11**(10), 1160–1167 (2002).
- ²⁸F. Bianconi and A. Fernandez, "Evaluation of the effects of Gabor filter parameters on texture classification," *Pattern Recogn.* **40**(12), 3325–3335 (2007).
- ²⁹R. M. Haralich, "Statistical and structural approaches to texture," *Proc. IEEE* **67**(5), 786–804 (1979).
- ³⁰W. Chen, M. L. Giger, and U. Bick, "Computerized interpretation of breast MRI: investigation of enhancement-variance dynamics," *Med. Phys.* **31**(5), 1076–1082 (2004).
- ³¹X. Yang and M. V. Knopp, "Quantifying tumor vascular heterogeneity with dynamic contrast-enhanced magnetic resonance imaging: A review," *J. Biomed. Biotechnol.* **2011**, 732848 (12pp.) (2011).
- ³²H. Mehrabian, R. Chopra, and A. L. Martel, "Calculation of intravascular signal in dynamic contrast enhanced-MRI using adaptive complex independent component analysis," *IEEE Trans. Med. Imaging* **32**(4), 699–710 (2013).
- ³³N. Bhooshan, M. L. Giger, S. A. Jansen, H. Li, L. Lan, and G. M. Newstead, "Cancerous breast lesions on dynamic contrast-enhanced MR images: computerized characterization for image-based prognostic markers," *Radiology* **254**(3), 680–690 (2010).
- ³⁴Y. Zheng, S. Englander, S. Baloch, E. I. Zacharaki, Y. Fan, M. D. Schnall, and D. Shen, "Step: Spatiotemporal enhancement pattern for MR-based breast tumor diagnosis," *Med. Phys.* **36**(7), 3192–3204 (2009).
- ³⁵C. Li, C. Xu, C. Gui, and M. D. Fox, "Distance regularized level set evolution and its application to image segmentation," *IEEE Trans. Image Process.* **19**(12), 3243–3254 (2010).
- ³⁶H. Peng, F. Long, and C. Ding, "Feature selection based on mutual information: Criteria of max-dependency, max-relevance, and min-redundancy," *IEEE Trans. Pattern Anal. Mach. Intell.* **27**(8), 1226–1238 (2005).
- ³⁷L. Breiman, "Random forests," *Mach. Learn.* **45**(1), 5–32 (2001).
- ³⁸J. P. W. Pluim, J. B. A. Maintz, and M. A. Viergever, "Mutual-information-based registration of medical images: A survey," *IEEE Trans. Med. Imaging* **22**(8), 986–1004 (2003).
- ³⁹J. Chappelow, A. Madabhushi, M. Rosen, J. E. Tomaszewski, and M. D. Feldman, "A combined feature ensemble based mutual information scheme for robust inter-modal, inter-protocol image registration," in *Proceedings of IEEE International Symposium on Biomedical Imaging: From Nano to Macro* (IEEE, Metro Washington DC, 2007), pp. 644–647.
- ⁴⁰Z. Xu, U. Bagci, B. Foster, A. Mansoor, and D. J. Mollura, "Spatially constrained random walk approach for accurate estimation of airway wall surfaces," in *Proceedings of MICCAI* (Springer, Berlin Heidelberg, Germany, 2013), Vol. 8150, pp. 559–566.
- ⁴¹D. Bagkavos and P. N. Patil, "Local polynomial fitting in failure rate estimation," *IEEE Trans. Reliab.* **57**(1), 41–52 (2008).
- ⁴²N. R. Draper and H. Smith, *Applied Regression Analysis*, 3rd ed. (John Wiley & Sons, Inc., New York, 1998).
- ⁴³S. Yan, D. Xu, B. Zhang, H. Zhang, Q. Yang, and S. Lin, "Graph embedding and extensions: A general framework for dimensionality reduction," *IEEE Trans. Pattern Anal. Mach. Intell.* **29**, 40–51 (2007).
- ⁴⁴R. E. Bellman, *Dynamic Programming* (Dover, New York, 2003).
- ⁴⁵S. Viswanath, B. N. Bloch, J. Chappelow, P. Patel, N. Rofsky, R. Lenkinski, E. Genega, and A. Madabhushi, "Enhanced multi-protocol analysis via intelligent supervised embedding (EMPrAvISE): detecting prostate cancer on multi-parametric MRI," *Proc. SPIE* **7963**, 79630U (2011).
- ⁴⁶M. D. Majmudar *et al.*, "Polymeric nanoparticle PET/MR imaging allows macrophage detection in atherosclerotic plaques," *Circ. Res.* **112**(5), 755–761 (2013).
- ⁴⁷A. Phinikaridou, K. J. Hallock, Y. Qiao, and J. A. Hamilton, "A robust rabbit model of human atherosclerosis and atherothrombosis," *J. Lipid Res.* **50**(5), 787–797 (2009).
- ⁴⁸A. Phinikaridou, F. L. Ruberg, K. J. Hallock, Y. Qiao, N. Hua, J. Viereck, and J. A. Hamilton, "In vivo detection of vulnerable atherosclerotic plaque by MRI in a rabbit model," *Circ. Cardiovasc. Imaging* **3**(3), 323–332 (2010).