The 2 most frequent underlying mechanisms for sudden cardiac death and acute coronary syndrome (ACS) are plaque rupture and plaque erosion.1–3 Plaque rupture has been well characterized both ex vivo and in vivo.1,4 However, an in vivo diagnosis of plaque erosion in patients with ACS had not been possible because of the lack of a diagnostic modality. Recently, our group reported an algorithm for in vivo diagnosis of plaque erosion using a high-resolution diagnostic technique, optical coherence tomography (OCT).5–7 However, the diagnostic algorithm used in the study was based on qualitative morphological assessment, which has potentially high inter- and intraobserver variability. Plaque erosion has distinct pathological properties, including proteoglycan-rich and smooth muscle cell–rich fibrous regions lacking a superficial endothelial layer.2,3,8 We hypothesized that quantitative diagnostic metrics of superficial tissue properties can provide more objective criteria, which may enhance in vivo diagnosis of plaque erosion. Furthermore, quantitative metrics can allow for multiple time point comparison of the same lesion, which may advance our understanding of natural history of plaque erosion and the response to treatment.

The aims of this study are to investigate the quantitative tissue properties that can differentiate plaque erosion from intact fibrous plaques and to develop a computer-aided classification model for in vivo diagnosis of plaque erosion.

Methods

Study Population

Patients with ACS who have undergone preintervention OCT imaging of the culprit lesion were identified from the Massachusetts General Hospital, Harvard Medical School, Boston, MA.

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General Hospital OCT Registry database. Patients with a prior stent implantation in the culprit vessel, the culprit lesion located in a bypass graft, massive residual thrombus overlying the eroded site, and poor image quality were excluded. Patients requiring balloon dilatation before OCT imaging were also excluded. Only patients imaged with frequency-domain OCT were included. Among 127 patients with ACS and evaluable OCT images, 42 patients with definite OCT erosion based on the previously established criteria were included in the final analysis. The culprit lesion was identified on the basis of the findings by coronary angiogram, stress test, ECG, left ventriculogram, or echocardiogram. The protocol for the OCT Registry was approved by each contributing site’s institutional review board, and all patients provided informed consent.

**OCT Image Acquisition**

OCT images of the culprit lesions were acquired using a commercially available frequency-domain OCT system (C7XR intravascular imaging system, St. Jude Medical Inc, St Paul, MN). Aspiration thrombectomy was performed if the thrombolysis in myocardial infarction flow grade was ≤2 before OCT imaging. A 2.7 F OCT catheter was advanced distal to the culprit lesion. Automated pullback was then performed at 20 mm/s, while blood was displaced by a short injection of contrast media prior to the culprit lesion. Automated pullback was then performed at 20 mm/s, while blood was displaced by a short injection of contrast media. After analysis, Z-offset was carefully corrected for each image. Before analysis, Z-offset was carefully corrected for each image. The raw linear-scale OCT data were then analyzed according to the following method. First, quantitative image features were extracted from each ROI. Then, effective features were selected and used to build a diagnostic model for plaque erosion using a training data set randomly pulled from the total data set. The classification accuracy of the model was tested in the remaining validation data set. The details of each step are described below.

**Image Analysis**

One cross-sectional frame with plaque erosion was selected from each lesion based on previously published OCT criteria for erosion. A region of interest (ROI) of each eroded plaque was traced manually by an experienced investigator. Two areas were selected: the focal region of erosion with mural thrombus (defined as erosion-focal) and the adjacent tissue without thrombus (defined as erosion-adjacent; Figure 1). For every eroded plaque, 1 cross-sectional frame of a typical fibrous plaque 25 mm away from the lesion in the same vessel was used as the control. A total of 42 ROIs for erosion-focal, erosion-adjacent, and control fibrous plaques were identified for subsequent image analysis.

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Pathologically, plaque erosion is defined as a loss of endothelial lining with lacerations of the superficial intimal layers in the absence of trans-cap ruptures. However, the limited axial resolution of OCT (10–15 μm) is unable to directly discern the loss of endothelium. To capture the surface signatures of plaque erosion but to include enough OCT signal for both intensity and texture analysis, we analyzed both the 50-μm superficial layer from the lumen boundary (defined as surface tissue) and the erosion ROI. In total, 7 features were extracted from each ROI. These features can be categorized into optical and morphological properties of tissue. The optical properties of tissue include the mean intensity of the surface tissue, mean intensity of the ROI, optical attenuation, and texture features characterized by the normalized SD (NSD) of both the surface tissue and the ROI. To account for intensity differences caused by different OCT machines and catheters used, all the intensity values of a lesion in every cross-sectional image were normalized to the mean intensity of the image foreground, which was generated by bimodal histogram thresholding. For this reason, all the intensity metrics derived in this study are relative intensity index as opposed to absolute intensity values. But for the sake of simplicity, we still use intensity throughout this article. For attenuation analysis, we computed the negative slope of the log-compressed signal of the first 250-μm deep tissue in the ROI, which is proportional to the attenuation coefficient of the tissue in this region. The morphological properties of tissue include the tissue protrusion area and roughness of the tissue surface. For computation of the 2 features, we first defined a smoothed convex hull of the lumen boundary (defined as smooth convex hull-lumen). This boundary was generated by first computing the convex hull of the real lumen boundary and then smoothing the boundary with splines. Effectively, the protruding region (eg, thrombus) was removed and the boundary was smoothed to the smoothed convex hull-lumen (Figure 2). Then, tissue protrusion area was simply defined as the area difference between the segmented real lumen boundary and the computed smooth convex hull-lumen in the ROI region. Roughness of tissue surface was defined as the SD of the distances between the real lumen and smooth convex hull-lumen in the ROI region. The available data were randomly partitioned into 50% training and 50% validation sets. Effective features were selected and were used to build a logistic regression classifier with the training data. The remaining 50% data set was used to test the classification accuracy. To avoid partition bias, 10-fold cross validation was also applied. Both binary (erosion versus nonerosion) and probabilistic output can be generated based on the definition of logistic regression.

To determine the interobserver variability of the algorithm, a second operator independently reselected the frames and retraced the ROI for all the lesions, and the performance of the algorithm was tested. To assess intraobserver variability, all lesions were reanalyzed by the same operator 2 months later. To compare the diagnostic accuracy between the quantitative algorithm and qualitative visual assessment by human experts, images from 36 lesions randomly selected from the total data set were deidentified and analyzed by the algorithm and by another independent operator. The operator performed binary classification by visually inspecting the focal, proximal, and distal regions of the lesion. The algorithm was trained using data from 24 eroded and 24 control lesions.

**Figure 1.** Representative cases of plaque erosion and a control fibrous plaque. Examples of plaque erosion and a control fibrous plaque included for analysis. Regions of interest were traced (blue contour) in the erosion-focal, erosion-adjacent region, and in a control fibrous plaque remote (≥5 mm) from the culprit site.
fibrous plaques different from the test data. The data were reviewed by 3 observers who were not involved in the initial analysis and their consensus was used as the gold standard.

Statistical Analysis

All measurements are presented as mean±SD. Plaque characteristics between erosion-focal, erosion-adjacent, and control fibrous plaques were compared using repeated measures ANOVA. A P value of <0.05 is considered statistically significant. A logistic regression model was built from the training data using the SimpleLogistic function in Weka. This function also has a built-in feature selection functionality, which starts with a univariate model and only adds more features if this improves the performance of the model based on cross validation. Logistic model-based receiver operating characteristics (ROC) were used to determine the predictability for plaque erosion. Cohen κ coefficient was used to assess intra- and interobserver variability. Statistical analyses were performed using SPSS (version 17.0, SPSS, Inc, Chicago, IL). Feature extraction was performed in MATLAB (The MathWorks, Inc). Model training and validation were performed in Weka.

Results

The clinical characteristics of patients included in this study are summarized in the Table. The optical and morphological characteristics of erosion-focal, erosion-adjacent, and control fibrous plaque are shown in Figure 3. Erosion-focal has significantly lower surface tissue intensity (0.941±0.320 versus 1.366±0.456; P<0.001), lower ROI intensity (1.008±0.354 versus 1.447±0.324; P<0.001), lower surface NSD (0.025±0.013 versus 0.041±0.023; P<0.001), lower ROI NSD (0.027±0.014 versus 0.040±0.017; P<0.001), higher tissue attenuation (1.658±0.523 versus 1.306±0.375; P<0.001), larger tissue protrusion area (0.181±0.136 versus 0.020±0.010 mm²; P<0.001), and greater surface roughness (0.078±0.039 versus 0.008±0.004 mm; P<0.001) when compared with control fibrous plaque. Erosion-adjacent plaque also has lower ROI NSD (0.031±0.015; P=0.008), higher attenuation (1.740±0.696; P<0.001), and greater surface roughness (0.011±0.007 mm; P=0.005) when compared with control. Erosion-focal region has significantly lower surface intensity (P<0.001), lower ROI intensity (P<0.001), lower surface NSD (P=0.003), lower ROI NSD (P=0.016), larger protrusion area (P<0.001), and greater surface roughness (P<0.001) when compared with erosion-adjacent region.

Three features were selected as the subset with the most predictive power. They are surface roughness, attenuation, and ROI intensity. With the training data, the logit-link generalized linear model to predict the plaque erosion Y (1=erosion; 0=noneroded fibrous plaque) that was built on the 3 features is

\[ \eta = \logit \left( \frac{\text{probability of plaque erosion } Y}{1 - \text{probability of plaque erosion } Y} \right) = -1.39 + 115.13 \times \text{surf}_\text{roughness} + 1.15 \times \text{attenuation} - 2.32 \times \text{ROI intensity} \]

The binary classification model is

\[ \eta = \ln \left( \frac{\pi}{1 - \pi} \right) > 0 : \text{erosion} (Y = 1) \]
\[ \eta = \ln \left( \frac{\pi}{1 - \pi} \right) < 0 : \text{noneroded fibrous plaque} (Y = 0) \]

The probabilistic logistic regression model is

Probability \( \text{plaque erosion}, Y = 1 \) = \( \pi = 1 / [1 + \exp(-\eta)] \)

Figure 4 presents some typical examples with plaque erosion (or control) labeled with different likelihood by the classification model.

With 50% data for training and the remaining data for validation, the binary classification model for erosion-focal versus control fibrous plaque achieved a classification accuracy of 100%, sensitivity of 100%, specificity of 100%, and area under the ROC curve of 1. With 10-fold cross validation, the model achieved an accuracy of 97.6%, sensitivity of 100%,
specificity of 95.2%, and area under the ROC curve of 0.997. The area under the ROC curve using this model (0.997) with selected features was superior to that of the full model using all features (0.984) and was better than that using only the morphological descriptors including the tissue protrusion area and surface roughness (0.982).

The inter- and intraobserver \( \kappa \) coefficients using the algorithm to assess plaque erosion were both 95.2%. For algorithm-visual assessment comparison in the randomly selected 36 lesions, the accuracies of the algorithm and the operator using the consensus results as the gold standard were 88.9% and 83.3%, respectively.

**Discussion**

The main findings of this study are (1) plaque erosion has significantly different optical and morphological properties in both the focal and nonfocal regions compared with remote, intact fibrous plaques and (2) with the computer-aided diagnostic
model, plaque erosion can be accurately classified based on the quantitative image features extracted from the lesion.

The quantitative features explored in this study are highly representative signatures for plaque erosion but may not be evidently noticeable by human eyes. The low intensity of eroded tissue surface and core, as well as the mass protrusion attributable to eroded surface or presence of mural thrombus, is expected and confirmed by the analysis. The high optical attenuation associated with erosion-focal region is mainly caused by the presence of thrombus, which strongly absorbs the near-infrared light of OCT. Interestingly, even erosion-adjacent area in the absence of obvious thrombus has high attenuation. It is possible that some platelet-rich thrombus is present on the surface around the erosion and causes the high attenuation of OCT signal. Alternatively, eroded plaques are characterized by proteoglycan-rich and smooth muscle cell-rich tissue, which may have low signal intensity. The low ROI NSD both in the erosion-focal and in the erosion-adjacent region suggests homogeneous texture of the eroded plaque composition, which is consistent with the pathology findings that plaque erosion has lacerated intima layer, less calcification, and less often macrophages and T cells compared with plaque ruptures.7 These features may be used to investigate the natural history of plaque erosion in longitudinal studies.

As OCT does not have sufficient resolution to detect individual endothelial cells, the OCT definition of plaque erosion was based primarily on exclusion criteria requiring the absence of fibrous cap rupture and calcified nodules. In this study, we focused primarily on the optical and morphological properties of tissue, and the resulting classification model has high accuracy for distinguishing definite OCT erosion from intact fibrous plaques. It is likely that combining the additional pathology information such as presence of calcified nodules or lipid plaques in regions proximal or distal to the lesion may even further improve the classification. For the same reason, we do not expect the algorithm in the current stage to be used in place of human experts in making the diagnosis. However, we think that by combining with expert knowledge of clinical information, the algorithm can effectively help reduce the uncertainty associated with visual inspections because of its consistency. The ability of the proposed method to generate probabilistic output is highly attractive for further incorporation of additional evidence into the model. In addition, the likelihood of plaque erosion may be used to develop a different treatment strategy (conservative antithrombotic therapy versus invasive coronary stenting) for that particular patient.

In this study, the ROIs of plaque erosion were traced manually to train the classifier with typical erosion characteristics. However, the ROIs can potentially be selected automatically for rapid plaque erosion screening during clinical practice. Figure 5 shows 2 examples where the algorithm was applied to every angular position of the vessel. For each position, the ROI was automatically selected as a 10-degree region and was bounded radially by the lumen boundary and the vessel wall (approximately by the adventitia boundary or noise floor because of insufficient penetration depth of OCT) using the segmentation methods described by Wang et al.19,20 The regions with high likelihood of plaque erosion can be more easily identified in the color-coded image as compared with the structural image alone.

Most existing imaging methods are unable to detect plaque erosion in vivo. Noninvasive imaging modalities such as computed tomography and MRI have insufficient resolution to characterize atherosclerotic plaques in the coronary arteries. Coronary angiography is considered the gold standard for the evaluation of patients presenting with ACS. However, angiography shows only the lumen and major stenoses but is unable to visualize individual plaques. Intravascular ultrasound is able to assess plaque burden and remodeling but has limited resolution and cannot detect thin-cap fibroatheroma or plaque erosion, both of which are considered major precursors of coronary thrombosis.1–3 Intravascular OCT has much higher resolution and can identify thin-cap fibroatheroma20,21 and detect plaque erosion in vivo.7 This makes OCT an ideal tool for assessing plaque vulnerability. As OCT is becoming more widely used during clinical practice, a rapid and effective method for diagnosis of plaque erosion with OCT is important. In this study, a simple yet highly accurate logistic regression model was proposed as the quantitative diagnostic model. This may dramatically ease the diagnosis of plaque erosion and reduce the associated intra- and interobserver variability. Computer-aided analysis can provide complementary criteria in addition to the qualitative diagnostic algorithm previously defined by Jia et al.7 Potentially, computer-aided diagnostic models can be made automatic, providing real-time feedback during the clinical procedure, facilitating timely diagnosis and treatment to improve patient care.

Figure 5. Automated labeling of plaque erosion. Two examples of optical coherence tomographic images are labeled automatically for the likelihood of plaque erosion using the proposed algorithm. At each angular position, the region of interest (ROI) was selected automatically as a 10-degree region bounded radially by the lumen boundary and the vessel wall. The algorithm was then applied to the ROI and the likelihood of plaque erosion can be generated for this position. The entire vessel can therefore be automatically labeled in a continuous colormap indicating the likelihood of plaque erosion.
Study Limitations
First, the sample size (n=42) of this study is relatively small. Second, the algorithm is only validated against human expert diagnosis, but not by histopathology. However, validation of the algorithm by pathology is difficult because of the lack of available histopathology from imaged coronary artery specimens from surviving subjects. Also, there would likely be fundamental differences in images of culprit lesion features between autopsy specimens in patients who died from sudden cardiac death and images of culprit lesions in vivo using OCT in those who survived ACS and were treated with antithrombotics.

Conclusions
Plaque erosion has distinctive optical and morphological properties compared with intact fibrous plaques. The quantitative logistic regression model may be used to enhance diagnostic accuracy for plaque erosion in vivo and to help cardiologists to develop a targeted therapy.

Sources of Funding
This work was supported by grants from LightLab Imaging/St. Jude Medical (Dr Jang), the National Science Foundation of China (Dr Jia and Dr Tian), and the Italian Society of Cardiology (Dr Vergallo) as well as by Dr John Nam optical coherence tomography fellowship grant and by Michael and Kathryn Park.

Disclosures
Dr Jang received grant support and consulting fees from LightLab Imaging/St. Jude Medical Inc. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE
Recently the in vivo diagnosis of erosion has become possible using a high-resolution imaging modality, optical coherence tomography. In the patients with erosion, it seems that vascular integrity is better preserved and the residual lumen is larger. Therefore, it is conceivable that this patient subset may be treated with antithrombotic therapy without coronary stenting, avoiding stent-related acute and late complications. However, a diagnosis of erosion may be challenging and is subject to variability depending on the operator’s experience. This newly developed algorithm will help us to make the diagnosis of erosion more accurate, consistent, and simple. With the ability to make this instant diagnosis, cardiologists will be able to develop treatment strategies tailored for each individual patient.
Computer-Aided Image Analysis Algorithm to Enhance In Vivo Diagnosis of Plaque Erosion by Intravascular Optical Coherence Tomography
Zhao Wang, Haibo Jia, Jinwei Tian, Tsunenari Soeda, Rocco Vergallo, Yoshiyasu Minami, Hang Lee, Aaron Aguirre, James G Fujimoto and Ik-Kyung Jang

Circ Cardiovasc Imaging. 2014;7:805-810; originally published online July 17, 2014; doi: 10.1161/CIRCIMAGING.114.002084
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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