Computer-Aided Image Analysis Algorithm to Enhance In Vivo Diagnosis of Plaque Erosion by Intravascular Optical Coherence Tomography

Wang et al: Computer-Aided Diagnosis of Plaque Erosion

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Abstract

Background—Recent reports show that plaque erosion can be diagnosed in vivo using optical coherence tomography (OCT) in patients with acute coronary syndromes (ACS). However, quantitative OCT image criteria for computer-aided diagnosis of plaque erosion have not been established.

Methods and Results—A total of 42 patients with ACS caused by plaque erosion were included. Plaque erosion was identified according to the previously established OCT criteria. Both optical properties and morphological features of the focal eroded region as well as erosion-adjacent region were analyzed using a custom designed computer algorithm. Non-eroded fibrous plaques remote from the erosion site within the same vessel were used as controls. Compared to control plaques, eroded plaques have significantly lower surface intensity (p<0.001), lower region of interest (ROI) intensity (p<0.001), lower surface normalized standard deviation (NSD) (p<0.001), lower ROI NSD (p<0.001), higher optical attenuation (p<0.001), larger tissue protrusion area (p<0.001) and greater surface roughness (p<0.001). Erosion-adjacent regions also have lower ROI NSD (p=0.008), higher attenuation (p<0.001), and greater surface roughness (p=0.005). Using a logistic regression model built upon the quantitative features, plaque erosion can be accurately classified against intact fibrous plaques. There was low inter- and intra-observer variability associated with the algorithm-assisted quantitative assessment.

Conclusions—Plaque erosion has distinctive optical properties and morphological features compared to non-eroded fibrous plaques. Quantitative image analysis may enhance diagnostic accuracy for plaque erosion in vivo.

Key Words: plaque erosion, optical coherence tomography, acute coronary syndrome
The two 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 due to 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 intra-observer variability. Plaque erosion has distinct pathologic 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 pre-intervention OCT imaging of the culprit lesion were identified from the Massachusetts General Hospital (MGH) 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 prior to OCT imaging were also excluded. Only patients imaged with frequency-domain OCT were included. Among 127 ACS patients with evaluable OCT images, 42 patients with definite OCT-erosion based on the previously established criteria [7] 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, USA). Aspiration thrombectomy was performed if the thrombolysis in myocardial infarction (TIMI) 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/sec, while blood was displaced by a short injection of contrast media or low molecular weight dextran through the guiding catheter. The images were de-identified and digitally stored for off-line analysis.

Image Analysis

One cross-sectional frame with plaque erosion was selected from each lesion based on previously published OCT criteria for erosion [7]. 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, one cross-sectional frame of a typical fibrous plaque at least 5mm 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, respectively, were identified for subsequent image analysis.

Before analysis, Z-offset was carefully corrected for each image [6, 9]. 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 dataset randomly pulled from the total dataset. The classification accuracy of the model was tested in the remaining validation dataset. The details of each step are described below.

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 [1]. 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), as well as the erosion ROI. In total, seven 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 [10, 11], and tissue texture features characterized by the normalized standard deviation (NSD) [12] 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 bi-modal histogram thresholding [13].
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 paper. For attenuation analysis, we computed the negative slope of the log-compressed signal of the first 250μm deep tissue in the ROI, which is proportional to the attenuation coefficient of the tissue in this region [10, 11]. The morphological properties of tissue include the tissue protrusion area and roughness of the tissue surface. For computation of the two features, we first defined a smoothed convex hull of the lumen boundary (defined as SCH-lumen). This boundary was generated by first computing the convex hull [14] of the real lumen boundary and then smoothing the boundary with splines [15]. Effectively, the protruding region (e.g. thrombus) was removed and the boundary was smoothed to the SCH-lumen (Figure 2). Then, tissue protrusion area was simply defined as the area difference between the segmented real lumen boundary and the computed SCH-lumen in the ROI region. Roughness of tissue surface was defined as the standard deviation of the distances between the real lumen and SCH-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 [16] with the training data. The remaining 50% dataset was used to test the classification accuracy. To avoid partition bias, 10-fold cross validation was also applied. Both binary (erosion vs. non-erosion) and probabilistic output can be generated based on the definition of logistic regression.

To determine the inter-observer variability of the algorithm, a second operator independently re-selected the frames and re-traced the ROI for all the lesions, and the performance of the algorithm was tested. In order to assess intra-observer variability, all lesions were re-analyzed by the same operator two 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 dataset were de-identified 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 fibrous plaques different from the test data. The data were reviewed by three 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 analysis of variance (RM-ANOVA). A p value <0.05 is considered statistically significant. A logistic regression model was built from the training data using the SimpleLogistic function in Weka [17]. 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 [18]. Logistic model based Receiver Operating Characteristics (ROC) were used to determine the predictability for plaque erosion. Cohen's kappa coefficient was used to assess intra- and inter-observer variability. Statistical analyses were performed using SPSS (version 17.0, SPSS, Inc., Chicago, Illinois). 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. Compared to control fibrous plaque, erosion-focal has significantly lower surface tissue intensity (0.941±0.320 vs. 1.366±0.456, p<0.001), lower ROI intensity (1.008±0.354 vs. 1.447±0.324, p<0.001), lower surface NSD (0.025±0.013 vs. 0.041±0.023, p<0.001), lower ROI NSD (0.027±0.014 vs. 0.040±0.017, p<0.001), higher tissue attenuation (1.658±0.523 vs. 1.306±0.375, p<0.001), larger tissue protrusion area (0.181±0.136mm$^2$ vs. 0.020±0.010mm$^2$, p<0.001) and greater surface roughness (0.078±0.039mm vs. 0.008±0.004mm, p<0.001). 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) compared to 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) 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=non-eroded fibrous plaque) that was built upon the three features is:

$$\eta = \logit[\text{Probability of Plaque Erosion } Y, \pi] = \ln[\pi /(1- \pi)]$$

$$= -1.39 + 115.13 \times \text{Surf Roughness} + 1.15 \times \text{Attenuation} - 2.32 \times \text{ROI Intensity}$$

The binary classification model is:
The probabilistic logistic regression model is:

Probability [Plaque Erosion, Y=1] = \frac{1}{1+\exp(-\eta)}

\eta = \ln[\pi/(1-\pi)] > 0: Erosion (Y = 1)
\eta = \ln[\pi/(1-\pi)] < 0: Non-eroded fibrous plaque (Y = 0)

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 vs. control fibrous plaque achieved a classification accuracy of 100%, sensitivity of 100%, specificity of 100%, and area under the ROC curve (ROC-AUC) of 1. With 10-fold cross validation, the model achieved an accuracy of 97.6%, sensitivity of 100%, specificity of 95.2%, and ROC-AUC of 0.997. The ROC-AUC 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 intra-observer Kappa coefficients by employing 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 non-focal region compared with remote, intact fibrous plaques; 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 due to eroded surface or presence of mural thrombus, are 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 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 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 [2]. 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 upon 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 don’t expect the algorithm in the current stage to be used in place of human experts in making the diagnosis. However, we believe that by combining with expert knowledge of clinical information, the algorithm can effectively help reduce the uncertainty associated with visual inspections due to its consistency. The ability of the proposed method to generate probabilistic output is highly attractive for further incorporation of additional evidence into the model. Additionally, the likelihood of plaque erosion may be used to develop a different treatment strategy (conservative antithrombotic therapy vs. 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 two 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 (approximated by the adventitia boundary or noise floor due to insufficient penetration depth of OCT) using the segmentation methods described in [19] and [20]. The regions with high likelihood of plaque erosion can be more easily identified in the color-coded image as compared to the structural image alone.

Most existing imaging methods are unable to detect plaque erosion in vivo. Non-invasive imaging modalities such as computed tomography (CT) and magnetic resonance imaging (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 (IVUS) is able to assess plaque burden and remodeling, but has limited resolution and cannot detect thin-cap fibroatheroma (TCFA) or plaque erosion, both of which are considered major precursors of coronary thrombosis [1, 3]. Intravascular OCT has much higher resolution and can identify TCFA [20, 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 inter-observer variability. Computer-aided analysis can provide complementary criteria in addition to the qualitative diagnostic algorithm previously defined in [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.

**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 difference 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

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Disclosures

Dr. Jang received grant support and consulting fees from LightLab Imaging/St. Jude Medical Inc.

References


Table. Baseline Characteristics of Patients with Plaque Erosion (n=42)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>55.3±12.5</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>30 (71.4%)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (45.2%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (28.6%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>28 (66.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (47.6%)</td>
</tr>
<tr>
<td>Family histology of CAD</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>6 (14.3%)</td>
</tr>
<tr>
<td>Statin</td>
<td>15 (35.7%)</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>10 (23.8%)</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>14 (33.3%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>18 (42.9%)</td>
</tr>
<tr>
<td><strong>Laboratory variables</strong></td>
<td></td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>131.4±55.1</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>73.3±29.7</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>63.9±31.7</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>178.1±204.5</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.95±0.26</td>
</tr>
</tbody>
</table>

Values are mean±SD or n(%).

CAD = coronary artery disease; MI = myocardial infarction; ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; STEMI = ST-segment elevation myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride
Figure Legends

**Figure 1. Representative cases of plaque erosion and a control fibrous plaque**
Examples of plaque erosion and a control fibrous plaque included for analysis. ROIs were traced (blue contour) in the erosion-focal, erosion-adjacent region, and in a control fibrous plaque remote (≥5mm) from the culprit site.

**Figure 2. Illustration of smoothed convex hull of lumen boundary (SCH-lumen)**
One example of SCH-lumen is illustrated. Left: Segmented real lumen boundary (blue contour) exactly follows the irregular surface of protruding tissues. Right: SCH-lumen derived from the real lumen by first computing the convex hull and then smoothing the boundary. The protrusion area and surface roughness can then be computed from the real and SCH-lumen.

**Figure 3. Quantitative comparison of optical and morphological properties between plaque erosion-focal, erosion-adjacent, and control fibrous plaques**
Significant optical and morphological differences are observed in all the metrics between erosion-focal and control regions. Erosion-adjacent regions also have significantly lower ROI NSD, higher attenuation and greater surface roughness compared with control. Erosion-focal regions have significantly lower surface intensity, lower ROI intensity, lower surface NSD, lower ROI NSD, larger protrusion area, and greater surface roughness compared with erosion-adjacent region. All the intensity values of a lesion are normalized to the intensity of the image foreground.
Figure 4. Classification of plaque erosion by the logistic regression model

Examples of plaque erosion (or non-eroded fibrous plaques) with likelihood ranging from 100% to 11% as determined by the logistic regression model. The likelihood of plaque erosion can be used to risk stratify the lesion progression. Definite erosion can be classified by simple thresholding (e.g., use 50% as the cut-off value).

Figure 5. Automated labeling of plaque erosion

Two examples of OCT 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.
Figure 1

Control

Erosion-focal

Erosion-adjacent

Circulation
Cardiovascular Imaging
Journal of the American Heart Association

1mm

5mm
Figure 2

Real lumen

SCH-lumen
Figure 4
Likelihood of Plaque Erosion

Figure 5
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