Coronary Plaque Classification With Intravascular Ultrasound Radiofrequency Data Analysis

Anuja Nair, MS; Barry D. Kuban, BS; E. Murat Tuzcu, MD; Paul Schoenhagen, MD; Steven E. Nissen, MD; D. Geoffrey Vince, PhD

Background—Atherosclerotic plaque stability is related to histological composition. However, current diagnostic tools do not allow adequate in vivo identification and characterization of plaques. Spectral analysis of backscattered intravascular ultrasound (IVUS) data has potential for real-time in vivo plaque classification.

Methods and Results—Eighty-eight plaques from 51 left anterior descending coronary arteries were imaged ex vivo at physiological pressure with the use of 30-MHz IVUS transducers. After IVUS imaging, the arteries were pressure-fixed and corresponding histology was collected in matched images. Regions of interest, selected from histology, were 101 fibrous, 56 fibrolipidic, 50 calcified, and 70 calcified-necrotic regions. Classification schemes for model building were computed for autoregressive and classic Fourier spectra by using 75% of the data. The remaining data were used for validation. Autoregressive classification schemes performed better than those from classic Fourier spectra with accuracies of 90.4% for fibrous, 92.8% for fibrolipidic, 90.9% for calcified, and 89.5% for calcified-necrotic regions in the training data set and 79.7%, 81.2%, 92.8%, and 85.5% in the test data, respectively. Tissue maps were reconstructed with the use of accurate predictions of plaque composition from the autoregressive classification scheme.

Conclusions—Coronary plaque composition can be predicted through the use of IVUS radiofrequency data analysis. Autoregressive classification schemes performed better than classic Fourier methods. These techniques allow real-time analysis of IVUS data, enabling in vivo plaque characterization. (Circulation. 2002;106:2200-2206.)

Key Words: atherosclerosis • coronary disease • Fourier analysis • plaque • ultrasonics

Rupture of vulnerable atherosclerotic plaque is the cause of most acute coronary syndromes.1 Atherosclerotic plaque stability is related to histological composition. Hence, accurate in vivo identification of plaque components may allow the detection of vulnerable atheroma before rupture. As a tomographic imaging technique, intravascular ultrasound (IVUS) allows the visualization of atherosclerotic plaques in vivo.2–6 In standard IVUS gray-scale images, calcified regions of plaque and dense fibrous components generally reflect ultrasound energy well and thus appear bright and homogeneous on IVUS images. Conversely, regions of low echo reflectance in IVUS images are usually labeled as “soft” or “mixed” plaque.7 However, the visual interpretation is limited and does not allow real-time assessment of quantitative plaque composition.8

Spectral analysis of the radiofrequency (RF) ultrasound signals allows detailed assessment of plaque composition. Previous studies by our group9 and others9,10,11 have demonstrated its potential for discerning plaque components in real time. However, few quantitative histological comparisons or validations exist.9–12 Therefore, the goal of this study was to compare real-time determination of plaque components, using easily accessible IVUS backscattered signals, with matched histology results.

With the use of a combination of previously identified13–17 spectral parameters, classification schemes were developed for the analysis of IVUS data. Various spectral algorithms were compared to assess those best suited for IVUS biological signals.9 The RF information was used to reconstruct tissue maps in an attempt to provide real-time classification of plaques.

Methods
Data were acquired from 51 human left anterior descending (LAD) coronary arteries obtained at autopsy, with Institutional Review Board approval from the Cleveland Clinic Foundation. The subjects were 39 men and 12 women (18 black, 33 white). The mean age was 56±12 years. The study sample was limited to those without prior cardiac percutaneous interventions or surgical revascularizations.

Tissue Preparation
The arteries were excised from the ostium to apex, including ~40 mm of surrounding fat and muscle tissue to maintain vessel support and mounted in a dissecting tray approximating their orientation in situ. A computer-controlled air valve system was used to maintain flow of PBS through the vessels. Side branches were
clamped to preserve the perfusion pressure of 100 mm Hg. A RADI wire (RADI Medical Systems) was used to monitor pressure. Figure 1 displays the experimental setup and conditions used while imaging the LAD. This setup has been tested and used by our group in previous studies.9,18

**Data Acquisition: IVUS and Histology**

IVUS data were acquired with a Hewlett-Packard SONOS clinical IVUS console (Hewlett-Packard Co) and 30-MHz, 2.9F, mechanically rotating IVUS catheters (Boston Scientific Corp). After interrogating each vessel with an IVUS catheter, sections with substantial plaque (on average 2 regions per vessel) were identified for data acquisition by manual pullback. Cross-sectional area stenosis >30% to 40%, as determined by IVUS, was considered significant for the study. RF data were digitized and stored in a Pentium PC for off-line analysis. The imaged plaque sites (n=88) were then marked with sutures for collecting the corresponding matched histology.

Each vessel was pressure-perfused with Histochoic fixative (Amresco) at 100 mm Hg to maintain its orientation and size for comparison with the IVUS images. Tissue was processed according to standard laboratory procedures. Two 4-μm sections were collected from each tissue block (at the suture site) and stained with hematoxylin and eosin and with Movat pentachrome stains.

**Histology Analysis**

Histology sections were digitized and analyzed by one of the authors, who was blinded to the IVUS data acquisition. Four plaque types (collagen, fibrolipid, calcium, and calcified necrosis) were defined.9 Areas of densely packed collagen were termed fibrous and those with significant lipid interspersed in collagen were labeled as fibrolipidic. Necrotic regions comprising cholesterol clefts, foam cells, and microcalcifications were termed calcified necrosis. Finally, calcium deposits without adjacent necrosis were identified as calcium. The Movat-stained sections were used as the gold standard for validations.

**IVUS–Histology Correlation**

IVUS B-mode images were reconstructed from the RF data by custom software (IVUSLab) written by our group.9 Software was also developed to maintain the 1:1 correspondence between the reconstructed IVUS and digitized histology images, which is essential for accurate selection of the regions of interest (ROI). The histology images were first registered, scaled, and warped by mathematical techniques9 to fit the corresponding IVUS-reconstructed image. The Movat images were used to identify homogeneous ROIs representing the four plaque components, and the corresponding regions were highlighted on the IVUS images in software. This allowed identification of the backscattered ultrasound signal data representative of the ROIs. Figure 2 provides a schematic of this procedure. Each ROI was 64 backscattered RF data samples in length (~480 μm), and 12–24 scan lines in width (240 scan lines form one IVUS image with the HP SONOS console).

**IVUS Data Analysis**

IVUS RF signal data for the ROIs identified from histology were processed in MATLAB (The MathWorks Inc) by previously developed routines9 such that the frequency spectrum is calculated by a mathematical autoregressive (AR) model for each line in an ROI and then averaged over the width of the ROI. AR processes are known to be more appropriate for short data records, such as IVUS signals, than discrete Fourier transforms and have been shown to result in high resolution of spectral estimates.19 Preliminary work in this study estimated the optimum AR model order (order 10) for characterizing plaque components, after testing several models. Further, the optimized AR spectra were normalized and then used to compute 8 spectral parameters (maximum power, corresponding frequency, minimum power, corresponding frequency, slope, y-intercept, mid-band fit, and integrated backscatter) for each ROI. Figure 3 describes parameter computation from normalized spectra. The more commonly used windowed fast Fourier transform (WFT) algorithm9–11 was also applied to calculate spectra and compared with the AR technique.

**Statistical Classification**

Seventy-five percent of the data (training set for model-building) representing each plaque component were randomly selected for validation.
computing classification trees with the statistics software S-Plus (Statistical Sciences, Inc). Classification tree modeling is an exploratory technique for discovering structure in data and can be used to devise prediction rules from multivariate data. Such classification schemes comprise a collection of guidelines that are determined by a procedure called recursive partitioning. At each juncture in a tree, unclassified data are separated based on one variable (spectral parameter) that displays maximum separation of the plaque types. Previous work has proven the advantage of these trees in plaque classification as opposed to studying separation of data by 1-way ANOVA. In addition, classification trees account for nonadditive behavior in data because they consider intervariable interactions that might be unknown and would be overlooked with linear regression techniques. In the context of plaque components, these interactions could include presence of microcalcifications in necrotic areas, even though necrosis could be present in absence of calcifications.

The trees were programmed in MATLAB and used to resolve the type of plaque in the remaining 25% of the test data. The results were validated with the corresponding histology to determine predictive accuracy, sensitivity, and specificity from widely accepted equations in biomedical literature. Two classification trees were computed, one for the spectral parameters from the WFT and the other for parameters from the mathematical AR spectra.

**Automated Plaque Characterization**

The classification schemes were built such that they could decipher plaque components in user-defined ROIs. Although this is useful, it requires user intervention to identify specific regions that should be classified. Therefore, the next goal in the study was to use these classification schemes to generate tissue maps of entire plaque cross sections. IVUS data from 3 complete vessel sections were analyzed in MATLAB to reconstruct tissue maps with the most accurate classification tree. The cases analyzed were not part of the training data that were used to compute the trees. Figure 4 illustrates the technique used. First, IVUSLab software was used to outline the plaque luminal and medial-adventitial borders. The IVUS data samples representing only the plaque area, delineated by the outlines,
were identified and isolated. Second, each scan line was analyzed separately with the use of a moving window 480 μm in length. Frequency spectra were calculated of samples within the window, and spectral parameters were derived (see Figure 3). The classification tree determined the plaque component type by using these parameters, and a plaque type was assigned to the center sample in the window. The window was then moved by one sample, and data were reanalyzed. Hence, each sample was given a particular value corresponding to a plaque component.

The plaque component values were assigned color codes and the tissue maps were reconstructed in IVUSlab software. Conforming with the typical Movat stains, fibrous regions were marked in yellow. Fibrolipidic, calcified, and calcified necrosis areas were labeled green, purple, and red, respectively. These tissue maps were then visually compared with the Movat stain histology sections to assess the accuracy of the plaque characterization.

Results

Eighty-eight plaque sections of interest were identified for data acquisition from the 51 vessels. ROIs were selected from histology sections for fibrous (n=101), fibrolipidic (n=56), calcified (n=50), and calcified necrotic (n=70) areas.

Statistical Classification With Frequency Spectra

Classification trees were computed for the AR and the WFT spectra with 75% of the ROIs (n=208) for each plaque component and then evaluated with the remaining 25% of test data (n=69). The predictive accuracy, sensitivity, and specificity for the training and test data sets for the AR and the WFT spectral trees are displayed in Figures 5 and 6, respectively. Both trees performed well, although the AR technique surpassed the WFT in the overall classification.

The AR tree classified fibrous, fibrolipidic, calcified, and calcified necrotic regions with high predictive accuracies of 90.4%, 92.8%, 90.9%, and 89.5%, respectively, for the training data and 79.7%, 81.2%, 92.8%, and 85.5%, respectively, for the test data. The corresponding results for the WFT tree were 88.9%, 92.3%, 91.8%, and 86.5% for training and 66.7%, 76.8%, 82.6%, and 72.5% for test data. This trend was also observed in the sensitivities and specificities (Figures 5 and 6) for characterizing the plaque components. All calcified regions were then combined as one plaque type (n=120), and the classification trees were reassessed (Figures 5 and 6). This increased the accuracies for AR and WFT to 94.7% and 91.8%, respectively, for training data, and 92.8% and 89.9% for test data.

Automated Plaque Characterization: Tissue Map Reconstruction

The AR classification scheme was used to assess the plaque composition of 3 random representative complete vessel sections that were not used as part of the training data. The predicted pathology was displayed as color-coded tissue maps (Figure 7) and was compared with the corresponding Movat-stained sections as the gold standard. There was good visual correlation between histology and the RF-reconstructed tissue maps. In contrast to the standard IVUS display, these tissue maps could differentiate areas of microcalcifications (case 1: 9 o’clock position; case 3: 12 o’clock position), heavy calcification (case 1: 12 to 2 o’clock position and 4 to 5 o’clock position), mixed fibrolipidic (case 2, green areas on tissue map corresponding to the lighter areas in the Movat stain), and areas of necrosis adjacent to calcification (case 3: 12 o’clock position, region below calcification separated by collagen).

Discussion

The results of our study show that classification trees based on AR spectral analysis of IVUS backscattered data allow reliable characterization of atherosclerotic coronary plaques. Composition could be predicted in individual ROIs in plaques as confirmed by histology. The computation of the classification schemes permitted reconstruction of tissue maps of plaques. Although overlap between fibrous and fibrolipidic regions still occurred, this technique provided an accurate differentiation of focal areas of microcalcification and necrosis. These results have important implications for in vivo assessment of atherosclerotic coronary plaques with IVUS.

Currently, standard clinical IVUS interpretation is limited to the evaluation of gray-scale images generated by ultrasound reflections at tissue interfaces, which differ in ultrasound propagation properties.7 There are limited data that suggest that the standard gray-scale images can be used reliably for identification of different plaque components. Although the gray-scale images indicate the overall composition of large homogeneous regions, such as a predominantly calcified area, they are unreliable in differentiating adjacent
smaller areas with heterogeneous composition. However, coronary atherosclerotic plaques are most frequently heterogeneous. In particular, plaques with a necrotic core, which is an accepted histological finding of unstable plaques, have adjacent areas of microcalcification and lipid.

Previous research by our group and other ex vivo studies have demonstrated that frequency domain analysis of IVUS RF data can provide information regarding the size and composition of plaque components. Such signal processing techniques combined with image analysis aim at accurate and high-resolution results for plaque typing. The multiple parameter approach enables gathering information from the entire frequency spectrum. Classification trees permit use of as many parameters as possible, and this characteristic can be further exploited to increase accuracy of the predictions. In addition, classification trees provide a simple means for real-time analysis by lending models that can be programmed in image analysis software. In contrast to previous studies, which mostly used analysis based on WFT, in this study we used and validated AR models. AR techniques are attractive for the study of biological signals such as IVUS RF data because they afford room for improvement by altering mathematical variables. More complex mathematical techniques can also be used to increase the resolution of predictions with AR methods. IVUS resolution is >480 μm (Figure 4), and we envisage the use of AR models to improve the resolution of the predictions.

Potential for Identification of Vulnerable Plaques

Acute coronary syndromes are usually caused by rupture or erosion of fibrous caps that cover the lipid-rich necrotic cores of “vulnerable plaques.” The lesions that harbor these plaques are frequently only mildly stenotic on angiographic examination. Identification of plaques that have a high likelihood of causing clinical events will undoubtedly create new opportunities for treatment before the onset of acute ischemic syndromes. Thus, techniques such as AR spectral tissue classification may gain clinical importance in the assessment of plaque composition. This study demonstrates high accuracy of discerning calcified necrotic and fibrolipidic regions (89.5%, 92.8% for training data and 85.5%, 81.2% for test data) with the AR classification scheme (Figure 5). This is exemplified in the reconstructed cross-section tissue map of case 3 (Figure 7), wherein the area of necrosis below the calcified region (12 o’clock position) is accurately predicted, including the fibrous layer separating the two. In accordance with other reports, it was observed that areas of necrosis seldom existed without the presence of microcalcifications. Therefore, the high accuracy of detecting calcified necrosis supports the premise that the AR classification tree developed in the study is suitable to identify key components of plaques that are vulnerable to rupture.
Other invasive techniques recently described include optical coherence tomography and near-infrared spectroscopy, which are far from being implemented in a clinical environment. Noninvasive techniques, in particular MRI and CT, have gained interest but are limited by their lower resolution.30–33 We envisage that IVUS spectral analysis would be an important tool in the identification of vulnerable plaques when used independently or in conjunction with other techniques such as thermography or elastography.

Study Limitations

The window size currently applied for selection of ROIs and eventual tissue map reconstructions is 480 μm in the radial direction. Therefore, detection of thin fibrous caps (<65 μm, below the resolution of IVUS) would be compromised, restricting the detection of vulnerable atheromas. However, efforts are underway to improve this and make full use of resolutions possible with commercially available IVUS systems (150 to 180 μm) by mathematical techniques. Similarly, in vessel wall sections with a low extent of disease, plaque classification depends on analysis of RF data spanning <480 μm and could cause errors in the predictions. However, the improvements to the AR models would help overcome this limitation. In addition, the current AR classification routine was calculated from 75% of data from 51 LADs. Increase in sample size would further lend statistical stability to this multiple spectral parameter approach to plaque classification, in addition to improvements in signal processing techniques that were previously disclosed.26 Furthermore, the low sample size for the fibrolipidic test data (n=14) might explain the low sensitivity with both the AR and WFT (Figures 5B and 6B) trees while displaying high specificity. However, this result could also be due to the definition of fibrolipidic regions used in the study. All areas that exhibited mild to heavy lipid accumulation were diagnosed as fibrolipidic from the histology images. This definition can therefore range from very mildly lipidic to heavy lipid presence in collagen, causing the low sensitivity in detection of these areas. As a result, some overlap was observed in the fibrous and fibrolipidic regions that were determined by the classification schemes. This error can be minimized by introduction of more plaque component types that are better suited to the various grades of lipid present in atherosclerotic plaques.

Conclusions

Mathematical modeling of IVUS backscattered signals is a robust technique for the classification of atheroma based on multiple spectral parameters. The autoregressive technique was better suited to discern plaque types (fibrous, fibrolipidic, calcified, and calcified necrosis) than the commonly used Fourier methods. These ex vivo histological validations display potential for assessment of plaque vulnerability. The developed classification trees make real-time analysis of IVUS data conceivable, enabling plaque characterization and further increasing the utility of IVUS.

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References

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