いてもプラーク容積の減少がなくても，血管内腔面積の有意な増加が認められたことから，probucol のリモデリング抑制効果が作用していると推測された．また，A＋P 群では有意なプラーク容積の減少による血管内腔容積の増加を認めた．以上より，atorvastatin，probucol おのおの単独では短期間の投与期間におけるプラークを安定化，退縮させることは困難であったが，atorvastatin に probucol を併用することにより，プラーク安定化が促進された結果として冠動脈内腔が拡大したと考えられた．

本研究の限界

今回の検討は，主としてプラークの量的変化を評価した．また，質的な評価法として，一部の症例で videodensitometric analysis を用いた．IVUS における tissue charactalization 法は最近進歩しており，radio-frequency の解析が可能となっている．プラーク性状変化の容積変化ばかりでなく質的な変化についても定量的な検討が今後必要と考えられた．

結　論

LDL 低下療法・抗酸化療法を併用することでプラークの安定化・退縮が期待される．

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Detection of Lipid-laden Atherosclerotic Plaque by Wavelet Analysis of Radio-frequency Intravascular Ultrasound Signals: In Vitro Validation and Preliminary In Vivo Application

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Short title: Detection of Lipid-rich Plaque by IVUS

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INTRODUCTION

Since a lipid-rich plaque with a thin fibrous cap has been shown to be vulnerable to rupture as a major cause of acute coronary events (1, 2), several attempts have been made to develop an imaging modality to identify such plaques before they rupture. Intravascular ultrasound (IVUS) imaging provides a detailed arterial cross-section with accurate morphometric representation of atherosclerotic plaque dimensions in vitro and in vivo (3-15). However, subsequent studies have demonstrated significant limitations in tissue characterization by IVUS intensity patterns alone, especially in discriminating fibrous and fatty tissues (16-19). To overcome these limitations, several methods of quantitative tissue characterization have been proposed to discriminate fibrous and fatty plaque (19- 24). However, none of these methods has yet been sufficiently well recognized for appropriate equipment to be installed in commercially available IVUS machines.

Wavelet analysis is a new mathematical model for assessing local changes in the geometrical profile of time-series signals (25). Wavelet analysis is one of the time-frequency domain analyses of signals. This method discriminates a local unique wave pattern within a complex signal. The purpose of this study was to investigate the feasibility of using wavelet analysis of radio-frequency (RF) IVUS signals to detect lipid-laden plaque. The reliability of this method was first examined with in vitro atherosclerotic plaque segments from human necropsy. The parameters evaluated in this

in vitro model were applied to an in vivo clinical setting and tested against the histology of the coronary segments excised with directional coronary atherectomy. The histology of the excised tissue was compared with the results of the wavelet analysis of radiofrequency IVUS signals.

METHODS

In Vitro IVUS Study. Twenty-seven formalin-fixed noncalcified atherosclerotic plaques which were obtained from human femoral and coronary arteries excised from 10 patients at necropsy were imaged using a 40 MHz Atlantis Plus^{TM} IVUS catheter (CVIS/Boston Scientific, Sunnyvale, CA, USA) in saline at room temperature. Eight patients died of heart failure with ischemic cardiomyopathy or old myocardial infarction, and two died of noncardiac events. The imaged arteries had plaques with a thickness greater than 0.5 mm. The lumen area of the examine vessel was 10.48 ±5.78 mm^2 (range 1.57–25.2 mm^2).

Calcified plaques were not studied in the present study, because calcified tissue is readily identified by visual inspection with high sensitivity and specificity (13). The current concern for tissue characterization of plaque is how to discriminate between fibrous and fatty tissue. An acoustic reference point was determined by suturing a surgical needle into the wall of the artery perpendicular to the long axis. This technique ensured that the same cross-section was imaged for all studies and that the ultrasound images corresponded exactly to the cross-section chosen for histologic analysis.

The entire length of the artery was initially imaged by visual inspection by use

of conventional IVUS video monitoring to find an optimal portion of atherosclerotic plaque which provided no significant change in tissue composition or structure within at least a 0.5 mm length of the artery. Care was taken to position the catheter centrally and coaxially. The ultrasound images were recorded on super VHS tape.

Data Acquisition. We sampled in vitro cross-sectional images of 27 noncalcified plaques in 21 atherosclerotic formalin fixed artery specimens (coronary: n=9 ; femoral: n=12) with a commercially available IVUS machine (ClearView Ultra System, CVIS/Boston Scientific, Sunnyvale, CA, USA) and a 40 MHz IVUS catheter. The RF IVUS signals of 256 radial vectors which completely surrounded (360 deg) the catheter center with an equal angle span (1.4 deg) were obtained from these plaques using an analog-to-digital converter installed inside the IVUS machine (Figure 1). The A/D board was specially designed and installed by the IVUS manufacturer. Each cross-section comprised these 256 RF IVUS signals which were sampled in real time at 500 MHz in 8-bit resolution with a digitizer, and then stored on hard disk for further analysis. Each cross-sectional IVUS image was also recorded on videotape. On a video screen, a radial line from the catheter center was superimposed on a conventional cross sectional IVUS image to enable recognition of the location of each vector. The vectors analyzed were first obtained from the thickest portion of the plaque imaged. We next selected another two or more vectors at least 15 degrees away from the vector first selected. In other words, there were at least 10 vectors in between these vectors. Only the plaque portions, the thickness of which was more than 0.5 mm, were selected. The RF signals were excluded when the signals were from the regions with significant

NURD, calcification, or drop-out in the conventional IVUS image. A total of 85 vectors could be finally analyzed from all plaques imaged.

Wavelet Analysis. IVUS RF signals were analyzed offline by wavelet analysis (25) using MATLAB data processing software (The MathWorks, Natick, MA, USA). Wavelet analysis is a signal processing tool that enables detection of a special geometric pattern within a localized area of a signal. A wavelet is a short segmental waveform of limited duration that has an average value of zero. Wavelet patterns which meet various mathematical criteria have been proposed for comparison, such as Daubechies, Meye, and Mexican hat. Wavelet analysis involves the breaking up of a signal into shifted and scaled versions of the original (or mother) wavelet. The continuous wavelet transform is defined as the sum over time of the signal multiplied by scaled, shifted versions of the wavelet function :

$$C(scale, position) = \int_{-\infty}^{\infty} f(t)\psi(scale, position, t)dt$$

This results in many wavelet coefficients, C, which are a function of scale and position. Multiplying each coefficient by the appropriately scaled and shifted wavelet yields the constituent wavelets of the original signal. Wavelet analysis then produces a time-scale view of a signal. "Scaling a wavelet" means stretching (or compressing) it. The greater the scale factor, the more the wavelet is stretched. This scale is related to the frequency of the signal. "Shifting a wavelet" simply means delaying (or hastening) its onset.

To obtain a Wavelet analysis, the following steps are performed (Figure 2).

1) Take a wavelet and compare it to a section at the start of the original signal.

2) Calculate C, the coefficient between the section and the wavelet, which represents how closely correlated the wavelet is with this section of the signal. The higher C is, the greater the similarity. The results will depend on the shape of the wavelet selected.

3) Shift the wavelet to the right and repeat steps 1 and 2 until the whole signal is covered.

4) Scale (stretch) the wavelet and repeat steps 1 through 3.

5) Repeat steps 1 through 4 for all scales.

This process produces wavelet coefficients (C) that are a function of scale and position. The commercially available program for wavelet analysis used in this study selected automatically the minimal scale of the wavelet to correspond to the minimum sampling interval.

After taking these steps, the coefficients are produced at different scales by different sections of the signal. The coefficients constitute a regression of the original signal performed on the wavelets. The results can be represented graphically, in which the x-axis represents position along the signal (time), the y-axis represents scale, and the color at each x-y point represents the magnitude of the wavelet coefficient C. In this map, correlation coefficients are shown using a blue-pink scale, in which pink represents higher values of the coefficient, and blue represents lower values.

Preliminary In Vivo Application . The same technique was applied in vivo to 29 coronary plaque segments from 13 patients (65 ± 6 years old, range 54–74) with coronary artery disease (7 patients with stable angina, 6 with acute coronary syndrome). The RF IVUS signals were obtained from the thickest part of the plaque imaged. These

segments were excised by directional coronary atherectomy (FLEXI-CUT/GUIDANT, Indianapolis, IN, USA), and processed for histologic analysis. Plaque segments were excluded, which were insuffciently debulked by the atherectomy leaving a residual plaque area of more than one-third of the original plaque area. In the histologic preparation, the specimens were stained with Hematoxylin-Eosin stain and Azan stain.

This study was approved by the institutional review committee and patients gave informed consent.

Histologic Study. In the in vitro study, after the arteries were imaged by intravascular ultrasound, the needle for acoustic reference was removed, and the needle site marked with india ink. The specimens were processed for histology and stained with Masson's trichrome stain. The IVUS and the histologic examinations were performed by different observers. A plaque was defined as lipid-laden by visual inspection, when a lipid-core was >50% of the total plaque area. A lipid core was defined as a contiguous area of lipid containing foam cells, extracellular lipids, cholesterol crystals, a lipid pool, or necrotizing material. A plaque was defined as fibrous, when it had no distinct lipid core but had fibro-acellular matrix with dense collagen bands. The thickness of the lipid core had to be more than 0.3 mm, and >50% of the total plaque area to be included in this study.

In the in vivo study, the DCA specimens were stained with Hematoxylin-Eosin and Azan stains. This study only included typical fatty-dominant or fibrous-dominant plaques. The fatty-dominant plaques contained a lipid core >80% of total plaque area. The fibrous-dominant plaques contained a fibrous area >80% of total plaque area.

Statistics. Values were expressed as means±standard deviation (SD). ROC analysis was performed in order to discriminate the optimal criteria in the interpretation of the results of this Wavelet analysis.

RESULTS

In Vitro Study. The mean thickness of plaque examined in this study was 1.42 ±0.47 mm. Histologic examination revealed that 29 of 85 vectors of RF signals analyzed were from a lipid-laden plaque.

Representative examples of wavelet analysis of RF IVUS signals from a lipid-laden plaque and from a fibrous plaque are shown in Figure 3. Wavelet analysis of the RF signals with a Daubechies-2 wavelet function provided an apparently different pattern in the color-coded mapping between scale 20 and scale 30. In this time-scale graphic representation of wavelet analysis of RF IVUS signals from a plaque with a lipid core, a different pattern of pink mapping was observed that was not observed from a fibrous plaque without a lipid core. A lipid-laden zone was frequently present, when the wavelet coefficient (C) was more than a certain value compared to a wavelet whose scale is between 20 and 30. The ROC analysis revealed that the optimal value of this wavelet coefficient was 0.6 in order to discriminate a lipid-laden plaque (Figure 4). Using this criteria, the lipid-laden plaque was detected in this in vitro setting with a sensitivity of 83% (24/29) and a specificity of 82% (46/56) (Table1).

Many other wavelet approaches (approximately 50 types) were analyzed and none provided the sensitivity and specificity of the Daubechies-2 method.

In Vivo Study. Histologic examination from the directional coronary atherectomies revealed that 16 of 29 coronary segments were fat-dominant (lipid-laden). No apparent fatty area was observed histologically in the remaining 13 segments. In the lipid-laden plaques, the Wavelet analysis with the Daubechies-2 wavelet function revealed a similar pattern as the in vitro results (Figure 5). Using the same criteria of the Wavelet analysis as in the in vitro study, fatty plaque could be detected from the clinical material with a sensitivity of 81% (13/16) and a specificity of 85% (11/13).

DISCUSSION

The present study is the first report of in vitro as well as in vivo tissue characterization of atherosclerotic plaque using a wavelet analysis of RF IVUS signals. The major finding of this study is that this wavelet method is accurate in detecting lipid-laden atherosclerotic plaque. This method may be useful in assessing plaque vulnerability in patients with coronary artery disease.

Advantages of Wavelet Analysis. The theoretical basis of wavelet analysis was first developed by Grossmann and Morlet in 1983 (25). Wavelet analysis is a time-frequency domain analysis of signals. The most well known of these is Fourier analysis, which breaks down a signal into constituent sinusoids of different frequencies. The Fourier transform was modified into a transform to analyze only a small section of the signal at a time by looking at 'windows' of the signal. This short-time Fourier transform provides some information about when and at what frequencies a signal event

occurs. The major drawback of this method is that once a particular size for the time window is chosen, that window is the same for all frequencies. If the window size is changed to a shorter one to increase time (space) resolution, the frequency resolution is compromised. Wavelet analysis was proposed in an attempt to overcome the problems in resolution.

Wavelet analysis represents a windowing technique with variable-sized regions. Wavelet analysis allows the use of long time intervals where we want more precise low-frequency information, and shorter regions where we want high-frequency information. One major advantage of wavelets is the ability to analyze a localized area of a larger signal. In this study, the Daubechies-2 wavelet proved best for detecting a lipid-laden plaque. An empirical selection of wavelet has to be made when applying wavelet analysis in a novel field of data. If a new wavelet family is developed, the sensitivity and specificity for detection of fatty tissue may be improved.

Wavelet scales 20 and 30, correspond to wavelengths of 32 and 47 μm, respectively. A scale of less than 20 is less than conventional IVUS resolution (26) or the ultrasound pulse wavelength. The results from wavelet analysis with a wavelet scale less than 20 would measure artificial noise only. A higher value of wavelet correlation coefficient represents an acoustic signal derived from a more complicated structure. Compared with a fibrous area, a fatty area is usually composed of various kinds of tissue, such as lipid-laden foam cells, cholesterol crystals, extracellular lipids, necrotizing material, and fibers, which may be intermingled in a way which could produce complex acoustic impedance mismatches inside the plaque (17). Therefore, a

lipid-laden area provides a higher value of wavelet correlation coefficient with a shorter scale of wavelet.

Comparison With Other Methods of Tissue Characterization. It was originally expected that tissue components within plaque could be identified from the videointensity pattern of IVUS images (4, 5, 7, 12-15). Subsequent studies, however, demonstrated significant limitations of tissue characterization by IVUS intensity patterns alone, especially in discriminating fibrous and fatty tissues or in assessing plaque vulnerability (16-19). To overcome the limitations, several methods of quantitative tissue characterization have been proposed to discriminate fibrous and fatty plaque. These included radio-frequency signal analysis, such as integrated backscatter analysis (20-23), attenuation slope mapping (19, 24) and spectral analysis (27). Recently, IVUS elastography was proposed as a novel modality of tissue characterization with IVUS(28). Our laboratory previously reported that color mapping of the angle-dependent echo-intensity was useful for detecting fibrous caps within plaques (29). But this method has difficulties in detecting other type of tissues. Since none of these previously reported techniques has become commercially available, no study has yet compared their clinical feasibility using the same subjects.

Study Limitations. For the in vitro study, the arteries were imaged after they were fixed in formalin at room temperature. It is unknown whether formalin fixation or change in temperature will alter the results of this analysis. Another limitation was the use of nonpressure distended arteries. When removed from physiologic pressure, atherosclerotic arteries contract. This could significantly alter the architecture which

might affect the wave pattern of the RF IVUS signal. However, the in vivo application of the Wavelet analysis also offered similar sensitivity and specificity for identifying a lipid-laden plaque as in the in vitro study. Therefore, these effects appear to be negligible in this study.

This wavelet analysis was performed for one single vector. The single vector analysis is subject to mismatch because of rotation of the images. To minimize any mismatch, a radial line from the catheter center was superimposed on a conventional cross sectional IVUS video image to enable recognition of the location of each vector. In the in vitro study, all the plaques analyzed had a thickness greater than 0.5mm, and any lipid core had a thickness greater than 0.3mm. Therefore, we do not know if it is possible to analyze thinner plaques, or to identify very thin lipid cores with this method. Furthermore, the presence of blood and phasic pressure within the lumen as well as any non coaxial alignment of the catheter may impair appropriate analysis in vivo with this method.

This study was performed on the off-line basis taking an hour or so to obtain each color map. Therefore, a further development is necessary to be able to provide an on-line plaque evaluation during the study so that immediate feedback is given to the operator.

Conclusions. The present study demonstrates the feasibility of in vitro as well as in vivo tissue characterization by wavelet analysis of RF IVUS signals. Using wavelet analysis, lipid-laden plaque could be detected with a sensitivity and specificity of more than 80%. This method may be useful in assessing plaque vulnerability in

patients with coronary artery disease. Currently, there is no reliable, commercially available device which is capable of discriminating fibrous and fatty areas within atherosclerotic plaque. Detection of vulnerable plaque, or sequential observations of the stabilizing effect of lipid-lowering therapy on plaque composition with acceptable accuracy in vivo could improve the management of patients with coronary artery disease. Further evaluation of wavelet analysis in comparison to clinical data and inflammatory markers will be necessary to assess its usefulness in clinical practice to predict future cardiac events in patients with coronary artery disease.

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FIGURE LEGENDS

Figure 1. Acquisition of RF IVUS Signals.

There are 256 radial vectors of RF signal sampled around the IVUS catheter.

Figure 2. Procedure of Wavelet analysis.

In this example, a wavelet is stretched twice and three times. At a time of t0, a high value of wavelet coefficient is provided (arrow). This suggests that a special wave pattern similar to the wavelet of scale 2 is included within the signal at the time.

Figure 3. Representative examples of in vitro Wavelet analysis of RF IVUS signals from a lipid-laden plaque (A) and from a fibrous plaque without a lipid core (B). The upper panel shows RF signals, the middle panel, the results of Wavelet analysis, the lower panel, histologic specimen of the corresponding arterial cross-section with Masson's trichrome. In the time-scale domain color-coded mapping of Wavelet analysis, a apparently different pattern of pink area from a RF signal vector of a lipid-laden plaque is observed between scale 20 and scale 30, compared to the fibrous plaque. F: Fibrous area, L: lipid core.

Figure 4. ROC analysis

ROC analysis was performed with varying degree of the wavelet coefficient in terms of the capability of the in vitro detection of lipid-laden plaque. This analysis revealed that

the optimal value of this wavelet coefficient in order to discriminate a lipid-laden plaque was 0.6.

C: the wavelet coefficient.

Figure 5. Representative examples of in vivo Wavelet analysis of RF IVUS signals from a lipid-laden plaque (A) and from a fibrous plaque without a lipid core (B). The left panel shows conventional IVUS images, the middle panel, the results of Wavelet analysis, the right panel, histologic cross section of the corresponding DCA specimen with Hematoxylin-Eosin and Azan stains. A similar pattern of color mapping was observed from the RF signal vector of a lipid-laden plaque as seen in the in vitro study.