積極的脂質低下による冠動脈病変の安定化と退縮についての検討

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はじめに

不安定狭心症や急性心筋梗塞の多くは，冠動脈プラークの破綻を契機に血栓が形成され，冠動脈の閉塞により発症することが明らかにされ，これらの疾患は同一の病態を基盤として発症するため急性冠症候群（acute coronary syndrome）と総称される[1,2]．一般的に破綻しやすいプラークの病理学的特徴としては，コレステロールエステル量が多く，脂質コアの占める割合が大きいソフトプラークであること，線維性被膜（fibrous cap）が薄いこと，マクロファージなどの炎症細胞の浸潤が強く，線維性被膜の傷害が進んでいることとされる[3]．冠動脈造影上，中等度病変であっても急性冠症候群の発症は多く，その発症予測や冠動脈プラークの退縮が冠動脈造影にて評価されてきたがそれには限界があり，血管内エコー法（IVUS）による観察が有用である．

近年，statin系抗高脂血症薬の投与による心血管イベントの抑制効果とIVUSによるプラークの安定化が報告された（GAIN）[4]．また，プラークの不安定化に酸化LDLの関与が指摘され，抗酸化薬の心血管イベント抑制効果が期待されている[5]．しかし，現在までのところプラークの安定化を証明する大規模脂質介入試験は行われておらず，IVUSにおけるプラークの退縮についても明らかにされていない．

そこで，今回われわれは，LDL低下療法ならびに抗酸化薬長期投与によるプラークの変化をIVUSにより観察した．

対象および方法

責任冠動脈病変に対するカテーテルインターベンションを施行した虚血性心疾患患者のうち，インターベンション非施行血管に定量的冠動脈造影法（QCA）上50％未満の病変に対し，初回造影時および遠隔期（6ヵ月以上）にIVUSによる観察を行った65症例（男性28例，平均年齢61歳）を対象とした．そして対象を3群に分類し，atorvastatin 10 mg/日（A群），probucol 500 mg/日（P群），atorvastatin 10 mg/日およびprobucol 500 mg/日併用（A＋P群）を6ヵ月間投与し，投与開始時および6ヵ月後においてIVUSによる観察を行った．

IVUSカテーテルはBoston Scientific社製30/40 MHzを使用し，観察病変の遠位部より0.5 mm/秒の速度でautomatic pullbackデバイスを用いて施行した．S-VHSビデオテープに記録されたIVUS画像はScImage社製Netra IVUSにて三次元再構築処理を行い，病変の最狭窄部を中心に15 mmの範囲においてminimum lumen diameter

[Key words]　脂質低下療法，プラーク，退縮

表1　患者背景

	A群	P群	A+P群
	(n=23)	(n=21)	(n=21)
年齢（平均）	62.2±12.0	64.4±8.3	57.6±5.2
観察期間	6.8±2.1	6.4±1.2	6.4±1.1
責任血管	5(50%)	8(80%)	6(60%)
LAD	10(40%)	8(20%)	7(30%)
LCX	7(40%)	6(20%)	5(20%)
RCA	6(20%)	7(60%)	9(50%)
喫煙	15(70%)	14(80%)	16(80%)
高脂血症	15(70%)	14(70%)	15(80%)
高血圧	14(70%)	9(40%)	10(40%)
糖尿病	5(0%)	7(40%)	5(20%)
家族歴	4(20%)	3(10%)	4(20%)

(MLD), vessel diameter，血管内腔面積，血管内腔容積，全血管面積，全血管容積，プラーク断面積，プラーク容積，面積狭窄率の計測を行った．また，提示症例においては，プラーク安定化の評価法としてtexture videodensitometric analysisを用いた．これには，フクダ電子社製解析ソフトCardio 2000に含まれるContrast time analistを使用し，黒から白までのgray scaleを256段階に分け，その値をプラーク輝度（gray value）とした．IVUS画像において中心部の小円（IVUSカテーテル自体に相当）を基準とし，同じイメージ上においてROIを設定し，おのおののgray valueを求め，抗高脂血症薬の投与前後において測定し比較検討した．

統計学的検討

コレステロール値，血管内エコーの計測値については，平均値±SDとし，平均値の差の検定はpaired t-testにて行い，$p<0.05$を有意とした．また，プラーク容積とIVUS計測値との相関については単回帰分析にて相関を求めた．

結　果

患者背景は（表1）に示す．3群間に有意差は認められなかった．

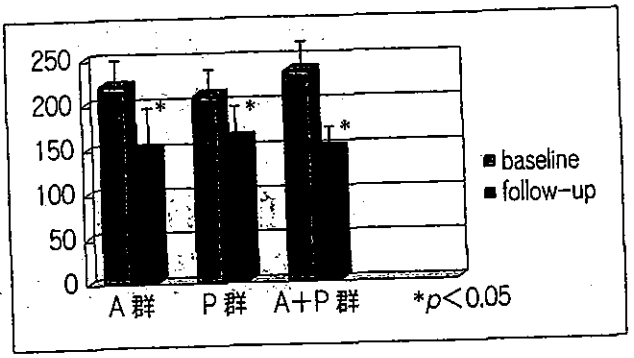

図1　血中総コレステロールの変化

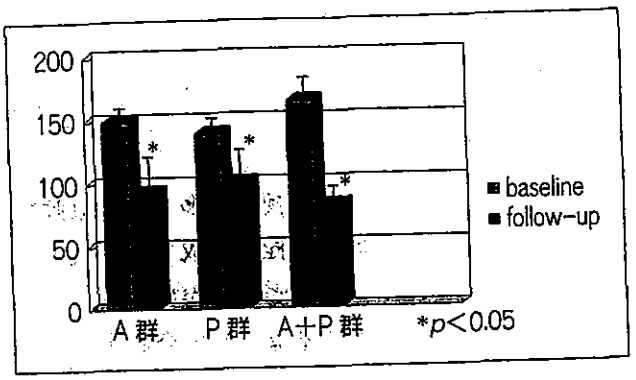

図2　LDLコレステロールの変化

血中総コレステロールの変化（図1）は，A群で228.0±22.0 mg/dlから147.01±36.0 mg/dl，P群で207.0±34.0 mg/dlから158.0±27.0 mg/dl，A+P群で233.0±39.0 mg/dlから140.14±10.0 mg/dlとすべての群で有意に減少した．また，LDL（図2）においては，A群で149.4±13.0 mg/dlから88.9±34.0 mg/dl，P群で138.0±25.0 mg/dlから99.0±32.0 mg/dl，A+P群で160.7±78.0 mg/dlから82.3±24.0 mg/dlとA群，A+P群で有意に減少し，A群，A+P群のLDL-Cが100 mg/dl以下となった．また，IVUS所見では，有意なMLD，プラーク面積，血管面積，内腔面積の変化はみられなかった．また，3Dによる検討（図3）で，プラーク容積の変化率はA群で−1.4%，P群で−2.0%，A+P群で−6.7%と，AP群で有意に減少した（$p<0.05$）．内腔容積はA群で4.1%，P群で4.0%増加，A+P群で8.2%とA+P群で有意に（$p<0.05$）増加

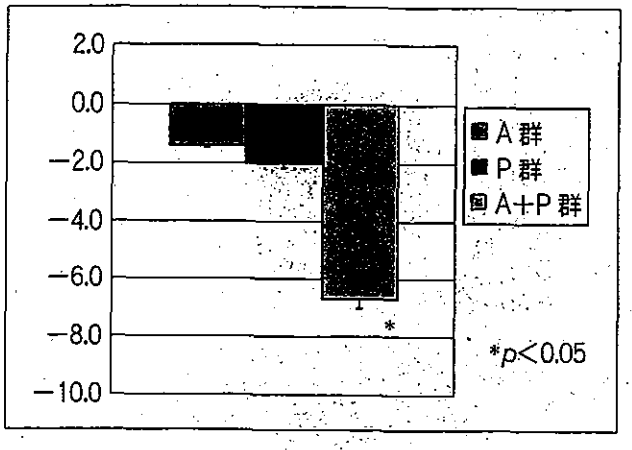

図3　アテロームの変化

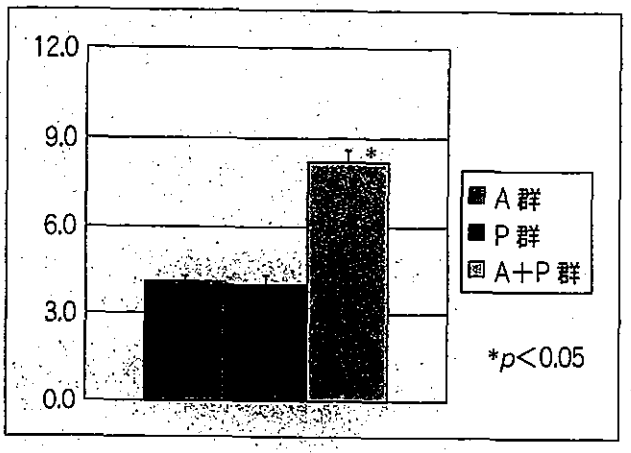

図4　内腔容積の変化

した（図4）．

症例提示（図5）

IVUS上プラーク安定化がみられた1例を提示する（A+P群）．本例はLDLが302 mg/dlから109 mg/dlまで63.9%減少し，6ヵ月後のIVUSにて，プラーク容積は減少し内腔容積が増加し，プラークの退縮が確認された．

考察　抗高脂血症薬投与によるプラークのIVUS所見の変化

statin投与によるlipid lowering therapyのプラーク安定化，退縮に関するIVUSを用いた研究はいくつか報告されており，Takagiら[6]は，statin投与群において冠動脈の血管面積の増加がなく血管内腔面積の増加が認められた．すなわちプラークの減少により血管内腔面積が増加したと報告した．また，Hamasakiら[7]はstatin投与によりコレステロールが十分にコントロールされていた群と不十分な群で，冠動脈の血管内腔面積を計測したが，コントロールされている群で有意に大きいことを報告した．Hagenaarsら[8]は下肢末梢血管を用いた検討であるが，1年間のstatin投与により血管リモデリングによる血管内腔面積の有意な増加が観察されたと報告している．Schartlら[4]はstatinを1年間投与しLDLを100 mg/dl以下にしIVUSによる検討を行った．それによると，プラーク容積の有意な減少はみられなかったものの，プラークのエコー輝度が有意にstatin投与群で上昇したことから，プラークの安定化が示唆されたと報告した．

今回のわれわれのIVUSによる検討では，A+P群で有意に血管内腔容積が増加し，かつ有意なプラーク容積の減少を示したということは，プラークの減少が内腔容積を増加させたと考えられる．A群においても有意ではなかったが，同様な傾向がみられた，これは，今までの報告では1年間という観察期間であったが，今回の検討は6ヵ月間であるためA群では有意な変化がみられなかったと考えられ，LDLがより低値であったこと，A+P群でのみ有意なプラーク退縮が起こり，従来の報告よりも退縮までの時間を短縮させたのではないかと思われた．また，コレステロール低下療法に基づくプラークの安定化のみならずprobucol併用により抗酸化作用の相乗効果の結果がプラーク退縮を促進したものとも考えられた．今回の検討ではechogenecityによる検討は全例に行われていないが，提示症例ではLDL-Cが68 mg/dlと著明に低下し，gray valueが上昇し，プラーク安定化が示唆された．今後は同様に多くの症例について検討する必要があると考えられた．

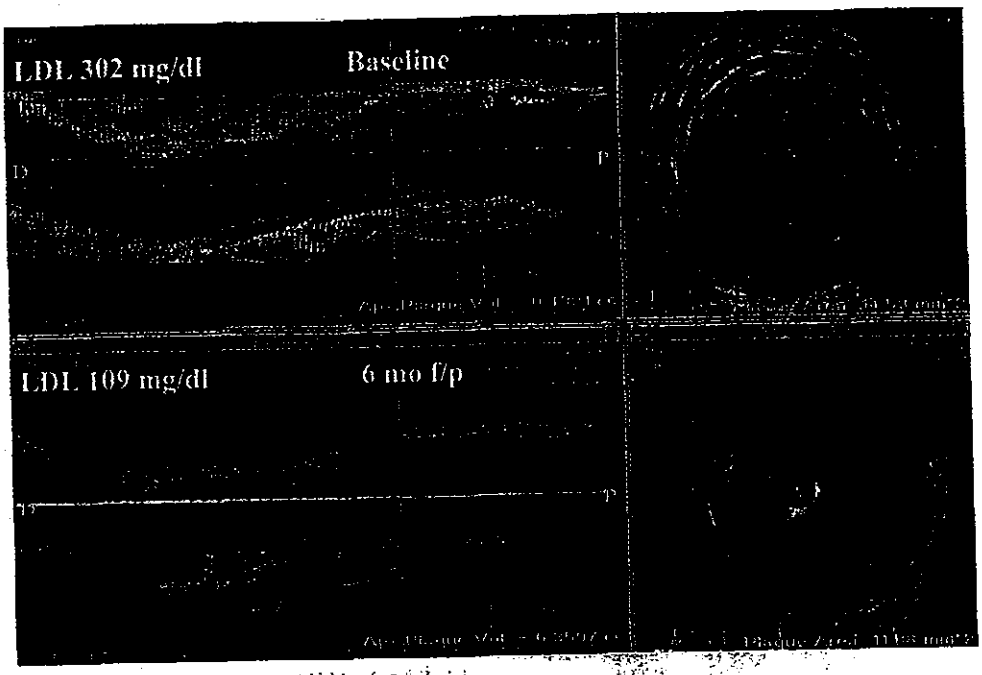

図5　3D-IVUS measurements

プラーク安定化・退縮の機序についての検討

プラーク安定化・退縮は，コレステロール低下，特にLDLが低下し，酸化LDLが減少することによりプラークの進展を防止し安定化させるとされる．さらに，statinはコレステロール低下作用による作用以外にもいろいろな直接効果が期待されている．Egashiraら[9]はpravastatin投与群と非投与（コントロール）群におけるアセチルコリンの反応性を検討したところ，コントロール群で冠動脈スパスムが有意に多く認められ，pravastatinによる内皮機能の改善を報告した．また，statinにはLDLの酸化遅延作用が報告されている．Girouxら[10]はsimvastatin投与によりdose dependentに36～54％のLDL酸化作用抑制効果を報告した．また，Ridkerら[11]は，5年間のpravastatinの投与によりCRPを有意に低下させることを報告した（CARE trial）．これらの酸化抑制作用，抗炎症作用とプラーク安定化の過程への関与についても現在さらに検討が進められている．Nissenら[12]は，REVERSAL studyにおいて，強力なstatin療法を行っても有意なプラークの退縮は認められなかったが，statinの抗炎症作用がプラークの安定化には重要な因子であることを示唆した．

一方，probucolはコレステロール低下作用のみならず強力な抗酸化作用を有する[13]．Sawayamaら[14]は，高脂血症患者をprobucol投与群，pravastatin投与群とプラセボ群で，投与前および2年を経過した時点で，probucol群およびpravastatin群で頸動脈の内膜-中膜厚が有意に減少した．さらに，多変量解析によりprobucol投与自体がLDLの低下とは独立してプラークの退縮と相関が認められたと報告した．また，心疾患の発症率がプラセボ群に比し有意に低値で，probucolの抗酸化作用がプラークの安定化に大きく寄与したものと結論した．MVP study[15]では，probucolの冠動脈形成術（PTCA）前30日よりPTCA後6ヵ月投与により，再狭窄率がプラセボ群で38.9％であったのに対しprobucol群で20.7％と有意に低い再狭窄率を示し，抗酸化作用による血管リモデリングの予防効果，新生内膜増殖抑制効果が報告された．われわれの今回の検討では6ヵ月間という短期間投与におけるIVUSによる検討であったにもかかわらず，probucol単独群にお

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

First author's surname: Murashige

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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