Many clinical studies have shown that coronary arteries respond to plaque growth by either outward expansion of the vessel wall (positive remodeling)\(^1\)\(^-\)\(^3\) or vessel shrinkage (negative remodeling)\(^4\)\(^,\)\(^5\). The difference in plaque morphology between positive and negative remodeling lesions in vivo has been investigated in several clinical studies using intravascular ultrasound (IVUS), but it is difficult to evaluate the detailed plaque composition with gray-scale IVUS.

Recently, spectral analysis of IVUS radiofrequency (RF) data was shown to provide detailed quantitative and qualitative information on coronary plaque composition in vivo\(^6\)\(^-\)\(^9\). A preliminary in vitro study showed that 4 components (eg, fibrous, fibrofatty, dense calcium components, and necrotic core) correlated with a specific spectrum of the RF signal\(^10\). Nasu et al used a color-coded mapping method by Virtual Histology (VH) that was able to identify atherosclerotic plaque composition of human coronary arteries in vivo\(^11\).

Previous studies using necropsy specimens or gray-scale IVUS have consistently found a large lipid burden in positive remodeling lesions\(^12\)\(^-\)\(^14\), but the role of calcium deposition in coronary artery remodeling is still controversial\(^2\)^\(^,\)\(^3\)\(^-\)\(^16\).

In the present study, we used spectral analysis of IVUS RF data to evaluate the relationship between coronary artery remodeling and culprit plaque composition in patients undergoing percutaneous coronary intervention (PCI) in order to confirm the findings of previous studies on lipid burden and to elucidate the role of calcium deposition.

### Methods

### Patients and Lesions

Between June 2005 and January 2006, a pre-interventional IVUS examination was performed prospectively in 93 consecutive de novo culprit lesions of 81 patients undergoing PCI; 18 lesions were excluded from analyses because we could not cross the lesion completely with the IVUS transducer; the images of 6 lesions could not be analyzed because of poor image quality; and for 13 lesions, no proximal reference site could be defined because the lesion involved the ostium (\(n=3\)) or a bifurcation (\(n=10\)). Finally, IVUS RF analyses were performed for 56 culprit lesions of 52 patients.

Informed, written consent was given by all the patients.

### Definitions

Hyperlipidemia was defined as total cholesterol level \(\geq 220\) mg/dl, high-density lipoprotein cholesterol level \(<40\) mg/dl, triglyceride level \(\geq 150\) mg/dl, low-density lipoprotein (LDL) level \(\geq 140\) mg/dl, or/and lipid-lowering medication use. Hypertension was defined as systolic blood pressure \(\geq 140\) mmHg, diastolic blood pressure \(\geq 90\) mmHg, or/and use of an antihypertensive drug. Diabetes mellitus was defined by a previous physician’s diagnosis and treatment with diet, oral hypoglycemic agents, or insulin.
IVUS RF Data Acquisition and Analysis

IVUS RF data were acquired with a 20-MHz 2.9Fr phased-array IVUS catheter (Eagle Eye\textsuperscript{TM} Gold, Volcano Corp, Rancho Cordova, CA, USA) and a dedicated console (IVG3\textsuperscript{TM}, Volcano Corp). An automated continuous pullback (0.5 mm/s) was performed after intracoronary administration of isosorbide dinitrate (2.5 mg). If thrombi were angiographically detected, percutaneous aspiration thrombectomy with TVACT\textsuperscript{TM} (Nipro Corporation, Osaka, Japan) was performed before IVUS interrogation to minimize any influence of thrombi on IVUS RF analysis.\textsuperscript{17} The IVUS RF data were stored on a hard disk for off-line analysis.

Manual contour detection of both the lumen and the media–adventitia interface was performed for the entire culprit lesion and the proximal reference segment. Subsequently, quantitative and qualitative analyses were done using VH software (VH IVUS Version 1.3j, Volcano Corp). We evaluated plaque morphology of the minimum lumen area (MLA) and entire culprit lesion.

The entire culprit lesion was defined as the segment that was treated by PCI following the pre-interventional IVUS examination. The treated segment was identified by post-interventional IVUS imaging. Using reproducible landmarks (eg, calcium deposit or a side branch), the same segment was determined on the pre-interventional IVUS run and subsequently the data from the pre-interventional IVUS run were used for analysis.

The MLA site was identified within the entire culprit lesion by IVUS quantitative analysis. If there were several MLA sites, the MLA site with the largest external elastic membrane (EEM) cross-sectional area (CSA) was chosen for evaluation\textsuperscript{18–20}.

The proximal reference segment was defined as the segment within 10 mm of the proximal border of the entire culprit lesion and distal to any major side branch. The proximal reference site was selected from the proximal reference segment as the site with the largest lumen and least plaque burden calculated as plaque plus media divided by EEM CSA\textsuperscript{20}.

VH uses IVUS RF data to classify plaques into 4 components. Fibrous, fibrofatty, dense calcium, and necrotic core components can be identified, which are validated by preliminary in vitro and in vivo study\textsuperscript{10,11}. The 4 components are color-coded green, greenish-yellow, white and red, respectively, and from these data color-coded tissue maps can be constructed.

Plaque composition was assessed as the percentage of plaque burden because an absolute value could be affected by plaque or vessel size.

IVUS Definitions of Remodeling

The remodeling index (RI) was defined as the ratio of the EEM area of MLA site to the EEM area of proximal reference site as previously described\textsuperscript{21,22}. Three remodeling categories were defined: positive remodeling, with a RI >1.05; intermediate remodeling, with a RI between 0.95 and 1.05; and negative remodeling, with a RI <0.95\textsuperscript{15,21,23,24}.

Inter- and Intra-Observer Variabilities of IVUS Analysis

The quantitative and qualitative measurements of IVUS data were reanalyzed in the first 15 consecutive patients by 2 independent observers (Y.H and H.Y) and by another observer at least 6 months later to assess the reproducibility of IVUS analysis.

The respective inter- and intra-observer correlation coefficients and absolute difference of area percentage of plaque composition were r=0.992, 0.933±1.223% and r=0.996, 0.600±0.910% for the fibrous component, r=0.988, 0.933±1.163% and r=0.998, 0.267±0.594% for the fibrofatty component, r=0.999, 0.267±0.458% and r=0.998, 0.267±0.594% for the dense calcium component, and r=0.993, 0.600±1.056% and r=0.996, 0.467±0.915% for the necrotic core component.

The respective inter- and intra-observer correlation coefficients and percent error obtained by taking the absolute difference divided by the initial measurements for EEM CSA, lumen CSA, plaque CSA and lesion length were r=0.995, 2.397±3.140% and r=1.000, 0.764±0.791%, r=0.994, 2.729±3.263% and r=0.996, 1.615±2.862%, r=0.995, 4.035±5.801% and r=0.999, 2.144±2.461%, and r=0.999, 2.506±1.922% and r=0.999, 2.140±2.061%.

Statistical Analysis

Continuous variables are expressed as mean±standard

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Table 1 Baseline Patient and Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Positive remodeling (n=24)</th>
<th>Intermediate remodeling (n=16)</th>
<th>Negative remodeling (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64.5±11.5</td>
<td>68.6±10.2</td>
<td>65.4±9.6</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Gender, male, n (%)</strong></td>
<td>22 (91.7)</td>
<td>15 (93.8)</td>
<td>14 (87.5)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>25.9±4.7</td>
<td>22.6±3.1</td>
<td>24.8±4.1</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Acute coronary syndrome, n (%)</strong></td>
<td>12 (50.0)</td>
<td>10 (62.5)</td>
<td>5 (31.3)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>15 (62.5)</td>
<td>8 (50.0)</td>
<td>11 (68.8)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>20 (83.3)</td>
<td>11 (68.8)</td>
<td>13 (81.3)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, n (%)</strong></td>
<td>8 (33.3)</td>
<td>5 (31.3)</td>
<td>7 (43.9)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Current smoker, n (%)</strong></td>
<td>8 (33.3)</td>
<td>4 (25)</td>
<td>6 (37.5)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Family medical history of CAD, n (%)</strong></td>
<td>11 (45.8)</td>
<td>6 (37.5)</td>
<td>8 (50.0)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Previous MI, n (%)</strong></td>
<td>4 (16.7)</td>
<td>2 (12.5)</td>
<td>4 (25.0)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Previous PCI, n (%)</strong></td>
<td>9 (37.5)</td>
<td>5 (31.3)</td>
<td>4 (25.0)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Multivessel disease, n (%)</strong></td>
<td>11 (45.8)</td>
<td>7 (43.8)</td>
<td>4 (25.0)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Target coronary artery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery, n (%)</td>
<td>9 (37.5)</td>
<td>6 (37.5)</td>
<td>5 (31.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Left circumflex artery, n (%)</td>
<td>5 (20.8)</td>
<td>1 (6.3)</td>
<td>7 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery, n (%)</td>
<td>9 (37.5)</td>
<td>9 (56.3)</td>
<td>3 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Left main coronary artery, n (%)</td>
<td>1 (4.2)</td>
<td>0 (0)</td>
<td>1 (6.3)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±standard deviation or number of patients/lesions (percentage). CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Patient and Lesion Characteristics

Table 2. Quantitative and Qualitative IVUS Data

<table>
<thead>
<tr>
<th></th>
<th>Positive remodeling (n=24)</th>
<th>Intermediate remodeling (n=16)</th>
<th>Negative remodeling (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal reference site</td>
<td>EEM CSA (mm²)</td>
<td>18.7±7.1</td>
<td>15.7±4.4</td>
<td>16.1±3.8</td>
</tr>
<tr>
<td></td>
<td>Lumen CSA (mm²)</td>
<td>9.8±3.9</td>
<td>8.7±3.2</td>
<td>8.0±3.3</td>
</tr>
<tr>
<td>MLA site</td>
<td>EEM CSA (mm²)</td>
<td>22.3±8.0</td>
<td>15.8±4.4</td>
<td>13.4±3.2</td>
</tr>
<tr>
<td></td>
<td>Lumen CSA (mm²)</td>
<td>3.7±0.2</td>
<td>3.9±1.0</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td></td>
<td>Plaque burden (%)</td>
<td>81.2±7.3</td>
<td>73.3±8.9</td>
<td>70.8±6.8</td>
</tr>
<tr>
<td>Plaque composition of MLA site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous (%)</td>
<td>63.6±8.8</td>
<td>65.3±12.6</td>
<td>63.4±14.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Fibrofatty (%)</td>
<td>22.5±10.3</td>
<td>13.6±8.1</td>
<td>10.4±6.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dense calcium (%)</td>
<td>2.8±2.9</td>
<td>4.8±7.8</td>
<td>8.4±7.0</td>
<td>0.016</td>
</tr>
<tr>
<td>Necrotic core (%)</td>
<td>11.5±7.8</td>
<td>16.4±11.2</td>
<td>17.7±10.3</td>
<td>0.086</td>
</tr>
<tr>
<td>Entire culprit lesion</td>
<td>Lesion length (mm)</td>
<td>17.7±12.5</td>
<td>14.6±8.0</td>
<td>17.3±9.8</td>
</tr>
<tr>
<td></td>
<td>Plaque volume (mm³)</td>
<td>236.4±193.6</td>
<td>131.8±110.9</td>
<td>155.1±126.9</td>
</tr>
<tr>
<td></td>
<td>Plaque burden (%)</td>
<td>66.8±8.0</td>
<td>59.6±9.9</td>
<td>59.3±8.0</td>
</tr>
<tr>
<td>Plaque composition of entire culprit lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous (%)</td>
<td>64.2±8.9</td>
<td>66.5±9.1</td>
<td>66.6±14.3</td>
<td>0.72</td>
</tr>
<tr>
<td>Fibrofatty (%)</td>
<td>18.6±7.5</td>
<td>13.5±5.3</td>
<td>10.0±5.4</td>
<td>0.0007</td>
</tr>
<tr>
<td>Dense calcium (%)</td>
<td>4.1±2.9</td>
<td>5.3±4.0</td>
<td>7.3±5.7</td>
<td>0.077</td>
</tr>
<tr>
<td>Necrotic core (%)</td>
<td>13.3±8.0</td>
<td>14.9±11.1</td>
<td>17.0±11.5</td>
<td>0.47</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>1.22±0.19</td>
<td>1.01±0.02</td>
<td>0.83±0.09</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2. Quantitative and Qualitative IVUS Data

Data are means±standard deviation.
IVUS, intravascular ultrasound; EEM, external elastic membrane; CSA, cross-sectional area; MLA, minimum lumen area.

The studied vessel was the left anterior descending artery in 20 lesions, the left circumflex artery in 13 lesions, the right coronary artery in 21 lesions, and the left main coronary artery in 2 lesions. There were 24 positive remodeling lesions, 16 intermediate remodeling lesions, and 16 negative remodeling lesions. Baseline characteristics were comparable among the 3 groups except for body mass index (25.9±4.7 kg/m² vs 22.6±3.1 kg/m² vs 24.8±4.1 kg/m², p=0.049).

Comparison of Quantitative and Qualitative IVUS Data of Proximal Reference Sites, MLA Sites and Entire Culprit Plaques Among the 3 Remodeling Groups

Quantitative and qualitative IVUS data are shown in Table 2. No significant difference was found in the proximal reference sites among the 3 remodeling groups.

There was a significant difference in EEM CSA and the plaque burden of MLA sites among the 3 groups. The EEM CSA of MLA sites in the positive remodeling lesions was larger than that in the intermediate remodeling lesions and in the negative remodeling lesions (22.3±8.0 mm² vs 15.8±4.4 mm² vs 13.4±3.2 mm², p<0.0001). Plaque burden at the MLA sites in the positive remodeling lesions was also larger than that in the intermediate and in the negative remodeling lesions (81.2±7.3% vs 73.3±8.9% vs 70.8±6.8%, p=0.0002). No significant difference was found in lumen CSA among the 3 groups.

As for the entire culprit lesions, there was a significant difference in total plaque burden calculated as plaque plus media volume divided by EEM volume. Positive remodeling lesions had a larger plaque burden than intermediate or negative remodeling lesions (66.8±8.0% vs 59.6±9.9% vs 59.3±8.0%, p=0.01). There was no significant difference in lesion length among the 3 groups.

Analysis of plaque composition of the MLA sites demonstrated that the percentages of fibrofatty and dense calcium components differed among the 3 groups (Fig 1). The percentage of the fibrofatty component at the MLA sites was larger than that in the intermediate remodeling lesions and in the negative remodeling lesions (89.1±8.9% vs 73.3±8.9% vs 70.8±6.8%, p=0.049).

Fig 1. Difference in plaque composition of minimum lumen area sites in the 3 remodeling groups. *Significant difference by multiple comparison test. FI, fibrous; FF, fibrofatty; DC, dense calcium; NC, necrotic core. Open square, positive remodeling group; stripe square, intermediate remodeling group; solid square, negative remodeling group.

deviation. Discrete variables are presented as numbers and percentages. Statistical differences in the means among groups were analyzed by one-way analysis of variance (ANOVA). When a significant difference was detected, multiple comparison test with the Tukey-Kramer method was performed to identify groups that showed a significant difference. Frequencies were compared with the chi-square test. Linear regression analysis was used to evaluate the correlation between RI and proportion of plaque components. A p-value of less than 0.05 indicated statistical significance. Statistical analyses were performed using Stat View software version 5.0 (SAS Institute, Cary, NC, USA).

Results

Patient and Lesion Characteristics

Patient and lesion characteristics are shown in Table 1.
higher in positive remodeling lesions than in intermediate or negative remodeling lesions (22.5±10.3% vs 13.6±8.1% vs 10.4±6.6%, p=0.0001). A larger percentage of the dense calcium component at the MLA sites was found in negative remodeling lesions than in positive remodeling lesions (2.8±2.9% vs 4.8±7.8% vs 8.4±7.0%, p=0.016). There was no difference in the other plaque components. Representative examples of gray-scale IVUS images and color-coded plaque compositional maps of MLA sites in positive and negative remodeling lesion are shown in Fig 2.

Analysis of plaque composition of the entire culprit lesions also showed a significant difference in the percentage of the fibrofatty component (Fig 3). Positive remodeling lesions contained a larger percentage of the fibrofatty component than negative remodeling lesions (18.3±7.5% vs 13.5±5.3% vs 10.0±5.4%, p=0.0007). No significant difference was found in the percentage of the dense calcium component in all plaques; however, there appeared to be a trend towards significance (4.1±2.9% vs 5.3±4.0% vs 7.3±5.7%, p=0.077). No significant difference was detected in the other plaque components.

**Correlation Between Coronary Artery Remodeling and Plaque Components**

There was a weak, but significant positive correlation between the RI and the percentage of the fibrofatty component at MLA sites (r=0.32, p=0.016; Fig 4A). Conversely, a weak, but significant negative correlation was found between the RI and the dense calcium component (r=−0.28, p=0.037; Fig 4B). No significant correlation was detected between the RI and the percentage of the fibrous and necrotic core components.
Using spectral analysis of IVUS RF data, we demonstrated that culprit plaques with positive remodeling have a larger amount of the fibrofatty component than those with negative remodeling, whereas those with negative remodeling contain a larger amount of the dense calcium component than those with positive remodeling.

To elucidate the mechanism of coronary artery remodeling and its clinical implications, the relationship between coronary artery remodeling and plaque morphology has been investigated in several studies using necropsy specimens or gray-scale IVUS.4,12–16 Previous studies have consistently revealed that positive remodeling lesions have a large lipid burden,12–14 but different results have been reported for calcium deposition and the role of calcium deposition in coronary artery remodeling remains controversial. Some studies have shown that a large amount of calcium deposition is related to negative remodeling,4,14,16 whereas other studies identified calcium deposition as an indicator of positive remodeling.13,15

Although gray-scale IVUS has played an important role in evaluating plaque morphology in vivo, it is difficult to perform a detailed assessment of plaque composition. Other modalities, such as angioscopy, optical coherence tomography and multidetector row computed tomography, are emerging as new tools for acquiring detailed quantitative and qualitative information of plaque morphology.25–27 VH is one of these and in vivo tissue characterization by VH has been demonstrated to correlate favorably with the results of in vitro histopathologic examinations of tissue samples obtained by directional coronary atherectomy.11

In previous studies using gray-scale IVUS, calcium deposition was often assessed by using a calcified arc; however, this method is not accurate and may have resulted in the different outcomes. Indeed, when calcium exists in a vessel as a large "chuck", no ultrasound signal can pass through. However, in many cases, there is micro-calcification and if the distance between calcium deposits is greater than 50 μm, then the wave can pass through. The signal intensity may get smaller, but the frequencies are unaffected. Therefore, tissues behind the calcium deposition can be assessed by IVUS RF analysis, which may lead to more detailed assessment of the calcified lesions in vivo.

In the present study, using IVUS RF data, we demonstrated that positive remodeling lesions have a large lipid burden, which supports the previous finding.20 The mechanism of positive remodeling has not been fully elucidated. Lipid-rich atherosclerotic plaques contain abundant oxidized LDL,28 accumulation of which may induce an inflammatory response leading to the production of proteolytic enzymes, such as matrix metalloproteinases and cysteine proteinases, by activated macrophages. These proteolytic enzymes may play an important role in the outward expansion of the coronary arterial wall,29,30 and the active biochemical reaction may lead to plaque instability and restenosis after PCI of positive remodeling lesions.18,19,31,32

Cholesterol crystallization...
zation may also be a mechanism of plaque instability in lipid-rich positive remodeling lesions.33

The mechanism of negative remodeling is also not fully understood. The present study revealed a linear negative correlation between coronary artery remodeling and the dense calcium component of the plaque. As plaque calcification has been shown to be an indicator of advanced atherosclerosis,3–8 there may be a transition from positive remodeling to negative remodeling in the progression of atherosclerosis. A reduction in lipid burden, an increase in calcification and apoptosis, together with regressive changes and a consecutive decrease in the volume of plaque, may be a contributory mechanism.

Study Limitations

The RI could be influenced by the degree of remodeling within the proximal reference segment, although there was no difference in the characteristics of the reference segment among positive, intermediate, and negative remodeling lesions. As contour detection of the media–adventitia interface was difficult in some cases with heavily calcified lesions, those lesions were excluded from the analysis and may have led to selection bias. In some cases of acute coronary syndrome, we found ruptured plaques, so some of the plaque content might have been lost and so the analyzed plaque composition would differ from the original plaque composition. As thrombi and blood are not validated on IVUS RF data, these components might be assigned to 1 of the 4 components; however, by performing percutaneous aspiration thrombectomy prior to IVUS data acquisition, this limitation would be minimized. Vasospasm during IVUS imaging could not be excluded completely despite intracoronary administration of nitrates before the procedure.

Conclusions

Spectral analysis of IVUS RF data showed detailed morphological differences of in vivo plaque according to the extent of arterial remodeling, which may help identify the mechanism of coronary artery remodeling.

References


