Relationship Between Arterial and Fibrous Cap Remodeling
A Serial Three-Vessel Intravascular Ultrasound and Optical Coherence Tomography Study

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Background—Positive arterial remodeling and thin fibrous cap are characteristics of rupture-prone or vulnerable plaque. The natural course of the fibrous cap thickness and the relationship between serial arterial remodeling and changes in fibrous cap thickness are unknown. Therefore, the purpose of this study was to evaluate the relationship between changes in fibrous cap thickness and arterial remodeling by using optical coherence tomography (OCT) and intravascular ultrasound (IVUS) during 6-month follow-up.

Methods and Results—Both IVUS and OCT examinations were performed on 108 vessels from 36 patients with ischemic heart disease who underwent percutaneous coronary intervention. Fifty-eight fibroatheromas were selected from 82 nonsignificant, nonculprit lesions (angiographic diameter stenosis, 25% to 75%; plaque burden, >40% by IVUS). Fibroatheroma was defined by OCT as lipid-rich plaque in <1 quadrant that has lipid. Thickness of the fibrous cap was measured by OCT. IVUS and OCT examinations were repeated at 6-month follow-up. Serial changes and relationships between IVUS indices and fibrous cap thickness were investigated. Overall, fibrous cap thickness (98.1 ± 38.9 to 96.9 ± 44.5 μm) as well as IVUS indices did not change significantly within 6 months. The percent changes in fibrous cap thickness correlated negatively and significantly (r = -0.54; P < 0.0001; generalized estimating equation adjusted, r = -0.42; P = 0.001) with the percent changes in external elastic membrane cross-sectional area.

Conclusions—Arterial remodeling is related to changes in fibrous cap thickness. Positive arterial remodeling is not only an adaptive process, but also related to thinning of the fibrous cap. (Circ Cardiovasc Interv. 2010;3:00-00.)

Key Words: natural history intravascular ultrasound optical coherence tomography thin cap fibroatheroma

Clinical Perspective on p ●●●
We hypothesized that arterial remodeling (ie, serial changes in vessel size) and changes in fibrous cap thickness may be associated with each other. Therefore, we conducted serial (baseline and 6-month) intravascular ultrasound (IVUS) and optical coherence tomography (OCT) imaging of nonostial, nontarget, intermediate coronary lesions and investigated the relationship between arterial and fibrous cap remodeling.

Methods

Study Population and Percutaneous Coronary Intervention Procedures
A total of 36 patients (24 men; mean age, 70 ± 8 years) with ischemic heart disease who underwent preintervention IVUS and OCT imaging of the 3 epicardial coronary vessels were enrolled in this study. Patients with acute myocardial infarction, chronic total occlusion,
Coronary angiography was performed after intracoronary injection of nitroglycerin (250 μg) or isosorbide dinitrate (1 mg). Dual antiplatelet therapy with aspirin (100 mg daily) and ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was started before stent deployment and continued for at least 12 months. Cardiac catheterization was performed by radial or femoral approach using a 6-F guiding catheter. Percutaneous coronary intervention (PCI) was performed to treat culprit lesions. After successful PCI, both IVUS and OCT examinations were performed in all 3 coronary arteries.

Study segments were selected based on the outcomes from angiography, IVUS, and OCT as follows: (1) angiographic diameter stenosis between 25% to 75%, (2) plaque burden >40% by IVUS,12,13 and (3) presence of fibroatheroma by OCT. The fibroatheroma was defined as lipid-rich plaque in >1 quadrant that has lipid, as previously reported.14,15 The arc of the lipid-rich plaque was measured from the lumen center (Figure 1). By OCT, plaques were classified into 3 types—fibrous, fibrocalcific, and lipid— as previously reported.16,17 In brief, lipid-rich plaque was defined as signal-poor regions with diffuse borders; fibrous plaque was defined as homogenous, signal-rich regions; and fibrocalcific plaque was defined as well-delineated, signal-poor regions with sharp borders. Fibrous cap was defined as the signal-rich layer from the coronary artery lumen to the inner border of the underlying lipid-rich plaque (Figure 1). Two independent investigators who were unaware of clinical presentation diagnosed presence or absence of fibroatheroma. When there was discordance between them, a consensus reading was obtained. After 6 months following PCI, IVUS and OCT examinations were repeated to evaluate the serial changes in fibroatheroma.

**IVUS Imaging**

IVUS imaging was performed using a commercially available catheter with an automatic pullback device at 0.5 mm/s, and the data were digitized for quantitative and qualitative analysis according to the criteria of the American College of Cardiology Clinical Expert Consensus document on IVUS.18 The acquired images were recorded on CD-ROM for offline analysis by echoPlaque software. External elastic membrane (EEM) and lumen cross-sectional area (CSA) were measured. Plaque plus media (P+M) CSA was calculated by EEM—lumen CSA. Percent plaque burden was calculated by (P+M CSA/EEM CSA)×100. The cross-section with the smallest lumen CSA was selected for analysis. If there were multiple cross-sections with the smallest lumen CSA, the image slice with the largest EEM and P+M CSA equaling the largest plaque burden was analyzed.18,19 The identical cross-section was carefully selected using intravascular or perivascular landmarks and a constant pullback speed.18,19 Remodeling index was defined as EEM CSA at the target lesion divided by EEM CSA at the reference. A remodeling index >1 was defined as positive remodeling.19-22 Interobserver variability for EEM CSA and lumen CSA were 4.3±5.4% and 4.2±5.1%, respectively. Intraobserver variability for EEM CSA and lumen CSA were 2.8±4.9% and 2.7±5.3%, respectively.

**OCT Imaging**

After the IVUS procedure, OCT examination was performed as previously described.16,23-26 The OCT system used in this study consisted of an electro-optical imaging engine, a computer, 2 monitor displays, a probe interface unit, and a 0.014-in wire-type imaging catheter. The entire vessel length was imaged with an automatic pullback device at 1 mm/s, and the OCT data were recorded on a CD-ROM for offline analysis, for which proprietary software from LightLab Imaging was used. The thickness of the fibrous cap was measured 3 times, and its average was defined as the minimum distance from the coronary artery lumen to inner border of the lipid pool, which was characterized by a signal-poor region in the OCT image.24,27 Inter- and intraobserver variability of this measurement was 8.8±7.8% and 8.5±7.3%, respectively.

**Laboratory Data**

Laboratory data were obtained 24 hours before the cardiac catheterization and at 6-month follow-up.

**Clinical Follow-Up**

Clinical follow-up data were obtained by either a chart review or a telephone contact at 12 months after the index PCI procedure. A composite of all-cause death, acute coronary syndrome (unstable angina pectoris, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) related to the analyzed segments, and revascularization of the analyzed segments was a prespecified clinical end point.

**Statistical Analysis**

Statistical analysis was performed with StatView version 5.0 and SPSS Statistics 18 software. Qualitative data are presented with frequencies, and quantitative data are shown as mean±SD, if indicated. Continuous variables are reported as mean±SD. Paired t tests were used to differentiate 2 sets of data with normal distribution. Wilcoxon signed rank test was performed when the data were not normally distributed. The association between IVUS and OCT indices was investigated with linear regression analysis. Multiple logistic regression analysis was used to determine whether baseline measures predicted fibrous cap thinning. Generalized estimating equations (GEE) modeling were performed to account for the
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Sample size</td>
<td>36</td>
</tr>
<tr>
<td>Male sex</td>
<td>24</td>
</tr>
<tr>
<td>Age, y</td>
<td>70±8</td>
</tr>
<tr>
<td>Mean follow-up, d</td>
<td>209±51</td>
</tr>
</tbody>
</table>

Vessels

- LAD: 18
- LCX: 8
- RCA: 32

Conditions

- Diabetes mellitus: 18 (50)
- Hyperlipidemia: 28 (78)
- Hypertension: 27 (75)
- Smoking: 8 (22)
- Myocardial infarction: 9 (25)
- PCI: 18 (50)
- CABG: 1 (3)

Medications

- ACE-I/ARB: 23 (64)
- Statin: 25 (69)
- Antidiabetics: 11 (31)
- β-blocker: 8 (22)
- Calcium channel blocker: 15 (42)
- Aspirin: 36 (100)
- Thienopyridines: 36 (100)

Data are presented as no. (%) or mean±SD. Unless otherwise indicated, ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CABG, coronary artery bypass graft surgery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Correlation between arteries and lesions within the same patients. A P<0.05 was considered statistically significant.

Results

Eighty-two nonsignificant, nonculprit lesions from 108 coronary arteries were selected. Fifty-eight from the 82 lesions were diagnosed as fibroatheroma based on OCT and thus enrolled in the study (1 lesion from 27 patients, 2 lesions from 7 patients, 3 lesions from 1 patient, and 5 lesions from 1 patient).

Patient characteristics and laboratory data are shown in Tables 1 and 2, respectively. Eighteen (31%) plaques were detected in the left anterior descending artery, 8 (14%) in the left circumflex artery, and 32 (55%) in the right coronary artery. All IVUS and OCT images were acquired successfully without any complications. The interval between PCI and follow-up angiographic examination was 209±51 days. During the follow-up period, dual antiplatelet therapy with use of aspirin and thienopyridine (ticlopidine or clopidogrel) were continued in all study patients. Statin was prescribed in 69%. Ten patients with baseline low-density lipoprotein (LDL) cholesterol level <100 mg/dL were not treated with statin. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was used in 64% of the study patients.

Table 2. Baseline and Follow-Up Laboratory Data

<table>
<thead>
<tr>
<th>Laboratory Data</th>
<th>Baseline (n=36)</th>
<th>Follow-Up (n=36)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL</td>
<td>131±60</td>
<td>129±77</td>
<td>-2.5±55</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.2±1.2</td>
<td>6.0±1.0</td>
<td>-0.1±0.5</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>103±24</td>
<td>90±24</td>
<td>-13±30</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>52±15</td>
<td>55±15</td>
<td>2.6±7.1</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>120 (89–154)</td>
<td>115 (78–149)</td>
<td>-0.5 (–21–14)</td>
</tr>
<tr>
<td>LDL/HDL cholesterol ratio</td>
<td>2.1±0.6</td>
<td>1.7±0.5</td>
<td>-0.3±0.6</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.4</td>
<td>1.0±0.9</td>
<td>0.1±0.6</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.8 (0.5–2.1)</td>
<td>0.7 (0.4–1.5)</td>
<td>0 (–0.6–0.3)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or median (interquartile range). CRP indicates C-reactive protein; HDL, high-density lipoprotein; TG, triglyceride.

IVUS and OCT Analysis

The total length of the coronary arteries examined by both IVUS and OCT was 54±18 mm in the left anterior descending artery, 58±10 mm in the left circumflex artery, and 69±12 mm in the right coronary artery.

Baseline and follow-up quantitative IVUS and OCT results are summarized in Table 3. Overall, EEM CSA, lumen CSA, remodeling index, and percent change in fibrous cap thickness significantly decreased during follow-up. Similarly, fibrous cap thickness and the arc of the lipid-rich plaque did not change significantly during follow-up (all P values nonsignificant).

Percent change in fibrous cap thickness [%Δ cap thickness=100×(fibrous cap thickness at follow-up–fibrous cap thickness at baseline)/fibrous cap thickness at baseline] by OCT correlated negatively and significantly (r = −0.54;
P<0.0001; GEE adjusted, r=-0.42; P=0.001) with %ΔEEM CSA (ΔEEM CSA=[EEM CSA at follow-up−EEM CSA at baseline]/EEM CSA at baseline) (Figure 4A). Similarly, absolute change (Δ) in fibrous cap thickness (Δcap thickness=fibrous cap thickness at follow-up−fibrous cap thickness at baseline) by OCT correlated negatively and significantly (r=−0.65; P<0.0001; GEE adjusted, r=−0.53; P<0.0001) with ΔEEM CSA (Figure 4B). Figure 5 is a representative case that shows positive remodeling and fibrous cap thinning during 6-month follow-up.

Baseline LDL cholesterol (r=0.01; P=0.91), baseline C-reactive protein (r=0.08; P=0.55), ΔLDL cholesterol (r=0.08; P=0.56), and ΔC-reactive protein (r=0.08; P=0.55) did not correlate with Δcap thickness. By multiple logistic regression analysis, no baseline IVUS indices predicted fibrous cap thinning (%Δ cap thickness <0%) during 6 months.

Clinical Follow-Up
At 12-month follow-up, no death was documented. Acute coronary syndrome related to the analyzed segments and revascularizations of the analyzed segments were observed in 2 (6%) patients. As a result, a composite end point was documented in 2 (6%) patients.

Discussion
The principal finding of this study is that arterial remodeling and serial changes in fibrous cap thickness are related. Fibrous cap thickness of the lesions with subsequent positive arterial remodeling decreased, and that with subsequent negative remodeling increased over time.

Pathological as well as serial IVUS studies have shown that positive arterial remodeling is an adaptive vascular response to accommodate for plaque accumulation.1−4,28 Lack of this adaptive process may be associated with atherosclerotic lesion progression29,30 or restenosis after balloon angioplasty.18 On the other hand, negative (inadequate) arterial remodeling or vessel shrinkage is associated with lumen narrowing in a majority of patients with stable angina pectoris.5−7,28,31

Although the exact mechanism for extent and direction of arterial remodeling is not fully understood, it is suggested that intraplaque cytokines such as matrix metalloproteinases may cause disruption of the media and induce subsequent positive arterial remodeling.5,10 On the other hand, it also is reported that matrix metalloproteinases may cause thinning and ultimate disruption of the fibrous cap, resulting in plaque rupture and acute coronary syndrome or sudden cardiac death.8,11,32−34

Therefore, our results showing that positive remodeling was associated with fibrous cap thinning are quite reasonable, considering the effect of matrix metalloproteinases. Although our results did not indicate the direct relationship between specific cytokines and arterial remodeling or fibrous cap remodeling, they did confirm the relationship between plaque accumulation and positive arterial remodeling or fibrous cap thinning. Because those plaques that increased during the 6-month follow-up may be biologically active, it is possible that soluble factors from such an active or “hot” plaque affected both arterial and fibrous cap remodeling.

IVUS and OCT studies have shown that positive arterial remodeling is related to unstable clinical presentation, increased arterial distensibility, and systemic inflammation.5−7,28,35,36 Furthermore, previous IVUS studies have consistently demonstrated that lesions with positive remodeling were associated with worse clinical outcomes.15,19,36−40 In our present study population, 12-month clinical follow-up did not show any prognostic impact of the arterial and fibrous cap remodeling because of the small sample size and short follow-up period. A larger study population with longer follow-up needs to be investigated to clarify the impact of serial arterial remodeling and changes in fibrous cap on long-term clinical outcomes.

A previous nonrandomized study showed that fibrous cap thickness increased over time more significantly in patients treated with statin.27 However, the present study did not find a relationship between statin treatment and the change of fibrous cap thickness (statin group, 11.9 ± 53.7%; nonstatin group, −0.4 ± 46.7%; P=0.28). One of the reasons might be the difference in patient characteristics. In our study population, statin was used only in patients with hyperlipidemia. Therefore, patients not on statins may have a better baseline lipid profile than those on statins. Furthermore, it is possible that the lack of association of statin use with change in cap thickness might represent a type II error. Further randomized study is needed to address the impact of aggressive lipid-lowering treatment and plaque stabilization assessed by OCT.

Clinical Implications
The present study results together with those of previous reports showing that both thin fibrous cap and positive
arterial remodeling are morphological findings of vulnerable plaque have important clinical implications. Although predictors and the prognostic role of serial fibrous cap thinning associated with positive arterial remodeling have not been elucidated in this study, future study with a larger population will clarify its clinical impact. Furthermore, it would be quite interesting to investigate whether specific medications or local intervention can modify arterial and fibrous cap remodeling. Thus, positive remodeling and fibrous cap thinning can be surrogate end points of such medical or interventional treatments.

Limitations
Our study was limited by its small sample size and a lack of longer-term clinical follow-up. Because we used a currently available OCT system, which requires balloon occlusion, the ostial part of each coronary artery could not be imaged and assessed.

Another limitation is possible selection bias. Because IVUS cannot cross the severely stenotic lesions, those lesions with a diameter stenosis $>75\%$ were excluded from this study. Therefore, our results may not be generalizable to such severely stenotic lesions.

Finally, plaque characterization (signal rich or signal poor) of the OCT images was based on visual interpretation, which sometimes can be subjective. To provide objective and quantitative measures of the plaque characterization, signal intensity of the visually diagnosed lipid-rich plaque also can be measured by Scion image software. Signal intensity of the visually diagnosed

Figure 4. Percent change in fibrous cap thickness was negatively and significantly correlated with the \(\%\Delta\text{EEM CSA} \quad (r=-0.54; \quad P<0.0001; \quad \text{GEE adjusted,} \quad r=-0.42; \quad P=0.001) \) (A). Absolute change in fibrous cap thickness was negatively and significantly correlated with \(\Delta\text{EEM CSA} \quad (r=-0.65; \quad P<0.0001; \quad \text{GEE adjusted,} \quad r=-0.53; \quad P<0.0001) \) (B).

Figure 5. Serial IVUS and OCT images of a case with positive remodeling and thinning of the fibrous cap during 6-month follow-up (baseline [left], follow-up [right]). Serial IVUS images demonstrated that EEM CSA increased from 13.8 to 15.0 mm$^2$ (positive remodeling) (C–G). Serial OCT images demonstrated that minimal thickness of the fibrous cap decreased from 130 to 60 μm during follow-up (fibrous cap thinning) (D–H). The images shown are as follows: A indicates a longitudinally reconstructed IVUS image at baseline; B, cross-sectional IVUS image of a reference segment with a small side branch at baseline; C, cross-sectional IVUS image of a target lesion at baseline; D, an OCT image of a target lesion at baseline; E, a longitudinally reconstructed IVUS image at follow-up; F, cross-sectional IVUS image of a reference segment with a small side branch at follow-up; G, cross-sectional IVUS image of a target lesion at follow-up; H, an OCT image of a target lesion at follow-up. *A small side branch.
lipid-rich plaques was well below a cut-off value to differentiate lipid from fibrous plaque (unpublished data).

Conclusions
Serial IVUS and OCT examinations demonstrate that positive arterial remodeling is not only an adaptive process, but also related to thinning of the fibrous cap.

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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

Thin fibrous cap and positive remodeling are 2 major morphological findings that frequently are observed at the culprit lesions in acute coronary syndrome. This study investigated the relationship between changes in fibrous cap thickness and arterial remodeling by using optical coherence tomography and intravascular ultrasound during 6-month follow-up in patients with ischemic heart disease. Fifty-eight fibroatheromas from 82 nonsignificant, nonculprit lesions were selected and studied. Although overall thickness of the fibrous cap and external elastic membrane cross-sectional area did not change significantly over time, the percent changes in fibrous cap thickness correlated negatively and significantly with percent changes in external elastic membrane cross-sectional area, suggesting that lesions with vessel dilatation equal to positive remodeling is associated with thinning of the fibrous cap. Although predictors and the prognostic role of fibrous cap thinning associated with positive arterial remodeling was not elucidated in this study, future study with a larger population will clarify its clinical impact on vulnerable or unstable plaque.
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