Clinical Characteristics and Prognosis of Peri-strut Low-intensity Area Detected by Optical Coherence Tomography

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Background: Peri-strut low-intensity area (PLIA) is a typical image pattern of neointima detected by optical coherence tomography (OCT) after stent implantation. However, few studies evaluated the predictors and prognosis of the PLIA; therefore, we aimed to explore the genesis and prognosis of PLIA detected by OCT in this study.

Methods: Patients presenting neointimal hyperplasia documented by OCT reexamination after percutaneous coronary intervention were prospectively included from 2009 to 2011. Peri-strut intensity was analyzed and classified into two patterns: Low-intensity and high-intensity. Clinical characteristics were analyzed to assess their contribution to peri-strut intensity patterns. Follow-up were performed in patients who did not receive revascularization during OCT reexamination, and the prognosis of the patients was evaluated.

Results: There were 128 patients underwent OCT reexamination after stent implantation included in the study. PLIA was detected in 22 (17.2%) patients. The incidence of PLIA was positively correlated with serum triglyceride (odds ratio [OR]: 2.11, 95% confidence interval [CI]: 1.14–3.90, P = 0.017), low-density lipoprotein (OR: 2.61, 95% CI: 1.22–5.66, P = 0.015), history of cerebrovascular disease (OR: 101.11, 95% CI: 6.54–1562.13, P < 0.001), and initial clinical presentation of acute coronary syndrome (ACS, OR: 18.77, 95% CI: 2.73–128.83, P = 0.003) while negatively correlated with stent implantation time (OR: 0.57, 95% CI: 0.33–0.98, P = 0.043). The median follow-up was longer than 3.8 years. Major adverse cardiovascular events (MACEs) occurred in 7 (7.3%) patients while showed no correlation with PLIA. A total of 17 (17.7%) patients experienced unstable angina (UA) and showed significant correlation with PLIA (hazard ratio: 6.16, 95% CI: 1.25–30.33, P = 0.025).

Conclusions: PLIA detected by OCT was positively correlated with higher serum lipid level, history of cerebrovascular disease and initial presentation of ACS, and negatively correlated with stent implantation time. Patients with PLIA were more likely to have UA than those with high-intensity while no significant difference was found in MACEs.

Key words: Optical Coherence Tomography; Peri-strut Low-intensity Area; Unstable Angina
plaque rupture. Moreover, recent studies showed typical image patterns in the restenotic tissues.[3–4] High intensity of peri-strut region is dominant in restenosis tissue, whereas some of the peri-strut tissues show low-intensity in OCT images. Previous studies explored the tissue characteristics of peri-strut low-intensity area (PLIA),[5–7] however, the predictors and prognosis of this typical image pattern is still unknown. Therefore, in this study, we compared clinical characteristics of patients with different patterns of peri-strut intensity and analyzed predictors and prognosis of these patients.

**Methods**

**Subjects and study design**

We prospectively enrolled patients accepted OCT examination at least 6 months after drug-eluting stents (DES) implantation from March 2009 to March 2011 in Fuwai Hospital. The patients with neointimal thickness of at least 100 μm in 5 consecutive cross-sectional images were included.

The exclusion criteria of our study were as follows: (1) age ≥80 years old or ≤18 years old; (2) untreated left main coronary artery disease; (3) underwent balloon predilatation before OCT examination; (4) poor OCT image; (5) left ventricle ejection fraction ≤30%; and (6) serum creatinine ≥2.0 mg/dl (150 μmol/L). This study was approved by the Institutional Ethics Committee of Fuwai Hospital, and written informed consent was obtained from each patient.

We assessed the OCT images and divided the patients into two groups according to peri-strut intensity: low-intensity group and high-intensity group [Figure 1]. Then we compared clinical characteristics of the two groups. We also performed a follow-up to compare prognosis of the two groups.

**Definitions**

Major adverse cardiac events (MACEs) were defined as all cause of death, nonfatal myocardial infarction, or target vessel revascularization. Clinical events were defined according to the Academic Research Consortium.[8] Myocardial infarction was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal image findings of myocardial infarction combined with an increase in creatine kinase myocardial band fraction >3 times the upper limit of the normal range or an increase in troponin T/troponin I to more than the 99th percentile of the upper limit of normal, all of which were unrelated to an interventional procedure.[8,9] Target vessel revascularization was defined as a repeat percutaneous intervention or bypass surgery of the target vessels with either of the following findings: Ischemic symptoms or a positive stress test and an angiographic minimal lumen diameter stenosis ≥50% assessed by quantitative coronary angiographic analysis or an angiographic diameter stenosis ≥70% assessed by quantitative coronary angiographic analysis without either ischemic symptoms or a positive stress test.[9] Symptoms including stable and unstable angina (UA) were acquired through questionnaire. Patients who had stable effort angina during follow-up were defined as stable angina, those with the initial issuance of effort angina, deterioration of exertional angina, resting angina, infarction angina, or variant angina were defined as UA.[10]

**Optical coherence tomography image acquisition**

OCT was performed according to the consensus standards for acquisition of OCT.[11] A 0.016-inch OCT catheter (ImageWire, LightLab Imaging Inc., Westford, MA, USA) was advanced distal to the culprit lesion, using an occlusion balloon catheter (Helios, Goodman Co., Ltd., Nagoya, Japan). To remove blood from the field of view, the occlusion balloon was inflated to a pressure of 0.5 atm (1 atm = 101.325 kPa) at a site proximal to the culprit lesion, and a mixture of dextran and lactate Ringer’s solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at a rate of 0.4–0.7 ml/s. Image acquisition was performed at an automated pull-back speed of 1–2 mm/s. OCT images were recorded and analyzed in LightLab Imaging System (LightLab Imaging Inc., Westford, MA, USA).[3,12]

**Optical coherence tomography image analysis**

OCT images were analyzed using proprietary off-line software (LightLab Imaging Inc). All of the OCT images were analyzed by two independent investigators who analyze more than 100 cases of OCT images per year, and were blinded to the clinical characteristics. Cross-sectional OCT images were analyzed at 1-mm intervals for qualitative and quantitative measurements. Stent area and luminal cross-sectional area (CSA) were measured. The neointimal area was calculated as the stent area minus luminal CSA. Restenosis ratio was defined as neointimal area divided by stent area. Image patterns were defined as validated criteria.[13] PLIA was defined as homogenous low-intensity around stent struts without significant signal attenuation behind the area on a strut basis [Figure 1a], while peri-strut high intensity was defined as homogenous high intensity around stent struts [Figure 1b]. Patients with one or more cross-sections presented with PLIA were classified into low-intensity group. Macrophage was defined as bright spot reside at the surface of a plaque [Figure 2a];[11,14] TCNA was defined as having an angle of signal-poor lipid pool in <2 quadrants and a fibrous cap thickness ≤65 μm in 3 consecutive images [Figure 2b].[17]
While an initial clinical presentation of acute coronary syndrome (ACS) at the time of stent implantation was more frequently observed in low-intensity group than that of high-intensity group (22.7% vs. 6.6%, \( P = 0.033 \)). Total cholesterol (5.46 ± 1.09 vs. 4.71 ± 0.97 mmol/L, \( P = 0.002 \)), LDL (2.39 ± 0.98 vs. 1.91 ± 0.62 mmol/L, \( P = 0.041 \)), and triglyceride (2.42 ± 1.03 vs. 1.87 ± 0.84 mmol/L, \( P = 0.010 \)) were also higher in low-intensity group compared with high-intensity group. Simultaneously, more patients experienced cerebrovascular disease in the low-intensity group than in the high-intensity group (22.7% vs. 1.9%, \( P = 0.002 \)).

**Optical coherence tomography assessment of neointima**

We analyzed 2202 cross-sections of the OCT image. There was no difference in average intimal thickness and restenosis ratio between the low- and high-intensity groups. Image patterns were qualitatively analyzed. Cross-sections with the presence of macrophage were similar in the two groups. Microvessel was more frequently detected in high-intensity group (4.8% vs. 23.8%, \( P< 0.001 \)), while TCNA was more frequently observed in low-intensity group compared with high-intensity group (22.7% vs. 6.6%, \( P = 0.039 \)) [Table 2].

**Factors related to peri-strut low-intensity area**

Through the initial univariate binary logistic regression model which included each of the possible coronary risk factors, we found that stent implantation time, history of ACS, cerebrovascular disease, triglyceride, total cholesterol, and LDL were potentially correlated with PLIA. Then using a multivariate binary logistic regression model, we found that factors related to PLIA were stent implantation time (OR: 0.57, 95% CI: 0.33–0.98), history of ACS (ACS, OR: 18.77, 95% CI: 2.73–128.83), cerebrovascular disease (OR: 101.11 95% CI: 6.54–1562.13), LDL (OR: 2.61, 95% CI: 1.22–5.66), and triglyceride (OR: 2.11, 95% CI: 1.14–3.90) [Table 3].

**Prognosis of the patients**

A total of 28 patients accepted PCI treatment once after OCT examination because of other target vessels, and they were excluded from the prospective study. Follow-up was completed in 96 patients. The median follow-up time was more than 3.8 years. No death or myocardial infarction was noted during the follow-up period. The follow-up group was divided into two groups: 0.37 years, IQR: 0.30–1.11 years vs. 1.07 years, IQR: 0.45–4.05 years, \( P = 0.004 \).

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A total of seven patients experienced target vessel revascularization (one with PLIA and six without PLIA). Cox regression analysis showed that there was no significant difference between the two groups in MACEs or rehospitalization. While we found that patients in low-intensity group were more likely to have UA during follow-up than in high-intensity group (38.9% vs. 12.8%, hazard ratio: 6.16, 95% CI: 1.25–30.33, P = 0.025) [Table 4].

**DISCUSSION**

PLIA was detected in 17.2% of the patients. It was positively correlated with the initial presentation of ACS, history of cerebrovascular disease, high serum LDL, and triglyceride while negatively correlated with stent implantation time. TCNA was more frequent in low-intensity OCT images while microvessel was less detected in low-intensity group. Patients with PLIA experienced more frequency of UA than that of high-intensity group while no significant difference was found in MACEs between the two groups.

OCT could provide a large amount of information during follow-up after stent implantation. Neointima shows different patterns in OCT images. Peri-strut intensity is one of the distinguishing features among the patterns. The
incidence of PLIA ranges from 6% to 40%,\(^{5,15}\) which is in consistency with our data. However, few studies researched the genesis and prognosis of PLIA.

We noticed that lipid plaque also showed low-intensity in OCT images. Given that, we hypothesized that PLIA was perhaps correlated with high serum lipid. Therefore, we compared the levels of serum total cholesterol, LDL, and triglyceride of patients with low or high intensity and proved the hypothesis. Considering that previous histological studies did not prove the presence of adipose tissue in swine models,\(^{5,6}\) we still need a pathological examination of human vessels to confirm the tissue components of neointima.

We also noticed that initial clinical presentation of ACS and shorter stent implantation history were independent risk factors of PLIA. Since inflammation is a key contributor to ACS, it could also provide a reasonable explanation for the detection of more peri-strut inflammation in PLIA pattern.\(^{[6]}\) These findings suggest that PLIA may be an immature pattern of neointimal which is associated with ACS or inflammation and appear more frequently in early phases after PCI. Besides, our data showed that patients with PLIA were more likely to be complicated with cerebrovascular disease. It suggests that PLIA may be correlated with vascular disease.

We analyzed the relationship between PLIA and other tissue characteristics. TCNA was found in more cross-sections of patients with PLIA. It suggests that PLIA may be associated with more lipid plaque, and it may be an unstable factor of neointima. The correlation of PLIA and microvessel we found in this study should be interpreted with caution for the reason that the image pattern of microvessel showed low-intensity in OCT images, and it might be hard to distinguish the microvessel patterns from low-intensity neointima. We did not find a correlation between PLIA and NIH, which was different from other studies.\(^{5,16}\)

Few studies explored the prognosis of patients with PLIA. We compared MACEs and rehospitalization between the two groups. However, no death or MI happened during the follow-up. Therefore, we found no significant difference in MACEs or rehospitalization. As a compromise, we compared the incidence of UA of the patients and found it was positively correlated with PLIA. It suggested that PLIA might lead to poor prognosis.

A possible explanation for PLIA is that patients with ACS or hyperlipidemia are in high inflammation state, after stent implantation, intima healing progression might be different, which would contain more lipid plaques or inflammation cells and with a tendency of more neatherosclerosis, this type of intima might show low-intensity in OCT images and lead to poor prognosis. We call this phenomenon intimal unhealthy healing. However, further studies are needed to verify this hypothesis in the future.

There are several limitations in this study. First, the limited sample size lead to low incidence of MACEs, hence we had to use UA as end points, which was not a strong enough evidence. Second, we did not quantitatively analyze the intensity of the OCT images which may lead to bias in the classification of intensity. Third, we did not perform serial OCT examinations for a single patient so that we could not explore the natural history of PLIA. Then, stent pressure and length play critical roles in the formation of PLIA, however, we were unable to collect detailed information of stents as most of the patients underwent PCI in other centers. Finally, we did not have a chance to perform pathological examinations of the target vessels so that we could not know the definite tissue components of PLIA tissue.

In conclusion, different types of OCT image patterns may provide meaningful information. PLIA was positively correlated with higher serum lipid level, history of

### Table 3: Factors related to peri-strut low-intensity detected by OCT

| Factors                        | OR   | 95% CI          | P  |
|-------------------------------|------|-----------------|----|
| ACS                           | 18.77| 2.73–128.83     | 0.003|
| Stent implantation time       | 0.57 | 0.33–0.98       | 0.043|
| LDL                           | 2.61 | 1.22–5.66       | 0.015|
| Triglyceride                  | 2.11 | 1.14–3.90       | 0.017|
| Cerebrovascular disease       | 101.11 | 6.54–1562.13 | <0.001|

ACS: Acute coronary syndrome; LDL: Low-density lipoprotein; OCT: Optical coherence tomography; OR: Odds ratio; CI: Confidence interval.

### Table 4: Major adverse cardiac events and angina pectoris during follow-up after OCT reexamination

| Endpoints                      | Low-intensity (n = 18) | High-intensity (n = 78) | HR   | 95% CI           | P  |
|--------------------------------|------------------------|-------------------------|------|-----------------|----|
| MACEs                          | 1 (5.6)                | 6 (7.7)                 | 1.63 | 0–138,424.6     | 0.932|
| Cardiac death                  | 0 (0)                  | 0 (0)                   |      |                 |    |
| MI                             | 0 (0)                  | 0 (0)                   |      |                 |    |
| TLR                            | 1 (5.6)                | 6 (7.7)                 | 1.63 | 0–138,424.6     | 0.932|
| All angina                     | 9 (50.0)               | 36 (46.2)               | 1.14 | 0.39–3.37       | 0.811|
| SAP                            | 5 (27.8)               | 29 (37.2)               | 0.32 | 0.07–1.50       | 0.149|
| UA                             | 7 (38.9)               | 10 (12.8)               | 6.16 | 1.25–30.33      | 0.025|
| Rehospitalization              | 7 (38.9)               | 26 (33.3)               | 0.96 | 0.23–4.01       | 0.955|

Values are n (%); After adjusted for age, gender, hypertension, diabetes, hyperlipidemia, smoke, history of cerebrovascular disease, initial presentation of ACS, TC, LDL, and triglyceride; MACEs: Major adverse cardiovascular events; MI: Myocardial infarction; TLR: Target lesion revascularization; SAP: Stable angina pectoris; UA: Unstable angina; ACS: Acute coronary syndrome; TC: Total cholesterol; LDL: Low-density lipoprotein; OCT: Optical coherence tomography; CI: Confidence interval; HR: Hazard ratio.
cerebrovascular disease and initial presentation of ACS, and negatively correlated with stent implantation time. Patients with PLIA were more likely to have UA than those with high intensity while no significant difference was found in MACEs between the two groups. Further large, randomized studies are needed to confirm these findings.

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Conflicts of interest
There are no conflicts of interest.

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