Association between non-culprit healed plaque and plaque progression in acute coronary syndrome patients: an optical coherence tomography study

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ABSTRACT

BACKGROUND   Healed plaques are frequently found in patients with acute coronary syndrome, but the prognostic value is debatable. This study investigated the clinical features of non-culprit healed plaques detected by optical coherence tomography (OCT) with the aim of predicting plaque progression of healed plaques.

METHODS   This study retrospectively analyzed 113 non-culprit lesions from 85 patients who underwent baseline OCT imaging and follow-up angiography from January 2015 to December 2019. Plaque progression predictors were assessed by multivariate analysis.

RESULTS   Among 113 non-culprit lesions, 27 healed plaques (23.9%) were identified. Patients with non-culprit healed plaques had prior antiplatelet therapy (65.0% *vs.* 33.8%, *P* = 0.019), hypertension (85.0% *vs.* 50.7%, *P* = 0.009), and dyslipidemia (70.0% *vs.* 41.5%, *P* = 0.04) which were more frequently than those without healed plaques. The thickness (*r* = 0.674, *P* < 0.001), arc (*r* = 0.736, *P* < 0.001), and volume (*r* = 0.541, *P* = 0.004) of healed plaque were correlated with minimum lumen diameter changes. At a mean follow-up of 11.5 months, the non-culprit healed plaques had a lower minimum lumen diameter (1.61 ± 0.46 mm *vs.* 1.91 ± 0.73 mm, *P* = 0.016), lower average lumen diameter (1.86 mm *vs.* 2.10 mm, *P* = 0.033), and a higher degree of diameter stenosis (41.4% ± 11.9% *vs.* 35.5% ± 13.1%, *P* = 0.031) when compared to baseline measurements. The plaque progression rate was higher in the healed plaque group (33.3% *vs.* 8.1%, *P* = 0.002), and multivariate analysis identified healed plaques [odds ratio (OR) = 8.49, 95% CI: 1.71−42.13] and lumen thrombus (OR = 10.69, 95% CI: 2.21−51.71) as predictors of subsequent lesion progression.

CONCLUSIONS   Healed plaques were a predictor for rapid plaque progression. The quantitative parameters of healed plaque showed a good agreement with plaque progression. Patients with healed plaque were associated with prior antiplatelet therapy and high level of low-density lipoprotein cholesterol. Bifurcation lesions might be the predilection sites of healed plaques.

Coronary artery diseases originate from pathological changes in the vessel endothelium, present as plaque development and lumen stenosis, that finally lead to clinical coronary symptoms.[1] Finding the ideal time to intervene in the atherosclerosis process is difficult, especially with non-culprit lesions.[2–4] Revascularization benefits are challenged by the quick progression of previously untreated mild to moderate lesions.[2] Several clinical trials suggested that the rapid step-wise pattern of plaque growth may play an important role in lumen narrowing.[5,6] This mechanism was described as a healing process that was initiated by a plaque rupture or erosion to protect the integrity of the vessel structure.[7,8] Re-endothelialization results in a new layer of organized thrombus and collagen distinguished from the underlying ruptured or eroded site,[9] and plaques with two or more layers of different densities are called healed plaques or layered plaques.[8,10] Autopsy studies found that healed plaques were frequent in patients dying of sudden death or asymptomatic myocardial infarction.[11] Optical coherence tomography (OCT) is a high-resolution intravascular imaging tool that is

highly sensitive and specific for *in vivo* identification of layered plaque patterns by histopathology.[12,13] A previous OCT study suggested that layered plaques at the culprit site were associated with more vulnerable features and a high degree of lumen stenosis in patients with acute coronary syndrome (ACS).[14] However, serial observations of plaque progression at the exact site were only reported in rare cases.[15] In this study, we investigated the OCT features, quantitative parameters, and predictive value of non-culprit healed plaques, which may help minimize plaque progression and stenosis risk.

METHODS

Study Population

From January 2015 to December 2019, patients with intra-coronary OCT imaging during baseline percutaneous coronary intervention and repeated angiography six to eighteen months later were selected from Chinese PLA General Hospital registry (ChiCTR2100041924). The repeated angiography was routine during follow-up. The inclusion criteria was ACS patients with non-culprit lesions detected by clinical standard (*n* = 137), culprit lesions were detected by clinical presentation, elevated leads, coronary angiogram or abnormalities of left ventricular wall motion.[8,16] Fifty-two patients were excluded for the following reasons: (1) severe heart

failure, chronic kidney failure or hypohepatia (*n* = 3); (2) previous coronary artery bypass grafting (*n* = 2); (3) insufficient length of pull-back to cover the whole lesions (*n* = 7); (4) massive lumen thrombus or artifacts with sub-optimal imaging (*n* = 5); (5) no culprit lesions were detected on OCT images (*n* = 32); and (6) total occlusion of detected lesions during follow-up (*n* = 3). Finally, a total of 85 patients with 113 non-culprit lesions were enrolled in the present study. The study protocol was showed in Figure 1.

Clinical data were collected based on the medical records. Patients with both healed plaque and non-healed plaque were included in healed plaque group. Patients without healed plaque in any lesions were included in non-healed plaque group. All images were anonymous and analyzed by two individual experts in core laboratory. Individual lesions were assessed and divided into healed plaque group and non-healed plaque group. Non-culprit lesions were defined as untreated lesions with abnormal architecture of the vessel wall on OCT images. Quantitative coronary angiography (QCA) analysis was performed to calculate the change of minimum lumen diameter (MLD) and diameter stenosis (DS) between healed plaque and non-healed plaque. Multivariate analysis was performed to find the predictors of lesion progression.

Clinical diagnose were made based on the novel international guideline and local expert consensus.[17,18] ACS represents an umbrella of ischemic myocardial
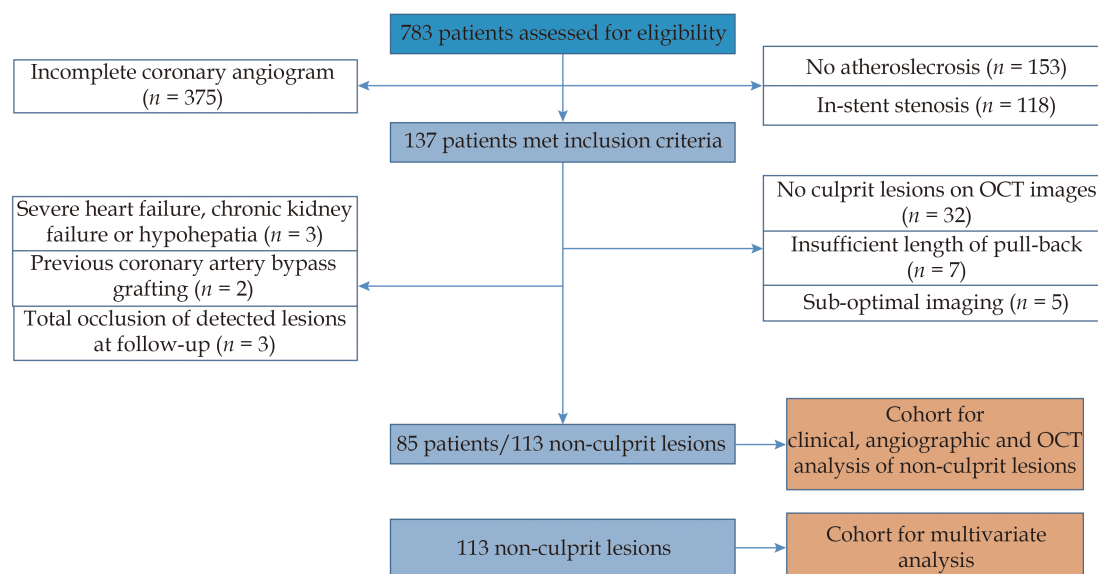

Figure 1 Study protocol. OCT: optical coherence tomography.

disease and diagnoses encompassing unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). STEMI was defined as long-last typical chest pain (> 30 min), elevated cardiac biomarkers and more than two contiguous leads ST-segment elevation > 0.1 mv or newly onset left bundle-branch block on the 12-lead electrocardiogram.[17] NSTEMI was defined as typical chest pain with elevated cardiac biomarkers in the absence of ST-segment elevation on electrocardiogram. Unstable angina was defined as long-last angina at rest, new-onset angina within two months, accelerated angina, angina after myocardial infarction.[18] Previous myocardial infarction was assured by the pathological Q waves or the abnormal ventricle wall motion. Other related complications were assured by medical examination report. Previous medical therapy were affirmed by certificate of diagnosis and inquiry. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) > 70 mg/dL in ACS patients, and the standard for LDL-C under control during follow-up was LDL-C < 70 mg/dL and LDL-C declining by 50% from baseline.[19] Information on tobacco smoking, blood lipids, diabetes mellitus or blood sugar disorder and blood pressure were collected during follow-up to estimate the cardiovascular risk factors.[20]

This study was approved by the Ethics Committee of Chinese PLA General Hospital (No.S2020-255-01) and was conducted according to the guidelines of the declaration of Helsinki Declaration. All patients provided written informed consent before enrollment.

Coronary Angiography Analysis

Offline angiograms were viewed by two independent investigators blinded to the clinical data and OCT results. All the significant non-culprit plaques were recorded using landmarks such as the side branch ostia, typical vessel structure and stent struts.[16] The follow-up angiography was performed at least six months later after the primary intervention. QCA was performed at the baseline and follow-up using QAngio® XA Medis Medical Imaging systems (B.V, Leiden, Netherlands). For each lesion, high-quality optimal angiography was selected for QCA analysis, the position of flat panel

and oblique was chosen according to the optimal analysis recommendation.[21] The target frame with minimize vessel movement and full-filled contrast in the end-diastolic phase was recorded and consistent between baseline and follow-up angiography. At least twice calculation was requested and the average value was recorded. The plaque length, MLD and DS were measured. Average lumen diameter (ALD), defined as the ALD of the whole lesions, was calculated automatically.[22] Plaque progression was defined as a decrease of MLD ≥ 0.4 mm during follow-up.[23–25]

OCT Image Acquisition and Analysis

OCT image was acquired using frequency domain OCT systems from either C7 OCT intravascular imaging system (St. Jude Medical, St. Paul, Minnesota) or ILUMIEN OPTIS OCT system (Abbott Vascular, Santa Clara, CA). OCT images were analyzed using an offline analysis software (Lightlab Imaging) in anonymous mode by two independent investigators blinded to clinical and laboratory data. A consensus reading was made in case of discordance. Random 30 images were selected to calculate the intra-observer and inter-observer deviation one month and two months later after completing analysis.

OCT analysis was conducted every one frame along the whole pull-back procedure, the definition and calculation conformed to the established criteria.[12,26,27] Any frame with more than 90° deficiency of vessel border was defined as invalid frame. Massive lumen thrombus or severe artifacts hampering the detection were excluded before the investigation. Significant plaque was defined as the loss of 3-layered vessel wall structure ≥ 90° on OCT image.[26] The OCT plaque frames corresponded with the angiography using the structural landmarks such as the side branches ostia, stent edges, dissection, luminal thrombosis and calcifications.[28] Given the situation of long diffused lesion, serial OCT pull-backs were combined with the mark of vessel structure and the average value of two pull-backs was calculated for the overlap segments.[29] The polygon of confluence (POC) began at the carina and ended at the contacting point of main vessel and side branch. The bifurcation lesion was defined as the POC and 5-mm

segment proximal and distal to the POC.[30]

Healed plaques were defined as a plaque with at least one heterogeneous sigh-rich layer of different optical signal intensity located close to the luminal surface and a clear demarcation from underlying tissues.[12-14] The measurements of healed plaque referred to the previous OCT studies.[14,31] Healed thickness was defined as the longest perpendicular distance between luminal surface and healed plaque boundary. Healed thickness was measured at three different points to calculate the average value. Healed length was measured on the longitudinal view. Healed arc and healed area were measured at 1-mm intervals. Healed volume index was calculated from mean healed area and healed area according to Simpson's rule.[32]

Plaques were classified as two kinds: (1) lipid (low-signal region with a diffusely border) or (2) fibrous (homogeneous, high backscattering region), calcified area were defined as a structure feature in avoidance of interference.[24,29] Lipid arc was measured every 1 mm, lipid index was calculated from lipid length and lipid arc.[28] The plaque with a lipid arc greater than 90° in any cross-sectional image was defined as lipid-rich plaque.[28] Fibrous cap was defined as an overlying signal-rich band upon the lipid core, the thickness of cap was measured 3 times at its thinnest part and defined as the average value. Thin-cap fibroatheroma (TCFA) was defined as lipid-rich plaque with an overlying fibrous cap thinner than 65 μmol/L.[33] Calcification was distinguished with sharped border and heterogeneous signal. Calcification with an arc less than 90° and the length less than 4 mm was defined as spotty calcification.[34] Macrophage accumulation appeared as high backscattering, strongly attenuating confluent area with a back shadowing.[28] Microvessels were defined as a non-signal intraplaque structure with a diameter of 50–300 μmol/L which could be seen in at least three continuous frames.[35] Thrombus was defined as an mass with minimum diameter of 250 μmol/L adherent to the vessel wall or floating within the lumen.[31,36] Plaque length was defined as the distance between the first and the last OCT frame where the plaque region was observed. Minimum lumen area was the smallest lumen area within the pull-back of the plaque. Reference lumen was the largest area within 10 mm distance to the plaque in the same segment without crossing large bifurcation. Mean reference lumen area was calculated from the largest distal and proximal reference lumen area.[31]

Statistical Analysis

Categorical variables were described as counts (percentages) and compared using the Pearson's chi-squared test or Fisher's exact probability test. At patient-level, all continuous variables were assessed by Kolmogorov-Smirnov test, normally distributed variables were expressed as mean ± SD and analyzed by Student's t-test, while non-normally distributed variables were expressed as medians (interquartile range) and analyzed by Mann-Whitney U test. At lesion-level, generalized estimating equations with an identity link for continuous variables and a logit link for the binary variables were used to take into account potential clustering of multiple plaques in a single patient. Correlation between healed plaque parameters and change of MLD was evaluated using Pearson's correlation coefficient and linear regression analysis. Predictors of plaque progression multivariate analysis was assessed by the multivariate logistic regression model with a generalized estimating equation. The OCT characters with P-value < 0.10 were selected into multivariate model and multi-collinearity were excluded by analyzing variance inflation factor. Kappa coefficient statistics were used for assessment of intra-observer and inter-observer agreements at a four-week interval, intraclass correlation coefficient with two-way random model and absolute agreement type were used to assess reproducibility. A two-sided P-value less than 0.05 was considered statistically significant, and odds ratio (OR) were presented with 95% confidence interval (CI). All statistical analyses were performed with SPSS 22.0 (SPSS Inc., IBM, Armonk, NY, USA).

RESULTS

Baseline Clinical Characteristics

In the healed plaque group, 19 patients (95.0%) were diagnosed with non-ST-segment elevation

ACS and 1 patient (5.0%) was diagnosed with acute STEMI at admission (Table 1). Patients with non-culprit healed plaques had prior antiplatelet therapy (65.0% *vs.* 33.8%, P = 0.019), hypertension (85.0% *vs.* 50.7%, P = 0.009), and dyslipidemia (70.0% *vs.* 41.5%, P = 0.04) which were more frequently than those without healed plaques. Patients with non-culprit healed plaques had high level of LDL-C (101.3 ± 32.4 mg/dL *vs.* 81.8 ± 32.9 mg/dL, P = 0.043) and C-reactive protein [0.21 (0.10−0.47) mg/dL *vs.* 0.10 (0.05−0.13) mg/dL, P = 0.008] than those without healed plaques. Overall, 97.6% of patients (83/85)

Table 1   Clinical characteristics of the patients.

Patient level	Patients with non-culprit healed plaque (*n* = 20)	Patients without non-culprit healed plaque (*n* = 65)	*P*−value
Follow-up period, month	14.0 (9.5−15.0)*	11.0 (7.8−15.3)*	0.12
Age, yrs	59.5 ± 8.6	58.2 ± 9.6	0.98
Male sex	11 (55.0%)	48 (73.8%)	0.11
Body mass index, kg/m^2	25.9 ± 3.0	24.9 ± 3.5	0.25
Mean SBP, mmHg	131.4 ± 19.0	130.6 ± 15.5	0.78
Mean DBP, mmHg	74.4 ± 13.2	74.1 ± 11.2	0.93
Mean heart rates, beat/min	74.4 ± 9.0	72.2 ± 11.1	0.42
Hypertension	17 (85.0%)	33 (50.7%)	< 0.05
Antihypertensive therapy	14 (70.0%)	30 (46.2%)	0.07
Diabetes mellitus	7 (35.0%)	26 (40.0%)	0.79
Hypoglycemic treatment	6 (30.0%)	23 (35.4%)	0.79
Dyslipidemia	14 (70.0%)	27 (41.5%)	< 0.05
Statins therapy	1 (5.0%)	2 (3.1%)	0.68
Current smoking	8 (40.0%)	23 (35.4%)	0.79
Prior myocardial infarction	4 (20.0%)	10 (15.4%)	0.73
Prior percutaneous coronary intervention	3 (15.0%)	18 (27.7%)	0.38
Prior antiplatelet therapy	13 (65.0%)	22 (33.8%)	< 0.05
Cerebrovascular or peripheral diseases	11 (55.0%)	20 (30.8%)	0.06
Clinical presentation			0.68
STEMI	1 (5.0%)	8 (12.3%)	−
NSTE-ACS	19 (99.5%)	57 (87.7%)	−
Left ventricular ejection fraction, %	58.0 ± 9.3	59.1 ± 8.2	0.61
Laboratory data on admission			
Total cholesterol, mg/dL	158.3 ± 33.6	144.9 ± 41.3	0.19
LDL-C, mg/dL	101.3 ± 32.4	81.8 ± 32.9	< 0.05
HDL-C, mg/dL	46.0 ± 15.2	38.1 ± 17.0	0.098
Triglyceride, mg/dL	109.4 (81.7−152.3)*	127.9 (106.1−179.4)*	0.58
Hemoglobin, g/L	130.8 ± 17.7	133.3 ± 22.5	0.65
Hypersensitive C-creative protein, mg/dL	0.21 (0.10−0.47)*	0.10 (0.05−0.13)*	< 0.05
HbA1c, %	6.5 ± 1.4	6.6 ± 1.4	0.73
Uric acid, μmol/L	351.5 ± 122.6	328.9 ± 86.1	0.36
Creatinine clearance, mL/min per 1.73 m^2	87.2 ± 31.4	92.7 ± 31.8	0.49
Coagulation index	−1.2 ± 1.7	−1.0 ± 2.3	0.81
Platelet inhibition ratio (ADP), %	72.1 (49.7−92.2)*	78.6 (56.6−90.2)*	0.48
Platelet inhibition ratio (AA), %	93.1 (87.7−95.7)*	91.4 (72.4−96.7)*	0.98

Continued

Patient level	Patients with non-culprit healed plaque (*n* = 20)	Patients without non-culprit healed plaque (*n* = 65)	*P*–value
Medication out of hospital			
Aspirin	19 (95.0%)	65 (100.0%)	0.24
Clopidogrel	17 (85.0%)	29 (44.6%)	< 0.05
Ticagrelor	4 (20.0%)	35 (53.8%)	< 0.05
Clinical presentation at follow-up			0.11
STEMI	0	1 (1.5%)	
NSTE-ACS	9 (18.0%)	17 (26.2%)	
Stable angina	1 (5.0%)	1 (1.5%)	
No symptoms	10 (50.0%)	46 (70.8%)	
Risk factors at follow-up			
Mean SBP, mmHg	131.40 ± 17.2	128.35 ± 17.1	0.54
Mean DBP, mmHg	76.3 ± 10.2	74.2 ± 9.0	0.44
LDL-C, mg/dL	82.1 ± 29.8	59.9 ± 20.5	< 0.05
LDL-C under control, mg/dL	9 (45.0%)	40 (61.5%)	0.79
Quit smoking	19 (95.0%)	63 (96.9%)	1.00
HbA1c, %	6.1 (5.9–7.2)[*]	6.2 (5.7–7.1)[*]	0.38

Data are presented as means ± SD or *n* (%). [*]Presented as median (interquartile range). AA: arachidonic acid; ADP: adenosine diphosphate; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; SBP: systolic blood pressure; STEMI: ST-segment elevation myocardial infarction.

received dual antiplatelet therapy. Patients with non-culprit healed plaques were administered clopidogrel outside of the hospital more often (85.0% *vs.* 44.6%, *P* = 0.002), but ticagrelor administration was lower (20.0% *vs.* 53.8%, *P* = 0.01) than those without healed plaques.

Angiographic Data

The lesion-level angiography data are presented in Table 2. The vessel location and the distribution of non-culprit lesions did not differ between patients with or without healed plaques. The baseline lesion length, reference lumen diameter, MLD, ALD, and percent of DS did not differ between the healed plaque and non-healed plaque groups, suggesting a similar degree of lumen stenosis.

OCT Characteristics

Lesion-level OCT characteristics are presented in Table 3, and a representative case is presented in Figure 1. Lipid plaques were found more frequently in healed plaques (92.6% *vs.* 69.8%, *P* = 0.012), as well as lipid-rich plaques (66.7% *vs.* 39.5%, *P* = 0.029), plaque rupture (44.4% *vs.* 26.7%,

P = 0.023) and macrophage accumulation (85.2% *vs.* 61.6%, *P* = 0.03) than in non-healed plaques. Healed plaques were more frequently found at POC of bifurcation lesions than non-healed plaque (48.1% *vs.* 23.2%, *P* = 0.008) (Figure 2). The maximum lipid arc (194.1 ± 61.3 *vs.* 152.6 ± 44.0, *P* < 0.001), mean lipid arc (129.4 ± 31.7 *vs.* 101.2 ± 32.0, *P* = 0.002), and the lipid index of healed plaque [984.34 (543.88−1 481.86) *vs.* 732.84 (553.55−1 105.86), *P* = 0.010] were significantly higher than those of non-healed plaques.

The healed plaque parameters were compared with changes of MLD and presented in Figure 3. Using MLD as reference (y-axis), the thickness (*r* = 0.674, *P* < 0.001), arc (*r* = 0.736, *P* < 0.001), and volume (*r* = 0.541, *P* = 0.004) of healed plaque were correlated with plaque progression (Figure 3).

The intra-observer and inter-observer Kappa coefficients for diagnosis were as follows: healed plaque (0.87 *vs.* 0.78), lipid plaque (0.88 *vs.* 0.90), TCFA (0.89 *vs.* 0.91), calcification (0.90 *vs.* 0.90), and macrophage (0.85 *vs.* 0.80). The intraclass correlation coefficient (ICC) for healed plaque parameters were as follows: healed plaque thickness (ICC = 0.982, *P* < 0.001), healed plaque arc (ICC = 0.990, *P* <

Table 2   Angiographic parameters.

Lesion level	Lesions with non-culprit healed plaque (n = 27)	Lesions with non-culprit non-healed plaque (n = 86)	P-value
Lesion location			0.25
Left main artery	1 (3.7%)	1 (1.2%)	
Left anterior descending artery	18 (66.7%)	53 (61.7%)	
Right coronary artery	7 (25.9%)	18 (20.9%)	
Left circumflex artery	1 (3.7%)	14 (16.3%)	
Distribution			0.79
Proximal	9 (33.3%)	22 (25.6%)	
Middle	5 (18.5%)	32 (37.2%)	
Distal	13 (48.2%)	32 (37.2%)	
Baseline			
Lesion length, mm	8.56 ± 3.67	8.19 ± 4.03	0.72
Reference diameter, mm	2.71 ± 0.52	2.90 ± 0.89	0.14
Minimum lumen diameter, mm	1.92 ± 0.46	2.07 ± 0.73	0.19
Average lumen diameter, mm	2.48 ± 0.45	2.59 ± 0.75	0.42
Diameter stenosis, %	29.1 ± 9.9	29.1 ± 11.5	0.95
Follow-up			
Lesion length, mm	9.05 ± 3.88	8.43 ± 4.01	0.47
Reference diameter, mm	2.74 ± 0.52	2.65 ± 0.72	0.61
Minimum lumen diameter, mm	1.61 ± 0.46	1.91 ± 0.73	< 0.05
Average lumen diameter, mm	1.86 ± 0.43	2.10 ± 0.70	< 0.05
Diameter stenosis, %	41.4 ± 11.9	35.5 ± 13.1	< 0.05
Comparison			
Decrease in minimum lumen diameter	0.31 ± 0.25	0.17 ± 0.15	< 0.001
Plaque progression	9 (33.3%)	7 (8.1%)	0.002

Data are presented as means ± SD or n (%).

0.001), and healed plaque volume (ICC = 0.945, $P < 0.001$).

Follow-up Data

The median angiography follow-up time was 11.5 months in the overall cohort [patients with non-culprit healed plaque: 14.0 (9.5–15.0) months, patients without non-culprit healed plaque: 11.0 (7.8–15.3) months, $P = 0.12$) (Table 1)]. LDL-C was significant higher in patients with non-culprit healed plaques (82.1 ± 29.8 mg/dL $vs.$ 59.9 ± 20.5 mg/dL, $P = 0.003$) than those without healed plaques, but the rate of LDL-C under control showed no significant difference. There were no significant differences in other patient characteristics during follow-up.

Coronary angiography was performed during follow-up, and the lesion-level data are presented in

Table 2. Lesions with non-culprit healed plaques had a significantly lower MLD at the exact site (1.61 ± 0.46 mm $vs.$ 1.91 ± 0.73 mm, $P = 0.016$) and whole lesion ALD (1.86 mm $vs.$ 2.10 mm, $P = 0.033$) than those without healed plaques, but percent of DS was significantly higher (41.4% ± 11.9% $vs.$ 35.5% ± 13.1%, $P = 0.031$). The follow-up of MLD significantly decreased from the baseline measurement in the healed plaque group (0.17 mm $vs.$ 0.31 mm, $P < 0.001$), and the healed plaque had a higher prevalence of defined plaque progression (33.3% $vs.$ 8.1%, $P = 0.002$) than non-healed plaque (Figure 4). A representative case with both non-culprit healed plaques and non-healed plaques is presented in Figure 5.

Plaque Progression Analysis

The differences in baseline OCT characteristics

Table 3   Optical coherence tomography findings.

Lesion level	Lesions with non-culprit healed plaque (*n* = 27)	Lesions with non-culprit non-healed plaque (*n* = 86)	*P*-value
Lesion length, mm	8.6 ± 3.2	8.7 ± 3.5	0.79
Plaque type			< 0.05
Fibrous plaque	2 (7.4%)	26 (30.2%)	
Lipid plaque	25 (92.6%)	60 (69.8%)	
Thinnest fibrous cap thickness, mm	64.0 (55.5–171.5)*	110.5 (61.0–156.0)*	0.46
Lipid length, mm	8.00 (5.37–9.66)*	7.80 (6.48–9.00)*	0.72
Maximum lipid arc, °	194.1 ± 61.3	152.6 ± 44.0	< 0.001
Mean lipid arc, °	129.43 ± 31.74	101.25 ± 32.05	< 0.05
Lipid index, mm	984.34 (543.88–1 481.86)*	732.84 (553.55–1 105.86)*	< 0.05
Thin-cap fibroatheroma	13 (48.1%)	27 (31.4%)	0.16
Lipid-rich plaque	18 (66.7%)	34 (39.5%)	< 0.05
Plaque rupture	12 (44.4%)	23 (26.7%)	< 0.05
Lumen thrombus	4 (14.8%)	11 (12.8%)	0.75
Macrophage accumulation	23 (85.2%)	53 (61.6%)	< 0.05
Cholesterol crystal	5 (18.5%)	9 (10.5%)	0.77
Microvessels	10 (37.0%)	35 (40.7%)	0.91
Bifurcation	13 (48.1%)	20 (23.2%)	< 0.05
Calcification	12 (44.4%)	46 (53.4%)	0.41
Calcification score	0.7 ± 1.2	0.6 ± 1.1	0.91
Spotty calcification	3 (11.1%)	21 (24.4%)	0.15
Minimum lumen area, mm²	4.31 ± 2.05	4.60 ± 2.75	0.57
Reference area, mm²	7.56 ± 2.80	6.49 ± 3.29	0.96
Area stenosis, %	41.95 ± 17.67	40.30 ± 16.98	0.51

Data are presented as means ± SD or *n* (%). *Presented as median (interquartile range).

between progressed plaques and other plaques were analyzed further (Table 4, Figure 4). After generalized estimating equation adjustment, multivariate analysis identified healed plaques (OR = 8.49, 95% CI: 1.71−42.13) and lumen thrombus (OR = 10.69, 95% CI: 2.21−51.71) as lesion progression predictors.

DISCUSSION

Previous studies focused on the layered phenotype of healed plaques detected by OCT.[8,10,12,28,37] Healed plaques were not an isolated phenomenon, but evidence of plaque injury and antithrombotic therapy.[9] The direct comparison of lumen stenosis at the exact site may help clarify the role of healed plaques in atherosclerosis progression. This study evaluated the clinical data and dynamic progression of healed plaques to elucidate the clinical features and prognostic value. Healed plaques were associated with a higher degree of lipid burden and were more prevalent at bifurcations, antiplatelet therapy, dyslipidemia, and hypertension may contribute to the formation of healed plaques. Lesions with healed plaque showed a greater morphology changes (MLD and percent of DS) and the thickness, arc, and volume of healed plaque were correlated with MLD decline. Finally, multivariate analysis found healed plaque and lumen thrombosis were the independent predictors of plaque progression.

Healed Plaques and Clinical Features

Coronary atherosclerosis originates from pathological changes to the vessel endothelium. Owing to lipid metabolism disorders and inflammatory activ-
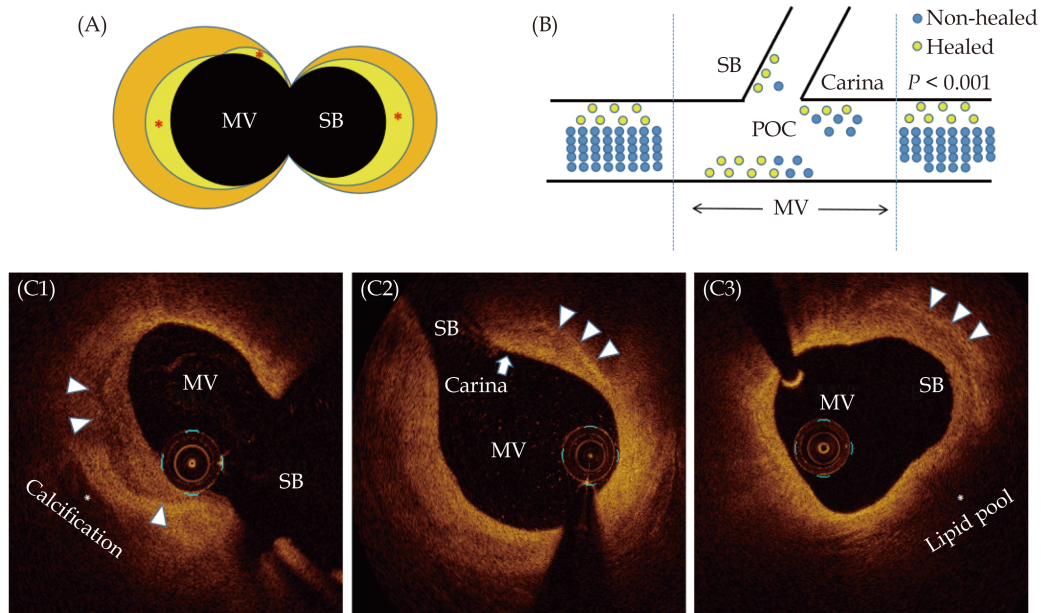
Figure 2 Healed plaques located at bifurcation. (A): Healed plaque at different site of bifurcation; (B): healed plaque were more frequent at bifurcation core (48.1% *vs.* 23.2%, *P* = 0.008); (C1): healed plaque at MV side; (C2): healed plaque at carina; and (C3): healed plaque at SB side. MV: main vessel; POC: polygon of confluence; SB: side branch.
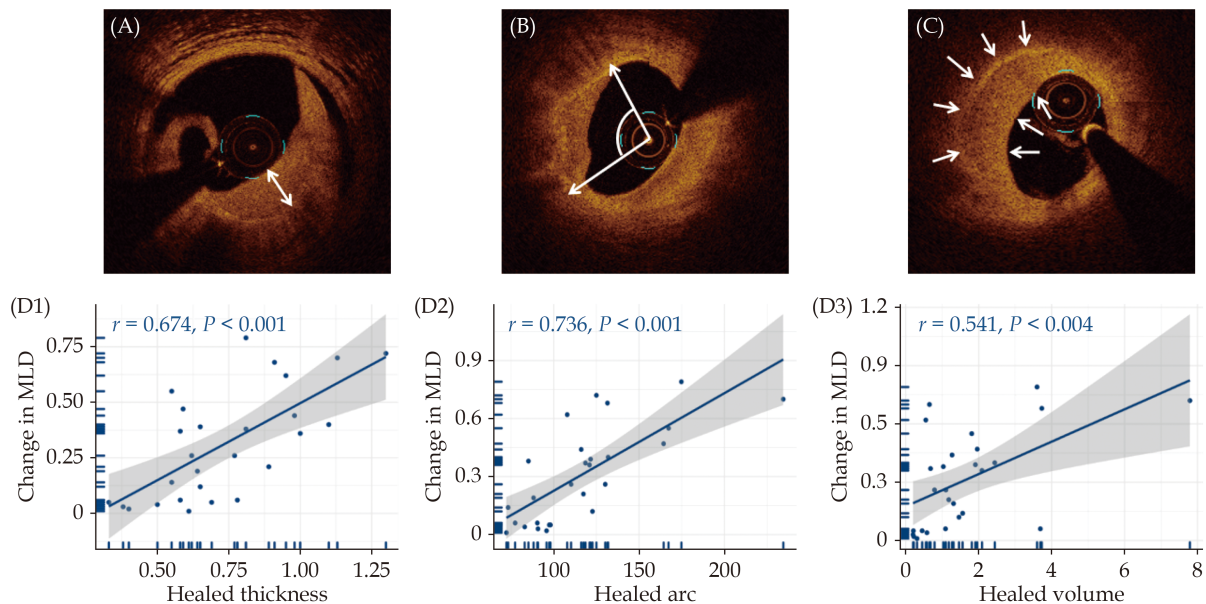

Figure 3 Representative optical coherence tomography images of healed plaques and the linear regression between healed plaque quantitative parameters and change in MLD. (A): Healed plaque with rupture at the star site; (B): healed plaque with an arc of 103.8°; (C): healed plaque area measured by underlying plaque and lumen boundary; and (D1–D3): healed thickness, healed arc and healed volume showed good correlation with change in MLD. MLD: minimum lumen diameter.

ation, intimal thickening gradually leads to lumen stenosis.[24] However, rapid plaque progression in patients with ACS implicates a different mechanism of plaque growth.[5] Abrupt changes to the vessel structures may cause no symptoms, but prompt a repair process called plaque healing.[3] Regarding plaque rupture or erosion, overactivated thrombotic function may contribute to occlusive thrombosis. Once thromboresistance prevails, the repair process initiates, and the subclinical residual thrombi gradually transform into an organized thrombus or collagen, appearing as a heterogeneous region dis-

Table 4 Predictors of plaque progression.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Healed plaque	4.85	1.45−16.17	< 0.05	8.49	1.71−42.13	< 0.05
Bifurcation	2.47	0.14−1.18	0.096	1.90	0.7−5.04	0.19
Thin-cap fibroatheroma	3.07	1.25−7.50	< 0.05	2.11	0.62−7.19	0.23
Rupture	4.83	1.67−13.97	< 0.05	1.03	0.30−3.52	0.96
Macrophage	2.61	0.82−8.23	0.10	0.69	0.12−4.16	0.69
Lumen thrombus	7.32	2.04−26.35	< 0.05	10.69	2.21−51.7	< 0.05
Cholesterol crystal	1.04	0.32−3.31	0.95			
Microvessels	0.91	0.31−2.74	0.87			
Spotty calcification	0.46	0.09−2.19	0.33			
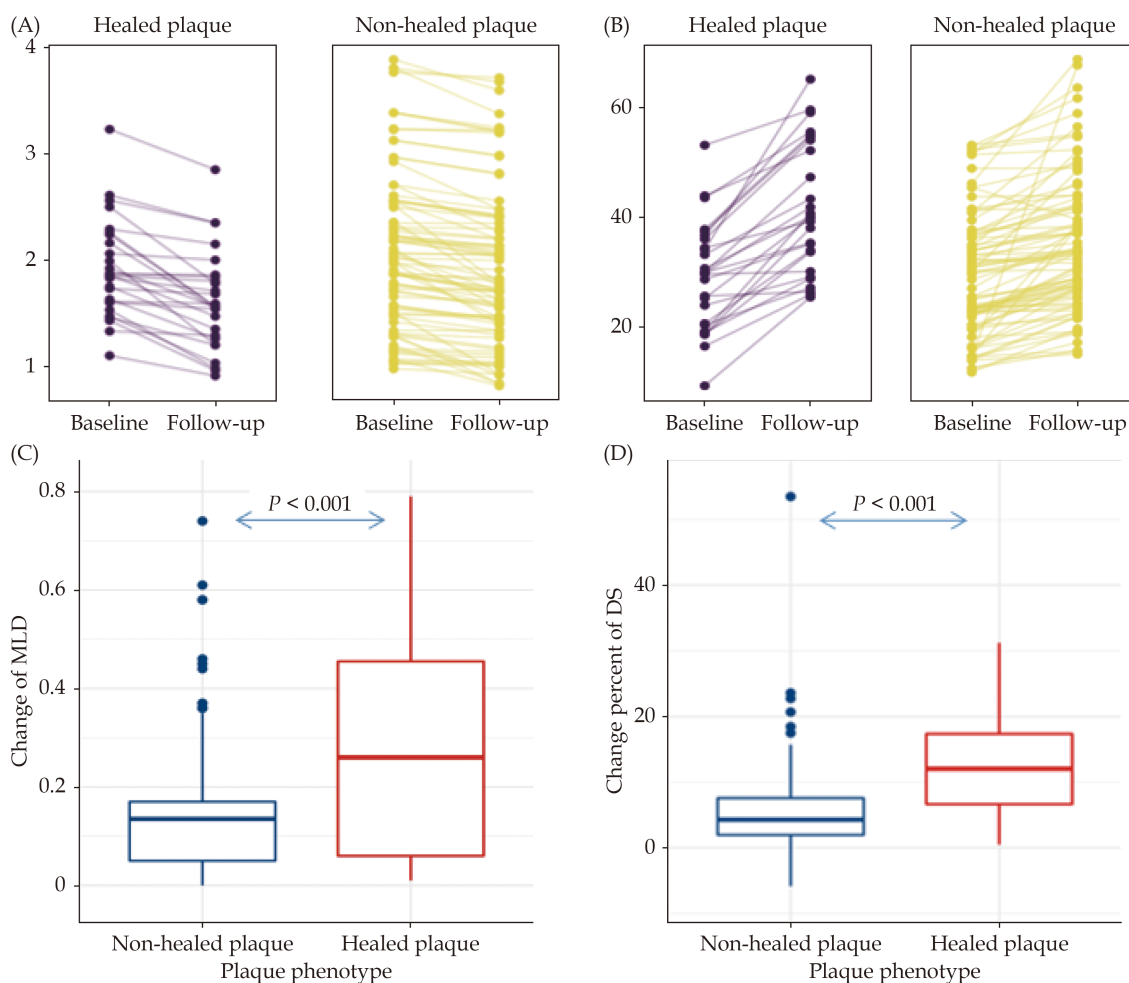
Figure 4 Evaluation of plaque progression between healed plaque and non-healed plaque groups. (A & C): Change of MLD (0.31 *vs.* 0.17, *P* < 0.001); and (B & D): change percent of DS (12.3 *vs.* 5.8, *P* < 0.001). *P*-value was adjusted by generalized estimating equation. DS: diameter stenosis; MLD: minimum lumen diameter.

tinguished from the underlying plaque.[12] This layered phenotype (i.e., layered plaque or healed plaque) was found in 61% of patients with sudden cardiac death.[11,14,16] OCT has high spatial resolu-

tion and has been histologically validated to identify healed plaques.[12] When light passes through two layers of different densities, backscatter beams produce a high signal band near the layer boundary on
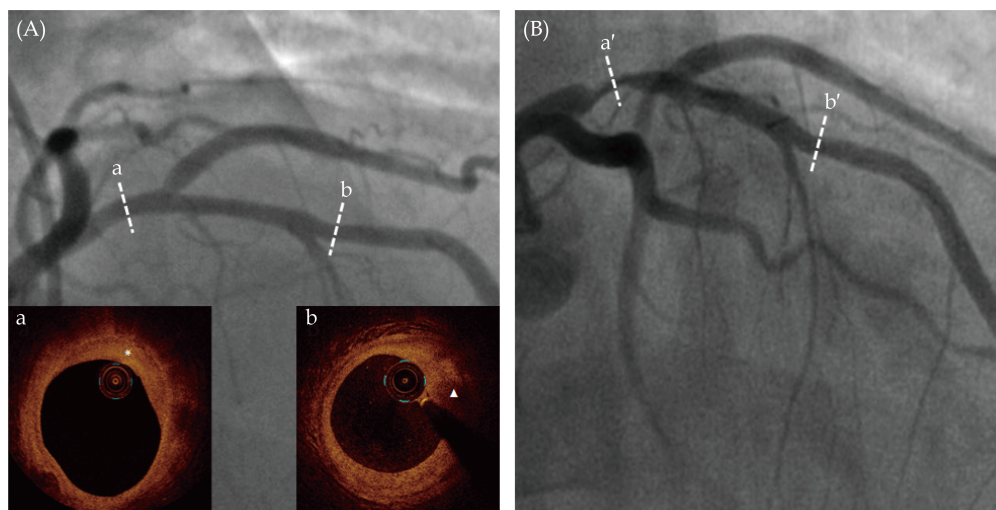
Figure 5 A representative case of a patient with both non-culprit healed plaque and non-healed plaque. (A): There was a healed plaque at a site and a fibrous plaque with a lipid core at b site; and (B): the exact site of healed plaque showed great reduction of the minimum lumen diameter at a 6-month follow-up while the non-healed plaque showed no significant progression.

an OCT image. A typical healed plaque is recognized by heterogeneous signal-rich layers of different optical signals with a clear demarcation.[26]

Previous studies showed differences in the prevalence of healed plaques among patient cohorts.[11,37] In our study, the clinical presentation was the same between the healed plaque group and non-healed plaque group, but antiplatelet therapy was used more in the healed plaque group. Large-scale clinical trials showed that unplanned interruption of antiplatelet therapy could lead to adverse events.[38–40] Our results indicate that antiplatelet therapy may have a protective effect and promote plaque healing.

LDL-C has a primary role in the formation of atherosclerosis plaque. High levels of serum LDL-C may lead to lipid deposition with macrophage accumulation,[19] and a large lipid pool underneath the endothelium has a high probability of necrosis,[23] accelerating endothelial injury and eventually ending with plaque rupture.[6] Our results showed that healed plaques were associated with higher serum LDL-C levels, and a higher lipid arc degree and lipid index underlined dyslipidemia in patients with healed plaques. These findings strongly support the hypothesis that healed plaques originate from the ruptured or eroded site of a large lipid core.[6,11] The association between healed plaques and dyslipidemia suggests that high serum lipid levels and a high lipid burden may contribute to plaque rupture or erosion, but the exact relationship between the healing process and the lipid burden against other plaque components remains unclear.

Healed Plaques and Plaque Progression

This study took detailed measurements of the healed plaques, such as the arc, thickness, and volume. Although OCT failed to recognize the deep inner component due to the attenuation of light in the tissues,[41] healed plaques were clearly bordered by the lumen boundary and underlying plaque. We found that a larger healed area was associated with a decline in MLD, suggesting that the healed plaque size was associated with plaque progression.[15] Healed plaque growth may be the primary reason for step-wise plaque progression.[5] A previous study by Usui, *et al*.[37] suggested that plaque healing may lead to the stabilization of ruptured or eroded sites. Our results provided another perspective on the mechanism of asymptomatic coronary events.

Although silent plaque rupture is reported more often in cases of low plaque burden,[42] *in vivo* OCT data showed that healed plaques are associated with more vulnerable features (macrophage accumulation, plaque rupture, lipid-rich plaque and bifurcation in Table 3) and a high degree of DS, indicated by the formation of a new atherosclerosis layer.[14] These results are contrasting, as healed plaques are consequences of coronary event stabilization, but a previous rupture or eroded site implicates vulnerabilities and potential plaque events. In this study, plaque rupture and macrophage accumulation were more frequent in healed plaques than in non-healed

plaques. Plaque rupture and healing are not individual events in the atherosclerosis process, but are in dynamic equilibrium, which partially supports the hypothesis that healed plaques have a higher possibility of recurrent plaque rupture, subsequently restarting the healing process.[14] Eventually, ischemic coronary stenosis ends circulation, and multiple-layer healed plaques were reported as evidence of recurrence coronary events.[8]

Bifurcation lesions were always the primary concern for surgeons. Due to its hemodynamic features, the bifurcation POC was prone to endothelium injury.[43] In this study, a higher prevalence of healed plaques at the POC and carina implied that the bifurcation vulnerability differed from the other structures. A high probability of plaque events and strengthening of the anti-thrombus mechanism may be why healing is more prevalent at the bifurcation core. This relationship between healed plaques and bifurcation may require a new comprehensive evaluation of bifurcation lesions.

Our study compared MLD and percent of DS changes at the exact culprit site and evaluated lesion progression. Univariate analysis showed that healed plaques, TCFA, plaque rupture, and lumen thrombus were predictors of plaque progression. Exchanging TCFA with lipid-rich plaque did not change the significance of the multivariate model. The predictive value of healed plaque was significant after adjustment with the multivariate model, together with lumen thrombus. The benefits of revascularizing non-culprit lesions are still debatable for surgeons facing multi-vessel disease. A new prognostic indicator could give surgeons more details about non-culprit lesions. Previous studies showed paradox conclusions on the prognostic value of healed plaques, but this may be owing to the analysis; qualitative analysis of only the healed area, not the exact healed site, was performed.[37] Our study explored the quantitative parameters of healed plaques, determining the prognostic value.

Healed plaques are evidence of previous plaque events and may predict further plaque growth. Healed plaque detection could be a reference for moderate coronary artery stenosis risks. Future studies are required to determine the association between healed plaques and vulnerable features,

lipid metabolism, and antithrombotic therapy, ultimately minimizing plaque progression.

LIMITATIONS

There were some mentionable limitations of the study. Firstly, this study was a single-center retrospective analysis, and the overall study group was small. To supplement this, our group is planning a cohort study that will include more patients and compare the serial changes of healed plaques with baseline and follow-up OCT imaging. Secondly, strict exclusion/inclusion criteria were applied. As a result, images with massive thrombus and artifacts were excluded, potentially creating a selection bias. Almost all healed plaques were observed near the lumen surface, and the exclusion criteria helped us accurately detect and measure the layered phenotype. Thirdly, the plaque burden analysis was restrained by the insufficient penetration of the OCT light source. For this reason, we also failed to detect plaques at endothelium depths. Fourthly, we included two kinds of OCT systems (C7 and OPTIS). However, all of the OCT pull-backs were performed using the novel frequency-domain OCT system, and OCT images were analyzed offline (remaining anonymous); the intra-observer and inter-observer results did not differ. Last but not least, the OCT pull-backs were not systematically performed on entire coronary trees in all patients. However, in practice, it was not necessary to examine the entire three vessels in every patient.

CONCLUSIONS

Healed plaques were a predictor for rapid plaque progression. Healed plaque parameters showed a good agreement with change of MLD. Patients with healed plaque were associated with prior antiplatelet therapy and high level of LDL-C. Healed plaques were more frequent at bifurcation lesions.

ACKNOWLEDGMENTS

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