Culprit and Non-Culprit Plaque Characteristics With vs. Without a Healed Phenotype in Patients With Acute Myocardial Infarction Caused by Plaque Erosion

— A 3-Vessel OCT Study —

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Background: Plaque erosion can occur quietly without causing clinical symptoms, followed by a healing process resulting in healed plaque. This study aimed to assess culprit and non-culprit plaque characteristics of patients with acute myocardial infarction (AMI) caused by plaque erosion with vs. without healed phenotype at the culprit plaque using optical coherence tomography (OCT).

Methods and Results: A total of 117 AMI patients caused by plaque erosion who underwent OCT imaging of 3 coronary arteries were included. Patients were divided into 2 groups based on presence or absence of a healed phenotype at the culprit site. Culprit and non-culprit plaque characteristics were compared between the 2 groups. A healed phenotype at the culprit lesion was identified in 47.9% of AMI patients caused by plaque erosion. Patients with a healed phenotype at the culprit site were more frequently with hyperlipidemia, and had a higher prevalence of macrophage infiltration, microchannels, cholesterol crystals, and calcification at the culprit lesion. Moreover, patients with a healed phenotype at the culprit site had more non-culprit plaques and more characteristics of plaque vulnerability at the non-culprit lesion. In addition, patients with a healed phenotype at the culprit site presented with more severe luminal stenosis at both the culprit and non-culprit lesion.

Conclusions: A healed phenotype was identified in 47.9% of AMI patients caused by plaque erosion at the culprit site. A healed phenotype within eroded culprit plaque was associated with signs of pancoronary vulnerability and advanced atherosclerosis.

Key Words: Acute myocardial infarction; Healed plaque; Optical coherence tomography; Plaque erosion

Plaque erosion and plaque rupture are the 2 most frequent causes of acute coronary syndrome (ACS), and plaque erosion is responsible for approximately one-third of patients.^{1,2} Previous pathological and in vivo studies have reported that plaque erosion can occur quietly without causing clinical symptoms followed by a healing process of the erosion site resulting in healed plaque.³⁻⁵ Silent plaque instability and the healing process can occur repeatedly, and eventually lead to culprit plaque formation. However, studies regarding the characteristics of plaque erosion with and without healed plaque are limited. Optical coherence tomography (OCT) is an intravascular imaging technique with excellent resolution, which can visualize detailed structures in the coronary

Editorial p????

arterial plaque.⁶ On OCT imaging, healed plaques appear as heterogeneous signal-rich layers with optical signal intensity that is different from the underlying plaque,^{3,7} and Shimokado et al demonstrated that OCT-derived healed plaques had good sensitivity and specificity (81% and 98%) to detect histologically defined healed plaques.⁵ Therefore, in this study, we sought to assess culprit and non-culprit plaque characteristics of culprit plaque erosion with vs. without a healed phenotype in patients with acute myocardial infarction (AMI).

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Methods

Study Population

Between January 2017 and August 2018, 582 patients with AMI who underwent pre-intervention OCT imaging of all 3 major epicardial coronary arteries were identified in the Cardiovascular Hospital of the Second Affiliated Hospital of Harbin Medical University (Harbin, China). Among them, 118 patients were excluded for: (1) residual massive thrombus or poor image quality (n=69); (2) short OCT pullbacks less than two-thirds of the lengths of the arteries (n=18); and (3) in-stent thrombosis, restenosis, or neoatherosclerosis (n=31). Therefore, 464 patients with 3-vessel OCT imaging were identified for this study. In addition, patients with plaque rupture (n=271), calcified nodule (n=11) and other lesion types (n=65), including tight stenosis (n=30), slight stenosis (n=11), coronary dissection (n=13), intimal tearing (n=2), myocardial bridge (n=2), fibrous calcified plaque (n=2), spasm or roughly normal blood vessels (n=4), and coronary embolism due to atrial fibrillation (n=1) were also excluded. Finally, 117 patients with AMI diagnosed as plaque erosion were included in the analysis (**Figure 1**). Pre-intervention OCT of the culprit vessel was carried out before treatment of the culprit plaque, whereas OCT of the non-culprit vessels was performed immediately after the culprit plaque was treated. Diagnosis of AMI included ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), as previously described.^{8,9}

The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Harbin, China), and all patients provided written informed consent.

Coronary Angiography Analysis

Quantitative coronary angiography analysis was performed by using a Cardiovascular Angiography Analysis System,

version 5.10.1 software (Pie Medical Imaging BV, Maastricht, The Netherlands). Coronary flow was assessed using the Thrombolysis in Myocardial Infarction (TIMI) flow grade classification. The minimal lumen diameter (MLD), reference vessel diameter (RVD), diameter stenosis (DS), and lesion length of the culprit and non-culprit lesions were measured.¹⁰

OCT Image Acquisition and Analysis

OCT was performed by using a commercially available frequency domain OCT system (ILUMIEN OPTIS or OPTIS Integrated System; Abbott Vascular, Santa Clara, CA, USA). In patients with TIMI flow grade ≤ 2 and large thrombus burden, aspiration thrombectomy was allowed before imaging, whereas patients with balloon pre-dilation were not enrolled. All OCT images were analyzed by 2 independent investigators blinded to clinical and angiographic data. In case of discordance, a consensus reading was achieved with a third investigator.

OCT images were analyzed using the previously established criteria.^{11,12} All plaques were identified by OCT as segments with luminal narrowing and a loss of the normal 3-layered structure of the vessel wall.¹¹ Culprit lesions were identified based on angiographic findings, electrocardiogram changes, and/or left ventricular wall motion abnormalities.¹¹ In patients with multiple stenoses, the plaque with the most severe stenosis or with evidence of acute thrombus on angiography or OCT was considered to be the culprit. Non-culprit lesions were identified by OCT by the presence of a plaque in ≥ 3 consecutively analyzed frames.¹¹ The reference was the site with the largest lumen area either proximal or distal to the stenosis, and plaque length was determined as the distance between the distal and proximal reference. A distance of at least 5 mm on the longitudinal view was considered 2 separated plaques, otherwise, separate plaques were considered to be one long plaque.¹¹⁻¹³ Cross-sectional OCT images were analyzed at 1-mm intervals. Minimal lumen area (MLA) was defined

	Healed phenotype group (n=56)	Non-healed phenotype group (n=61)	P value
Age, years	53.0±10.3	52.4±11.1	0.748
Male	47 (83.9)	51 (83.6)	0.962
Risk factors			
Hypertension	18 (32.1)	13 (21.3)	0.185
Hyperlipidemia	31 (55.4)	23 (37.7)	0.056
Current smoking	35 (62.5)	42 (68.9)	0.469
Diabetes mellitus	10 (17.9)	9 (14.8)	0.649
Chronic kidney disease	0 (0.0)	5 (8.2)	0.083
Clinical presentation			0.739
STEMI	36 (64.3)	41 (67.2)	
NSTEMI	20 (35.7)	20 (32.8)	
Laboratory data			
Triglyceride, mg/dL	144.2±78.7	121.6±52.3	0.08
TC, mg/dL	179.8±38.1	170.6±33.8	0.176
LDL-C, mg/dL	110.2±29.7	102.6±27.8	0.166
HDL-C, mg/dL	50.2±10.3	52.8±11.0	0.202
HbA1c, %	6.2±1.2	5.8±0.9	0.086
Hs-CRP, mg/L	5.5 (1.6–10.3)	4.6 (2.5–8.3)	0.736
Creatinine, μ mol/L	75 (63.3–85.3)	78 (68–94)	0.062
CK-MB, μ g/L	14.2 (2.7–63.8)	16 (2.1–96.0)	0.766
CTnI, μ g/L	2.7 (1.1–13.4)	2.0 (0.3–24.7)	0.798
Medication history			
Antiplatelet therapy	4 (7.1)	8 (13.1)	0.367
Aspirin	2 (3.6)	6 (9.8)	0.275
Clopidogrel	2 (3.6)	2 (3.3)	1.000
Statin	5 (8.9)	2 (3.3)	0.257
ACEI/ARB	6 (10.7)	3 (4.9)	0.308
β -blockers	1 (1.8)	2 (3.3)	1.000

Data are presented as n (%), mean±SD, or median (25th–75th percentiles). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; β -blockers, β -receptor blockers; CK-MB, creatine kinase isoenzyme MB; CTnI, cardiac troponin I; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; TC, total cholesterol.

as the smallest lumen area within the length of the plaque. Percent area stenosis (AS%) was calculated as [(Mean Reference Lumen Area – MLA)/Mean Reference Lumen Area]×100.

Plaque erosion was defined and categorized according to the absence of fibrous cap disruption and the presence of a thrombus. Definite erosion was identified by the presence of an attached thrombus overlying an intact and visualized plaque. Probable erosion was defined by: (1) luminal surface irregularity at the culprit lesion in the absence of thrombus; or (2) attenuation of underlying plaque by a thrombus without superficial lipid or calcification immediately proximal or distal to the site of a thrombus.¹

Plaque rupture was identified by the presence of fibrous cap discontinuity with a cavity formed inside the plaque. A calcified nodule was defined by fibrous cap disruption detected over a calcified plaque characterized by protruding calcification, superficial calcium, or the presence of substantive calcium proximal and/or distal to the lesion.

Plaques were classified as fibrous plaques (homogeneous, high backscattering region) or lipid plaques (low signal region with diffuse border).¹¹ For each lipid plaque, the thinnest fibrous cap thickness (FCT) and the maximal arc of lipid

were measured. Lipid length was obtained on the longitudinal view, and the lipid index was calculated as the product of mean lipid arc and lipid length. Thin-cap fibroatheroma (TCFA) was defined as a plaque with a maximal lipid arc >90° and thinnest FCT <65 μ m. Macrophage accumulation was defined as the presence of highly backscattering focal regions within the fibrous cap. Microchannels were defined as the presence of signal-poor structures with vesicular or tubular shapes. Cholesterol crystals were identified as thin and linear regions of high signal intensity with high backscattering within a plaque. Calcification was defined as a signal-poor or heterogeneous region with a sharply delineated border. Thrombus was defined as an irregular mass with minimum diameter at least 250 μ m adherent to the vessel wall or floating within the lumen. Healed plaque was defined as a plaque with heterogeneous signal-rich layered tissue of different optical signal intensity located close to the luminal surface that was clearly demarcated from the underlying tissue.⁵ The maximum area and thickness of healed tissue was determined from the cross-sectional OCT images.

The inter-observer kappa coefficients for plaque erosion and healed plaque were 0.92 and 0.88, respectively. The

	Healed phenotype group (n=56)	Non-healed phenotype group (n=61)	P value
Plaque length, mm	22.3 (17.2–25.7)	18.0 (16.2–21.5)	0.003
Plaque type			0.035
Fibrous	16 (28.6)	29 (47.5)	
Lipid	40 (71.4)	32 (52.5)	
FCT, μm	100 (84.2–139.2)	100 (77.5–121.7)	0.398
Mean lipid arc, $^{\circ}$	205.7 $\pm$ 43.0	203.0 $\pm$ 44.5	0.801
Max lipid arc, $^{\circ}$	349.6 (238.8–360)	287.5 (239.3–360)	0.355
Lipid length, mm	13.6 $\pm$ 7.3	11.8 $\pm$ 6.4	0.262
Lipid index, mm°	2,893.7 $\pm$ 1,744.4	2,422.4 $\pm$ 1,383.4	0.217
TCFA	4 (7.1)	3 (4.9)	0.907
Macrophage	49 (87.5)	36 (59.0)	0.001
Microchannel	30 (53.6)	18 (29.5)	0.008
Cholesterol crystals	14 (25.0)	6 (9.8)	0.03
Calcification	26 (46.4)	7 (11.5)	<0.001
Thrombus	56 (100)	58 (95.1)	0.273
MLA, mm^2	1.6 (1.1–2.4)	2.1 (1.7–3.2)	0.007
AS, %	79.3 (68.4–84.7)	73.3 (57.4–79.3)	0.035
Mean RLA, mm^2	8.1 (6.1–9.0)	8.5 (6.6–10.8)	0.144

Data are presented as n (%), median (interquartile range), or mean $\pm$ SD. AS, area stenosis; FCT, fibrous cap thickness; MLA, minimal lumen area; OCT, optical coherence tomography; RLA, reference lumen area; SD, standard deviation; TCFA, thin cap fibroatheroma.

Figure 2. OCT analysis of culprit plaques in patients with vs. without healed phenotype at the culprit site. Patients with healed phenotype at the culprit site had higher prevalence of lipid plaque, macrophage infiltration, microchannel, cholesterol crystals, and calcification and had longer plaque length, smaller minimal lumen area and greater degree of area stenosis than those without healed phenotype. OCT, optical coherence tomography; PE, plaque erosion.

intra-observer kappa coefficients for plaque erosion and healed plaque were 0.95 and 0.92, respectively.

Clinical Follow up

Patients were followed for 2 years after discharge at either a hospital visit or via a phone call. Major adverse cardiac events (MACE) were a composite of cardiac death, non-fatal recurrent myocardial infarction (MI), ischemia-driven revascularization, or rehospitalization due to unstable or progressive angina. Detailed definitions of individual outcome measures are provided in **Supplementary Methods**.

Statistical Analyses

Statistical analyses were performed by using SPSS version 21.0 (IBM, Armonk, NY, USA). Data distribution was assessed by using the Kolmogorov-Smirnov test. Continuous variables have been shown as mean $\pm$ SD or as median (25th–75th percentiles) and compared with the independent sample t-test or the Mann-Whitney U-test. Categorical data have been presented as counts (proportions) and compared using the chi-squared or Fisher's exact test. For plaque level data, a model with generalized estimating equations was used to take into account potential cluster

Figure 3. Representative OCT images of eroded plaque with or without healed phenotype. Healed phenotype was a plaque with heterogeneous signal-rich layered tissue (yellow arrow) of different optical signal intensity located close to the luminal surface and clearly demarcated from the underlying tissue. The white arrow refers to the plaque erosion site with thrombus, and the yellow arrow refers to the healed plaque. PE, plaque erosion.

	Healed phenotype group (n=230)	Non-healed phenotype group (n=167)	P value
Plaque length, mm	14.1 (10.6–19.3)	13.2 (10.2–17.5)	0.340
Plaque type			0.120
Fibrous	71 (30.9)	66 (39.5)	
Lipid	159 (69.1)	101 (60.5)	
Lipid length, mm	9.0±6.4	9.0±6.7	0.992
Mean lipid arc, °	146.1±41.3	153.4±39.4	0.186
Lipid index, mm°	1,405.8±1,219.7	1,429.4±1,172.0	0.898
FCT, μm	103.3 (80.0–150.0)	116.7 (85.0–165.0)	0.184
Mean RLA, mm ²	7.8 (5.7–10.2)	8.3 (6.2–10.3)	0.120
MLA, mm ²	3.6 (2.4–5.5)	4.3 (2.6–6.2)	0.037
AS, %	50.1 (38.7–61.9)	46.3 (34.3–61.0)	0.045
TCFA	20 (8.7)	11 (6.6)	0.485
Macrophage	181 (78.7)	112 (67.1)	0.044
Microvessels	115 (50.0)	75 (44.9)	0.604
Cholesterol crystals	24 (10.4)	3 (1.8)	0.003
Thrombus	5 (2.2)	6 (3.6)	0.463
Calcification	77 (33.5)	37 (22.2)	0.043
Healed plaque	75 (32.6)	45 (26.9)	0.284
Healed tissue thickness, μm	596.9±182.2	504.4±170.9	0.004
Healed tissue area, mm ²	1.5±0.9	1.1±0.6	0.015

Data are presented as n (%), median (interquartile range), or mean ± SD. Abbreviations as in Table 2.

effects of multiple plaques in a single patient. Inter- and intra-observer agreement were assessed by kappa coefficient statistics. A 2-tailed $P < 0.05$ was considered statistically significant.

Results

Patients and Baseline Characteristics

Among 117 AMI patients caused by plaque erosion, 67 (57.3%) patients were with definite plaque erosion and 50 (42.7%) patients were with probable plaque erosion. Moreover, in 117 patients, 56 (47.9%) patients with healed

plaque at the culprit lesion had 230 non-culprit plaques and 61 (52.1%) patients without healed plaque at the culprit lesion had 167 non-culprit plaques.

Patient characteristics are listed in **Table 1**. Although the difference did not reach statistical significance, patients with healed phenotype at the culprit site had a higher incidence of hyperlipidemia (55.4% vs. 37.7%, $P = 0.056$) than those without. No significant differences were found in other baseline characteristics between the 2 groups.

Angiographic Findings

Angiographic findings are summarized in **Supplementary**

Table 4. Patient-Level OCT Analysis of Non-Culprit Plaques in Patients With vs. Without Healed Phenotype at the Culprit Site

	Healed phenotype group (n=56)	Non-healed phenotype group (n=61)	P value
Lipid plaque	51 (91.1)	46 (75.4)	0.025
TCFA	15 (26.8)	8 (13.1)	0.063
Macrophage	49 (87.5)	48 (78.7)	0.206
Microchannel	44 (78.6)	36 (59.0)	0.023
Cholesterol crystals	14 (25.0)	3 (4.9)	0.003
Thrombus	4 (7.1)	5 (8.2)	1.000
Calcification	33 (58.9)	24 (39.3)	0.034
Healed plaque	39 (69.6)	26 (42.6)	0.003

Data are presented as n (%). OCT, optical coherence tomography; TCFA, thin cap fibroatheroma.

Table 1 and Supplementary Table 2. Lesion distribution of culprit and non-culprit lesions was not significantly different between the 2 groups. Patients with healed phenotype at the culprit site had smaller RVD in culprit (3.0 ± 0.5 mm vs. 3.3 ± 0.6 mm, $P=0.017$) and non-culprit lesions (3.1 ± 0.7 mm vs. 3.3 ± 0.6 mm, $P=0.048$) compared with those without healed phenotype.

OCT Findings at the Culprit Lesion

OCT characteristics of culprit lesions are listed in **Table 2** and **Figure 2**. Patients with healed phenotype at the culprit site had longer plaque length (22.3 [17.2–25.7] mm vs. 18.0 [16.2–21.5] mm, $P=0.003$), higher prevalence of lipid plaque (71.4% vs. 52.5%, $P=0.035$), macrophage infiltration (87.5% vs. 59.0%, $P=0.001$), microchannel (53.6% vs. 29.5%,

$P=0.008$), cholesterol crystals (25% vs. 9.8%, $P=0.03$), and calcification (46.4% vs. 11.5%, $P<0.001$). Patients with healed phenotype at the culprit site also had smaller MLA (1.6 [1.1–2.4] mm² vs. 2.1 [1.7–3.2] mm², $P=0.007$) and greater degree of AS (79.3 [68.4–84.7]% vs. 73.3 [57.4–79.3]%, $P=0.035$) than those without healed phenotype. The representative OCT image is presented in **Figure 3**.

OCT Characteristics of Non-Culprit Lesions in Patients With or Without Healed Phenotype at the Culprit Site

OCT characteristics of non-culprit lesions are summarized in **Table 3**, **Table 4** and **Figure 4**. Patients with healed phenotype at the culprit site had more non-culprit plaque (4.1±2.2 vs. 2.7±1.8, $P<0.001$).

For plaque-based analysis of non-culprit lesions (**Table 3**, **Figure 4**), culprit plaque erosion with healed phenotype group had higher incidence of macrophage infiltration (78.7% vs. 67.1%, $P=0.044$), cholesterol crystals (10.4% vs. 1.8%, $P=0.003$), calcification (33.5% vs. 22.2%, $P=0.043$) and had smaller MLA (3.6 [2.4–5.5] mm² vs. 4.3 [2.6–6.2] mm², $P=0.037$) and greater degree of AS% (50.1 [38.7–61.9] % vs. 46.3 [34.3–61.0] %, $P=0.045$) than culprit plaque erosion without healed phenotype group. The prevalence of non-culprit healed plaque in both groups was similar; however, culprit plaque erosion with healed phenotype had larger non-culprit healed tissue thickness (596.9±182.2 μm vs. 504.4±170.9 μm, $P=0.004$) and healed tissue area (1.5±0.9 mm² vs. 1.1±0.6 mm², $P=0.015$).

For patient-based analysis of non-culprit lesions (**Table 4**, **Figure 4**), patients with healed plaque at the culprit site had higher incidence of lipid plaque (91.1% vs. 75.4%, $P=0.025$), microchannels (78.6% vs. 59.0%, $P=0.023$), cholesterol crystals (25.0% vs. 4.9%, $P=0.003$), calcification (58.9% vs. 39.3%, $P=0.034$) and healed plaque (69.6% vs. 42.6%, $P=0.003$) than those without healed plaque at the culprit site.

Clinical Outcomes

Clinical follow-up data were available for 115 (98.3%) patients, and the mean follow-up time was 25.2±3.9 months. The overall incidence of MACE was 16.5%, and there was no significant difference between patients with vs. without healed phenotype at the culprit site (22.2% vs. 11.5%, $P=0.138$). The incidence of cardiac death, non-fatal MI, ischemia-driven revascularization and rehospitalization were similar between the 2 study groups (**Supplementary Table 3**).

Discussion

In the current study, we compared the characteristics of culprit and non-culprit plaques in AMI patients caused by plaque erosion with and without healed plaque at the culprit site. Our study demonstrated that patients with healed phenotype at the culprit site: (1) were identified in 47.9% of AMI patients caused by plaque erosion and had a higher incidence of hyperlipidemia; (2) had higher levels of local inflammation and plaque vulnerability at both the culprit and non-culprit lesions; and (3) presented with more severe luminal stenosis at both culprit and non-culprit lesions than patients without healed phenotype at the culprit site.

Prevalence and Baseline Characteristics of Patients With Healed Phenotype

Healed plaques represent signs of previous plaque instability, morphologically characterized by distinct layers of collagen

in histopathology^{14,15} and appear as heterogeneous signal-rich layers with optical signal intensity that is different from the underlying plaque on OCT.⁵ In an autopsy study, Burke et al reported that healed plaque had been found in 53% of subjects who suffered from sudden coronary death, who had no evidence of previous myocardial infarction.¹⁵ Recently, Dai et al found 40.3% of AMI patients had healed culprit plaques in an OCT study.¹⁶ In the present study, we reported that the prevalence of healed plaques at the culprit lesion was 47.9% in AMI patients caused by plaque erosion, which was similar to the findings of previous studies. In another OCT study, however, Fracassi et al reported that 29% of patients had healed phenotype at the culprit lesion in 376 ACS patients, which was lower than our study.⁷ This difference may be due to the patients enrolled being identified from 21 sites over 6 years, which indicates a highly selected cohort. In our study, patients with healed phenotype at the culprit lesion were more frequent with hyperlipidemia. Previous studies revealed that hyperlipidemia was associated with a higher risk of thrombosis.¹⁷ Under a hypercoagulable state, thrombus stimulation will exceed the endogenous thrombolytic activity, leading to mural thrombosis, followed by the healing process, resulting in healed plaques.

Culprit Plaque Characteristics in AMI Patients Caused by Plaque Erosion With or Without Healed Phenotype at the Culprit Site

In the present study, patients with healed phenotype at the culprit site had higher prevalence of lipid plaque, macrophage infiltration, microchannel, and cholesterol crystals than patients without healed phenotype, indicating higher plaque vulnerability at the culprit lesion. Previous OCT studies have found similar findings.⁷ Russo et al had reported that plaques with healed phenotype at the culprit site showed more signs of vulnerability (more lipid plaque, greater lipid burden, and more macrophage infiltration) than non-healed ones.¹⁸ Shimokado et al also found that microvessels and macrophages were more frequently identified in OCT-derived healed plaque.⁵ Macrophages indicating higher local inflammation are the sign of plaque activity and play an important role in extracellular matrix degradation and fibrous cap disruption, as well as plaque progress.¹⁹ The formation of microvessels is a common feature during thrombus organization and is observed more frequently in healed plaques than in non-healed plaques, and plays an important role in thrombus organization for providing oxygen and nutrients to the healing tissue.²⁰ Cholesterol crystallization is thought to be the result of accumulation of free cholesterol in macrophages and destruction of cholesterol homeostasis. Excess esterified cholesterol and crystals are released from the dead foam cells into the extracellular space, and then identified as cholesterol crystals in coronary plaques.^{21,22} Sugane et al found that cholesterol-crystallized coronary atheroma was a potential precursor lesion causing plaque instable, leading to obstructive and non-obstructive thrombosis.²³ In addition, patients with healed phenotype at the culprit site had a higher incidence of calcification than those without. Russo et al¹⁸ also showed a higher prevalence of calcifications in healed culprit plaques compared with non-healed ones. As we know, in the process of plaque healing, especially in the late stage, type 2 macrophages can promote the calcification of plaque by promoting the differentiation of osteoblasts and maturation of vascular smooth muscle

cells.³ Moreover, Burke et al suggested that previous plaque instability, especially plaque rupture, via hemorrhage and cellular breakdown, resulted in coronary calcification.²⁴

Non-Culprit Plaque Characteristics in AMI Patients Caused by Plaque Erosion With or Without Healed Phenotype at the Culprit Site

In the current study, we found that patients with healed phenotype at the culprit site had more non-culprit plaques and a higher incidence of macrophages, cholesterol crystals and calcification at plaque level, and higher prevalence of lipid plaque, microchannels, cholesterol crystals, calcification and healed plaque at the patient level, all of which indicated that patients with healed phenotype at the culprit site also had higher plaque vulnerability in non-culprit lesions. Russo et al reported that patients with healed culprit plaque had more non-culprit plaque, and had higher prevalence of lipid plaque and macrophage infiltration than those without in patients with ACS or stable angina pectoris (SAP),^{18,25} which was similar with our results. Moreover, multiple studies demonstrated that the vulnerability of non-culprit plaque was consistent with the vulnerability of culprit plaque in the same patients.^{26,27} These results revealed that the presence of healed phenotype at the culprit site in patients with ACS or SAP represented a higher level of pan-coronary plaque vulnerability through previous plaque destabilization, indicating higher instability in the future.

Lumen Stenosis in AMI Patients Caused by Plaque Erosion With or Without a Healed Phenotype at the Culprit Site

In our study, patients with healed phenotype at the culprit site had a more severe degree of lumen stenosis in the culprit and non-culprit lesions, indicating greater plaque burden and a more advanced atherosclerosis process. Mann and Davies reported that >70% of plaques with a diameter stenosis $\geq 51\%$ had a healed pattern in men who died from ischemic heart disease.¹⁴ Burke et al found that the mean percent luminal narrowing increased in both acute and stable plaque sites with increased numbers of healed plaques.¹⁵ Yamamoto et al demonstrated that healed non-culprit plaques represented rapid progression with a greater increase in plaque volume compared with non-healed phenotype.⁴ These findings suggested the potential contribution of plaque healing to progression of coronary atherosclerosis. In addition, we also found the healed tissue thickness and healed tissue area in non-culprit healed plaques was greater in patients with healed phenotype at the culprit site than those without. We considered this phenomenon may attribute to higher plaque vulnerability in non-culprit plaques, and there may also be multiple healing processes in single non-culprit coronary lesions, which might not be visible due to the limited penetrability of OCT.

Clinical Significance

In our study, although not statistically significant, the overall incidence of MACE in patients with healed phenotype was nearly twice as high as that of patients without healed phenotype. We considered that the reason for this phenomenon may come from patients with healed phenotype at the culprit site having higher levels of local inflammation and plaque vulnerability at both culprit and non-culprit lesions. Moreover, patients with healed phenotype at the culprit site had more severe luminal stenosis at both culprit and non-culprit lesions than for those without healed pheno-

type, indicating greater plaque burden and a more advanced atherosclerosis process. Therefore, for AMI patients caused by plaque erosion with a healed phenotype, stronger anti-thrombotic and lipid-lowering therapy might have more clinical benefits. However, as the sample size of our study is small and follow-up time is relatively short, studies with larger samples and longer follow-up time are needed.

Study Limitations

This study had several limitations. First, this study was a retrospective single-center study and patients with highly unstable clinical conditions and cases with massive thrombus or poor image quality were excluded. Therefore, selection bias cannot be excluded. Second, this study lacked histopathologic correlation, and we cannot exclude other potential mechanisms of atherosclerosis progression (i.e., neointimal hyperplasia, lipid, or calcification) that may lead to intraplaque heterogeneity with a healed appearance on OCT. Third, the OCT definition of plaque erosion was a diagnosis of exclusion requiring the absence of fibrous cap disruption. Fourth, manual thrombectomy may have altered the underlying plaque morphology, although extreme care was taken to avoid excess trauma. Finally, despite the high specificity of OCT-defined healed plaques to detect histologically defined healed plaques, sensitivity was slightly lower. Moreover, in the presence of lipid plaques, OCT showed lower concordance with histology.

Conclusions

In patients with AMI caused by plaque erosion, healed phenotype was identified in 47.9% of patients at the culprit site. Healed phenotype within eroded culprit plaque was associated with signs of pancoronary vulnerability and advanced atherosclerosis.

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Disclosures

All authors declared that they had nothing to disclose regarding conflict of interest with respect to this manuscript. B.Y. is an International Associate Editor of *Circulation Journal*.

Author Contributions

Yanwei Yin, Chao Fang, Senqing Jiang: the design of research, data acquisition analysis, and manuscript drafting; Jifei Wang, Yidan Wang, Junchen Guo, Fangmeng Lei, Sibao Sun, Xueying Pei, Ruyi Jia, Caiying Tang, Yini Wang: data acquisition; Lulu Li: statistical analysis; Huai Yu: patient enrollment and performing cardiac intervention; Jiannan Dai, Bo Yu: substantial contribution to the design of the research and critical manuscript revision.

IRB Information

The original study was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Reference number: No. KY2017-249).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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