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Plaque characteristics in patients with ST-segment elevation myocardial infarction and early spontaneous reperfusion

Jincheng Guo[1], MD, PhD; Jun Chen[2], MD; Guozhong Wang[1], MD; Zhi Liu[2], MD, PhD; Dan Niu[1], MD; Yongxia Wu[1], MD; Jiahui Song[1], MD; Jing Gao[2], MD, PhD; Zhenxing Fan[2], MD, PhD; Yinghua Zhang[2], MD; Jin Si[2], MD; Xuebing Zuo[2], MD; Ning Shi[2], MD; Zupei Miao[2], MD; Zhaorun Bai[2], MD; Leimin Zhang[2], MD; Binyu Liu[2], MD; Jing Li[2,3]*, MD, PhD

1. Department of Cardiology, Beijing Luhe Hospital, Capital Medical University, Beijing, China; 2. Department of Cardiology, Xuanwu Hospital, Capital Medical University, Beijing, China; 3. National Clinical Research Center for Geriatric Diseases, Beijing, China

J. Guo, J. Chen and G. Wang contributed equally to this work.

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KEYWORDS

- optical coherence tomography
- plaque rupture
- STEMI

Abstract

Background: Early spontaneous reperfusion (ESR) is not an uncommon phenomenon in clinical settings.

Aims: The aim of this study was to detect potential mechanisms of ESR in patients with STEMI.

Methods: This prospective study enrolled a total of 241 consecutive patients with STEMI undergoing optical coherence tomography (OCT) from July 2016 to August 2019. Forty-five patients (18.7%) met angiographic ESR criteria (TIMI 3 flow on the initial angiogram). Among those without ESR (TIMI 0 flow on initial angiogram), 45 patients were assigned to the control group according to propensity score matching with the ESR group.

Results: Although the baseline characteristics of the groups were comparable, non-ruptured plaque (62.2% vs 35.6%) predominated and plaque rupture (37.8% vs 64.4%) was less common in the ESR group (p=0.011). Red thrombus (44.4% vs 77.8%) was also less common in the ESR group (p=0.001). Lastly, compared to the control group, the ESR group underwent fewer emergent stent placements (68.9% vs 91.1%, p=0.008).

Conclusions: Relief of coronary occlusion induced by a non-ruptured plaque may contribute to ESR in patients with STEMI.

**Corresponding author: Department of Cardiology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases, No. 45 Changchun Street, Xicheng District, Beijing, 100053, China. E-mail: shpxbb@sina.com*

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Abbreviations

ACS acute coronary syndrome
ESR early spontaneous reperfusion
IVUS intravascular ultrasound
MACE major adverse cardiovascular events
OCT optical coherence tomography
PCI percutaneous coronary intervention
STEMI ST-segment elevation myocardial infarction

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is a life-threatening situation. Reperfusion, using techniques such as primary percutaneous coronary intervention (PCI), is recommended by the current guidelines to restore coronary blood flow promptly and save the maximum amount of jeopardised cardiomyocytes[1,2]. Interestingly, up to 30% of patients with STEMI have an initial Thrombolysis In Myocardial Infarction (TIMI) 3 flow during emergent angiography, without undergoing any invasive intervention or fibrinolytic therapy. This is known as early spontaneous reperfusion (ESR) and has been examined in previous studies[3-6]. ESR is associated with smaller infarct size, less stent placement as well as favourable short-term outcomes[7]. Although endogenous lysis of thrombi or relief of coronary spasms can cause ESR[4], its pathologic and pathophysiologic mechanisms remain undefined. Furthermore, PCI timing (immediate or delayed) in patients with ESR is debatable; no specific recommendations are included in the current guidelines.

Optical coherence tomography (OCT) is an intracoronary imaging modality with a tenfold higher resolution (10-15 μm) compared to intravascular ultrasound (IVUS)[8]. OCT is recommended in the current guidelines for optimising stent implantation in selected patients[9]. OCT has also been used to identify potential mechanisms (such as plaque rupture, plaque erosion and calcified nodule) of STEMI[10-12]. OCT is more accurate than angiography or IVUS for detecting subtle morphological details of the culprit lesion and is both feasible and reproducible.

We sought to identify the potential mechanisms of ESR using OCT. We hypothesised that ESR may possess unique morphological characteristics.

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Methods

STUDY DESIGN AND PATIENTS

This prospective study enrolled consecutive patients with STEMI who underwent OCT in a single centre from July 2016 to August 2019. Patients whose coronary blood flow of the culprit vessel achieved TIMI 3 flow on the initial angiogram, followed by OCT assessment, were assigned to the ESR group. The control group consisted of patients who had TIMI 0 flow, and who underwent OCT after achieving TIMI 3 flow by thrombus aspiration. The ESR and control groups were propensity score matched for age, sex, hypertension, diabetes mellitus, the location of the infarct-related artery, time from dual antiplatelet therapy (DAPT) to procedure and duration from the onset of symptoms to performance of coronary angiography. All patients underwent immediate OCT assessments. The exclusion criteria are reported in **Supplementary Appendix 1**.

This study was approved by the Xuanwu Hospital's institutional review board, and informed consent was obtained from all patients.

CATHETERISATION PROCEDURES

All catheterisation procedures were carried out by experienced operators according to the hospital's standard protocol. Coronary angiography was performed via a transradial or transfemoral approach with the use of a 6 Fr sheath and the default right radial access. Manual thrombus aspiration was performed in non-ESR patients using the Export Advance™ aspiration catheter (Medtronic, Minneapolis, MN, USA). After OCT assessment, the decision whether or not to stent the culprit lesion was based on the operator's discretion, according to visual estimation of diameter stenosis ≥70%. ESR was defined as a culprit coronary vessel blood flow of TIMI 3 on the initial angiogram[13]. The definition of vasospasm is reported in **Supplementary Appendix 1**.

OCT IMAGING ANALYSIS

Intracoronary images of the culprit lesion were acquired using frequency domain OCT (FD-OCT) through a non-occlusive technique with the C7XR™ system (Abbott Vascular, Santa Clara, CA, USA). The OCT images were identified by two experienced physicians using offline software (Abbott Vascular). The details of plaque characteristics and thrombus analysis are shown in **Supplementary Appendix 1**.

MEDICAL TREATMENT (Supplementary Appendix 1)

STATISTICAL ANALYSIS

Continuous variables are shown as means±SDs for normally distributed data or medians (25th-75th percentiles) for non-normally distributed data. Between-group differences were tested using an independent samples t-test or the Mann-Whitney U test. Categorical data are presented as counts (proportions) and compared using the χ^2 test or Fisher's exact test (if the expected cell value was <5). The propensity score analysis used a logistic regression model. We included age, sex, hypertension, diabetes mellitus, the location of the infarct-related artery, time from DAPT to the procedure, and the duration from symptom onset to coronary angiography. The variables with significant between-group differences – as indicated by $p<0.05$ during univariate analysis – were propensity score matched using a 1:1 ratio and based on an estimated calliper width of 0.1. The balance was deemed satisfactory when the standard mean differences were less than 10% **(Supplementary Table 1)**. Statistical analysis was performed with SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA).

ENDPOINTS

The primary endpoint was culprit lesion morphology in patients with ESR, as identified by OCT.

Results

BASELINE CHARACTERISTICS

The study flow chart is provided in **Figure 1**. Among the 241 patients with STEMI and analysable OCT images, 45 (18.7%) met the angiographic ESR criteria. Patients in the ESR group were younger (53.0 [43.0-62.5] vs 58 [49.0-66.0] years, p=0.035). After propensity score matching, there were no significant between-group differences in baseline characteristics between the ESR (n=45) and control groups (n=45). The baseline characteristics of all patients are included in **Table 1**, **Supplementary Table 2** and **Supplementary Table 3**.

ANGIOGRAPHIC FINDINGS

The coronary angiography data for all patients are shown in **Table 2**. Emergent stent placement was significantly less frequent in the ESR group compared to controls (68.9% vs 91.1%, p=0.008). The minimal lumen diameter was significantly larger in the ESR group than in controls (0.53±0.53 vs 0.01±0.58, p<0.001). The TIMI thrombus classification was lower in the ESR group than that in controls (p<0.001).

OCT FINDINGS

The OCT findings in matched and unmatched populations are presented in **Table 3** and **Supplementary Table 4**. ESR group patients had more non-plaque ruptures (62.2% vs 35.6%), whereas plaque

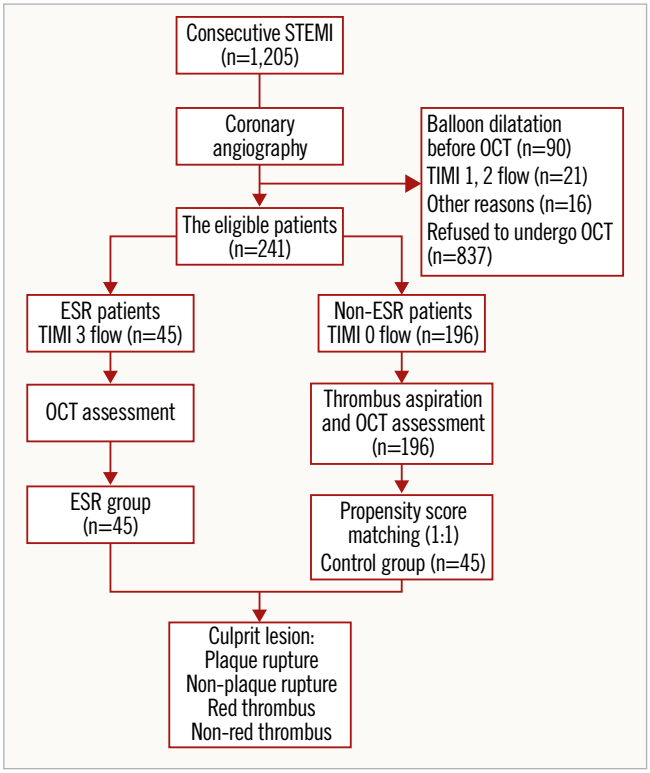

Figure 1. *Study flow chart. ESR: early spontaneous reperfusion; OCT: optical coherence tomography*

Table 1. Baseline characteristics.

		Unmatched cohort			Matched cohort	
		ESR group (n=45)	Non-ESR (n=196)	*p*-value*	Control group (n=45)	*p*-value†
Age, years		53.0 (43.0-62.5)	58 (49.0-66.0)	0.035	56.0 (46.0-64.5)	0.367
Male		38 (84.4)	168 (85.7)	0.827	38 (84.4)	N/A
Smoking		36 (80.0)	134 (68.4)	0.123	34 (75.6)	0.612
Diabetes mellitus		13 (28.9)	46 (23.5)	0.446	13 (28.9)	N/A
Hypertension		27 (60.0)	102 (52.0)	0.334	27 (60.0)	N/A
Blood glucose, mmol/L		8.1 (6.3-12.1)	8.8 (7.2-12.0)	0.630	8.4 (6.6-10.5)	0.615
DAPT to procedure, min		45.0 (32.0-65.0)	42.0 (30.0-60.0)	0.243	42 (27.5-63.0)	0.604
Symptom onset to PCI, hrs		3.5 (3.0-6.0)	3.2 (2.2-5.0)	0.071	3.5 (2.3-5.0)	0.160
In-hospital medication	Aspirin	45 (100.0)	196 (100.0)	N/A	45 (100.0)	N/A
	Ticagrelor/clopidogrel	45 (100.0)	196 (100.0)	N/A	45 (100.0)	N/A
	Beta-blockers	31 (68.9)	156 (79.6)	0.120	34 (75.6)	0.336
	ACEI or ARB	29 (64.4)	139 (70.9)	0.394	26 (57.8)	0.442
	Statins	42 (93.3)	185 (94.4)	0.729	44 (97.8)	0.306
WBC, $\times 10^9$/L		10.2 (8.7-12.1)	9.4 (7.1-13.1)	0.423	10.8 (8.7-13.4)	0.706
Neutrophil, $\times 10^9$/L		8.2 (6.8-9.6)	7.4 (5.5-10.2)	0.462	8.3 (6.3-10.1)	0.786
PLT, $\times 10^9$/L		212.3±89.5	227.2±53.8	0.238	215.1±66.6	0.874
LDL-cholesterol, mmol/L		2.9±1.1	3.0±0.9	0.633	3.0±0.8	0.456
HDL-cholesterol, mmol/L		1.0±0.3	1.06±0.30	0.592	1.0±0.3	0.958
D-dimer, ug/ml		0.2±0.2	0.2±0.2	0.438	0.1±0.1	0.110

Values shown are n (%), mean±SD or median (interquartile range). * *p*-value was the analytic comparison between the ESR group and the unmatched non-ESR patients. † *p*-value was the analytic comparison between the ESR group and the matched control group. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; DAPT: dual antiplatelet therapy; ESR: early spontaneous reperfusion; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PCI: percutaneous coronary intervention; PLT: platelets; WBC: white blood cell

Table 2. Angiographic findings.

		Unmatched cohort			Matched cohort	
		ESR group (n=45)	Non-ESR (n=196)	*p*-value	Control group (n=45)	*p*-value#
Infarct-related artery	LAD	24 (53.3)	102 (52.0)	0.708	24 (53.3)	0.918
	LCX	3 (6.7)	21 (10.7)		4 (8.9)	
	RCA	18 (40.0)	73 (37.2)		17 (37.8)	
Number of diseased vessels	One	13 (28.9)	60 (30.6)	0.764	11 (24.4)	0.308
	Two	15 (33.3)	73 (37.3)		22 (48.9)	
	Three	17 (37.8)	63 (32.1)		12 (26.7)	
Number of stents placed in emergent procedure		1.0±0.9	1.3±0.9	0.062	1.3±0.7	0.081
Emergent stent placement		31 (68.9)	179 (91.3)	0.001	41 (91.1)	0.008
Stent diameter, mm		3.5 (3.0-4.0)	3.5 (3.0-3.5)	0.519	3.5 (3.0-4.0)	0.065
Total stent length, mm		23.5 (18.0-33.0)	23.0 (18.0-30.0)	0.753	24.0 (18.0-33.0)	0.148
Vascular access site	Radial	44 (97.8)	189 (96.4)	0.649	43 (95.6)	0.616
	Femoral	1 (2.2)	7 (3.6)		2 (4.4)	
Reference lumen diameter, mm		3.5±0.4	3.4±0.4	0.320	3.5±0.4	0.803
Minimal lumen diameter, mm	Baseline	0.53±0.53	N/A	N/A	N/A	N/A
	After thrombus aspiration	N/A	0.97±0.59	0.001*	0.95±0.62	0.001$
Diameter stenosis, %	Baseline	82.4±14.6	N/A	N/A	N/A	N/A
	After thrombus aspiration	N/A	71.9±16.6	0.001*	72.7±16.0	0.001$
TIMI thrombus classification	Grade 0-2	9 (20.0)	0 (0)	0.001	0 (0)	0.001
	Grade 3	10 (22.2)	5 (2.5)		2 (4.4)	
	Grade 4	26 (57.8)	17 (8.7)		2 (4.4)	
	Grade 5	0 (0)	174 (88.8)		41 (92.2)	

Values shown are n (%), mean±SD or median (interquartile range). # *p*-value was the analytic comparison between the ESR group and the matched control group. * *p*-value was the analytic comparison between baseline in the ESR group and characteristics after thrombus aspiration in the non-ESR patients. $ *p*-value was the analytic comparison between baseline in the ESR group and characteristics after thrombus aspiration in the control group. Control group: non-spontaneous reperfusion; ESR: early spontaneous reperfusion; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction

ruptures (37.8% vs 64.4%) were less common in the ESR group. Moreover, non-red thrombi (55.6%) were more frequent in the ESR group, while red thrombi (77.8%) were frequent in the control group. The minimal lumen area was significantly larger in the ESR group than in the control group (2.5±1.7 vs 1.8±1.0 mm², p=0.025) **(Figure 2, Figure 3)**.

Discussion

In this prospective study, we defined ESR in 20% of patients with STEMI. Compared with controls, the ESR group demonstrated a lower rate of plaque rupture and a higher rate of plaque erosion. In the ESR group, non-red thrombi were more common, whereas red thrombus accounted for 77.8% of control group cases. Significantly fewer patients in the ESR group underwent emergent stent implantation compared to the control group.

ESR is not an uncommon phenomenon in the clinical setting. We previously reported that 18.4% of patients with STEMI had angiographic patency in the infarct-related artery within 12 hours of chest pain onset[7]. Four primary angioplasty in myocardial infarction (PAMI) primary PCI trials found that 16.0% of patients had ESR[13]. A recent large-scale study found that the prevalence of ESR was 17.0% among patients with ST-segment elevation acute coronary syndrome (ACS).

Although some factors – such as endogenous activity of thrombolysis, the size of thrombus, atherosclerotic conditions and vasomotor tone – were believed to be associated with ESR[4,7,14], the mechanisms of plaque morphology remain uncertain. Generally, coronary occlusion due to a ruptured atherosclerotic plaque followed by immediate thrombosis was regarded as the main cause (70.0%) of STEMI[12]. Also, plaque erosion and calcified nodules contributed to thrombi formation in STEMI without plaque rupture. These patients exhibited either missed endothelium replaced by exposed intima or disruptive nodular calcifications that protruded into the lumen[13]. In the current study, non-ruptured plaque (62.2%) was predominant in the ESR group. To our knowledge, this is the first report which suggests that ESR is mainly a result of non-ruptured plaque-related transient coronary occlusion.

There are four potential explanations for our findings. In coronary thrombosis, the initial flow obstruction is usually caused by an early and fragile platelet thrombus. The fate of thrombus is largely determined by the balance among platelet activation, pro-coagulant factors, antithrombotic therapy and the fibrinolytic system.

Table 3. OCT findings.

Plaque characteristics	Unmatched cohort			Matched cohort	
	ESR group (n=45)	Non-ESR (n=196)	*p*-value	Control group (n=45)	*p*-value#
Plaque rupture	17 (37.8)	111 (56.6)	0.022	29 (64.4)	0.011
Non-ruptured plaque	28 (62.2)	85 (43.4)	–	16 (35.6)	–
Plaque erosion	26 (57.8)	85 (100)	–	16 (35.6)	–
Probable	10 (38.5)	34 (40.0)	–	3 (18.7)	–
Definite	16 (61.5)	51 (60.0)	–	13 (81.3)	–
Vasospasm	1 (2.2)	0 (0)	–	0 (0)	–
Calcified nodule	1 (2.2)	0 (0)	–	0 (0)	–
Thrombus type					
Red thrombus	20 (44.4)	121 (61.7)	0.034	35 (77.8)	0.001
Non-red thrombus	25 (55.6)	75 (38.3)	–	10 (22.2)	–
White thrombus	12 (26.7)	38 (19.4)	–	5 (11.1)	–
Mixed thrombus	3 (6.7)	37 (18.9)	–	5 (11.1)	–
No thrombus	10 (22.2)	0 (0)	–	0 (0)	–
Plaque rupture	1 (10.0%)	0 (0)	–	0 (0)	–
Plaque erosion	7 (70.0%)	0 (0)	–	0 (0)	–
Calcified nodule	1 (10.0%)	0 (0)	–	0 (0)	–
Vasospasm	1 (10.0%)	0 (0)	–	0 (0)	–
Quantitative thrombus analysis					
Thrombus volume, mm^3	3.0±7.3	N/A	–	5.3±10.2	0.216
Thrombus burden, %	12.2±9.2	N/A	–	17.7±16.9	0.058
Max thrombus area, mm^2	0.9±1.1	N/A	–	1.7±1.7	0.019
Thrombus length, mm	3.6±3.9	N/A	–	5.6±4.4	0.026
Thrombus score	28.7±32.2	N/A	–	52.1±42.3	0.004
Lesion length, mm	18.7±6.8	21.1±8.8	0.091	22.0±9.7	0.067
Reference lumen area, mm^2	7.6±2.7	6.9±1.5	0.107	6.9±1.5	0.133
Minimal lumen area, mm^2 *	2.5±1.7	1.9±1.4	0.025	1.8±1.0	0.025
Area stenosis, % *	66.0±18.6	71.3±16.4	0.062	72.9±13.3	0.047

Values shown are n (%) or mean±SD. # *p*-value was the analytic comparison between the ESR group and the matched control group. * The minimal lumen area and area stenosis were measured post thrombus aspiration in the patients with non-ESR. ESR: early spontaneous reperfusion; Non-red thrombus: white thrombus, vasospasm; Non-ruptured plaque: plaque erosion, vasospasm, calcified nodule; OCT: optical coherence tomography

Non-ruptured plaques usually do not contain a large necrotic core exposed to circulating blood[10]. This results in lower local thrombogenicity[15]. A previous study indicated that white thrombus, identified by OCT, was predominant in plaque erosion and calcified nodules[16]. Our ESR patients exhibited results similar to ACS patients in a previous study. The occurrence of ESR has been associated with antithrombotic and vasodilator drug treatment before primary PCI in previous studies[17]. The dissolution of the white thrombus following re-opening of the infarct-related artery might be one of the main mechanisms underlying ESR. Moreover, in non-ruptured plaque-related STEMI, the thrombus volume and degree of lumen stenosis are smaller. Both of these factors might contribute to a higher incidence of ESR in this group[4]. Kramer et al demonstrated that plaque erosion (60.0%) had a higher incidence of <75.0% area stenosis when compared with plaque rupture (35.4%)[18]. Jia et al reported that the mean diameter stenosis in plaque erosion was 55.4% and about 70.0% of patients had diameter stenosis <70.0%[10]. In our study, the ESR patients had a higher minimal lumen diameter and minimal lumen area. Also, 2.2% of ESR cases were diagnosed with coronary spasm, yet this was not the case for the control group. ESR may be followed by prompt relief of coronary spasm. Lastly, lower thrombus burden was another likely mechanism of ESR. The study by Lee et al indicated that heavy thrombi were independent predictors of less frequent ESR in patients with STEMI[4], in agreement with our findings.

Patients with ESR usually have resolved symptoms and normalised ST segments, similar to "transient STEMI"[19,20]. Patients with transient STEMI had more rapid efficient endogenous fibrinolysis and reduced platelet reactivity[21]. Clinically, these patients had less extensive coronary artery disease, better coronary flow on angiography, lower peak creatine kinase levels, and higher left ventricular ejection fractions[22]. Another plaque feature of ESR was analogous to "non-ST-segment elevation ACS". In a previous study[23], plaque erosion (61.5% vs 38.5%) and calcified nodules (100% vs 0%)

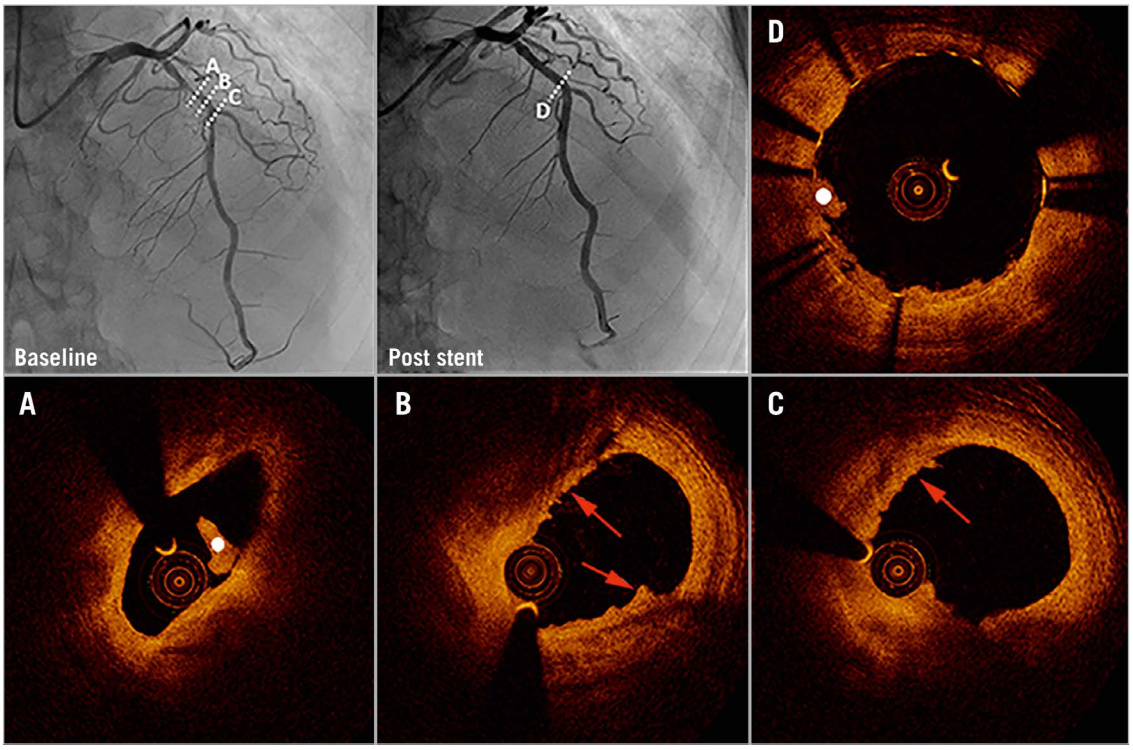

Figure 2. *Coronary angiography and optical coherence tomography in early spontaneous reperfusion. Baseline angiography (upper left) shows a patient with TIMI 3 flow. Optical coherence tomography (OCT) shows plaque erosion (red arrows) and white thrombus (white dot) (A-C). Coronary angiography (upper middle) and OCT show imaging of the region after stent implantation (D).*

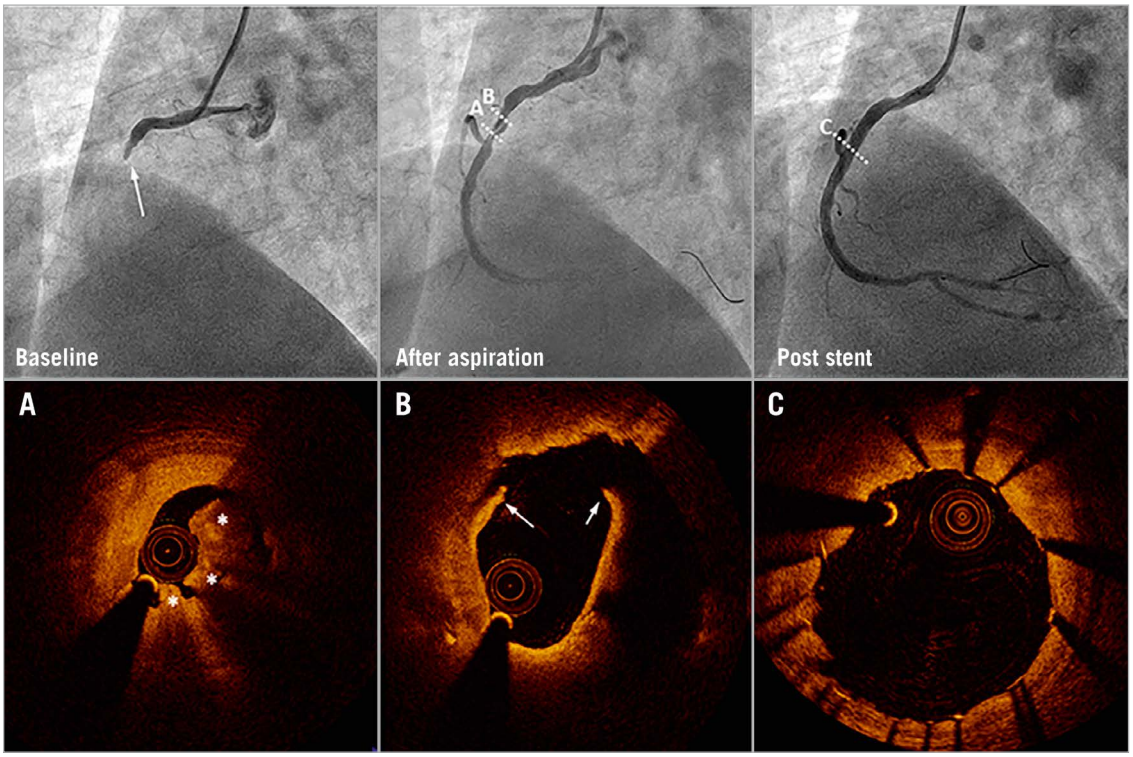

Figure 3. *Coronary angiography and optical coherence tomography in a control patient. Baseline angiography (upper left) shows a patient with complete occlusion and TIMI 0 flow. After thrombus aspiration, the coronary arterial flow was restored to TIMI 3 flow. Optical coherence tomography (OCT) shows plaque rupture (white arrows) and red thrombus (white stars) (A & B). Angiography and OCT show imaging of the region after stent implantation (C).*

were more common, but there were fewer instances of plaque rupture (29.1% vs 70.9%) in patients with non-ST-segment elevation ACS compared to STEMI.

Although our ESR group had a higher percentage of three-vessel disease, the difference was non-significant. Lee et al[4] also reported that the number of diseased vessels had no significant relationship with the occurrence of ESR. Moreover, we found that the lumen area and diameter stenosis were associated with ESR prevalence. Therefore, the relation between the number of diseased vessels and ESR may be influenced by other factors. According to the clinical manifestation, morphological features, and prognosis, ESR seems to be an intermediate state between STEMI and non-ST-segment elevation ACS.

Jian Wang et al[17] found that most cases of ESR were not actually spontaneous but rather the result of antithrombotic and vasodilator drug treatment before primary PCI. However, our data did not show a significant difference in pre-hospital antiplatelet drug treatment between the ESR group and the control group. Therefore, future studies should examine whether antithrombotic drugs are associated with ESR occurrence. Moreover, both the TRANSIENT trial[19,20] and the EROSION study[10] showed no differences in short-term outcomes between primary and delayed PCI in patients with either transient STEMI or non-ruptured plaque-induced acute myocardial infarction. OCT was performed in our study, but the invasive strategy was still left to the operator's discretion, according to angiographic images. Therefore, our results suggest that more clinical studies should explore whether plaque morphology could guide the decision concerning interventional treatment in ESR patients.

Study limitations

Limitations of the study should be acknowledged. First, the data were collected at a single medical centre from a relatively small study cohort. Second, it was performed in a heterogeneous, non-selected population within a clinical setting. Propensity score matching may mitigate bias after adjusting for confounding factors, but unmeasured indicators leave room for residual bias. Third, thrombus aspiration was performed in the non-ESR patients, resulting in plaque modification and inaccurate assessment. Fourth, due to the balloon dilatation that would affect the plaque morphologic characteristics by OCT, we excluded patients with more severe stenosis, and a selection bias might have existed. Fifth, because OCT was not covered by health insurance, about 70 percent of the 1,205 STEMI patients were unable to complete OCT; this could also have influenced patient selection. Sixth, we excluded patients with TIMI 1 or 2 flow; this constitutes an additional source of potential selection bias.

Conclusions

Non-ruptured plaque is closely involved in the potential mechanism of ESR. Since ESR is associated with favourable clinical outcomes, future studies should explore whether plaque morphology assessment could guide the decision concerning interventional treatment in these patients.

Impact on daily practice

Non-ruptured plaque is a potential mechanism of ESR. Future studies should explore whether plaque morphology could guide therapeutic strategy in ESR patients.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Table 1. Standard mean difference after propensity score matching.

Supplementary Table 2. Baseline characteristics of total patients.

Supplementary Table 3. Baseline characteristics.

Supplementary Table 4. OCT findings.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00812

Supplementary data

Supplementary Appendix 1. Methods

Exclusion criteria

1) Receiving fibrinolytic therapy; 2) prior PCI or CABG; 3) duration from onset of symptoms to emergent angiography over 12 hrs; 4) cardiogenic shock; 5) declined or unsuitable for OCT assessment; 6) undergoing balloon dilatation before OCT.

Diagnostic criteria for STEMI

The presence of continuous chest pain lasting ≥20 minutes; and either 1) ST-segment elevation of ≥2 mV in at least two contiguous precordial leads, and 2) ST-segment elevation of ≥1 mV in at least two inferior leads, or 3) new left bundle branch block [24]. The STEMI was later confirmed by elevated myocardial biomarkers (CK-MB or troponin) ≥2-fold or 99 percentiles of normal value.

Diagnostic criteria of vasospasm

The vasospasm was defined by the following two criteria [25]: 1) spontaneous coronary artery spasm (producing >90% narrowing in the infarct-related vessel identified by angiography) associated with chest pain and ischaemic ST-segment changes (transient ST-segment elevation or depression ≥0.1 mV, recorded on at least two contiguous leads on the 12-lead electrocardiogram [ECG]); and 2) normal or insignificant coronary artery disease (diameter stenosis <50%) after intracoronary nitroglycerine injection.

OCT images were analysed at spasm sites that extended 5 mm proximally and distally from the maximal spasm segments.

Medical treatment

All patients immediately received a loading dose of 300 mg of aspirin and 600 mg of clopidogrel (or ticagrelor 180 mg), followed by 100 mg of aspirin maintenance dose daily and 75 mg of clopidogrel (or ticagrelor 180 mg) daily. Unfractionated heparin (100 IU/kg) was given intravenously prior to the catheterisation procedure, and the use of glycoprotein IIb/IIIa inhibitors (GPI, tirofiban, bolus of 25 mg/kg administered over 3 min followed by continuous intravenous infusion of 0.15 mg/kg/min) was decided by the operator. After the emergent procedure, a standard protocol of medical treatment was implemented according to the recommendation of current guidelines.

The culprit lesion

The culprit lesion was identified by two experienced physicians in combination with ECG and images (angiogram and OCT images).

Coronary angiogram analysis

A quantitative coronary angiography (QCA) analysis was performed using the Cardiovascular Angiography Analysis System (CAAS) 5.10 (Pie Medical Imaging, Maastricht, the Netherlands).

Minimum lumen diameter (MLD) was defined as the smallest lumen diameter from one intimal leading edge to another along any line passing through the centre of the lumen. Reference lumen diameter was defined as the average diameter of the lumen assumed without atherosclerotic disease. Diameter stenosis (%) = (reference lumen diameter – minimal lumen diameter) / reference lumen diameter × 100%.

The TIMI thrombus burden classification

Grade 0: no angiographic characteristics of thrombus are present.

Grade 1: possible thrombus is present with angiographic features such as decreased contrast density, haziness of contrast, irregular lesion contour, a smooth convex meniscus at the site of a total occlusion, suggestive, but not firmly diagnostic of thrombus.

Grade 2: definite thrombus is present with greatest dimension of thrombus (1/2 to 2 vessel diameters).

Grade 3: definite thrombus appears in multiple angiographic views (greatest dimension from >1/2 to 2 vessel diameters).

Grade 4: definite large size thrombus is present (greatest dimension >2 vessel diameters).

Grade 5: definite complete thrombotic occlusion of a vessel (a convex margin that stains with contrast, persisting for several cardiac cycles); angiographic detection of a grade 5 TIMI thrombus leads to further exploration of the occlusive thrombotic content. Either a PCI guidewire or a small balloon is advanced across the thrombotic total occlusion. Crossing the thrombus results in restoration of antegrade flow in the treated vessel. Consequently, the ensuing coronary angiogram enables restratification of the underlying residual thrombus (final TIMI thrombus grade).

OCT imaging analysis

Analysis of plaque characteristics

Based on the established OCT diagnostic criteria, plaque rupture was of discontinuous fibrous cap from the surface of the vessel wall and a clear cavity formed inside the plaque. Plaque erosion was identified by the presence of attached thrombus overlying an intact and visualised plaque, luminal surface irregularity at the culprit lesion in the absence of thrombus, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus, and categorised according to the absence of fibrous cap disruption and the presence of thrombus. Definite plaque erosion was identified by the presence of attached thrombus overlying an intact and visualised plaque. Probable plaque erosion was defined by: 1) luminal surface irregularity at the culprit lesion in the absence of thrombus; or 2) attenuation of

underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus. Calcified nodule was defined when fibrous cap disruption was detected over a calcified plaque characterised by protruding calcification, superficial calcium, and the presence of substantive calcium proximal and/or distal to the lesion [23].

Analysis of thrombus characteristics

Thrombus was defined as an irregular mass (diameter >250 μm) either attached to the luminal surface or floating within the lumen, including erythrocyte-rich (red) thrombus or platelet-rich (white) thrombus. Red thrombus contains mainly red blood cells, relevant OCT images characterised by high-backscattering protrusions with signal-free shadowing. Platelet-rich (white) thrombus contains mainly platelets characterised by signal-rich, low-backscattering protrusions into the lumen [26].

Thrombus area (TA) was calculated as lumen area (LA) minus flow area (FA). Lumen area (LA) and flow area (FA) were measured by planimetry in each OCT frame, i.e., TA (mm^2) = LA (mm^2) – FA (mm^2).

Thrombus volume (TV) was calculated as the mean TA multiplied by the thrombus length.

The thrombus length was measured as the longitudinal distance between the most distal and the most proximal frame that showed intraluminal thrombus, i.e., TV (mm^3) = mean TA (mm^2) × Thrombus length (mm).

Thrombus burden (TB) was defined as the mean TA divided by the mean LA, i.e., TB (%) = mean TA (mm^2) / mean LA (mm^2) × 100%.

Luminal area stenosis was defined as the relative decrease in luminal area of the target lesion, in percent, when compared with a reference lumen area in the same vessel segment.

Reference lumen area was defined as the area with the largest reference lumen either proximal or distal to a stenosis, but within the same segment (usually within 10 mm of the stenosis with no major intervening branches).

Length of lesion was defined as the distance from the culprit lesion to the normal site (proximal and distal).

Maximum lumen diameter was defined as the largest lumen diameter from one intimal leading edge to another along any line passing through the centre of the lumen.

Minimal lumen area (MLA). Minimal lumen area along the length of the target lesion.

Supplementary Table 1. Standard mean difference after propensity score matching.

Variables	Standard mean difference (after PSM)
Age, years	0.058
Male	0.000
Smoking	0.095
Hypertension	0.000
Diabetes	0.000
Blood glucose	0.081
Symptom onset to PCI, hrs	0.055
DAPT to procedure, mins	0.079
WBC, $x10^9$/L	0.083
Neutrophil, $x10^9$/L	0.061
Uric acid, μmol/L	0.002
PLT, $x10^9$/L	-0.035
LDL-cholesterol, mmol/L	0.041
HDL-cholesterol, mmol/L	0.034
D-dimer, ug/ml	-0.071

Values shown are standard mean difference.

PSM: propensity score matching

Supplementary Table 2. Baseline characteristics of total patients.

Variables	Total patients (n=241)
Age, years	56.0 (46.0-64.0)
Male	206 (85.5)
Smoking	170 (70.5)
Diabetes mellitus	59 (24.5)
Hypertension	129 (53.5)
Systolic blood pressure, mmHg	126.6±20.7
Diastolic blood pressure, mmHg	79.87±20.0
DAPT to procedure, min	45.0 (33.7-68.0)
Symptom onset to PCI, hrs	3.5 (2.5-5.0)
Pre-hospital medication	
Aspirin	74 (30.7)
Ticagrelor/clopidogrel	55 (22.8)
Nitroglycerine	16 (6.6)
In-hospital medication	
Aspirin	241 (100)
Ticagrelor/clopidogrel	241 (100)
Beta-blockers	187 (77.6)
ACEI or ARB	168 (70.0)
Statins	227 (94.2)
Medication during PCI	
GP IIb/IIIa inhibitor	69 (28.6)
Heparin	166 (68.9)
Bivalirudin	75 (31.1)
Blood glucose, mmol/L	8.2 (6.5-11.1)
WBC, $x10^9$/L	10.2 (8.2-12.7)
Neutrophil ($x10^9$/L)	8.0 (6.2-10.3)
PLT, $x10^9$/L	214.5±78.0
LDL-cholesterol, mmol/L	3.3±1.3
HDL-cholesterol, mmol/L	1.2±0.4
Serum creatinine, μmol/L	73.6±17.0
Uric acid, μmol/L	335.7±84.5
D-dimer, ug/ml	0.2±0.2

Values shown are n (%), mean±SD or median (interquartile range). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; DAPT: dual antiplatelet therapy; PLT: platelets; WBC: white blood cell

Supplementary Table 3. Baseline characteristics.

	Unmatched cohort			Matched cohort	
Variables	ESR group (n=45)	Non-ESR (n=196)	*p*-value[&]	Control group (n=45)	*p*-value[#]
Systolic blood pressure, mmHg	127.6±22.5	129.8±19.3	0.583	125.5±19.6	0.633
Diastolic blood pressure, mmHg	80.3±16.4	81.9±13.8	0.567	80.1±14.4	0.946
Pre-hospital medication					
Aspirin	14 (31.1)	60 (30.6)	0.948	18 (40)	0.378
Ticagrelor/clopidogrel	13 (28.9)	42 (21.4)	0.282	12 (26.7)	0.814
Nitroglycerine	1 (2.2)	15 (7.7)	0.187	5 (11.1)	0.091
Medication during PCI					
GP IIb/IIIa inhibitor	8 (17.8)	61 (31.1)	0.074	16 (35.6)	0.057
Heparin	34 (75.6)	132 (67.3)	0.388	27 (60.0)	0.114
Bivalirudin	11 (24.4)	64 (32.7)	0.283	18 (40.0)	
Serum creatinine, μmol/L	73.0±16.0	76.5±16.9	0.286	71.5±16.6	0.660
Uric acid, μmol/L	329.3±74.6	341.0 83.9	0.429	329.3±86.8	0.990

Values shown are n (%), mean±SD or median (interquartile range). [#] p-value was the analytic comparison between the ESR group and the matched control group. [&] p-value was the analytic comparison between the ESR group and the unmatched non-ESR patients. ESR: early spontaneous reperfusion; NSR: non-spontaneous reperfusion

Supplementary Table 4. OCT findings.

Variables	ESR group n=45	Control group n=45	*p*-value
Mean minimal lumen diameter, mm	1.7±0.8	1.3±0.2	0.001
Mean reference lumen diameter, mm	3.2±0.7	3.3±0.5	0.239
Mean diameter stenosis, %	44.6±15.9	60.8±7.7	0.001

Values shown are mean±SD.