

Renal Dysfunction as a Predictor of Slow-Flow/No-Reflow Phenomenon and Impaired ST Segment Resolution After Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction With Initial Thrombolysis in Myocardial Infarction Grade 0

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Background: The slow-flow/no-reflow phenomenon and impaired ST segment resolution (STR) following primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) predict unfavorable prognosis and are characterized by obstruction of the coronary microvascular. Several predictors of slow-flow/no-reflow have been revealed, but few studies have investigated predictors of slow-flow/no-reflow and STR exclusively in acute myocardial infarction patients with initial Thrombolysis in Myocardial Infarction (TIMI) Grade 0.

Methods and Results: In all, 279 STEMI patients with initial TIMI Grade 0 were enrolled in the study. Slow-flow/no-reflow was defined as TIMI Grade <3 by angiography after PCI, and impaired STR was defined as STR <50% on an electrocardiogram after PCI. Slow-flow/no-reflow was observed in 31 patients. In multivariate analysis, estimated glomerular filtration rate (eGFR; odds ratio [OR] 0.97; $P=0.007$), a history of cerebrovascular disease (OR 4.65, $P=0.007$), time to recanalization ≥ 4 h (OR 2.76, $P=0.023$), and systolic blood pressure ≤ 90 mmHg (OR 3.45, $P=0.046$) were independent predictors of slow-flow/no-reflow. Impaired STR was observed in 102 of 248 patients with TIMI Grade 3. In multivariate analysis, eGFR (OR 0.94, $P<0.001$) and occlusion of the left anterior descending artery (OR 4.48, $P<0.001$) were independent predictors of impaired STR; eGFR was the only independent predictor of both slow-flow/no-reflow and impaired STR.

Conclusions: Renal dysfunction may be related to coronary microvascular dysfunction and obstruction.

Key Words: No reflow; Renal dysfunction; ST-elevation myocardial infarction (STEMI)

ST segment elevation myocardial infarction (STEMI) remains one of the leading causes of death worldwide.¹ Primary percutaneous coronary intervention (pPCI) is associated with improved prognosis in patients with STEMI. However, the benefits of this procedure are limited by the incidence of the slow-flow/no-reflow phenomenon. The concept of “slow-flow/no-reflow” refers to a state of myocardial tissue hypoperfusion in the presence of a patent epicardial coronary artery.² Slow-flow/no-reflow results from obstruction of the myocardial microcirculation, defined as vessels $<200\mu\text{m}$ in diameter, and is caused by various mechanisms.³ Suggested etiologic factors include ischemia–reperfusion injury, myocardial edema, endothelial swelling, capillary obstruction, vasospasm, inflammatory response, and distal coronary embolization.³ Slow-flow/no-reflow is closely related to worse clinical out-

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comes.⁴ Furthermore, ST segment resolution (STR) after pPCI is also a well-established parameter for evaluating microvascular dysfunction and obstruction.⁵ Impaired STR after pPCI has also been shown to be associated with an adverse clinical outcome.⁶

Several studies have reported predictors of slow-flow/no-reflow, such as age, male sex, diabetes, hypertension, onset to reflow time, Killip class, blood glucose, creatinine, peak creatine kinase, initial Thrombolysis in Myocardial Infarction (TIMI) grade, and thrombus score.⁷ In a meta-analysis of the predictors of slow-flow/no-reflow, initial TIMI Grade ≤ 1 and a high thrombus burden had the most impact.⁷ We wanted to evaluate the principal mechanisms

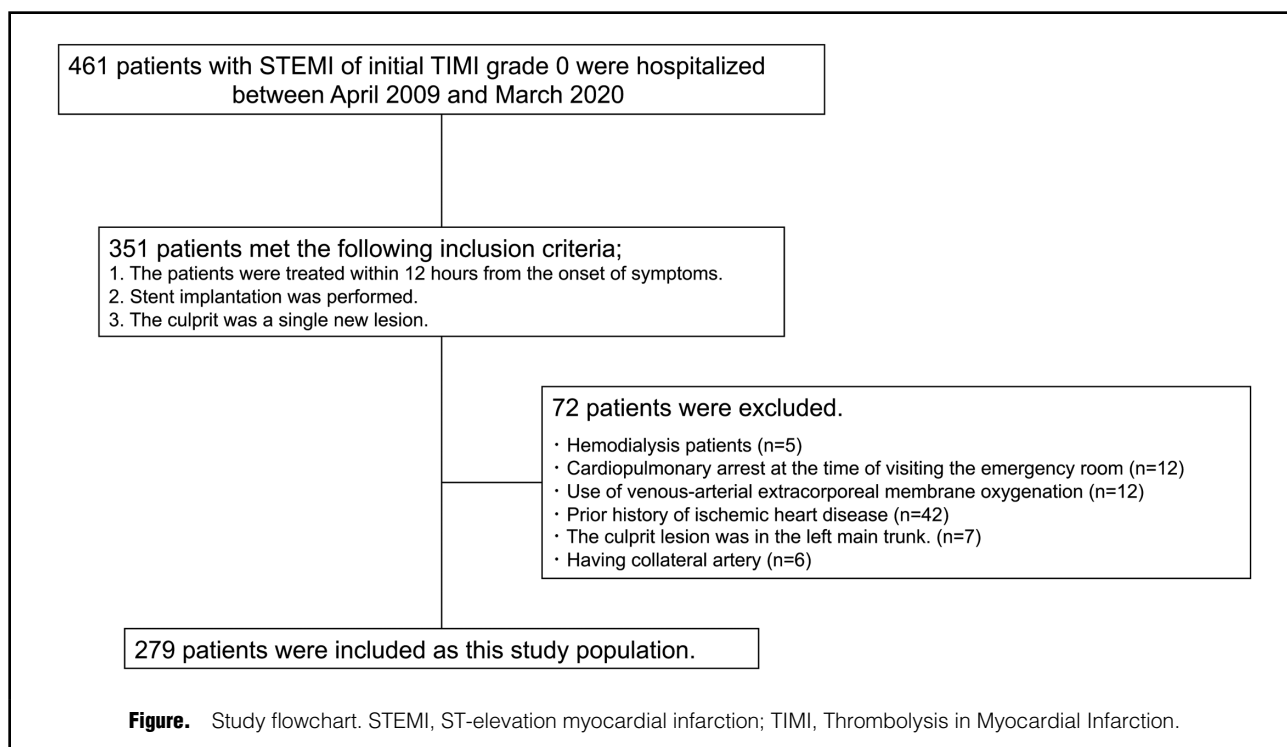
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leading to slow-flow/no-reflow separate from the effect of low initial TIMI grade and a high thrombus burden. Therefore, we investigated the predictors of slow-flow/no-reflow exclusively in STEMI patients with initial TIMI Grade 0. The aim of this study was to evaluate the predictors of slow-flow/no-reflow and impaired STR in STEMI patients with initial TIMI Grade 0.

Methods

Study Design

This study was a retrospective single-center case-control study. In all, 461 patients who underwent percutaneous coronary intervention (PCI) for STEMI of initial TIMI Grade 0 at Fujieda Municipal General Hospital between April 2009 and March 2020 were recruited to the study. Eligible patients had ST segment elevation ≥ 0.1 mV in at least 2 limb leads and/or ≥ 0.2 mV in 2 contiguous precordial leads. The inclusion criteria were as follows: (1) patients had to have been treated within 12 h from the onset of symptoms; (2) a stent had to have been implanted; and (3) the culprit lesion must have been a single new lesion. Patients undergoing hemodialysis, those experiencing cardiopulmonary arrest when presenting to the emergency room, those receiving venous-arterial extracorporeal membrane oxygenation, and those with a prior history of ischemic heart disease, a culprit lesion in the left main trunk, or with a collateral artery were excluded from the study. Finally, 279 patients who met the inclusion criteria were included in the study.

Angiographic Analysis

All patients underwent baseline coronary angiography using standard techniques (Allura Xper FD10/10 [Philips, Amsterdam, Netherlands] between April 2009 and October

2019; Azurion7B12 [Philips] between November 2019 and March 2020). TIMI grade was assessed according to a previous study.⁸ Slow-flow/no-reflow was defined as TIMI Grade <3 on the angiogram after stent implantation despite residual stenosis $<50\%$ and the absence of significant dissection or visible thrombus. Slow-flow/no-reflow also included transient flow worsening after stent implantation. Normal flow was defined as TIMI Grade 3. Patients were into 2 groups, a slow-flow/no-reflow group and a normal-flow group, and the predictors of slow-flow/no-reflow were evaluated.

This study was performed in accordance with the 1975 Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Fujieda Municipal General Hospital (No. R02-08).

Electrocardiogram Analysis

Electrocardiograms (ECGs) were measured on admission and immediately after pPCI in the intensive care unit; STR was calculated by comparing the 2 electrocardiograms. Single-lead STR was measured by comparing 1 ECG lead with the most prominent ST segment deviation.⁹ With anterior acute myocardial infarction (AMI), ST elevation in any of leads I, aVL, or V1–6 was taken into account; with non-anterior AMI, ST elevation was assessed in either leads II, III, and aVF, or in leads V5 and V6.⁹ STR was measured only in patients in the normal-flow group. Patients were divided into 2 groups, the high-STR group (STR $\geq 50\%$) and the low-STR group (STR $<50\%$), and evaluated the predictors of low STR.

Laboratory Analysis

Blood samples were obtained from the peripheral artery or vein on admission before the administration of any medication. The estimated glomerular filtration rate (eGFR)

was calculated using serum creatinine (Cr) concentrations, age, weight, and sex using the following formulas:¹⁰

$$eGFR = 194 \times Cr^{-1.094} \times age^{-0.287} \text{ (in males)}$$

$$eGFR = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739 \text{ (in females)}$$

Intervention Procedure

All patients received oral aspirin (162mg) and clopidogrel (300mg) or prasugrel (20mg) in the emergency room. Intravenous unfractionated heparin (2,000 U) was injected before baseline coronary angiography. After total occlusion of the main branch (left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) was found, heparin (6,000–10,000 U, depending on the patient's weight) was injected. The PCI procedures were performed according to the standard femoral or

radial approach with a 6-Fr guiding catheter. Decisions regarding the use of balloon for pre- or post-dilatation, a thrombus aspiration device, and the type of stent (bare metal or drug eluting) were made by each operator.

Statistical Analysis

Continuous variables are expressed as the median with interquartile range and categorical variables are expressed as frequencies and percentages. The significance of differences was evaluated using Mann-Whitney non-parametric U tests for continuous variables and the χ^2 test for categorical variables. Univariate and multivariate logistic regression analyses were used to investigate predictors of slow-flow/no-reflow and low STR. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Two-sided $P < 0.05$ was considered significant. All analyses were per-

	Normal flow (n=248)	Slow flow/no reflow (n=31)	P value
Age (years)	67 [58–74]	72 [62–80]	0.008
Male sex	197 (79)	24 (77)	0.79
SBP (mmHg)	134 [114–154]	118 [101–145]	0.03
DBP (mmHg)	83 [70–95]	72 [61–91]	0.06
SBP $\leq$ 90 mmHg	17 (6.9)	6 (19)	0.02
NYHA classification			0.01
I	207 (84)	24 (77)	
II	12 (4.8)	6 (19)	
III	4 (1.6)	0 (0)	
IV	25 (10.1)	1 (3.2)	
NYHA classification $\geq$ II	41 (17)	7 (23)	0.4
BMI (kg/m ²)	23.5 [21.4–25.5]	22.7 [20.8–25.0]	0.43
Hypertension	191 (77)	22 (71)	0.46
Diabetes	77 (31)	11 (36)	0.62
History of cerebrovascular disease	12 (4.8)	7 (23)	<0.001
Primary Vf	6 (2.4)	0 (0)	0.38
Smoking status			0.48
Current smoker	108 (44)	10 (32)	
Ex smoker	62 (25)	9 (29)	
Never smoked	78 (32)	12 (39)	
WBC ($\times 1,000/\mu\text{g}$)	9.5 [8.1–11.6]	8.9 [8.4–11.0]	0.67
Neutrophils ($\times 1,000/\mu\text{g}$)	6.1 [4.0–8.6]	6.9 [5.2–7.4]	0.46
Lymphocytes ($\times 1,000/\mu\text{g}$)	2.4 [1.5–3.8]	1.7 [1.3–2.9]	0.08
NLR	2.5 [1.2–5.3]	4.1 [1.6–6.2]	0.17
Hb (g/dL)	14.4 [13.3–15.6]	14.1 [12.0–15.0]	0.056
RDW-SD (fL)	43.2 [41.2–45.1]	44 [42.3–46.5]	0.07
RDW-CV (%)	13.1 [12.7–13.6]	13.3 [12.9–13.9]	0.15
Platelets ($\times 1,000/\mu\text{g}$)	214 [183–252]	225 [178–269]	0.56
PDW (fL)	11.3 [10.4–12.5]	11.3 [10.4–12.3]	0.54
MPV (fL)	10.1 [9.6–10.7]	10 [9.5–10.5]	0.42
TG (mg/dL)	81 [50–130]	67 [50–96]	0.19
HDL-C (mg/dL)	47 [41–57]	45 [39–54]	0.34
LDL-C (mg/dL)	123 [98–143]	117 [91–144]	0.32
HbA1c (%)	5.8 [5.5–6.3]	5.8 [5.6–6.5]	0.84
Glucose (mg/dL)	159 [138–199]	169 [145–221]	0.42
BNP (pg/mL)	37 [14–100]	74 [25–149]	0.054
Maximum CPK (IU/L)	2,967 [1,844–4,801]	3,957 [2,305–5,956]	0.08

(Table 1 continued the next page.)

	Normal flow (n=248)	Slow flow/no reflow (n=31)	P value
eGFR (mL/min/1.73 m ²)	68.3 [55.9–84.0]	51.2 [39.3–66.8]	<0.001
Medication on admission			
Prasugrel (20 mg loading)	92 (37)	12 (39)	0.86
Clopidogrel (300 mg loading)	152 (61)	18 (58)	0.73
ACEI	4 (1.6)	0 (0)	0.48
ARB	40 (16)	10 (32)	0.03
β -blockers	11 (4.4)	2 (6.5)	0.62
Calcium channel blockers	65 (26)	9 (29)	0.74
Statin	29 (12)	5 (16)	0.48
Insulin	6 (2.4)	3 (9.7)	0.03
Culprit lesion			0.65
LAD	125 (50)	17 (55)	
RCA	104 (42)	13 (42)	
LCX	19 (7.7)	1 (3.2)	
Syntax score	14.5 [9–21.5]	15.5 [10–20]	0.9
Type of stent deployed			
BMS	118 (48)	11 (36)	0.19
DES	130 (52)	20 (65)	0.2
Stent length (mm)	20.5 [18–28]	23 [18–28]	0.45
Stent diameter (mm)	3 [2.75–3.5]	3 [3–3.5]	0.78
Procedural characteristics			
Use of IVUS	132 (53)	18 (58)	0.61
Predilatation	184 (74)	27 (87)	0.11
Post-dilatation	51 (21)	5 (16)	0.56
Temporary pacemaker support	34 (14)	5 (16)	0.71
Use of IABP	43 (17)	18 (58)	<0.001
Use of thrombectomy	48 (19)	5 (16)	0.67
Time from onset to recanalization (min)	175 [135–269]	247 [145–322]	0.25
Time from onset to recanalization ≥ 4 h	77 (31)	16 (52)	0.02

Unless indicated otherwise, data are presented as the median [interquartile range] or n (%). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BMS, bare-metal stent; BNP, B-type natriuretic peptide; CPK, creatine phosphokinase; DBP, diastolic blood pressure; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; IABP, intra-aortic balloon pump; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; NYHA, New York Heart Association; PDW, platelet distribution width; RCA, right coronary artery; RDW-CV, red cell distribution width-coefficient of variation; RDW-SD, red cell distribution width-standard deviation; SBP, systolic blood pressure; TG, triglyceride; Vf, ventricular fibrillation; WBC, white blood cell.

Table 2. Univariate and Multivariate Logistic Regression Analysis Predicting Slow Flow/No Reflow

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.05 (1.01–1.09)	0.008	1.02 (0.98–1.07)	0.34
Male sex	0.89 (0.36–2.18)	0.79	1.49 (0.51–4.31)	0.46
SBP ≤ 90 mmHg	3.26 (1.18–9.03)	0.02	3.45 (1.02–11.6)	0.046
eGFR	0.96 (0.94–0.98)	<0.001	0.97 (0.94–0.99)	0.007
Insulin (on admission)	6.54 (1.39–30.7)	0.02	2.95 (0.5–17.5)	0.24
History of cerebrovascular disease	5.74 (2.06–15.9)	<0.001	4.65 (1.51–14.3)	0.007
Time from onset to recanalization ≥ 4 h	2.37 (1.11–5.04)	0.03	2.76 (1.15–6.63)	0.023

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SBP, systolic blood pressure.

formed using Bellcurve for Excel (Social Survey Research Information, Tokyo, Japan).

Results

Of the 461 patients with STEMI of initial TIMI Grade 0

who were admitted to Fujieda Municipal General Hospital between April 2009 and March 2020, 279 were included in the present study (Figure). Slow-flow/no-reflow was observed in 31 patients (11%). Patient characteristics in slow-flow/no-reflow and normal-flow groups are presented in Table 1. Compared with patients in the normal-flow group,

those in the slow-flow/no-reflow group were older, had a lower systolic blood pressure (SBP) at admission, and had a higher percentage of previous cerebrovascular disease and insulin use (**Table 1**). The time from onset to recanalization was comparable between the 2 groups, but the percentage of patients in whom the time from onset to reperfusion was >4 h was higher in the slow-flow/no-reflow than normal-flow group (**Table 1**). eGFR was significantly lower in the slow-flow/no-reflow than normal-flow group (**Table 1**).

The results of univariate and multivariate logistic regression analyses evaluating the predictors of slow-flow/no-reflow are presented in **Table 2**. Multivariate logistic regression analysis revealed that eGFR, previous cerebrovascular disease, the time from onset to recanalization ≥ 4 h, and SBP ≤ 90 mmHg were independent predictors of slow-flow/no-reflow (**Table 2**).

Of the 248 patients in the normal-flow group, low STR (i.e., STR <50%) was observed in 102 (41%). **Table 3** shows patient characteristics in the high- and low-STR groups. Compared with the high-STR group, patients in the low-

STR group were older, had lower hemoglobin and eGFR values, and had higher B-type natriuretic peptide (BNP) concentrations (**Table 3**). Regarding the location of culprit lesions, the left descending artery was significantly the most frequently affected among the 3 vessels (**Table 3**).

Table 4 provides results of univariate and multivariate logistic regression analyses used to identify the predictors of low STR. Multivariate logistic regression analysis revealed that eGFR and involvement of the left anterior descending artery were independent predictors of low STR (**Table 4**). eGFR was the only predictor common to both slow-flow/no-reflow and impaired STR.

Discussion

The present study demonstrated that eGFR was the sole predictor of both slow-flow/no-reflow and low STR after pPCI for STEMI of initial TIMI Grade 0 on admission. Both the lack of reflow and the impairment of STR are well-established parameters for evaluating coronary microvascular dysfunction and obstruction. TIMI Grades 0–3

	STR $\geq 50\%$ (n=146)	STR <50% (n=102)	P value
Age (years)	64 [56–73]	70 [61–78]	<0.001
Male sex	122 (84)	75 (74)	0.054
SBP (mmHg)	137 [113–154]	133 [115–154]	0.94
DBP (mmHg)	82 [69–94]	86 [70–98]	0.36
SBP ≤ 90 mmHg	13 (8.9)	4 (3.9)	0.13
NYHA classification			0.06
I	127 (87)	80 (78)	
II	7 (4.8)	5 (4.9)	
III	0 (0)	4 (3.9)	
IV	12 (8.2)	13 (13)	
NYHA classification $\geq$ II	19 (13)	22 (22)	0.07
BMI (kg/m ²)	23.4 [21.5–25.9]	23.6 [21.3–24.9]	0.42
Hypertension	108 (74)	83 (81)	0.17
Diabetes	44 (30)	33 (32)	0.71
History of cerebrovascular disease	6 (4.1)	6 (5.9)	0.52
Primary Vt	2 (1.4)	4 (3.9)	0.2
Smoking status			0.01
Current smoker	75 (51)	33 (32)	
Ex smoker	33 (23)	29 (28)	
Never smoked	38 (26)	40 (39)	
WBC ($\times 1,000/\mu\text{g}$)	9.6 [8.2–12.1]	9.1 [7.9–11.4]	0.25
Neutrophils ($\times 1,000/\mu\text{g}$)	6.3 [4.1–8.8]	6.1 [3.9–7.9]	0.15
Lymphocytes ($\times 1,000/\mu\text{g}$)	2.4 [1.5–3.8]	2.6 [1.7–3.8]	0.51
NLR	2.8 [1.2–5.7]	2.3 [1.3–4.3]	0.28
Hb (g/dL)	14.7 [13.5–15.8]	14.0 [12.8–15.4]	0.03
RDW-SD (fL)	42.9 [41.3–44.6]	43.7 [41.2–45.4]	0.23
RDW-CV (%)	13.1 [12.6–13.7]	13.1 [12.8–13.4]	0.86
Platelets ($\times 1,000/\mu\text{g}$)	222 [190–258]	204 [177–249]	0.051
PDW (fL)	11.3 [10.3–12.5]	11.4 [10.5–12.4]	0.56
MPV (fL)	10.1 [9.6–10.7]	10.1 [9.7–10.7]	0.57
TG (mg/dL)	82 [51–133]	79 [49–123]	0.48
HDL-C (mg/dL)	47 [42–58]	47 [40–56]	0.69
LDL-C (mg/dL)	124 [99–142]	123 [97–143]	0.76

(Table 3 continued the next page.)

	STR ≥50% (n=146)	STR <50% (n=102)	P value
HbA1c (%)	5.7 [5.4–6.3]	5.9 [5.6–6.5]	0.07
Glucose (mg/dL)	156 [137–189]	162 [138–227]	0.28
BNP (pg/mL)	28 [12–93]	57 [22–145]	<0.001
eGFR (mL/min/1.73 m ²)	77.3 [63.9–89.1]	58.9 [49.6–70.5]	<0.001
Medication on admission			
Prasugrel (20 mg loading)	54 (37)	38 (37)	0.97
Clopidogrel (300 mg loading)	90 (62)	62 (61)	0.89
ACEI	3 (2.1)	1 (1)	0.51
ARB	18 (12)	22 (22)	0.052
β-blockers	2 (1.4)	9 (8.8)	0.005
Calcium channel blockers	32 (22)	33 (32)	0.07
Statin	19 (13)	10 (10)	0.44
Insulin	2 (1.4)	2 (2)	0.72
Culprit lesion			
LAD	59 (40)	66 (65)	<0.001
RCA	72 (49)	32 (31)	
LCX	15 (10)	4 (3.9)	
Syntax score	10 [9–20]	16.5 [10–18.5]	0.06
Type of stent deployed			
BMS	73 (50)	45 (44)	0.31
DES	73 (50)	57 (56)	0.36
Stent length (mm)	20 [18–24]	22 [18–28]	0.14
Stent diameter (mm)	3 [2.75–3.5]	3 [2.75–3.5]	0.5
Procedural characteristics			
Use of IVUS	71 (49)	61 (60)	0.08
Predilatation using additional balloon	108 (74)	76 (75)	0.92
Post-dilatation using additional balloon	32 (22)	19 (19)	0.53
Temporary pacemaker support	21 (14)	13 (13)	0.71
Use of IABP	24 (16)	19 (19)	0.65
Use of thrombectomy	32 (22)	16 (16)	0.22
Time between 2 ECGs (min)	125 [105–142]	129 [108–152]	0.06
Time from onset to recanalization (min)	191 [145–299]	156 [131–247]	0.046
Time from recanalization to second ECG (min)	49 [38–65]	53 [41–72]	0.09

Unless indicated otherwise, data are presented as the median [interquartile range] or n (%). ECG, electrocardiogram. Other abbreviations as in Table 1.

Table 4. Univariate and Multivariate Logistic Regression Analysis Predicting Low ST Segment Resolution				
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.04 (1.02–1.07)	<0.001	1.00 (0.97–1.03)	0.84
Male sex	0.55 (0.29–1.02)	0.06	0.71 (0.34–1.49)	0.36
Hemoglobin	0.94 (0.87–1.02)	0.15		
eGFR	0.95 (0.94–0.97)	<0.001	0.94 (0.93–0.96)	<0.001
BNP pg/mL >18.4	2.33 (1.32–4.12)	0.004	1.93 (0.97–3.83)	0.06
LAD	2.7 (1.6–4.56)	<0.001	4.48 (2.36–8.51)	<0.001

Abbreviations as in Tables 1,2.

refer to levels of coronary blood flow assessed during percutaneous coronary angioplasty. TIMI Grade 0 refers to the absence of any antegrade flow beyond a coronary occlusion; therefore, the decision to use TIMI Grade 0 is the easiest and most appropriate among TIMI Grades 0, 1, 2, and 3. Therefore, only patients with TIMI Grade 0 were included in the present study.

STR is a non-invasive, widely available, inexpensive, and powerful prognostic tool for AMI.⁹ When STR is used to assess microvascular dysfunction and obstruction, there are 3 issues to be considered: (1) the method used to determine STR; (2) the degree of STR; and (3) the timing of ECG measurement. Generally, there are 2 different ways to determine STR. One is the sum of ST segment elevation

(sum STR), which is measured by comparing all leads related to infarct location after reperfusion therapy to the ECG at baseline; the other methods involves comparing 1 ECG lead with the most prominent ST segment deviation at baseline.⁹ In most studies, sum STR after reperfusion therapy has been used to predict infarct size, left ventricular function, epicardial vessel patency, and mortality.^{6,11,12} However, measuring ST segment elevations from all leads related to infarct location is time consuming. Furthermore, the assessment of a single-lead STR showing maximum ST elevation at baseline seems to be as accurate as sum STR measurements.¹³ Therefore, single-lead STR was used in the present study. Regarding the degree of STR, 2 different methods have been proposed to measure STR; STR <50% or 70% is considered an established marker of impaired STR because its predictive value was demonstrated at the start of the pharmacological reperfusion era and has been confirmed in the contemporary mechanical reperfusion era.⁹ Because we wanted to assess STR more simply, the binary method for STR (i.e., STR <50% vs. ≥50%) was used. Regarding the timing of ECG recording, ECGs in most studies were performed at 60 or 90 min or 3 h after thrombotic and pPCI.^{14–16} In the present study, an ECG was performed as soon as the patient was admitted to the intensive care unit after pPCI, and there was no differences between the 2 groups (i.e., STR <50% vs. ≥50%) in the time between coronary recanalization and the second ECG measurement (**Table 3**). STR was assessed only in the normal-flow group because STR in the slow-flow/no-reflow group was thought to be obviously low. In order to specifically clarify the predictors of slow-flow/no-reflow and low STR (i.e., the predictors of coronary microvascular dysfunction and obstruction), 2 different methods were used.

In the present study, renal dysfunction was demonstrated to be a predictor of coronary microvascular dysfunction and obstruction in patients with STEMI treated with pPCI. The pathophysiology of slow-flow/no-reflow has not been fully elucidated yet, but several studies have summarized the complex mechanisms responsible for coronary microvascular dysfunction and obstruction in AMI.^{17–19} Chronic kidney disease (CKD) is a major risk factor for worse cardiovascular outcomes.²⁰ Kurtul et al studied the predictors of no reflow in 3 groups according to eGFR.²¹ In that study, eGFR was also an independent factor for no reflow.²¹ Conversely, the relationship between CKD and STR remains unclear. From a pathological point of view, CKD may be related to coronary microvascular dysfunction and obstruction in 3 respects: pre-existing coronary microvascular dysfunction, differential leukocyte count, and platelet activity.

There are 2 invasive techniques for the evaluation of coronary microvascular function, namely Doppler flow wire-derived coronary flow reserve (CFR) and pressure wire-derived index of microcirculatory resistance (IMR). Coronary blood flow normally increases automatically from the resting to peak level in response to an increase in myocardial oxygen demand.²² Such a change in coronary blood flow is regarded as CFR. Several studies have demonstrated that CFR is significantly associated with renal dysfunction; that is, reduced renal function is associated with attenuated coronary vasodilator capacity in patients without obstructive coronary artery disease.^{23–25}

Leukocytosis (and increased differential counts) is a hallmark of the inflammatory process and is closely associ-

ated with cardiovascular risk.²⁶ The neutrophil/lymphocyte ratio (NLR), which is derived from the leukocyte count, has been investigated with regard to cardiovascular risk and was found to be an important marker of inflammation.^{27–29} A previous study reported that the NLR was associated with an increased mortality rate and poor prognosis in acute coronary syndrome, especially when ST segment elevation is present.³⁰ Furthermore, Machado et al demonstrated that a high NLR on admission was an independent predictor of no reflow after pPCI in patients with STEMI.³¹ Surprisingly, Sevcenkan et al demonstrated that the NLR was higher in patients with Stage 3 CKD than in those with Stage 1 or 2 CKD.³² In the present study, there was no difference in the NLR between the slow-flow/no-reflow and normal flow groups.

Platelets play an important role in the pathophysiology of coronary artery disease.³³ Currently, it is assumed that platelet size is a sensitive indicator of their reactivity.³⁴ Mean platelet volume (MPV) is a marker of platelet activation, and an elevated preprocedural MPV is associated with increased mortality in STEMI patients who have undergone pPCI.³⁵ Machado et al also demonstrated that high MPV on admission was an independent predictor of no reflow after pPCI in patients with STEMI.³¹ Moreover, Verdoia et al demonstrated that CKD patients had a significantly larger platelet volume, and observed a weak positive inverse association between MPV and the decay of renal function (as eGFR).³⁶ Renal impairment may cause platelet activation and increase coagulability, leading to the slow-flow/no-reflow phenomenon. In the present study there were no differences in MPV and NLR between the slow-flow/no-reflow and normal-flow groups.

Finally, CKD has been considered to be related to slow-flow/no-reflow from the viewpoint of diagnostic imaging, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Soeda et al showed that the morphological predictors for no reflow after pPCI in patients with STEMI are caused by plaque rupture.³⁷ In addition, they showed that a larger lipid index (calculated as the average of lipid arc multiplied by lipid length) derived from OCT and the plaque burden derived from IVUS were critical morphological discriminators between no reflow and normal flow.³⁷ Importantly, it was demonstrated that non-culprit plaques had a larger lipid index in patients with than without CKD.³⁸ Moreover, it was demonstrated that non-culprit lesions had a greater plaque burden in patients with than without CKD.³⁹

Study Limitations

This study has several limitations. First, because the measurement of eGFR was based on the serum Cr value on admission, this assessment may be affected by hemodynamic instability in some patients. Second, angiographic assessments, such as the myocardial blush and TIMI frame count, were not used. Although the conventional TIMI grade classification has played a major role in comparing angiographic and clinical outcomes following STEMI, the quality and magnitude of such assessments are limited. Third, the time between reperfusion and the second ECG measurement was different in all patients, although the time did not differ significantly between the low- and high-STR groups. Fourth, proteinuria was not determined in all patients in this study even though the classification of the severity of renal failure is based on eGFR and proteinuria determination.

Conclusions

This study showed that CKD is a predictor of slow-flow/no-reflow and impaired STR after PCI in STEMI. Renal dysfunction may be one of the risk factors for coronary microvascular dysfunction and obstruction.

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Disclosures

The authors have no conflicts of interest directly relevant to the content of this article.

IRB Information

This study was approved by the Ethics Committee of Fujieda Municipal General Hospital (No. R02-08).

Data Availability

The deidentified participant data will not be shared.

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