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Long-Term Clinical Outcomes of Transient and Persistent No Reflow Phenomena following Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction

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Background and Objectives: There is limited information on the transient or persistent no reflow phenomenon in patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI).
Subjects and Methods: The study analyzed 4329 patients with AMI from a Korean multicenter registry who underwent PCI using coronary stents (2668 ST-elevation and 1661 non-ST-elevation myocardial infarction [MI] patients): 4071 patients without any no reflow, 213 with transient no reflow (no reflow with final thrombolysis in myocardial infarction [TIMI] flow grade 3), and 45 with persistent no reflow (no reflow with final TIMI flow grade≤2). The primary endpoint was all-cause mortality during 3-year follow-up. We also analyzed the incidence of cardiac mortality, non-fatal MI, re-hospitalization due to heart failure, target vessel revascularization, and stent thrombosis.
Results: The persistent no reflow group was associated with higher all-cause mortality (hazard ratio [HR] 1.98, 95% confidence interval [CI] 1.08-3.65, p=0.028) and cardiac mortality (HR 3.28, 95% CI 1.54-6.95, p=0.002) compared with the normal reflow group. Transient no reflow increased all-cause mortality only when compared with normal reflow group (HR 1.58, 95% CI 1.11-2.24, p=0.010). When comparing transient and persistent no reflow, persistent no reflow was associated with increased all-cause mortality (46.7 vs. 24.4%, log rank p=0.033).
Conclusion: The persistent no reflow phenomenon was associated with a poor in-hospital outcome and increased long-term mortality mainly driven by increased cardiac mortality compared to the transient no reflow phenomenon or normal reflow. **(Korean Circ J 2016;46(4):490-498)**

KEY WORDS: Myocardial infarction; No-reflow phenomenon; Percutaneous coronary interventions.

Introduction

The no reflow phenomenon is a serious complication following percutaneous coronary intervention (PCI). It is defined as a state of myocardial hypoperfusion in the presence of a patent epicardial coronary artery.[1)2)] No reflow negatively affects the clinical outcome in patients with acute myocardial infarction (AMI),[3-6)] and it is associated mainly with increased mortality or left ventricular remodeling, despite its relatively low incidence.[7)]

The pathomechanism of no reflow includes ischemia-reperfusion injury, myocardial edema, endothelial swelling, capillary obstruction, vasospasm, inflammatory response, and distal coronary embolization.[1)] Although interventional cardiologists try to overcome no reflow using

various methods and drugs,[2] persistent no reflow often remains despite adequate revascularization of coronary stenosis. However, few studies have described the incidence and prognosis of transient or persistent no reflows in patients with AMI.[8-11] Furthermore, no studies have examined the long-term clinical outcomes according to the persistence of no reflow.

Therefore, this study investigated the incidence of transient or persistent no reflow during PCI, its clinical and angiographic characteristics, and the long-term clinical outcomes in patients with AMI based on a Korean multicenter registry.

Subjects and Methods

Study population

The Convergent Registry of Catholic and Chonnam University for AMI (COREA-AMI) is a Korean prospective, multicenter, observational registry that was designed to reflect real-world practice in Korean AMI patients at nine centers with facilities for primary PCI, representing two universities, between January 2004 and December 2009. Of the 4748 patients in the COREA-AMI registry, 4329 who underwent PCI with coronary stents were analyzed. We excluded 419 patients, including 184, 17, and 97 patients without any no reflow who achieved post-procedural thrombolysis in myocardial infarction (TIMI) flow grades 0, 1, or 2, respectively, 28 patients who did not have coronary stents implanted, and 93 patients with insufficient data. The remaining subjects were divided into three groups according to the presence of no reflow and post-procedural TIMI flow grade: the normal reflow group was defined as patients without any no reflow who achieved final TIMI flow grade 3 (n=4071); the transient no reflow group was defined as patients having no reflow during PCI who achieved final TIMI flow grade 3 after adequate management of the no reflow (n=213, 4.9% of all patients); and the persistent no reflow group was defined as patients having no reflow whose final TIMI flow grade was ≤2 despite of management for no reflow (n=45, 1.0% of all patients). The no reflow phenomenon was defined as the disruption of coronary flow distal to a treatment segment following initial procedure despite patency of the epicardial coronary arteries after PCI. An operator at each center confirmed no reflow during PCI. Patients with vasospasm, distal embolism or coronary dissection were excluded. The ethics committee of each participating hospital approved the study protocol, and all patients provided written informed consent.

Study definitions and outcomes

The patients' demographics, vital signs on admission, and medical history were compared among groups. A history of renal insufficiency included a history of chronic kidney disease and patients receiving chronic dialysis. The diagnosis of ST-segment elevation myocardial infarction (STEMI) was based on ST-segment elevation>2 mm in at least two precordial leads, ST-segment elevation>1 mm in at least two limb leads, or new left bundle branch block on a 12-lead electrocardiogram in the infarct-related artery distribution, as determined by coronary angiography with increased cardiac-specific biomarkers. All laboratory findings were performed upon admission, except for lipid profiles, which were obtained after at least 9 hours of fasting within 24 hours of hospitalization. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease study equation.[12] Baseline left ventricular ejection fraction was determined using two-dimensional echocardiography performed before or after PCI.

Multi-vessel coronary artery disease was defined as significant stenosis (disease stenosis≥70%) of more than one epicardial coronary artery, including the culprit artery. The coronary blood flow before and after PCI was classified using the TIMI score, and coronary lesion complexity was based on the American College of Cardiology (ACC)/ American Heart Association (AHA) definitions.[13][14] Patients who underwent PCI were given 300 mg aspirin and 600 mg clopidogrel as a loading dose before PCI. Doses of 50-70 U/kg of unfractionated heparin were used before or during PCI to maintain the activated clotting time at 250-300 seconds. Low-molecular-weight heparin, drug-eluting stent implantation, and the overlapping stent technique were used at the discretion of the clinician. Thrombus aspiration or use of a glycoprotein IIb/IIIa inhibitor in patients with large thrombotic burdens and insertion of an intra-aortic balloon pump in patients with cardiogenic shock were also performed at the discretion of the interventional cardiologists. After PCI, 100-300 mg aspirin and 75 mg clopidogrel were prescribed daily.

The follow-up duration was 3-years after AMI. While the primary endpoint was all-cause mortality, we also evaluated the incidence of cardiac mortality, re-hospitalization due to congestive heart failure (CHF), non-fatal myocardial infarction (MI), target vessel revascularization, and stent thrombosis. Cardiac mortality was registered when a definite cardiac cause was identified; other causes of mortality were considered non-cardiac mortality. Non-fatal recurrent MI was defined as the development of recurrent angina symptoms with new 12-lead electrocardiographic changes or increased cardiac specific biomarkers. Target vessel revascularization was defined as repeated PCI for any segment of the entire coronary artery, including the segments treated using coronary stents, and stent thrombosis was defined as definite and probable stent thrombosis, according to the Academic Research Consortium definition.[15]

Table 1. Baseline characteristics

	Normal reflow (n=4071)	Transient no reflow (n=213)	Persistent no reflow (n=45)	p*	p†
Baseline clinical characteristics					
Age (years)	62.4±12.5	64.6±13.2	67.2±12.5	0.002	0.210
Male	2922 (71.8)	149 (70.0)	28 (62.2)	0.171	0.310
Systolic blood pressure (mmHg)	129.1±30.3	125.9±28.9	111.9±44.9	<0.001	0.008
Diastolic blood pressure (mmHg)	79.2±18.7	78.3±18.2	70.3±28.3	0.006	0.017
Heart rate (/min)	76.1±19.9	74.2±16.5	72.1±25.3	0.172	0.485
Current or ex-smoke	2379 (58.4)	118 (55.4)	28 (62.2)	0.774	0.401
Atrial fibrillation	166 (4.1)	6 (2.8)	3 (6.7)	0.945	0.201
Hypertension	2023 (49.7)	111 (52.1)	28 (62.2)	0.104	0.216
Diabetes mellitus	1290 (31.7)	51 (23.9)	18 (40.0)	0.364	0.027
Familial history of coronary artery disease	220 (5.4)	15 (7.0)	2 (4.4)	0.582	0.523
Renal insufficiency	166 (4.1)	6 (2.8)	1 (2.2)	0.277	0.823
Cerebrovascular accident	182 (4.5)	7 (3.3)	1 (2.2)	0.277	0.708
Previous myocardial infarction	146 (3.6)	6 (2.8)	1 (2.2)	0.447	0.823
Previous percutaneous coronary intervention	159 (3.9)	7 (3.3)	2 (4.4)	0.839	0.700
ST-segment elevation myocardial infarction	2493 (61.2)	136 (63.8)	39 (86.7)	0.004	0.003
Killip class≥3	453 (11.1)	24 (11.3)	9 (20.0)	0.192	0.111
Left ventricular ejection fraction (%)	54.0±11.7	53.1±11.7	47.0±14.6	0.001	0.019
Laboratory findings					
Estimated glomerular filtration rate (ml/min)	82.2±35.5	81.3±37.2	77.2±38.1	0.602	0.519
Peak troponin-I (mg/dL)	43.9±79.5	55.7±70.6	51.1±45.8	0.107	0.606
Peak creatine kinase (mg/dL)	1575.3±2326.3	1729.5±1856.6	2263.1±2434.7	0.107	0.186
Peak CK-MB (mg/dL)	103.1±134.7	135.8±179.9	137.0±137.1	0.001	0.957
Total cholesterol (mg/dL)	181.7±41.4	179.9±39.6	164.8±41.6	0.037	0.043
Triglyceride (mg/dL)	123.9±90.8	116.8±88.1	110.1±64.1	0.361	0.579
HDL-C (mg/dL)	1575.3±2326.3	1729.5±1856.6	2263.1±2434.7	0.048	0.358
LDL-C (mg/dL)	116.6±36.5	116.4±33.5	102.1±34.8	0.051	0.023
Serum glucose (mg/dL)	173.0±82.4	163.9±67.9	204.5±105.8	0.015	0.002
N-terminal pro-BNP (pg/mL)	2685.9±6120.2	3433.1±6752.7	4958.9±8078.6	0.041	0.322
High sensitivity C-reactive protein (mg/L)	1575.3±2326.3	1729.5±1856.6	2263.1±2434.7	<0.001	0.024
Medication history (at discharge time)					
Aspirin	4057 (99.7)	212 (99.5)	44 (97.8)	0.108	0.319
Clopidogrel	4048 (99.4)	211 (99.1)	43 (95.6)	0.082	0.142
Cilostazol (triple antiplatelet therapy)	1976 (48.5)	93 (43.7)	14 (31.1)	0.010	0.120
Statin	3496 (85.9)	179 (84.0)	33 (73.3)	0.032	0.088
Beta blocker	3118 (76.6)	161 (75.6)	18 (40.0)	<0.001	<0.001
ACE inhibitor or ARB	3139 (77.1)	173 (81.2)	24 (53.3)	0.123	<0.001

Data are expressed as mean±standard deviation or number (percentage). *p for trend, which compared patients with normal reflow, transient no reflow, and persistent no reflow. †p, which compared patients with transient no reflow and persistent no reflow. HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, CK-MB: creatine kinase-myocardial band isoenzyme, BNP: brain-type natriuretic peptide, ACE: angiotensin-converting enzyme, ARB: angiotensin-II receptor blocker

Statistical analysis

Continuous variables are presented as the means±standard deviations and were compared using the Student's t-test or Mann-Whitney U-test. Comparisons among the three groups were performed using one-way analysis of variance. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test to determine the significance of differences. The 3-year mortality was estimated by the Kaplan-Meier method, and curves were compared with the log-rank test. Cox-regression analysis was done to compare study outcomes between normal reflow and transient or persistent no reflow after adjusting confounding variables which were known to be associated with the study outcomes. Logistic regression analysis was performed to evaluate independent predictors of transient or persistent no reflow. Among variables predicting no reflow, clinically relevant variables with marginal significance (defined as p<0.2) in the univariate analysis were entered into multivariate models to determine predictors of transient and persistent no reflow.

All analyses were two-tailed, and all variables were considered significant when p<0.05. Statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics

The persistent no reflow group had more STEMI patients and a lower admission blood pressure than did the other groups. The medical histories and proportions of male patients and those with a higher Killip class (≥3) were comparable among groups. The levels of creatine kinase-myocardial band isoenzyme, high density lipoprotein-cholesterol, and N-terminal pro-brain type natriuretic peptide and the prescription rates of triple antiplatelet agents and statins were higher in the no reflow group, but there was no difference between the transient and persistent no reflow groups. The persistent no reflow group had lower levels of total cholesterol,

Table 2. Angiographic and procedural characteristics

	Normal reflow (n=4071)	Transient no reflow (n=213)	Persistent no reflow (n=45)	p*	p†
Infarct-related coronary artery					
Left-anterior descending	1951 (47.9)	86 (40.4)	21 (46.7)	0.096	0.436
Right	1357 (33.3)	90 (42.3)	19 (42.2)	0.005	0.997
Left circumflex	670 (16.5)	32 (15.0)	2 (4.4)	0.062	0.057
Left main	80 (2.0)	5 (2.3)	3 (6.7)	0.075	0.129
Multivessel disease	2087 (51.3)	122 (57.3)	28 (62.2)	0.026	0.541
ACC/AHA B2/C lesion	3190 (78.4)	184 (86.4)	40 (88.9)	0.001	0.652
Pre-procedural TIMI flow grade					
0	1577 (38.7)	111 (52.1)	36 (80.0)	<0.001	0.001
1	253 (6.2)	9 (4.2)	2 (4.4)	0.235	0.947
2	872 (21.4)	41 (19.2)	4 (8.9)	0.054	0.096
3	1275 (31.3)	45 (21.1)	3 (6.7)	<0.001	0.024
Drug-eluting stent implantation	3675 (90.3)	174 (81.7)	41 (91.1)	0.005	0.123
Total no. of stents	1.6±0.9	1.7±0.9	1.4±0.7	0.101	0.031
Total stent length (mm)	37.6±23.5	39.7±24.7	33.7±20.2	0.239	0.096
Mean stent diameter (mm)	3.2±0.4	3.3±0.4	3.2±0.5	<0.001	0.080
Stent overlapping	329 (8.1)	17 (8.0)	3 (6.7)	0.786	0.764
Thrombus aspiration	169 (4.2)	24 (11.3)	9 (20.0)	<0.001	0.111
Intra-aortic balloon counterpulsation	214 (5.3)	27 (12.7)	10 (22.2)	<0.001	0.097
Use of glycoprotein IIb/IIIa inhibitor	718 (17.6)	105 (49.3)	23 (51.1)	<0.001	0.825
Use of inotropics	765 (18.8)	53 (24.9)	22 (48.9)	<0.001	0.001

Data are expressed as mean±standard deviation or number (percentage). *p for trend, which compared patients with normal reflow, transient no reflow, and persistent no reflow. †p, which compared patients with transient no reflow and persistent no reflow. ACC: American college of cardiology, AHA: American heart association, TIMI: thrombolysis in myocardial infarction

serum glucose, low-density lipoprotein-cholesterol, left ventricular ejection fraction, and were more likely to include patients who were prescribed a beta blocker and angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker (Table 1).

Coronary angiographic and procedural characteristics

Table 2 summarizes the coronary angiographic and procedural findings. The prevalence of multi-vessel disease, B2 or C coronary lesion, and mean stent diameter were higher in the no reflow group than in the normal reflow group. The no reflow group also experienced more thrombus aspiration and insertion of an intra-aortic balloon pump and received more glycoprotein IIb/IIIa inhibitor during the procedure, while these treatments were similar for the transient and persistent no reflow groups. The persistent no reflow group had more pre-procedural TIMI flow grade 0, but less pre-procedural TIMI flow grade 3. The persistent no reflow group received more inotropics during the procedure. However, similar results were observed among groups for the distribution of the infarct-related artery, total stent length, and rate of patients receiving overlapping stents.

In-hospital outcomes and study endpoints

During the in-hospital stay, the persistent no reflow group experienced more peri-procedural cardiogenic shock and multi-organ failure and had higher in-hospital mortality than did the other groups. The persistent group had poorer outcomes in terms of in-hospital mortality, fatal ventricular arrhythmia, and cardiogenic shock than did the transient no reflow group (Fig. 1).

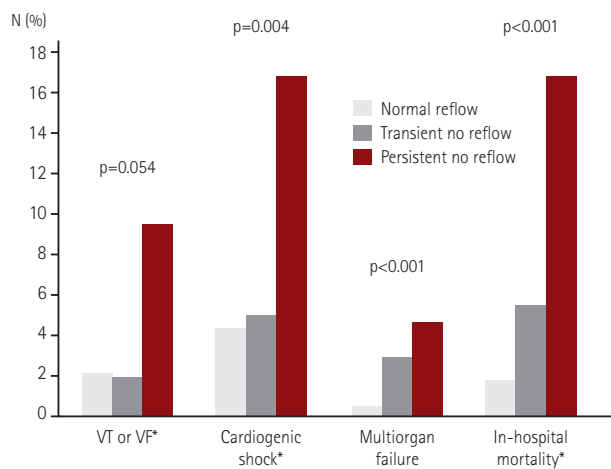The primary endpoint occurred in 811 patients (18.7%) during the

follow-up period. The persistent no reflow group had the highest all-cause (738 [18.1%] vs. 52 [24.4%] vs. 21 patients [46.7%]) and cardiac (321 [7.9%] vs. 28 [13.1%] vs. 18 patients [40.0%]) mortality rates. Between the transient and persistent no reflow groups, the persistent group had higher all-cause mortality (Fig. 2). However, the incidences of secondary endpoints did not differ among the groups (Fig. 3). Table 3 shows the adjusted risks for the study endpoints. Persistent no reflow increased the risks of all-cause mortality (hazard ratio [HR] 1.98, 95% confidence interval [CI] 1.08-3.65, p=0.028), cardiac mortality (HR 3.28, 95% CI 1.54-6.95, p=0.002), and re-hospitalization due to CHF (HR 12.05, 95% CI 4.26-34.14, p<0.001). Transient no reflow was not associated with cardiac
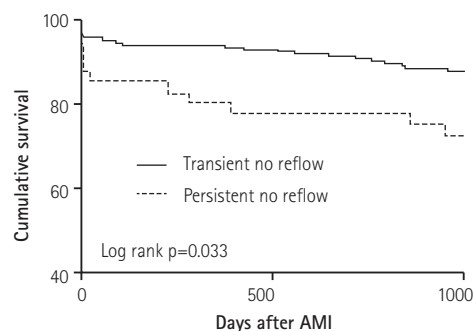
Fig. 2. 3-year all-cause mortality between patients with transient and persistent no reflow. AMI: acute myocardial infarction.

Fig. 1. In-hospital outcomes among normal reflow, transient no reflow, and persistent no reflow groups. Data are presented as a percentage. *p≤0.05, comparison between transient and persistent no reflow groups. VT: ventricular tachycardia, VF: ventricular fibrillation.
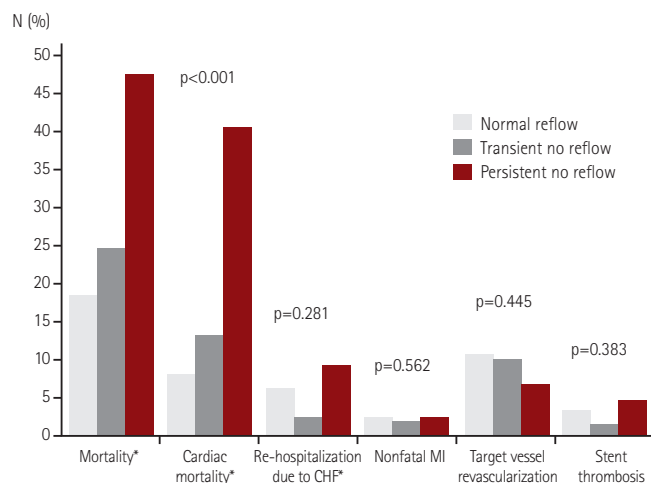
Fig. 3. Clinical outcomes among normal reflow, transient no reflow, and persistent no reflow groups during follow-up period. *p≤0.05, comparison between transient and persistent no reflow group. Data are presented as percentages. CHF: congestive heart failure, MI: myocardial infarction.

mortality (HR 1.45, 95% CI 0.84-2.49, p=0.186), but was associated with all-cause mortality (HR 1.58, 95% CI 1.11-2.24, p=0.010), compared to the normal reflow group. Neither the transient nor the persistent no reflow group had an increased risk of non-fatal MI, target vessel revascularization, or stent thrombosis. However, the risk of early stent thrombosis (within 30 days after PCI) was higher in the persistent no reflow group.

Independent predictors of no reflow phenomenon

To determine independent predictors of no reflow, logistic regression analysis was performed (Table 4). Among variables predicting no reflow phenomenon, variables with p≤0.2 in the univariate model (except for use of glycoprotein IIb/IIIa inhibitor and thrombus aspiration which might be associated with management for no reflow) were tested to identify predictors of both transient and persistent no reflow in the multivariate analysis. The result determined that old age, multi-vessel disease, B2 or C lesion, and stent diameter were all related to the development of transient no reflow. However, only old age and pre-procedural TIMI 0 were predictors of persistent no reflow.

Table 3. Risks for study outcomes in patients with transient or persistent no reflow

	Normal eflow (reference)	Transient no reflow		p	Persistent no reflow		p
		HR	95% CI		HR	95% CI	
Mortality from any cause	1	1.58	1.11-2.24	0.010	1.98	1.08-3.65	0.028
Cardiac mortality	1	1.45	0.84-2.49	0.186	3.28	1.54-6.95	0.002
Re-hospitalization due to CHF	1	0.92	0.38-2.22	0.846	12.05	4.26-34.14	<0.001
Non-fatal myocardial infarction	1	0.56	0.17-1.83	0.334	0.83	0.45-1.51	0.537
Target vessel revascularization	1	0.78	0.46-1.32	0.351	1.21	0.38-3.83	0.747
Stent thrombosis	1	0.27	0.06-1.09	0.067	1.78	0.43-7.48	0.429
Early stent thrombosis	1	0.38	0.05-2.94	0.354	5.19	1.10-24.46	0.037

HR: hazard ratio, CI: confidence interval, CHF: congestive heart failure

Table 4. Predictors of transient or persistent no reflow during percutaneous coronary intervention

	No reflow		p	Transient no reflow		p	Persistent no reflow		p
	OR	95% CI		OR	95% CI		OR	95% CI	
Age≥65	1.42	1.10-1.83	0.007	1.34	1.02-1.77	0.039	1.83	1.05-3.29	0.025
Diabetes mellitus	0.71	0.48-1.05	0.087	0.74	0.52-1.06	0.101	1.85	0.87-3.89	0.108
History of coronary artery bypass graft	3.17	0.58-17.21	0.182	0.96	0.12-7.89	0.968	6.33	0.69-58.04	0.102
ST-segment elevation myocardial infarction	1.11	0.78-1.58	0.575						
Multivessel disease	1.69	1.19-2.42	0.003	1.35	1.01-1.80	0.044	1.41	0.76-2.62	0.273
LAD as a culprit artery	1.09	0.67-1.81	0.716						
RCA as a culprit artery	1.22	0.74-2.02	0.433						
ACC/AHA B2/C coronary lesion	2.45	1.47-4.08	0.001	1.88	1.25-2.82	0.002	2.12	0.83-5.43	0.117
Pre-procedural TIMI flow grade 0	1.36	0.89-2.08	0.150	1.08	0.78-1.50	0.647	3.18	1.34-7.58	0.009
Pre-procedural TIMI flow grade 3	1.19	0.71-2.01	0.494						
Use of glycoprotein IIb/IIIa inhibitor	3.34	2.30-4.83	<0.001						
Thrombus aspiration	2.75	1.68-4.51	<0.001						
Use of intra-aortic balloon counterpulsation	1.13	0.64-1.99	0.685						
Drug-eluting stent implantation	1.26	0.81-1.95	0.301						
Stent diameter per mm increase	1.76	1.13-2.72	0.012	1.89	1.34-2.65	<0.001	0.80	1.75-8.27	0.581
Peri-procedural shock	0.66	0.31-1.44	0.301						
Left ventricular ejection fraction ≤ 40%	1.45	0.93-2.26	0.103	1.23	0.74-1.71	0.580	1.89	0.82-4.36	0.138

OR: odds ratio, CI: confidence interval, LAD: left-anterior descending coronary artery, RCA: right coronary artery, ACC: American college of cardiology, AHA: American heart association, TIMI: thrombolysis in myocardial infarction

Discussion

This study investigated the long-term clinical outcomes of transient or persistent no reflow in patients with AMI who underwent PCI. The principal findings of our study were that poor in-hospital and long-term outcomes were associated with persistent no reflow during PCI compared to patients with normal reflow or transient no reflow despite its low incidence. However, the transient no reflow group had lower reduced all-cause mortality only, not cardiac mortality, compared to the normal reflow group.

In this study, the incidence of the no reflow phenomenon in AMI was similar to that in a large population study.[7] However, the majority of the no reflow cases was transient no reflow. The published incidence of persistent no reflow is 0.7-2.0%,[8)9)16] which is comparable to our series. Several studies have investigated the impact of transient or persistent no reflow in AMI populations.[8)10] Mehta et al.[8] reported a low incidence of transient no reflow (1.3%) in patients with STEMI who underwent primary PCI. Patients with transient no reflow had higher in-hospital (2 vs. 13%, p=0.04) mortality compared to those with normal reflow. Data from the Melbourne Interventional Group (MIG) compared the clinical outcomes among normal reflow and transient and persistent no reflow patients undergoing PCI. Interestingly, transient or persistent no reflow increased the target vessel failure as well as mortality at the 30-day follow-up.[10] Other small single-center studies reported higher short-term mortality in the persistent no reflow groups.[9)11] However, few studies have compared transient and persistent no reflow in patients with AMI over the long-term.

In our study, the in-hospital and long-term mortalities were higher in the persistent no reflow group. Based on the result of 30-day mortality among groups (2.5 vs. 5.2 vs. 22.2%, p<0.001, data not shown), higher long-term mortality in the persistent no reflow group might be due to higher early mortality. Unlike other studies, transient no reflow was only associated with increased all-cause mortality in our study, not cardiac mortality. A previous study reported higher short-term all-cause or cardiac mortality in the transient no reflow group than in a normal reflow group.[10] This landmark analysis showed that the transient group was associated with more in-hospital adverse cardiac events such as contrast-induced acute kidney injury, peri-procedural MI, and in-hospital mortality. In the present study, in-hospital outcomes were the same for patients with normal reflow and transient no reflow except for higher in-hospital mortality in the transient group. These differences of in-hospital outcomes might be associated with similar cardiac mortality between the normal and transient no reflow groups in our study. Furthermore, the comparison of long-term mortality between the two groups was not evaluated

in prior studies. The difference in the repeat target vessel PCI outcome between our study and the prior report might result from a lower implantation rate of coronary stents, longer mean length of the implanted stents, or higher incidence of bifurcation lesions in the persistent no reflow group of the MIG study.[10] The above-mentioned factors are all associated with repeat target vessel revascularization.[17-19] Notably, our study showed that persistent no reflow increased the risk of early stent thrombosis compared with normal or transient no reflow. Brodie et al.[20] evaluated predictors of early stent thrombosis and found that STEMI, small stent size, Killip class III or IV, and reperfusion time≤2 hours were all associated with the development of early stent thrombosis. In our study, the persistent no reflow group also had a higher prevalence of STEMI and higher Killip class, and these factors might increase the risk of early stent thrombosis. Although other factors related to early stent thrombosis were similar to prior reports, the reason for the correlation of shorter reperfusion time to early stent thrombosis is uncertain. Further research is needed to confirm the relation between persistent no reflow and early stent thrombosis.

Studies have established clinical and angiographic factors that predict the no reflow phenomenon in patients with acute coronary syndrome. The clinical predictors include initial shock, age, STEMI diagnosis, longer symptoms-to-admission time, and higher level of N-terminal pro brain-type natriuretic peptide.[7)21)22] The angiographic factors include a complex coronary lesion based on the ACC/AHA definition, lesion length, use of a glycoprotein IIb/IIIa inhibitor during PCI, pre-procedural TIMI flow grade 0, bifurcation lesion, coronary anatomical scoring system, amount of attenuated plaque, larger necrotic core, and more thin-cap fibroatheroma on intravascular ultrasound.[7)10)23-25] In our patients, similar factors were associated with the development of no reflow. However, few studies have analyzed the predictors of transient and persistent no reflow. In our series, several factors predicted transient no reflow: old age, multi-vessel disease, complex coronary lesion, and stent diameter. In comparison, only old age and pre-procedural TIMI flow 0 predicted the development of persistent no reflow. This suggests that there is a relationship between pre-procedural TIMI flow grade and persistent no reflow, consistent with a prior report.[26]

There are several limitations to our study. Despite its prospective, consecutive data collection, this was a non-randomized retrospective analysis which resulted in differences in the baseline clinical and angiographic findings among groups. This study also used a small number of patients with persistent no reflow. Although we performed Cox-regression analysis adjusting 5 variables (age, STEMI diagnosis, Killip class≥3, left ventricular ejection fraction and multivessel disease) to avoid overfitting, the small number of patients in the persistent no reflow group might

be related to overfitting in the multivariate analysis. In addition, no information on the use of intracoronary agents to reverse no reflow was available because our registry does not contain this data. Furthermore, confirmation of no reflow might vary among the interventional cardiologists at each participating center, because there is no verification of catheterization laboratory data at every center. Although several studies reported on the importance of a core laboratory to verify coronary flow,[27)28)] angiographic reperfusion assessment by both an operator and a core laboratory correlated with survival.[29)] Finally, our registry does not include detailed information on coronary lesion anatomy. Although previous studies identified several coronary anatomy factors related to no reflow, our study was limited in the ability to analyze this association.

In conclusion, this study determined that persistent no reflow in patients with AMI who underwent PCI with coronary stents was associated with poor in-hospital outcomes and increased long-term mortality mainly driven by increased cardiac death despite its low incidence.

Acknowledgments

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