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ORIGINAL ARTICLE

Left circumflex coronary artery is protected against no-reflow phenomenon following percutaneous coronary intervention for coronary artery disease

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Abstract Despite the positive impact of percutaneous coronary intervention (PCI) on reducing mortality, a small percentage of patients experience poor myocardial reperfusion following PCI. However, factors associated with no-reflow remain unclear. We investigated clinical factors associated with no-reflow following PCI for coronary artery disease (CAD). We retrospectively analyzed 1622 consecutive CAD patients who underwent PCI over a 5-year period at our institution. Patients were divided into two groups according to the presence (n = 31) or absence (n = 1591) of no-reflow, defined as Thrombolysis in Myocardial Infarction flow grade <3 after PCI. No significant differences in patient characteristics or PCI strategy were seen between the no-reflow and normal flow groups. The incidence of no-reflow was significantly lower in the left circumflex artery (LCx) than in the left anterior descending artery (LAD) (P = 0.0015), with no differences in characteristics or PCI strategy between these two target vessels. Multivariate analysis revealed that involvement of the LCx was an independent protective factor against no-reflow (odds ratio 0.14, 95 % confidence interval 0.02–0.98, P = 0.044). In conclusion, LCx as the target vessel was protective against no-reflow compared with LAD following PCI for CAD. Our results suggest that embolic protection devices may be unnecessary in CAD patients with involvement of LCx.

Keywords Coronary artery disease · No-reflow phenomenon · Percutaneous coronary intervention · Target vessel

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Introduction

Although percutaneous coronary intervention (PCI) has dramatically improved survival rates after acute myocardial infarction (AMI), a small proportion of patients with coronary artery disease (CAD) experience poor myocardial reperfusion following PCI, a phenomenon that is termed "no-reflow" [1, 2]. No-reflow, whose reported incidence ranges between 3 % and 5 % for all types of PCI [3–5], is independently associated with increased in-hospital mortality, cardiac dysfunction and failure, and poor long-term prognosis [6–9]. Although a number of intervention strategies to improve reperfusion in AMI patients before and after PCI have been implemented [10], no significant change in the incidence of no-reflow has been obtained, and factors underlying the increased susceptibility to this phenomenon are poorly understood.

The main approaches to preventing or treating no-reflow following PCI include the use of vasodilators [11–13], antiplatelet therapy [14], calcium-channel blockers [15, 16], nicorandil [17, 18], and embolic protection devices [19]. Although these various approaches have led to improvements in mortality outcomes, the frequency of no-reflow has not significantly improved, and no standardized treatment for this phenomenon has been established. In

general, when plaque instability is identified in CAD patients by intravascular ultrasonography (IVUS), embolic protection devices are used as a preventative measure against no-reflow. However, three major trials [20–22] found that the use of such devices did not lead to significant differences in myocardial reperfusion or microvascular flow. These findings indicate that the optimum use of these protection devices awaits a better understanding of the underlying clinical factors associated with the development of no-reflow following PCI.

In our clinical experience, the incidence of no-reflow is lower in patients who receive PCI for CAD involving the left circumflex artery (LCx). Although in Japan embolic protection devices are often implanted in response to the detection of lesions without distinction of the type of vessel, outcome benefits based on target vessel have not been conclusively demonstrated. Recently, Ndrepepa et al. [23] reported that the incidences of no-reflow among patients with ST-elevation myocardial infarction (STEMI) treated with PCI varied considerably among target vessels, albeit without statistical significance. It therefore remains unclear as to whether the target vessel influences the development of no-reflow in the setting of PCI for CAD.

Here, we retrospectively analyzed patients with CAD who had undergone PCI to determine the incidence of no-reflow with respect to target vessel.

Patients and methods

Patients

In total, 1622 consecutive CAD patients who underwent PCI for either stable CAD (n = 749) or acute coronary syndrome (ACS) (n = 873) at our institution between January 2006 and December 2010 were retrospectively analyzed. Data were obtained from clinical records, which included clinical history, and all patients provided written informed consent to undergo the procedure.

Angiographic analyses

Patients were divided into two groups according to the presence or absence of no-reflow, defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade <3 after PCI. All coronary angiograms were analyzed using quantitative coronary analysis (QCA) software (CAAS V; Pie Medical Imaging, Maastricht, The Netherlands) and plaque areas were calculated. For each lesion, an end-diastolic frame from the angiogram was selected with identical angulations that best showed the stenosis at its greatest severity with minimal foreshortening and branch overlap.

Clinical data collection and biochemical measurements

We collected the following data: age, sex, coronary risk factors (smoking and hypertension, as defined by the Joint National Committee VII [24, 25], diabetes mellitus, as defined by the World Health Organization study group [26], and dyslipidemia), and cardiovascular medications before PCI. Serum creatinine before PCI was measured by the creatinase–sarcosine oxidase–peroxidase method. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation, as follows: eGFR = 175 $\times$ serum creatinine level $(\mathrm{mg/dl})^{-1.154}$ $\times$ age $(\mathrm{years})^{-0.203}$ (if female, $\times$0.742) [27]. The ethnicity factor used in this equation for the Japanese population was 0.741 [28].

Medications and follow-up

All patients in this study underwent PCI. Aspirin (100 mg for stable CAD patients; 162–200 mg for ACS patients) was administered before PCI. Intravenous heparin (10,000 IU) was administered once arterial access had been obtained to achieve an activated clotting time of 200–300 s. Postprocedural antithrombotic therapy consisted of aspirin (81–100 mg/day) and ticlopidine (100 mg twice daily) or clopidogrel (75 mg daily). We followed the patients for 30 days after PCI, observing for in-hospital cardiac deaths.

Statistical analyses

For continuous variables, comparisons between the no-reflow and normal flow, and LAD and LCx groups were performed using Student's t test and Fisher's exact test. Continuous data are expressed as the mean $\pm$ standard deviation (SD). Categorical variables are reported as frequencies with percentages, and were compared between the two groups using the Chi-squared test. Comparisons between the incidences of no-reflow based on the target vessel of PCI were performed using the Chi-squared and post hoc Bonferroni multiple-comparison tests. Kaplan–Meier curves were drawn to compare mortality outcomes between the no-reflow and normal-flow patient groups. Univariate analysis of variance was performed to assess the effects of various factors on the development of no-reflow, with variables with a P value of less than 0.10 in the univariate analysis included in the multivariate logistic regression analysis. All statistical analyses were performed using SPSS statistical software (SPSS, Chicago, IL, USA), with P values of less than 0.05 considered statistically significant.

Results

Patients' baseline characteristics and incidence of no-reflow

Baseline characteristics of the 1622 study patients are summarized in Table 1. The patients were predominantly male (77 %) and had a mean age of 67 ± 11 years. Over 80 % of all patients received aspirin prior to PCI; however, nearly half were also treated with statins (51 %). Among the 1622 patients, 31 (1.9 %) experienced no-reflow following PCI. No significant differences were detected between patients with normal (n = 1591) and no-reflow in any of the examined variables.

The incidence of no-reflow based on PCI strategy is summarized in Table 2. Drug-eluting stents (DES) were the most common PCI procedure (85 %). No significant differences in the rates of no-reflow were detected for DES, bare-metal stents, or plain balloon angioplasty. In addition, the incidences of no-reflow and normal flow did not significantly differ based on the implantation of an embolic protection device, or the use of aspiration.

Kaplan–Meier estimates of in-hospital mortality during the 30 days after PCI were 6.5 % in patients with no-reflow and 0.6 % in patients with normal flow ($P < 0.001$; Fig. 1).

Incidence of no-reflow by target vessel of PCI

We also examined the incidence of no-reflow based on the target vessel of PCI (Table 3). For the LAD, a significantly higher incidence of no-reflow was detected in comparison with all patients with normal flow. The inverse association was detected for LCx, with patients displaying a markedly lower incidence of no-reflow. Only a single case of no-reflow was found among the 351 patients who underwent PCI for the LCx, in contrast to the 20 cases detected

Table 1 Baseline characteristics of study patients

Variables	Overall (n = 1622)	No-reflow (n = 31)	Normal flow (n = 1591)	P value
Age (years)	67 ± 11	69 ± 7	67 ± 11	0.12
Male, n (%)	1241 (77)	24 (77)	1217 (76)	0.90
BMI	24.3 ± 3.4	24.7 ± 2.9	24.3 ± 3.4	0.52
Smoking, n (%)	828 (51)	11 (35)	817 (51)	0.09
Hypertension, n (%)	1100 (68)	19 (61)	991 (62)	0.86
Diabetes mellitus, n (%)	661 (41)	17 (55)	644 (40)	0.09
Dyslipidemia, n (%)	1122 (69)	23 (74)	1099 (69)	0.45
Acute coronary syndrome, n (%)	873 (54)	20 (65)	853 (54)	0.23
STEMI	471 (29)	10 (32)	461 (29)	0.69
NSTEMI	97 (6)	4 (13)	93 (6)	0.21
UA	305 (19)	6 (19)	299 (19)	0.94
Medications before PCI				
Aspirin, n (%)	1346 (83)	25 (81)	1321 (83)	0.73
Dual antiplatelet, n (%)	895 (55)	18 (58)	875 (55)	0.73
Beta-blocker, n (%)	569 (35)	12 (39)	557 (35)	0.67
ACE-I or ARB, n (%)	699 (43)	15 (48)	684 (43)	0.55
Calcium antagonist, n (%)	177 (11)	2 (5)	175 (11)	0.61
Statin, n (%)	825 (51)	14 (45)	811 (54)	0.52
eGFR (ml/min/1.73 m^2)	69.1 ± 25.1	70.2 ± 28.5	68.9 ± 25.2	0.78
Hemoglobin (g/dl)	13.6 ± 1.9	13.3 ± 2.0	13.6 ± 1.9	0.40

Continuous variables are presented as the mean ± SD. Categorical variables are presented as numbers (percentage)

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, *UA* unstable angina

Table 2 Incidence of no-reflow based on PCI strategy

PCI procedure	Overall (n = 1622)	No-reflow (n = 31)	Normal flow (n = 1591)	P value
DES, n (%)	1384 (85)	26 (84)	1358 (85)	0.95
BMS, n (%)	161 (10)	3 (10)	158 (10)	0.73
POBA, n (%)	77 (5)	2 (6)	75 (5)	0.66
Direct stenting, n (%)	232 (14)	5 (16)	227 (14)	0.79
Embolic protection, n (%)	27 (2)	1 (3)	26 (2)	0.41
Aspiration, n (%)	228 (14)	8 (26)	220 (14)	0.07

BMS bare-metal stent, *DES* drug-eluting stent, *POBA* plain old balloon angioplasty

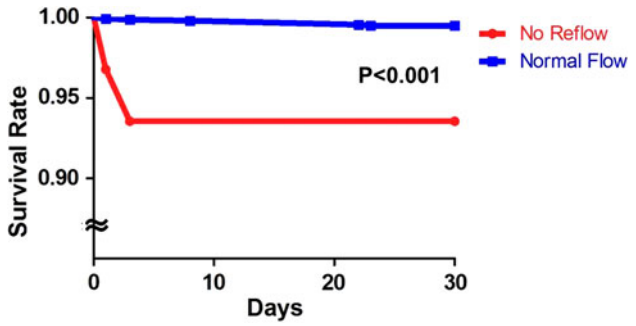

Fig. 1 Kaplan–Meier estimates of in-hospital mortality for CAD patients with no-reflow (n = 31) and normal flow (n = 1591). Patient mortality during the 30 days following PCI is shown

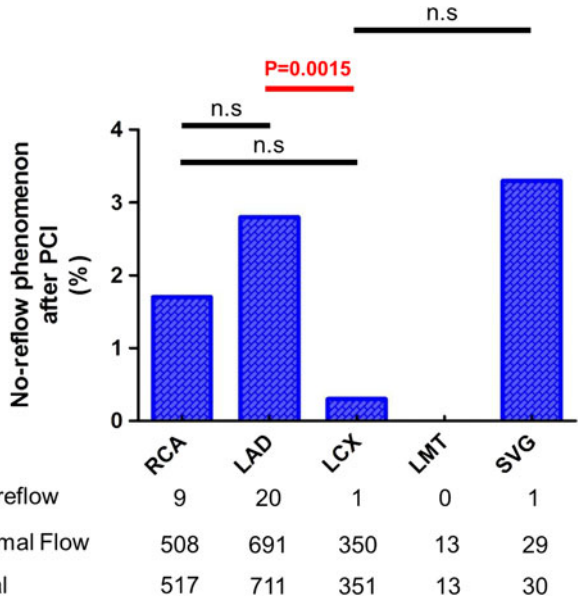

Fig. 2 Incidence of no-reflow based on the target vessel of percutaneous coronary intervention (PCI). The percentage of total patients with coronary artery disease experiencing no-reflow after PCI involving the left anterior descending artery (*LAD*), left circumflex artery (*LCx*), left main trunk coronary artery (*LMT*), right coronary artery (*RCA*), or saphenous vein graft (*SVG*) are shown. The Chi-squared and post hoc Bonferroni multiple-comparison tests were used to evaluate statistical significance. *ns* not significant

when the LAD was the target vessel. We directly compared the relationship between the development of no-reflow following PCI for each target vessel using the Chi-squared and post hoc Bonferroni multiple-comparison tests (Fig. 2). A significant difference in the incidence of no-reflow was detected only between the LCx and LAD (P = 0.0015), with no-reflow occurring less frequently in patients with LCx as the target vessel (<0.5 %).

Protective factors against no-reflow phenomenon

Univariate analysis was performed to identify potentially protective factors against no-reflow (Table 4). Three variables with a P value of less than 0.10 were identified: a history of hypertension (P = 0.05), and either the LCx (P = 0.03) or the LAD as a target vessel (P = 0.02). To identify factors that were independently associated with the development of no-reflow, multivariate logistic regression analysis was conducted (Table 4). The analysis revealed that only LCx was independently associated with a reduced incidence of no-reflow following PCI.

LCx-patient and LAD-patient groups

Following the identification of the LCx and LAD as being significantly associated with lower and higher incidences of no-reflow, respectively, we further examined the background characteristics of CAD patients with involvement of either the LCx (n = 351) or LAD (n = 711) (Table 5). There were no significant differences in background characteristics, including plaque burden calculated by the QCA method and collateral source contributions, between the two patient groups. Of note, the two groups had similar rates of ACS including STEMI, non-STEMI and unstable angina, and the rates of medication use were nearly identical before PCI. Furthermore, we confirmed that there were no significant differences in PCI strategies between these two groups (Table 6).

Discussion

In the present study of consecutive CAD patients who underwent PCI for either stable CAD or ACS, the

Table 3 Incidence of normal and no-reflow by target vessel following PCI

Target vessel, n (%)	Overall (n = 1622)	No-reflow (n = 31)	Normal flow (n = 1591)	P value
LAD	711 (45)	20 (65)	691 (43)	0.019
LCx	351 (22)	1 (3)	350 (22)	0.012
RCA	517 (32)	9 (29)	508 (32)	0.73
LMT	13 (1)	0 (0)	13 (1)	1.0
SVG	30 (2)	1 (3)	29 (2)	0.44

LAD left anterior descending artery, *LCx* left circumflex artery, *LMT* left main trunk coronary artery, *RCA* right coronary artery, *SVG* saphenous vein graft

Table 4 Multiple logistic regression analysis for protective factors against no-reflow

Variables	Univariate analysis *P* value	Multivariate analysis		
		Odds ratio	95 % CI	*P* value
LCx target	0.03	0.14	0.02–0.98	0.044
History of hypertension	0.05	0.48	0.23–1.13	0.07
LAD target	0.02	1.50	0.69–3.24	0.30
History of dyslipidemia	0.18	–	–	–
History of diabetes mellitus	0.54	–	–	–
Acute coronary syndrome	0.23	–	–	–
Direct stenting	0.22	–	–	–

CI confidence interval, *LAD* left anterior descending artery, *LCx* left circumflex artery

incidence of no-reflow was significantly lower when the LCx was the target vessel, compared with that associated with the LAD. This is the first report to identify a relationship between the development of no-reflow and the target vessel of PCI in the setting of stable CAD and ACS. In addition, no differences in baseline characteristics or PCI strategies were detected between the LCx and LAD patient groups. Our findings suggest that the use of embolic protection devices may not be warranted in PCI treatment of the LCx in CAD.

It is noteworthy that the LAD and LCx patient groups had similar baseline characteristics, particularly with regard to the incidence of ACS, which tends to be associated with the development of no-reflow [29, 30], and furthermore did not differ with respect to PCI strategy. Although it is possible that the placement of the embolic protection device itself may influence the no-reflow phenomenon, we found no difference in the incidence of no-reflow between patients who underwent direct stenting, embolic protection, or aspiration. The overall incidence of no-reflow among our consecutive CAD patients was 1.9 %; however, when the LAD was the target vessel, the rate increased to 2.8 %, which was 10-fold higher than that associated with the LCx. Although the reason for this finding is presently unclear, we speculate that the large difference may be related to factors associated with vessel morphology, such as the degree of septal branching and propensity to form atheromatous coronary lesions [31]. In the present study, we analyzed plaque burden by the QCA method and found no significant differences between the LCx and LAD patient groups. However, the QCA method is unsatisfactory for evaluating actual plaque characteristics and amount. For this purpose, IVUS is preferable to QCA. A full understanding of this difference awaits further prospective clinical studies, employing IVUS analyses, in both Western and Japanese CAD patients.

A number of studies have examined predictors of the no-reflow phenomenon [23, 32–34]; however, our present

Table 5 Baseline characteristics of the LCx and LAD groups of patients

Variables	LCx (n = 351)	LAD (n = 711)	*P* value
Age (years)	69 ± 10	67 ± 11	0.006
Male, *n* (%)	278 (79)	522 (73)	0.04
BMI	24.3 ± 3.5	24.2 ± 3.6	0.72
Smoking, *n* (%)	185 (52)	346 (48)	0.21
Hypertension, *n* (%)	219 (62)	422 (59)	0.06
Diabetes mellitus, *n* (%)	149 (42)	277 (39)	0.27
Dyslipidemia, *n* (%)	248 (71)	485 (68)	0.42
Acute coronary syndrome, *n* (%)	222 (63)	424 (60)	0.26
STEMI	116 (33)	242 (34)	0.75
NSTEMI	24 (7)	35 (5)	0.20
UA	82 (23)	147 (21)	0.32
Medications before PCI			
Aspirin, *n* (%)	298 (85)	590 (83)	0.43
Dual antiplatelet, *n* (%)	179 (51)	398 (56)	0.13
Beta-blocker, *n* (%)	147 (42)	277 (39)	0.36
ACE-I or ARB, *n* (%)	151 (43)	313 (44)	0.76
Calcium antagonist, *n* (%)	25 (7)	36 (5)	0.17
Statin, *n* (%)	170 (48)	370 (52)	0.27
Plaque area calculated by QCA (mm^2)	12.9 ± 6.3	13.3 ± 6.7	0.31
Collateral source, *n* (%)	20 (6)	34 (5)	0.52
eGFR (ml/min/1.73 m^2)	68.9 ± 20.3	70.8 ± 24.6	0.62
Hemoglobin (g/dl)	13.5 ± 1.9	13.8 ± 1.9	0.03

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *NSTEMI* non-ST-elevation myocardial infarction, *QCA* quantitative coronary analysis, *STEMI* ST-elevation myocardial infarction, *UA* unstable angina

Table 6 PCI strategy for LCx and LAD patient groups

PCI procedure	LCx (n = 351)	LAD (n = 711)	*P* value
DES, *n* (%)	294 (84)	595 (84)	0.97
BMS, *n* (%)	21 (6)	57 (8)	0.23
POBA, *n* (%)	15 (4)	23 (3)	0.39
Direct stenting, *n* (%)	41 (12)	99 (14)	0.31
Embolic protection, *n* (%)	1 (0.2)	12 (2)	0.07
Aspiration, *n* (%)	24 (7)	74 (10)	0.06

BMS bare-metal stent, *DES* drug-eluting stent, *POBA* plain old balloon angioplasty

study is the first to identify an association between the development of no-reflow and type of target vessel. Recently, Ndrepepa et al. [23] found no significant association between the incidence of no-reflow and target vessel, which included the LAD (9.3 %) and LCx (7.4 %), among 1140 STEMI patients treated with PCI. Although the overall incidence of no-reflow observed here was markedly lower for all examined target vessels than for those of Ndrepepa et al. [23], a direct comparison between the two study populations is not possible because of differences in ethnic composition, type of CAD, and the potential influence of country-based differences in PCI techniques and treatment strategies. Of note, our study included CAD patients with either stable CAD or ACS, while that of Ndrepepa et al. [23] consisted exclusively of STEMI patients.

Although our findings, together with the clinical evidence reported to date [20, 21], generally support the routine use of embolic protective devices during PCI, their use may not be warranted in patients with CAD associated with the LCx. Approaches for predicting patients at risk of developing no-reflow, such as examining lesion morphology [35] using IVUS [36] and angioscopy [37], although often unreliable, may also provide useful information. Our findings should aid physicians when deciding a PCI strategy for CAD patients, particularly concerning the use of embolic protective devices for involvement of the LCx. However, further prospective studies examining revascularization outcomes after insertion of embolic protection devices in such patients are needed to confirm the present results.

Our study has several strengths. First, this represents the first identification of the LCx being resistant to the no-reflow phenomenon, a finding that has important clinical implications. Second, our study population consisted of clinical cases that were continuous over a 5-year period at a single facility. Thus, the quality and type of PCI procedure and patient care remained relatively consistent throughout the study period, thereby limiting the potential impact of this confounding factor on the study results. Finally, our study population was relatively large and consisted of CAD patients with either stable CAD or ACS, thus increasing the generalizability of our findings.

A few limitations of the present study also warrant mention. First, the number of patients in the no-reflow group was small, thus limiting the significance of the results. Given that the overall incidence of no-reflow is low [38], pooled analysis may provide further insights into the factors associated with this phenomenon. Second, as the CAD patients analyzed in this study included those with either stable CAD or ACS, it is possible that thrombus formation and the properties of plaques may have differed between the patients. Third, our study population was enrolled at a single institution, and even after 5 years the incidence of the no-reflow phenomenon was relatively low. Finally, as only a limited number of patients underwent IVUS, data relating to vessel diameter and plaque characteristics were not available for all patients.

In conclusion, our analysis of CAD patients has revealed that the incidence of no-reflow was lower when the LCx was the target vessel for PCI than when the LAD was the target. Our findings suggest that the use of embolic protection devices may be unnecessary in CAD patients with involvement of the LCx. However, further prospective studies examining reperfusion outcomes after insertion of embolic protection devices in such patients are needed to confirm the present findings.

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Conflict of interest None.

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