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CLINICAL STUDIES **Myocardial Infarction and Acute Coronary Syndromes**

Association Between Hyperglycemia and the No-Reflow Phenomenon in Patients With Acute Myocardial Infarction

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OBJECTIVES We investigated the association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction (AMI).

BACKGROUND Hyperglycemia is associated with increased risks of heart failure, cardiogenic shock, and death after AMI, but its underlying mechanism remains unknown.

METHODS A total of 146 consecutive patients with a first AMI were studied by intracoronary myocardial contrast echocardiography (MCE) after successful reperfusion within 24 h after symptom onset. Two-dimensional echocardiography was recorded on day 1 and three months later to determine the change in the wall motion score (ΔWMS; sum of 16 segmental scores; dyskinesia = 4 to normokinesia = 0).

RESULTS The no-reflow phenomenon was found on MCE in 49 (33.6%) of 146 patients; their glucose level on hospital admission was significantly higher than that of patients who did not exhibit this phenomenon (209 ± 79 vs. 159 ± 56 mg/dl; $p < 0.0001$). There was no difference in glycosylated hemoglobin or in the incidence of diabetes mellitus between the two subsets. The no-reflow phenomenon was more often observed in the 75 patients with hyperglycemia (≥160 mg/dl) than in those without hyperglycemia (52.0% vs. 14.1%; $p < 0.0001$). Patients with hyperglycemia had a higher peak creatine kinase level (2,497 ± 1,603 vs. 1,804 ± 1,300 IU/l; $p = 0.005$) and a lower ΔWMS (3.7 ± 4.8 vs. 5.7 ± 4.3; $p = 0.01$) than did those without hyperglycemia. The blood glucose level was an independent prognostic factor for no reflow, along with age, gender, absence of pre-infarction angina, complete occlusion of the culprit lesion, and anterior AMI.

CONCLUSIONS Hyperglycemia might be associated with impaired microvascular function after AMI, resulting in a larger infarct size and worse functional recovery. (J Am Coll Cardiol 2003;41: 1–7) © 2003 by the American College of Cardiology Foundation

Hyperglycemia can be observed in patients with acute myocardial infarction (AMI), irrespective of a history of diabetes mellitus (DM) (1–3), and is associated with increased mortality after AMI (3–7). The decrease in blood glucose, by an insulin-glucose infusion, during the first 24 h after AMI decreases mortality in patients with DM (7). The increased mortality in patients with hyperglycemia might be explained by a larger infarct size (5), a high incidence of congestive heart failure, and cardiogenic shock (6,8). However, the underlying mechanisms of these deleterious effects of hyperglycemia are not well understood.

Impaired microvascular function, or the no-reflow phenomenon, determines functional and clinical outcomes after AMI (9,10). Myocardial contrast echocardiography (MCE) has revealed that the no-reflow phenomenon is found in 25% to 30% of patients with AMI, despite successful coronary recanalization, as shown by angiography (11,12), and is associated with a larger infarction (11–13), poorer functional recovery, and more frequent post-AMI complications (14). This study was conducted to investigate the association between hyperglycemia and the no-reflow phenomenon in patients with AMI.

METHODS

Study population. Between February 1999 and August 2001, 185 consecutive patients with a first AMI underwent a primary percutaneous coronary intervention (PCI; angioplasty and/or stenting) for arteries exhibiting Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 within 24 h after symptom onset, and subsequently, they were studied by MCE. The diagnosis of AMI was based on prolonged chest pain lasting ≥30 min, ST-segment elevation ≥2 mm in at least two contiguous electrocardiographic (ECG) leads, and a more than threefold increase in serum creatine kinase (CK) levels. Thirty-nine patients were excluded because of poor echocardiographic images (n = 11), cardiogenic shock (n = 2), spontaneous recanalization of the culprit lesion (TIMI flow grade ≥2) at the time of initial coronary angiography (n = 19), allergy to ioxaglate (n = 4), and unsuccessful PCI (n = 3). Therefore, the final study

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Abbreviations and Acronyms

AMI = acute myocardial infraction
CK = creatine kinase
DM = diabetes mellitus
ECG = electrocardiogram or electrocardiographic
HbA_{1c} = glycosylated hemoglobin
MCE = myocardial contrast echocardiography
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction
WMS = wall motion score

population consisted of 146 patients. The study protocol was approved by the hospital's Ethics Committee, and patients gave written, informed consent.

Study protocol. Just after hospital admission, a 12-lead ECG was recorded and the blood glucose level was measured in each patient. All patients underwent two-dimensional echocardiography with a SONOS 5500 system (Philips Medical Systems, Andover, Massachusetts). All patients received an intravenous infusion of nicorandil at 6 mg/h for 24 h after admission (15). Aspirin (243 mg) was given orally at least 30 min before coronary angiography, which was performed to find the culprit lesion and collateral channels. Collateral channels were graded according to the report by Rentrop (16), and good collateral flow was defined as grade 2 or 3. We performed coronary angioplasty on the culprit lesion by using appropriate-sized balloon catheters. We repeated angioplasty or implanted a stent to reduce the residual diameter stenosis to <50%. A repeat 12-lead ECG was obtained during and after each PCI procedure. Coronary reperfusion was achieved in all patients within 90 min of blood glucose measurement. We did not treat hyperglycemia until the PCI procedure was completed and the patient returned to coronary care unit.

At a mean time of 15 min after the last PCI procedure, we performed MCE as previously reported (11,14). In brief, we injected 2 ml sonicated ioxaglate (Hexabrix-320, Tanabe, Osaka, Japan) containing microbubbles of a mean size of 12 μm into the coronary artery and recorded two-dimensional echocardiograms. The MCE images, including the parasternal short-axis view at the mid-papillary muscle level and the apical two- and four-chamber views, were recorded on videotape. We measured glycosylated hemoglobin (HbA_{1c}) and total cholesterol and triglyceride levels on the next day. We performed echocardiography at a mean period of three months later to determine the wall motion recovery.

Analysis of echocardiographic data. Two observers blinded to the patients' data independently evaluated wall motion in 16 myocardial segments (17). Wall thickening of each segment was scored as follows: 4 = dyskinesia; 3 = akinesia; 2 = severe hypokinesia; 1 = hypokinesia; and 0 = normokinesia or hyperkinesia. We defined the risk area as myocardial segments showing dyskinesia, akinesia, or severe hypokinesia on hospital admission. The wall motion score (WMS) was calculated as the sum of the scores within the area at risk. The difference between WMS on admission and that three months later was defined as ΔWMS.

An experienced echocardiographer analyzed the MCE images to determine the presence of the no-reflow phenomenon. We defined the no-reflow zone in end-diastolic images as a contrast perfusion defect after PCI. We quantified the area of no reflow as the ratio of it to the risk area at baseline. When the ratio exceeded 25%, myocardial reperfusion was considered incomplete (i.e., no reflow) (11,14). We have reported the reproducibility of measuring the size of the contrast defect (11). We also scored the degree of contrast enhancement within the risk area as follows: 1 = good enhancement; 0.5 = patchy or endocardial enhancement; 0 = no enhancement (18).

Analysis of patient data. A physician obtained a detailed clinical history for each study patient. Cardiac symptoms lasting <30 min were defined as a sign of angina pectoris, and angina occurring within 48 h before the onset of infarction was defined as pre-infarction angina (19,20). A clinical history of risk factors such as DM, hypertension, hyperlipidemia, and smoking was determined from a patient interview or medical records. Diabetes mellitus was considered present if this diagnosis and treatment, including diet, drugs, or insulin, had been given to the patient or if an abnormal oral glucose tolerance test or HbA_{1c} ≥6.5% was found after admission. We measured fasting blood glucose in each patient at least twice during the hospital stay, and if the patient without a history of risk factors or high HbA_{1c} showed fasting blood glucose ≥110 mg/dl, we performed a glucose tolerance test. The patients who showed a high blood glucose level on admission but who did not fulfill the aforementioned criteria were classified as not having DM. Re-elevation of the ST segment was defined as additional ST-segment elevation on the ECG at reperfusion, compared with that before PCI.

Statistics. All data are expressed as the mean value ± SD. We made comparisons by one-way analysis of variance (ANOVA) for continuous variables, and significance of difference was calculated by using the Scheffé F test. Categorical variables were compared by the chi-squared test. To define hyperglycemia, we constructed receiver-operating characteristic curves and determined the suitable cutoff point where sensitivity for the prediction of no reflow is nearly equal to specificity. The association between hyperglycemia and ΔWMS or contrast enhancement score was analyzed by analysis of co-variance (ANCOVA), with the presence or absence of hyperglycemia as a fixed factor and the peak CK value as a co-variate to adjust the differences in infarct size. Multivariate logistic regression analysis was used to identify independent predictors for the development of the no-reflow phenomenon. Differences were considered significant at $p < 0.05$. Statistical analysis was performed with StatView, version 5.0 (SAS Institute, Cary, North Carolina).

Table 1. Clinical Characteristics of the Study Patients

	All Patients (n = 146)	MCE Findings		p Value*
		Reflow (n = 97)	No-Reflow (n = 49)	
Age (yrs)	60 ± 11	58 ± 11	64 ± 11	0.003
Gender (male/female)	116/30	76/21	40/9	0.64
Height (cm)	163 ± 8	163 ± 7	163 ± 8	0.82
Weight (kg)	64.6 ± 11.9	64.4 ± 12.4	65.3 ± 10.8	0.72
Peak creatine kinase (IU/l)	2,160 ± 1,499	1,719 ± 1,177	3,032 ± 1,688	< 0.0001
Blood glucose (mg/dl)	176 ± 69	159 ± 56	209 ± 79	< 0.0001
HbA_{1c} (%)	5.7 ± 1.3	5.6 ± 1.3	5.9 ± 1.3	0.12
Total cholesterol (mg/dl)	199 ± 45	201 ± 44	194 ± 47	0.38
Triglycerides (mg/dl)	113 ± 91	119 ± 99	100 ± 72	0.26
Risk factors (%)				
Diabetes mellitus	28.1	23.7	36.7	0.10
Hypertension	50.0	51.5	46.9	0.28
Hyperlipidemia	40.4	45.3	30.6	0.08
Smoking	66.4	72.2	55.1	0.06
Symptom onset to reflow time (h)	6.9 ± 5.7	7.2 ± 6.2	6.3 ± 4.4	0.41
Incidence of pre-infarction angina (%)	43.2	47.4	20.4	0.14
Killip class (I/II/III)	132/12/2	95/2/0	37/10/2	0.03
Hemodynamic data on admission				
Systolic blood pressure (mm Hg)	138 ± 27	136 ± 29	141 ± 23	0.34
Heart rate (beats/min)	80 ± 18	77 ± 17	85 ± 20	0.01
Rate–pressure product	11,155 ± 3,903	10,684 ± 3,635	12,148 ± 4,290	0.04
Hemodynamic data after PCI				
Systolic blood pressure (mm Hg)	124 ± 24	126 ± 25	121 ± 21	0.32
Heart rate (beats/min)	83 ± 12	83 ± 12	85 ± 13	0.24
Rate–pressure product	10,483 ± 3,052	10,383 ± 2,718	10,695 ± 3,684	0.57
ST-segment re-elevation (%)	38.4	34.0	46.9	0.13
Stent implantation (%)	49.3	46.4	55.1	0.32
Anterior wall MI (%)	63.7	53.6	83.7	0.0002
TIMI flow grade 0 on initial CAG (%)	76.7	70.1	89.8	0.005
Good collateral channels† (%)	29.5	28.1	32.7	0.57
WMS on admission	14.9 ± 5.6	13.8 ± 5.4	17.0 ± 5.4	0.0009
ΔWMS	4.7 ± 4.7	5.6 ± 4.6	2.8 ± 4.4	0.0006
Medication after AMI				
ACE inhibitor (%)	91.1	92.8	87.8	0.59
Beta-blocker (%)	28.8	25.8	34.7	0.26

*P values for the differences between reflow and no reflow by MCE. †Good collateral channels indicate collateral flow graded as 2 or 3. Data are presented as the mean value ± SD or number or percentage of patients.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CAG = coronary angiogram; HbA_{1c} = glycosylated hemoglobin; MCE = myocardial contrast echocardiography; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction trial; WMS = wall motion score on echocardiogram.

RESULTS

Patient characteristics. Among the 146 study patients (mean age 60 ± 11 years; 116 men and 30 women), 93 had the culprit lesion in the left anterior descending coronary artery, 15 in the left circumflex artery, and 38 patients in the right coronary artery. The mean time from the symptomatic onset to coronary reperfusion was 6.9 ± 5.7 h. A stent was implanted in 72 patients. The peak CK level was 2,160 ± 1,499 IU/l for the entire group. The blood glucose level on admission was 176 ± 69 mg/dl (range 79 to 549). Blood glucose on admission was weakly but significantly correlated with the heart rate on admission ($r = 0.28$, $p = 0.0004$) and with the rate–pressure product ($r = 0.30$, $p = 0.0002$), but not with systolic blood pressure ($p = 0.09$), suggesting that the blood glucose level might somehow reflect an adrenergic drive after AMI.

Diabetes was diagnosed in 41 patients, as described earlier: 25 patients had a previous diagnosis of DM, nine had a high HbA_{1c} value, and seven were diagnosed on the basis of the glucose tolerance test. Among 25 patients with a clinical history of DM, two received insulin, six received glibenclamide, three received gliclazide, and one received nateglinide. The remaining 13 patients were controlled by diet alone. Among 10 patients receiving oral antidiabetic agents, 9 showed hyperglycemia on admission, and 4 (3 receiving glibenclamide and 1 receiving gliclazide) showed no reflow by MCE. An angiotensin-converting enzyme inhibitor was administered in 133 patients (91.1%) after AMI, and a beta-blocker was used in 42 patients (28.8%) (Table 1).

The no-reflow phenomenon and blood glucose level. Patients with AMI were classified into two groups according to myocardial perfusion patterns; those without no reflow (n = 97 [66%]) and those with it (n = 49 [34%]). The peak CK value was higher and ΔWMS was lower in the no-

Table 2. Clinical Characteristics of Patients With or Without Hyperglycemia

	With Hyperglycemia (≥160 mg/dl)	Without Hyperglycemia (<160 mg/dl)	p Value
No. of patients	75	71	
Age (yrs)	61 ± 10	58 ± 11	0.10
Gender (male/female)	57/18	59/12	0.28
Peak creatine kinase (IU/l)	2,497 ± 1,603	1,804 ± 1,300	0.005
No reflow on MCE (%)	52.0	14.1	< 0.0001
Blood glucose (mg/dl)	221 ± 69	128 ± 18	< 0.0001
HbA_{1c} (%)	6.2 ± 1.6	5.1 ± 0.5	< 0.0001
Total cholesterol (mg/dl)	194 ± 45	204 ± 45	0.23
Triglycerides (mg/dl)	109 ± 103	117 ± 78	0.59
Risk factors (%)			
Diabetes mellitus	45.3	9.9	< 0.0001
Hypertension	49.3	50.7	0.86
Hyperlipidemia	40.0	40.8	0.92
Smoking	62.7	70.4	0.32
Symptom onset to reflow time (h)	6.1 ± 4.9	7.8 ± 6.3	0.06
Incidence of pre-infarction angina (%)	44.0	42.3	0.83
Killip class (I/II/III)	64/9/2	68/3/0	0.03
Hemodynamic data on admission			
Systolic blood pressure (mm Hg)	139 ± 25	137 ± 29	0.66
Heart rate (beats/min)	82 ± 20	77 ± 16	0.12
Rate–pressure product	11,579 ± 4,203	10,732 ± 3,558	0.20
Hemodynamic data after PCI			
Systolic blood pressure (mm Hg)	124 ± 23	124 ± 25	0.98
Heart rate (beats/min)	87 ± 18	81 ± 12	0.04
Rate–pressure product	10,834 ± 3,286	10,133 ± 2,778	0.17
ST-segment re-elevation (%)	49.3	26.8	0.005
Stent implantation (%)	45.3	53.5	0.32
Anterior wall MI (%)	66.7	60.6	0.44
TIMI flow grade on initial CAG (%)	80.0	73.2	0.33
Good collateral channels* (%)	29.3	30.0	0.93
WMS on admission	14.8 ± 5.6	14.9 ± 5.6	0.94
ΔWMS	3.7 ± 4.8	5.7 ± 4.3	0.01
Medication after AMI			
ACE inhibitor (%)	88.7	93.3	0.53
Beta-blocker (%)	28.0	29.6	0.83

*Good collateral channels indicate collateral flow graded as 2 or 3. Data are presented as the mean value ± SD or number or percentage of patients.
Abbreviations as in Table 1.

reflow group (3,032 ± 1,688 vs. 1,719 ± 1,177 IU/l, $p < 0.0001$ and 2.8 ± 4.4 vs. 5.6 ± 4.6, $p = 0.0006$, respectively). The patients with no reflow showed a significantly higher blood glucose level on admission than did those without it (209 ± 79 vs. 159 ± 56 mg/dl; $p < 0.0001$). There were no differences in HbA_{1c} or in the frequency of DM between the two groups (no reflow vs. reflow: 5.9 ± 1.3% vs. 5.6 ± 1.3%, $p = 0.12$ and 36.7% vs. 23.7%, $p = 0.10$, respectively). Also, there were no differences in DM therapy received before hospital admission between the two groups. Patients with no reflow showed a higher heart rate and a larger rate–pressure product on admission, although no differences were observed in these values after successful PCI. There were no differences in medication (angiotensin-converting enzyme inhibitor and beta-blocker) after AMI between the two subsets (Table 1).

We defined hyperglycemia as a blood glucose level ≥160 mg/dl, which was the optimal cutoff point to differentiate the patients showing no reflow, based on the receiver-operating characteristic curve analysis. The mean blood glucose level of the 75 patients (51.4%) with hyperglycemia on admission was 221 ± 69 mg/dl. There were no significant differences in age, gender, time from symptom onset to coronary reperfusion, or coronary risk factors, except for DM, between the patients with and those without hyperglycemia (Table 2). Although the heart rate on admission was significantly higher in patients with hyperglycemia, no differences were observed in the hemodynamic data between the two subsets after PCI. There were no differences in medication between the two groups. Re-elevation of the ST-segment was more frequently observed in patients with hyperglycemia. The incidence of no reflow was significantly higher in patients with hyperglycemia than in those without it (52.0% vs. 14.1%; $p < 0.0001$). Patients with hyperglycemia also showed a lower contrast enhancement score than did those without it, even after adjusting for differences in the peak CK value (0.6 ± 0.4 vs. 0.9 ± 0.3; $p < 0.0001$ by ANCOVA). The hyperglycemia group also showed a significantly higher peak CK value (2,497 ± 1,603 vs. 1,804 ± 1,300 IU/l; $p < 0.0001$) and a

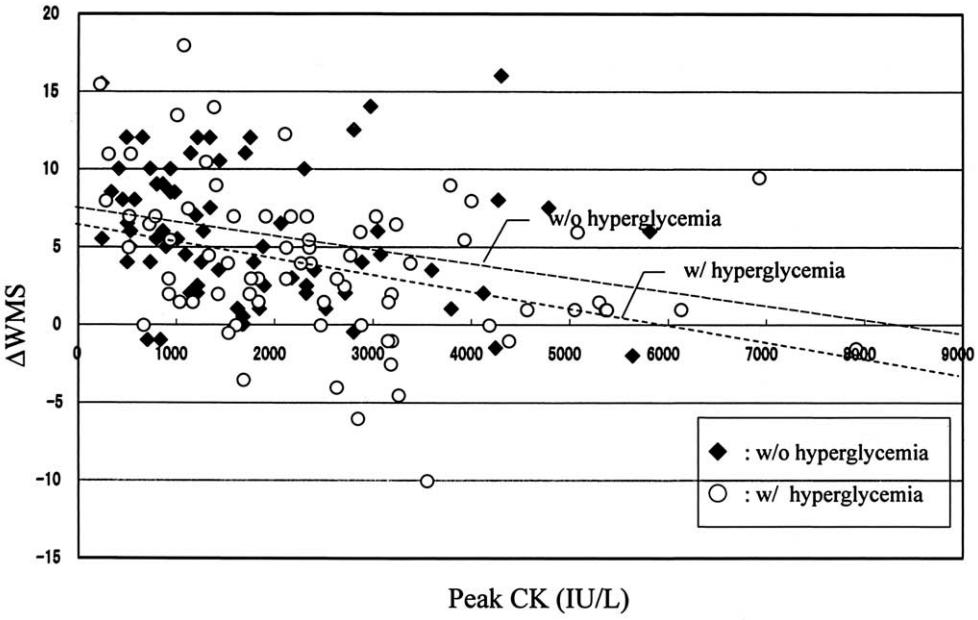

Figure 1. Relationship between peak creatine kinase (CK) value and Δ wall motion score (WMS) in patients with or without hyperglycemia. Both patients with hyperglycemia **(open circles)** and those without it **(solid squares)** showed a weak but significant relationship between peak CK and ΔWMS ($r = 0.35$, $p = 0.002$ and $r = 0.28$, $p = 0.04$, respectively). The hyperglycemia group showed a significantly lower ΔWMS, even after adjusting for differences in peak CK ($p = 0.009$ by analysis of covariance).

smaller ΔWMS (3.7 ± 4.8 vs. 5.7 ± 4.3; $p = 0.01$). The hyperglycemia group showed a significantly lower ΔWMS, even after adjusting for differences in the peak CK value ($p = 0.009$ by ANCOVA) (Fig. 1).

Determinants of the no-reflow phenomenon. We performed multivariate logistic regression analysis to determine the independent factors related to the development of the no-reflow phenomenon. Along with the blood glucose level on admission and HbA_{1c}, we used the following variables: age, gender, coronary risk factors, Killip class, pre-infarction angina, location of infarction, elapsed time from symptom onset to reperfusion, ST-segment re-elevation after reperfusion, WMS on admission, presence of good collateral channels, TIMI grade at initial coronary angiography, and use of stenting.

The blood glucose level is one of the independent predictive factors for no reflow, along with age, male gender, absence of pre-infarction angina, complete occlusion (TIMI flow grade 0) of the infarct-related artery, and anterior AMI (Table 3). Diabetes and HbA_{1c} were not selected as independent predictive factors. Among these factors, the blood glucose level had the highest Wald's chi-square value, followed by anterior wall AMI, complete occlusion, and male gender, indicating that the blood glucose level is the strongest factor to predict the no-reflow phenomenon. Even in the model using only the factors that were significant predictors in the univariate logistic analysis (i.e., age, blood glucose, gender, smoking, Killip class, location of infarction, ST-segment re-elevation, WMS on admission, and initial TIMI grade), we obtained the same results, except that the absence of pre-infarction angina was not a significant factor. When we used the incidence of hyperglycemia (≥160 mg/dl) instead of the blood glucose level, we also obtained the same result, with a 12.1 risk ratio of hyperglycemia for the no-reflow phenomenon (95% confidence interval 2.7 to 61.2).

DISCUSSION

In the present study, we investigated the relationship between hyperglycemia and the no-reflow phenomenon in 146 patients with a first AMI. The patients with no reflow showed a higher blood glucose level on admission than did those without it, whereas the DM frequency and HbA_{1c} values were comparable between the two groups. Patients with blood glucose ≥160 mg/dl on admission showed a higher incidence of the no-reflow phenomenon, along with a higher peak CK level and poorer recovery of wall motion. Multivariate analysis revealed that a high blood glucose level on admission was an independent predictive factor for the no-reflow phenomenon.

Hyperglycemia and the no-reflow phenomenon. In a previous study, we reported the independent predictors related to the no-reflow phenomenon: initial WMS as the size of the risk area, development of Q waves on admission, patent infarct-related artery, and preconditioning angina (20). Hyperglycemia in the present study was the strongest predictive factor for no reflow, compared with these factors.

Several mechanisms might explain the association between hyperglycemia and the no-reflow phenomenon. First, large infarcts are more likely to cause catecholamine release, which is known to affect fatty acid and glucose homeostasis. Acute hyperglycemia also increases intercellular adhesion molecule-1 levels (21) or P-selectin (22), which would augment plugging of leukocytes in the capillaries. Leukocytes trapped in the

Table 3. Multivariable Predictors of the No-Reflow Phenomenon

	Chi-Squared Statistic*	p Value	Odds Ratio (95% CI)
Age	5.61	0.02	1.08 (1.01–1.16)
Male gender	2.81	0.09	4.96 (0.76–32.24)
Blood glucose	8.96	0.003	1.02 (1.01–1.04)
HbA_{1c}	0.78	0.37	0.73 (0.36–1.48)
Diabetes mellitus	0.55	0.46	2.11 (0.30–15.08)
Hypertension	0.87	0.35	0.57 (0.18–1.86)
Hyperlipidemia	1.89	0.17	0.43 (0.13–1.44)
Smoking	0.16	0.69	0.75 (0.18–3.13)
Symptom onset to reflow time	0.59	0.44	1.03 (0.96–1.10)
Absence of pre-infarction angina	5.42	0.02	4.96 (1.29–19.11)
Systolic blood pressure	0.58	0.45	1.01 (0.99–1.03)
Heart rate	0.57	0.45	1.01 (0.98–1.05)
Killip class	1.93	0.17	6.04 (0.48–76.52)
ST-segment re-elevation	0.93	0.33	0.54 (0.16–1.88)
Stent implantation	0.89	0.35	1.74 (0.55–5.46)
Anterior wall AMI	5.09	0.02	4.86 (1.23–19.19)
TIMI flow grade on initial CAG	4.96	0.03	6.28 (1.25–31.60)
Good collateral channels†	5.74	0.02	0.04 (0.003–0.55)
WMS on admission	0.11	0.74	1.02 (0.91–1.14)
Peak CK liter	4.434	0.04	1.00 (1.00–1.001)
Oral antidiabetic agents	0.67	0.41	2.56 (0.27–25.36)

*Wald's chi-square value. †Good collateral channels indicate collateral flow graded as 2 or 3.
CI = confidence interval; other abbreviations as in Table 1.

coronary capillaries and venules early after coronary reperfusion are much more frequently observed in the diabetic rat heart than in the nondiabetic heart (23). Plugging of enhanced leukocytes in the microcirculation might further contribute to the no-reflow phenomenon (24).

Hyperglycemia may also augment thrombus formation. A recent clinical study suggests that a microthrombus in the capillaries plays a crucial role in the no-reflow phenomenon after AMI (25). Blood glucose is an independent predictor of platelet-dependent thrombosis, even in the normal range (26). Hyperglycemia may also attenuate the impact of ischemic preconditioning, which is an independent predictor of the no-reflow phenomenon (20). Acute hyperglycemia is known to abolish the effect of ischemic preconditioning (27), probably through attenuation of mitochondrial adenosine triphosphate–regulated potassium channel activation (28). Hyperglycemia could also reduce collateral flow to the risk area (29), resulting in greater myocardial damage before reperfusion and, subsequently, the no-reflow phenomenon (20).

Finally, hyperglycemia is likely to be associated with reperfusion injury. In the rat heart, diabetic blood enhances myocardial reperfusion injury through enhancement of both leukocyte adhesion to capillaries and free radical production (30). Re-elevation of the ST-segment, which could be a clinical sign of reperfusion injury, is associated with poor functional outcomes in patients with AMI (31). In this study, 56 patients with ST-segment re-elevation had a higher peak CK value (2,580 ± 1,490 vs. 1,899 ± 1,452 IU/l; $p = 0.007$) than did those without ST-segment re-elevation, and the hyperglycemia group showed a higher incidence of ST-segment re-elevation after coronary reperfusion (Table 2).

In turn, the possibility that hyperglycemia may be a consequence of a large infarct size, which is associated with the no-reflow phenomenon (20), could not be denied. Stress hyperglycemia itself is an imperfect marker of cardiac damage (6), as many other factors in addition to stress hormones contribute to the regulation of glucose concentration. The Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction (DIGAMI) study demonstrated that controlling blood glucose before reperfusion could reduce the infarct size (7). The blood glucose level was correlated with the heart rate and rate–pressure product, which implies that hyperglycemia may be a consequence of high adrenergic stress. Neither the heart rate nor blood pressure was an independent predictor of the no-reflow phenomenon in this study. Moreover, patients with hyperglycemia had a lower contrast enhancement score and lower ΔWMS than did those without it, even after adjusting for differences in the peak CK value. These results indicate that the effects of hyperglycemia on microvascular integrity and WMS could be independent from the infarct size. Still, we could not definitely determine whether hyperglycemia was a cause or consequence of a large infarct size that could be related to the no-reflow phenomenon. Further prospective studies in which the blood glucose level was controlled before coronary reperfusion would be required to clarify these associations.

Study limitations. Although all patients underwent coronary reperfusion within 90 min after blood glucose measurement at hospital admission, we do not know how the blood glucose level had changed before coronary reperfu-

sion. We also did not investigate how long hyperglycemia persisted before reperfusion. We did not perform the glucose tolerance test in all patients without a history of DM or a high HbA_{1c} value, and the incidence of DM in the hyperglycemia group (45.3%) might be underestimated. However, several previous reports have demonstrated that >40% of patients with AMI, but without DM, had hyperglycemia on admission (3,8), as in the present study. We did not measure serum catecholamine levels, free fatty acids, blood viscosity, or red-cell deformability, which might be useful to clarify the relationship between the blood glucose level and infarct size. We could not successfully analyze the effects of the sulfonylurea agents, which might affect microvascular integrity, because of the small number of patients receiving these drugs.

The present study was based on a retrospective analysis of the patients and was only a descriptive study in which we established an association between hyperglycemia and the no-reflow phenomenon. Prospective studies are required to determine the effect of hyperglycemia on the no-reflow phenomenon, independent of the infarct size and the effect of controlling blood glucose levels on this phenomenon.

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