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Hyperglycemia Is an Important Predictor of Impaired Coronary Flow Before Reperfusion Therapy in ST-Segment Elevation Myocardial Infarction

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OBJECTIVES	This study was designed to investigate whether elevated glucose is associated with impaired Thrombolysis In Myocardial Infarction (TIMI) flow before primary percutaneous coronary intervention (PCI).
BACKGROUND	Reperfusion before primary PCI in patients with ST-segment elevation myocardial infarction (STEMI) is associated with an improved outcome. Hyperglycemia in patients with STEMI is associated with an adverse prognosis. Hyperglycemia may induce a pro-thrombotic state and therefore be of influence on TIMI flow before PCI.
METHODS	A total of 460 consecutive patients with STEMI treated with primary PCI were included in this analysis. Hyperglycemia was defined as a glucose ≥ 7.8 mmol/l (140 mg/dl).
RESULTS	Hyperglycemia was observed in 70% and TIMI flow grade 3 before primary PCI in 17% of the patients. Patients with hyperglycemia less often had TIMI flow grade 3 before primary PCI (12% vs. 28%, $p < 0.001$). After adjustment for differences in baseline variables, hyperglycemia was a strong predictor of absence of reperfusion before primary PCI (odds ratio 2.6, 95% confidence interval 1.5 to 4.5).
CONCLUSIONS	Hyperglycemia in patients with STEMI is an important predictor of impaired epicardial flow before reperfusion therapy has been initiated. Investigation of methods improving coronary flow before primary PCI in these patients is warranted. (J Am Coll Cardiol 2005;45:999–1002) © 2005 by the American College of Cardiology Foundation

Patients with ST-segment elevation myocardial infarction (STEMI) who already have normal Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 of the infarct-related artery before primary percutaneous coronary intervention (PCI) have improved left ventricular function, lower incidence of congestive heart failure, and decreased mortality compared to patients without initial TIMI flow grade 3 (1,2). This background is the basis for facilitated primary PCI, aiming at early reperfusion through administration of pharmaceutical agents before mechanical intervention. Identification of patients without TIMI flow grade 3 on admission may provide insight on the mechanism of spontaneous reperfusion and identify subjects who benefit most from additional pharmacologic or mechanical strategies. Hyperglycemia during STEMI is associated with an increased mortality (3). Although hyperglycemia may induce a pro-thrombotic state, no data with regard to admission glucose and initial TIMI flow are present. Therefore we investigated

whether admission glucose is associated with TIMI flow on admission.

METHODS

Patients. This study concerns a post-hoc analysis of the Ongoing Tirofiban in Myocardial Infarction Evaluation (ON-TIME) trial, a randomized controlled trial of tirofiban including patients with STEMI treated with primary PCI (4). In this trial, before-hospital administration of tirofiban was compared with administration in the hospital. Inclusion criteria were the presence of chest pain for more than 30 min together with more than 0.2 mV (anterior myocardial infarction) or 0.1 mV (non-anterior myocardial infarction) ST-segment elevation in two contiguous electrocardiogram leads and the ability to perform primary angioplasty within 6 h after the start of symptoms. Patients >80 years of age, women <50 years of age, patients who were treated with thrombolytic therapy in the previous 24 h, patients receiving warfarin or acenocoumarol within the past 7 days, and patients with a contraindication to glycoprotein IIb/IIIa blockade were excluded. Patients with severe heart failure or cardiogenic shock (Killip class III or IV) and patients who were receiving hemodialysis were also excluded. All patients

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Abbreviations and Acronyms

- OR = odds ratio
- PCI = percutaneous coronary intervention
- STEMI = ST-segment elevation myocardial infarction
- TIMI = Thrombolysis In Myocardial Infarction

received a bolus of 5,000 IU of unfractionated heparin intravenously together with 250 mg of aspirin intravenously. Before transportation, oral informed consent was obtained in all patients by either a physician or a specialized ambulance crew. The protocol was approved by each institution's review board or ethical committee. Patients were transported to the catheterization laboratory as soon as possible, where both coronary arteries were visualized. Percutaneous coronary intervention was performed with standard techniques if the coronary anatomy was suitable for angioplasty. After PCI, all patients were treated with tirofiban (maintenance infusion, 0.15 µg/kg/min) for 24 h, clopidogrel (300 mg loading dose followed by 75 mg daily for one month), aspirin, beta-blockade, statin therapy and angiotensin-converting enzyme inhibition. Baseline characteristics, clinical data, angiographic data, and outcomes were recorded prospectively in a dedicated database.

Measurements and definitions. Core laboratory analysts (DIAGRAM, Zwolle, the Netherlands) who were unaware of the clinical history and outcome of the patients assessed TIMI flow quantitatively according to the TIMI classification (5). Hyperglycemia was defined as glucose levels on admission of ≥7.8 mmol/l (140 mg/dl) (whole blood: Modular system, Roche Analytics, Mannheim, Germany)

as stated by the American Diabetes Association (6). Diabetes was defined as a history of diabetes on admission with the use of oral hypoglycemic agents or insulin.

Statistical analysis. Differences between group means at baseline were assessed with the two-tailed Student *t* test. Chi-square analysis was used to test differences between proportions. When the expected frequency of a variable was <5, the Fisher exact test was used. To study independent predictors of TIMI flow, multivariate logistic regression analysis was performed comparing TIMI flow grade 3 with TIMI flow grade 0 to 2. To exclude confounding effects of diabetes, additional stratified analyses were performed, with separate analyses in patients without diabetes. Statistical significance was considered a two-tailed *p* value <0.05. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois) version 10.1 was used for all statistical analysis.

RESULTS

Baseline characteristics. The ON-TIME trial included 507 patients with STEMI treated with primary PCI. Admission glucose was measured in 477 patients (94%), and TIMI flow before primary PCI was scored in 487 patients (96%). In 460 (91%) patients both admission glucose and TIMI flow was present and these patients were included in the final analysis. A TIMI flow grade 3 before primary PCI was present in 76 patients (17%). These patients were younger (58.9 ± 11.7 years vs. 62.1 ± 10.2 years, *p* = 0.01), were more often smokers (77% vs. 63%, *p* = 0.02), and less often had anterior infarction (31% vs. 49%, *p* < 0.01). Patients were divided into groups with normoglycemia (*n* =

Table 1. Baseline Characteristics of the Patient Groups According to Presence of Hyperglycemia

	Normoglycemia <7.8 mmol/l (<140 mg/dl) (n = 138)	Hyperglycemia ≥7.8 mmol/l (≥140 mg/dl) (n = 322)	<i>p</i> Value
Age (yrs)	58.9 ± 10.7	62.3 ± 10.3	<0.001
Male gender	120 (87%)	249 (77%)	0.02
Risk factors (%)			
Diabetes mellitus	2 (1%)	44 (14%)	<0.001
Hypertension	34 (25%)	93 (29%)	0.35
Family history	60 (44%)	125 (39%)	0.39
Hypercholesterolemia	36 (26%)	67 (21%)	0.22
Smoking	98 (73%)	200 (63%)	0.04
Heart rate (beats/min)	75 ± 20	72 ± 19	0.13
Blood pressure (mm Hg)			
Systolic ≤ 100	10 (8%)	34 (12%)	0.27
Diastolic ≤ 60	11 (9%)	47 (16%)	0.05
Ischemic time ± SD	228 ± 143	217 ± 83	0.32
Ischemic time ≤ 3 h	44 (37%)	120 (40%)	0.59
Coronary history			
Previous AMI	10 (7%)	27 (8%)	0.67
Previous CABG*	3 (2%)	8 (3%)	1.00
Previous PCI	10 (7%)	15 (5%)	0.26
Multi-vessel disease	65 (47%)	172 (53%)	0.73
Anterior infarction	63 (46%)	145 (46%)	0.92

Comparison of proportions was done by chi-square analysis, except when stated otherwise. *Calculated with Fisher exact test. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

138) and with hyperglycemia (n = 322). Baseline characteristics are shown in Table 1. Hyperglycemic patients were older (p < 0.001), were more often women (p = 0.02), and more often had diabetes (p < 0.001) compared with patients with normoglycemia. The prevalence of a Killip class >1 was comparable between the patient groups.

Glucose levels and TIMI flow. Patients with hyperglycemia less often had TIMI flow grade 3 before primary PCI compared with patients without hyperglycemia (12% vs. 28%, p < 0.001). A TIMI flow grade of 0 to 1 before primary PCI was more often present in patients with hyperglycemia (Table 2). With decreasing TIMI flow before primary PCI, the percentage of patients with hyperglycemia increased (TIMI flow grade 3 = 50%, TIMI flow grade 2 = 67%, TIMI flow grade 0 to 1 = 76%). In patients without diabetes, hyperglycemia was also associated less often with TIMI flow grade 3 before PCI (11% vs. 27%, p < 0.001). No differences in TIMI flow grade 3 before primary PCI were present between patients with and without diabetes (p = 0.86). We divided the patient group into quartiles according to their admission glucose. The presence of TIMI flow grade 3 on admission was 28.7%, 14.4%, 13.8%, and 10.2%, respectively, in the lowest to the highest quartile.

Multivariate analysis. Multivariate analysis was performed to investigate whether hyperglycemia on admission was independently associated with TIMI flow before primary PCI. We included age, gender, and all other variables that were significantly different between patients with and without hyperglycemia (diabetes and smoking). After multivariate analysis, hyperglycemia (odds ratio [OR] 2.6, p = 0.001) was an independent predictor of initial TIMI flow grade 0 to 2 (Table 3). Inclusion of surrogate measures of physical stress (heart rate, blood pressure, and Killip class) did not change these results (OR 2.3; p = 0.004). Continuous glucose was also independently associated with initial TIMI flow grade 0 to 2 (OR 1.2 mmol/l, p = 0.002). Separate analyses for hyperglycemia and diabetes revealed that only hyperglycemia was independently associated with initial TIMI flow. Exclusion of patients with diabetes did not influence the association of hyperglycemia with TIMI flow grade 0 to 2 (OR 2.7; 95% confidence interval 1.5 to 4.6, p < 0.001).

Tirofiban administration. There was no influence of early versus late administration of tirofiban with regard to initial TIMI flow grade 3 in the total study group (19% vs. 15%, p = 0.22). In patients with normal glucose levels, initial TIMI flow grade 3 was nonsignificantly higher after early treatment with tirofiban (32% vs. 23%, p = 0.24), whereas no association between early treatment and TIMI flow grade 3 was present in patients with hyperglycemia (13% vs. 11%). In both patients with and without early tirofiban administration, there was a significant association between hyperglycemia and, less often, TIMI flow grade 3 on admission.

Table 2. Initial TIMI Flow Grade According to Admission Glucose

	Glucose <7.8 mmol/l (<140 mg/dl)	Glucose ≥7.8 mmol/l (≥140 mg/dl)	p Value
TIMI flow grade 3	38 (28%)	38 (12%)	<0.001*
TIMI flow grade 2	32 (23%)	65 (20%)	
TIMI flow grade 1	7 (5%)	42 (13%)	
TIMI flow grade 0	61 (44%)	177 (55%)	0.03†

*As compared to TIMI flow grade 2 to 0. †As compared to TIMI flow grade 1 to 3. Table shows a transition of better initial TIMI flow grade in patients with normoglycemia and worse initial TIMI flow grade in those with hyperglycemia.

TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

This is the first study to investigate the association between TIMI flow before reperfusion therapy and admission glucose in patients with STEMI. Hyperglycemia was a strong predictor of the absence of TIMI flow grade 3 of the infarct-related vessel before primary PCI. Further investigation with regard to glycometabolic status and initial TIMI flow should be initiated.

Explanations for the findings. First, patients with reduced TIMI flow may represent a sicker patient population. Stress is accompanied by high levels of catecholamines such as cortisol and adrenaline. These hormones increase glycogenolysis and lipolysis and reduce insulin sensitivity, resulting in elevated glucose levels (7). Therefore, patients with elevated glucose levels could represent patients with an increased response to stress, for example owing to more severe hemodynamic compromise or more extensive myocardial damage. However, after inclusion of systolic and diastolic blood pressure, heart rate, and Killip class on admission, hyperglycemia was independently associated with TIMI flow. Another explanation can be prothrombotic properties associated with hyperglycemia. Gesele et al. (8) showed that acute hyperglycemia increased platelet activation in diabetic patients. Nondiabetic patients with hyperglycemia may also have increased activation of platelets. Furthermore, recent evidence showed that acute hyperglycemia increased inflammatory responses during STEMI (9,10). As systemic inflammation is a potent prothrombotic stimulus, promoting procoagulant factors and inhibiting natural anticoagulants, elevation of inflammatory responses in hyperglycemic subjects may partly explain our observations with regard to initial TIMI flow (11). Although diabetes has been associated with reduced myocardial reperfusion after STEMI

Table 3. Multivariate Analysis of Initial TIMI Flow Grade 0 to 2

	Odds Ratio	95% CI	p Value
Hyperglycemia*	2.6	1.5–4.5	0.001
Non-smoking	1.6	0.9–3.0	0.13
Male gender	1.1	0.5–2.1	0.96
Age (per yr)	1.0	0.9–1.0	0.17
Diabetes	0.5	0.2–1.3	0.15

*Hyperglycemia was defined as a glucose level ≥7.8 mmol/l (140 mg/dl).

CI = confidence interval; TIMI = Thrombolysis In Myocardial Infarction.

(12), in our study diabetes was not associated with initial TIMI flow. Possibly, acute hyperglycemia is more important than chronic hyperglycemia in predicting TIMI flow before PCI.

Implications for treatment. The majority of patients (70%) in our analysis were hyperglycemic on admission. In these patients, only 12% had TIMI flow grade 3 on admission. Whether early reduction of glucose levels through insulin administration improves TIMI flow is unknown. Treatment with glucose-insulin and potassium infusion by this mechanism may be beneficial and should be further studied. Resolving this issue would be of interest from both a clinical and an experimental point of view. Furthermore, additional pharmacologic interventions to achieve early adequate TIMI flow should be investigated in these patients. Methods of implementing facilitated PCI through early administration of thrombolysis are a topic of growing clinical importance. Identification of patients with absent or reduced initial TIMI flow may be of help in selecting patients for facilitated PCI. Patients with early diagnosed hyperglycemia (e.g., in the ambulance) may benefit from more aggressive treatment before PCI, with potential use of thrombolytic agents or higher dosage of glycoprotein IIb/IIIa inhibitors (13). In our study, before-hospital treatment with a regular dosage of tirofiban was not associated with better TIMI flow in patients with hyperglycemia. However, analyses of a limited number of patients in non-prespecified subgroups should be interpreted with caution.

Study limitations. Our study involves a subanalysis of a prior performed trial. As HbA1c levels were not available it remains unclear whether acute or chronic hyperglycemia is most important with regard to initial TIMI flow. Furthermore, our observation could have been caused by confounding. Patients with reduced TIMI flow before primary PCI were older, whereas advanced age was also associated with hyperglycemia. However, after multivariate analysis hyperglycemia remained associated with a decreased TIMI flow. Other unmeasured variables may also be of importance with regard to initial TIMI flow.

Conclusions. Hyperglycemia on admission is an important predictor of reduced TIMI flow before primary PCI. Fur-

ther investigation to improve coronary flow of the infarct-related artery before mechanistic reperfusion is warranted in hyperglycemic patients.

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