Effect of stress hyperglycaemia on monocyte chemoattractant protein-1 levels and the short-term prognosis of patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Abstract. The present study prospectively investigated the effect of blood glucose level at admission on monocyte chemoattractant protein-1 levels at different time points before and after primary percutaneous coronary intervention, and the postoperative 1-year prognosis of patients with acute ST-segment elevation myocardial infarction. The 146 patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention were divided into three groups: Group 1, non-diabetic, non-hyperglycemic group; group 2, stress hyperglycemia group; and group 3, diabetic group. Serum monocyte chemoattractant protein-1 levels before and after percutaneous coronary intervention (PCI), and the incidence of major adverse cardiovascular events 1-year post PCI were observed. The increase in monocyte chemoattractant protein-1 levels 24 h after percutaneous coronary intervention, compared with those before percutaneous coronary intervention, was significantly correlated with the blood glucose level at admission. Furthermore, the 1-year postoperative major adverse cardiovascular events rates were significantly higher in groups 2 and 3 compared with group 1. Logistic regression analysis demonstrated that a high blood glucose level at admission, diabetes, and high preoperative monocyte chemoattractant protein-1 levels were risk factors for major adverse cardiovascular events 1-year post-percutaneous coronary intervention. Stress hyperglycemia and diabetes may contribute to high monocyte chemoattractant protein-1 levels and prolonged inflammation. These symptoms are associated with poor prognosis of acute ST-segment elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention.

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Introduction

Primary percutaneous coronary intervention (PCI) rapidly and completely restores blood flow in occluded coronary arteries in patients with acute myocardial infarction (AMI), thus effectively enabling the reperfusion of the infarcted myocardium, reducing the mortality rate and the incidence of cardiac endpoint events in AMI patients (1,2). However, for diabetic and non-diabetic patients, a high blood glucose level during AMI is associated with a poor AMI prognosis and somewhat affects the benefits of primary PCI (3-6). A random high blood glucose level at admission in non-diabetic patients with AMI is known as stress hyperglycemia (3).

It is not fully understood how stress hyperglycemia affects the prognosis of primary PCI (4,6,7). Previous studies have demonstrated that inflammation serves an important role in this process (8-10). Monocyte chemoattractant protein 1 (MCP-1) is an important inflammatory cytokine during the inflammatory response. MCP-1 serves roles in chemotaxis and the activation of monocytes/macrophages, the upregulation of the expression of monocyte/macrophage adhesion molecules and the production of inflammatory cytokines including interleukin (IL) 1 and 6, chemotaxis and the activation of basophils (11-13). These result in the release of histamine and inflammatory responses that may be associated with vascular injury, the development of atherosclerosis, plaque instability and restenosis following coronary stenting (14,15). MCP-1 may serve an important role in the mechanism by which stress hyperglycemia affects the prognosis of AMI, but limited data are available regarding these associations and further studies are required to confirm this.

A prospective study was conducted to investigate MCP-1 levels at different time points before and after primary PCI, and the prognosis of patients with acute ST-segment elevation

myocardial infarction (ASTEMI) 1-year post-PCI. Blood glucose levels were also measured at admission to explore how stress hyperglycemia affects the prognosis of primary PCI.

Materials and methods

Subjects. A total of 146 patients (age range, 35-80 years; average age, 60.1 years) with ASTEMI who successfully underwent primary PCI within 12 h of onset at the Second Affiliated Hospital of Anhui Medical University between December 2014 and December 2016 were included in the present study. Each patient and/or his/her family provided informed consent for PCI and written informed consent for the present study. Ethics approval for the study was granted from the Second Affiliated Hospital of Anhui Medical University Ethics Committee. ASTEMI was diagnosed according to the Third Universal Definition of the myocardial infarction document, as described previously (16). ASTEMI was defined as complaints of chest pain with ECG signs compatible with AMI (ST-segment elevation >2 mm in precordial leads and >1 mm in limb leads). Patients were included in the current study if they were diagnosed with ASTEMI, over the age of 18 years and were successfully treated with PCI. Patients with the following conditions were excluded: Severe peripheral vascular disease, peptic ulcer, coagulation disorders, severe infections, tumors, and connective tissue diseases, along with patients who succumbed within 48 h of admission or did not successfully undergo PCI (as the study required monitoring of MCP-1 levels for 48 h post-operatively).

Group assignment. Eligible patients with ASTEMI were divided into three groups (groups 1, 2 and 3), according to history of diabetes, blood glucose level at admission, and glycated hemoglobin A1c (HbA1c) level. The glucose oxidase method by automated analyzer was utilized to measure blood glucose levels (17). Group 1 was the non-diabetic, non-hyperglycemic group (blood glucose at admission <8.0 mmol/l); group 2 was the stress hyperglycemia group (non-diabetic, hyperglycemic group; blood glucose at admission ≥8.0 mmol/l); and group 3 was the diabetic group. Non-diabetic patients were defined by having no history of diabetes, with fasting blood glucose levels 24 h after admission, 2-h postprandial blood glucose levels and HbA1c levels that were incompatible with the diagnostic criteria of diabetes. Diabetes was diagnosed according to the Standards of Medical Care in Diabetes (2014) from the American Diabetes Association (18).

Perioperative medications. Prior to PCI, patients were routinely given 300 mg aspirin (Bayer AG, Leverkusen, Germany) and 300 mg clopidogrel (Sanofi S.A., Paris, France) by oral administration. Upon successful puncture, 3,000 IU unfractionated heparin was given via an arterial sheath. After coronary angiography and before PCI, additional unfractionated heparin was given via an arterial sheath (until 100 IU/kg). Additionally, 2,000 IU heparin was given each additional hour during PCI to maintain an activated clotting time ≥300 sec. Following PCI, aspirin, clopidogrel, angiotensin-converting enzyme inhibitors (Perindopril, 2-8 mg daily according to patient blood pressure; Servier, Suresnes, France) and β-blockers (Metoprolol succinate, 23.75-95 mg daily according to patient heart rate; Astrazeneca, Cambridge, UK) were routinely administered, unless otherwise contraindicated.

Cardiovascular events. The incidence of cardiovascular events during hospitalization (severe arrhythmias intra-PCI, severe heart failure and mortality) and of major adverse cardiovascular events (MACEs), including cardiogenic death, non-fatal myocardial infarction, target vessel revascularization, and severe heart failure occurring within one year after PCI were observed. Severe arrhythmia was defined as sinus arrest for ≥3 sec, grade 2 (or above) type II atrioventricular block, ventricular tachycardia and ventricular fibrillation. Severe heart failure was defined as class IV, according to the criteria of the New York Heart Association (19).

MCP-1 sample collection and testing. Blood samples (3 ml) were collected from the cubital vein prior to PCI (at admission), 24 and 48 h after PCI into a standard serum tube (no anticoagulant), followed by centrifugation at 1,006.2 x g for 10 min at room temperature. The upper layer of serum was collected into a test tube, which was sealed and stored at -80˚C for later use. The MCP-1 level was measured by ELISA (cat. no. SEA087Hu; Cloud-Clone Corp., Wuhan, China).

Statistical analysis. Data are expressed as the mean ± standard deviation. A Kolmogorov-Smirnov test was performed to verify the normality of the distribution. For normally distributed data, one-way analysis of variance was performed to analyze differences among the groups and the least significant difference was calculated to analyze between-group differences. Non-normally distributed measurement data or measurement data with heterogeneous variance were analyzed using the K independent samples method. Count data were analyzed with a χ^2 test. Correlations of measurement data with a normal distribution were analyzed with Pearson's correlation analysis. For non-normally distributed measurement data, Spearman's rank correlation analysis was used. Partial correlation analysis was applied to eliminate the influence of certain factors. $P<0.05$ was considered to indicate a statistically significant difference. Risk factors for MACEs 1-year post-PCI were analyzed using binary logistic regression analysis. SPSS V19.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

General information. A total of 146 patients with ASTEMI were eligible to participate, of which 128 were men and 18 women, with an average age of 60.1±11.0 years. Groups 1, 2, and 3 included 56, 50 and 40 patients, respectively. No significant differences among the groups were observed in age, sex, peak creatine kinase level, blood lipid profile, smoking history, history of hypertension or history of cerebrovascular disease. Blood glucose level at admission was significantly higher in group 3 (diabetic group) compared with groups 1 and 2 ($P<0.05$; Table I).

Coronary intervention-associated data. The comparison of coronary angiography results of each group during primary PCI reveled that more patients had multivessel lesions in

Table I. Baseline clinical characteristics.

Variables	Group 1 (n=56)	Group 2 (n=50)	Group 3 (n=40)
Male sex (%)	52 (92.9)	40 (80.0)	36 (90.0)
Female sex (%)	4 (7.1)	10 (20)	4 (10)
Age (years)	58.9±11.0	61.2±10.1	60.5±12.0
Smoking history (%)	26 (46.4)	26 (52.0)	20 (50.0)
Hypertensive disease (%)	22 (39.3)	24 (48.0)	24 (60.0)
Cerebrovascular disease (%)	6 (10.7)	6 (12.0)	4 (10.0)
Blood glucose on admission (mmol/l)	6.73±0.92	9.61±1.40[a]	12.78±3.32[a,b]
Total cholesterol (mmol/l)	4.31±0.90	4.59±0.96	4.52±0.85
TG (mmol/l)	1.52±0.70	1.61±0.91	1.79±0.78
HDL (mmol/l)	1.05±0.35	0.99±0.25	1.02±0.30
LDL (mmol/l)	2.66±0.70	2.89±0.72	2.73±0.65
VLDL (mmol/l)	0.42±0.27	0.44±0.27	0.46±0.21
LP-a (mmol/l)	0.19±0.16	0.17±0.11	0.18±0.09
CK (U/l)	2699±1419	2744±1510	2866±1323

[a]P<0.05 vs. group 1, [b]P<0.05 vs. group 2. CK, creatine kinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, triglyceride; VLDL, very-low-density lipoprotein; LP-a, lipoprotein-a.

Table II. Characteristics of primary PCI.

		Infarction-related artery					
Group	n	LAD	RCA	LCX	Multivessel disease (%)	Time of onset to reperfusion (h)	Maximum pressure of expansion (kPa)
Group 1	56	26	6	24	30 (53.6)	5.61±2.01	1,432.75±256.32
Group 2	50	30	6	14	28 (56.0)	5.83±1.61	1,408.25±262.38
Group 3	40	20	2	18	36 (90.0)[a,b]	5.97±1.79	1,418.4±256.26

[a]P<0.05 vs. group 1, [b]P<0.05 vs. group 2. LAD, left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

group 3 (diabetic group) compared with groups 1 and 2 (P<0.05). No significant among-group differences were observed in infarction-related artery, from AMI onset to reperfusion treatment, or maximum dilating pressure during PCI (P<0.05; Table II). This indicates that these factors do not affect the differences in MCP-1 levels among groups.

MCP-1 levels. The MCP-1 levels were higher 24 h following PCI compared with prior to PCI in all three groups (P<0.05), particularly in group 2 (stress hyperglycaemia group) and group 3 (diabetic group; P<0.001; Fig. 1). High MCP-1 levels 48 h after PCI were sustained, whereas the MCP-1 levels significantly decreased 48 h after PCI compared with 24 h after PCI in group 1 (non-diabetic, non-hyperglycemic group; P<0.05; Fig. 1).

Significant differences were observed in MCP-1 levels at different time points: MCP-1 levels were significantly higher in groups 2 and 3 compared with group 1, both before PCI and 24 and 48 h after PCI (P<0.05; Fig. 1).

Cardiovascular events during hospitalization. No patients with ASTEMI succumbed during hospitalization. The incidences of intraoperative severe arrhythmias and severe heart failure during hospitalization were higher in groups 2 and 3 compared with group 1, but the differences did not reach statistical significance (P>0.05; Fig. 2).

One-year post-PCI MACEs. The 1-year postoperative MACE rate was higher in groups 2 and 3 compared with group 1 (P<0.05), with no significant difference between groups 2 and 3 (Table III). Variables including blood glucose level at admission, age, diabetes, hypertension, smoking history, history of cerebrovascular diseases, infarction-related artery, multivessel lesions, time from AMI onset to reperfusion treatment, MCP-1 levels before PCI and 24 and 48 h after PCI, and blood lipids were incorporated into binary logistic regression analysis. The results demonstrated that blood glucose level at admission (Wald=4.286, β=2.146, P=0.038), diabetes (Wald=9.165, β=58.086, P=0.002), and preoperative MCP-1 levels (Wald=15.991, β=1.024, P<0.001) were risk factors for MACEs occurring within 1 year after PCI. This indicates that the increased level of blood glucose and MCP-1 at admission, as well as diabetes, were the risk factors for the

Table III. MACE in the 1-year postoperative period.

Group	n	MACE (%)	Cardiac deaths (%)	Non-death AMI (%)	Target vessel revascularization (%)	Severe heart failure (%)
Group 1	56	14 (25.0)	5 (8.9)	6 (10.7)	4 (7.1)	9 (16.1)
Group 2	50	22 (44.0)[a]	6 (12.0)	8 (16.0)	8 (16.0)	12 (24.0)
Group 3	40	20 (50.0)[a]	5 (12.5)	8 (20.0)	6 (15.0)	14 (35.0)

[a]P<0.05 vs. group 1. AMI, acute myocardial infarction; MACE, major adverse cardiovascular events.

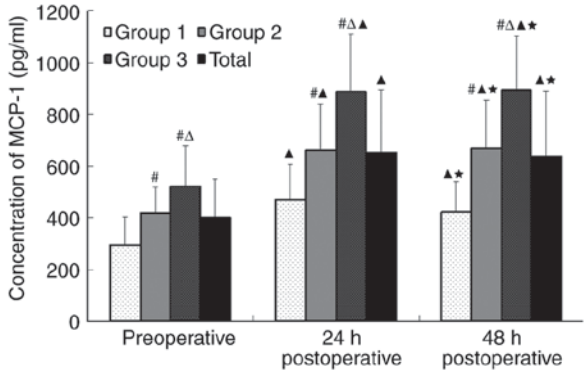

Figure 1. Concentration of MCP-1 preoperative and postoperative PCI. MCP-1 levels were significantly higher in groups 2 and 3 compared with group 1, both before PCI and 24 and 48 h after PCI. #P<0.05 vs. group 1, ΔP<0.05 vs. group 2, ▲P<0.05 vs. preoperative, ★P<0.05 vs. 24 h postoperative. MCP-1, Monocyte chemoattractant protein 1; PCI, percutaneous coronary intervention.

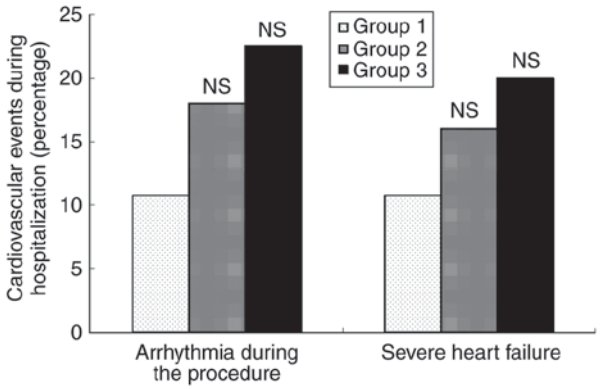

Figure 2. cardiovascular events during hospitalization. There was no change among groups, in terms of arrhythmia during the procedure and severe heart failure in hospital. NS, not significant.

occurrence of MACE 1 year following primary PCI in patients with ASTEMI.

Discussion

The present study demonstrated that the blood glucose level can be higher at admission not only for patients with ASTEMI with diabetes, but also for certain patients with ASTEMI without diabetes. The latter condition is called stress hyperglycaemia (3), which is defined as the first random blood glucose level tested post-admission being no less than 8.0 mmol/l. Among non-diabetic patients, patients with stress hyperglycaemia had higher preoperative and postoperative MCP-1 levels compared with those without hyperglycaemia at admission. Furthermore, patients with stress hyperglycaemia and diabetes had a higher rate of MACEs occurring within 1 year after PCI compared with non-hyperglycemic patients. This result indicated that for patients with ASTEMI, stress hyperglycaemia and diabetes are associated with a poor prognosis post-PCI.

Diabetes is an independent risk factor for coronary heart disease (20). Patients with coronary heart disease and diabetes frequently have multiple, severe and complicated coronary artery lesions (21). The present study also demonstrated that the incidence of multivessel lesions was significantly higher in diabetic patients with AMI compared with non-diabetic patients with AMI. Furthermore, patients with diabetes are characterized by chronic hyperglycaemia; during AMI, glucose metabolism disorders may worsen, resulting in a further increase in the blood glucose level at admission (3,4). It is known that patients with AMI and diabetes have a poor prognosis following PCI (22-24). However, in the case of AMI, not only patients with diabetes have elevated blood glucose, but patients who have not been previously diagnosed with diabetes may have elevated blood glucose at admission (4-6). This is termed stress hyperglycaemia.

During AMI, this stress hyperglycaemia is usually transient and is eliminated as AMI is stabilized. However, certain patients may develop diabetes in the future due to insulin resistance (25,26), while a previous study reported that high blood glucose at admission is unrelated to diabetes in the future (27). Regardless of the association between stress hyperglycaemia and diabetes, a number of studies have demonstrated that stress hyperglycaemia is associated with a poor prognosis in AMI (4,6,7).

Researchers continue to debate whether stress hyperglycaemia indicates the severity of the condition of patients with AMI or if hyperglycaemia itself may damage cardiac function (28,29). The mechanism by which stress hyperglycaemia affects the prognosis of AMI is not fully understood (6,7). Studies have shown that inflammation serves an important role in this process (8-10,30,31). The study of Marfella *et al* (31) demonstrated that during AMI, hyperglycaemia was associated with increased levels of inflammatory markers, enhanced expression of cytotoxic T-cells, and reduced expression of suppressor T-cells. There was a positive correlation between stress hyperglycaemia and poor cardiac outcomes in patients

with AMI (31). The study primarily confirmed the involvement of lymphocytes in the effects of stress hyperglycaemia on cardiac function in AMI. However, monocytes/macrophages are important immune cells in the body, similar to lymphocytes. Following AMI, monocytes/macrophages are rapidly recruited to the infarct zone, where they promote wound healing and ventricular remodeling (32,33). MCP-1 is an important inflammatory cytokine during the process of monocyte/macrophage activation. To the best of our knowledge, there is a lack of studies investigating the effect of stress hyperglycaemia on perioperative MCP-1 levels in patients with AMI undergoing PCI and the associated dynamic changes, thus the present study focused on this.

Patients with diabetes frequently have high baseline levels of MCP-1 (34,35). The present study also demonstrated that for patients with ASTEMI, the MCP-1 levels pre-PCI were significantly higher in patients with diabetes compared with non-diabetic patients. Furthermore, due to AMI and PCI, the MCP-1 levels increased more significantly following PCI in patients with diabetes, indicating that patients with diabetes were more sensitive to certain inflammatory stimuli.

In addition, the present study indicated that MCP-1 levels at different time points before and after PCI were higher. It also demonstrated that high MCP-1 levels lasted longer (maintained for 48 h after PCI) in patients with stress hyperglycaemia compared with non-diabetic and non-hyperglycemic patients, with no significant difference from the trend observed in patients with diabetes. Stress hyperglycaemia is usually transient; the blood glucose level usually returns to normal at discharge, indicating that stress hyperglycaemia is unrelated to the sustained expression of inflammatory cytokines due to chronic hyperglycaemia (36). El-Osta *et al* (37) described that transient hyperglycaemia induces long-lasting activating epigenetic alterations in the promoter of nuclear factor-κ B subunit p65 in aortic endothelial cells, which causes p65 gene expression to increase. The epigenetic and gene expression alterations persist for at least 6 days after normal physiological glucose levels are restored, inducing increases in MCP-1 and vascular cell adhesion molecule 1 expression. The study of El-Osta *et al* (37) reported that hyperglycaemia in patients with stress hyperglycaemia, although transient, may still result in days of activation of the upstream signaling pathway of MCP-1 expression. This observation was confirmed by the serum MCP-1 levels in the patients with ASTEMI in the present study.

Furthermore, the present study demonstrated that for non-diabetic patients, the increase in MCP-1 levels after PCI compared with those prior to PCI was significantly associated with blood glucose level at admission in a dose-dependent manner, indicating that hyperglycaemia itself may be associated with elevated chemokine levels and may prolong the effects of chemokines. Hyperglycaemia may increase the expression levels of MCP-1 and MCP-1-induced protein, thereby enhancing the effects of reactive oxygen species, endoplasmic reticulum and autophagy, resulting in myocardial apoptosis (30). This enhancement may increase the incidence of no-reperfusion during primary PCI in patients with AMI, resulting in myocardial microcirculation thrombosis (38-40), an increase in the area of AMI (41). It could also have an effect on the post-PCI cardiac recovery of patients with AMI (42), and subsequently higher post-PCI MACE rate in patients with hyperglycemia compared with non-hyperglycemic patients. These effect of hyperglycaemia on the expression of MCP-1 may represent one of the mechanisms by which stress hyperglycaemia affects the prognosis of AMI.

In conclusion, the present study demonstrated that stress hyperglycaemia was associated with elevated serum MCP-1 levels in patients with ASTEMI undergoing primary PCI and may enhance and prolong MCP-1-associated inflammatory responses resulting in a poor prognosis post-PCI. This indicates that stress hyperglycaemia may affect the prognosis of patients with ASTEMI undergoing primary PCI via elevated MCP-1 levels. Thus, blocking excessively high MCP-1 levels may become a potential option for improving the prognosis of patients with ASTEMI following primary PCI, though further research is required to validate these results.

In the present study, patients with unsuccessful PCI or those who succumbed within 48 h of admission were excluded, as this study required monitoring of MCP-1 levels for 48 h after PCI; this exclusion may result in selection bias. As for ethical considerations, no interventions were given for MCP-1 levels to further verify the association between MCP-1 levels and poor prognosis. In addition, the sample size was small, and the study period was short. Thus, the long-term prognoses of the subjects in this study should be monitored and large multicenter studies are required to further validate these results. The current study revealed that stress hyperglycemia and high monocyte chemoattractant protein-1 levels at admission are risk factors for the adverse prognosis of patients with ASTEMI undergoing primary PCI. Therefore, patients with ASTEMI exhibiting such biochemical abnormalities should have more medical attention paid to them.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YW conceived and designed the current study, and revised the manuscript critically for important intellectual content. NL and JS collected, analyzed and interpreted the data. NL wrote the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethics approval for the study was granted from the Second Affiliated Hospital of Anhui Medical University Ethics Committee. Each patient and/or his/her family provided written informed consent for the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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