Persistent Hyperglycemia is Associated With Left Ventricular Dysfunction in Patients With Acute Myocardial Infarction

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Background  The relationship of changes in blood glucose concentrations after admission to left ventricular (LV) dysfunction in patients with recanalized anterior acute myocardial infarction (AMI) remains unclear.

Methods and Results  Blood glucose concentrations were measured on admission and 24h after symptom onset in 210 patients with recanalized anterior AMI within 6h of symptom onset. Of them, 142 had hyperglycemia on admission, defined as a blood glucose ≥8.9 mmol/L, and 68 patients did not. Among the patients with admission hyperglycemia, 49 had persistent hyperglycemia, defined as a blood glucose ≥8.9 mmol/L 24h after onset, and 93 did not. The incidences of myocardial blush grade of 0/1 after recanalization indicating impaired myocardial perfusion (71%), and peak creatine kinase concentration (5,631±2,855 mU/ml) were higher and predischarge LV function (43±11%) was lower in patients with persistent hyperglycemia than in those without (p<0.01). Multivariate analysis showed that persistent hyperglycemia was independently associated with LV dysfunction, defined as a predischarge LV ejection fraction ≤40% (odds ratio 7.38, p=0.001).

Conclusions  Persistent hyperglycemia at 24h after symptom onset is associated with LV dysfunction before discharge in patients with recanalized anterior AMI. (Circ J 2005; 69: 23–28)

Key Words: Glucose; Infarct size; Myocardial infarction

A cute hyperglycemia, irrespective of a previous diagnosis of diabetes mellitus, is associated with increased risks of congestive heart failure, cardiogenic shock, and death after acute myocardial infarction (AMI). Recent studies have shown that not only restoration of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the epicardial infarct-related artery, but also complete and sustained myocardial reperfusion of the jeopardized myocardium are required to maintain left ventricular (LV) function and improve the outcome for patients with AMI. In addition, it has been recently demonstrated that hyperglycemia (≥8.9 mmol/L) on admission is associated with the no-reflow phenomenon on myocardial contrast echocardiography after recanallized AMI, resulting in a larger infarct and worse functional recovery. Previous studies assessing the significance of acute hyperglycemia in patients with AMI have focused mainly on the blood glucose concentration on admission, but the association of a change in the blood glucose concentration after admission with LV function remains to be elucidated and was the aim of the present study.

Methods

We enrolled 210 consecutive patients with an anterior wall AMI (mean age 59±11 years; range 29–84); 167 men and 43 women) who fulfilled the following criteria: (1) no history of prior myocardial infarction; (2) absence of conditions precluding electrocardiographic (ECG) evaluation of ST-segment changes (ie, left or right bundle-branch block, ventricular pacing); (3) achievement of TIMI grade 3 flow of the left anterior descending (LAD) coronary artery as confirmed by coronary angiography within 6h of symptom onset; (4) adequate assessment of myocardial blush grade after recanalization; (5) measurement of blood glucose concentration on admission and fasting blood glucose concentrations 24 and 48h after symptom onset, and on day 7; and (6) a patent infarct-related artery and left ventriculograms obtained a median of 14 days after AMI. Patients receiving oral hypoglycemic drugs or insulin during the first 48h and those with cardiogenic shock were excluded. The diagnosis of anterior AMI was based on typical chest pain lasting ≥30min, ≥2 mm ST-segment elevation in at least 2 contiguous precordial leads, and a typical increase in serum creatine kinase to more than twice the upper limit of normal. All patients were informed that some results of their general examinations during hospitalization may be used for research purposes. Informed consent was obtained before the data were included in analysis.

Coronary Angiography

Coronary angiography was performed immediately after admission. In the right coronary artery and the left circumflex coronary artery, stenosis was considered clinically...
significant if the lumen diameter was narrowed by ≥75% in any projection. The grade of collateral filling in the LAD coronary artery was evaluated as described by Rentrop et al.,11 a good collateral channel was defined as grade 2 or 3. Recanalization was defined as TIMI grade 3 flow. The allocation of recanalization therapy was left to the doctor’s discretion. Myocardial blush was graded immediately after recanalization by 2 observers who were unaware of all data apart from the coronary angiograms. The following grading scale was used: 0, no myocardial blush; 1, minimal myocardial blush; 2, moderate myocardial blush; and 3, normal myocardial blush.10

**ECG Analysis**
A 12-lead ECG was recorded on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The isoelectric line was defined as the level of the preceding TP segment. The 32-point Selvester QRS score was also calculated12 (this score has been validated in patients with AMI and strongly correlates with infarct size).13

**Patient Data**
A physician obtained a detailed clinical history for each patient. Cardiac symptoms lasting <30 min were defined as symptoms of angina pectoris, and angina occurring within 48 h before the onset of infarction was defined as previous angina.9 The presence or absence of the following risk factors was recorded: currently or previously treated hypertension, hypercholesterolemia, defined as a previous total serum cholesterol concentration >220 mg/dl when known; and smoking during the preceding 2 years. Diabetes mellitus (DM) was considered present if this diagnosis and antidiabetic treatment (ie, diet, drugs, or insulin) had been given to the patient, or if the glycosylated hemoglobin (HbA1c) was ≥6.5% after admission. Patients with a high blood glucose concentration on admission who did not fulfill the aforementioned criteria were classified as not having DM. Blood glucose concentration was measured immediately after admission and fasting blood glucose concentrations were measured 24 and 48 h after symptom onset, and on day 7. Blood glucose was analyzed immediately in plasma by means of GlcK-G6PD (HITACHI 7600, Japan). HbA1c was analyzed by high-performance liquid chromatography with an upper limit of 5.8% (Arkray, Hitachi-8150, Japan).

**Cardiac Enzyme Study**
Blood samples were obtained on admission and at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge.

**Analysis of LV Function**
LV function was evaluated on right anterior oblique views of left ventriculograms obtained at a median time of 14 days (interquartile range; 11–16 days) after AMI. LV end-diastolic volume index, end-systolic volume index, and LV ejection fraction (LVEF) were determined by the area–length method as described by Sandler and Dodge14 Regional wall motion in the territory of the LAD coronary artery was assessed with the centerline method15 and expressed as standard deviation/chord. Infarct size was assessed by calculating the percentage of chords in the infarct zone that were ≥2 standard deviations below normal wall motion (percent abnormally contracting segment).

**Statistical Analysis**
Data are expressed as mean ± standard deviation values for continuous variables and as percentages for categorical variables. We made comparisons by one-way analysis of variance (ANOVA) for continuous variables, and the statistical significance of differences was calculated by using the Scheffe F test. Chi-square analysis or Fisher’s exact test was used to compare categorical variables. A two-tailed p<0.05 was considered statistically significant. Multiple logistic regression analysis was used to examine determinants of LV dysfunction. LV dysfunction, defined as a predischARGE LVEF ≤40%, was the dependent variable. The independent variables were age ≥70 years16 female gender, time to recan- alization ≥2 h17 heart rate on admission >100 beats/min16 absence of previous angina within 48 h before AMI, multi-
血管病变，DM，入院时高血糖，定义为入院时血葡萄糖浓度≥8.9 mmol/L，以及持续高血糖，定义为入院时和24小时后的血葡萄糖浓度≥8.9 mmol/L。计算了 odds ratios (OR) 和 95% confidence intervals (CI)。分析使用 SPSS PC 软件。

**Results**

研究组的 142 名患者有入院高血糖，定义为入院时血葡萄糖浓度≥8.9 mmol/L，68 名患者没有。入院高血糖组的 49 名患者有持续高血糖，定义为入院时和24小时后的血葡萄糖浓度≥8.9 mmol/L，93 名患者没有。

**Patient Characteristics**

入院临床特征和 ECG 发生率在表 1 中总结。心率在入院时更高，无论有无持续高血糖。DM、使用口服降糖药物史前AMI，和 QRS 纵上入院时更高在患者有持续高血糖。其他入院临床特征在 3 组相似。

**Angiographic Findings (Table 2)**

从症状发生到再灌注的时间更长和再灌注后心肌血流受损的几率更高在患者有持续高血糖。其他血管造影的发现在 3 组中类似。

**Infarct Size and LV Function (Table 3)**

高峰 creatine kinase 浓度更高，入院时 LVEF 和区域心室肌运动损害的几率也更高。LV 灌流量评估基线百分比不正常收缩的段落下，表面积分数和 LV 灌流量基线百分比不正常收缩的段落下，入院时 LV 胶体和 LV 基线百分比不正常收缩的段落下。

**Blood Glucose Concentrations (Table 4)**

HbA1c 在 157（74%）入院时测量。入院时血葡萄糖浓度在院时，和在第 48 小时后症状发生时，以及在第 7 天更高在患者有持续高血糖。HbA1c。

**Determinants of Predischarge LV Dysfunction (Table 5)**

多变量分析表明持续高血糖独立地与入院时 LV 功能不全相关。
Admission Hyperglycemia in Patients With AMI

Several mechanisms explain the occurrence of hyperglycemia early after AMI. First, patients with admission hyperglycemia had a higher heart rate than did those without it, suggesting that admission hyperglycemia may be a consequence of high adrenergic stress. Second, patients with persistent hyperglycemia were likely to have had DM, even if it had not been diagnosed, as reflected by a higher HbA1c value on admission and a higher blood glucose concentration after admission. Admission hyperglycemia in such ‘non-diabetic’ patients may have simply been a sign of undiagnosed DM. Recent studies have shown that abnormal glucose metabolism is very common in patients with AMI and approximately two-thirds of patients with no previous diagnosis of DM could be classified as having undetected diabetes or impaired glucose tolerance.18,19 Furthermore, those studies showed that the standard measurements of fasting blood glucose concentration and HbA1c in the acute phase were poor tools for predicting future DM and impaired glucose tolerance. It is possible that admission hyperglycemia is associated with DM or impaired glucose tolerance. A third possible explanation for hyperglycemia early after AMI is that more severe myocardial damage may lead to a greater rise in stress hormones, which can promote glycogenolysis and hyperglycemia. However, the severity of myocardial damage on admission as indicated by QRS score were similar between patients with transient hyperglycemia on admission and those without admission hyperglycemia. It is thus unlikely that admission hyperglycemia simply reflects severe myocardial damage.

Severity and Duration of Hyperglycemia and Impaired Myocardial Perfusion

Impaired myocardial perfusion despite successful recanalization is associated with a larger infarct size and increased mortality after AMI.2-8 Recently, Iwakura et al demonstrated that in patients with angiographically successful recanalization, admission hyperglycemia is associated with impaired myocardial perfusion (ie, the no-reflow phenomenon) on myocardial contrast echocardiography.9 Hyperglycemia has been shown to increase intercellular adhesion molecule-1, which increases leukocyte plugging in the capillaries,20,21 augments platelet-dependent thrombus formation22 and attenuates endothelium-dependent vasodilation.23 Although these findings may explain why hyperglycemia is associated with impaired myocardial perfusion after recanalization, the effects of hyperglycemia on the microvascular circulation may depend on its severity and duration. In patients with transient hyperglycemia on admission myocardial perfusion was relatively well preserved, similar to those without admission hyperglycemia. These findings suggest that admission hyperglycemia itself does not necessarily contribute to impaired myocardial perfusion. Patients with persistent hyperglycemia had a higher incidence of DM and a higher HbA1c value on admission than those with transient hyperglycemia, perhaps reflecting a longer duration of elevated blood glucose (ie, chronic hyperglycemia), which may have led to increased endothelial damage and an increased risk of microvascular morbidity.

Discussion

The present study has demonstrated that despite having admission hyperglycemia, patients who did not have persistent hyperglycemia 24 h after symptom onset had a lower incidence of impaired myocardial perfusion, a smaller infarct size and better LV function before discharge, similar to those in patients without admission hyperglycemia. Our findings suggest that persistent hyperglycemia is associated with LV dysfunction before discharge in patients with recanalized anterior AMI.
ity. Furthermore, acute episodes of hyperglycemia in patients with chronic hyperglycemia might produce a greater rise in blood glucose than that occurring in patients without chronic hyperglycemia. Experimental studies have shown that infarct size is linearly related to blood glucose concentration during acute or chronic hyperglycemia, suggesting that the severity of hyperglycemia is related to infarct size.

Hyperglycemia and Severe Myocardial Damage

In the present study, patients with persistent hyperglycemia had a longer time from symptom onset to recanalization and more severe myocardial damage on admission as indicated by a higher QRS score than did those without admission hyperglycemia. Patients with persistent hyperglycemia might already have severe myocardial damage before recanalization. Iwakura et al reported that more severe myocardial damage before recanalization is closely related to the no-reflow phenomenon in patients with successful coronary recanalization29 and other studies. Previous studies have suggested that microvascular damage can develop even after recanalization27,28 Persistent hyperglycemia may have additionally increased the microvascular damage thereafter. Our results indicate that persistent hyperglycemia is independently associated with LV dysfunction before discharge, which is a strong predictor of long-term prognosis.30,31 The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study reported that an insulin–glucose infusion reduced mortality in patients with acute hyperglycemia, especially those who had higher blood glucose concentrations.32 Other studies have shown that a glucose–insulin–potassium infusion reduces mortality associated with AMI, especially in patients who receive reperfusion therapy despite not having signs of heart failure.33,34 The available evidence thus suggests that acute hyperglycemia may be causally related to adverse outcomes and that aggressive management of plasma glucose concentrations by treatment with insulin early after AMI could improve outcomes in patients with acute hyperglycemia.

Study Limitations

We call for caution in interpreting the results of this study. It was a retrospective analysis limited to patients with a first AMI in whom TIMI grade 3 flow of the LAD coronary artery was achieved within 6h from symptom onset in order to evaluate precisely the effect of hyperglycemia on LV dysfunction. Furthermore, to evaluate the clinical significance of untreated acute hyperglycemia, patients who received oral hypoglycemic drugs or insulin during the first 48h were excluded. Therefore, the incidence of DM in the present study (23%) was lower than that in previous studies. Another limitation is that oral glucose tolerance tests were not routinely performed; consequently, DM may not have been diagnosed in some diabetic patients. We also did not measure plasma concentrations of norepinephrine, cortisol, or angiotensin II, which might be useful to clarify the relationship between blood glucose concentration and myocardial damage. Finally, the use of different criteria for admission hyperglycemia might lead to disparate results. Further prospective studies with more patients are required to confirm the effect of acute hyperglycemia on LV dysfunction after recanalization.

Conclusions

Persistent hyperglycemia 24h after symptom onset was associated with LV dysfunction before discharge in patients with recanalized anterior AMI.

References


