Impact of Admission Glycemic Variability, Glucose, and Glycosylated Hemoglobin on Major Adverse Cardiac Events After Acute Myocardial Infarction

GONG SU, MD, PhD1 SHU-HUA MI, MD1 HONG TAO, MD, PhD2 ZHAO LI, MD3 HONG-XIA YANG, MD1 HONG ZHENG, MD1 YUN ZHOU, MD1 LEI TIAN, MD1

OBJECTIVE—Dysglycemia is associated with poorer prognosis in patients with acute myocardial infarction (AMI). Whether admission glycemic variability (GV) has important value in prognosis of AMI patients is still unknown. The aim of study is to investigate the prognostic value of admission GV, glucose, and glycosylated HbA1c in AMI patients.

RESEARCH DESIGN AND METHODS—We measured blood glucose, HbA1c, and GV on admission in 222 consecutive patients with diagnosed AMI. GV, indicated as the mean amplitude of glycemic excursions (MAGE), was determined by a continuous glucose-monitoring system. MAGE was categorized as 3.9 or 8.61 or >8.61 mmol/L, admission glucose as 3.9 or <8.61 or >8.61 mmol/L; and HbA1c as 6.5% or <6.5%. Participants were followed up prospectively for 12 months. The relationship of admission MAGE, glucose, and HbA1c to the major adverse cardiac event (MACE) of AMI patients was analyzed.

RESULTS—In 222 enrolled patients with AMI, the rate of MACE by MAGE category (<3.9 or 3.9 or >3.9 mmol/L) was 8.4 and 24.1%, respectively (P = 0.001), by admission glucose category (<8.61 or 8.61 mmol/L) was 10.1 and 21.6%, respectively (P = 0.020), and by HbA1c category (<6.5 or 6.5%) was 10.7 versus 18.7%, respectively (P = 0.091). In multivariate analysis, high MAGE level was significantly associated with incidence of MACE (hazard ratio 2.419 [95% CI 1.273–9.100]; P = 0.017) even after adjusting for Global Registry of Acute Coronary Events risk score, but admission glucose and HbA1c was not.

CONCLUSIONS—Elevated admission glycemic variability appears more important than admission glucose and prior long-term abnormal glycometabolic status in predicting 1-year MACE in patients with AMI.

Hyperglycemia is associated with a poor prognosis in patients with an acute myocardial infarction (AMI) (1). Some evidence has shown that chronic glucose dysregulation, as assessed by glycosylated HbA1c levels, is a prognostic factor for mortality in patients with or without diabetes after myocardial infarction (2,3). However, more acute glycometabolic disturbances may also have a negative impact on patients' outcomes. It is evident that admission hyperglycemia is of independent prognostic value with regard to future cardiovascular disease in patients with AMI, irrespective of diabetes status (4,5). Glycemic variability (GV) is also one component of the dysglycemia, which includes both upward and downward acute glucose changes. Recent studies have shown that GV might play an important role in the pathogenesis of atherosclerosis and may be an independent risk factor for cardiovascular complications in diabetic patients (6–8). However, it still remains unclear whether acute GV has the same prognostic significance as admission glucose or HbA1c levels in AMI patients. The purpose of the current study is therefore to investigate the independent prognostic value of admission GV determined by a continuous glucose-monitoring system (CGMS), admission glucose, and HbA1c levels in patients with AMI.

RESEARCH DESIGN AND METHODS—This was a single-center, prospective follow-up study. Consecutive patients admitted to the cardiology department of Beijing An Zhen Hospital of Capital Medical University for AMI between July 2010 and February 2011 were selected. The inclusion criteria were: 1) confirmed admission diagnosis of AMI; 2) admission glucose <16.7 mmol/L; and 3) without diabetic ketosis or nonketotic hyperosmolar coma. AMI was defined according to the universal definition of myocardial infarction. Myocardial infarction was defined as acute if the time elapsed between the first symptom and admission was ≤72 h. To enable long-term follow-up and repeated visits to our outpatient clinic, only patients under the age of 80 years and living within the hospital’s catchment area were eligible. The exclusion criteria were severe noncardiac disease with expected survival of <1 year and unwillingness to participate. A patient could only be included once. Data, including information on previous clinical history, cardiovascular risk factors, and medication, were collected in hospital. Type 2 diabetes mellitus (T2DM) was diagnosed according to the American Diabetes Association criteria or the use of insulin or glucose-lowering medication. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with oral antihypertension drugs. Hyperlipidemia was diagnosed according to the modified National Cholesterol Education Program-Adult Treatment Panel III. The estimated

From the 1Department of Cardiology, Beijing An Zhen Hospital, Capital Medical University, Beijing, China; the 2Department of Endocrinology, Beijing An Zhen Hospital, Capital Medical University, Beijing, China; and the 3Beijing Emergency Center of Heart, Lung and Blood Vessel Diseases, Beijing, China. Corresponding authors: Gong Su, su_gong@yahoo.com, and Shu-hua Mi, mishuhua@hotmail.com. Received 13 May 2012 and accepted 28 September 2012.

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Glomerular filtration rate (eGFR) value was calculated by Modification of Diet in Renal Disease equation (9). The Global Registry of Acute Coronary Events (GRACE) risk score was calculated as admission (10), which is recommended by the National Institute for Health and Clinical Excellence to assess risk in patients with acute coronary syndrome. Patients were categorized according to the mean amplitude of glycemic excursions (MAGE) level on admission (<3.9 and ≥3.9 mmol/L), based on reference values for continuous glucose monitoring in Chinese subjects (11), according to admission glucose levels (the upper tertile ≥8.61 mmol/L and the other two-thirds <8.61 mmol/L), and according to HbA1c (<6.5 and ≥6.5%) (12). The study protocol was approved beforehand by the Medical Ethics Committee of Beijing An Zhen Hospital of Capital Medical University, and the procedures followed were in accordance with the institutional guidelines. The study complied with the Declaration of Helsinki, and informed consent was obtained from all patients.

All patients were equipped with a CGMS (Medtronic Minimed; Medtronic) and monitored for 48 consecutive h after admission. A CGMS sensor was inserted into the subcutaneous abdominal fat tissue, calibrated according to the standard Medtronic MiniMed (Medtronic) operating guidelines. During CGMS monitoring, patients checked their blood glucose level with a self-monitoring of blood glucose device (Medisafe Mini; Terumo, Tokyo, Japan) at least four times per day. Then, they entered the self-monitoring of blood glucose data and time of each meal into the CGMS. After monitoring for 48 h, the recorded data were downloaded into a personal computer for analysis of the glucose profile and glucose excursion parameters with MiniMed Solutions software. After downloading the recorded data, the MAGE was analyzed from the intermediate 24 h of recording to avoid bias due to insertion and removal of the CGMS or insufficient stability of the monitoring system (13). Since measurable range of glucose by CGMS was mechanically limited from 2.2 to 22.2 mmol/L, the case showing the data out of this range was excluded from the study. The MAGE was calculated by measuring the arithmetic mean of the differences between consecutive peaks and nadirs, provided that the differences are >1 SD of the mean glucose value. Patients would maintain antihyperglycemic therapy as usual and avoid glucose infusion during the CGMS monitoring period. Otherwise, the patient would be excluded from the study.

Blood samples were collected on admission and after overnight fasting and stored at −70°C prior to analysis. Blood glucose, creatinine, total cholesterol, and triglyceride levels were measured by automatic biochemical analyzer (Hitachi 747; Hitachi, Tokyo, Japan). Serum concentration of HbA1c was determined by high-performance liquid chromatographic method using an automatic HbA1c analyzer (Tosoh HLC-723G7; Tosoh Corporation, Tokyo, Japan).

Patients were followed up prospectively for about 12 months. During the follow-up period, incidences of major adverse cardiac event (MACE) were registered, including new-onset myocardial infarction, acute heart failure, and cardiac death. All MACE data were adjudicated by an experienced cardiovascular physician blinded to clinical details and outcomes.

Statistical analysis
All statistical analyses were performed by using SPSS for Windows 13.0 (SPSS Inc, Chicago, IL). Data are presented as frequencies and percentages for categorical variables and mean ± SD for continuous variables, unless otherwise indicated. Differences between two groups were assessed by using the χ² and unpaired t tests. Correlation between continuous variables was determined by Spearman correlation coefficients. Admission MAGE was included as a continuous and as a categorized (<3.9 and ≥3.9 mmol/L) variable. Admission glucose and HbA1c levels were also included as continuous and categorized (admission glucose: <8.61 and ≥8.61 mmol/L; HbA1c: <6.5 and ≥6.5%) variables. Kaplan-Meier survival curve analysis was used to represent the proportional risk of MACE for the admission MAGE, glucose, and HbA1c values, and the log-rank test was performed to assess differences between high levels and low levels of those variables. To ascertain the independent contribution to MACE, multivariate regression analysis was made. A value of P < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics
During the study period, 222 patients with complete data were included in the final analysis. Mean age was 62 ± 10 years, 62.6% were male, and 53.6% had diabetes. Participants were treated conservatively (7%), with percutaneous coronary intervention (77%), or with coronary artery bypass surgery (16%). MAGE level was <3.9 mmol/L in 143 patients (64.4%) and ≥3.9 mmol/L in 79 (35.6%). Admission glucose level was <8.61 mmol/L in 148 patients (66.7%) and ≥8.61 mmol/L in 74 (33.3%). HbA1c was <6.5% in 132 (59.5%) and ≥6.5% in 90 (40.5%). The GRACE risk score ranged from 75 to 235 with a mean of 142 ± 34. Baseline characteristics of patient groups based on admission MAGE, glucose, and HbA1c are shown in Table 1. The correlation of admission MAGE with admission glucose and HbA1c were significant (Spearman r = 0.570 and r = 0.355, respectively; all P < 0.001).

Incidence of MACEs
At the end of 12-month follow-up, 10 patients had died (4.5%) for cardiac causes, 12 patients had new-onset myocardial infarction (5.4%), and 9 patients had acute heart failure (4.1%). AMI patients with high admission MAGE (≥3.9 mmol/L) levels had a significantly higher incidence of MACE compared with low MAGE level patients (24.1 vs 8.4%; P = 0.001). The higher rates of MACE were also observed in AMI patients with admission glucose level ≥8.61 mmol/L (21.6 vs. 10.1%; P = 0.020). No significant rates of adverse cardiovascular events were observed between patients with HbA1c levels ≥6.5% and patients with HbA1c levels ≤6.5% (18.7 vs. 10.7%; P = 0.091). AMI patients with a higher MAGE level had significantly higher cardiac mortality compared with AMI patients with MAGE levels <3.9 mmol/L (8.9 vs. 2.1%; P = 0.02). There were not significantly different rates of cardiac mortality, new-onset myocardial infarction, and acute heart failure in AMI patients between high and low levels of admission glucose or HbA1c (Fig. 1). Kaplan-Meier survival curves for the two patient groups by admission MAGE, admission glucose, and HbA1c are shown in Fig. 2.

Multivariate analysis
To investigate the associations of admission MAGE, glucose, and HbA1c, with incidences of MACE with respect to baseline characteristics, we used multivariate analysis. Include variables were:
Table 1: Baseline characteristics in AMI patients according to admission MAGE, glucose, and HbA1c level

<table>
<thead>
<tr>
<th>Groups</th>
<th>MAGE (mmol/L)</th>
<th>Glucose (mmol/L)</th>
<th>HbA1c (%)</th>
<th>P value Group 1</th>
<th>P value Group 2</th>
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ACEI, angiotensin-converting enzyme inhibitor; TC, total cholesterol; TG, triglyceride.

Diabetes

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Diabetes
We investigated the association between admission GV, glucose, HbA1c level, and 1-year MACE in patients with AMI. Our study demonstrated that elevated MAGE on admission was a strong and independent predictor of increased risk of MACEs in patients with AMI, but HbA1c was not.

There were major differences in baseline characteristics according to admission MAGE. Patients with MAGE ≥3.9 mmol/L more often had diabetes or a history of CAD. They had lower LVEF and eGFR levels. There were also differences in baseline characteristics according to admission glucose or HbA1c levels. Patients with higher glucose or HbA1c levels were more found to have diabetes or CAD history, lower LVEF and eGFR, and higher total cholesterol and triglyceride levels. There are a higher proportion of patients with high MAGE, glucose, or HbA1c level on diuretic therapy. Many diuretics, particularly thiazide diuretics that act on a particular part of the kidneys, have the potential to cause hyperglycemia (14), so we have adjusted the models by diuretics to prevent its affection. After adjusting for these different baseline characteristics, admission MAGE was significantly associated with poor outcomes, but HbA1c was not.

Numerous prior studies have established that elevated admission glucose and HbA1c are powerful predictors of survival and increased risk of cardiovascular complications in AMI patients both with...
and without diabetes (4,5,15). However, glycemic disorders are not solely limited to sustained hyperglycemia but can be extended to glycemic excursions that include both upward and downward acute glucose changes. Admission glucose is only a blood glucose value of point-in-time, which cannot reflect the status of acute glucose swings. HbA1c is a convenient marker of long-term glycometabolic status. Patients with similar mean glucose or HbA1c levels can have markedly different glycemic excursions (16). Fluctuations of glucose seem to have more deleterious effects than sustained hyperglycemia in the development of cardiovascular complications as acute glucose excursions activate the oxidative stress (17,18).

More and more evidences have been found that glycemic variability may be an important role in resolving potential vascular problems in diabetes. Some researchers suggested that postchallenge glucose excursion is independently related to carotid intima-media thickness and may contribute to the development of atherosclerosis in individuals with T2DM independent of other risk factors (6,19). In our previous study, we found that GV is an important contributing factor in the severity of CAD, which is independent of the average level of blood glucose (7). The Verona Diabetes study (20) reported that fasting GV is an independent predictor of mortality in T2DM patients. Some studies concluded that GV was a significant predictor of mortality in critically ill patients independently from mean glucose level and severity of illness (21–23). In the current study, patients with a higher MAGE level ($\geq 3.9 \text{ mmol/L}$) have higher GRACE risk scores. After 1-year follow-up, a significantly higher incidence of MACEs and cardiac mortality was found in those patients. The results indicate that high glucose fluctuations may be associated with the risk of future adverse cardiovascular events in patients with AMI. Multivariate analysis disclosed that in the AMI population, GV (i.e., MAGE $\geq 3.9 \text{ mmol/L}$) was an independent predictor of MACEs, even after adjusting for GRACE risk score.

Although stress-induced hyperglycemia can partly explain the relation between admission GV and outcomes, glucose excursion itself can also be harmful. Ceriello et al. (17) reported that intermittent hyperglycemia induced a higher degree of apoptosis in endothelial cells than chronic hyperglycemia. Quagliaro et al. (24) showed that the apoptosis of endothelial cells exposed to

Figure 2—A: Kaplan-Meier event-free survival curves for freedom from MACE in two patient groups by admission MAGE levels. The event-free survival rate was significantly lower in the high MAGE level patients (log-rank test, $P < 0.001$) (green dashed line: MAGE level $< 3.9 \text{ mmol/L}$; blue solid line: MAGE level $\geq 3.9 \text{ mmol/L}$). B: Kaplan-Meier event-free survival curves for freedom from MACE in two patient groups by admission glucose levels. The event-free survival rate was significantly lower in the high admission glucose level patients (log-rank test, $P = 0.011$).
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Table 2—Multivariate analysis of determinants of MACE

<table>
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<tr>
<th>Independent variables</th>
<th>Unstandardized coefficients</th>
<th>95% CI for Exp (B)</th>
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<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Constant</td>
<td>-8.476</td>
<td>3.405</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.120</td>
<td>0.045</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>1.254</td>
<td>0.446</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.062</td>
<td>0.019</td>
</tr>
<tr>
<td>MAGE ≥3.9 mmol/L</td>
<td>2.140</td>
<td>0.834</td>
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Exp(B): the exponentiation of the B coefficient.

Multivariate analysis of determinants of MACE

Intermittent high glucose may be related to a reactive oxygen species overproduction, through protein kinase C–dependent activation of NADPH-oxidase. Glucose excursion may also be an important mediator in inflammatory responses (25). In vitro studies indicate that glucose fluctuations can activate the nuclear factor-kB and protein kinase C pathway, leading to a greater expression of the adhesion molecules and excess formation of advanced glycation end products than stable high glucose (26,27). Moreover, severe glycemic disorders may adversely affect sympathetic dysfunction, which is associated with mortality and morbidity of cardiovascular disease (28); the thronbotic properties of platelets are increased in a hyperglycemic environment, and this can result in additional cardiovascular complications (29).

Although admission glucose, HbA1c, and GV may all be associated with adverse prognosis, our study shows that increased admission MAGE is more important. A significantly lower rate of event-free survival in patients with high admission glucose levels was observed in our Kaplan-Meier survival analysis. That result has confirmed the prognostic influence of admission glucose on outcomes of AMI patients as findings of previous trials. However, in the multivariate analysis, admission glucose was not found to be associated with the incidence of MACE, especially after adjustment for GRACE risk score. Acute hyperglycemia is an important contributing factor in glycemic excursions on admission. So there may be some interaction between admission glucose and GV. As a blood glucose value of point-in-time, admission glucose cannot accurately show dynamic changes of blood glucose as GV and can be influenced by many random factors. That may be why admission glucose does not show the independent association with incidence of MACE when analyzed with MAGE together in our study. Increased HbA1c represents long-term glucose regulation, whereas elevated admission glucose excursion is not only a symptom of glucose dysregulation, but also of stress and general poor health. Carmen Wong et al. (30) found cortisol level is correlated with acute hyperglycemia in patients with AMI. In our Kaplan-Meier survival-curve analysis, only a trend toward lower event-free survival rate in AMI patients with HbA1c ≥6.5% (P = 0.055) was observed. The less clear association between HbA1c and MACE could be due to a limited number of patients with a relatively short follow-up in present study. There is a clear association to be found between HbA1c and long-term outcome in AMI patients after 3.3 years of follow-up (31). So HbA1c may have limited predictive power on short-term prognosis in patients with AMI, but its association with long-term prognosis may be stronger.

There is still an extensive debate about GV as a risk factor for cardiovascular complications independent of HbA1c (32). Siegelaar et al. (33) performed reanalysis of the data of the HEART2D study, which shows that targeting postprandial glucose—decreased intraday GV would not be beneficial in reducing adverse cardiovascular events in AMI patients. However, the HEART2D study was not designed to determine the impact of GV on the risk of MACEs, and the MAGE and SD levels were not found significantly different between two contrasting groups in the study. In addition, the method of calculating GV from self-measured blood glucose profiles may be not very accurate.

Study limitations

The sample size was relatively small, so that some subgroup comparisons may have lacked power to detect significant differences for selected variables. Due to the lack of microvascular complications data, we did not include those risk factors in analysis. Although we had maintained the patients’ antihyperglycemic therapy as usual and avoided glucose infusion during the CGMS monitoring period, some factors, such as different diets, physical and emotional stress, etc., which may affect levels of admission glucose fluctuations, could not all be prevented. In addition, tests to detect diabetes were not routinely done, so some cases of diabetes may have been missed. However, if the observed relation between glucose excursion and MACE was due to undiagnosed diabetes, one would have expected a more distinct association between HbA1c and outcomes.

Elevated admission MAGE might predict risk of MACE in our AMI patients, but HbA1c did not. Acute glucose excursion in glycemic metabolism would seem to be of greater importance than admission glucose and long-term derangements of glucose metabolism in predicting 1-year outcomes in AMI. The results of this study further support the view that glucose variability should be one of the targets of treatment for the glycemic disorders encountered in AMI patients.

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G.S. designed the study, collected data, analyzed data statistically, and drafted the manuscript. S.-h.M. designed the study, contributed to the analysis with suggestions and advice, and critically reviewed and edited the manuscript. H.T. designed the study, contributed to the analysis with suggestions and advice, and critically reviewed and edited the manuscript.
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