Glycemic Variability on Continuous Glucose Monitoring System Predicts Rapid Progression of Non-Culprit Lesions in Patients With Acute Coronary Syndrome

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Background: Although rapid progression (RP) of coronary artery disease (CAD) has been shown to be a powerful predictor of cardiovascular events, predictors of RP are not fully understood in patients with acute coronary syndrome (ACS).

Methods and Results: We prospectively investigated the clinical impact of glycemic variability (GV), as determined on continuous glucose monitoring system (CGMS), on RP of non-culprit lesions in 88 patients with ACS. RP was defined as ≥10% diameter reduction in a pre-existing stenosis ≥50%; ≥30% diameter reduction in a stenosis <50%; development of a new stenosis ≥30% in a previously normal segment; or progression of any stenosis to total occlusion. Patients were classified into 2 groups according to the presence (progressor, n=20) or absence (non-progressor, n=68) of RP. All patients were equipped with a CGMS during the stable phase, and mean amplitude of glycemic excursion (MAGE) was calculated as a marker of GV. Mean MAGE was significantly higher in progressors than in non-progressors (55±19 mg/dl vs. 37±18 mg/dl, P<0.01). On multiple logistic regression analysis, MAGE was an independent predictor of RP (odds ratio, 1.06 per 1 mg/dl; P<0.01).

Conclusions: MAGE early after the onset of ACS is a predictor of RP of non-culprit lesions. (Circ J 2015; 79: 2246–2254)

Key Words: Acute coronary syndrome; Glycemic variability; Rapid progression

Although rapid progression (RP) of coronary artery disease (CAD) has been shown to be a powerful predictor of cardiovascular events,1 RP is unpredictable, even after the first coronary angiography (CAG). It does not appear to be associated solely with the severity of stenosis.2 In particular, RP of non-culprit lesions remains a residual issue in patients with acute coronary syndrome (ACS) because they have already had diseased vessels with culprit lesions.3–5 The ability to differentiate patients likely to have RP from those at low risk for RP would allow patients to be closely followed up while they receive optimal medical therapy. Monocyte/macrophage activation and systemic inflammation have been shown to play important roles in the progression of coronary atherosclerosis.6,7 The detailed mechanisms and predictors of RP, however, are not fully understood.

Impaired glucose metabolism is also associated with heart failure8 and is an established risk factor for CAD. Hyperglycemia and hypoglycemia are determined only at 1 time point and represent 2 extremes; therefore interest has focused on glycemic variability (GV). Monnier et al showed that activation of oxidative stress caused by GV is greater than that caused by sustained hyperglycemia.9 To evaluate GV accurately, the continuous glucose monitoring system (CGMS), a recent advance, provides continuous measurement of interstitial glucose, with correction by self-monitoring of blood glucose (SMBG).10 The aim of this study was to investigate whether GV as assessed on CGMS is a clinically useful predictor of RP of non-culprit lesions in patients with ACS.
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Glycemic Variability in ACS

Methods

Patients
We studied 88 patients with ACS who underwent percutaneous coronary intervention (PCI) in Yokohama City University Medical Center between April 2012 and February 2014. ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA; Supplementary Methods). Patients with any of the following characteristics were excluded: (1) lack of informed consent; (2) history of ACS; (3) history of coronary artery bypass grafting (CABG); (4) inability to detect clinically significant stenosis on initial CAG; (5) any medication use (including insulin) for diabetes mellitus (DM) or hyperglycemia; (6) serious clinical conditions. The study protocol was approved by the Yokohama City University Medical Center Institutional Review Board, and all patients gave written informed consent (UMIN-CTR ID: UMIN000010620).

CAG Analysis
We evaluated RP of non-culprit lesions not treated by PCI that occurred between initial and follow-up CAG (average, 11 ± 2 months later). Follow-up CAG was performed earlier if patients were readmitted for recurrence of ACS. Clinical management and the decision to proceed to CAG and PCI were left to the discretion of the attending cardiologist.

After direct intracoronary injection of 2.5 mg isosorbide dinitrate into the coronary arteries to exclude potential effects of coronary spasm, CAG was obtained in routine standardized projections with the use of an Infinix Cleva system (Toshiba, Tokyo, Japan). Quantitative CAG (QCA-CMS; QAngio XA 7.1; Medis Medical Imaging Systems, Leiden, the Netherlands) was performed to analyze the images of the coronary tree. Pairs of initial and follow-up CAG obtained in the same projection were quantitatively assessed by 2 cardiologists who were blinded to all other clinical data. The stem of a Judkins coronary catheter was used for calibration to determine absolute measurements in millimeters. For each segment, measurements were performed on end-diastolic frames in which the severity of stenosis appeared maximal. Stenosis >50% was considered clinically significant. The culprit lesion was considered the lesion with the most severe narrowing or the lesion with complex morphology, intracoronary thrombus, or both. PCI-treated lesions located within 20 mm of culprit lesions or within 20 mm of non-culprit lesions were excluded from analysis. Stenosis morphology was assessed in coronary lesions associated with ≥30% reduction in diameter. Stenosis was defined as complex (eccentric; with overhanging edges; irregular borders; and/or showing ulceration or thrombus). Similar to a previous study, RP was diagnosed in the presence of any of the following: ≥10% reduction in the diameter of a pre-existing ≥50% stenosis; ≥30% reduction in the diameter of <50% stenosis; development of a new stenosis with ≥30% reduction in the diameter of a segment that was normal on initial CAG; or progression of any lesion to total occlusion on follow-up CAG.

Patients were classified into 2 groups according to the presence or absence of RP of non-culprit lesions.

CGMS Protocol
All patients were equipped with a CGMS (iPro2, Medtronic, Minneapolis, MN, USA) in the stable phase after admission and were monitored for at least 24 consecutive hours. The CGMS sensor was inserted into the subcutaneous abdominal fat tissue. During CGMS monitoring, blood glucose level was checked at least 4 times per day with an SMBG device (Medisafe Mini, Terumo, Japan) to calibrate the CGMS data. We excluded patients who were receiving medication for DM or hyperglycemia to eliminate the effects of such drugs on GV; therefore, none of the subjects was receiving anti-diabetic medications (including insulin) before admission, during hospitalization, or between discharge and follow-up CAG in the present study. The data obtained by CGMS were recorded and analyzed offline (Figure 1). Analysis was based on data obtained during a 24-h period of monitoring, including 3 regular meals in the most stable phase of the patient’s condition as interpreted by 2 experienced observers (average of 926 days after admission). Mean amplitude of glycemic excursion (MAGE) was determined by calculating the arithmetic mean of the difference between consecutive peaks and nadirs if the difference is >1 SD of the mean glucose.

We examined the mean difference of glucose level between CGMS and SMBG device. The mean difference was ±7 mg/dL, and there was strong correlation between CGMS-derived glucose level and SMBG-derived glucose level (r=0.93, P<0.01).

Figure 1. Glycemic variability measured using continuous glucose monitoring system (CGMS). CGMS can visualize glycemic variability. Mean amplitude of glycemic excursion is calculated by measuring the arithmetic mean of the difference between consecutive peaks and nadirs (red arrows) if the difference is >1 SD of the mean glucose. ● Self monitoring of blood glucose.
75-g Oral Glucose Tolerance Test Protocol

All patients who had not been given a diagnosis of DM underwent a standard 75-g oral glucose tolerance test between the 4th hospital day and discharge, after their condition had stabilized (average of 11±7 days after admission). After an overnight fast, venous blood samples for the measurement of plasma glucose were taken at baseline and 30 min, 60 min, and 120 min after oral glucose load. DM, impaired glucose tolerance, and normal glucose tolerance were classified according to the American Diabetes Association criteria. HOMEostasis model assessment for insulin resistance (HOMA-R) and homeo-
sis model assessment β cell function (HOMA-β) were calculated according to the following formulae: HOMA-R=fasting insulin (µU/ml)×fasting glucose (mg/dl)/405; HOMA-β=[fasting insulin×360 (µU/ml)]/fasting glucose (mg/dl)–63.

Biochemical Markers

Blood samples for the measurement of plasma high-sensitivity C-reactive protein (hs-CRP) were serially taken on admission and then daily until discharge and 1 month after the onset of ACS. hs-CRP was measured using Nanopia CRP (Sekisui Medical, Tokyo, Japan). Lipid profiles were measured on admission, at 1 month after the onset of ACS and at follow-up CAG. Renal function, glucose, and hemoglobin A1c (HbA1c) were measured on admission. We excluded patients with any conditions known to modify hs-CRP level (cancer and inflammatory disease) from the assessment of hs-CRP.

Statistical Analysis

Continuous variables are expressed as mean±SD. Student’s t-test was used to compare differences in continuous variables among groups. For categorical variables, Fisher’s exact test or chi-squared test were used. Variables with P<0.05 on univariate analysis were entered into multiple logistic regression analysis using a forward stepwise algorithm. We then performed multivariate logistic regression analysis using forced inclusion models (model-1: age, male sex, body mass index, and MAGE level; model-2: hypertension, dyslipidemia, diabetes mellitus and MAGE level; model-3: current smoker, multiple complex lesion, MAGE level, and hs-CRP level at 1 month; model-4;
HbA1c, admission glucose level, and MAGE level) to identify clinical predictors of RP. Then, receiver operating characteristics (ROC) curves were constructed. The area under the curve (AUC), sensitivity, and specificity for predicting RP were calculated, with AUC=0.50 representing no accuracy, and AUC=1.00 indicating maximum accuracy. We defined the optimal thresholds of MAGE and hs-CRP by maximizing the sums of sensitivity and specificity. Positive and negative predictive values were also calculated. All statistical tests were 2-tailed, and P<0.05 was considered to indicate statistical significance. SPSS version 20.0 (SPSS Japan, Tokyo, Japan) was used for all statistical analysis.

**Results**

During an average follow-up of 11 months, 20 (23%) of the 88 patients had RP of non-culprit lesions: 2 patients had ≥10% reduction in the diameter of a pre-existing ≥50% stenosis, 4 had ≥30% reduction in the diameter of a pre-existing <50% stenosis, 12 had a new lesion with ≥30% stenosis in a previously normal segment, and 2 had progression of a lesion to total occlusion on follow-up CAG. If at least 1 lesion showed RP, we classified the patient as a progressor (n=20). No patient had ≥2 lesions with RP. Patients without RP were classified as non-progressors (n=68).

### Baseline Characteristics

Baseline patient characteristics are listed in Table 1. The only significant differences between the groups were in hs-CRP level at 1 month and medication at follow-up (Table 1).

### Glycemic Metabolism

Glycemic metabolism markers are given in Table 2. The only significant difference between the groups was in MAGE. MAGE was higher in the progressor group than in the non-progressor group (all P<0.01).
was significantly higher in the progressor group than in the non-progressor group (55±19 mg/dl vs. 37±18 mg/dl, P<0.01; Table 2; Figure 2).

In this population, asymptomatic hypoglycemia (<70 mg/dl) occurred in 7 patients. We could detect hypoglycemia in only 1 patient on SMBG; in the other 6 patients it was detected using CGMS. Hypoglycemia was not a predictor of RP in this study (odds ratio [OR], 1.36; 95% confidence interval [CI]: 0.24–7.59; P=0.73).

Angiography
On the basis of angiography, there were no significant differences between the groups except for coronary stenosis morphology (Table 3). We evaluated coronary stenosis morphology in a total of 241 lesions with ≥30% reduction in lumen diameter (mean, 2.7 per patient), consisting of 88 culprit lesions and 153 non-culprit lesions. Among the 241 lesions, 155 complex lesions (64%) were identified. Multiple complex lesions (64%) were observed in a higher proportion of patients with RP than in those without RP (70% vs. 40%, P<0.02; Table 3).

Assessment
In the present study, MAGE and hs-CRP at 1 month were higher in the progressor group than in the non-progressor group (both P<0.01; Figure 2). On univariate logistic regression analysis, DM, multiple complex lesions, admission glucose level, fasting glucose level, MAGE, hs-CRP at 1 month, and β-blocker use at follow-up were predictors of RP. Multivariate logistic regression analysis using a forward stepwise algorithm showed that MAGE was an independent predictor of RP (OR, 1.05 per 1 mg/dl; 95% CI: 1.02–1.08; P<0.01), model 2 (OR, 1.05 per 1 mg/dl; 95% CI: 1.02–1.08; P<0.01) and model 3 (OR, 1.05 per 1 mg/dl; 95% CI: 1.02–1.09; P<0.01; Table 4). In model 4, we included glycemic metabolism markers (HbA1c, admission glucose and MAGE). Only MAGE was an independent predictor of RP in model 4 (OR, 1.05 per 1 mg/dl; 95% CI: 1.02–1.08; P<0.01; Table 4).

ROC Analysis for the Prediction of RP
We defined the optimal thresholds of hs-CRP and MAGE by maximizing the sums of sensitivity and specificity. On ROC analysis, hs-CRP at 1 month was a significant predictor of RP (AUC, 0.735; 95% CI: 0.614–0.856; P=0.001; Figure 3A). When hs-CRP>0.1355 at 1 month was used as the cut-off, the sensitivity and specificity for the prediction of RP were 70% and 69%, respectively, with positive and negative predictive values of 40% and 89%, respectively. In addition, ROC analysis showed that MAGE was a significant predictor of RP (AUC, 0.780; 95% CI: 0.672–0.887; P<0.001; Figure 3B). When MAGE >44.035 was used as the cut-off, the sensitivity and specificity for the prediction of RP were 80% and 75%, respectively, with positive and negative predictive values of 48% and 93%, respectively.

When we divided all patients into 4 groups according to the cut-offs for hs-CRP at 1 month and MAGE, 58% of patients with both higher hs-CRP at 1 month and higher MAGE had RP. In contrast, only 3% of patients with both lower hs-CRP at 1 month and lower MAGE had RP (Figure 4).

Clinical Outcome
During follow-up, no patient died, underwent CABG, or was...
To our knowledge, this is the first study to show that MAGE is an independent predictor of RP of non-culprit lesions. Lichtlen et al reported that progression of coronary artery stenosis was more common than regression in patients with moderate lesions during 3 years of follow-up.

Subsequently, Kaski et al reported that complex lesions are associated with RP in patients with stable angina.

Zouridakis et al reported that RP is related to elevated hs-CRP, endothelial function, and elevated biochemical markers of macrophage activity.

Our previous study showed that RP is related to high hs-CRP and the presence of multiple complex lesions in patients with non-ST-

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†From the onset of acute coronary syndrome. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

Discussion

To our knowledge, this is the first study to show that MAGE is an independent predictor of RP of non-culprit lesions. Lichtlen et al reported that progression of coronary artery stenosis was more common than regression in patients with moderate lesions during 3 years of follow-up. Subsequently, Kaski et al reported that complex lesions are associated with RP in patients with stable angina. Zouridakis et al reported that RP is related to elevated hs-CRP, endothelial function, and elevated biochemical markers of macrophage activity. Our previous study showed that RP is related to high hs-CRP and the presence of multiple complex lesions in patients with non-ST-admitted because of stent thrombosis. Two patients (2%) were admitted because of recurrence of ACS involving another culprit lesion, and 1 patient (1%) was admitted because of recurrence of ACS involving the same culprit lesion. These 3 patients underwent follow-up CAG at an early timepoint. Twelve patients (14%) had initial target lesion restenosis at follow-up CAG, but there was no significant difference between the progressor group and non-progressor group (P=0.84; Table 3).

Among the 20 patients with RP, a total of 6 patients (4 patients with stable angina and 2 patients with ACS involving another culprit lesion) underwent PCI for clinically significant stenotic lesions that did not show appreciable stenosis on initial CAG.
RP in non-culprit lesions. We found that GV is a clinically significant predictive marker of RP of non-culprit lesions in patients with ACS, as well as a marker of the need for more aggressive therapy.

**GV in ACS**

GV reflects daily glycemic excursions including episodes of hyperglycemia and hypoglycemia. Hyperglycemia causes oxidative-stress-induced abnormalities in immune response and promotes vascular inflammation, a thrombogenic tendency, endothelial dysfunction, myocardial microangiopathy, and decreased collateral circulation. Acute hyperglycemia is also thought to abolish ischemic preconditioning. In contrast, hypoglycemia induces inflammation and triggers abnormal platelet function and fibrinolytic activity, endothelial dysfunction, and vasoconstriction and arrhythmias caused by the release of epinephrine. Recently, attention has focused on GV as a new index of risk. We recently reported that GV is associated with left ventricular remodeling in patients with STEMI. According to the current guideline for secondary prevention of MI, the only target value for glycemic control is HbA1c <7.0% but the inhibition of hyperglycemia and avoidance of hypoglycemia achieved by the suppression of GV is expected to lead to improved outcome in patients with ACS. Lipska et al reported that GV is unrelated to outcome in patients with acute MI but they did not assess GV on CGMS. CGMS is a prerequisite for the accurate evaluation of GV. Studies using CGMS to accurately evaluate GV in patients with ACS, however, remain scarce and have examined only the relationship of GV to in-hospital outcome, 1-year outcome, myocardial salvage index on cardiac magnetic resonance imaging, or coronary plaque rupture in culprit lesions. To our knowledge, this is the first to demonstrate an association between MAGE and RP.

**MAGE and RP**

GV is thought to be related to inflammation and endothelial dysfunction which contribute to the progression of atherosclerosis. GV is also a strong inducer of oxidative stress,
which directly promotes atherosclerosis.9 Taken together with the results of previous studies, the present findings suggest that increased GV augments inflammation, endothelial dysfunction, and oxidative stress and thereby leads to RP of CAD.

In the present study, the use of β-blockers during follow-up was also an independent predictor of RP. This might be due to the fact that the attending physicians considered patients with RP to be at high risk and therefore aggressively used β-blockers in such patients.

Clinical Implications
This study showed that GV is an independent predictor of RP. The recent advent of drug-eluting stents has markedly reduced the rate of restenosis of culprit lesions after PCI. An unresolved problem is whether GV contributes to the RP of non-culprit lesions in ACS, which is difficult to predict. Treatment with statins lowered low-density lipoprotein cholesterol and hs-CRP and inhibited the development of cardiovascular events in healthy adults with no history of cardiovascular disease.31 Prophylactic treatments that suppress RP by directly inhibiting inflammation, however, have yet to be established. In the present study, nearly all subjects received statins in accordance with treatment guidelines. The present results suggest that interventions designed to decrease GV might lead to the inhibition of RP. In the future, intervention studies should be performed to investigate whether the correction of GV effectively prevents RP in patients with ACS.

Study Limitations
The present study had some limitations. First, it was a small, prospective, observational trial conducted at a single center. Second, we did not measure markers of oxidative stress. Previous studies, however, have demonstrated that GV triggers oxidative stress,9 and this mechanism is now widely accepted. Third, patients who met the exclusion criteria were not included as subjects in the present study. It is therefore unclear whether the present results are applicable to such patients. For example, we studied only patients who were not receiving anti-diabetic medications. Clinically, patients with DM who are receiving anti-diabetic agents comprise an important high-risk group. But, even though we studied only patients who were not receiving anti-diabetic drugs, we consider it meaningful that RP could be accurately predicted on the basis of GV in a high proportion of patients. Fourth, inclusion criteria were different from our previous study.12 Fifth, in patients who have non-culprit lesions in the same culprit coronary artery as culprit lesions, injury to plaque or the coronary artery wall caused by the PCI guidewire might lead to RP. In the present study, however, the incidence of RP of non-culprit lesions did not differ between the culprit and non-culprit coronary artery (data not shown).

Conclusions
GV as defined by MAGE is an independent predictor of RP of non-culprit lesions in ACS. Measurement of GV using MAGE in addition to hs-CRP (high levels of which have previously been shown to be related to RP), can further enhance the ability to accurately predict RP and thus may identify patients who require more aggressive therapy.

Disclosures
Grant Support: None.

References

Supplementary Files
Supplementary File 1
Supplementary Methods