

[ORIGINAL ARTICLE]

Coronary Flow Reserve and Glycemic Variability in Patients with Coronary Artery Disease

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Abstract:

Objective Glycemic variability is being increasingly recognized as an early indicator of glucose metabolic disorder and may contribute to the development of diabetic vascular complications, such as coronary microvascular dysfunction. The present study sought to investigate the relationship between coronary microvascular function assessed by intracoronary thermodilution method and glycemic variability on a continuous glucose monitoring system (CGMS).

Methods We prospectively enrolled 40 patients with or without known diabetes mellitus who had epicardial coronary artery disease referred for coronary angiography and were not treated with diabetic medications. Of these, two had a significant stenosis in the left main coronary artery and were therefore excluded from the analyses. In the end, 38 patients were equipped with a CGMS and underwent intracoronary physiological assessments in the unobstructed left anterior descending artery. The mean amplitude of glycemic excursion (MAGE) and standard deviation were calculated from the obtained CGMS data as indicators of glucose variability.

Results Coronary flow reserve (CFR) was negatively correlated with MAGE ($r=-0.328$, $p=0.044$) and standard deviation ($r=-0.339$, $p=0.037$) on CGMS, while the index of microcirculatory resistance showed no such correlation. Multivariable linear regression analyses showed that MAGE on CGMS was significantly associated with CFR after adjusting for age, sex, fractional flow reserve and hemoglobin A1c.

Conclusion Higher MAGE on CGMS was associated with reduced CFR in stable patients with coronary artery disease, suggesting a potential effect of glycemic variability on coronary microvascular flow regulation. A further study with a larger sample size needs to be conducted to confirm our findings.

Key words: coronary flow reserve, diabetes mellitus, glycemic variability

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Introduction

Diabetes mellitus (DM) is a major risk factor for ischemic heart disease, and its prevalence is increasing worldwide. A large contribution to morbidity and mortality of patients with DM can be attributed to the accelerated development of obstructive coronary artery disease (CAD) (1). However, it is increasingly recognized that coronary microvascular dysfunction is an early feature of DM that may precede macrovascular disease and constitutes a major component of DM-associated CAD (2-5). Previous studies have demon-

strated that coronary flow reserve (CFR) was impaired in patients with DM and angiographically normal coronary arteries (6-9), suggesting that not only atherosclerosis of epicardial coronary arteries but also dysfunction of coronary microvascular function may play a significant role in the development of DM-related CAD.

The development of DM is usually preceded by a variable interlude of prediabetes, characterized by impaired fasting glucose or impaired glucose tolerance (IGT) (10-12). Previous studies have indicated that the microvascular complications of DM can manifest even during the prediabetes stage (13-15).

The diagnosis of glucose intolerance or prediabetes is traditionally based on the 75-g oral glucose tolerance test (OGTT) and hemoglobin A1c (HbA1c) (16). Recently, the importance of impaired glucose homeostasis and glycemic variability as an early indicator of glucose metabolic disorder has been highlighted (17-20). With the introduction of reliable and comfortable continuous glucose monitoring system (CGMS), it became possible to accurately investigate the glycemic variability (21). In fact, glycemic variability as measured by CGMS was shown to be associated with epicardial CAD (22-26). However, its contribution to coronary microvascular function remains unclear.

A validated thermodilution-derived method for assessing coronary microvascular function by measuring coronary flow and pressure simultaneously with a single coronary wire enables measurement of CFR and the index of microcirculatory resistance (IMR), which are commonly used to assess coronary microvascular function and have been shown to have prognostic implications in various cardiac conditions (27-31).

The present study sought to investigate the relationship between glycemic variability and CFR and microvascular resistance as assessed by the invasive intracoronary thermodilution-derived method.

Materials and Methods

This was a prospective, cross-sectional, observational study designed to evaluate the relationship between coronary microvascular function and glucose metabolism, particularly glycemic variability. We recruited patients who were ≥ 20 years old, had been referred to the cardiac catheterization laboratory for follow-up coronary angiography (CAG) 9 months after stent implantation and were willing and able to give their written informed consent. Exclusion criteria included any of the following: prior myocardial infarction in the left anterior descending artery (LAD) territory; acute decompensated heart failure; acute coronary syndrome; and any contraindication to CGMS (e.g. severe skin disease and severe blood disorder). If CAG revealed significant stenosis in the left main coronary artery or the LAD [defined as $> 50\%$ diameter stenosis and/or fractional flow reserve (FFR) < 0.75], patients were excluded from the analyses.

The protocol was approved by the institutional review boards, and the study was conducted in accordance with regulatory standards. All patients provided their written informed consent. The present study was registered at the University Hospital Medical Information Network Clinical Trials Registry (number: UMIN000022401).

CAG was performed in the standard fashion via the radial or brachial artery on the second day of hospitalization. Quantitative coronary angiography (QCA) was performed with a contour-detection QCA system (QAngioXA V.7.1; Medis, Leiden, The Netherlands). Parameters, including percent diameter stenosis, minimum lumen diameter, reference vessel size and vessel size of the most proximal part of the

LAD, were reported.

After coronary angiography, CFR, IMR and FFR were measured in the LAD by methods previously described using a 6-F guiding catheter without side holes and a 0.014-inch pressure-temperature sensor guidewire (PressureWire Certus; St. Jude Medical, St. Paul, USA) (32-34). Intracoronary isosorbide dinitrate (at least 0.5 mg) was administered prior to wire advancement. Maximal hyperemia was induced using either a single bolus of 12 mg of intracoronary papaverine or 140 $\mu\text{g}/\text{kg}/\text{min}$ of intravenous adenosine or adenosine 5'-triphosphate via a central venous catheter. The mean transit time (Tmn), which is inversely proportional to flow, was calculated as an average of three transit time of room-temperature saline manually injected via the guiding catheter. Tmn and the mean aortic (Pa) and distal coronary pressures (Pd) were measured at rest and during peak hyperemia. FFR was calculated by the ratio of Pd/Pa at hyperemia. CFR was calculated as resting Tmn divided by hyperemic Tmn. IMR was calculated as Pd at hyperemia multiplied by hyperemic Tmn. The cut-off values for abnormal findings were set as follows in the present study: IMR ≥ 25 (high IMR), FFR ≤ 0.80 (low FFR) and CFR ≤ 2.5 (low CFR) (31, 35, 36).

Reactive hyperemia index (RHI) was measured by reactive hyperemia peripheral arterial tonometry (RH-PAT) using an Endo-PAT2000 (Itamar Medical, Caesarea, Israel). (34) RHI assesses the extent of digital reactive hyperemia which is considered to be associated with peripheral endothelial function. An RHI of 1.67 was recommended as a cut-off for a normal endothelial function in the user manual of the EndoPAT 2000. RH-PAT studies were carried out in the fasting state in the early morning.

Blood samples were taken in the morning after 12 hours of fasting, and a 75-g OGTT was performed to diagnose DM. DM was defined as a 2-hour plasma glucose level following the 75-g OGTT of ≥ 200 mg/dL (11.1 mmol/L) or a fasting plasma glucose (FPG) level of ≥ 126 mg/dL (7.0 mmol/L), IGT as a 2-hour OGTT of 140-199 mg/dL (7.8-11.0 mmol/L) and normal glucose tolerance (NGT) as a 2-hour OGTT of < 140 mg/dL (7.8 mmol/L) (37). Immune reactive insulin (IRI), HbA1c, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride values were evaluated. The homeostasis model assessment (HOMA) was used to evaluate pancreatic β cell function (HOMA- β) and insulin resistance (HOMA-IR), which were mathematically calculated by the following formulae (38): HOMA-IR = FPG (mg/dL) \times fasting IRI ($\mu\text{U}/\text{mL}$)/405; HOMA- β (%) = IRI $\times 360$ / FPG-63.

CGM was performed under stable conditions without any treatment with anti-diabetic drugs during hospital admission. Study patients were equipped with a fourth-generation CGMS (iPro2, Medtronic, USA). A CGMS sensor was inserted into the subcutaneous abdominal fat tissue. The i-Pro 2 uses a retrospective algorithm to convert sensor signals to glucose levels based on self-monitored capillary blood glucose readings; therefore, the blood glucose values were

checked at least four times per day using the finger-stick test. The median duration of CGM was 45.0 hours [interquartile range (IQR) of 39.9-46.0 hours]. CGMS data obtained on the second day of monitoring were used for the evaluation. The mean and max glucose level and percentage of time spent in hypoglycemia (<70 mg/dL) and hyperglycemia (>140 mg/dL) were evaluated from the CGMS data. The mean amplitude of glycemic excursion (MAGE) and standard deviation (SD) of glucose were calculated as indicators of glycemic variability. The MAGE was calculated by measuring the arithmetic mean of differences between consecutive peaks and nadirs, provided that the differences were greater than one SD of the mean glucose value; measurements in the peak-to-nadir or nadir-to-peak directions were determined by the first qualifying excursion (39). In addition, we evaluated the area under the curve (AUC) above the limit and AUC below the limit, which provide a relative indication of the overall extent and duration of high and low glucose excursions over the entire day, respectively.

End points and statistical analyses

The predefined primary outcome was the difference in the IMR between high and low glycemic variability based on the median MAGE value. The key predefined secondary outcome was the correlation between the coronary physiological indices (i.e. IMR, CFR, and FFR) and CGMS findings, HbA1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglyceride and RHI. The other analyses were exploratory ones decided after data collection.

Based on previous studies (40, 41), we estimated that a between-group difference in IMR of approximately 10 (20 vs. 30 with SD of 9.1) would be clinically relevant. Based on these assumptions, we estimated that 40 patients would be required for a power of 80% and a 2-sided α level of 0.05, assuming a dropout rate of 10%. Continuous data are expressed as the mean \pm SD or median (IQR) with analyses conducted using Student's *t*-test or the Mann-Whitney *U* test as appropriate. Categorical variables were expressed as numbers or percentages. The correlation between two quantitative variables was assessed by Pearson's correlation or Spearman's correlation, as appropriate. Multivariable linear regression models were used to evaluate whether or not glucose metabolic indices on the CGMS that were significantly correlated with CFR in the univariable analysis remained significantly associated after adjusting for age, sex, variables with a *p* value of <0.1 in the univariable analyses and FFR as an indicator of physiological severity of the epicardial artery. A 2-sided *p* value <0.05 was considered significant. Statistical analyses were performed using the SPSS software program, version 24 (IBM, Armonk, USA).

Results

A total of 40 subjects were enrolled between June 2015 and June 2016 at Chiba University Hospital. Of these, two

subjects had a significant stenosis in the left main coronary artery and were thus excluded from the analyses. The clinical and angiographic characteristics, laboratory data, CGMS data and coronary physiological indices of the examined 38 subjects are shown in Table 1. Based on the 75-g OGTT, 9 patients were diagnosed with DM (3 had been previously diagnosed, and 6 were newly diagnosed); 16 patients were considered to have an IGT, and the remaining 13 were considered to have an NGT. The median HbA1c was 5.8% (IQR 5.68%, 6.10%) ranging from 5.3% to 6.9%. The MAGE was 84.4 \pm 35.9 mg/dL [median 84.7 (IQR 51.2, 108.8)]. No significant difference in the coronary indices was found between the high (\geq the median of 84.7) and low (<84.7) MAGE groups, including in the CFR (3.2 \pm 1.4 vs. 3.9 \pm 1.3, *p*=0.15), FFR (0.89 \pm 0.04 vs. 0.88 \pm 0.06, *p*=0.38) and IMR [16.0 (11.0, 25.0) vs. 13.0 (11.0, 24.0), *p*=0.39]. In addition, baseline and hyperemic Tmn were not significantly different between the high and low MAGE groups [0.82 (0.59, 1.08) vs. 0.88 (0.55, 1.12), *p*>0.99; 0.28 (0.20, 0.39) vs. 0.18 (0.15, 0.36), *p*=0.065]

Of the 38 patients, low CFR (\leq 2.5) and high IMR (\geq 25) were observed in 10 (26%) and 9 patients (24%), respectively. MAGE (106.6 \pm 35.1 vs. 76.4 \pm 33.3, *p*=0.020) and SD (42.1 \pm 14.9 vs. 31.7 \pm 12.4, *p*=0.037) were higher in patients with low CFR than in those with high CFR, while there were no significant differences in MAGE (92.2 \pm 41.3 vs. 81.9 \pm 34.5, *p*=0.46) or SD (36.6 \pm 16.0 vs. 33.8 \pm 13.1, *p*=0.60) between the high and low IMR groups.

CFR showed a negative correlation with MAGE, SD, max glucose level and AUC above limit (Table 2), whereas FFR, IMR, resting Tmn and hyperemic Tmn did not significantly correlate with those variables. RHI did not significantly correlate with CFR or IMR. In multivariable linear regression analyses, high MAGE, max glucose level and AUC above limit on the CGMS remained significantly associated with reduced CFR after adjusting for age, sex, FFR and HbA1c (Table 3).

Discussion

The present study investigated the relationship between indicators of glucose metabolism and coronary physiological parameters in patients with or without known DM who were not taking diabetic medication and demonstrated that low CFR was associated with impaired glucose metabolism, including high MAGE, max glucose level and AUC above limit on the CGMS.

Previous studies have shown that larger glycemic variability on CGM is associated with a higher rate of adverse cardiac events in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome and stable CAD (42-45). This is likely due to the accelerated development of diabetic coronary vascular complications. In fact, recent studies have shown that glycemic variability is associated with the progression of coronary macrovascular disease, including the presence and severity of CAD as well as the

Table 1. Clinical and Angiographic Characteristics, Laboratory and CGMS Data and Coronary Physiological Indices.

Age, years	68±9
Male	35 (92%)
BMI, kg/m ²	23.8±3.0
Hypertension	27 (71%)
Dyslipidemia	26 (68%)
Chronic kidney disease	5 (13%)
Current smoking	3 (8%)
Formerly diagnosed diabetes mellitus	3 (8%)
Family history of CAD	6 (16%)
Prior MI (Non-LAD territory)	10 (26%)
Prior PCI	38 (100%)
Vessels treated with PCI	
Right coronary artery	18 (47%)
LAD	28 (74%)
Left circumflex	13 (34%)
Left main coronary artery	5 (13%)
LVEF, %	62.7 [60.1, 65.4]
Medications	
Statins	34 (90%)
Beta blocker	15 (40%)
Calcium channel blocker	19 (50%)
ACEI or ARB	18 (47%)
Angiographic data	
LAD maximum diameter, mm	3.7±0.6
MLD, mm	2.3±0.6
%diameter stenosis, %	25±9
Laboratory data	
Total cholesterol	146.2±24.0
LDL cholesterol	82.6±21.9
HDL cholesterol	44.0 [39.3, 53.3]
Triglyceride	120.9±42.6
Hemoglobin A1c, %	5.9±0.3
Fasting plasma glucose level, mg/dL	96.7±13.0
1-h plasma glucose level during OGTT, mg/dL	184.3±45.9
2-h plasma glucose level during OGTT, mg/dL	168.8±47.5
Fasting IRI	5.9 [4.2, 7.3]
HOMA-β, %	66.2 [43.0, 83.9]
HOMA-IR	1.41 [0.93, 1.76]
CGMS data	
Standard deviation	34.5±13.7
MAGE, mg/dL	84.4±35.9
Maximum glucose level	208.8±45.3
Mean glucose level	118.5 [109.5, 127.3]
AUC above limit	7.0 [2.3, 13.0]
AUC below limit	0.0 [0.0, 0.4]
Peripheral endothelial function	
RHI	1.82±0.51
Coronary physiological indices	
Resting Pd	79.58±13.39
Hyperemic Pd	66.82±12.229
Resting Tmn	0.84 [0.58, 1.09]
Hyperemic Tmn	0.22 [0.17, 0.37]
CFR	3.5±1.4
FFR	0.88±0.05
IMR	14.0 [11.0, 24.3]

Data are expressed as the mean±standard deviation, median values [interquartile range], or number (percentage). ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, AUC: area under the curve, CAD: coronary artery disease, CCB: calcium channel blocker, CFR: coronary flow reserve, CGMS: continuous glucose monitoring system, FFR: fractional flow reserve, HDL: high-density lipoprotein, HOMA: Homeostatic Model Assessment, IMR: the index of microcirculatory resistance, IRI: immunoreactive insulin, LAD: left anterior descending coronary artery, LDL: low-density lipoprotein, LVEF: left ventricular ejection fraction, MAGE: mean amplitude of glycemic excursion, MI: myocardial infarction, MLD: minimum lumen diameter, OGTT: oral glucose tolerance test, PCI: percutaneous coronary intervention, RHI: reactive hyperemia index

Table 2. Correlation between CFR and Indicators of Glucose Metabolism, Lipid Profile and RHI.

	CFR		IMR		FFR	
	Correlation coefficient	p value	Correlation coefficient	p value	Correlation coefficient	p value
MAGE	-0.328	0.044	0.201*	0.23	0.233	0.16
Standard deviation on CGMS	-0.339	0.037	0.167*	0.32	0.168	0.31
Maximum glucose level	-0.405	0.012	0.156*	0.35	0.195	0.24
Mean glucose level	-0.311*	0.057	0.034*	0.84	0.120*	0.47
Minimum glucose level	-0.064	0.703	-0.120*	0.47	-0.064	0.70
AUC above limit	-0.359*	0.027	0.159*	0.34	0.253*	0.13
AUC below limit	-0.111*	0.51	0.262*	0.112	-0.101*	0.55
Hemoglobin A1c, %	-0.354*	0.029	0.067*	0.69	-0.145*	0.39
Fasting plasma glucose level	-0.096	0.57	0.100*	0.55	0.054	0.75
1-h plasma glucose level during OGTT	-0.151	0.37	0.130*	0.44	0.096	0.57
2-h plasma glucose level during OGTT	-0.088	0.60	0.312*	0.057	0.044	0.79
Fasting IRI	-0.048*	0.78	0.074*	0.66	-0.062*	0.71
HOMA- β	-0.007*	0.97	0.061*	0.72	-0.085*	0.61
HOMA-IR	-0.048*	0.77	0.112*	0.51	0.026*	0.88
Total cholesterol	-0.216	0.19	0.250*	0.13	0.192	0.25
LDL cholesterol	-0.187	0.26	0.262*	0.11	0.101	0.55
HDL cholesterol	-0.199*	0.23	-0.071*	0.67	0.118*	0.48
Triglyceride	0.027	0.87	-0.051*	0.76	0.017	0.92
RHI	-0.134	0.42	-0.063*	0.71	0.041	0.81

AUC: area under the curve, CFR: coronary flow reserve, CGMS: continuous glucose monitoring system, HDL: high-density lipoprotein, HOMA: Homeostatic Model Assessment, IMR: the index of microcirculatory resistance, IRI: immunoreactive insulin, LDL: low-density lipoprotein, LVEF: left ventricular ejection fraction, MAGE: mean amplitude of glycemic excursion, OGTT: oral glucose tolerance test, RHI: reactive hyperemia index

*Spearman's correlation coefficient, otherwise: Pearson's correlation coefficient.

coronary plaque volume and vulnerability assessed by intra-coronary imaging (22-26). DM-related vascular dysfunction is not limited to the epicardial coronary arteries but extends to the coronary microvasculature. In a similar way, glycemic variability can affect both the epicardial coronary arteries and coronary microvasculature. The present study provides additional evidence of the link between glycemic variability and coronary microvascular dysfunction in the early stages of glycemic disorder by showing a significant correlation between CFR impairment and MAGE on the CGMS.

In patients with no significant epicardial stenosis, both CFR and IMR are commonly used to assess the microvascular status, with impairment of either described as microvascular dysfunction. CFR represents the flow ratio between hyperemic and resting states, while IMR represents microvascular resistance in a hyperemic state. Therefore, some patients have discordant results, as observed in the present study where impairment of CFR, but not IMR, was associated with higher glycemic variability and higher max glucose level on the CGMS. A previous cross-sectional study in which thermodilution-derived CFR and IMR were assessed in 13 and 17 patients with and without a history of DM, respectively, showed that CFR was significantly lower in those with a history of DM than in those without such a history, whereas IMR was not significantly different (8). Of note, that study included patients in the early stage of glucose metabolic impairment or DM, suggesting a link between

glucose metabolic disorder and functional microvascular dysfunction or impairment of the coronary flow regulation in such populations when obvious increased hyperemic microvascular resistance does not exist. DM-related coronary microvascular impairment may occur in a time-dependent manner; structural microvascular dysfunction may be observed in the late phase of DM, preceded by functional microvascular dysfunction in the early phase (46).

Although many factors are involved in the pathophysiology of DM-related microvascular dysfunction, hyperglycemia is known to be the primary culprit in the pathogenesis of diabetic microvascular complications. This induces acute changes in cellular metabolism, such as glycation and consequent inactivation of proteins involved in the control of the microvascular function. In addition, hyperglycemia can activate and be activated by several other mechanisms, such as the generation of advanced glycation end products, polyol, activation of the diacylglycerol-protein kinase C pathways and inflammation (47). Increased oxidative stress is the unifying element common to all pathways through which the various mechanisms interact to cause DM-related cardiomyopathy and endothelial dysfunction, which is likely the primary mechanism responsible for the development of coronary microvascular dysfunction (47).

Previous studies have suggested that glycemic variability has a more powerful effect on oxidase stress and endothelial dysfunction than constant hyperglycemia. A case control

Table 3. Relationship between CFR and the Indicators of Glucose Metabolism on CGMS in Multivariable Linear Regression Models.

	Beta	95% CI Lower	95% CI Upper	p value
Model 1				
MAGE	- 0.01	- 0.03	0.00	0.049
Age	- 0.02	- 0.07	0.03	0.51
Sex (male)	1.06	- 0.52	2.64	0.18
Hemoglobin A1c	- 0.83	- 2.17	0.51	0.22
FFR	3.92	- 6.03	13.86	0.43
Model 2				
Standard deviation	- 0.03	-0.07	0.002	0.063
Age	- 0.01	-0.06	0.04	0.69
Sex (male)	1.13	-0.47	2.72	0.16
Hemoglobin A1c	- 0.80	-2.17	0.56	0.24
FFR	3.64	-6.34	13.61	0.46
Model 3				
Maximum glucose level	- 0.01	- 0.02	-0.001	0.031
Age	- 0.02	- 0.07	0.03	0.51
Sex (male)	0.93	- 0.63	2.48	0.23
Hemoglobin A1c	- 0.47	- 1.91	0.97	0.51
FFR	4.35	-5.53	14.22	0.38
Model 4				
AUC above limit	- 0.06	-0.12	-0.003	0.041
Age	- 0.02	-0.07	0.03	0.47
Sex (male)	1.11	-0.47	2.68	0.16
Hemoglobin A1c	- 0.33	-1.86	1.21	0.67
FFR	3.36	-6.39	13.1	0.49

In the multivariable linear regression models, CFR is a dependent variable, and the key independent variables are CGMS parameters with a significant association with CFR in the univariable analysis, including the MAGE, standard deviation, max glucose level and AUC above the limit on the CGMS. Because those variables have significant and strong mutual correlations (all correlation coefficients > 0.80, all $p < 0.001$), we put those variables into separate models (Model 1, 2, 3 and 4). All models were adjusted for age, sex, physiological severity of the epicardial coronary artery as assessed by FFR and variables with a p value of < 0.1 in the univariable analysis (i.e. hemoglobin A1c).

AUC: area under the curve, CFR indicates coronary flow reserve, CI: confidence interval, CGMS: continuous glucose monitoring system, MAGE: mean amplitude of glycemic excursion

study (48) reported that glycemic variability on CGMS showed a more specific triggering effect of oxidative stress, as estimated from 24-hour urinary excretion rates of free 8-iso prostaglandin F₂α, than chronic sustained hyperglycemia. In addition, an *in vitro* study explored the effect of fluctuating glucose levels on endothelial cells, showing that both intermittent and high glucose concentrations stimulated apoptosis in human umbilical vein endothelial cells, although intermittent glucose concentrations appeared to worsen the proapoptotic effects of high glucose (49). These findings suggest that glucose fluctuations may play a significant role in the pathogenesis of DM-related coronary microvascular as well as macrovascular dysfunction, likely contributing to the incidence of adverse cardiac events. Further studies are warranted to determine whether or not addi-

tional glycemic variability control will decrease the diabetic coronary microvascular dysfunction and improve clinical outcomes.

Limitations

Several limitations associated with the present study warrant mention. First, this was a single-center study with a relatively small number of subjects. Extensive multivariable adjustment was unable to be performed due to the small sample size in the linear regression models. Our findings will need to be confirmed in further investigations with a larger sample size. Second, we investigated the coronary physiology only in the LAD because variations in the coronary tree might rarely be expected in the LAD compared with the left circumflex and right coronary arteries. This limits the generalizability of the results to other coronary territories. Third, all of the subjects enrolled in the present study had established epicardial CAD previously treated with percutaneous coronary intervention. They likely had a greater risk for diabetic vascular complications than the general population referred to the catheterization laboratory for coronary artery evaluations. Fourth, this study was a cross-sectional study in which both CGM and coronary physiological evaluations were performed during the same time period; the analysis was based on the assumption that a glycemic assessment during hospitalization would reflect prior glycemic variability affecting the coronary physiology, although this assumption might not be necessarily the case. Therefore, we were unable to confirm a causal relationship between glycemic metabolic disorder assessed by the CGMS and the CFR impairment. Finally, the patients included in the present study were heterogeneous in terms of their diabetic status; in particular, we included 13 NGT patients. In addition, the diabetic patients included in the present study (16 FGT and 9 DM patients based on the 75-g OGTT) represent those in the early stage of glucose metabolic impairment. Had we included more severe diabetic patients, the results might have been different; both IMR and CFR might correlate with the indicators of glycemic disorder.

Conclusions

In conclusion, impaired glucose metabolism, including higher MAGE, max glucose level and AUC above the limit on the CGMS, were associated with reduced CFR in stable patients with CAD who were not taking anti-diabetic medications. This suggests a potential effect of glycemic variability as well as hyperglycemia on impairment of coronary flow regulation. However, the correlation was modest in the present study, which had a small sample size and heterogeneity of diabetic conditions. A further study with a larger sample size will need to be conducted to confirm our findings.

Author's disclosure of potential Conflicts of Interest (COI).

Yoshio Kobayashi: Honoraria, Abbott Medical Japan, DAIICHI SANKYO, Bayer Yakuhin, Bristol-Myers Squibb and Nippon

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