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【 ORIGINAL ARTICLE 】

Association between Changes in the Systolic Blood Pressure from Evening to the Next Morning and Night Glucose Variability in Heart Disease Patients

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Abstract:

Objectve To assess the impact of glycemic variability on blood pressure in hospitalized patients with cardiac disease.

Methods In 40 patients with cardiovascular disease, the glucose levels were monitored by flash continuous glucose monitoring (FGM; Free-Style Libre™ or Free-Style Libre Pro; Abbott, Witney, UK) and self-monitoring blood glucose (SMBG) for 14 days. Blood pressure measurements were performed twice daily (morning and evening) at the same time as the glucose level measurement using SMBG.

Results The detection rate of hypoglycemia using the FGM method was significantly higher than that with the 5-point SMBG method (77.5% vs. 5.0%, p<0.001). Changes in the systolic blood pressure from evening to the next morning [morning - evening (ME) difference] were significantly correlated with night glucose variability (r=0.63, P<0.001). A multiple regression analysis showed that night glucose variability using FGM was more closely correlated with the ME difference [r=0.62 (95% confidence interval, 0.019-0.051); p< 0.001] than with the age, body mass index, or smoking history. Night glucose variability was also more closely associated with the ME difference in patients with unstable angina pectoris (UAP) than in those with acute myocardial infarction (AMI) or heart failure (HF) (r=0.83, p=0.058).

Conclusion Night glucose variability is associated with the ME blood pressure difference, and FGM is more accurate than the 5-point SMBG approach for detecting such variability.

Key words: cardiovascular diseases, flash continuous glucose monitoring system, glycemic variability

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Introduction

Several studies have recently addressed the importance of glycemic variability in heart disease (1-5). Optimal glycemic control in the acute phase after myocardial infarction improves cardiac outcomes, although poor glycemic control increases the risk of heart failure caused by metabolic disturbance, interstitial fibrosis, microcirculation disturbances, and cardiac autonomic neuropathy (1, 6, 7). Conversely, strict glycemic control increases the risk of hypoglycemia, which can induce adverse events (8). An increased blood pressure can be induced by hypoglycemia through sympathetic nerve activation in type 2 diabetic patients (9).

Flash glucose monitoring (FGM) is one why by which individuals can determine their own glucose levels (10).

The present study assessed the impact of glycemic variability assessed using FGM on blood pressure and determined the incidence of hypoglycemia in such patients compared with those using self-monitored blood glucose (SMBG) levels among hospitalized patients with cardiac disease.

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Materials and Methods

Subjects

We studied 40 patients admitted to the University of Fukui with cardiovascular disease between September 2017 and March 2018. Smoking was defined as having a current or previous smoking habit. Diabetes was defined as ≥1 of the following: self-reported diabetes, the use of diabetes medication, fasting plasma glucose level ≥126 mg/dL, or hemoglobin A1c (National Glycohemoglobin Standardization Program) value ≥6.5%. The clinical histories of the patients were obtained from interviewing the patients' own doctors.

Study protocol

After the purpose and methods of this study had been explained to patients, they provided their written informed consent for participation in this study.

Continuous glucose levels were monitored in the present study by FGM (Free-Style Libre™ or Free-Style Libre Pro; Abbott, Witney, UK) and SMBG. All patients had Free-Style Libre™ or Free-Style Libre Pro™ sensors implanted in their left upper arm within a few days after hospitalization. Glucose levels were recorded by the FGM system for up to 14 days, excluding the first 2 days after sensor implantation because of the risk of errors due to inflammatory reactions, which might have resulted in unstable glucose data (10). We excluded patients with unstable hemodynamics (using catecholamine, sedation, having ventricular arrhythmia, and ventilator management), receiving insulin treatment, and with infection disease from this study.

As hypoglycemia was defined as a glucose level <70 mg/dL, the detection rate of hypoglycemia was estimated for both FGM and 5-point SMBG (5 timepoints: early morning; before breakfast, lunch, and dinner; and before bedtime). Glucose variability was expressed as the standard deviation (SD). Blood pressure measurements were performed twice daily (morning and evening) at the same time as the glucose level measurement using SMBG. In this study, the difference in the morning and evening values (ME difference) was defined as the morning systolic blood pressure minus the evening systolic blood pressure.

This study was approved by the ethics committee of our institution and complied fully with the Declaration of Helsinki. A series of patients who underwent a diagnostic procedure were used as the controls, and the follow-up results were registered in the Universal Hospital Medical Information Network Clinical Trials Registry (UMIN000023837)

Statistical analyses

All statistical analyses were performed using the EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria), and Statcel 4 software, OMS Publishing, Saitama, Japan (11). Data are presented as frequencies and percentages for categorical variables, the median for abnormal distributed parameters, and the mean±SD for continuous distributed variables. Differences between categorical variables were assessed using the χ^2 test. The correlation between continuous variables was determined by Spearman's rank-order correlation coefficient. To ascertain the independent contribution to the ME blood pressure difference, a multiple regression analysis was made. A value of $p<0.05$ was considered statistically significant.

Results

Patients' characteristics

This study included 40 patients (23 with ST-elevated acute myocardial infarction, 6 with unstable angina, and 11 with heart failure caused by non-ischemic disease). Twenty-one patients with acute myocardial infarction and six with unstable angina underwent percutaneous coronary intervention (PCI), while two patients with acute myocardial infarction did not undergo PCI due to old age and renal dysfunction. The patient characteristics are listed in Table 1. Diabetes mellitus was observed in 47.5% of patients, and 27 patients (67.5%) had a history of hypertension. Seventeen patients (42.5%) were taking ≥1 antidiabetic medication (Table 1). All patients were taking one or more cardioprotective medications [avoid prescribing an angiotensin-converting enzyme-inhibitor (ACE-I), angiotensin receptor blocker (ARB), β-blockers] in the morning.

Detection rate of hypoglycemia

We estimated the detection rate of hypoglycemia (glucose <70 mg/dL) with both FGM and 5-point SMBG, and the rate was significantly higher using FGM than 5-point SMBG (77.5% vs. 5.0%, $p<0.001$). Furthermore, glucose levels <50 mg/dL, which can cause neurogenic symptoms, were detected in 11 patients (27.5%) with FGM (Fig. 1). Fig. 2 shows the frequency of hypoglycemia per unit time from 0:00 to 23:00 during the total observation period (396 days) for all patients.

The correlation between the ME difference and night glucose variability

Night glucose variability was defined as SD from 22:00 to the next morning at 6:00 during the period when glucose levels were continuously monitored by FGM. Changes in the systolic blood pressure from evening to the next morning (ME difference) were significantly correlated with the night glucose variability ($r=0.63$, $p=0.000015$) (Fig. 3).

We examined the factors affecting the ME blood pressure differences using a multiple regression analysis and found that the night glucose variability determined using FGM was more closely correlated with the ME difference than the age, body mass index, or smoking history [total patients: $r=0.62$ (95% confidence interval {CI}, 0.019-0.051), $p=0.0001$; DM

Table 1. Patients' Characteristics.

	Total (n=40)	DM (n=19)	Non-DM (n=21)
Age, years old	70.0±11.0	72.0±8.4	68.0±12.6
Sex(male), n(%)	31(77.5)	14(73.7)	17(90.0)
Myocardial infarction, n(%)	23(57.5)	8(42.1)	15(71.4)
max CK(U/I)	2,358.9±2,746.9	1,402.1±768.4	2,869.0±3,280.3
Unstable angina, n(%)	6(15.0)	4(21.1)	2(9.5)
Heart failure, n(%)	11(27.5)	7(36.8)	4(19.0)
BMI(kg/m^2)	22.7±3.4	22.1±4.4	23.2±2.3
Smoker, n(%)	23(57.5)	11(57.9)	12(57.1)
HbA1c(%, mmol/mol)	6.3±0.7, 45±7	6.8±0.6, 51±6	5.9±0.3, 40±3*
Diabetes mellitus, n(%)	19(47.5)	19(100)	0(0)
Hypertension, n(%)	27(67.5)	12(63.2)	15(71.4)
β-blocker, n(%)	25(62.5)	10(52.6)	15(71.4)
ACE inhibitor or ARB, n(%)	32(80.0)	17(89.5)	15(71.4)
CCB, n(%)	8(20.0)	4(21.6)	4(19.0)
Statin, n(%)	30(75.0)	16(84.2)	14(66.7)
Atorvastatin, n(%)	5(12.5)	2(10.5)	3(14.3)
Rosuvastatin, n(%)	8(20.0)	4(21.1)	4(19.0)
Pitavastatin, n(%)	17(42.5)	10(52.6)	7(33.3)
Antidiabetic medications, n(%)	17(42.5)	17(89.5)	0(0)
DPP-4 inhibitor, n(%)	15(37.5)	15(78.9)	0(0)
Meglitinide, n(%)	4(10.0)	4(21.1)	0(0)
α-glucosidase inhibitors, n(%)	4(10.0)	4(21.1)	0(0)
Sulfonylurea, n(%)	1(2.5)	1(5.3)	0(0)
SGLT2 inhibitor, n(%)	5(12.5)	5(26.3)	0(0)
Metformin, n(%)	2(5.0)	2(10.5)	0(0)

* p<0.001 compared with DM group.

ACE: angiotensin-converting-enzyme, ARB: Angiotensin II receptor blockers, BMI; body mass index, CCB: Calcium channel blockers, DPP-4: Dipeptidyl Peptidase-4, SGLT-2: Sodium-glucose co-transporter-2

group: r=0.61 (95% CI, 0.0004-0.049), p=0.047; non-DM group: r=0.56 (95% CI, 0.003-0.069), p=0.034] (Table 2). Furthermore, night glucose variability was more closely associated with the ME difference in patients with unstable angina pectoris (UAP) than in those with acute myocardial infarction (AMI) or heart failure (HF), although it was not considered statistically significant in patients with UAP (r=0.83, p=0.058). In addition, the night glucose variability in patients with HbA1c ≥6.5% (47 mmol/mol) was larger than that in patients with HbA1c <6.5% (HbA1c ≥6.5%: 23.8±1.4 mg/dL vs. HbA1c <6.5%: 17.1±2.2 mg/dL, p<0.05). Nevertheless, there was a significant correlation between the ME difference and night glucose variability in patients with HbA1c <6.5% (47 mmol/mol) but no correlation in patients with HbA1c ≥6.5%.

We also assessed the influence of the 24-hour average glucose levels on the ME difference and noted a significant difference and small correlation between the 24-hour average glucose levels and the ME difference. However, in the multiple regression analysis to which we added the 24-hour average glucose level as a covariate, the levels were not correlated with the ME difference (p=0.74). In addition, nearly the same results were obtained in the multiple regression analysis to which the 24-hour average glucose levels were added instead of the night glucose variability (p=0.09).

Discussion

The main findings of the present study are as follows: In patients with cardiovascular disease, the detection rate of hypoglycemia (glucose levels <70 mg/dL) using FGM was significantly higher than that using 5-point SMBG; furthermore, the night glucose variability from 22:00 to the next morning at 6:00 monitored by FGM was significantly correlated with changes in the systolic blood pressure from evening to the next morning.

Detection of hypoglycemia in coronary artery disease (CAD) patients

In CAD patients, hypoglycemia might be an important factor associated with risk management (8, 9), such as arrhythmia and a prolonged QT interval. Furthermore, chronic hypoglycemia accelerates atherosclerosis, leading to the development of CAD (8). Hypoglycemia stimulates the autonomic system, which accelerates the release of epinephrine and glucagon secretion, resulting in vasoconstriction, increased intravascular coagulability, and exacerbated viscosity (increased platelet counts, neutrophil activation, and an ele-

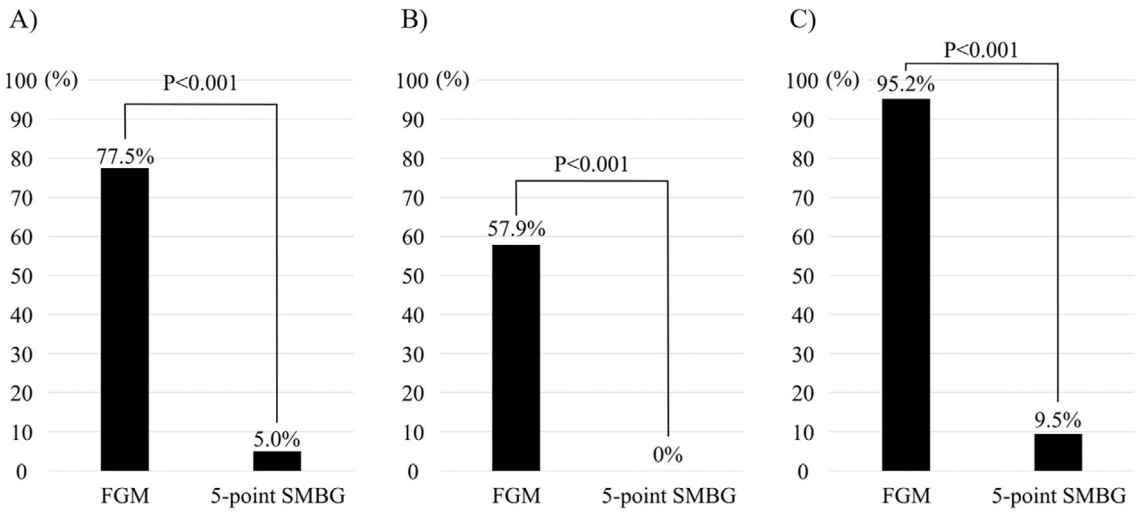

Figure 1. **Detection rate of hypoglycemia (glucose levels <70 mg/dL). Detection rate in A) total patients, B) DM group, C) non-DM group. The detection rate of hypoglycemia using the FGM method was significantly higher than that with the 5-point SMBG method (total patients: 77.5% vs. 5.0%, p<0.001; DM group: 57.9% vs. 0%, p<0.001; non-DM group: 92.5% vs. 9.5%, p<0.001). FMG: flash glucose monitoring system, SMBG: self-monitored blood glucose**

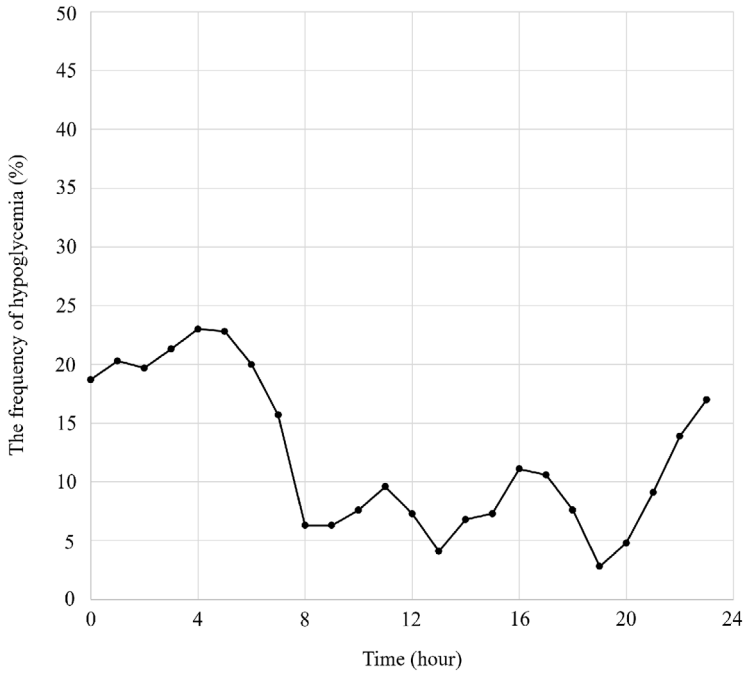

Figure 2. **Frequency of hypoglycemia (glucose levels <70 mg/dL) per unit time from 0: 00 to 23:00 during the total observation period. The frequency of hypoglycemia between 4:00 and 5:00 was the highest across 24 h (23.0%).**

vated endothelial function), all of which influence CAD (8, 9, 12).

Several studies have suggested that the presence of hypoglycemia might worsen the prognosis of patients with CAD (8, 9). Particularly in the acute phase after coronary syndrome, hypoglycemia and serious hypoglycemia were associated with MACE (13). Studies have suggested the importance of detecting hypoglycemia correctly in patients after acute coronary syndrome and treating it immediately. In the present study, we evaluated the usefulness of FGM for detecting hypoglycemia and found that the detection rate with FGM was significantly higher than that with SMBG. The high detection rate of hypoglycemia using FGM might be due to the glucose levels being recorded every 15 minutes, capturing up to 1,340 glucose results every 14 days. Furthermore, assessing glucose levels on a continuous 24-hour basis, which shows day-to-day trends in glucose variability, enables the appropriate treatment of diabetes.

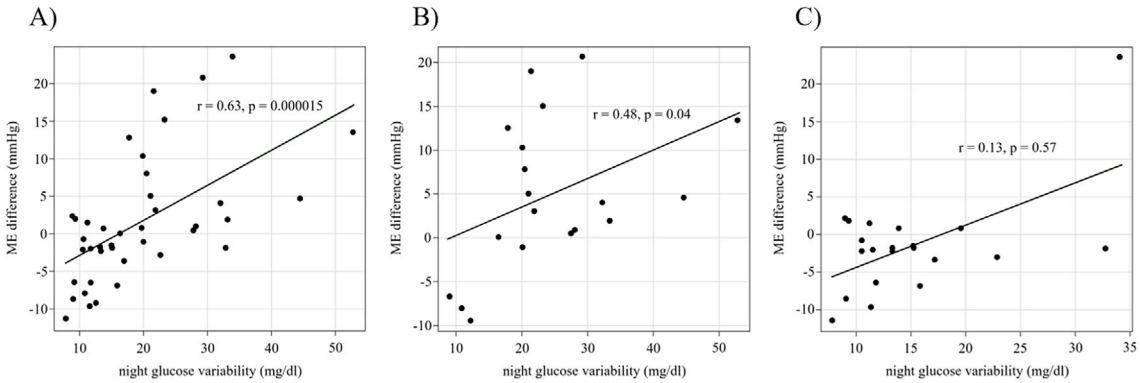

Figure 3. **The correlation of ME difference and night glucose variability (SD) from 22:00 to next morning. Correlation in A) total patients, B) DM group, C) non-DM group. Changes in the systolic blood pressures from evening to the next morning (ME difference) were significantly correlated with the night glucose variability in total patients and the DM group (total patients; r=0.63, p=0.000015, DM group; r=0.48, p=0.04), whereas there was no correlation in the non-DM group (r=0.13, p=0.57). ME: blood pressure from the evening to the next morning**

Table 2. **Multiple Regression Analysis for ME Difference.**

	Unstandarized Coefficients			Standarized Coefficients		
	B	Std. Error	95%CI	Beta	t	p value
constant	1.939	0.807	0.300 to 3.578		2.402	0.0217
Age (y.o.)	-0.007	0.006	-0.021 to 0.005	-0.1970	-1.189	0.2423
BMI (kg/m^2)	0.026	0.023	-0.267 to 0.312	0.0187	1.126	0.2676
Smorker	0.022	0.142	-0.267 to 0.312	-0.0270	0.126	0.8737
Night glucose variability	0.035	0.007	0.019 to 0.051	0.6097	4.551	0.0001

BMI: body mass index, ME: evening to next morning

Multiple regression analysis for ME difference (DM, n=19)						
	Unstandarized Coefficients			Standarized Coefficients		
	B	Std. Error	95%CI	Beta	t	p value
constant	2.968	1.662	-0.596 to 6.534		1.786	0.0957
Age (y.o.)	-0.014	0.014	-0.045 to 0.017	-0.2486	-0.960	0.3531
BMI (kg/m^2)	0.019	0.030	-0.046 to 0.086	0.1703	0.646	0.5282
Smorker	-0.206	0.226	-0.691 to 0.279	-0.2367	-0.911	0.3774
Night glucose variability	0.025	0.011	0.0004 to 0.049	0.5078	2.182	0.0466

Multiple regression analysis for ME difference (non-DM, n=21)						
	Unstandarized Coefficients			Standarized Coefficients		
	B	Std. Error	95%CI	Beta	t	p value
constant	2.166	1.272	-0.531 to 4.863		1.702	0.1080
Age (y.o.)	-0.007	0.008	-0.025 to 0.009	-0.2329	-0.957	0.3523
BMI (kg/m^2)	0.009	0.049	-0.095 to 0.113	0.0465	0.186	0.8543
Smorker	0.172	0.202	-0.256 to 0.601	0.2083	0.852	0.4066
Night glucose variability	0.036	0.015	0.003 to 0.069	0.5010	2.315	0.0341

Blood pressure surge and glucose variability

The morning surge in blood pressure is associated with cardiovascular events and is closely related to the early-phase events after acute coronary syndrome. This surge may be caused by various factors, including aging, smoking, alcohol intake, obstructive sleep apnea syndrome, and glucose abnormality (14). In a previous study, the morning surge

was attributed to the activation of neurohumoral factors, including the renin-angiotensin system (RAS) and sympathetic nervous system, which might increase the vascular tonus in the small arteries and cardiac output. Furthermore, it was reported that arterial stiffness might reduce the sensitivity of the cardiovagal baroreflex, which regulates the blood pressure thorough the sympathetic nervous system, leading to an increase in blood pressure in the morning (14). We demonstrated the association between an increase in blood pressure in the morning and glucose variability at night (22:00 to 6: 00) in this study. We suspect that the autonomic nervous system and catecholamines might be involved in the mechanism by which glucose variability induces the morning-time elevation of the blood pressure, although we were unable to directly evaluate this in our study.

Several studies have examined the association between glucose abnormalities and the autonomic nervous system (15-17). Camargo et al. reported that an elevation in the glucose concentration in the lateral ventricles of the brain reduces the firing rate of the vagus nerve and increases the sympathetic nerve activity. In an animal model, a glucose infusion for 48 hour increased the firing rate of the vagus nerve and decreased the cervical ganglion firing rate in rats (17). Furthermore, in humans without glucose abnormalities, an increase in blood glucose levels induced by intravenous infusion of glucose increased the heart rate, suggesting that glucose variability might affect the autonomic nervous system (18).

Glucose variability may alter the levels of counterregulatory hormones, such as catecholamines, cortisol, and other hormones. It was reported that hypoglycemia might increase aldosterone secretion, depending on the activation of the renin-angiotensin-aldosterone system (19). Lee et al. demonstrated the correlation between the cortisol levels and acute hyperglycemia (20). Furthermore, adrenaline secretion might be increased during hypoglycemia, whereas postprandial glucose may increase the serum adrenaline level (21).

In contrast, hypoglycemia might blunt counterregulatory hormones, such as adrenaline and noradrenaline, in patients with type 1 diabetes (22). Uncontrolled and long-term diabetes reportedly causes autonomic neuropathy and reduces counterregulatory hormones, such as catecholamine responses. In contrast, in healthy individuals and patients with early-stage diabetes, the changes in the glucose levels and hypoglycemia alter the firing rate of glucose-responsive neurons within areas of the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH) in the brain, resulting in autonomic responses sensitively and counterregulatory hormone release (23, 24). These previous findings support our present results, which showed a significant correlation between the ME difference and night glucose variability in patients with HbA1c <6.5% (47 mmol/mol) but not in those with HbA1c ≥6.5%. In the present study, sensitive autonomic responses and counterregulatory hormones release caused by the change in glucose levels in patients with HbA 1c <6.5% (47 mmol/mol) might have resulted in the observed significant correlation between the ME difference and night glucose variability.

We examined the association between the ME difference and night glucose variability in patients with AMI, UAP, and HF and found a positive correlation in each group (UAP: r= 0.83, p=0.058, AMI: r=0.47, p=0.022, HF: r=0.81, p=0.004). Although there was no statistically significant correlation between each group, there was a stronger correlation in patients with UAP than in the other groups. Initially, we anticipated that the relevance in the AMI group would be highest, but our findings unexpectedly showed a high relevance in the UAP and chronic HF groups instead. The reason for this is that although norepinephrine is released from sympathetic nerves in AMI, it triggers sympathetic nerve remodeling to promote sympathetic hyperinnervation, therefore the direct influence of the changes in the glucose levels on autonomic nervous system was reduced, resulting in a weak correlation in patients with AMI (25). For this reason, the influence of changes in blood sugar values on autonomic nervous system was lower in the AMI group than in the other two groups. In patients with UAP and HF, glucose variability might influence the increase in the blood pressure in the morning because of the lower sympathetic nerve activity in these patients than in those with AMI. This point may be able to be clarified if the sympathetic nerve index is estimated by other methods, such as measuring the serum catecholamine.

Limitations

Several limitations associated with the present study warrant mention. There were a limited number of cases in our study. Therefore, we were unable to examine the influence of drugs, such as antihypertensive agents and antidiabetic agents. Antidiabetic medications in particular were expected to be an important factor influencing the correlation between the ME difference and night glucose variability. However, in the present study, 17 of the 19 patients with diabetes mellitus were taking ≥1 antidiabetic medication, as shown in Fig. 1 [dipeptidyl peptidase (DPP)-4 inhibitor: n=15, 78.9%, Meglitinide: n=4, 21.1%, α-glucosidase inhibitors: n=4, 21.1%, Sulfonylurea: n=1, 5.3%, sodium-glucose transport protein 2 (SGLT2) inhibitor: n=5, 26.3%, Metformin: n=2, 10.5%]. We were thus unable to clarify the effect of antidiabetic medications on the correlation between the ME difference and night glucose variability due to the small sample size. We cannot deny the possibility of the difference in blood glucose levels between the FGM and SMBG methods, which may have led to the false detection of hypoglycemia. In addition, we were unable to evaluate extreme dippers of nocturnal blood pressure because we did not measure the blood pressure at night. Long-term studies will be needed to examine the usefulness of these measurements for prognostic prediction.

Conclusion

In conclusion, FGM was useful for detecting hypoglycemia in the night phase, and the night glucose variability measured by FGM was correlated with an increase in the blood pressure in the morning, suggesting that continuous glucose monitoring at night might be a novel method of detecting a risk of heart failure and coronary event recurrence in CAD patients.

The authors state that they have no Conflict of Interest (COI).

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