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Associations of Glucose and Blood Pressure Variability with Cardiac Diastolic Function in Patients with Type 2 Diabetes Mellitus and Hypertension: A Retrospective Observational Study

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Abstract: We evaluated the effects of glucose metabolism and blood pressure (BP) variability on cardiac diastolic function in patients with type 2 diabetes mellitus (T2DM) and hypertension. A total of 23 inpatients with T2DM underwent ambulatory BP monitoring (ABPM) and echocardiography. BP variability was assessed by measuring the mean BP and the standard deviation (SD) of systolic and diastolic BP over 24 hours, as well as daytime and nighttime ABPM. Cardiac diastolic function was assessed using the echocardiography E/e' ratio. Participants had a mean age of 69.0 ± 10.6 years, disease duration of 11.0 ± 10.5 years, glycated hemoglobin (HbA1c) of $8.2\% \pm 1.3\%$, and glycated albumin (GA) of $22.0\% \pm 4.2\%$. Univariate analysis showed that the nighttime systolic BP, nighttime SDs of systolic and diastolic BP, urinary albumin, estimated glomerular filtration rate, and GA/HbA1c ratio were all significantly correlated with the E/e' ratio. Moreover, stepwise multiple regression analysis identified nighttime SD of diastolic BP, urinary albumin, and GA/HbA1c ratio as independent contributors to the E/e' ratio. In patients with T2DM and hypertension, cardiac diastolic function was associated with nighttime diastolic BP variability and the GA/HbA1c ratio.

Key words: blood pressure variability, cardiac diastolic function, glycated albumin / glycated hemoglobin ratio, ambulatory blood pressure monitoring, type 2 diabetes mellitus

Introduction

The coexistence of diabetes and hypertension is common and associated with an increased risk of death and cardiovascular events as well as the progression of microvascular complications, such as nephropathy and retinopathy^{1,2}. Type 2 diabetes mellitus (T2DM) is also a major cause of heart failure, with reduced or preserved ejection fraction³. The Framingham Heart Study demonstrated that the frequency of heart failure is five times higher in women with diabetes

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and two times greater in men with diabetes compared with age-matched controls⁴). It was recently reported that the most frequent heart alteration in T2DM is heart failure with preserved ejection fraction⁵). It was also reported that around 50% of patients with hypertension suffer heart failure with preserved ejection fraction⁶).

The short and long-term variability of glucose and blood pressure (BP) levels have been studied. Recently, long-term variability in visit-to-visit glucose levels, as well as BP, was shown to be related to macrovascular and microvascular complications in patients with T2DM^{7,8}). Advances in medical technology, such as continuous glucose monitoring (CGM) and 24-hr ambulatory BP monitoring (ABPM), have enabled short-term glucose and BP variability to be detected in greater detail. The mean amplitude of glycemic excursions (MAGE) is a short-term glucose variability index that has been associated with oxidative stress⁹), vascular endothelial dysfunction¹⁰), and narrowing of the coronary artery¹¹). Nighttime BP variability, a short-term BP variability index, is also reported to be a strong predictor for cardiovascular disease in patients with T2DM and hypertension¹²). However, few studies have investigated the relationship between glucose variability, BP variability, and heart failure.

Therefore, the present study aimed to determine whether glucose and BP variability, measured using the glycated albumin (GA) /glycated hemoglobin (HbA1c) ratio and ABPM, respectively, are associated with the early diastolic (E) /spectral pulsed-wave Doppler-derived lateral early diastolic velocity (e') ratio, an index of heart failure with preserved ejection fraction in patients with T2DM and hypertension.

Patients and methods

Participants

This retrospective, observational study included 23 inpatients with T2DM and hypertension recruited from among patients treated at Showa University Hospital from May 2017 to October 2018. The patients were admitted to the hospital to achieve glycemic control due to poor current control. The inclusion criteria were as follows: a diagnosis of T2DM and hypertension, age over 20 years, and stable diabetes and hypertension treatment for ≥ 3 months prior to the study. T2DM was defined according to the Japan Diabetes Society. Hypertension was defined as a systolic BP (SBP) ≥ 140 mmHg and /or diastolic BP (DBP) ≥ 90 mmHg on at least two occasions according to the current guidelines, or a previous diagnosis of hypertension and treatment with antihypertensive medication. The exclusion criteria for patients were: 1) ejection fraction $< 50\%$; 2) shift to a different medicine within the last month; 3) use of steroid anti-inflammatory drugs; 4) secondary diabetes; 5) malignancy; 6) liver disease; 7) valvular heart disease; 8) myocardial infarction with asynergy; and 9) estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m².

Study design

Figure 1 shows a summary of the study protocol. This was a retrospective observational analysis of patients with T2DM who underwent a 24-hr period of ABPM and echocardiography

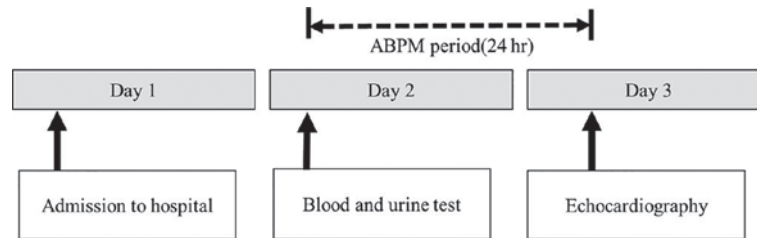


Fig. 1. Study protocol. Laboratory parameters were measured before breakfast on Day 2. Parameters of blood pressure variability were measured for 24 hours, starting on Day 2. Echocardiography was performed on Day 3. ABPM, ambulatory blood pressure monitoring.

monitoring. Clinical and laboratory parameters, including body mass index (BMI), fasting plasma glucose, HbA1c, GA, eGFR, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured before breakfast on Day 2. We used the GA / HbA1c ratio as a marker of glucose variability. Clinical data (age, sex, smoking status, duration of diabetes, diabetes therapy, and the use of antihypertensive and lipid-lowering drugs) were retrieved from medicals records. Parameters of BP variability, such as mean and standard deviation (SD) of BP, and percentage coefficient of variation for BP (%CV) were measured for 24 hr, starting on Day 2. All patients continued their usual treatment during ABPM. Echocardiography was performed on Day 3. E/e' was used as a parameter of cardiac diastolic function. The study protocol was approved by the School of Medicine, Showa University Ethical Committee (Permit Number: 2465) and was designed in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants after receiving an explanation of the study protocol.

Procedures and measurements

Venous blood samples were taken for laboratory analysis on Day 2 before breakfast. All patients received a weight-maintaining diet (25–30 kcal/kg of ideal body weight) with salt restriction (< 6 g/day). After attaching the ABPM device (Mobil-O-graph; I.E.M. GmbH, Stolberg, Germany) on Day 2, BP was measured in the left upper extremity using the oscillometric method and pulse rate at 30 min intervals for 24 hr. Daytime and nighttime were defined based on the patients' written diaries recorded during ABPM. BP variability was estimated using the SD of SBP and DBP during the daytime and nighttime. The %CV was calculated using the coefficient of variation obtained by dividing the SD by the mean BP and multiplying by 100. Mean SBP and DBP during the daytime and nighttime were also determined.

Echocardiography was performed using commercially available ultrasound systems (iE33; Philips, Amsterdam, Netherlands; Vivid E9; GE Healthcare UK, Ltd., Amersham, England, UK). Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography / European Association of Cardiovascular Imaging¹³). Specifically, the early diastolic (E) velocities and the E-wave deceleration time were measured using the pulsed-wave Doppler recording from the apical four chamber view. Spectral

pulsed-wave Doppler-derived lateral early diastolic velocity (e') was considered as the lateral mitral annulus, and the E/e' ratio was calculated to estimate the left ventricular filling pressure.

Laboratory measurements

The serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and creatinine levels were measured using an automated analyzer (BM6070; Japan Electron Optics Laboratory, Tokyo, Japan). Plasma glucose was measured using the glucose oxidase method, whereas HbA1c was measured using high-performance liquid chromatography¹⁴⁾ while GA was detected using the bromocresol purple method.

Statistical analysis

Data are expressed as mean \pm SD. Spearman's rank correlation coefficient was used to determine univariate analysis. Multiple stepwise regression analysis (forward-backward stepwise selection method) was used to assess independent contributors to the E/e' ratio. Analyses were performed using IBM SPSS, version 22, for Windows (IBM Corp; Armonk, NY, USA) with p -values < 0.05 indicating statistical significance.

Results

Clinical characteristics

Table 1 shows the clinical and laboratory characteristics of the 23 participants. Participants had a mean age of 69.0 ± 10.6 years, diabetes duration of 11.0 ± 10.5 years, and HbA1c level of $8.2\% \pm 1.3\%$. The study group included more men ($n=14$) than women ($n=9$), and participants were slightly overweight ($BMI=24.2 \pm 4.7$ kg/m²). The left ventricular ejection fraction was $63.6\% \pm 6.1\%$ and the E/e' ratio was 7.1 ± 2.0 . At baseline, 56.5% of the patients were on diet therapy, 39.1% were taking angiotensin II receptor blockers, 30.4% were taking calcium channel blockers for hypertension treatment, 47.8% were taking dipeptidyl peptidase 4 inhibitors, and 43.5% were on insulin therapy for diabetes treatment.

Table 1. Baseline clinical characteristics of the study participants

Clinical characteristics	Mean \pm SD, n (%)
Age (years)	69.0 \pm 10.6
Sex (male)	14 (60.9)
Body mass index (kg/m ²)	24.2 \pm 4.7
Smoking	4 (17.4)
Duration of diabetes (years)	11.0 \pm 10.5
Dyslipidemia	22 (95.7)
Low-density lipoprotein cholesterol (mg/dl)	98.0 \pm 30.5
High-density lipoprotein cholesterol (mg/dl)	46.1 \pm 13.1
Triglycerides (mg/dl)	134.4 \pm 60.3
Estimated glomerular filtration rate (ml/min/1.73 m ²)	69.2 \pm 19.7
Urinary albumin-to-creatinine ratio (mg/g)	68.3 \pm 188.6
Fasting plasma glucose (mg/dl)	132.4 \pm 30.8
HbA1c (%)	8.2 \pm 1.3

Clinical characteristics	Mean \pm SD, n (%)
1.5-anhydro-D-glucitol ($\mu\text{g/dl}$)	4.9 \pm 8.2
GA (%)	22.0 \pm 4.2
GA/HbA1c ratio	2.7 \pm 0.4
Markers of BP variability	
24-hr mean SBP (mmHg)	124.5 \pm 12.2
24-hr SD of SBP (mmHg)	12.6 \pm 3.6
24-hr %CV of SBP	10.0 \pm 2.6
24-hr mean DBP (mmHg)	77.0 \pm 7.6
24-hr SD of DBP (mmHg)	9.6 \pm 2.4
24-hr %CV of DBP	12.6 \pm 3.1
Daytime mean SBP (mmHg)	125.5 \pm 12.0
Daytime SD of SBP (mmHg)	12.3 \pm 3.9
Daytime %CV of SBP	9.7 \pm 2.8
Daytime mean DBP (mmHg)	78.1 \pm 7.7
Daytime SD of DBP (mmHg)	9.2 \pm 2.6
Daytime %CV of DBP	11.8 \pm 3.2
Nighttime mean SBP (mmHg)	119.1 \pm 16.2
Nighttime SD of SBP (mmHg)	8.9 \pm 4.3
Nighttime %CV of SBP	7.4 \pm 3.2
Nighttime mean DBP (mmHg)	72.0 \pm 9.3
Nighttime SD of DBP (mmHg)	7.8 \pm 2.8
Nighttime %CV of DBP	11.1 \pm 4.2
24-hr pulse pressure (mmHg)	47.5 \pm 9.0
Daytime pulse pressure (mmHg)	47.3 \pm 8.9
Nighttime pulse pressure (mmHg)	47.1 \pm 10.4
Ejection fraction (%)	63.6 \pm 6.1
E/e'	7.1 \pm 2.0
Macroangiopathy	7 (23.3)
Nephropathy	5 (21.7)
Neuropathy	15 (65.2)
Retinopathy	2 (8.7)
Diabetes therapy	
Diet alone	3 (13.0)
Metformin	6 (26.1)
Sulfonylurea	4 (17.4)
Glinide	0 (0.0)
α -Glucosidase inhibitor	3 (13.0)
Thiazolidine	1 (4.3)
Dipeptidyl peptidase 4 inhibitor	11 (47.8)
Sodium glucose cotransporter 2 inhibitors	5 (21.7)
Glucose-like peptide 1 receptor agonist	0 (0.0)
Insulin	12 (52.2)
Antihypertensive drugs	
Diet alone	13 (56.5)
Angiotensin II receptor blocker	9 (39.1)
Calcium channel blocker	7 (30.4)
Diuretic	1 (4.3)
α -blocker	0 (0.0)
β -blocker	3 (12.0)
Other treatments	0 (0.0)
Lipid-lowering drugs (statins)	13 (56.5)

Data represent mean \pm SD, or n (%). SD, standard deviation; HbA1c, glycated hemoglobin; GA, glycated albumin; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; %CV, percentage coefficient of variation; E/e', early diastolic transmitral inflow velocity/lateral early diastolic mitral annular velocity.

Relationship between E/e' ratio, E, and e' and markers of BP variability glucose metabolism, and non-glycemic clinical and laboratory variables

Table 2 shows the correlations between the E/e' ratio, E, and e' and the markers of BP variability, glucose metabolism, and non-glycemic clinical and laboratory variables. Significant correlations were observed between the E/e' ratio and ejection fraction ($p=0.047$), nighttime mean SBP ($p=0.031$), nighttime SD of SBP ($p=0.019$), nighttime SD of DBP ($p=0.023$),

Table 2. Correlations between E/e', E, and e' and markers of BP control, glycemic control, and non-glycemic metabolic variables

Variable	r		
	E/e'	E	e'
Age (years)	0.360	-0.091	-0.594**
Body mass index (kg/m ²)	-0.261	0.096	0.473*
Duration of diabetes (years)	0.255	0.203	-0.089
Fasting plasma glucose (mg/dl)	-0.039	-0.065	0.055
HbA1c (%)	-0.298	-0.233	-0.099
1.5-anhydro-D-glucitol (μ g/dl)	0.148	0.029	-0.195
GA (%)	0.156	-0.013	-0.376
GA / HbA1c ratio	0.550**	0.140	-0.476*
Markers of BP variability			
24-hr mean SBP (mmHg)	0.257	0.203	-0.191
24-hr SD of SBP (mmHg)	0.041	-0.184	-0.458*
24-hr %CV of SBP	-0.114	-0.281	-0.392
24-hr mean DBP (mmHg)	-0.168	0.216	0.105
24-hr SD of DBP (mmHg)	-0.024	-0.102	-0.272
24-hr %CV of DBP	-0.048	-0.143	-0.249
Daytime mean SBP (mmHg)	0.230	0.197	-0.173
Daytime SD of SBP (mmHg)	0.094	-0.343	-0.600**
Daytime %CV of SBP	-0.029	-0.445*	-0.639**
Daytime mean DBP (mmHg)	-0.245	0.138	0.121
Daytime SD of DBP (mmHg)	0.001	-0.120	-0.357
Daytime %CV of DBP	-0.010	-0.176	-0.393
Nighttime mean SBP (mmHg)	0.450*	0.150	-0.385
Nighttime SD of SBP (mmHg)	0.484*	0.183	-0.159
Nighttime %CV of SBP	0.266	0.177	0.055
Nighttime mean DBP (mmHg)	0.307	0.032	-0.302
Nighttime SD of DBP (mmHg)	0.473*	0.084	-0.237
Nighttime %CV of DBP	0.250	0.081	-0.020
24-hr pulse pressure (mmHg)	0.492*	0.117	-0.430*
Daytime pulse pressure (mmHg)	0.463*	0.112	-0.405
Nighttime pulse pressure (mmHg)	0.529**	0.099	-0.441*
Low-density lipoprotein cholesterol (mg/dl)	0.126	0.073	-0.045
High-density lipoprotein cholesterol (mg/dl)	-0.359	-0.153	0.173
Triglycerides (mg/dl)	-0.278	0.064	0.135
Estimated GFR (ml/min/1.73 m ²)	-0.425*	-0.040	0.236
Urinary albumin-to-creatinine ratio (mg/g)	0.438*	0.359	-0.043
Ejection fraction (%)	-0.418*	-0.123	0.100

* $p < 0.05$, ** $p < 0.01$. BP, blood pressure; E, early diastolic transmitral inflow velocity; e', lateral early diastolic mitral annular velocity; HbA1c, glyated hemoglobin; GA, glyated albumin; SBP, systolic blood pressure; SD, standard deviation; %CV, percentage coefficient of variation; DBP, diastolic blood pressure; GFR, glomerular filtration rate.

GA/HbA1c ratio ($p=0.007$), 24-hr pulse pressure ($p=0.017$), daytime pulse pressure ($p=0.026$), nighttime pulse pressure ($p=0.009$), urinary albumin-to-creatinine ratio ($p=0.037$), and eGFR ($p=0.043$). However, no significant correlation was observed between the E/e' ratio and fasting plasma glucose, HbA1c, and non-glycemic variables.

E/e' showed a positive correlation with the GA/HbA1c ratio, as depicted in Table 2. In addition, the E/e' ratio in patients with a GA/HbA1c ratio ≥ 2.8 was more than that in patients with a GA/HbA1c ratio < 2.8 (Fig. 2).

Significant correlations were also observed between E and daytime %CV of SBP ($p=0.034$), and between e' and 24-hr SD of SBP ($p=0.032$), daytime SD of SBP ($p=0.003$), daytime % CV of SBP ($p=0.001$), 24-hr pulse pressure ($p=0.046$), nighttime pulse pressure ($p=0.040$), age ($p=0.004$), BMI ($p=0.026$), and GA/HbA1c ratio ($p=0.025$; Table 2).

Multivariate analysis identified the GA/HbA1c ratio, urinary albumin-to-creatinine ratio, and nighttime SD of DBP as independent and significant determinants of the E/e' ratio (adjusted multiple $R^2 = 0.526$; Table 3).

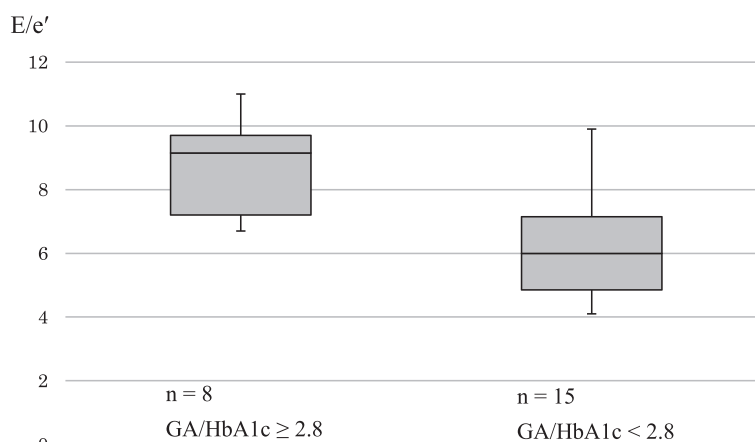


Fig. 2. E/e' ratio in patients with GA/HbA1c ratio ≥ 2.8 or < 2.8 . E/e', early diastolic transmitral inflow velocity/lateral early diastolic mitral annular velocity; GA, glycated albumin; HbA1c, glycated hemoglobin.

Table 3. Linear multivariate analyses with E/e' as dependent variable

	Dependent variable: E/e'			
	β Coefficient	t-value	p-value	Full-model R^2
			< 0.001	0.526
GA/HbA1c ratio	0.519	3.525	0.002	
Urinary albumin-to-creatinine ratio	0.398	2.708	0.014	
Nighttime SD of DBP	0.332	2.252	0.036	

E/e', early diastolic transmitral inflow velocity/lateral early diastolic mitral annular velocity; GA, glycated albumin; HbA1c, glycated hemoglobin; SD, standard deviation; DBP, diastolic blood pressure.

Discussion

To the best of our knowledge, no previous studies have investigated the relationship between cardiac diastolic function, glucose, and BP variability in patients with T2DM with hypertension. Our findings are pertinent to the clinical management of T2DM with hypertension and highlight the importance of GA and BP variability, in addition to glucose and BP levels.

Hypertension induces endothelial dysfunction via oxidative stress¹⁵. In cardiomyocytes, hypertension-induced oxidative stress causes S-glutathionylation of the myofibrillar protein, cardiac myosin binding protein C, leading to diastolic dysfunction¹⁶. Previous studies have reported that T2DM and hypertension are closely associated with heart failure with preserved ejection fraction^{17,18}. T2DM and hypertension increases oxidative stress in the heart and blood vessels and leads to vascular endothelial dysfunction, left ventricular hypertrophy, and interstitial fibrosis¹⁹. The extent of microalbuminuria is correlated with the level of endothelial cell injury; hence, the urinary albumin-to-creatinine ratio is thought to be correlated with the E/e' ratio. Therefore, it is speculated that increased oxidative stress ultimately leads to the onset of cardiac diastolic dysfunction.

Postprandial plasma glucose is reported to be more closely related to cardiovascular disease than fasting plasma glucose. Furthermore, glucose variability is important in patients with T2DM¹¹ as it induces endothelial dysfunction via oxidative stress, as well as the progression of arteriosclerosis that causes cardiovascular disease²⁰. In clinical studies, MAGE calculated using CGM is used as a glucose variability index. Indeed, we previously reported a relationship between MAGE and oxidative stress⁹. Recently, the GA/HbA1c ratio has been shown to be a reliable marker of glucose variability, regardless of the degree of glycemic control²¹. Albumin is glycosylated much more easily than hemoglobin²², and as blood glucose levels increase, the GA/HbA1c ratio also increases. Furthermore, patients with a GA/HbA1c ratio ≥ 2.8 show the highest SD²³. Our study demonstrated that E/e' is associated with the GA/HbA1c ratio; furthermore, patients with a GA/HbA1c ratio ≥ 2.8 had a high E/e' ratio. Therefore, we propose that chronic hyperglycemia is not the cause, but that glucose variability leads to oxidative stress and, ultimately, cardiac dysfunction.

Studies have reported a relationship between cardiovascular disease and BP variability evaluated via ABPM. Accordingly, several studies have demonstrated that nighttime SBP variability is a risk factor for cardiovascular disease²⁴. However, the present study showed that nighttime DBP variability was associated with cardiac function. This mechanism is unknown, but could be explained by the following pathophysiological mechanism. Low DBP may compromise blood flow to target organs and impair coronary perfusion, causing cardiac ischemia²⁵. Therefore, a large DBP variability is considered to be related to cardiac function due to the impairment of coronary perfusion.

The present study has several limitations. First, this was a cross-sectional study, precluding the evaluation of any cause and effect relationship between glucose and BP variability and cardiac diastolic function. Further studies are necessary to examine whether interventions to reduce

glucose and BP variability are required. Second, we did not evaluate the relationship between cardiac diastolic function and oxidative stress. Third, the sample size was relatively small and any subgroup comparison may lack statistical power. Significant correlations were observed between E/e' and nighttime mean SBP, nighttime SD of SBP, and nighttime SD of DBP. Conversely, significant correlations were observed between e' and 24-hr SD of SBP and daytime SD of SBP. The reason that the result differs between E/e' and e' may be because e' is influenced by age. However, because the sample size is small, we found it difficult to study this in detail. Fourth, we were unable to use CGM to evaluate glucose variability. Fifth, since the glycemic control of the patients was poor, hyperglycemia and glucose variability may have had a significant effect on the results of our study. Future studies are necessary to examine patients with good glycemic control. Sixth, sleep apnea, which causes sympathetic activation, may have been a factor in the present study. Seventh, few patients had poorly controlled hypertension in the study. Therefore, it is difficult to compare patients with poorly controlled hypertension with patients with well-controlled hypertension. Eighth, there was no patient with an E/e' ratio > 14 , which is the cut-off level of E/e' for diastolic dysfunction, according to the Japanese guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure. Finally, it has been reported that %CV of BP is useful as a BP variability index²⁶⁾. However, there was no significant relationship between %CV of BP and E/e' . Hence, the relationship between the SD of BP and E/e' is likely important, but the SD of BP positively correlates with the mean BP. In the future, it will be necessary to investigate an increased number of cases with these relationships in order to draw a firm conclusion.

In conclusion, the present study demonstrates that cardiac diastolic function is associated with the GA/HbA1c ratio and nighttime DBP variability in patients with T2DM and hypertension. While further intervention studies are required to determine whether reducing glucose variability as well as BP variability is associated with improved cardiac diastolic function, our results imply that glucose and BP variability are important factors affecting cardiac diastolic function.

Conflict of interest

The authors have no conflicts of interest to disclose.

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