



# Association of left ventricular myocardial dysfunction with diabetic polyneuropathy

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## Abstract

**Background** The pathogenesis of left ventricular (LV) dysfunction in diabetes has been attracting attention. It has been reported that LV longitudinal systolic myocardial function determined by speckle tracking echocardiography (STE) is associated with diabetic polyneuropathy (DPN). However, the relationship between the severity of peripheral neuropathy and LV myocardial dysfunction is unknown. This study examined the relationship between the severity of DPN and echocardiographic parameters as well as clinical features.

**Methods** The subjects were 166 patients ( $57 \pm 14$  years old) with diabetes who had a normal LV ejection fraction ( $\geq 55\%$ ). To assess LV longitudinal systolic function, global longitudinal strain (GLS) was calculated by two-dimensional STE as the average peak strain of 18 LV segments in three standard apical views. A nerve conduction study (NCS) was performed in each subject to assess the severity of neuropathy based on the NCS Baba Classification (Grade 0: no apparent abnormalities–Grade IV: abolition). Three nerves in the lower extremity were examined: tibial nerve (F-wave latency, motor nerve conduction velocity, and amplitude), sural nerve (sensory conduction velocity and amplitude), and peroneal nerve (motor nerve conduction velocity and amplitude).

**Results** Of the 166 subjects, 112 subjects (67.5%) were confirmed to have DPN, and all the subjects were divided into two groups according to the presence/absence of DPN. When multivariate analysis was performed using significant factors from univariate logistic regression analysis as explanatory variables, GLS was found to be an independent determinant of DPN (odds ratio: 0.55,  $p < 0.001$ ). In multivariate analysis of NCS data, F-wave latency was the most important determinant of DPN (odds ratio: 1.43,  $p < 0.001$ ). There was a significant negative correlation between F-wave latency and GLS ( $r = -0.43$ ,  $p < 0.001$ ). Regarding the relation between GLS and the severity of DPN, GLS was significantly lower in patients with Grade I or higher DPN than in patients without DPN, but showed no significant difference between the grades of neuropathy. In addition, GLS was significantly lower when 2–3 lower extremity nerves were affected by DPN than in patients without DPN.

**Conclusion** Patients with diabetes may already have subclinical LV myocardial dysfunction when DPN is Grade I. Assessment of LV longitudinal systolic function by GLS may be important in diabetic patients with DPN.

**Keywords** Diabetic cardiomyopathy · Diabetic polyneuropathy · Echocardiography · Nerve conduction study · Global longitudinal strain

## Introduction

The pathogenesis of left ventricular (LV) dysfunction in diabetes mellitus has been attracting attention. It is known that patients with diabetes can develop LV dysfunction even in the absence of hypertension (HT) or significant coronary artery stenosis, and diabetes itself is considered to be a risk factor for heart failure, and especially LV diastolic failure [1, 2]. Recently, it has been reported that LV longitudinal systolic myocardial function determined by speckle tracking echocardiography (STE) is associated with diabetic

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nephropathy or diabetic polyneuropathy (DPN) [3]. However, the relation between the severity of peripheral neuropathy and LV myocardial dysfunction is unknown. The aim of this study was to examine the relationship between the severity of DPN determined by nerve conduction studies and clinical features or echocardiographic parameters.

## Methods

### Study population

This retrospective study was performed in 166 patients with diabetes (average age:  $57 \pm 14$  years; male/female: 108/58) who had normal systolic function on echocardiography [LV ejection fraction (LVEF)  $\geq 55\%$ ] during the period between March 2014 and December 2017. Diagnosis of diabetes was based on the criteria in the Japan Diabetes Society clinical practice guideline [4]. The subjects included both patients who are and not undergoing medical treatment for diabetes. The following clinical parameters were investigated based on the medical records: age, sex, body mass index (BMI), office blood pressure, heart rate, coefficient of variation of the R–R interval (CVR-R), fasting blood sugar (FBS), Hemoglobin A1c (HbA1c), duration of diabetes, total cholesterol (T-CHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), urinary microalbumin (uALB), estimated glomerular filtration rate (eGFR), and the presence/absence of complications [HT; hyperlipidemia (HL); chronic kidney disease (CKD)]. Patients with atrial fibrillation, coronary artery disease, clinically significant valvular heart disease, or renal dysfunction (eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>) were excluded.

### Echocardiographic examinations

Transthoracic echocardiography (TTE) was performed using a Vivid E9 (GE Healthcare, Horten, Norway) with a sector array transducer (M5S-D). The following echocardiography parameters were determined: LVEF by the modified Simpson's method, the peak velocity of early rapid filling (*E*) and atrial filling (*A*) by pulsed Doppler echocardiography in the apical long-axis view, as well as *E/A* ratio, and septal early diastolic mitral annular velocity (*e'*) by tissue Doppler echocardiography in the apical four-chamber view. The *E/e'* ratio was then calculated. The LA volume index (LAVI) was calculated as the LA volume obtained by the modified Simpson's method using the LV end-systolic apical two-chamber view and four-chamber view divided by the body surface area. LV end-diastolic dimension (LVDD), interventricular septal thickness (IVST), and posterior wall thickness (PWT) were measured by M-mode method or two-dimensional

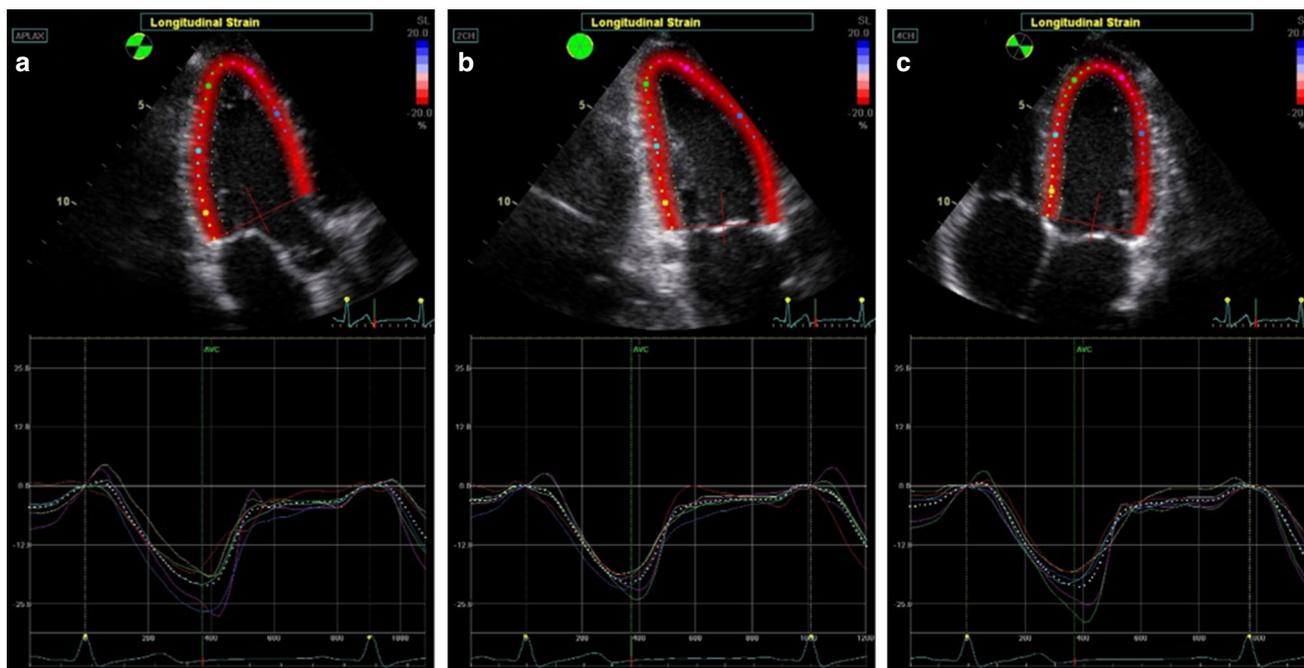
(2D) echocardiographic image in the parasternal LV long-axis view, and relative wall thickness (RWT) and LV mass index (LVMI) were calculated. LVMI was calculated using the formula in the American Society of Echocardiography guideline [5]. To assess LV longitudinal systolic function, global longitudinal strain (GLS) was calculated as the average peak strain in three standard apical views by 2D-STE (Fig. 1) using an EchoPAC PC (Version 112, GE Healthcare) on offline analysis. Similarly, global circumferential strain (GCS) and global radial strain (GRS) were calculated as the average peak strain in short-axis views at the papillary muscle levels.

### Nerve conduction study

A nerve conduction study (NCS) was performed in each subject within 1 week after TTE to assess three lower extremity nerves: the tibial nerve (F-wave latency (Fig. 2), motor nerve conduction velocity, and amplitude), the sural nerve (sensory conduction velocity and amplitude), and the peroneal nerve (motor nerve conduction velocity and amplitude). The severity of neuropathy was determined according to the NCS Baba Classification [6] using the following five grades: Grade 0, No apparent abnormalities; Grade I, Mild; Grade II, Moderate; Grade III, Severe; Grade IV, Abolition (Table 1). Because the upper limit of normal for the F-wave latency varies with the body height, a cutoff value was calculated using the following correction formula: latency (ms) = body height (cm)  $\times 0.22 + 12.8$ .

### Statistical analysis

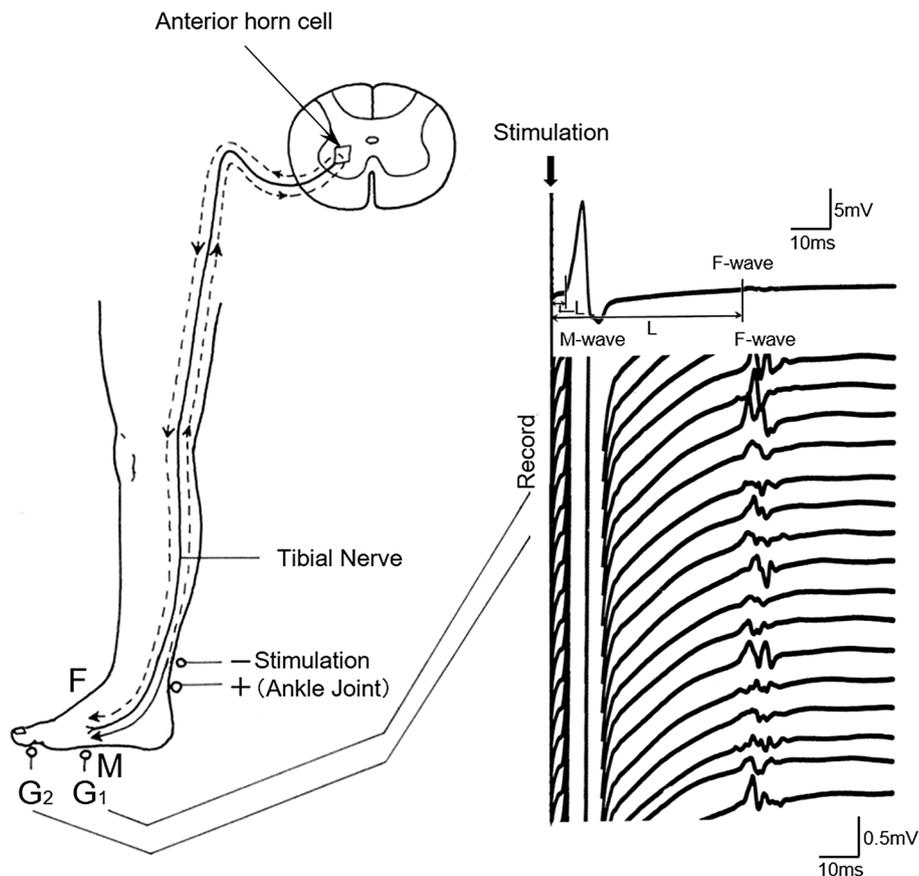
Numerical data are presented as the mean  $\pm$  standard deviation or as percentages. The Chi square test and the Mann–Whitney *U* test were used for comparison between two groups. To assess association between the severity of DPN and the number of nerves with neuropathy, Scheffe's multiple comparison test was performed after determining the significance of differences by analysis of variance (Kruskal–Wallis test). To identify factors that were relevant to DPN, univariate logistic regression analysis was conducted with background factors, echocardiographic parameters, and NCS indexes as the independent variables and the presence/absence of DPN as the dependent variable. Multivariate analysis was then conducted by stepwise logistic regression models (forward selection; likelihood ratio) using variables that were statistically significant ( $p < 0.1$ ) in the univariate analysis. All analyses were performed with statistical software (Dr. SPSS II; SPSS Japan Inc., Tokyo, Japan), and  $p < 0.05$  was considered to indicate statistical significance.



**Fig. 1** Measurement of global longitudinal strain (GLS) using two-dimensional speckle tracking in the apical long-axis (a), two-chamber (b), and four-chamber (c) views, respectively. The waveforms in the figure represent the longitudinal strain curves obtained from each

view. The white dotted line strain curve shows the average peak strain of six segments in each view, and GLS was calculated as the average peak strain in three standard apical views

**Fig. 2** The tibial nerve was stimulated at the ankle joint 16 times consecutively with the maximum stimulus and the F-wave minimum latency was measured



**Table 1** NCS Baba classification

NCS parameters/severity	Grade 0 (none)	Grade I (mild)	Grade II (moderate)	Grade III (severe)	Grade IV (abolition)
Tibial F-wave latency extension (> 45.8–52.4 ms/1.5–1.8 m height)	–	○			
And/or MCV delay (> 42 m/s)	–	○			
And/or appearance of A-wave	–	○			
And/or sural SCV delay (> 42 m/s)	–	○			
And/or peroneal CMAP low amplitude (> 2 mv)	–	○			
And/or peroneal MCV delay (> 42 m/s)	–	○			
Sural SNAP low amplitude (> 5 μV)	–	–	○		
Peroneal CMAP low amplitude (> 2–5 mV)	–	–	–	○	
Peroneal CMAP severe low amplitude (> 2 mV)	–	–	–	–	○

NCS nerve conduction study, MCV motor nerve conduction velocity, SCV sensory nerve conduction velocity, CMAP compound muscle action potential, SNAP sensory nerve action potential

<sup>a</sup>Quotes form NCS Baba classification and modified [6]

## Reproducibility

Intraobserver variability for GLS, GCS, and GRS was assessed in 15 randomly chosen echocardiograms on two separate occasions separated by several weeks in time. Interobserver measurements in these 15 patients were repeated by a blinded second reviewer (M.H.) and by the primary reviewer (S.T.) on two separate occasions. The intraclass correlation coefficient (ICC) was used to assess the reliability of the intra- and interobserver measurements.

## Results

### Baseline characteristics in patients with and without DPN

Based on the NCS Baba Classification, the subjects were classified into two groups, including 54 subjects in the non-DPN group (Grade 0) and 112 subjects in the DPN group (Grade I–IV). Comparison of clinical and echocardiographic characteristics between the two groups is presented in Table 2. Significant differences were noted between the DPN group and the non-DPN group with regard to age ( $p < 0.001$ ), BMI ( $p = 0.027$ ), duration of diabetes ( $p = 0.023$ ), CVR-R ( $p = 0.008$ ), diabetic retinopathy ( $p < 0.001$ ), diabetic nephropathy ( $p < 0.001$ ), uALB ( $p < 0.001$ ), insulin ( $p = 0.015$ ), and sodium–glucose cotransporter-2 inhibitor (SGLT-2i) ( $p = 0.023$ ), while there were no significant differences in FBS, HbA1c, and lipid metabolism parameters.

### Comparison of echocardiographic and NCS parameters in patients with and without DPN

Echocardiographic parameters showed no significant differences between the DPN group and non-DPN group, while there were significant differences in RWT ( $p = 0.021$ ),  $E/A$  ( $p < 0.001$ ),  $e'$  ( $p = 0.001$ ),  $E/e'$  ( $p = 0.039$ ), and GLS ( $p < 0.001$ ). To select variables for multivariate analysis, univariate logistic regression analysis was performed with clinical background factors and echocardiographic parameters as independent variables and the presence/absence of DPN as the dependent variable, resulting in 17 factors being identified that showed significance at  $p < 0.1$  (Table 3). Subsequently, multivariate analysis was performed by forward selection (likelihood ratio), revealing that age and GLS were independent determinants of DPN (GLS; odds ratio: 0.55,  $p < 0.001$ ). NCS parameters are compared between the two groups in Table 4. All NCS parameters were significantly different between the two groups. Similarly, multivariate analysis revealed that F-wave latency was most closely related to DPN among the NCS parameters (odds ratio: 1.43,  $p < 0.001$ ) (Table 4). There was a significant negative correlation between GLS and F-wave latency ( $r = 0.43$ ,  $p < 0.001$ ) (Fig. 3).

### Relationship between GLS and DPN severity, number of nerves affected by neuropathy

The relationship between the severity of DPN and GLS was investigated (Fig. 4). GLS tended to decrease as the severity of DPN increased from Grade I to IV. A significant difference in GLS was observed between Grade 0 and Grade I or higher DPN, while there was no significant difference

**Table 2** Clinical and echocardiographic characteristics of patients

Variable	Patients ( <i>n</i> = 166)	DPN (–) ( <i>n</i> = 54)	DPN (+) ( <i>n</i> = 112)	<i>p</i> value
<b>Clinical data</b>				
Age (year)	57.0 ± 14.0	50.6 ± 13.6	60.1 ± 13.1	< 0.001
Men, <i>n</i> (%)	108 (65.1)	33 (61.1)	75 (67.0)	0.549
Body mass index	2.5 ± 4.4	26.6 ± 4.4	25.0 ± 4.4	0.027
Body surface area (m <sup>2</sup> )	1.73 ± 0.21	1.76 ± 0.21	1.72 ± 0.21	0.126
Systolic blood pressure (mmHg)	120.6 ± 15.7	119.5 ± 12.7	121.2 ± 17.0	0.883
Diastolic blood pressure (mmHg)	68.9 ± 10.4	69.9 ± 8.9	68.5 ± 11.1	0.351
Heart rate (bpm)	70.0 ± 10.0	69.3 ± 10.0	70.3 ± 10.1	0.427
CVR-R (%)	2.83 ± 1.62	3.22 ± 1.60	2.65 ± 1.60	0.008
Diabetes duration (year)	8.9 ± 7.3	6.7 ± 5.2	10.0 ± 8.0	0.023
Type 2 diabetes, <i>n</i> (%)	155 (93.4)	50 (92.6)	105 (93.8)	0.790
Hypertension, <i>n</i> (%)	70 (42.2)	17 (31.5)	53 (47.3)	0.052
Dyslipidemia, <i>n</i> (%)	90 (54.2)	33 (61.1)	57 (50.9)	0.219
Chronic kidney disease, <i>n</i> (%)	29 (17.5)	6 (11.1)	23 (20.5)	0.138
Diabetic polyneuropathy, <i>n</i> (%)	112 (67.5)	–	–	–
Diabetic retinopathy, <i>n</i> (%)	47 (28.3)	5 (9.3)	42 (37.5)	< 0.001
Diabetic nephropathy, <i>n</i> (%)	47 (28.3)	6 (11.1)	41 (36.6)	< 0.001
<b>Biochemistry</b>				
Fasting blood glucose (mg/dl)	172.0 ± 74.0	163.2 ± 67.1	176.2 ± 77.0	0.215
Hemoglobin A1c (%)	9.5 ± 2.4	9.2 ± 2.6	9.7 ± 2.2	0.065
Total cholesterol (mg/dl)	199.0 ± 44.1	202.3 ± 38.8	197.5 ± 46.5	0.427
LDL cholesterol (mg/dl)	119.0 ± 40.9	123.6 ± 37.8	116.7 ± 42.3	0.164
HDL cholesterol (mg/dl)	52.9 ± 15.5	51.0 ± 13.0	53.8 ± 16.5	0.440
Triglyceride (mg/dl)	148.8 ± 85.4	156.1 ± 102.4	145.3 ± 76.2	0.676
Creatinine clearance (mg/dl)	0.76 ± 0.24	0.74 ± 0.22	0.77 ± 0.25	0.744
eGFR (ml/min/1.732 m <sup>2</sup> )	81.7 ± 23.8	83.2 ± 20.6	80.9 ± 25.3	0.478
Urinary microalbumin	125.0 ± 476.1	33.0 ± 102.9	168.1 ± 568.2	< 0.001
<b>Medical treatment</b>				
CCb, <i>n</i> (%)	45 (27.1)	11 (20.4)	34 (30.4)	0.180
ACEi/ARB, <i>n</i> (%)	55 (33.1)	13 (24.1)	42 (37.5)	0.085
β-blocker, <i>n</i> (%)	8 (4.8)	1 (1.9)	7 (6.3)	0.216
Statin, <i>n</i> (%)	48 (28.9)	16 (29.6)	32 (28.6)	0.884
Insulin, <i>n</i> (%)	55 (33.1)	11 (20.4)	44 (39.3)	0.015
SGLT-2i, <i>n</i> (%)	9 (5.4)	6 (11.1)	3 (2.7)	0.023
DPP-4i, <i>n</i> (%)	68 (41.0)	20 (37.0)	48 (42.9)	0.479
GLP-1RA, <i>n</i> (%)	3 (1.8)	0 (0.0)	3 (2.7)	0.216
Sulfonylurea, <i>n</i> (%)	30 (18.1)	8 (14.8)	22 (19.6)	0.439
α-GI, <i>n</i> (%)	23 (13.9)	6 (11.1)	17 (15.2)	0.472
Thiazolidine, <i>n</i> (%)	13 (7.8)	4 (7.4)	9 (8.0)	0.902
Metformin, <i>n</i> (%)	56 (33.7)	20 (37.0)	36 (32.1)	0.528
<b>Echocardiography</b>				
Left ventricular ejection fraction (%)	69.8 ± 5.9	69.1 ± 5.7	70.2 ± 6.0	0.232
LVDd (mm)	43.6 ± 4.8	43.9 ± 4.4	43.4 ± 4.9	0.534
IVST (mm)	9.3 ± 1.3	9.1 ± 1.2	9.4 ± 1.3	0.122
PWT (mm)	9.4 ± 1.2	9.2 ± 1.2	9.5 ± 1.2	0.109
Relative wall thickness	0.43 ± 0.06	0.42 ± 0.06	0.44 ± 0.06	0.021
Left ventricular mass index (g/m <sup>2</sup> )	78.5 ± 19.9	75.3 ± 18.1	80.0 ± 20.7	0.163
Left atrial volume index (ml/m <sup>2</sup> )	23.0 ± 7.0	21.9 ± 6.5	23.6 ± 7.1	0.195
<i>E</i> (cm/s)	69.2 ± 14.7	71.6 ± 14.2	68.1 ± 14.8	0.103
Dct (ms)	235.1 ± 55.4	221.2 ± 42.9	241.9 ± 59.6	0.056

**Table 2** (continued)

Variable	Patients ( <i>n</i> = 166)	DPN (–) ( <i>n</i> = 54)	DPN (+) ( <i>n</i> = 112)	<i>p</i> value
<i>E/A</i>	0.99 ± 0.34	1.11 ± 0.35	0.93 ± 0.32	< 0.001
<i>E'</i> (cm/s)	6.80 ± 2.17	7.56 ± 2.26	6.43 ± 2.03	0.001
<i>E/E'</i>	10.9 ± 3.4	10.2 ± 3.2	11.3 ± 3.4	0.039
Global longitudinal strain (%)	– 20.2 ± 2.0	– 21.2 ± 1.6	– 19.2 ± 1.6	< 0.001
Global circumferential strain (%)	– 20.8 ± 3.1	– 21.1 ± 2.6	– 20.7 ± 3.3	0.411
Global radial strain (%)	55.4 ± 17.6	56.2 ± 17.9	55.0 ± 17.5	0.592

*CVR-R* coefficient of variation of R–R intervals, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *CCB* calcium channel blocker, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon like peptide-1 receptor agonist, *α-GI* α-glucosidase inhibitor, *LVDd* left ventricular diastolic dimension, *IVST* intraventricular septal thickness, *PWT* posterior wall thickness, *Dct* deceleration time E-wave, *E* peak velocity of early rapid filling, *A* peak velocity of atrial filling, *E'* early diastolic mitral annular velocity

**Table 3** Univariate and multivariate analysis of clinical and echocardiographic characteristics

Variable	DPN (–) ( <i>n</i> = 54)		DPN (+) ( <i>n</i> = 112)		<i>p</i> value	
	Univariate analysis		Multivariate analysis			
	$\beta$	OR (95% CI)	$\beta$	OR (95% CI)		
Age (year)	0.05	1.05 (1.03–1.08)	< 0.001	0.05	1.05 (1.02–1.08)	0.003
Body mass index	–0.08	0.92 (0.85–0.99)	0.030			
<i>CVR-R</i> (%)	–0.21	0.81 (0.66–0.99)	0.040			
Diabetes duration (year)	0.07	1.08 (1.02–1.14)	0.012			
Hypertension	0.67	1.96 (0.99–3.87)	0.055			
Diabetic retinopathy	1.77	5.88 (2.17–15.9)	< 0.001			
Diabetic nephropathy	1.51	4.52 (1.78–11.5)	0.002			
Urinary microalbumin (mg/day)	0.01	1.00 (1.00–1.01)	0.099			
ACEi/ARB	0.64	1.89 (0.91–3.93)	0.088			
Insulin	0.93	2.53 (1.18–5.43)	0.017			
SGLT-2i	–1.51	0.22 (0.05–0.92)	0.038			
Relative wall thickness	5.47	237 (0.92–61,380)	0.054			
<i>Dct</i> (ms)	0.01	1.01 (1.00–1.01)	0.027			
<i>E/A</i>	– 1.63	0.20 (0.07–0.54)	0.002			
<i>E'</i> (cm/s)	– 0.24	0.78 (0.67–0.92)	0.002			
<i>E//E'</i>	0.10	1.11 (1.00–1.23)	0.060			
Global longitudinal strain (%)	– 0.65	0.52 (0.41–0.67)	< 0.001	– 0.59	0.55 (0.43–0.72)	< 0.001

$\beta$  partial regression coefficient, *CI* confidence intervals, *OR* odds ratios, *CVR-R* coefficient of variation of R–R intervals, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin blocker, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor, *Dct* deceleration time of E-wave, *E* peak velocity of early rapid filling, *A* peak velocity of atrial filling, *E'* early diastolic mitral annular velocity

in GLS between the grades from Grade I to IV. Similarly, the relationship between the number of nerves affected by neuropathy and GLS was investigated (Fig. 5). It was found that GLS tended to decrease as the number of affected nerves increased. GLS was significantly lower in patients with more than two nerves affected by neuropathy than in those without DPN, while there was no significant difference in GLS between patients with one or two nerves affected by

neuropathy. The patients with and without DPN are shown in Fig. 6.

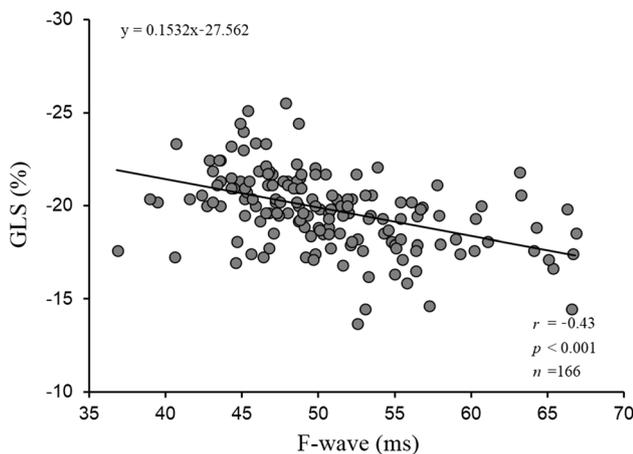
### Intra- and interobserver variability

The ICC and 95% confidence intervals [CI] for the intra- and interobserver agreement for the GLS measurements were 0.95 (95% CI 0.88–0.98) and 0.93 (95% CI 0.82–0.97),

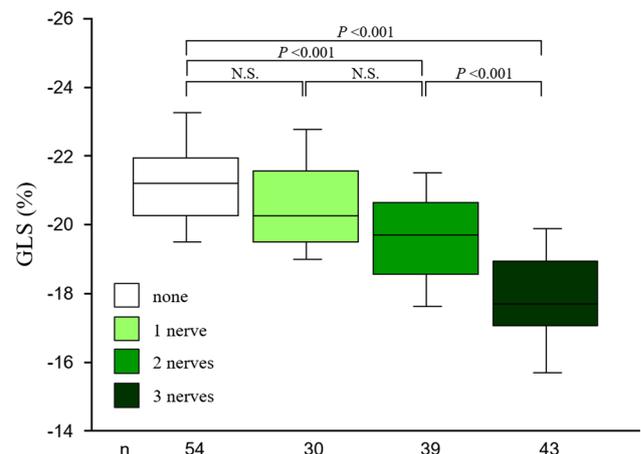
**Table 4** Nerve conduction study of patients

Variable	Comparison in both groups			Multivariate analysis		
	DPN (-) (n=54)	DPN (+) (n=112)	p value	$\beta$	OR (95% CI)	p value
Tibial F-wave latency (ms)	45.8 ± 2.5	52.7 ± 5.9	< 0.001	0.36	1.43 (1.20–1.70)	< 0.001
Tibial MCV (m/s)	47.7 ± 3.2	40.5 ± 4.7	< 0.001	- 0.29	0.75 (0.62–0.91)	0.004
Tibial CMAP (mV)	10.3 ± 3.1	6.9 ± 3.4	< 0.001			
Sural SCV (m/s)	52.0 ± 5.0	45.4 ± 6.8	< 0.001			
Sural SNAP ( $\mu$ V)	16.5 ± 7.6	8.7 ± 5.5	< 0.001	- 0.15	0.87 (0.78–0.96)	0.004
Peroneal MCV (m/s)	47.0 ± 2.9	39.9 ± 5.8	< 0.001	- 0.20	0.82 (0.69–0.97)	0.020
Peroneal CMAP (mV)	4.3 ± 2.5	2.3 ± 1.9	< 0.001			

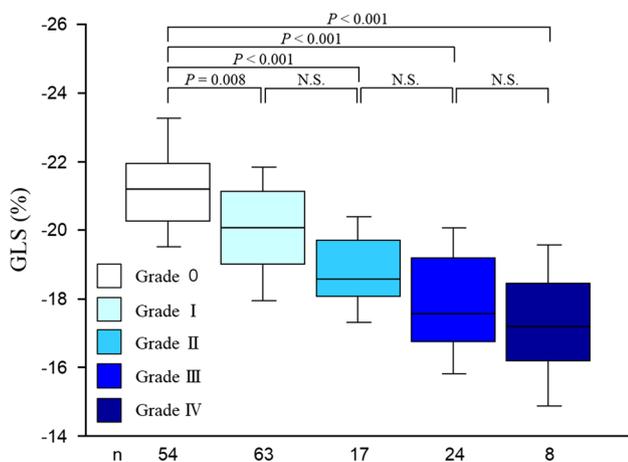
$\beta$  partial regression coefficient, CI confidence intervals, OR odds ratio, MCV motor nerve conduction velocity, SCV sensory nerve conduction velocity, CMAP compound muscle action potential, SNAP sensory nerve action potential



**Fig. 3** Correlation between GLS and F-wave latency



**Fig. 5** Relationship between GLS and number of nerves affected by neuropathy



**Fig. 4** Relationship between GLS and diabetic polyneuropathy severity

respectively. The ICC and 95% CI for the intra- and interobserver agreement for the GCS measurements were 0.97 (95% CI 0.93–0.99) and 0.92 (95% CI 0.86–0.95), respectively.

The ICC and 95% CI for the intra- and interobserver agreement for the GRS measurements were 0.93 (95% CI 0.85–0.96) and 0.90 (95% CI 0.77–0.94), respectively.

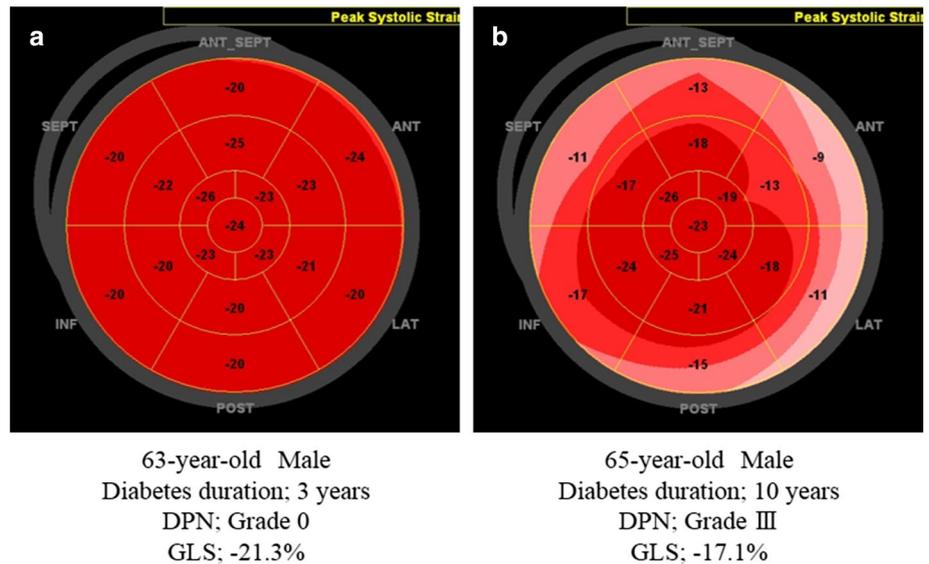
## Discussion

The number of patients with diabetes worldwide has been reported to be 425 million, accounting for 8.8% of the world’s adult population [7]. In Japan, an estimated 20 million people either have diabetes or are at risk of developing diabetes [8]. As the number of patients with diabetes and diabetic complications increases, patients with heart failure and diabetes are also expected to increase annually.

### Diabetic cardiomyopathy

Coronary artery disease was originally thought to be the main cardiac disease associated with diabetes. However, Rubler et al. [1] reported that LV hypertrophy and

**Fig. 6** Strain values for all 18 myocardial segments represented on bull's eye plots. The plots also provide longitudinal strain values for each of the three views and an average value, which is the primary variable of interest for longitudinal surveillance. **a** A patient with diabetes for 3 years and grade 0 diabetic polyneuropathy (DPN) has normal GLS. **b** A patient with diabetes for 10 years and grade III DPN showed a decrease in GLS



myocardial fibrosis were observed at autopsy in patients with diabetes who experienced heart failure without coronary artery disease, valvular heart disease, or HT, leading to the concept that diabetic cardiomyopathy may cause severe myocardial damage in patients without coronary artery disease. Diabetic cardiomyopathy is characterized by the development of cardiomyocyte hypertrophy, interstitial fibrosis, and/or small vessel wall thickening despite the absence of apparent coronary atherosclerosis or significant coronary artery stenosis. It is assumed that vascular endothelial cell dysfunction is caused by multiple factors, including accumulation of fatty acids in the myocardium, abnormal glucose metabolism, autonomic neuropathy, increased oxidative stress, or deposition of advanced glycation end products (AGE), resulting in damage to the intramyocardial arterioles [9–12].

### STE for assessment of LV myocardial systolic function

It is known that some patients have systolic dysfunction due to abnormalities of the LV myocardium, even with a normal LVEF [13, 14].

The LV is composed of three myocardial layers with the inner oblique, circular, and outer oblique muscles. Contraction of the heart is complex, with muscular components contracting in the longitudinal, circumferential, and radial directions [15]. In patients with heart failure, myocardial dysfunction initially occurs in the subendocardial layer due to myocardial ischemia, leading to a reduction of GLS [16, 17]. Recently, Stokke et al. [18] reported that LVEF is mainly dependent on circumferential shortening, and less sensitive to a reduction in longitudinal shortening. Our study was consistent with their results that GLS worsened

in diabetic patients with DPN despite of the preservation of LVEF and GCS.

### LV longitudinal systolic dysfunction in DM patients with preserved LVEF

It was recently reported that STE revealed reduction of LV longitudinal systolic myocardial function in patients with diabetes despite the absence of coronary artery disease and a normal LVEF ( $\geq 50\%$ ) [19–21]. Liu et al. [22] performed a cohort study of 224 patients with type II diabetes without a history of cardiac disease in whom LVEF was preserved, and found that cardiovascular events were significantly more frequent in the group with  $GLS > -17.9\%$ . Also, Holland et al. [23] performed a 10-year follow-up study of 230 patients with type II diabetes without coronary artery disease and with maintenance of LVEF, which revealed that death or hospitalization for heart failure was significantly more frequent in the group with  $GLS > -18.9\%$ . It has been reported that LV diastolic dysfunction occurs at a relatively early stage in patients with diabetes mellitus [2, 24]. In the present study, patients with or without DPN showed significant differences in diastolic function parameters, including  $E/A$  ratio,  $e'$ , and  $E/e'$  ratio. However, the  $E/A$  ratio that is markedly influenced by preload [25, 26] and  $e'$  only partially assesses LV diastolic function. On the other hand, GLS assesses myocardial function for the whole LV and may be a stronger determinant than those diastolic parameters. Hayashi et al. [27] reported that GLS was more strongly correlated with LV relaxation than  $e'$ , and the  $E/GLS$  ratio showed a closer correlation with LV filling pressure than the  $E/e'$  ratio. Thus, reduction of GLS is already observed at the asymptomatic stage in patients whose LVEF is still normal, and therefore it may be important to investigate GLS

to detect LV myocardial dysfunction earlier for the prevention of cardiovascular events and heart failure.

### Diabetic polyneuropathy

DPN is due to microangiopathy and is a complication of diabetes that develops at the earliest stage with a high incidence. According to an epidemiological investigation conducted in Japan using simple diagnostic criteria advocated by the “Japanese study group of diabetic polyneuropathy,” 35.8% of patients with diabetes have DPN, and the prevalence is 36.7% according to the Japan Physicians Association [28, 29]. In our study, 67.5% of the subjects had DPN, which was a higher prevalence compared to previous reports. The probable reason is that many of our subjects had poor glycemic control as their average HbA1c was 9.5%.

### Impact of GLS on diabetic polyneuropathy

Enomoto et al. [3] reported a relatively good correlation between GLS and CVR-R ( $r=0.58$ ,  $p<0.001$ ). However, the correlation between GLS and CVR-R was weak in our study ( $r=0.19$ ,  $p=0.016$ ). Since the frequency of diabetic retinopathy (35%) and diabetic nephropathy (83%) among the patients studied by Enomoto et al. was higher than in our subjects, it seems likely that there were also differences in the duration and progression of diabetes. Currently, the Mayo Clinic Neuropathy Impairment Score of the lower limbs plus seven tests [NIS(LL)+7 tests] is considered to be the most accurate method for diagnosis of DPN. It was reported that, if this method is taken as the gold standard, the sensitivity would be 81% and the specificity would be 91% for criteria that use abnormalities of two or more nerves on NCS to indicate “neuropathy present” [30]. Regarding the relationship between the number of nerves affected by neuropathy and GLS, we found that GLS was significantly lower in patients with involvement of 2–3 lower extremity nerves, suggesting that myocardial damage may progress as the number of affected nerves increases. NCS is considered to be a gold standard method for diagnosis of neuropathy [31]. In our study, we investigated DPN using the NCS Baba Classification [6], which is an objective clinical index for stratification of neuropathy based on NCS data for lower extremity nerves. We found that GLS was significantly lower in subjects with Grade I or higher DPN than those without DPN. We also found that GLS tended to decrease as the severity of DPN increased from Grade I to IV, although no significant differences were found between the grades of neuropathy. Possible reasons for this result could include the small number of subjects with DPN of Grade II or higher. It has been reported that the hemodynamic burden such as afterload caused by increased central blood pressure or aortic stiffness affects GLS and the GCS [32–34].

Additionally, approximately half of the patients in this study had concurrent HT, and there is also a possibility that it has been affected by blood pressure. However, there was no significant difference in systolic and diastolic blood pressure between the patients with or without DPN. As patients with diabetes often have HT, dyslipidemia, and other complications, it would be difficult to clinically evaluate LV myocardial dysfunction in patients with diabetes alone.

### F-wave latency and GLS

Because DPN progresses from distal to proximal, NCS is considered to be able to detect early lesions since measurements are made more distally, and it has been reported that F-wave latency is an acute indicator of early abnormalities [35]. Mochizuki et al. [36] found a significant negative correlation between GLS and F-wave latency ( $r=-0.34$ ,  $p<0.001$ ). In our study, a similar relationship was also observed between F-wave latency and GLS ( $r=0.43$ ,  $p<0.001$ ), and multivariate analysis demonstrated that GLS was the independent determinant most closely related to the presence/absence of DPN.

### Clinical implications

Thus, GLS obtained by 2D-STE is associated with DPN. Considering that reduction of blood flow and abnormalities of metabolism due to impairment of the blood supply to the nerves (e.g., oxidative stress, AGE accumulation, activation of protein kinase C, and abnormal fat metabolism) are assumed to be involved in the pathogenesis of DPN [37–42], there are many mechanisms common to diabetic cardiomyopathy, suggesting that these two types of microangiopathy may occur and progress together. However, there are still many unknown factors regarding the detailed mechanisms of DPN and diabetic cardiomyopathy, and further investigation is required. The mean GLS in the DPN group was 19.2% in the present study, but this is normal using GE equipment, with the reported normal value of GLS being  $-21.3 \pm 2.1\%$  (mean  $\pm$  SD) [43]. Also, the reported normal range of GLS in a meta-analysis was from  $-15.9$  to  $-22.1\%$  [44]. It seems to be difficult to predict the presence/absence of DPN based on GLS data. However, GLS was already significantly lower in the patients with Grade I DPN, so it can be assumed that patients with DPN already have a high prevalence of subclinical LV myocardial dysfunction. Attention is also required with regard to the risk of heart failure in patients with advanced DPN because they may already have marked myocardial damage even if the LVEF is maintained. Considering that reduction of GLS is not only related to LV myocardial dysfunction but also to the severity of DPN, assessment of LV longitudinal systolic function by

determining GLS using STE may be important in diabetic patients with DPN.

### Study limitations

In this study, we excluded patients with coronary artery disease based on their medical records and laboratory findings. However, rigorous exclusion was not achieved because coronary angiography or coronary CT angiography was not performed. With regard to the NCS Baba Classification, the standard values may differ among ethnic groups, and our research was only conducted on Japanese subjects. Furthermore, this was a cross-sectional study. A prospective study needs to be conducted in the future to determine whether GLS is related to cardiac events caused by diabetic heart failure and progression of microangiopathy.

### Conclusion

Our findings suggested that patients with diabetes and Grade I DPN may already have subclinical LV myocardial dysfunction. Assessment of LV longitudinal systolic function by determining GLS using STE may be important in diabetic patients with DPN.

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### Compliance with ethical standards

**Conflict of interest** None of the authors has any conflict of interest in the research associated with this article.

**Ethical standards** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This research was approved by the Ethics Committee of Toho University Medical Center Omori Hospital (approval No. M17264) and was conducted after the Committee made a decision that informed consent was not required.

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