JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Fragmented QRS on electrocardiography as a predictor for diastolic cardiac dysfunction in type 2 diabetes

Kunimasa Yagi[1,2]*, Teruhiko Imamura[3], Hayato Tada[2], Jianhui Liu[1,2], Yukiko Miyamoto[2], Azusa Ohbatake[2], Naoko Ito[2], Masataka Shikata[1], Asako Enkaku[1], Akiko Takikawa[1], Hisae Honoki[1], Shiho Fujisaka[1], Daisuke Chujo[1,2], Hideki Origasa[4], Koichiro Kinugawa[3], Kazuyuki Tobe[1]

[1]1st Department of Internal Medicine, University of Toyama, Toyama, Japan, [2]2nd Department of Internal Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan, [3]2nd Department of Internal Medicine, University of Toyama, Toyama, Japan, and [4]Biostatistics and Clinical Epidemiology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan

Keywords
Diabetic microvascular diseases, Diastolic cardiac dysfunction, Fragmented QRS

***Correspondence**
Kunimasa Yagi
Tel.: +81-76-434-7287
Fax: +81-76-434-5025
E-mail address: yagikuni@med.u-toyama.ac.jp

J Diabetes Investig 2022; 13: 1052–1061

doi: 10.1111/jdi.13759

ABSTRACT

Aims/Introduction: Diastolic cardiac dysfunction in type 2 diabetes (DD2D) is a critical risk of heart failure with preserved ejection fraction. However, there is no established biomarker to detect DD2D. We aimed to investigate the predictive impact of fragmented QRS (fQRS) on electrocardiography on the existence of DD2D.

Materials and Methods: We included in-hospital patients with type 2 diabetes without heart failure symptoms who were admitted to our institution for glycemic management between November 2017 and April 2021. An fQRS was defined as an additional R′ wave or notching/splitting of the S wave in two contiguous electrocardiography leads. DD2D was diagnosed according to the latest guidelines of the American Society of Echocardiography.

Results: Of 320 participants, 122 patients (38.1%) had fQRS. DD2D was diagnosed in 82 (25.6%). An fQRS was significantly associated with the existence of DD2D (odds ratio 4.37, 95% confidence interval 2.33–8.20; $p < 0.0001$) adjusted for seven potential confounders. The correlation between DD2D and diabetic microvascular disease was significant only among those with fQRS. Classification and regression tree analysis showed that fQRS was the most relevant optimum split for DD2D.

Conclusions: An fQRS might be a simple and promising predictor of the existence of DD2D. The findings should be validated in a larger-scale cohort.

INTRODUCTION

Patients with type 2 diabetes mellitus and heart failure (HF) with preserved ejection fraction (HFpEF) have a poorer prognosis and quality of life, as well as higher hospitalization and cardiovascular mortality compared with their counterparts without diabetes[1]. Diastolic cardiac dysfunction in type 2 diabetes (DD2D) is a critical risk for HFpEF[2]. As the clinical course of DD2D has been reported as adjustable[3], screening DD2D in the early stage of diabetes is crucial.

Currently, modalities, such as transthoracic echocardiograms (TTE)[4] and cardiac magnetic resonance imaging[5], are applied for the diagnosis of diastolic cardiac dysfunction. However, these modalities require expert techniques for the assessments. Thus, a reliable, simple and quickly-applicable biomarker is required for DD2D screening in daily clinics.

Fragmented QRS (fQRS) on a standard resting 12-lead electrocardiogram (ECG) includes various QRS complex morphologies as follows: various RSR′ patterns; additional R wave (R′) or notching in the nadir of the S wave; the presence of >1 R′ (fragmentation) in two contiguous leads; and corresponding to a significant coronary artery territory[6]. We recently reported a higher prevalence of fQRS in patients with diabetes than patients with metabolic syndrome without diabetes[7].

A few studies examined the relationship between fQRS and diastolic function in diabetes. One showed the correlation between fQRS and diastolic function parameters on TTE, not

Received 13 December 2021; revised 21 January 2022; accepted 23 January 2022

in diastolic dysfunction, in type 2 diabetes patients[8]. The other showed that those with diastolic dysfunction, including 41% of type 2 diabetes patients, were more likely to be diagnosed as HFpEF when accompanying fQRS[9]. However, to our knowledge, little data exist regarding the relationship between the presence of fQRS and DD2D. The present study aimed to investigate whether fQRS could be a predictor of DD2D among patients with type 2 diabetes.

MATERIALS AND METHODS

Study population

This was a retrospective cross-sectional observational study on a hospital-based cohort. We analyzed data of patients who were hospitalized for glycemic management in Toyama University Hospital, Toyama, Japan, between November 2017 and April 2021. The inclusion criteria were as follows: (i) type 2 diabetes with evaluation data of diabetic microvascular diseases (MVDs), ECG and TTE; (ii) left ventricular ejection fraction ≥40%; (iii) no symptomatic HF; and (iv) no persistent atrial fibrillation. MVD included neuropathy, retinopathy or nephropathy[10]. The exclusion criteria were as follows: (i) type 1 diabetes; (ii) secondary diabetes; (iii) refractory malignant diseases; (iv) dependency on hemodialysis; (v) cardiac deposition diseases; (vi) symptomatic coronary artery disease or percutaneous coronary intervention within a year; (vii) severe valvular disease or valve replacement/implantation within a year; and (viii) severe hepatic dysfunction (Child–Pugh score ≥10).

Medical record review and variable definitions

We reviewed the data of comprehensive examinations including MVD evaluation. The examination also contained a self-reported health questionnaire that included information on diabetes onset and previous histories. The diagnoses of type 2 diabetes were based on the American Diabetes Association diagnostic criteria; diagnosed using hemoglobin A1c ≥6.5% (National Glycohemoglobin Standardization Program), a fasting blood glucose concentration of ≥126 (7.0 mol/L) mg/dL or a random blood glucose concentration of ≥200 mg/dL[11], or if the health questionnaire showed current medications for diabetes. Diabetic retinopathy was diagnosed by ophthalmologists using standardized stereoscopic seven-field fundus photographs. Diabetic neuropathy was defined as established autonomic neuropathy with the coefficient of variation of R-R interval <2.5% or positive orthostatic distention evaluated with the Schellong test. Diabetic nephropathy was defined with urinary albumin excretion ≥30 mg/g creatinine or estimated glomerular filtration ratio <60 mL/min/1.73 m^2. The patients' blood pressures were measured by ward nurses, with patients in the sitting position in the early morning within 1 h of waking up on the second day of admission. Hypertension was diagnosed if peripheral blood pressure was ≥140/90 mmHg, or if the health questionnaire showed current antihypertensive medications[12]. Coronary artery disease was diagnosed if significant coronary artery stenoses existed as ≥75% on coronary cine angiography and ≥50% on coronary computed tomography angiography. Peripheral arterial disease was diagnosed if the lowest resting ankle-brachial index was <0.9[13].

ECG acquisition and evaluation of fQRS

ECG record was obtained on admission in the supine position with electrocardiogram FCP-7431 (Fukuda Denshi Co. Ltd., Tokyo, Japan; filter range 0.16–100 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV). An fQRS was defined as follows[6]: QRS complex morphologies included various RSR′ patterns, including an additional R wave (R′), notching of the R wave or the S wave, or the presence of more than one R′ (fragmentation) in two continuous leads corresponding to a major lead set for major coronary artery territory. An fQRS was present if alterations were found in two or more contiguous anterior leads, lateral leads or inferior leads.

We followed the fQRS evaluation in cases with bundle branch block[14]. Right and left bundle branch blocks were defined by the standard ECG criteria (QRS duration ≥120 ms), and f-bundle branch block was defined as various RSR′ patterns with or without a Q wave, with more than two R waves (R′) or more than two notches in the R wave, or more than two notches in the downstroke or upstroke of the S wave in two contiguous leads corresponding to a major coronary artery territory. All ECGs were assessed by a single cardiologist blinded to the patients' clinical and laboratory characteristics. The concordance rate for detecting fQRS was 97% to the previously published studies[7,15,16].

TTE Data collection and diagnosis of DD2D

All echocardiographic examinations were carried out at clinically stable conditions by the cardiologists who were blinded to the clinical data. Echocardiographic image recordings and measurements were obtained using a 3.75-MHz standard probe (EPIQ G7; Philips Inc., Amsterdam, the Netherlands). Standard echocardiographic parameters were measured including the ratio of peak early diastolic (E) and peak atrial systolic (A) transmitral flow velocities (E/A) and the E-wave to E′ ratio (E/E′) on tissue Doppler imaging.

We diagnosed DD2D as satisfying both left ventricular ejection fraction ≥40% and two abnormal parameters among E/E′ ratio, E′ velocity and tricuspid regurgitation velocity[17]. An average E/E′ ratio >14, a lateral E/E′ ratio >13 or a septal E/E′ >15 was considered abnormal. Septal E′ velocity <7 cm/s or lateral E′ velocity <10 cm/s was considered abnormal. Tricuspid regurgitation velocity >2.8 m/s was considered abnormal.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers and percentages. Continuous variables were compared using an unpaired *t*-test or a Mann–Whitney *U*-test. A comparison of the categorical variables between the groups was carried out using a χ^2-test. Multivariable logistic regression analysis was

carried out to assess the predictive impact of fQRS on the existence of DD2D adjusted for other potential confounders. For the stepwise analysis, parameters associated with fQRS with $p < 0.10$ were included in the analysis. The classification and regression tree analysis was carried out to investigate the predictive impact of independent variables, including fQRS, on DD2D. Classification and regression tree analysis was carried out recursively to form a tree of decision rules for powerful modeling, and $p < 0.05$ was considered statistically significant. The number of optimal splits was determined with k-fold cross-validation ($k = 5$). Statistical analysis was carried out using JMP Pro 15.2.1 on Mac (SAS Institute Inc., Cary, NC, USA).

Power analysis

Our previous study showed the ratio of fQRS was 36.0% in the participants with type 2 diabetes[7]. Using this ratio and χ^2-test sample size calculations, evaluation of 302 patients in total allowed detection of 30% difference in the prevalence of DD2D between 60% in the participants with fQRS and 30% in those without fQRS at 99% power and 0.005 significance level.

RESULTS

A total of 547 in-hospital diabetes patients were admitted. We excluded 227 patients according to the exclusion criteria: admitted in emergency or semi-emergency ($n = 33$); type 1 diabetes ($n = 20$); under immunosuppression ($n = 5$); diabetes after the surgical resection of the pancreas ($n = 10$); permanent hemodialysis ($n = 6$); refractory malignant diseases ($n = 27$); less than one year from cardiac intervention ($n = 8$); persistent atrial fibrillation ($n = 20$); no ankle-brachial index evaluation ($n = 14$); no examinations by ophthalmologists ($n = 18$); lacking ECG ($n = 4$); lacking TTE ($n = 27$); inability to evaluate E/E′ ratio ($n = 27$); and left ventricular ejection fraction <40% ($n = 8$). We finally included 320 patients in the present study.

Table 1 presents baseline characteristics, and Table 2 presents electrocardiogram findings. fQRS was observed in 38.1% of patients. A total of 82 patients (25.6%) had DD2D. fQRS was mainly observed in the inferior region. Patients with DD2D were older and had more comorbidities than those without DD2D. Of note, 79 out of 82 (96%) DD2D participants had multiple MVDs.

Multivariate analysis showed that fQRS was an independent predictor of DD2D (odds ratio 4.37, 95% confidence interval 2.33–8.20, $p < 0.0001$) after adjusting for potential confounders: age, sex and the number of MVDs (Table 3).

The classification and regression tree analysis showed the most relevant optimum split of DD2D versus fQRS and other potential confounders (Figure 1). As the cross-validation R^2 value increment between eight and nine splits was not >0.005, eight was considered optimal. The eight-node classification model showed an R^2 of 0.263. The optimal tree showed a correct classification rate of 79.7% and a negative predictive value of 93.7%. In patients without fQRS, female sex and age ≥65 years were associated with DD2D.

The prevalence of DD2D increased along with the number of MVDs (Figure 2). DD2D showed a tight association with MVD, because the MVD paralleled with the prevalence of DD2D ($R^2 = 0.0611$, $p < 0.0001$), and almost all DD2D cases possessed at least one MVD. This tendency between DD2D and the number of MVDs was observed significantly only in patients with fQRS ($R^2 = 0.1095$, $p = 0.0004$), but not those without fQRS ($R^2 = 0.0189$, $p = 0.3293$), showing fQRS correlated with DD2D associated with MVD. The relationships between each of the MVD and DD2D are shown in Figure 3. Nephropathy correlated most significantly with diastolic dysfunction among MVDs.

DISCUSSION

In the present study, we showed statistically that an fQRS was the most significant determinant of DD2D with high specificity. The prevalence of fQRS of 38.1% in the current study was quite similar to the prevalence of fQRS in type 2 diabetes; 36.0%[7], 28.1%[8], 33.1%[18] and 37.5%[19] in previous reports. As ECG is available at any clinic or medical checkup, it can be a simple and useful modality to estimate the presence of DD2D among diabetes patients. The screening for DD2D through ECG evaluation should be routine, especially for older female patients with MVD. Patients with fQRS should be further examined with TTE and other modalities. We suppose that the clinical significance of fQRS will change the consensus toward implementing routine ECG evaluation in diabetes.

Interstitial fibrosis, capillary endothelial changes and capillary basal laminar thickening are often observed from the very early stage of diabetes[20]. Chronic hyperglycemia can activate extracellular signal-regulated protein kinase 1/2 and p38 mitogen-activated protein kinase-mediated intracellular signaling, thereby regulating procollagen gene expression, resulting in cardiac fibroblasts activation[21,22]. fQRS was shown to be a valid biomarker for cardiac fibrosis[14]. Among the two possible underlying mechanisms of diastolic cardiac dysfunction (stiff cardiomyocytes and interstitial fibrosis)[23], from the current results, it is conceivable that DD2D is mainly attributed to interstitial fibrosis. Also, the finding that nephropathy most significantly correlated with DD2D is interesting. The diastolic cardiac dysfunction is markedly more progressed in patients with diabetic nephropathy than those with chronic glomerulonephritis independent of cardiac hypertrophy[24]. Procollagen gene expression, which plays a significant role in interstitial fibrosis progression in DD2D, could contribute to glomerular and tubulointerstitial fibrosis in diabetic nephropathy[25].

This is the first study showing the association between fQRS and diagnosed diastolic cardiac dysfunction according to the American Society of Echocardiography 2016 guideline[17]. The cut-off values of E/E′ ratio and E′ velocity for diagnosing DD2D were determined with the hemodynamic significance as the values reflecting the elevation of end-diastolic pressure of the left ventricles[26]. Until the update of the guidelines, there were differences in the parameters, and cut-off values in the

Table 1 | Baseline characteristics

	Total (n = 320)	DD2D (+) (n = 82)	DD2D (–) (n = 238)	p-value
Age (years)	67.3 ± 12.6	72.4 ± 9.6	65.5 ± 13	<0.0001
Male sex, n (%)	193 (60.3%)	38 (46.3%)	155 (65.1%)	0.0027
Duration of diabetes (years)	15.7 ± 11.8	20 ± 11.7	14.2 ± 11.4	<0.0001
Medical history				
Aortic stenosis	8 (2.5%)	6 (7.3%)	2 (0.8%)	0.0012
Coronary artery disease	73 (22.8%)	23 (28.1%)	50 (21.0%)	0.1901
Hypertension	247 (77.2%)	71 (86.6%)	176 (74.0%)	0.0187
Paroxysmal atrial fibrillation	14 (4.4%)	4 (4.9%)	10 (4.2%)	0.7962
Prior stroke	41 (12.8%)	15 (18.3%)	26 (10.9%)	0.0851
Peripheral arterial disease	50 (15.6%)	25 (30.5%)	25 (10.5%)	<0.0001
Systolic BP (mmHg)	134 ± 18	139 ± 18	133 ± 17	0.0041
Diastolic BP (mmHg)	81 ± 12	80 ± 13	81 ± 12	0.5698
BMI (kg/m^2)	25.2 ± 4.9	25.5 ± 5	25.3 ± 4.9	0.9618
eGFR (mL/min/1.73 m^2)	73.5 ± 25.9	63.2 ± 23.6	77 ± 25.7	<0.0001
Laboratory				
HbA1c (%)	9.6 ± 1.6	9.5 ± 1.7	9.7 ± 1.6	0.4001
TC (mg/dL)	180 ± 40	173 ± 42	183 ± 39	0.0663
Triglyceride (mg/dL)	141 ± 81	145 ± 86	140 ± 80	0.5941
HDL-C (mg/dL)	48 ± 14	47 ± 15	48 ± 14	0.6145
ALT	27.7 ± 21.6	25.1 ± 21.2	28.5 ± 21.7	0.2232
gGTP	47.9 ± 58.2	45.9 ± 60.6	48.6 ± 57.5	0.723
BNP	38.2 ± 58.4	61.2 ± 81	30 ± 45.3	<0.0001
UAE	198 ± 527	344 ± 781	148 ± 395	0.0036
Medication, n (%)				
ACEi or ARB	125 (39.1%)	44 (53.7%)	81 (34.0%)	0.0017
β-Blocker	49 (15.3%)	20 (24.4%)	29 (12.2%)	0.0081
MRA	10 (3.1%)	6 (7.32%)	4 (1.7%)	0.0114
Any diuretics	74 (23.2%)	24 (29.3%)	50 (21.1%)	0.1308
Any oral antidiabetic medication	268 (83.8%)	65 (79.3%)	203 (85.3%)	0.2021
Insulin	26 (39.4%)	47 (57.3%)	79 (33.2%)	0.0001
No. diabetic microvascular diseases				
0	50 (15.6%)	3 (3.7%)	47 (19.7%)	<0.0001
1	110 (34.4%)	23 (28.0%)	87 (36.6%)	
2	115 (35.9%)	36 (43.9%)	79 (33.2%)	
3	45 (14.1%)	20 (24.4%)	25 (10.5%)	
Any diabetic microvascular diseases	270 (84.4%)	79 (96.3%)	191 (80.3%)	0.0003
TTE parameter				
LAD	36.9 ± 5.9	38.5 ± 5.7	36.3 ± 5.9	0.0044
LVDd	45.2 ± 5	45.3 ± 5.4	45.1 ± 4.8	0.8242
IVS	9.4 ± 1.3	9.45 ± 1.45	9.36 ± 1.26	0.5725
LVEF	67 ± 7.7	65.3 ± 9	67.5 ± 7.1	0.0268
Septal E/E′	12.1 ± 4	17.3 ± 3.2	10.3 ± 2.4	<0.0001
Lateral E/E′	9.1 ± 3.3	12.9 ± 3.4	7.8 ± 2.1	<0.0001
Average E/E′	10.6 ± 3.4	15.1 ± 2.7	9.1 ± 2	<0.0001
Septal E′	5.6 ± 1.8	4.2 ± 1	6 ± 1.8	<0.0001
Lateral E′	7.5 ± 2.5	5.9 ± 1.6	8 ± 2.5	<0.0001

echocardiographic evaluation of diastolic dysfunction. The mean prevalence of DD2D in a recent meta-analysis was 46% with a wide variation between 21% and 81%[27]. The prevalence of DD2D was 55% in 113 participants in the previous hospital-based evaluation for Japanese patients with type 2 diabetes in 2011[28]. We consider that the updated guideline allows universal evaluation of DD2D with diagnosing the advanced cases with E/E′ cut-off values with high specificity.

Last, we discuss diabetic cardiomyopathy, characterized by diastolic cardiac dysfunction from the early stage of

Table 1. (*Continued*)

	Total (n = 320)	DD2D (+) (n = 82)	DD2D (–) (n = 238)	p-value
TRV (measured in 49 patients)	2.25 ± 0.36	2.49 ± 0.55	2.21 ± 0.3	0.0538
E/A	0.8 ± 0.25	0.84 ± 0.27	0.79 ± 0.25	0.1071
Diastolic dysfunction	82 (25.6%)	–	–	–

Continuous data given as the mean ± standard deviation, n (%) or median (interquartile range) unless otherwise specified. Hypertension was diagnosed if peripheral blood pressure (BP) was ≥140/90 mm Hg or if the health questionnaire showed current antihypertensive medications. Coronary artery disease was diagnosed if significant coronary artery stenoses existed as ≥75% on coronary cine angiography and ≥50% on coronary computed tomography angiography. Peripheral arterial disease was diagnosed if the lowest resting ankle-brachial index was <0.9. ACEi angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; DD2D, diastolic cardiac dysfunction in type 2 diabetes; eGFR, estimated glomerular filtration rate; gGTP, gamma-glutamyl transpeptidase; GLP-1, glucagon like peptide −1; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IVS, interventricular septal thickness; LAD, left atrial diameter; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineral receptor antagonists; TC, total cholesterol; TRV, tricuspid valve regurgitation velocity; TTE, transthoracic echocardiography; UAE, urinary albumin excretion.

Table 2 | Electrocardiogram findings

	Total (n = 320)	DD2D (+) (n = 82)	DD2D (–) (n = 238)	p-value
CVRR (%)	2.66 ± 1.72	2.22 ± 1.38	2.81 ± 1.81	0.0072
Heart rate (b.p.m.)	73 ± 12.5	73.9 ± 13.3	72.6 ± 12.3	0.4229
Blocks				
1′ AVB	5 (1.6%)	2 (2.4%)	3 (1.3%)	0.4580
RBBB	20 (6.3%)	3 (3.7%)	17 (7.1%)	0.2610
LBBB	4 (1.3%)	2 (2.4%)	2 (0.8%)	0.2611
fQRS	122 (38.1%)	49 (59.8%)	73 (30.7%)	<0.0001
fQRS region				
Inferior leads	104 (32.5%)	45 (54.9%)	59 (24.8%)	<0.0001
Anterior leads	47 (14.7%)	18 (22.0%)	29 (12.2%)	0.0312
Lateral leads	13 (4.1%)	6 (7.3%)	7 (2.9%)	0.0835
Multiple regions	35 (10.9%)	15 (18.3%)	20 (8.4%)	0.0133
fQRS morphologies				
Fragmented QRS	21 (6.6%)	7 (8.5%)	14 (5.9%)	0.4026
rSr′	9 (2.8%)	4 (4.9%)	5 (2.1%)	0.1896
Notched S	90 (28.1%)	37 (45.1%)	53 (22.3%)	<0.0001
RSR′	12 (3.8%)	6 (7.3%)	6 (2.5%)	0.0487
Notched R	92 (28.8%)	38 (46.3%)	54 (22.7%)	<0.0001
RSR′ with ST elevation	4 (1.3%)	1 (1.2%)	3 (1.3%)	0.9770

Continuous data given as the mean ± standard deviation, n (%) or median (interquartile range) unless otherwise specified. Fragmented QRS (fQRS) finding was categorized following Das et al.[6] 2006 and Das et al.[14] 2008. AVB, atrioventricular block; CVRR, coefficient of variation of R-R interval; DD2D, diastolic cardiac dysfunction in type 2 diabetes; LBBB, left bundle branch block; RBBB, right bundle branch block.

diabetes[29,30]. The precise diagnosis of diabetic cardiomyopathy is quite challenging in real-world settings due to the high frequency of accompanying hypertension and subclinical coronary heart diseases in diabetes. Recent considerations show that diabetic cardiomyopathy could be a microvascular manifestation of diabetes[31]. Then, diabetic cardiomyopathy and DD2D could share interstitial fibrosis mediated by microvascular inflammation by hyperglycemia. Recent studies have shown that the number of MVDs paralleled the prevalence of DD2D, HFpEF[32] and the hazard ratio for hospitalization for HF[33]. MVD is well-correlated with the elevated risk of incident HF[34]. In addition, HFpEF with MVD shows an increased incidence of HF hospitalization and HF death among type 2 diabetes patients[35]. Furthermore, as MVD is robustly associated with glycemic management, it is acceptable that tight glycemic management could be the therapeutic option for preventing the onset and progression of HF[32,36]. Further large-scale trials should be carried out to validate the intensive glycemic management on HF prevention with high-risk individuals screened by fQRS in type 2 diabetes.

Table 3 | Potential predictors of diastolic cardiac dysfunction in type 2 diabetes including fragmented QRS

Independent variables	Univariate analysis		Multivariate analysis		CART model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
fQRS	3.36 (1.99–5.65)	<0.0001	4.37 (2.33–8.20)	<0.0001	4.45 (2.40–8.24)	<0.0001
Female sex	2.16 (1.30–3.60)	0.0027	3.00 (1.60–5.64)	0.0005	2.85 (1.54–5.24)	0.0006
Age (every 10 years)	1.73 (1.34–2.25)	<0.0001	1.57 (1.17–2.17)	0.0023	1.62 (1.21–2.18)	0.0006
No. diabetic microvascular complication, every 1 complication	2.00 (1.48–2.70)	<0.0001	1.47 (1.04–2.10)	0.029	1.55 (1.11–2.18)	0.0095
Aortic stenosis	9.32 (1.84–47.12)	0.0012	12.02 (1.89–76.62)	0.0049		
PAD	3.74 (2.00–6.99)	<0.0001	2.80 (1.29–6.–06)	0.0096	2.87 (1.36–6.07)	0.0059
Insulin treatment	2.70 (1.62–4.52)	0.0001	2.09 (1.14–3.84)	0.0168		
Systolic BP (every 10 mmHg)	1.24 (1.07–1.44)	0.004	1.22 (1.03–1.45)	0.0228	1.22 (1.04–1.45)	0.0158
CAD	1.47 (0.83–2.60)	0.1901				
Prior stroke	1.83 (0.91–3.65)	0.0851				
eGFR (every 5 mL/min/1.73 m^2)	0.89 (0.84–0.94)	<0.0001				
BMI (every 1 kg/m^2)	0.96 (0.95–1.05)	0.9616				
HbA1c (every 1%)	0.93 (0.80–1.09)	0.394				
Heart rate (every 10 b.p.m.)	1.09 (0.89–1.33)	0.4222				
Duration of diabetes (every 5 years)	1.22 (1.10–1.36)	<0.0001				

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CART, classification and regression tree analysis; CI, confidence interval; eGFR, estimated glomerular filtration rate; fQRS, fragmented QRS; HbA1c, hemoglobin A1c; OR, odds ratio; PAD, peripheral artery disease.

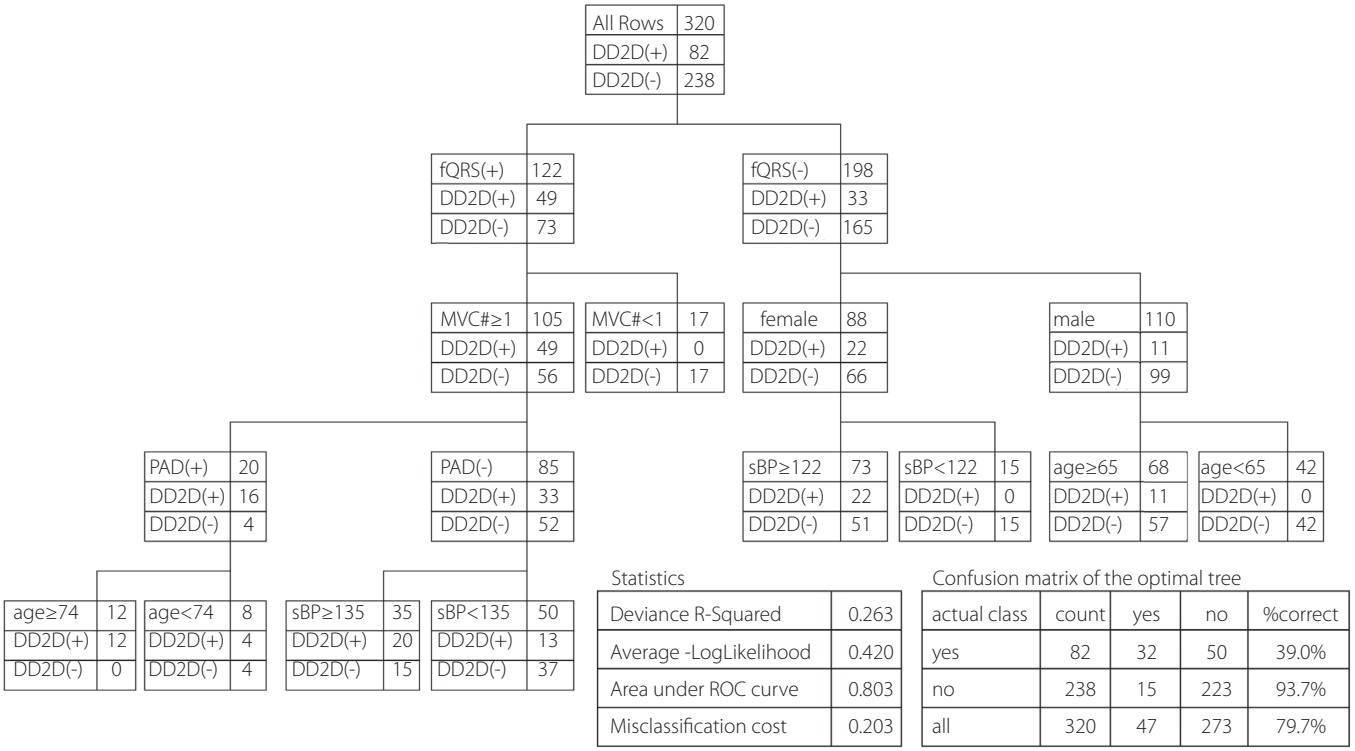
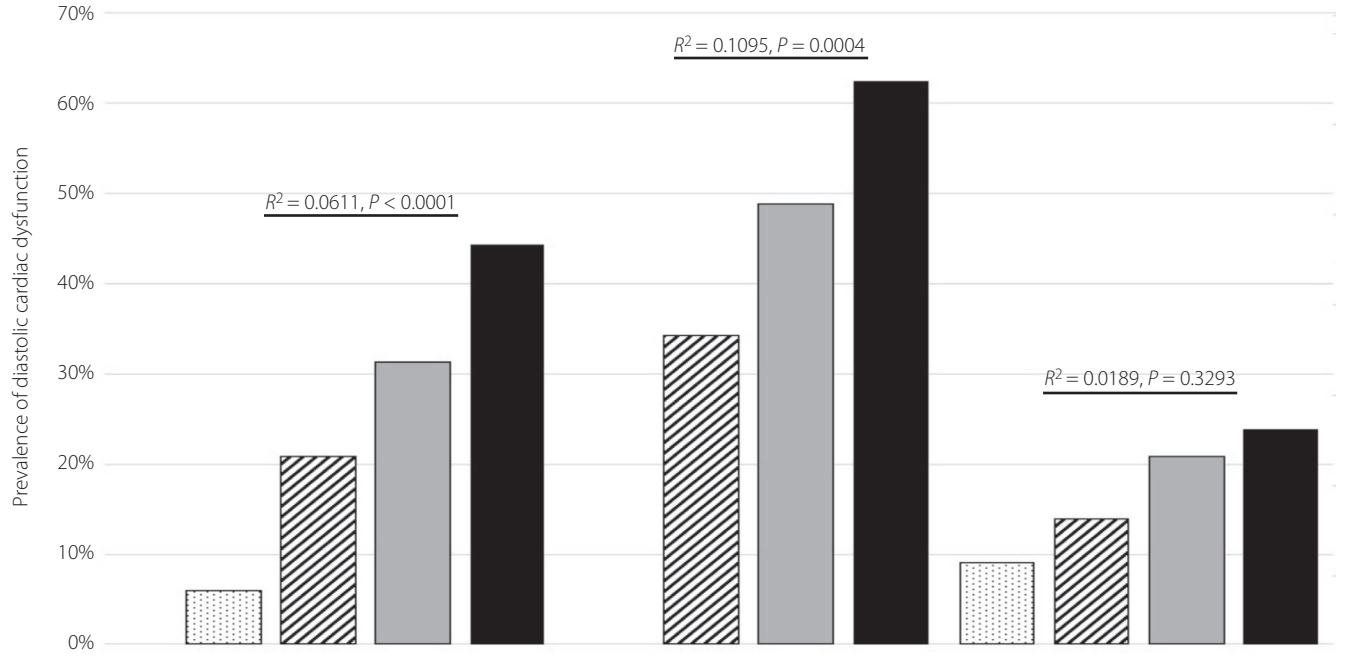


Figure 1 | Classification and regression tree analysis of 320 patients with diabetes for diastolic cardiac dysfunction in type 2 diabetes (DD2D) with eight candidates as fragmented QRS (fQRS), age, aortic stenosis, sex, insulin treatment, peripheral artery disease (PAD), systolic blood pressure (sBP) and the number of diabetic microvascular diseases (MVD); ROC, receiver operating characteristic.



	total	total	total	total	fQRS(+)	fQRS(+)	fQRS(+)	fQRS(+)	fQRS(-)	fQRS(-)	fQRS(-)	fQRS(-)
Number of MVD	0	1	2	3	0	1	2	3	0	1	2	3
Number of subjects	50	110	115	45	17	38	43	24	33	72	72	21
Number of DD2D	3	23	36	20	0	13	21	15	3	10	15	5
DM duration (years)	8.1±6.9	13.4±10.7	17.8±11.6	24.1±12.7	8.4±8.6	14.2±11.4	18.3±11.2	25.7±13.1	9.9±1.4	13.0±10.3	17.6±11.8	22.3±12.2
HbA1c (mmol/mol)	85.8±6.0	78.1±6.0	82.5±6.0	83.6±3.8	86.9±2.8	78.1±8.2	82.5±7.1	83.6±3.8	63.9±42.1	78.1±4.9	82.5±4.9	84.7±4.9

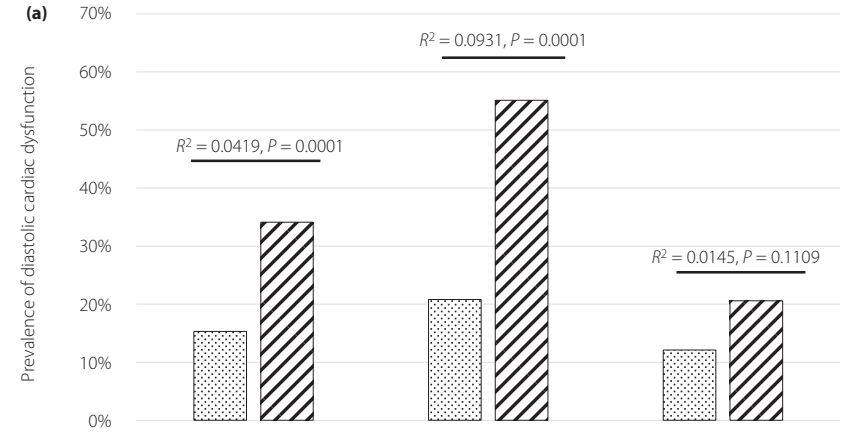
Figure 2 | The relationship between the percentages of participants with diastolic cardiac dysfunction was stratified according to the number of diastolic cardiac dysfunction in type 2 diabetes (DD2D). The number of diabetic microvascular diseases (MVD) and rates of DD2D observed in the total patients (left), fragmented QRS (fQRS) (+) patients (middle) and fQRS (–) patients (right). White bar with dots represents no MVD; striped bar, one MVD; dark gray bar, two MVDs; and black bar, three MVDs. The predictive ability of the number of MVDs for the presence of DD2D was calculated using Pearson's χ^2 analysis. R^2-value and *p*-value over subject group reflected the intragroup difference. DM, type 2 diabetes; HbA1c, hemoglobin A1c.

This was a single-center retrospective study with a cross-sectional study design, so there was only a little evidence of the relationship between fQRS and DD2D. Thus, prospective multicenter studies with larger patient populations and longitudinal data are required to assess the present findings further. We did not carry out cardiac magnetic resonance imaging and histopathological evaluation. Another limitation was the relatively small sample size cohort; however, we believe that the restricted sample size contributed to maintaining the reliability of this study. All MVDs were supported with objective evaluation, not self-reported. All the participants who undertook TTE were closely examined by qualified cardiologists, and the possibility of overlooked silent ischemia was rare. Finally, we should mention the exclusion of type 1 diabetes patients. One previous report showed that the prevalence of diastolic cardiac dysfunction in type 1 diabetes patients was 14.4% in patients with a mean age of 50 years[37]. We excluded patients with type 1 diabetes due to low numbers in the Japanese population and the significant difference in mean age compared with patients with type 2 diabetes.

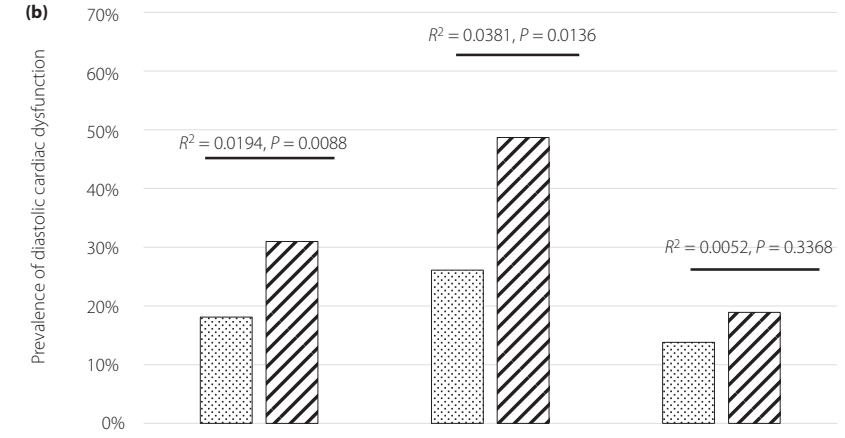
In summary, the present results show that fQRS is a predictor for DD2D. The result recommends that diabetologists consider the routine evaluation of fQRS through ECG in all patients with diabetes and its complications. Further investigation in a prospective study is required to prevent HF progression and clarify optimal glycemic management for HF prevention in patients with type 2 diabetes with fQRS.

ACKNOWLEDGMENTS

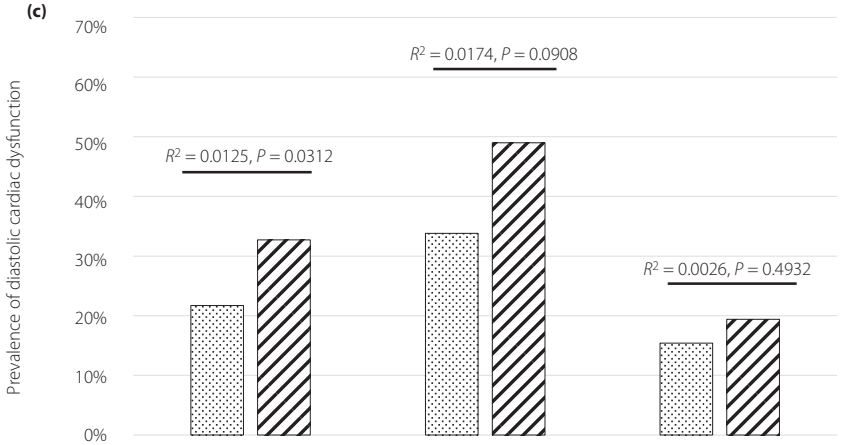
The authors express their gratitude to Dr Tetsuo Konno, a former research director in the Department of Cardiology, Kanazawa University, for inspiring our interest in fQRS. This work



	total	total	fQRS(+)	fQRS(+)	fQRS(-)	fQRS(-)
Nephropathy	-	+	-	+	-	+
Number of subjects	144	176	53	69	91	107
Number of DD2D	22	60	11	38	11	22



	total	total	fQRS(+)	fQRS(+)	fQRS(-)	fQRS(-)
Neuopathy	-	+	-	+	-	+
Number of subjects	133	187	46	76	87	111
Number of DD2D	18	31	12	37	12	21



	total	total	fQRS(+)	fQRS(+)	fQRS(-)	fQRS(-)
Retinopathy	-	+	-	+	-	+
Number of subjects	207	113	71	51	136	62
Number of DD2D	45	37	24	25	21	12

Figure 3 | The relationship between the percentages of participants with diastolic cardiac dysfunction was stratified according to each diabetic microvascular disease (MVD). The existence of (a) nephropathy, (b) neuropathy and (c) retinopathy. Each figure shows the total patients (left), fragmented QRS (fQRS) (+) patients (middle) and fQRS (–) patients (right). White bar with dots represents each MVD (–); striped bar, each MVD (+). The predictive ability of the existence of each MVD for the presence of diastolic cardiac dysfunction in type 2 diabetes (DD2D) was calculated using Pearson's χ^2 analysis. R^2-value and *p*-value over subject group reflected the intragroup difference. DM, type 2 diabetes.

was supported by JSPS KAKENHI (grant number JP18K08505 and JP21K10300). The study sponsor was not involved in the study's design or the collection, analysis, interpretation of data, writing the report or the decision to submit the report for publication.

DISCLOSURE

DC received honoraria from Eli Lilly Japan K.K., research funding from Sanofi and Novo Nordisk Pharm Ltd., and donations from Novo Nordisk Pharm Ltd. KT received honoraria from MSD K.K., Novo Nordisk Pharm Ltd, and Kowa Pharm Co. Ltd., and donations from Daiichi Sankyo Co. Ltd., Ono Pharm Co. Ltd., Takeda Pharm Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., MSD K.K., Mitsubishi Tanabe Pharm Co., Teijin Pharm Ltd., Eli Lilly Japan K.K., Asahi Kasei Pharm Co., The Mitsubishi Foundation, and Suntory Global Innovation Center Ltd.). The other authors declare no conflict of interest.

Approval of the research protocol: All procedures were carried out following the ethical standards of the responsible committee on human experimentation, and with the Helsinki Declaration of 1964 and later versions. The Ethics Committee of Toyama University Hospital approved the study protocol (IRB# R2020141). Web notifications informed all participants that they could opt out at any time.

Informed consent: Obtained from all participants.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

REFERENCES

1. Kristensen SL, Mogensen UM, Jhund PS, *et al*. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation* 2017; 135: 724–735.
2. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 2010; 55: 300–305.
3. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. *J Am Coll Cardiol* 2014; 63: 407–416.
4. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol* 2006; 48: 1548–1551.
5. Chamsi-Pasha MA, Zhan Y, Debs D, *et al*. CMR in the evaluation of diastolic dysfunction and phenotyping of HFpEF: current role and future perspectives. *JACC Cardiovasc Imaging* 2020; 13: 283–296.
6. Das MK, Khan B, Jacob S, *et al*. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation* 2006; 113: 2495–2501.
7. Yagi K, Nagata Y, Yamagami T, *et al*. High prevalence of fragmented QRS on electrocardiography in Japanese patients with diabetes irrespective of metabolic syndrome. *J Diabetes Investig* 2021; 12: 1680–1688.
8. Bayramoğlu A, Taşolar H, Kaya Y, *et al*. Fragmented QRS complexes are associated with left ventricular dysfunction in patients with type-2 diabetes mellitus: a two-dimensional speckle tracking echocardiography study. *Acta Cardiol* 2018; 73: 449–456.
9. Onoue Y, Izumiya Y, Hanatani S, *et al*. Fragmented QRS complex is a diagnostic tool in patients with left ventricular diastolic dysfunction. *Heart Vessels* 2016; 31: 563–567.
10. Fowler M. Microvascular and macrovascular complications of diabetes. *Clin Diabetes* 2008; 26: 77–82.
11. Araki E, Goto A, Kondo T, *et al*. Japanese clinical practice guideline for diabetes 2019. *Diabetol Int* 2020; 11: 165–223.
12. Shimamoto K, Ando K, Fujita T, *et al*. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2014). *Hypertens Res* 2014; 37: 253–390.
13. Hirsch AT, Haskal ZJ, Hertzer NR, *et al*. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)–summary of recommendations. *J Vasc Interv Radiol* 2006; 17: 1383–1397; quiz 1398.
14. Das MK, Suradi H, Maskoun W, *et al*. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. *Circ Arrhythm Electrophysiol* 2008; 1: 258–268.
15. Konno T, Hayashi K, Fujino N, *et al*. Electrocardiographic QRS fragmentation as a marker for myocardial fibrosis in hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2015; 26: 1081–1087.
16. Nomura A, Konno T, Fujita T, *et al*. Fragmented QRS predicts heart failure progression in patients with hypertrophic cardiomyopathy. *Circ J* 2015; 79: 136–143.

17. Nagueh SF, Smiseth OA, Appleton CP, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; 29: 277–314.
18. Cetin S, Yıldız SS, Mazı EE, *et al*. Relationship between a fragmented QRS and microalbuminuria in patients with type 2 diabetes mellitus. *Endocrinol Diabetes Nutr* 2017; 64: 464–470.
19. Eren H, Kaya Ü, Öcal L, *et al*. Presence of fragmented QRS may be associated with complex ventricular arrhythmias in patients with type-2 diabetes mellitus. *Acta Cardiol* 2021; 76: 67–75.
20. Fischer VW, Barner HB, Leskiw ML. Capillary basal laminar thichness in diabetic human myocardium. *Diabetes* 1979; 28: 713–719.
21. Bugyei-Twum A, Advani A, Advani SL, *et al*. High glucose induces Smad activation via the transcriptional coregulator p300 and contributes to cardiac fibrosis and hypertrophy. *Cardiovasc Diabetol* 2014; 13: 89.
22. Papakrivopoulou J, Lindahl GE, Bishop JE, *et al*. Differential roles of extracellular signal-regulated kinase 1/2 and p38MAPK in mechanical load-induced procollagen alpha1(I) gene expression in cardiac fibroblasts. *Cardiovasc Res* 2004; 61: 736–744.
23. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; 62: 263–271.
24. Miyazato J, Horio T, Takiuchi S, *et al*. Left ventricular diastolic dysfunction in patients with chronic renal failure: impact of diabetes mellitus. *Diabetes Med* 2005; 22: 730–736.
25. Maezawa Y, Takemoto M, Yokote K. Cell biology of diabetic nephropathy: roles of endothelial cells, tubulointerstitial cells and podocytes. *J Diabetes Investig* 2015; 6: 3–15.
26. Almeida JG, Fontes-Carvalho R, Sampaio F, *et al*. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. *Eur Heart J Cardiovasc Imaging* 2018; 19: 380–386.
27. Bouthoorn S, Valstar GB, Gohar A, *et al*. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: a systematic review and meta-analysis. *Diab Vasc Dis Res* 2018; 15: 477–493.
28. Shimabukuro M, Higa N, Asahi T, *et al*. Impaired glucose tolerance, but not impaired fasting glucose, underlies left ventricular diastolic dysfunction. *Diabetes Care* 2011; 34: 686–690.
29. Shimizu M, Umeda K, Sugihara N, *et al*. Collagen remodelling in myocardia of patients with diabetes. *J Clin Pathol* 1993; 46: 32–36.
30. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res* 2018; 122: 624–638.
31. Laakso M. Heart in diabetes: a microvascular disease. *Diabetes Care* 2011; 34(Suppl 2): S145–S149.
32. Tromp J, Lim SL, Tay WT, *et al*. Microvascular disease in patients with diabetes with heart failure and reduced ejection versus preserved ejection fraction. *Diabetes Care* 2019; 42: 1792–1799.
33. Brownrigg JRW, Hughes CO, Burleigh D, *et al*. Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. *Lancet Diabetes Endocrinol* 2016; 4: 588–597.
34. Kaze AD, Santhanam P, Erqou S, *et al*. Microvascular disease and incident heart failure among individuals with type 2 diabetes mellitus. *J Am Heart Assoc* 2021; 10: e018998.
35. Sandesara PB, O'Neal WT, Kelli HM, *et al*. The prognostic significance of diabetes and microvascular complications in patients with heart failure with preserved ejection fraction. *Diabetes Care* 2018; 41: 150–155.
36. Paulus WJ, Dal Canto E. Distinct myocardial targets for diabetes therapy in heart failure with preserved or reduced ejection fraction. *JACC Heart Fail* 2018; 6: 1–7.
37. Jensen MT, Sogaard P, Andersen HU, *et al*. Prevalence of systolic and diastolic dysfunction in patients with type 1 diabetes without known heart disease: the Thousand & 1 Study. *Diabetologia* 2014; 57: 672–680.