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

Kunimasa Yagi1,2*, Teruhiko Imamura3, Hayato Tada2, Jianhui Liu1,2, Yukiko Miyamoto2, Azusa Ohbatake2, Naoko Ito2, Masataka Shikata1, Asako Enkaku1, Akiko Takikawa1, Hisae Honoki1, Shiho Fujisaka1, Daisuke Chuo1,2, Hideki Origasa4, Koichiro Kinugawa3, Kazuyuki Tobe1

11st Department of Internal Medicine, University of Toyama, Toyama, Japan, 22nd Department of Internal Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan, 32nd Department of Internal Medicine, University of Toyama, Toyama, Japan, and 4Biostatistics and Clinical Epidemiology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan

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

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INTRODUCTION
Patients with type 2 diabetes mellitus and heart failure (HF) with preserved ejection fraction (HFP EF) have a poorer prognosis and quality of life, as well as higher hospitalization and cardiovascular mortality compared with their counterparts without diabetes1. Diastolic cardiac dysfunction in type 2 diabetes (DD2D) is a critical risk for HFP EF2. As the clinical course of DD2D has been reported as adjustable3, screening DD2D in the early stage of diabetes is crucial.

Currently, modalities, such as transthoracic echocardiograms (TTE)4 and cardiac magnetic resonance imaging5, 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 territory6. We recently reported a higher prevalence of fQRS in patients with diabetes than patients with metabolic syndrome without diabetes7.

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
in diastolic dysfunction, in type 2 diabetes patients. 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. 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. The exclusion criteria were as follows: (i) type 1 diabetes; (ii) secondary diabetes; (iii) refractory malignant diseases; (iv) dependency in 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, 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 m². 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. 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.

**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: 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. 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.

**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) mitral 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. 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 χ²-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 \( \chi^2 \)-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 \( \geq 65 \) 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
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%. The prevalence of DD2D was 55% in 113 participants in the previous hospital-based evaluation for Japanese patients with type 2 diabetes in 2011. 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 | 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/m²)      | 25.2 ± 4.9       | 25.5 ± 5          | 25.3 ± 4.9 | 0.9618 |
| eGFR (mL/min/1.73 m²) | 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%) | 0.0627 |
| 2                | 115 (35.9%)      | 36 (43.9%)        | 79 (33.2%) | 0.1308 |
| 3                | 45 (14.1%)       | 20 (24.4%)        | 25 (10.5%) | 0.0003 |
| Any diabetic microvascular diseases | 270 (84.4%) | 79 (96.3%) | 191 (80.3%) | <0.0001 |
| 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 |
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. 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 and the hazard ratio for hospitalization for HF. MVD is well-correlated with the elevated risk of incident HF. In addition, HFpEF with MVD shows an increased incidence of HF hospitalization and HF death among type 2 diabetes patients. 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. 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 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 ± 125 | 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%) | <0.0010 |
| FQRS region          |              |                  |                   |         |
| Inferior leads       | 104 (32.5%) | 45 (54.9%) | 59 (24.8%) | <0.0010 |
| 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. 2006 and Das et al. 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.
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 |
| 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 |
| Systolic BP (every 10 mmHg)                                 | 1.73 (1.34–2.25)    | <0.0001               | 1.57 (1.17–2.17) | 0.0023 | 1.62 (1.21–2.18) | 0.0006 |
| Diabetes duration (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.
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. 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.

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Prevalence of diastolic cardiac dysfunction

Nephropathy

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

Neuropathy

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

Retinopathy

|                | total | total | fQRS(+) | fQRS(+) | fQRS(-) | fQRS(-) |
|----------------|-------|-------|---------|---------|---------|---------|
| Number of subjects | 207   | 113   | 71      | 51      | 136     | 62      |
| Number of DD2D   | 45    | 37    | 24      | 25      | 21      | 12      |
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 χ² analysis. R²-value and p-value over subject group reflected the intragroup difference. DM, type 2 diabetes.

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DISCLOSURE
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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.

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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. Chrysler-Chapman 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. Bayramoglu A, Tasolar 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, Izumiyare 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, Hertzler 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 Arhythm 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. Norumara 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. Petrucci P, Valenza M, Del Vecchio F, et al. Prognostic implications of reduced microvascular blood flow in chronic kidney disease not otherwise specified (CKD-NOS) and diabetic nephropathy: roles of endothelial cells, tubulointerstitial cells and podocytes. J Diabetes Investig 2015; 6: 3–15.

19. Neumann IJ, Siegenthaler U, Schomig A, et al. Acute myocardial infarction management in Europe: results from the EURObservatório registry. Eur Heart J 2016; 37: 131–140.

20. 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.

21. Miyazato J, Horio T, Takaichi S, et al. Left ventricular diastolic dysfunction in patients with chronic renal failure: impact of diabetes mellitus. Diabetes Med 2005; 22: 730–736.

22. Maenza A, Takemoto M, Yokote K. Cell biology of diabetic nephropathy: roles of endothelial cells, tubulointerstitial cells and podocytes. J Diabetes Investig 2015; 6: 3–15.

23. 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.