| タイトル | Title |
|---------|-------|
| Effect of heart rate on left ventricular longitudinal myocardial function in type 2 diabetes mellitus |

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|------|-----------|
| Yamauchi, Yuki / Tanaka, Hidekazu / Yokota, Shun / Mochizuki, Yasuhide / Yoshigai, Yuko / Shiraki, Hiroaki / Yamashita, Kentaro / Tanaka, Yusuke / Shono, Ayu / Suzuki, Makiko / Sumimoto, Keiko / Matsumoto, Kensuke / Hirota, Yushi / Ogawa, Wataru / Hirata, Ken-ichi |

| 掲載誌・巻号・ページ | Citation |
|----------------|---------|
| Cardiovascular Diabetology, 20(1):87 |

| 刊行日 | Issue date |
|-------|------------|
| 2021-04-24 |

| 資源タイプ | Resource Type |
|-----------|--------------|
| Journal Article / 学術雑誌論文 |

| 版区分 | Resource Version |
|--------|------------------|
| publisher |

| 権利 | Rights |
|------|--------|
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| DOI | 10.1186/s12933-021-01278-7 |

| JaLCDOI |
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| URL | http://www.lib.kobe-u.ac.jp/handle_kernel/90008292 |

PDF issue: 2021-07-16
Effect of heart rate on left ventricular longitudinal myocardial function in type 2 diabetes mellitus

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Abstract
Background: Left ventricular (LV) longitudinal myocardial dysfunction is considered a marker of preclinical LV dysfunction in patients with type 2 diabetes mellitus (T2DM). High heart rate (HR) is associated with cardiovascular outcomes, but the effect of HR on LV longitudinal myocardial function in T2DM patients is uncertain.

Methods: We studied 192 T2DM patients with preserved LV ejection fraction (LVEF), and 81 age-, sex-, and LVEF-matched healthy volunteers. HR was measured as the average HR during echocardiography, and high HR was defined as resting HR ≥ 70 beats/minute. LV longitudinal myocardial function was assessed as global longitudinal strain (GLS). The predefined cutoff for subclinical LV dysfunction was set at GLS < 18%.

Results: GLS in T2DM patients with high HR was significantly lower than that in T2DM patients with low HR (16.3% ± 4.2% vs. 17.8% ± 2.8%; P = 0.03), whereas GLS in normal subjects with high and low HR was similar (20.3 ± 1.7% vs. 20.3 ± 2.0%; P = 0.99). Multivariable logistic regression analysis showed that high HR (odds ratio: 1.04; 95% confidence interval: 1.01–1.07; P = 0.01) was independently associated with GLS < 18% in T2DM patients as well as HbA1c, T2DM duration, LVEF, body mass index, and mitral inflow E and mitral e' annular velocity ratio. One sequential logistic model evaluating the associations between GLS < 18% and clinical variables in T2DM patients showed an improvement with the addition of LVEF and E/e' (P < 0.001) and a further improvement with the addition of high HR (P < 0.001).

Conclusion: Compared with normal subjects, resting HR was associated with LV longitudinal myocardial function in asymptomatic T2DM patients with preserved LVEF. Our findings provide new insights on the management of T2DM patients.

Keywords: Type 2 diabetes mellitus, Heart rate, Global longitudinal strain, Echocardiography
progression. Stage B HF patients are ideal targets for HF prevention. Type 2 diabetes mellitus (T2DM) is another well-known risk factor for HF and is an important comorbid disease of Stage A HF, similar to hypertension. Left ventricular (LV) longitudinal myocardial dysfunction, assessed in terms of low global longitudinal strain (GLS), is a sensitive marker for early subtle abnormalities in LV myocardial performance, helpful for predicting outcomes for various cardiac diseases, and superior to conventional echocardiographic indices such as LV ejection fraction (LVEF) and mitral inflow E and mitral e’ annular velocity ratio (E/e’) [1–5]. In addition, LV longitudinal myocardial dysfunction is altered in Stage A HF patients and can be an early marker of LV dysfunction, which in turn indicates cardiovascular morbidity and mortality. Thus, LV longitudinal myocardial dysfunction is also considered a sensitive marker of a preclinical form of LV dysfunction in patients with T2DM and preserved LVEF without overt HF [6–12]. Therefore, LV longitudinal myocardial dysfunction should be considered the first marker of a preclinical form of T2DM-related cardiac dysfunction, known as diabetic cardiomyopathy.

High resting heart rate (HR) is a known marker of cardiovascular outcomes for various categories of HF patients, especially HFrEF patients, and HR-lowering therapy has a positive impact on outcomes in HFrEF patients [13]. However, the effect of resting HR on LV longitudinal myocardial function in T2DM patients is unclear. Therefore, this study aimed to investigate the association of resting HR with LV longitudinal myocardial function in asymptomatic T2DM patients with preserved LVEF without coronary artery disease.

Methods

Study population

In this study, a total of 192 asymptomatic T2DM patients with preserved LVEF who were admitted to Kobe University Hospital between June 2013 and March 2020 were retrospectively enrolled. The preliminary exclusion criteria were as follows: (1) history of coronary artery disease, (2) LVEF <50%, (3) previous history of open-heart surgery or congenital heart disease, (4) severe renal dysfunction defined as a glomerular filtration rate < 30 mL/min/1.73 m², (5) uncontrolled hypertension with blood pressure ≥180/100 mmHg, (6) more than moderate valvular heart disease, and (7) atrial fibrillation. All enrolled patients underwent an exercise stress screening test such as a treadmill exercise test or stress myocardial perfusion scintigraphy during hospitalization, and patients with an ischemic response were excluded. We excluded patients with atrial fibrillation because the irregular rhythm effects on the speckle-tracking evaluation. The diagnosis of T2DM was based on the World Health Organization criteria [14]. The mean patient age was 61 ± 13 years, 92 (48%) patients were women, and the mean LVEF was 66% ± 5% (all ≥ 55%). For comparison, a control group including 81 age-, sex-, and LVEF-matched normal subjects were randomly chosen from our database by the observers who were not involved in echocardiographic analysis. All normal subjects did not have a history of T2DM or cardiovascular disease. This study was approved by the local ethics committee of our institution (No. B200306).

Echocardiographic examination

All T2DM patients and normal controls underwent transthoracic echocardiography. All echocardiographic data were obtained using a commercially available echo-cardiographic system (Vivid E9; GE-Vingmed, Horten, Norway). Digital routine grayscale two-dimensional cine loops from three consecutive heart beats were obtained at end-expiratory apnea from standard parasternal and apical views. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography [4].

Two-dimensional speckle-tracking strain analysis was performed for each patient using a dedicated software (EchoPAC version 113; General Electric Medical Systems) to evaluate LV longitudinal myocardial function, which was assessed in terms of GLS. In summary, apical 4-, 2-, and long-axis views were uploaded for subsequent offline GLS analysis. Longitudinal speckle-tracking strain was calculated using an automated contouring detection algorithm, and manual adjustments of the region of interest were performed, if necessary. Longitudinal strain results for the individual clips were visualized in a color-coded format and combined in a bull’s eye plot. GLS was then determined as the averaged peak longitudinal strain of 18 LV segments and was expressed as an absolute value in accordance with current guidelines [4], which also recommend expressing all strain values as absolute values, as was done in our study, to avoid confusion regarding magnitude relationships. The pre-defined cutoff for LV longitudinal myocardial dysfunction was set at GLS < 18% [4].

Assessment of resting HR

Resting HR was determined as the average HR during echocardiography. High HR was defined as resting HR ≥ 70 beats/minute (bpm) [13, 15].

Statistical analysis

Continuous variables are expressed as mean values with standard deviation for normally distributed data and
Results

Baseline characteristics of T2DM patients and controls

The baseline clinical and echocardiographic characteristics of the 192 T2DM patients and 81 normal controls are summarized in Table 1. Clinical data showed that T2DM patients were more likely to have a higher body weight, body mass index, systolic blood pressure, heart rate, HbA1c, and prevalence of hypertension and dyslipidemia than normal controls, while echocardiographic data showed that T2DM patients were more likely to have a larger left atrial volume index, LV mass index, and E/e’ and a smaller GLS and E/A than normal controls. In addition, the comparison baseline clinical and echocardiographic characteristics of T2DM patients and normal controls according to HR quartiles are shown in Table 2 and Additional file 1.

Association between HR and LV longitudinal myocardial function

Resting HR ≥ 70 bpm was observed in 101 T2DM patients, whereas it was observed in 33 normal controls. LV longitudinal myocardial function, assessed in terms of GLS, in normal controls with high and low HR was similar (20.3% ± 1.7% vs. 20.3% ± 2.0%; P = 0.99), whereas GLS in T2DM patients with high HR was significantly lower than that in T2DM patients with low HR (16.3% ± 4.2% vs. 17.8% ± 2.8%; P = 0.03; Fig. 1).

Table 3 shows the results of univariable and multivariable logistic regression analysis to identify LV
longitudinal myocardial dysfunction in T2DM patients. In univariable logistic regression analysis, age, body mass index, T2DM duration, HR ≥ 70 bpm, HbA1c, E/e’, and LVEF were associated with LV longitudinal myocardial dysfunction. Multivariable logistic regression analysis showed that HR ≥ 70 bpm (odds ratio: 1.04; 95% confidence interval: 1.01–1.07; P = 0.01) was independently associated with LV longitudinal myocardial dysfunction in T2DM patients. Table 4 shows the results of univariable and multivariable logistic regression analysis to identify LV longitudinal myocardial dysfunction in normal controls. Unlike in T2DM patients, none of the parameters, including HR ≥ 70 bpm, were associated with LV longitudinal myocardial dysfunction in multivariable logistic regression analysis.

The incremental benefits determined using sequential logistic models to identify the association between GLS and clinical variables are shown in Fig. 2. One model, based on clinical variables including age, sex, hypertension, and HbA1c ($\chi^2 = 10.6$), showed an improvement with the addition of LVEF and E/e’’ ($\chi^2 = 33.4$,

### Table 2 Baseline characteristics of T2DM patients according to the HR quartiles

| Variables                             | HR:44-62 bpm (n = 48) | HR:63-69 bpm (n = 48) | HR:70-77 bpm (n = 48) | HR:78-109 bpm (n = 48) | P value |
|---------------------------------------|------------------------|------------------------|------------------------|------------------------|---------|
| **Clinical characteristics**          |                        |                        |                        |                        |         |
| Age, years                            | 61 ± 14                | 61 ± 13                | 63 ± 12                | 58 ± 13                | 0.24    |
| Gender (female), n (%)                | 19 (40)                | 23 (48)                | 25 (52)                | 25 (52)                | 0.58    |
| DM duration, years                    | 10 (8–13)              | 9 (7–11)               | 10 (7–13)              | 11 (8–13)              | 0.85    |
| Body weight, kg                       | 67 ± 15                | 66 ± 15                | 66 ± 17                | 68 ± 17                | 0.97    |
| Body mass index                       | 25.7 ± 5.7             | 25.9 ± 4.8             | 24.8 ± 6.3             | 25 ± 5.0               | 0.77    |
| Systolic blood pressure, mmHg         | 129 ± 22               | 132 ± 19               | 134 ± 20               | 130 ± 19               | 0.56    |
| Heart rate, bpm                       | 56 ± 5                 | 67 ± 2                 | 74 ± 2                 | 85 ± 7                 | < .0001 |
| eGFR, mL/min/1.73 m\(^2\)            | 76.4 ± 23.2            | 70.1 ± 24.5            | 74.2 ± 22.5            | 75.3 ± 26.1            | 0.6     |
| HbA1c, %                              | 8.8 ± 2.3              | 8.3 ± 1.7              | 9.2 ± 1.9              | 8.6 ± 2.0              | 0.2     |
| **Comorbidities, n (%)**              |                        |                        |                        |                        |         |
| Hypertension                          | 28 (58)                | 30 (6)                 | 31 (65)                | 28 (58)                | 0.92    |
| Dyslipidemia                          | 28 (58)                | 25 (52)                | 29 (60)                | 35 (73)                | 0.15    |
| **Antidiabetic drugs, n (%)**         |                        |                        |                        |                        |         |
| DPP-4I                                | 26 (54)                | 17 (35)                | 31 (65)                | 23 (48)                | 0.04    |
| GLP-1 RA                              | 2 (4)                  | 9 (19)                 | 7 (15)                 | 10 (21)                | 0.09    |
| SU                                    | 10 (21)                | 8 (17)                 | 12 (25)                | 12 (25)                | 0.7     |
| α-Gl                                  | 13 (27)                | 8 (17)                 | 9 (19)                 | 10 (21)                | 0.65    |
| Thiazalidine                          | 3 (6)                  | 7 (15)                 | 4 (8)                  | 5 (10)                 | 0.57    |
| Metformin                             | 20 (42)                | 19 (40)                | 30 (63)                | 26 (54)                | 0.07    |
| SGLT2 inhibitor                       | 4 (8)                  | 4 (8)                  | 6 (13)                 | 6 (13)                 | 0.83    |
| Statin                                | 20 (42)                | 21 (44)                | 18 (38)                | 21 (44)                | 0.9     |
| Calcium channel blocker               | 18 (38)                | 21 (44)                | 20 (42)                | 11 (23)                | 0.16    |
| β-blocker                             | 5 (10)                 | 9 (19)                 | 6 (13)                 | 7 (15)                 | 0.68    |
| **Echocardiographic parameters**      |                        |                        |                        |                        |         |
| LV end-diastolic volume, mL           | 73.4 ± 19.5            | 70.8 ± 19.9            | 70.6 ± 26.0            | 61.8 ± 19.8            | 0.05    |
| LV end-systolic volume, mL            | 25.4 ± 8.5             | 25.3 ± 9.5             | 24.4 ± 11.7            | 21.9 ± 9.5             | 0.26    |
| LVEF, %                               | 66 ± 5                 | 65 ± 6                 | 66 ± 5                 | 66 ± 5                 | 0.82    |
| LVMI, g/m\(^2\)                      | 86.8 ± 20.7            | 80.7 ± 19.5            | 82.7 ± 22.1            | 75.5 ± 21.4            | 0.08    |
| LAVI, mL/m\(^2\)                     | 315 ± 8.0              | 293 ± 9.0              | 307 ± 8.9              | 265 ± 7.2              | 0.02    |
| E/A                                   | 0.9 ± 0.3              | 0.8 ± 0.2              | 0.7 ± 0.2              | 0.8 ± 0.2              | 0.001   |
| E/e’                                  | 110 ± 3.6              | 111 ± 3.5              | 116 ± 5.4              | 101 ± 3.6              | 0.36    |
| Tricuspid regurgitation velocity      | 1.6 ± 0.9              | 1.5 ± 1.0              | 1.5 ± 1.0              | 0.9 ± 1.1              | 0.005   |
| GLS                                   | 18.0 ± 3.0             | 18.0 ± 2.8             | 16.8 ± 2.9             | 17.4 ± 3.5             | 0.65    |

All abbreviations as in Table 1
P < 0.001) and a further improvement with the addition of HR ≥ 70 bpm (χ² = 44.6, P < 0.001).

Figure 3 shows representative cases of GLS in a bull’s eye plot of high and low HR subjects in a T2DM patient and a normal control.

### Table 3: Associated factor of GLS in T2DM patients

|                          | Univariable |          |          |          | Multivariable |          |          |
|--------------------------|-------------|----------|----------|----------|---------------|----------|----------|
|                          | OR          | 95% CI   | P value  | OR       | 95% CI       | P value  |          |
| Age                      | 0.97        | 0.95–1.00| 0.02     | 1.14     | 1.07–1.23    | 0.0002   |          |
| Body mass index          | 1.13        | 1.06–1.21| 0.0002   | 1.14     | 1.07–1.23    | 0.0002   |          |
| T2DM duration            | 1.00        | 1.0–1.01 | 0.05     | 1.0      | 1.0–1.01     | 0.01     |          |
| Heart rate ≥ 70 bpm      | 1.03        | 1.00–1.05| 0.04     | 1.04     | 1.01–1.07    | 0.01     |          |
| HbA1c                    | 1.17        | 1.01–1.37| 0.04     | 1.27     | 1.06–1.51    | 0.01     |          |
| LVEF                     | 0.89        | 0.84–0.95| 0.0003   | 0.86     | 0.8–0.93     | 0.0001   |          |
| E/e’                     | 1.04        | 1.01–1.04| 0.0007   | 1.11     | 1.01–1.22    | 0.03     |          |
| E/A                      | 0.71        | 0.23–2.2 | 0.56     |          |               |          |          |
| TR velocity              | 0.89        | 0.69–1.18| 0.44     |          |               |          |          |
| Hypertension             | 1.08        | 0.60–1.94| 0.8      |          |               |          |          |
| Using AV node blockers   | 1.42        | 0.79–2.54| 0.24     |          |               |          |          |

OR: odds ratio, CI: confidential interval
All other abbreviations as in Table 1

### Discussion

In our study, resting HR was associated with LV longitudinal myocardial function in T2DM patients, but such a phenomenon was not observed in age-, sex-, and LVEF-matched normal controls.

**Association between LV longitudinal function and T2DM**

T2DM is a well-known risk factor for HF and is an important comorbid disease of Stage A HF, similar to
hypertension. Lack of T2DM control is an important predictor of new-onset HF, with every 1% increase in HbA1c correlating to an 8%-19% increase in the incidence of HF [16, 17]. The presence of LV longitudinal myocardial dysfunction has been identified in T2DM patients with preserved LVEF without overt coronary artery disease or HF [6–12]. In addition, T2DM is a major cause of HFpEF, similar to hypertension, with HFpEF usually presenting as LV diastolic dysfunction. Some researchers have maintained that LV longitudinal myocardial dysfunction, rather than LV diastolic dysfunction, should be considered the first marker of a preclinical form of T2DM-related cardiac dysfunction in T2DM patients with preserved LVEF without overt HF [8, 18]. Ernande et al. showed that LV longitudinal dysfunction, assessed as GLS < 18%, was even present in T2DM patients with preserved LVEF and normal LV diastolic function [8]. Thus, it has been suggested that progression of uncontrolled T2DM leads to LV longitudinal myocardial dysfunction and LV diastolic dysfunction, that GLS is associated with

Table 4  Associated factor of GLS in normal controls

|                | Univariable |          |          |          |          |          | Multivariable |          |          |          |          |
|----------------|-------------|----------|----------|----------|----------|----------|--------------|----------|----------|----------|----------|
|                | OR          | 95% CI   | P value  | OR       | 95% CI   | P value  |
| Age            | 1.02        | 0.97 to 1.08 | 0.43    | 0.97        | 0.94 to 1.01 | 0.43 |
| Heart rate ≥ 70 bpm | 0.55        | 0.10 to 3.05 | 0.50    | 0.61        | 0.29 to 1.35 | 0.33 |
| HbA1c          | 1.46        | 0.24 to 8.69 | 0.68    | 1.60        | 0.29 to 8.2 | 0.62 |
| LVEF           | 0.85        | 0.72 to 1.00 | 0.05    | 0.91        | 0.78 to 1.05 | 0.30 |
| LAVI           | 0.98        | 0.89 to 1.07 | 0.61    | 0.80        | 0.67 to 1.07 | 0.20 |
| E/e’           | 0.84        | 0.58 to 1.20 | 0.33    | 0.78        | 0.52 to 1.18 | 0.24 |

OR odds ratio, CI confidential interval
All other abbreviations as in Table 1

Fig. 2  Bar graphs of sequential logistic regression models showing that one model, based on clinical variables including age, sex, hypertension, and HbA1c, showed an improvement with the addition of LVEF and E/e’ and a further improvement with the addition of HR ≥ 70 bpm
LV diastolic function, and that reduced GLS can coexist with LV diastolic dysfunction in T2DM patients with preserved LVEF, leading to HFpEF. Therefore, assessment of LV longitudinal myocardial function is promising strategy for detection of LV myocardial damage due to T2DM, known as diabetic cardiomyopathy.

Impact of HR on LV function in T2DM
Poanta et al. evaluated the association of HR with LV diastolic function in 58 T2DM patients without signs of cardiovascular disease [19]. They showed that HR in T2DM patients with impaired relaxation pattern of LV diastolic dysfunction was significantly higher than that in T2DM patients without LV diastolic dysfunction (91 ± 10 bpm vs. 88 ± 11 bpm, P < 0.05). Other studies focusing on the association between HR variability and LV diastolic function in T2DM patients without overt HF [19–21] have reported that HR variability parameters in T2DM patients with LV diastolic dysfunction were significantly lower than those in T2DM patients without LV diastolic dysfunction. As described above, limited studies have evaluated the association between HR with LV diastolic function in T2DM patients and the effect of HR on LV longitudinal myocardial function in asymptomatic T2DM patients with preserved LVEF is unclear. In this study, we showed that LV longitudinal myocardial function in T2DM patients with HR ≥ 70 bpm was significantly worse than that in T2DM patients with HR < 70 bpm, but this finding was not observed in normal controls. In addition, HR ≥ 70 bpm was independently associated with LV longitudinal myocardial dysfunction in T2DM patients in multivariable logistic regression analysis. LV longitudinal myocardial function in T2DM patients with preserved LVEF was already impaired compared to normal controls in this study so that T2DM patients may be susceptible to the adverse effect of high HR, leading to further early LV damage caused by high HR. However, our speculation seems to be insufficient to ascertain the existence of a true differential GLS behavior by HR between T2DM patients and normal controls. Thus, further investigation is necessary to confirm our findings.

In addition, other investigators have reported the association of exercise-induced hemodynamics evaluation with impaired HR adjustment in HFpEF patients and T2DM patients [22–25]. Borlaug et al. showed that exercise-induced elevation in pulmonary capillary wedge pressure in HFpEF patients was confirmed by greater increases in LV end-diastolic pressure and was associated with blunted increases in HR [22]. O'Connor et al. showed that a slower kinetics of adjustments of HR was more evident in older T2DM male patients with longer T2DM duration or with suboptimal glycemic control [24]. On the contrary, Caron et al. reported that well-controlled T2DM male patients and with relatively short T2DM duration did not show significant HR abnormalities with respect to control subjects [25].

Clinical implication
High resting HR is a known marker of cardiovascular outcomes in HF patients, especially HFrEF patients and general populations [13, 15, 26]. In addition, a high
HR was associated with a significantly high risk of all-cause death or cardiovascular hospitalization in HFrEF patients in sinus rhythm, similar to that observed in HFrEF patients [27]. However, it is unclear whether HR-lowering therapy is beneficial for patients with HFrEF, including those with Stage A HF. There are no large randomized controlled trials to evaluate HR lowering with β-blockers or ivabradine in HFrEF with LVEF ≥ 50% [28]. Moreover, ivabradine is currently restricted to off-label use in HFrEF patients with HR ≥ 70 bpm. Thus, we are conducting a multi-center prospective study (IVA-PEF study) to evaluate the effect of ivabradine on LV function such as LV diastolic function and LV longitudinal myocardial function in HFrEF patients, including those with Stage A HF [29]. Our findings suggest that careful observation or early therapeutic intervention with established cardioprotective medications, including ivabradine, may avoid or limit the progression of Stage A HF to Stage B HF for patients with HR ≥ 70 bpm.

**Study limitations**

There were the following limitations in this study. First, this was a single-center retrospective study; hence, prospective multicenter studies with larger patient populations are needed to further assess our findings. Second, only a small number of patients were currently available for follow-up; hence, the effect of HR changes on LV longitudinal myocardial function is unclear. Third, a control group consisted of age-, sex-, and LVEF-matched normal subjects who were randomly chosen from our database, however, there were significant differences of body weight, systolic blood pressure, and the prevalence of hypertension and dyslipidemia between two groups. These parameters can effect on LV longitudinal myocardial function (GLS). Finally, high HR was defined as resting HR ≥ 70 bpm based on the previous registry for HFrEF [13, 15] in this study, but there is currently no established optimal cutoff value of high HR for predicting cardiovascular events for HFrEF patients.

**Conclusion**

Compared with normal subjects, resting HR was associated with LV longitudinal myocardial function in asymptomatic T2DM patients with preserved LVEF. Our findings provide new insights on the management of T2DM patients.

**Abbreviations**

Bpm: Beats/minute; E/e': Mitral inflow E and mitral E' annular velocities ratio; GLS: Global longitudinal strain; HF: Heart failure; HFrEF: Heart failure with preserved ejection fraction; HR: Heart rate; HFrEF: Heart failure with reduced ejection fraction; LV: Left ventricular; LVEF: Left ventricular ejection fraction; T2DM: Type 2 diabetes mellitus.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12933-021-01278-7.

**Additional file 1:** Baseline characteristics of normal patients according to the HR quartiles.

**Acknowledgements**

The authors are grateful for the support of the entire staff of the Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine Kobe Japan.

**Authors’ contributions**

HT designed the study, carried out subject recruitment, performed echocardiography, analysed the data, and wrote the manuscript. YY, SY, YM, YY, HS, KY, YT, AS, MS, KS, KM, YH and WO assisted recruitment and manuscript revision. HT and HK assisted in study design, data interpretation and manuscript revision. All authors read and approved the final manuscript.

**Funding**

The authors declare that they have no funding.

**Availability of data and materials**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the local ethics committee of Kobe University Hospital (No. B200306).

**Consent for publication**

The consent to publish was obtained from all participants in this study.

**Competing interests**

The authors declare that they have no competing interests.

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**Received:** 17 February 2021   **Accepted:** 15 April 2021  
**Published online:** 24 April 2021

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