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

Cardiac electrophysiology, structure and diastolic function in patients with diabetic foot versus those without diabetic foot

Mingxin Bai[1], Dawei Chen[1], Yan Liu[2], Xingwu Ran[1], Chun Wang[1], Lihong Chen[1], Donge Yan[3], Sen He[3], Murong Wu[1], Bo Luo[1], Wen Wang[4], Zhiyi Lei[5], Yun Gao[1]*

[1]Department of Endocrinology and Metabolism, Diabetic Foot Care Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [2]Department of Endocrinology, Chengdu Eighth People's Hospital, Chengdu, Sichuan, China, [3]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [4]Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China, and [5]West China Medical School, Sichuan University, Chengdu, Sichuan, China

Keywords
Diabetic foot, Heart rate variability, Left ventricular diastolic dysfunction

***Correspondence**
Yun Gao
Tel.: +86-189-8060-6855
Fax: +86-28-8542-2982
E-mail address:
gaoyun@wchscu.cn

J Diabetes Investig 2024; 15: 1276–1286

doi: 10.1111/jdi.14250

ABSTRACT

Aims/Introduction: To evaluate the differences in cardiac autonomic function, cardiac structure and diastolic function between individuals with diabetic foot (DF) and those with diabetes but without DF.

Materials and Methods: A total of 413 individuals with DF and 437 without DF who underwent a 24-h electrocardiogram Holter and a Doppler echocardiogram were included. The heart rate variability parameters to evaluate cardiac autonomic function, and the indices for the assessment of cardiac structure and left ventricular (LV) diastolic function, including left atrium, LV posterior wall thickness, interventricular septum and *E/e'* ratio, were measured or calculated. Propensity score matching was used for the sensitivity analysis to minimize potential imbalance.

Results: In both the crude and propensity score matching analyses, significant differences were observed in heart rate variability between individuals with and without DF, as evidenced by lower standard deviation of the normal sinus interval, lower low-frequency power/high-frequency power ratio, lower standard deviation of the 5-min average RR intervals, lower low-frequency power, lower percentage of normal adjacent RR interval difference >50 ms, lower root mean square of successive RR interval differences and lower high-frequency power (all $P < 0.05$). In multivariate analysis, DF showed an independent negative correlation with the aforementioned indices of heart rate variability (all $P < 0.05$). Individuals with DF showed higher left atrium, LV posterior wall thickness, interventricular septum and a higher *E/e'* ratio than those without DF in the crude analysis (all $P < 0.05$), whereas these indices were no longer associated with DF in the multivariate analysis and the propensity score matching analyses.

Conclusions: Cardiac autonomic modulation was more severely impaired in individuals with DF than in their counterparts without DF. There has been insufficient evidence to demonstrate the independent association of DF and LV diastolic dysfunction.

INTRODUCTION

Diabetic foot (DF) is a common and serious complication of diabetes mellitus, which is a growing public health concern that imposes a severe socioeconomic burden with high morbidity and mortality[1]. Compared with those with diabetes mellitus, but without DF, patients with DF had a higher mortality rate, which can be mainly attributed to the excess cardiovascular disease risk[2–5]. The risk of cardiovascular disease death in individuals with DF is 2.22–3.27-fold higher than that in those with diabetes mellitus only[5,6]. In individuals with DF, the elevated mortality rates from cardiovascular complications can be attributed not only to a higher prevalence of coronary atherosclerotic heart

Received 7 October 2023; revised 10 May 2024; accepted 24 May 2024

disease and ischemic cerebrovascular disease, but also to the presence of cardiomyopathy and cardiac autonomic neuropathy (CAN), both of which significantly increase the risk of cardiac-related mortality[7,8].

DF can be divided into two main entities: neuropathic foot and ischemic foot (including neuroischemic foot). Unquestionably, patients with ischemic foot have a higher risk of cardiovascular death due to ischemic cardio-cerebrovascular diseases. For neuropathic foot with palpable pulses, however, it has not yet been clarified whether neuropathic DF patients and their counterparts without DF have different changes in cardiac electrophysiology, cardiac structure, and function independent of atherosclerotic disease and myocardial ischemia.

CAN, a prominent complication arising from diabetic autonomic neuropathy, arises due to impaired autonomic nerve fibers that supply the heart and blood vessels. Analysis of heart rate variability (HRV) serves as a dependable method for evaluating cardiac autonomic function, effectively capturing the dynamic interplay between the sympathetic and parasympathetic systems regulating cardiovascular activity[9]. Reduced HRV has been observed in individuals with type 2 diabetes mellitus[10,11]. Furthermore, some studies have reported individuals with DF had a higher prevalence of CAN[12,13]. Nevertheless, these studies were insufficient to control for confounding factors, such as the higher prevalence of myocardial ischemia in ischemic foot due to small sample sizes.

Additionally, previous studies have shown that individuals with diabetes remain at significantly higher risk of heart failure than controls without diabetes, even in the absence of hypertension (HBP) and coronary artery disease (CAD)[14], suggesting a direct detrimental effect of hyperglycemia on cardiac structure and function beyond the adverse effect of coronary atherosclerosis. Early cardiac damage in individuals with diabetes always manifests as diastolic dysfunction[15,16]. However, few studies have analyzed the cardiac diastolic function in individuals with DF compared with those with diabetes without DF complications.

Thus, we used HRV analysis and cardiac echocardiography to evaluate the differences in cardiac electrophysiology, structure and diastolic function between patients with type 2 diabetes mellitus with and without DF.

MATERIALS AND METHODS

Study population

We retrospectively reviewed the medical records of 2,446 individuals with type 2 diabetes mellitus (768 with DF and 1,678 without DF) who visited the Diabetic Foot Care Center of West China Hospital, Sichuan University (Chengdu, China) between January 2016 and January 2022, excluding 1,354 individuals with incomplete records or left ventricular (LV) ejection fraction (LVEF) <50%. Diabetes mellitus was diagnosed based on the diagnostic criteria proposed by the World Health Organization in 1999[17]. DF disease was defined as foot infection, ulcer or tissue destruction in patients with a current or previous diagnosis of diabetes, usually accompanied by lower-extremity neuropathy and/or peripheral arterial disease (PAD)[18]. All patients with type 1 or special types of diabetes, other endocrine and metabolic diseases, severe organic heart diseases, severe renal and hepatic insufficiency, hematological diseases, autoimmune and/or rheumatic diseases, neoplasms, neurological or respiratory disorders, and inflammatory or infectious diseases were excluded from the study. Individuals were also excluded if they had a fever, arrhythmia, a history of myocardial infarction, were pregnant or lactating, or were taking medication that might influence cardiac autonomic function (e.g., metoprolol, amiodarone, propranolol, bisoprolol). According to these criteria, 850 individuals with type 2 diabetes mellitus (413 with DF and 437 without DF) were included in the study (Figure 1). The study was reviewed and approved by the Institutional Ethics Committee of the West China Hospital, and was registered in the Clinical Trial Registry (registration number: ChiCTR1900025899). All patients provided written informed consent.

Assessment of sympathovagal balance

Holter electrocardiogram monitoring with a 24-h recording was carried out using a GE Marquette MARS PC ambulatory electrocardiogram Holter system (GE Healthcare, Chicago, IL, USA). Before collection, participants were familiar with the device, the staff and the procedures. To obtain reliable HRV data, participants were asked to abstain from alcohol and stimulant intake, such as caffeine, nicotine and chocolate, and to refrain from vigorous physical activity for 24 h before and during the 24 h of the recording period. The device was placed in the precordial region at the same hour (8:00–9:00 a.m.), with the patients undertaking normal daily activities during hospitalization. During monitoring, patients were informed about keeping dry skin, having a good night's sleep and staying away from electromagnetic fields.

A Holter Analysis Workstation (GE Medical Systems Information Technologies, Inc., El Paso, TX, USA) was used to calculate the HRV indices. HRV analyses were carried out by a trained professional to obtain reproducible data. The following time-domain indices of HRV were computed: the standard deviation of the normal sinus interval (SDNN), the standard deviation of the 5-min average RR intervals (SDANN), the root mean square of successive RR interval differences (rMSSD) and the percentage of normal adjacent RR interval difference >50 ms (PNN50). Frequency domain indices include the low-frequency power (LF), the high-frequency power (HF) and the LF/HF ratio.

SDNN is a marker of total tension of sympathetic and vagal nerves, and reflects both sympathetic and parasympathetic modulation of heart rate. In the present study, SDNN <100 ms was defined as CAN[19]. It is also a strong predictor of an impaired cardiac autonomic system, malignant arrhythmia and sudden death[20]. The LF/HF ratio, an index of the interaction between sympathetic and vagal activity, is also regarded as a valuable assessment of sympathovagal balance[19]. PNN50, rMSSD and HF are associated mainly with parasympathetic

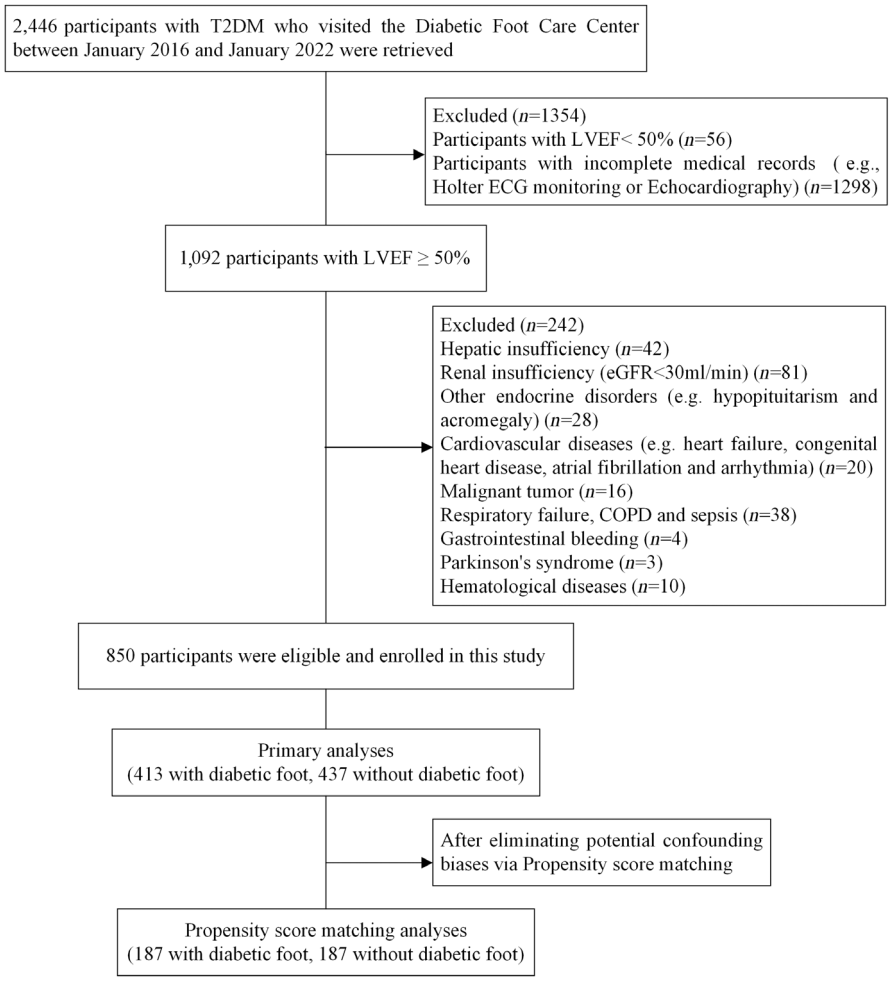

Figure 1 | Flow chart of the study. COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; T2DM, type 2 diabetes mellitus.

modulation, whereas SDANN and LH are considered quantitative markers for sympathetic modulation[19, 21].

Echocardiographic examination

Echocardiography is the most commonly used noninvasive means of evaluating cardiac structure and function. For accurate results, all participants requested an echocardiogram after stabilization from clinical treatment. All echocardiographic examinations were carried out from 9:00 to 12:00 a.m. of the day and using the Philips EPIQ 7C and IE33 platforms (Amsterdam, the Netherlands). Echocardiographic parameters were measured and calculated by an experienced operator.

With the participants in the supine left-sided position, standard parasternal long- and short-axis, and apical two- and four-chamber views were obtained to measure the left atrium (LA), LV posterior wall thickness (LVPW), interventricular septum (IVS) and LV internal diameter at end-diastole (LVIDd). LV mass (LVM) was calculated using the Devereux formula: LVM (g) = $0.8 \times 1.04 \times [(\text{LVIDd} + \text{IVS} + \text{LVPW})^3 - \text{LVIDd}^3] + 0.6$ and indexed per square meter of body surface area (LVMI)[22]. The peak early diastolic mitral inflow velocity (E) was recorded from pulse-wave Doppler, and the average mitral annulus early diastolic velocity (e') was calculated from pulsed wave tissue Doppler, then the average E/e' ratio was derived. The tricuspid regurgitation velocity maximum was obtained in the apical four-chamber view with continuous-wave Doppler. We defined LV diastolic dysfunction as an average E/e' ratio >14 according to the recommendation from the American Society of Echocardiography and the European Association of Cardiovascular Imaging[23].

Assessment of diabetes mellitus-related clinical features

The diagnosis of diabetic peripheral neuropathy was based on neuropathy symptoms, signs and neurophysiologic test abnormalities[24]. HBP was diagnosed based on the Guidelines in 2018[25]. CAD could be diagnosed when patients had a history of angina excluding other diseases, previous myocardial infarction, current acute myocardial infarction or coronary artery

stenosis >50%. Ischemic cerebrovascular disease refers to the degeneration, necrosis or transient loss of function of local brain tissue due to stenosis or occlusion of cerebral arteries[26]. PAD was defined by the presence of ankle brachial index <0.9, confirmed imaging examination or history of revascularization therapy[27,28]. Biochemical indices (e.g., glycated hemoglobin, liver and renal function, glucose and lipids) were also measured at baseline.

Statistical analysis

Statistical analysis was carried out using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as the mean ± standard deviation or medians with interquartile ranges, and were compared using Student's *t*-test or Wilcoxon's rank-sum test. Categorical variables were described as frequencies and percentages, and differences were compared using the χ^2-test and Fisher's exact test when appropriate. Multiple linear regression models were used to analyze the independent correlation between DF and indices of HRV, cardiac structure and function after adjustment for covariates. Additionally, we used multivariable logistic regression models to compute adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) relating DF to CAN and LV diastolic dysfunction.

Additionally, a propensity score (PS) was developed as a sensitivity analysis to minimize the potential imbalance of confounding factors between groups. Based on the use of PS matching (PSM), patients with DF were matched 1:1 with controls without DF using the nearest neighbor caliper width of 0.05. This matching procedure was carried out using the MatchIt package for R (RStudio, PBC, Boston, MA, USA). Correspondingly, univariate and multivariate regression analyses were also carried out after PSM. All statistical analyses were two-sided with a significance level of 0.05.

RESULTS

Table 1 shows the baseline demographic and clinical characteristics of all participants before and after PSM. Individuals with

Table 1 | Baseline demographic and clinical characteristics of all participants before and after propensity score matching

Variables	Before PSM			After PSM		
	DF group	Non-DF group	*P*	DF group	Non-DF group	*P*
No. patients (*n*)	413	437		187	187	
Sex, men (%)	271 (65.6)	253 (57.9)	0.021	120 (64.2)	123 (65.8)	0.745
Age (years)	64.5 ± 12.1	58.9 ± 13.8	<0.001	61.9 ± 12.4	61.6 ± 12.6	0.814
Diabetes duration (years)	11 (6, 17)	10 (4, 16)	0.019	12 (7, 18)	11 (6, 17)	0.259
Alcohol consumption (%)						
Never	254 (61.5)	295 (67.5)	0.190	119 (63.6)	118 (63.1)	0.811
Occasional	65 (15.7)	59 (13.5)		24 (12.8)	28 (15.0)	
Frequent	94 (22.8)	83 (19.0)		44 (23.5)	41 (21.9)	
Current smoking (%)	182 (44.1)	154 (35.2)	0.009	79 (42.2)	80 (42.8)	0.917
BMI (kg/m^2)	23.5 ± 3.4	24.6 ± 4.7	<0.001	24.0 ± 3.7	24.1 ± 3.7	0.861
Family history of DM (%)	148 (35.8)	168 (38.4)	0.430	78 (41.7)	76 (40.6)	0.834
SBP (mmHg)	141.3 ± 22.8	136.0 ± 20.3	0.001	141.3 ± 22.8	137.0 ± 21.3	0.366
DBP (mmHg)	80.5 ± 12.6	83.3 ± 11.9	0.001	82.3 ± 13.1	81.8 ± 11.2	0.681
MBP (mmHg)	100.8 ± 13.7	100.8 ± 12.8	0.940	101.2 ± 14.1	100.2 ± 12.7	0.458
HbA1c (%)	7.8 (6.8, 9.5)	8.8 (7.3, 10.9)	<0.001	8.4 (7.1, 9.9)	8.1 (6.8, 9.8)	0.862
FPG (mmol/L)	8.5 (6.4, 11.6)	8.4 (6.3, 11.8)	0.850	8.8 (6.6, 12.4)	8.2 (6.1, 11.4)	0.097
TC (mmol/L)	3.88 ± 1.10	4.34 ± 1.18	<0.001	4.0 (3.2, 4.8)	3.9 (3.3, 4.8)	0.912
TG (mmol/L)	1.30 (0.99, 1.83)	1.53 (1.05, 2.36)	0.001	1.4 (1.1, 2.1)	1.4 (0.9, 2.2)	0.709
HDL-C (mmol/L)	1.06 ± 0.34	1.13 ± 0.40	0.011	1.06 (0.85, 1.35)	1.04 (0.86, 1.28)	0.773
LDL-C (mmol/L)	2.16 ± 0.89	2.49 ± 0.97	<0.001	2.21 (1.50, 2.86)	2.08 (1.61, 2.85)	0.838
eGFR (mL/min/1.73 m^2)	79.4 ± 23.8	87.5 ± 24.1	<0.001	87.3 (63.8, 101.3)	89.5 (67.6, 100.6)	0.697
DPN (%)	398 (96.4)	249 (57.0)	<0.001	174 (93.0)	171 (91.4)	0.562
PAD (%)	205 (49.6)	33 (7.6)	<0.001	35 (18.7)	30 (16.0)	0.495
HBP (%)	260 (63.0)	256 (58.6)	0.190	113 (60.4)	111 (59.4)	0.833
CAD (%)	81 (19.6)	57 (13.0)	0.009	25 (13.4)	26 (13.9)	0.880
CVD (%)	32 (7.8)	24 (5.5)	0.190	10 (5.3)	10 (5.3)	>0.999

Data are mean (standard deviation), median (interquartile range) or *n* (percentage). BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DF, diabetic foot; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HBP, hypertension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MBP, mean blood pressure; PAD, peripheral arterial disease; PSM, propensity score matching; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

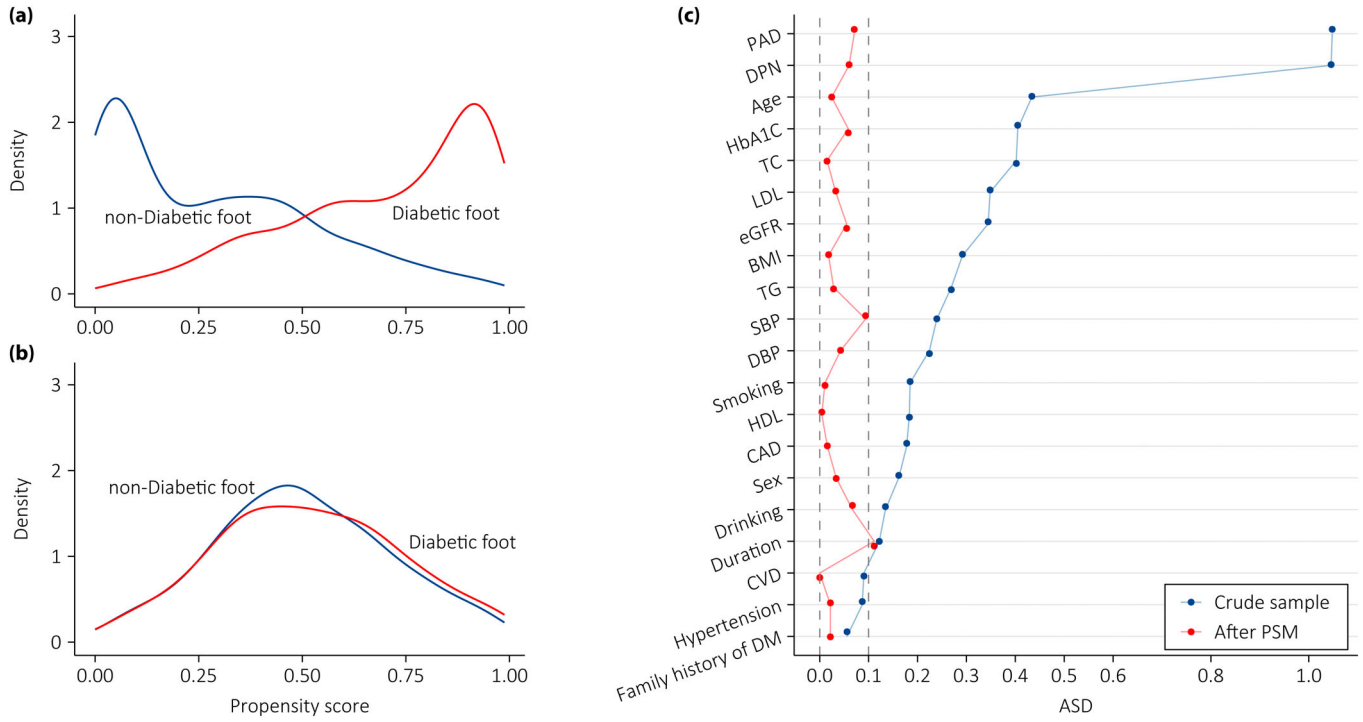

Figure 2 | Propensity scores (PS) distributional overlap and absolute standardized differences (ASD) in participants with diabetic foot (DF) and without diabetic foot (non-DF). (a, b) Present PS distributions between individuals with or without DF in the crude sample and the sample after propensity score matching (PSM). For intervals along the *x*-axis, the area under the probability density curve represents the probability of those PSs, and smoothing was through the kernel density estimate. Greater overlap of PS curves of the two groups indicates a lesser risk of confounding. (c) ASD in individuals stratified by DF. The dashed line indicates >0.1 imbalance between the variable's value, which is a commonly used metric of significant imbalance. BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-, low-density lipoprotein cholesterol; PAD, peripheral arterial disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

DF were older, had a longer diabetes duration, and had a higher prevalence of drinking and smoking. Furthermore, individuals with DF tended to have a faster heart rate and higher SBP. Additionally, individuals with DF had a greater prevalence of diabetic peripheral neuropathy, PAD, HBP, CAD and cerebrovascular disease than those without DF. Figure 2a shows the distribution of PS in individuals with and without DF before PSM. The smaller the overlap between the PS curves of the two groups, the greater the risk of confounding is suggested. After PSM, the PS curves of the groups with and without DF were highly overlapping, which indicated well-balanced baseline covariates between the two groups (Figure 2b). Several unbalanced variables with the absolute standardized difference ≥0.1, including SBP and diabetic duration (Figure 2c), were further adjusted in the multivariate analysis.

Within the time and frequency domain, measures of HRV, SDNN and LF/HF reflect the total cardiac autonomic tone, and serve to assess the overall damage and recovery of the cardiac autonomic nerve. Compared with individuals without DF, SDNN and LF/HF in the DF group were significantly lower, and the differences were statistically significant (all $P < 0.05$). Indicators assessing cardiac vagal tone (PNN50, rMSSD, HF) and cardiac sympathetic tone (SDANN, LF) were significantly lower in the DF group than in the non-DF group (all $P < 0.05$; Table 2). For all enrolled participants, the multivariate linear regression analysis showed that DF was independently negatively associated with all the abovementioned HRV measures: SDNN (β −0.311; 95% CI −0.377, 0.246; $P < 0.001$), LF/HF (β −0.131; 95% CI −0.164, 0.098; $P < 0.001$), SDANN (β −20.854; 95% CI −25.646, 16.061; $P < 0.001$), LF (β −0.472; 95% CI −0.563, 0.382; $P < 0.001$), PNN50 (β −0.265; 95% CI −0.434, 0.095; $P = 0.002$), rMSSD (β −3.596; 95% CI −5.306, 1.885; $P < 0.001$) and HF (β −0.266; 95% CI −0.342, 0.190; $P < 0.001$). After eliminating or reducing potential confounding biases via PSM, these independently negative associations between DF and HRV indices remained in both univariable and multivariable linear regression analyses (Table 3). CAN, defined by SDNN <100 ms, was more prevalent in the DF group than in the group without DF (350/413 [84.7] vs 239/437 [54.7], $P < 0.001$; Figure 3a). Furthermore, DF was independently associated with higher odds of CAN (OR 3.62; 95% CI 2.40–5.45; $P < 0.001$) after adjustment for

Table 2 | Indices of heart rate variability, cardiac structure and diastolic function in participants with and without diabetic foot

Variables	Before PSM			After PSM		
	DF group	Non-DF group	*P*	DF group	Non-DF group	*P*
No. patients (*n*)	413	437		187	187	
HR (bpm)	80.6 ± 11.0	76.4 ± 10.6	<0.001	80.6 ± 11.0	75.3 ± 11.0	<0.001
SDNN (ms)	64 (48, 86)	95 (76, 118)	<0.001	66.0 (51.0, 88.0)	94.0 (74.0, 118.0)	<0.001
SDANN (ms)	63.0 ± 27.5	88.4 ± 29.7	<0.001	60.0 (46.0, 80.0)	83.0 (65.0, 107.0)	<0.001
PNN50 (%)	0.4 (0.0, 2.7)	1.9 (0.4, 5.8)	<0.001	0.5 (0.0, 3.1)	1.5 (0.2, 5.5)	0.005
rMSSD (ms)	16.5 ± 10.4	21.1 ± 10.0	<0.001	14.0 (10.0, 21.0)	19.0 (13.0, 26.0)	<0.001
HF (ms^2)	4.6 (3.2, 7.1)	7.3 (5.4, 10.3)	<0.001	4.9 (3.3, 7.8)	7.0 (5.1, 9.7)	<0.001
LF (ms^2)	4.9 (3.0, 9.0)	10.9 (7.5, 15.2)	<0.001	5.2 (2.9, 9.2)	10.2 (7.1, 14.0)	<0.001
LF/HF	1.1 (0.8, 1.5)	1.4 (1.2, 1.8)	<0.001	1.1 (0.8, 1.5)	1.4 (1.1, 1.7)	<0.001
LA (mm)	34.34 ± 5.28	33.41 ± 4.07	0.004	34.26 ± 4.34	33.75 ± 4.06	0.238
LVPW (mm)	9.62 ± 1.28	9.41 ± 1.65	0.040	9.57 ± 1.11	10.85 ± 1.92	0.876
IVS (mm)	11.06 ± 1.76	10.63 ± 1.84	0.001	10.98 ± 1.69	10.63 ± 1.84	0.484
LVMI (g/m^2)	108.9 (93.2, 126.0)	101.6 (86.7, 118.3)	<0.001	108.9 (95.1, 126.0)	105.0 (90.1, 123.4)	0.714
E (m/s)	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	0.008	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	0.663
e′ (cm/s)	5.80 ± 1.95	6.23 ± 2.01	0.002	6.0 (5.0, 7.0)	6.0 (5.0, 7.0)	0.371
E/e′	12.9 (10.0, 16.0)	12.0 (10.0, 14.5)	<0.001	12.0 (10.0, 15.0)	12.0 (10.0, 15.0)	0.256
TRVmax (m/s)	2.4 (2.2, 2.7)	2.3 (2.1, 2.5)	0.003	2.3 (2.2, 2.6)	2.4 (2.2, 2.6)	0.817

Data are mean (standard deviation), median (interquartile range) or *n* (percentage). DF, diabetic foot; *E*, the peak early diastolic mitral inflow velocity; *e′*, the mitral annulus early diastolic velocity; HF, high-frequency power; HR, heart rate; IVS, interventricular septum; LA, left atrium; LF/HF, rate of low-frequency power between high-frequency power; LF, low-frequency power; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; PNN50, the percentage of normal adjacent RR interval difference >50 ms; PSM, propensity score matching; rMSSD, the root mean square of successive RR interval differences; SDANN, the standard deviation of the 5-min average RR intervals; SDNN, the standard deviation of normal sinus interval; TRVmax, tricuspid regurgitation velocity maximum.

possible confounders. Further PSM analysis also showed an independent association of DF and CAN (OR 3.19; 95% CI 1.99–5.12; $P < 0.001$; Table 4).

Indicators of cardiac structure and function obtained from echocardiography are shown in Table 2. Before PSM, compared with those without DF, individuals with DF were characterized by a larger LA, thicker LVPW, thicker IVS, higher LVMI and higher tricuspid regurgitation velocity maximum (all $P < 0.05$), which indirectly suggests the possible abnormality of LV diastolic dysfunction (Table 2). Thus, we used the average *E/e′* ratio as a direct assessment index of LV diastolic function. Individuals with DF had higher *E/e′* than those without DF (12.9 vs 12.0, $P < 0.001$; Table 2). Furthermore, compared with those without DF, individuals with DF had more LV diastolic dysfunction, which was defined by an average *E/e′* ratio >14 (136/413 [33.2] vs 109/437 [25.0], $P = 0.009$; Figure 3b). Before PSM, the multiple linear regression analysis showed that DF tended to be independently associated with E/e' (β 0.051; 95% CI −0.002, −0.104; $P = 0.058$) after adjusting for potential confounding factors (Table 3). After PSM, however, the average *E/e′* ratio and the proportion of LV diastolic dysfunction were similar between individuals with DF and without DF (Table 2). Furthermore, in the PSM analysis, the association of DF and average *E/e′* ratio became nonsignificant (β 0.026; 95% CI −0.037, 0.089; $P = 0.419$; Table 3). Additionally, DF did not increase the likelihood of having LV diastolic dysfunction in both multivariate logistic regression analysis (OR 1.413; 95% CI 0.936, 2.133; $P = 0.100$) and PSM analysis (OR 1.107; 95% CI 0.701, 1.748; $P = 0.663$; Table 4).

DISCUSSION

The current study showed that the HRV indices of individuals with DF were significantly lower than those of individuals without DF. Furthermore, an independently negative association was observed between DF and the aforementioned HRV indices after adjustment for potential confounding factors, such as demographic and lifestyle factors, diabetic duration, chronic comorbidities or complications, and other relevant biomarkers. Even after carrying out PSM and further eliminating probable confounding biases, the results remained unchanged.

HRV analysis is a useful means to identify diabetic cardiac autonomic neuropathy (DCAN)[29], and a decreased HRV suggests an impairment in cardiac autonomic regulation, thereby contributing to an increased risk of cardiovascular diseases, such as arrhythmia and sudden cardiac death[20,30,31]. Individuals with DF had a significantly lower SDNN and LF/HF ratio, which suggested more severe overall regulatory dysfunction of the cardiac autonomic nervous system in individuals with DF[32–34]. Usually, cardiac autonomic dysfunction is characterized by diminished activity of vagal nerves and/or increased activity of sympathetic nerves[35]. The present study showed significantly lower rMSSD, PNN50 and HF in individuals with DF. After adjusting for potential confounding factors, DF was independently negatively associated with rMSSD, PNN50 and HF,

Table 3 | The association of diabetic foot and indices of heart rate variability, cardiac structure and diastolic function among participants with type 2 diabetes

	Crude analysis models (before PSM)				Propensity-score analysis models (after PSM)			
	Univariate analysis		Multivariable analysis[†]		With PSM (univariate)		With PSM (multivariable)[‡]	
	β, 95%CI	*P*-value	β, 95% CI	*P*-value	β, 95% CI	*P*-value	β, 95% CI	*P*-value
SDNN	−0.377 (−0.430, −0.324)	<0.001	−0.311 (−0.377, −0.246)	<0.001	−0.333 (−0.412, −0.254)	<0.001	−0.329 (−0.408, −0.250)	<0.001
LF/HF	−0.140 (−0.167, −0.113)	<0.001	−0.131 (−0.164, −0.098)	<0.001	−0.129 (−0.171, −0.087)	<0.001	−0.126 (−0.168, −0.084)	<0.001
SDANN	−25.31 4 (−29.172, −21.456)	<0.001	−20.854 (−25.646, −16.061)	<0.001	−22.016 (−27.692, −16.341)	<0.001	−21.642 (−27.316, −15.967)	<0.001
LF	−0.584 (−0.659, −0.508)	<0.001	−0.472 (−0.563, −0.382)	<0.001	−0.484 (−0.602, −0.366)	<0.001	−0.476 (−0.594, −0.358)	<0.001
PNN50	−0.404 (−0.542, −0.267)	<0.001	−0.265 (−0.434, −0.095)	0.002	−0.278 (−0.469, −0.086)	0.005	−0.280 (−0.472, −0.087)	0.005
rMSSD	−4.653 (−6.032, −3.274)	<0.001	−3.596 (−5.306, −1.885)	<0.001	−3.845 (−5.659, −2.031)	<0.001	−3.869 (−5.691, −2.046)	<0.001
HF	−0.352 (−0.414, −0.290)	<0.001	−0.266 (−0.342, −0.190)	<0.001	−0.265 (−0.357, −0.173)	<0.001	−0.263 (−0.355, −0.171)	<0.001
LVMI	0.066 (0.031, 0.102)	<0.001	0.018 (−0.024, 0.059)	0.399	0.010 (−0.044, 0.065)	0.714	0.007 (−0.046, 0.060)	0.801
Average E/e' ratio	0.103 (0.058, 0.149)	<0.001	0.051 (−0.002, 0.104)	0.058	0.038 (−0.027, 0.102)	0.256	0.026 (−0.037, 0.089)	0.419

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CVD, cerebrovascular disease; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; *E*, the peak early diastolic mitral inflow velocity; e', the mitral annulus early diastolic velocity; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HBP, hypertension; HF, high-frequency power; LF/HF, rate of low-frequency power between high-frequency power; LF, low-frequency power; LVMI, left ventricular mass index; MBP, mean blood pressure; PAD, peripheral arterial disease; PNN50, the percentage of normal adjacent RR interval difference >50 ms; PSM, propensity score matching; rMSSD, the root mean square of successive RR interval differences; SBP, systolic blood pressure; SDANN, the standard deviation of the 5-min average RR intervals; SDNN, the standard deviation of normal sinus interval; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides. [†]Adjustment for imbalance variables, including age, sex, diabetic duration, BMI, MBP, current smoking, alcohol consumption; family history of DM, HBP, PAD, CAD, CVD, DPN, eGFR, TC, TG and HbA1C. [‡]Adjustment for imbalance variables after PSM, including SBP and diabetic duration.

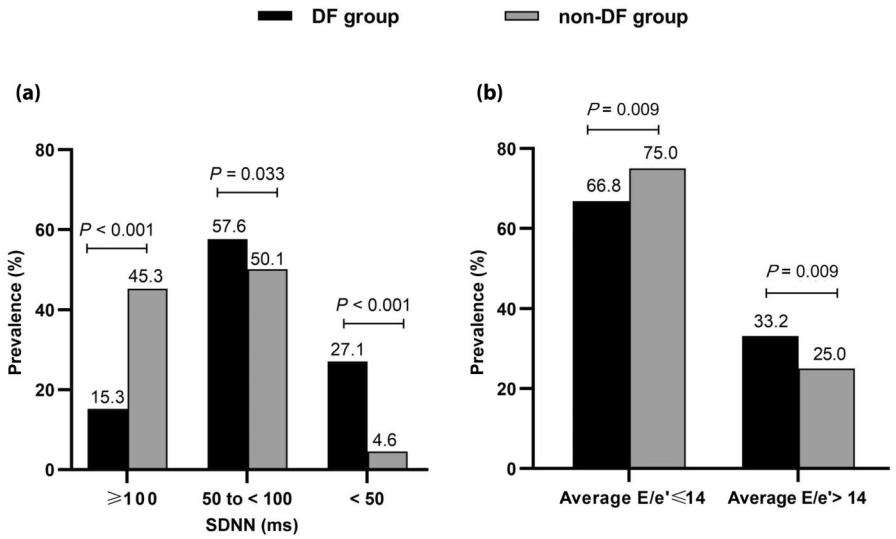

Figure 3 | The prevalence of (a) cardiovascular autonomic neuropathy and (b) left ventricular diastolic dysfunction in participants with and without diabetic foot. DF, diabetic foot; *E*, the peak early diastolic mitral inflow velocity; *e′*, the mitral annulus early diastolic velocity; SDNN, the standard deviation of normal sinus interval.

Table 4 | The odds ratios and 95% confidence intervals of cardiovascular autonomic neuropathy and left ventricular diastolic dysfunction among participants with type 2 diabetes mellitus, according to diabetic foot status

	CAN[†]		LV diastolic dysfunction[‡]	
	OR, 95% CI	*P*-value	OR, 95% CI	*P*-value
Crude analysis models				
Univariate analysis	4.602 (3.316, 6.387)	<0.001	1.489 (1.104, 2.007)	0.009
Multivariate analysis[§]	3.618 (2.402, 5.451)	<0.001	1.413 (0.936, 2.133)	0.100
Propensity-score analyses models				
With PSM (univariate)	3.220 (2.009, 5.161)	<0.001	1.170 (0.747, 1.831)	0.493
With PSM (multivariate)[¶]	3.189 (1.987, 5.117)	<0.001	1.107 (0.701, 1.748)	0.663

BMI, body mass index; CAD, coronary artery disease; CAN, cardiovascular autonomic neuropathy; CI, confidence interval; CVD, cerebrovascular disease; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; *E*, the peak early diastolic mitral inflow velocity; *e′*, the mitral annulus early diastolic velocity; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HBP, hypertension; LV, left ventricular; MBP, mean blood pressure; PAD, peripheral arterial disease; PSM, propensity score matching; SBP, systolic blood pressure; SDNN, the standard deviation of normal sinus interval; TC, total cholesterol; TG, triglycerides. [†]CAN was identified by SDNN <100 ms. [‡]LV diastolic dysfunction was identified by average *E/e′* ratio >14. [§]Adjustment for imbalance variables, including age, sex, diabetic duration, BMI, MBP, smoking history, drinking history, family history of DM, HBP, PAD, CAD, CVD, DPN, eGFR, TC, TG and HbA1c. [¶]Adjustment for imbalance variables after PSM, including SBP and diabetic duration.

suggesting more severe impairment and diminishment of vagal tone in individuals with DF. In addition, in the present study, we observed individuals with DF had significantly lower SDANN and LF, which indicated that cardiac sympathetic function was more severely impaired in individuals with DF than those without DF. Considering the marked impact of confounding factors, such as age, diabetic duration, HBP and CAD, on cardiac autonomic modulation, PSM presented a more robust result. Thus, the present study showed that both vagal and sympathetic nerves were more severely damaged in patients with DF than in those without DF. However, the results from the current study did not interpret the sequential order of or susceptibility to vagal and sympathetic damage in individuals with DF compared with those without DF, which will be investigated in our future study.

The reasons for the significant differences in cardiac autonomic dysfunction might be considered from the pathogenesis of DCAN. Reduced nerve blood flow caused by endothelial damage and/or vasoconstriction, and direct neuronal damage through cell necrosis, hypoxia and apoptosis lead to the development of DCAN[36,37]. For instance, hyperglycemic activation of the polyol pathway induces both direct neuronal damage and reduced neuronal blood flow. Hyperglycemia-induced increased oxidative stress and the production of oxygen free

radicals damage vascular endothelial cells and neurons, also contributing to the development of DF. The formation of advanced glycation end-products and activation of protein kinase C reduce the neuronal blood supply by thickening the basement membrane of the neurotrophic vessels. Altered fatty acid metabolism induced by hyperinsulinism promotes vasoconstriction and excessive production of inflammatory mediators, such as interleukin-6, interleukin-8 and tumor necrosis factor-α, which have shown significant correlation with decreased HRV. Previous studies have shown that patients with DF presented significantly elevated levels of lipid peroxides, 8-hydroxy-2′-deoxyguanosine, skin autofluorescence, advanced glycation end-products and a higher degree of endothelial function impairment[13,38,39]. Thus, in terms of pathogenesis, multiple more severe pathological processes occur in patients with diabetic neuropathic foot disease than in patients with diabetes, but without DF. However, considering the similar diabetes duration and disease background, further studies are warranted to investigate whether intrinsic disease susceptibility or extrinsic differences in glycemic control, or a combination of multiple risk factors are responsible for the divergence in adverse outcomes of DCAN.

Additionally, we found that the parameters of cardiac structure related to LV diastolic dysfunction, such as LA, LVPW, IVS and LVMI, were larger or thicker in individuals with DF than in those without DF through the crude analysis of all enrolled participants. Furthermore, individuals with DF had more LV diastolic dysfunction than those without DF. When achieving the basic balance of potential confounding factors through PSM between the two groups, however, the aforementioned differences in related indices or abnormal proportions of LV diastolic function were no longer significant. Previous studies have established that diabetes mellitus is a major contributor to the development of LV diastolic dysfunction and heart failure in patients with preserved LVEF, even in the absence of CAD and HBP[40,41]. This could be explained by the fact that participants with DF were older and had a longer diabetes duration, were more likely to be smokers, and had higher proportions of HBP, CAD, PAD and/or diabetic peripheral neuropathy, which are well-known risk factors for LV diastolic dysfunction. After eliminating or reducing potential confounding biases through PSM, individuals with DF had similar cardiac structure and diastolic function. Thus, the reason that individuals with DF seem to have a higher proportion of LV diastolic dysfunction might be mainly attributed to more concomitant diseases, resulting in an elevated risk of LV diastolic dysfunction instead of possible disease susceptibility.

Some potential limitations of the study warrant discussion. First, the causality of the observed association in the present study could not be established because of the cross-sectional nature of the study. Second, as most of the enrolled participants did not have an indication for coronary angiography or computed tomography angiography, relevant data on the severity of coronary stenosis were not available, which might affect cardiac autonomic function, cardiac structure and diastolic function. Third, although the current study showed more severe CAN in people with DF than in those without DF, the extent to which an impairment of cardiac autonomic function significantly increases cardiovascular mortality is unclear. Thus, we are carrying out a prospective cohort study to determine the answer.

In conclusion, we found that cardiac autonomic modulation was more severely impaired in people with DF than in their counterparts without DF, reflected by more severe autonomic imbalance and significantly lower parasympathetic activity. DF is independently associated with a higher risk of having CAN. There has been insufficient evidence to show the independent association of DF and LV diastolic dysfunction.

ACKNOWLEDGMENTS

This study was supported by Chengdu Science and Technology Bureau (Grant No. 2022YFS0308), National Natural Science Foundation of China (Grant No. 81700087) and West China Hospital, Sichuan University (Grant No. ZYGD18025).

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The present study was approved by the Institutional Ethic Committee of West China Hospital, Sichuan University, and it conformed to the provisions of the Declaration of Helsinki.

Informed consent: Written informed consent was obtained from all participants.

Approval date of Registry and the registration No. of the study/trial: 13 September 2019, No. ChiCTR1900025899.

Animal Studies: N/A.

REFERENCES

1. Lim JZ, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. *J R Soc Med* 2017; 110: 104–109.
2. Preis SR, Hwang SJ, Coady S, *et al*. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham heart study, 1950 to 2005. *Circulation* 2009; 119: 1728–1735.
3. Boyko EJ, Ahroni JH, Smith DG, *et al*. Increased mortality associated with diabetic foot ulcer. *Diabet Med* 1996; 13: 967–972.
4. Young MJ, McCardle JE, Randall LE, *et al*. Improved survival of diabetic foot ulcer patients 1995-2008: Possible impact of aggressive cardiovascular risk management. *Diabetes Care* 2008; 31: 2143–2147.
5. Brownrigg JR, Davey J, Holt PJ, *et al*. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: A meta-analysis. *Diabetologia* 2012; 55: 2906–2912.
6. Qiu L, Li Y, Yang C, *et al*. Influence of foot ulceration on all-cause and cardiovascular mortality in diabetic patients: A case-control study. *J Wound Ostomy Continence Nurs* 2022; 49: 175–179.

7. Gilmore JE, Allen JA, Hayes JR. Autonomic function in neuropathic diabetic patients with foot ulceration. *Diabetes Care* 1993; 16: 61–67.
8. Murtaza G, Virk HUH, Khalid M, *et al*. Diabetic cardiomyopathy - a comprehensive updated review. *Prog Cardiovasc Dis* 2019; 62: 315–326.
9. Lewis MJ. Heart rate variability analysis: A tool to assess cardiac autonomic function. *Comput Inform Nurs* 2005; 23: 335–341.
10. John APP, Udupa K, Avangapur S, *et al*. Cardiac autonomic dysfunctions in type 2 diabetes mellitus: An investigative study with heart rate variability measures. *Am J Cardiovasc Dis* 2022; 12: 224–232.
11. Benichou T, Pereira B, Mermillod M, *et al*. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS One* 2018; 13: e0195166.
12. Aso Y, Fujiwara Y, Inukai T, *et al*. Power spectral analysis of heart rate variation in diabetic patients with neuropathic foot ulceration. *Diabetes Care* 1998; 21: 1173–1177.
13. Tuttolomondo A, Del Cuore A, La Malfa A, *et al*. Assessment of heart rate variability (HRV) in subjects with type 2 diabetes mellitus with and without diabetic foot: Correlations with endothelial dysfunction indices and markers of adipo-inflammatory dysfunction. *Cardiovasc Diabetol* 2021; 20: 142.
14. Pop-Busui R, Januzzi JL, Bruemmer D, *et al*. Heart failure: An underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care* 2022; 45: 1670–1690.
15. Ernande L, Audureau E, Jellis CL, *et al*. Clinical implications of echocardiographic phenotypes of patients with diabetes mellitus. *J Am Coll Cardiol* 2017; 70: 1704–1716.
16. Karamitsos TD, Karvounis HI, Dalamanga EG, *et al*. Early diastolic impairment of diabetic heart: The significance of right ventricle. *Int J Cardiol* 2007; 114: 218–223.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
18. van Netten JJ, Bus SA, Apelqvist J, *et al*. Definitions and criteria for diabetic foot disease. *Diabetes Metab Res Rev* 2020; 36(Suppl 1): e3268.
19. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Task force of the European Society of Cardiology and the north American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; 17: 354–381.
20. Kleiger RE, Miller JP, Bigger JT Jr, *et al*. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59: 256–262.
21. Shah AS, El Ghormli L, Vajravelu ME, *et al*. Heart rate variability and cardiac autonomic dysfunction: Prevalence, risk factors, and relationship to arterial stiffness in the treatment options for type 2 diabetes in adolescents and youth (TODAY) study. *Diabetes Care* 2019; 42: 2143–2150.
22. Devereux RB, Alonso DR, Lutas EM, *et al*. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450–458.
23. 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. *Eur Heart J Cardiovasc Imaging* 2016; 17: 1321–1360.
24. Xue P, Covassin N, Ran X, *et al*. Association of parameters of nocturnal hypoxemia with diabetic microvascular complications: A cross-sectional study. *Diabetes Res Clin Pract* 2020; 170: 108484.
25. Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021–3104.
26. Liu L, Chen W, Zhou H, *et al*. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: Executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke Vasc Neurol* 2020; 5: 159–176.
27. Hinchliffe RJ, Brownrigg JR, Apelqvist J, *et al*. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. *Diabetes Metab Res Rev* 2016; 32(Suppl 1): 37–44.
28. Kohler TR, Nance DR, Cramer MM, *et al*. Duplex scanning for diagnosis of aortoiliac and femoropopliteal disease: A prospective study. *Circulation* 1987; 76: 1074–1080.
29. Roy B, Ghatak S. Nonlinear methods to assess changes in heart rate variability in type 2 diabetic patients. *Arq Bras Cardiol* 2013; 101: 317–327.
30. Lucini D, Mela GS, Malliani A, *et al*. Impairment in cardiac autonomic regulation preceding arterial hypertension in humans: Insights from spectral analysis of beat-by-beat cardiovascular variability. *Circulation* 2002; 106: 2673–2679.
31. Tarvainen MP, Laitinen TP, Lipponen JA, *et al*. Cardiac autonomic dysfunction in type 2 diabetes - effect of hyperglycemia and disease duration. *Front Endocrinol (Lausanne)* 2014; 5: 130.
32. McFadden JP, Corrall RJ, O'Brien IA. Autonomic and sensory nerve function in diabetic foot ulceration. *Clin Exp Dermatol* 1991; 16: 193–196.
33. Malpas SC, Maling TJ. Heart-rate variability and cardiac autonomic function in diabetes. *Diabetes* 1990; 39: 1177–1181.
34. Xhyheri B, Manfrini O, Mazzolini M, *et al*. Heart rate variability today. *Prog Cardiovasc Dis* 2012; 55: 321–331.
35. Zandstra TE, Notenboom RGE, Wink J, *et al*. Asymmetry and heterogeneity: Part and parcel in cardiac autonomic innervation and function. *Front Physiol* 2021; 12: 665298.

36. Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nat Rev Endocrinol* 2012; 8: 405–416.
37. Hoeldtke RD, Bryner KD, McNeill DR, *et al*. Nitrosative stress, uric acid, and peripheral nerve function in early type 1 diabetes. *Diabetes* 2002; 51: 2817–2825.
38. Bolajoko EB, Mossanda KS, Adeniyi F, *et al*. Antioxidant and oxidative stress status in type 2 diabetes and diabetic foot ulcer. *S Afr Med J* 2008; 98: 614–617.
39. Vouillarmet J, Maucort-Boulch D, Michon P, *et al*. Advanced glycation end products assessed by skin autofluorescence: A new marker of diabetic foot ulceration. *Diabetes Technol Ther* 2013; 15: 601–605.
40. 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.
41. Poirier P, Bogaty P, Garneau C, *et al*. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: Importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 2001; 24: 5–10.