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ORIGINAL RESEARCH

Relationship Between Index of Cardiac Electrophysiological Balance, Frontal QRS-T Angle and Retinopathy in People with Type 2 Diabetes

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Background: Diabetic retinopathy (DR) is strongly associated with cardiovascular disease, which is a risk factor for sudden cardiac death (SCD). The index of cardiac electrophysiological balance (iCEB) and the frontal QRS-T angle are recommended to predict the risk of ventricular arrhythmias more than other ECG parameters. However, the relationships between these two markers and DR have not yet been explored. The aim of this study was to investigate the variation in the iCEB, corrected iCEB (iCEBc) and frontal QRS-T angle in different stages of DR and determine whether there are associations between these markers and DR.

Methods: The sample comprised 665 patients with Type 2 diabetes mellitus (T2DM) who were classified into three groups: no DR (NDR), mild to moderate non-proliferative DR (NPDR), and vision-threatening DR (VTDR). Twelve-lead ECG was performed and the QT, QTc, QRS duration, iCEB, iCEBc and frontal QRS-T angle were recorded and compared across the groups.

Results: The VTDR group had a significantly higher iCEBc and frontal QRS-T angle than the NDR and NPDR groups. After controlling for confounding variables, the correlations between the iCEBc (OR=2.217, 95% CI=1.464–3.358, P<0.001), frontal QRS-T angle (OR=1.017, 95% CI=1.008–1.025, P<0.001) and DR risk remained (P<0.05). Subjects in the fourth iCEBc quartile (adjusted OR=2.612, 95% CI=1.411–4.834, p=0.002) had a much higher chance of developing DR compared to those in the first quartile. In comparison to the first frontal QRS-T angle quartile, subjects in the third (adjusted OR=1.998, 95% CI=1.167–3.422, P=0.012) and fourth (adjusted OR=2.430, 95% CI=1.420–4.160, P=0.001) frontal QRS-T angle quartiles had significantly greater risks of DR.

Conclusion: With the progression of DR, the iCEBc and frontal QRS-T angle increase. An increased iCEBc and frontal QRS-T angle are associated with an increased risk of DR.

Keywords: type 2 diabetes mellitus, diabetic retinopathy, index of cardiac electrophysiological balance, iCEB, frontal QRS-T angle, ventricular arrhythmia

Introduction

Diabetes mellitus (DM) is a serious long-term disease and among the top 10 causes of death in adulthood. According to the International Diabetes Federation, five million people globally died from diabetes in 2017, accounting for 10.7% of all deaths from all causes among people aged 20 to 99 years.[1] Obesity often coexists with diabetes. Previous research has confirmed that obesity is associated with an increased risk of cardiovascular disease.[2] Esben et al[3] found that rapid weight loss can cause cardiac repolarization changes and an increased risk of arrhythmias. Louise et al[4] found that both postprandial hypoglycaemia and hyperglycaemia can affect the QT interval in patients with long QT-syndrome type 2 (LQT2). Thus, patients with LQT2 may be at a further increased risk of cardiac events during glucose fluctuations. Diabetes has been shown to be associated with increased cardiovascular disease mortality and sudden cardiac death (SCD).[5] In patients with diabetes, approximately 50% of deaths from cardiovascular causes are SCD.[6] SCD is defined as

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death within one hour of the onset of acute cardiac symptoms; the main causes of SCD include ventricular tachycardia, ventricular fibrillation and pulseless electrical activity.[7] Several large-scale epidemiological studies have shown that diabetes is an independent risk factor for SCD.[5,8–10] A meta-analysis by Aune et al[11] found that diabetes is associated with a more than two-fold increased risk of SCD in the general population. Moreover, in a population of patients with atrial fibrillation, coronary artery disease, myocardial infarction, heart failure or haemodialysis, the risk of SCD was increased by 75% in patients with diabetes.

Diabetic retinopathy (DR) is one of the most serious and common microvascular complications of diabetes and is an important cause of adult vision loss in developed countries.[12] Jouven et al[13] found a significantly increased risk of SCD in diabetes mellitus patients with microangiopathy (including DR and proteinuria), as compared to those without microangiopathy over a 14-year follow-up. The Tp-e interval, QT interval, QTc interval, Tp-e/QT ratio and Tp-e/QTc ratio are indicators of ventricular arrhythmias.[14–16] However, there is inconsistency in the results of previous studies in relation to the Tp-e interval, QTc interval and Tp-e/QTc ratio in patients with DR.[17,18] Therefore, further research is necessary.

The cardiac wavelength (λ) is an electrophysiological measure of the distance a depolarizing wave travels through a functional nonresponse cycle. It is determined by the product of the conduction velocity (CV) and effective nonresponse cycle (ERP). However, the invasive nature of the measurement of the ERP may limit the use of λ as a screening tool/biomarker in the clinical setting.[19] The index of cardiac electrophysiological balance (iCEB), a new predictor of ventricular arrhythmias, is calculated by dividing the QT interval by the QRS duration (QT/QRS). It is considered a simple and effective non-invasive alternative to the λ.[20] Due to its non-invasive nature and ease of measurement, it has attracted much attention in clinical practice. Recently, the iCEB was found to be a better predictor of arrhythmia risk as compared to the Tp-e interval, QTc interval and Tp-e/QTc ratio.[19]

The frontal QRS-T angle is the angle between the direction of ventricular depolarization and the direction of repolarization. It is a novel marker of ventricular repolarization heterogeneity. Abnormal prolongation of ventricular repolarization markers predicts an increased risk of ventricular arrhythmias.[21] The frontal QRS-T angle can be obtained directly from automated ECG reports and is easier to calculate in clinical practice than the more complex spatial QRS-T angle.[22] Among the various ECG markers, the frontal QRS-T angle is the most powerful predictor of cardiovascular death, all-cause mortality[23] and SCD.[24] Previous studies have revealed that the frontal QRS-T angle is wider in patients with diabetes than in those without diabetes;[25] however, the relationship between the QRS-T angle and DR has not yet been reported.

The pathogenesis of DR is intricate, sharing some of the pathophysiological mechanisms implicated in cardiovascular diseases, such as a dysfunction of the endothelium, chronic inflammation, oxidative stress, increased late glycosylation end products, neovascularization and hypercoagulable states.[26–28] Additionally, known cardiovascular risk factors, such as hyperglycaemia, hyperlipidaemia, hypertension and diabetic nephropathy (DN), are also risk factors for the progression of DR.[29] However, the relationships between DR and the iCEB, corrected iCEB (iCEBc) and frontal QRS-T angle have not yet been explored. Thus, the purpose of this study was to investigate the changes in the iCEB, iCEBc and frontal QRS-T angle at different stages of DR and to identify whether the above indicators are associated with the occurrence of DR.

Materials and Methods

Subjects

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University. Written informed consent was obtained from all participants. The sample comprised 665 individuals with type 2 diabetes (T2DM). All subjects were hospitalized in the Department of Endocrinology at the First Affiliated Hospital of Harbin Medical University from June 2016 to October 2022. The inclusion criteria for this study were as follows: (1) diagnosis of T2DM in accordance with the 1999 World Health Organization criteria,[30] (2) sinus rhythm, (3) heart rate between 60–100 bpm, (4) 12-lead ECG on admission, (5) completed fundus photography and optical coherence tomography (OCT). If fundus photography was unable to clarify

DR staging, a further fundus fluorescein angiography (FFA) examination was performed. The exclusion criteria were as follows: (1) history of coronary artery disease, (2) previous history of pacemaker implantation, (3) various arrhythmias, such as congenital long QT syndrome, bradycardia, tachycardia, atrial fibrillation, atrial flutter or cardiac conduction abnormalities, (4) cancer, (5) abnormal thyroid function test, (6) chronic liver disease, (7) chronic renal failure, (8) abnormal electrolyte values, (9) taking antiarrhythmic drugs, antipsychotic drugs, antihistamines or beta-blockers, (10) severe cataract, glaucoma or other eye disease affecting the diagnosis of DR.

Collection of Basic Information and Laboratory Tests

Relevant demographic information was obtained and recorded for all patients, including age, gender, disease duration, use diabetes treatment combination of insulin and oral medication, history of smoking and history of hypertension. All included patients had their weight and height measured, and their body mass index (BMI) was calculated as the ratio of their weight to the square of their height (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by a research nurse. The subjects were fasted for more than 10 hours before blood samples were collected for the measurement of glycated haemoglobin (HbA1c), fasting blood glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C). Blood samples were collected at 6:00 am by a research nurse.

Related Diagnostic Criteria

Diabetic nephropathy (DN) is a clinical diagnosis based on a persistent increase in the urinary albumin/creatinine ratio (UACR). Specifically, the clinical diagnosis of DN is made based on a random urine UACR $\geq$ 30 mg/g, with the exclusion of other chronic kidney diseases.[31]

The diagnostic criteria for diabetic peripheral neuropathy (DPN) are as follows: a clear history of diabetes, clinical symptoms consistent with the presentation of DPN, and the exclusion of neuropathy from other aetiologies. The signs of DPN include a diminished or absent ankle reflex and pins and needles, vibration, pressure and/or temperature pain. The clinical symptoms include bilateral distal symmetric limb pain, numbness and abnormal sensations. Diabetic patients with neurological symptoms and one or more positive signs can be clinically diagnosed with DPN; if there are no clinical symptoms, two or more positive signs can also be used for the clinical diagnosis of DPN.[32]

A fundus examination was performed based on fundus photographs, OCT and FFA. The severity of DR was assessed using the modified Airlie House classification. Subjects in this study were divided into three groups: no diabetic retinopathy (NDR), mild to moderate non-proliferative diabetic retinopathy (NPDR), and vision-threatening diabetic retinopathy (VTDR). VTDR is considered to consist of severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and/or clinically significant macular oedema (CSME). CSME was defined as oedema or hard exudate within 500 mm of the central macular recess.[33] If the severity assessments obtained from the two eyes were inconsistent, the assessment for the worst eye was used for the analysis. If an assessment could not be performed for one eye, the other eye was used. Two ophthalmologists from the First Affiliated Hospital of Harbin Medical University diagnosed DR; a third ophthalmologist was consulted in the case of differing diagnoses between the two ophthalmologists.

ECG Measurement

A 12-lead resting ECG was performed using an ECG machine (ECG-2360, Nihon Kohden Co, Tokyo, Japan). The QRS duration and QT interval were calculated from the ECG data. The QT interval is the amount of elapsed time between the beginning of the QRS wave and the termination of the T wave. The QTc interval was computed based on Bazett's formula ($QTc = QT/ [RR]^{1/2}$). A prolonged QTc interval is defined as $\geq$ 440 ms. The ECG measurements in this study were performed by two independent cardiovascular physicians who were blind to the participants' clinical information. The frontal QRS angle was obtained from the automated ECG report. The frontal QRS-T angle is equal to the absolute value of the QRS electrical axis minus the T electrical axis, or 360° minus the above result if the value of the above result is > 180°. A frontal QRS-T angle $\geq$ 73° in men and $\geq$ 67° in women is considered abnormal.[34] The iCEB was calculated

as follows: QT/QRS. The iCEBc was calculated as follows: QTc/QRS. Finally, the QT and QTc intervals and the iCEB, iCEBc and frontal QRS-T angle were recorded.

Statistical Analysis

Statistical analyses were performed using SPSS 26. The Kolmogorov–Smirnov test was used to examine the normality of continuous numerical variables. Non-normally distributed continuous numerical variables are presented as the median (interquartile range) [M (P25, P75)], and the Kruskal–Wallis H-test was utilized for the comparison of multiple groups while the Kruskal–Wallis one-way ANOVA (k samples) was used for pairwise comparisons between groups. Categorical variables are expressed as percentages, and between-group comparisons of categorical variables were performed using the chi-square test. The associations between the iCEBc, frontal QRS-T angle and other variables were examined with Spearman correlation analysis. For univariate and multifactorial analyses, binary logistic regression analysis was performed.

Results

Comparison of the Characteristics of the Participant Groups

A total of 665 patients were enrolled in this study, including 287 in the NDR group, 131 in the NPDR group, and 247 participants in the VTDR group. Compared to the NDR group, patients in the DR group had a longer disease duration, higher prevalence of DPN and DN, higher use of insulin in combination with oral medication, and higher HbA1c, FPG, SBP and BMI ($P<0.05$). Further, disease duration, DN, use of insulin in combination with oral medication and HbA1c significantly differed between the VTDR and the mild to moderate NPDR groups ($P<0.05$). Subjects in the VTDR group were more likely to have a higher prevalence of hypertension and higher TG and TC, as compared to subjects in the mild to moderate NPDR group ($P<0.05$). However, there was no significant difference between the mild to moderate NPDR and NDR groups ($P>0.05$). Additionally, the other variables did not significantly differ among the three groups (all $P>0.05$) (Table 1).

Table 1 Comparison of General and Clinical Data of Study Subjects

Variables	NDR	Mild to Moderate NPDR	VTDR	*P*
N	287	131	247	
Sex, % male	193(67.2)	83(63.4)	151(61.1)	0.331
Age, years	57(51–62)	57(49–63)	56(48–62)	0.397
Duration of diabetes, years	6(2–12)†	10(5–17)§	13(7–20)*	<0.001
Hypertension, % yes	111(38.7)	57(43.5)§	138(55.9)*	<0.001
Peripheral neuropathy, % yes	114(39.7)†	83(63.4)	160(64.8)*	<0.001
Diabetic nephropathy, % yes	13(5.8)†	35(18.9)§	65(33.7)*	<0.001
Diabetes treatment, % combine insulin +oral medication	129(45.1)†	79(60.3)§	207(83.8)*	<0.001
Current smoker, n %	86(30.0)	38(29.0)	67(27.1)	0.767
HbA1c, %	7.6(6.8–9.1)†	8.2(7.1–9.9)§	9.1(7.8–10.5)*	<0.001
Fasting blood glucose, mmol/L	7.52(6.35–9.13)†	8.06(6.59–10.47)	8.92(6.65–11.60)*	<0.001
TC, mmol/L	4.66(4.12–5.37)	4.62(3.96–5.32)§	4.97(4.30–6.06)*	<0.001
TG, mmol/L	1.58(1.08–2.37)	1.53(1.20–2.11)§	1.88(1.32–3.25)*	<0.001
HDL-C, mmol/L	1.13(0.97–1.36)	1.15(0.97–1.29)	1.10(0.93–1.31)	0.321
LDL-C, mmol/L	2.93(2.45–3.40)	2.82(2.40–3.27)	3.01(2.39–3.75)	0.089
SBP, mmHg	131(120–141) †	140(125–154)	140(127–152) *	<0.001
DBP, mmHg	80(73–87)	80(74–89)	80(74–89)	0.632
BMI, kg/m^2	23.94(22.49–25.39) †	25.10(23.14–27.55)	25.26(23.67–27.12) *	<0.001

Notes: Data are expressed as n (%) and median (25 and 75 interquartile). No DR group vs Mild to moderate NPDR group, †Represents $p<0.05$. Mild to moderate NPDR group vs VTDR group, §Represents $p<0.05$. No DR group vs VTDR group, *Represents $p<0.05$.

Abbreviations: TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

ECG Indicators

The QTc interval, iCEBc and frontal QRS-T angle were significantly increased in the VTDR group compared to the NDR and NPDR groups (all P<0.05). There was an increase in iCEB in the VTDR group as compared to the NDR group, but no significant difference between the mild to moderate NPDR and VTDR groups (P>0.05). Compared with the NDR patients, the DR patients had a prolonged QTc interval and an increased rate of widened frontal QSR-T angle, but there was no statistically significant difference between the mild to moderate NPDR and VTDR groups (P>0.05) (Table 2).

Associations Between DR, iCEBc, Frontal QRS-T Angle and the Other Variables

Table 3 shows that the associations between DR, iCEBc, frontal QRS-T angle and the other variables respectively. Spearman correlation analysis showed that the duration of disease (r= 0.325, P < 0.001), FPG (r= 0.177, P < 0.001), HbA1c (r= 0.207, P < 0.001), BMI (r= 0.248, P < 0.001), TC (r= 0.083, P < 0.05), SBP (r= 0.211, P < 0.001), QTc interval (r=0.301, P<0.001), iCEBc (r=0.205, P<0.001) and frontal QRS-T angle (r=0.217, P<0.001) were significantly and positively associated with DR. Age (r=0.114, P<0.05), disease duration (r=0.144, P<0.05), HbA1c (r=0.127, P<0.05), TC (r=0.078, P<0.05) and SBP (r=0.083, P<0.05) were significantly positively associated with iCEBc (Table 3). FPG

Table 2 Comparison of Electrocardiographic Indices of Participants

Variables	NDR	Mild to Moderate NPDR	VTDR	*P*
QT interval, ms	376(360–392)	380(364–396)	374(358–398)	0.297
QTc interval, ms	420(405–435)†	430(415–445)§	434(423–452)*	<0.001
Prolonged QTc interval, n %	53(18.5)†	41(31.3)	98(39.7)*	<0.001
QRS, ms	94(86–100)	94(84–100)	92(84–98)	0.102
iCEB	4.06(3.75–4.33)	4.13(3.77–4.47)	4.10(3.82–4.56)*	0.035
iCEBc	4.50(4.18–4.91)†	4.64(4.30–5.11)§	4.76(4.41–5.21)*	<0.001
Frontal QRS-T angle, °	16(9–30)†	22(9–47)§	30(15–49)*	<0.001
Widened frontal QRS-T angle, n %	41(14.3)†	33(25.2)	70(28.3)*	<0.001

Notes: Data are expressed as n (%) and median (25 and 75 interquartile). No DR group vs Mild to moderate NPDR group, †Represents p<0.05. Mild to moderate NPDR group vs VTDR group, §Represents p<0.05. No DR group vs VTDR group, *Represents p<0.05. Prolonged QTc interval was defined as ≥ 440ms, widened frontal QRS-T angle was defined as ≥73° in men and ≥67° in women.
Abbreviations: QTc interval, corrected QT interval; iCEB, index of cardiac electrophysiological balance; iCEBc, corrected index of cardiac electrophysiological balance.

Table 3 Associations Between DR, iCEBc, Frontal QRS-T Angle and the Other Variables

Variables	DR		iCEBc		Frontal QRS-T Angle	
	r	*P*	r	*P*	r	*P*
Age, years	−0.024	0.532	0.114	0.003	0.013	0.728
Duration of diabetes, years	0.325	<0.001	0.144	<0.001	0.035	0.362
Fasting blood glucose, mmol/L	0.177	<0.001	0.066	0.088	0.140	<0.001
HbA1c, %	0.270	<0.001	0.127	0.001	0.108	0.005
BMI, kg/m^2	0.248	<0.001	−0.014	0.291	0.067	0.084
TC, mmol/L	0.083	0.003	0.078	0.045	0.052	0.343
TG, mmol/L	0.099	0.143	0.057	0.143	0.037	0.143
HDL-C, mmol/L	−0.040	0.302	0.105	0.054	−0.005	0.901
LDL-C, mmol/L	0.025	0.516	0.064	0.098	0.034	0.384
SBP, mmHg	0.211	<0.001	0.083	0.033	0.131	0.001
DBP, mmHg	0.037	0.343	0.079	0.052	0.084	0.003
QTc interval, ms	0.301	<0.001				
iCEBc	0.205	<0.001				
Frontal QRS-T angle, °	0.217	<0.001				

Abbreviations: TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; QTc interval, corrected QT interval; iCEBc, corrected index of cardiac electrophysiological balance.

(r=0.140, P<0.001), HbA1c (r=0.108, P<0.05), SBP (r=0.131, P<0.05) and DBP (r=0.084, P<0.05) were significantly positively associated with the frontal QRS-T angle (Table 3).

Relationships Between DR, iCEBc and the Frontal QRS-T Angle

As shown in Table 4, without adjusting for confounders (Table 4, model 1), both the iCEBc (OR=2.284, 95% CI=1.696–3.077, P<0.001) and frontal QRS-T angle (OR=1.020, 95% CI=1.013–1.027, P<0.001) were correlated with DR. In model 2, with adjustment for confounding variables, iCEBc (OR=2.135, 95% CI=1.447–3.150, P<0.001), frontal QRS-T angle (OR=1.020, 95% CI=1.011–1.028, P<0.001) and DR risk were still correlated. After further adjustment for confounding variables in model 3, the iCEBc (OR=2.217, 95% CI=1.464 −3.358, P<0.001) and frontal QRS-T angle (OR=1.017, 95% CI=1.008–1.025, P<0.001) remained correlated with DR risk (P<0.05) (Table 4). Logistic regression analysis was then performed with gender stratification and the inclusion of all confounders. The results revealed that the iCEBc was associated with DR in both male patients (OR=2.090, 95% CI=1.244–3.512, P=0.005) and female patients (OR=3.227, 95% CI=1.436–7.253, P=0.005); in the analysis of the association between the frontal QRS-T angle and DR, the frontal QRS-T angle was also associated with DR in both male patients (OR=1.013, 95% CI=1.003–1.023, P=0.011) and female patients (OR=1.028, 95% CI=1.009–1.048, P=0.004) (Table 4).

Correlations Between DR and the iCEBc and Frontal QRS-T Angle Quartiles

Subjects were classified into four groups according to the quartiles of iCEB and frontal QRS-T angle. We classified iCEB levels into four categories based on quartiles: first quartile ≤4.28, second quartile 4.29–4.63, third quartile 4.64–5.05, fourth quartile ≥5.06; and the frontal QRS-T angle was also grouped into four groups according to the quartiles: first quartile ≤10°, second quartile 11–30°, third quartile 31–40°, fourth quartile ≥41°. The findings revealed that the incidence of DR increased with increases in both the iCEBc and frontal QRS-T angle quartiles (all P<0.001; Figures 1 and 2). In the multifactorial logistic regression analysis (Table 5), subjects in the fourth iCEBc quartile had a statistically significant increased risk of DR (adjusted OR=2.612, 95% CI=1.411–4.834, p=0.002) compared to subjects in the first quartile.

Table 4 Logistic Regression Analysis of Frontal QRS-T Angle and iCEBc with DR Risk

Model	OR	95%CI	*P*
iCEBc			
Model 1	2.284	1.696 –3.077	<0.001
Model 2	2.135	1.447–3.150	<0.001
Model 3	2.217	1.464–3.358	<0.001
Model 4			
Male	2.090	1.244–3.512	0.005
Female	3.227	1.436 –7.253	0.005
Frontal QRS-T angle			
Model 1	1.020	1.013–1.027	<0.001
Model 2	1.020	1.011–1.028	<0.001
Model 3	1.017	1.008 –1.025	<0.001
Model 4			
Male	1.013	1.003 –1.023	0.011
Female	1.028	1.009–1.048	0.004

Notes: iCEBc, corrected index of cardiac electrophysiological balance; model 1: Crude model; model 2: adjusted for age, sex, diabetes duration, hypertension, current smoker, peripheral neuropathy, diabetic nephropathy and use of combined diabetes treatment; model 3: additionally adjusted for SBP, DBP, BMI, HbA1c, FPG, TC, TG, HDL and LDL at the base of model 2. Model 4 is stratified according to gender.

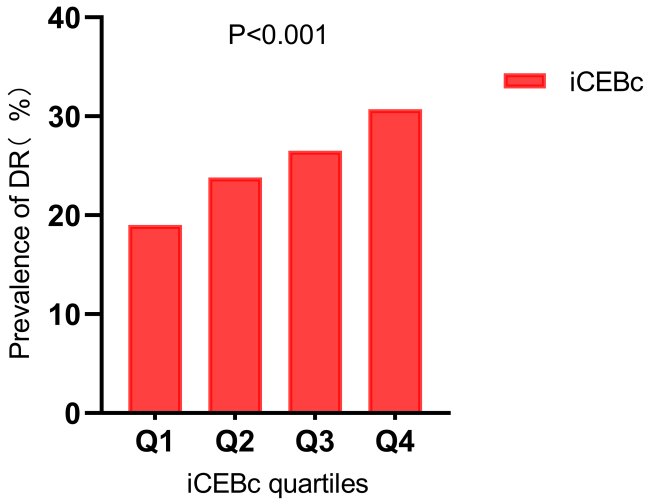

Figure 1 Relationship between iCEBc quartiles and the prevalence of DR.

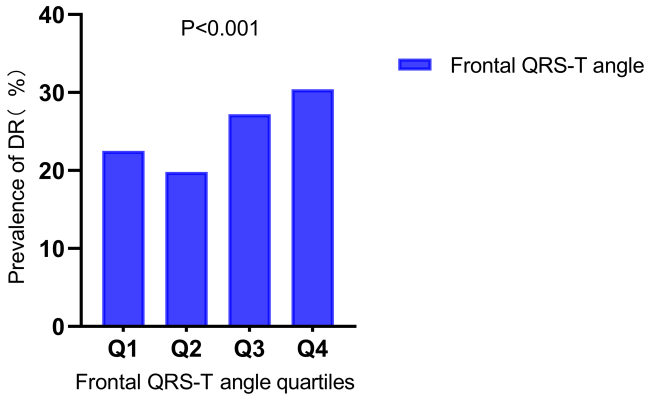

Figure 2 Relationship between frontal QRS-T angle quartiles and the prevalence of DR.

Further, compared to the first quartile of the frontal QRS-T angle, subjects in the third (adjusted OR= 1.998, 95% CI=1.167–3.422, P=0.012) and fourth (adjusted OR=2.430, 95% CI=1.420–4.160, P=0.001) quartiles had significantly increased risks of DR.

Table 5 Correlation Analysis of Quartiles of iCEBc and Frontal QRS-T Angle with DR Risk

Variables	Prevalence of DR (%)	Univariate			Multivariate		
		OR	95% CI	P	OR	95% CI	P
iCEBc							
Q1, ≤4.28	72(19.0)	Reference		<0.001	Reference		0.016
Q2, 4.29–4.63	90(23.8)	1.526	0.990 –2.351	0.055	1.248	0.725–2.149	0.424
Q3, 4.64–5.05	100(26.5)	1.978	1.278–3.062	0.002	1.743	0.996 –3.053	0.052
Q4,≥5.06	116(30.7)	3.029	1.928–4.759	<0.001	2.612	1.411–4.834	0.002
Frontal QRS-T angle, °							
Q1, ≤10	85(22.5)	Reference		<0.001	Reference		0.002
Q2, 11–23	75(19.8)	1.106	0.720–1.698	0.646	1.067	0.627–1.814	0.811
Q3, 24–40	103(27.2)	1.967	1.280 –3.021	0.002	1.998	1.167–3.422	0.012
Q4,≥41	115(30.4)	2.790	1.789–4.352	<0.001	2.430	1.420 –4.160	0.001

Note: iCEBc, corrected index of cardiac electrophysiological balance.

Discussion

This study is the first to assess the associations between DR and both the iCEBc and frontal QRS-T angle. The findings demonstrated that 1) with the progression of DR, the iCEBc and frontal QRS-T angle gradually increase, and the percentage of individuals with an abnormal widening of the frontal QRS-T angle is significantly increased, suggesting a possible increased risk of ventricular arrhythmias; 2) An increased iCEBc and frontal QRS-T angle are associated with an increased risk of DR.

The iCEB is a new predictor of ventricular arrhythmias; it reflects the balance between ventricular depolarization and repolarization. The cardiac wavelength λ is an electrophysiological measurement, and since the iCEB can respond to the cardiac wavelength, significant changes in iCEB may reflect cardiac electrophysiological imbalances, and therefore, may predict arrhythmias. The iCEB provides information on the depolarization and repolarization phases of the cardiac action potential, and thus, is a better predictor of arrhythmia risk than the Tp-e interval, Tp-e/QT ratio and QT interval, which only reflect repolarization.[19]

The frontal QRS-T angle is a new marker of ventricular repolarization heterogeneity. A recent study showed that the frontal QRS-T angle is a suitable alternative for risk prediction to the spatial QRS-T angle.[34] May et al found that the predictive value of the QRS-T angle for long-term mortality in diabetes mellitus patients was equivalent to that of cardiovascular autonomic neuropathy and that a larger frontal QRS-T angle was a powerful long-term predictor of all-cause mortality in diabetes.[35]

Our research revealed that the QTc interval was progressively prolonged with increasing severity of DR. Erken Pamukcu et al[17] used the International Clinical Diabetes Retinopathy Disease Severity scale of the American Academy of Ophthalmology to grade patients into mild NPDR, moderate NPDR and severe NPDR/ proliferative DR (PDR), and found no significant difference in the QTc interval between the NDR, NPDR and PDR groups; however, this study was limited by the small sample of PDR patients. Kobayashi et al[18] classified the severity of DR according to Davis' criteria[36] and found that the QTc interval was significantly prolonged when DR reached the proliferative phase. Different criteria for DR classification and different ethnicities of the subjects may explain the differences in the results. Thus, more research is needed.

Our study also revealed that the frontal QRS-T angle and iCEBc were significantly positively correlated with HbA1c and SBP, which both play a role in the occurrence and development of DR. The pathophysiological mechanisms underlying the increased risk of ventricular arrhythmias in patients with DR may include the following: (1) the pathogenesis of DR includes an inflammatory response, and inflammation can cause extensive endothelial dysfunction and reduced vascular nitric oxide (NO) bioavailability. Decreased NO can lead to suppression of Ca^{2+}-adenosine triphosphatase and K^{+}/Na^{+}-adenosine triphosphatase enzyme activities in cardiomyocytes and increased cytoplasmic free calcium, which leads to prolonged myocardial repolarization,[37] as evidenced by a prolonged QTc and increased frontal QRS-T angle. (2) Excessive production of oxygen radicals leads to impaired function of proteins involved in excitation-contraction coupling; Ca^{2+} ATPase (SERCA2a) in the sarcoplasmic reticulum exhibits a high oxidation rate, and the reuptake of Ca^{2+} by SERCA2a is reduced, resulting in elevated Ca^{2+} levels and changes in intracellular Ca^{2+} homeostasis, thus triggering ventricular arrhythmias.[38,39]

In our study, there was no difference in QRS waves among the groups, thus, the iCEBc was mainly dependent on differences in the QTc interval. There were significant differences in the iCEBc and frontal QRS-T angle among the DR groups. Logistic regression analysis revealed that the frontal QRS-T angle and iCEBc were associated with DR. All subjects in this study underwent a comprehensive eye examination, and thus, the diagnosis of DR was accurate. ECG is a simple, convenient and non-invasive test. All T2DM patients admitted to the Endocrinology Department are routinely screened with ECG; therefore, the iCEB and frontal QRS-T angle can be used for clinical DR screening. Patients with VTDR also had a more pronounced increase in the iCEBc and frontal QRS-T angle, suggesting that these indices may have some clinical significance in determining the severity of DR. DR is one of the most typical microvascular complications of diabetes, and its presence is closely related to cardiovascular autonomic neuropathy (CAN) in diabetes.[40] The presence of diabetic autonomic neuropathy accelerates or worsens DR, with impaired haemodynamics/ autoregulation and abnormal parasympathetic/sympathetic balance due to diabetic autonomic neuropathy.[42] Previous

studies have also found that the QTc interval and QRS-T angle are associated with diabetic autonomic neuropathy.[41,43] However, there is also evidence of autonomic dysregulation in prediabetes, especially involving the cardiovascular system.[44] Loss of the parasympathetic vagus nerve leads to sympathetic overactivity which, in turn, may lead to arrhythmias by prolonging the QT interval.[42]

At present, the pathogenesis of DR is unclear and the mechanism of abnormalities in myocardial repolarization parameters and the electrophysiological balance index is still unclear. The correlations between these parameters and DR may reflect a common or similar pathogenesis. For example, (1) hyperglycaemia causes an increase in metabolic pathways such as the polyols and hexosamine pathways, which induces oxidative stress as well as inflammatory responses; these are common pathogenic mechanisms underlying chronic complications such as microvascular and macrovascular diabetes. The upregulation of inflammatory factors can simultaneously promote myocardial hypertrophy, fibrosis and electrophysiological remodelling.[45–47] (2) Hypertension is positively correlated with DR. Hypertension can lead to increased retinal blood flow, and retinal hyperperfusion is closely associated with capillary shear injury in DR.[48] On the other hand, hypertension can lead to enhanced renin-angiotensin system activity, and Ang II activation of the angiotensin receptor 1 (AT-1) can promote vascular smooth-muscle cell senescence and endothelial dysfunction, thereby mediating myocardial remodelling and myocardial hypertrophic fibrosis.[49]

This study has several limitations that should be noted. First, this was a cross-sectional study, and no causal inferences can be made with respect to the relationships between the ECG metrics and DR. Second, asymptomatic patients with atherosclerosis and DR were not excluded; it is not clear whether asymptomatic myocardial ischemia could also prolong ECG indices. Third, this was a retrospective study. Prospective studies are needed in the future to investigate changes in ECG indicators before and after the onset of retinopathy.

Conclusions

With the progression of DR, the iCEBc and frontal QRS-T angle increased, and the proportion of patients with an abnormally wide frontal QRS-T angle increased, which may place these patients at increased risk of ventricular arrhythmias. Meanwhile, clinicians should be alert to the occurrence of DR, and especially VTDR, in diabetes patients who have an increased iCEBc and frontal QRS-T angle during ECG examination.

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Disclosure

The authors report no conflicts of interest in this work.

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