ORIGINAL ARTICLE

Changes of Virtual Planar QRS and T Vectors Derived from Holter in the Populations with and without Diabetes Mellitus

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Aims: Research related to type 2 diabetes mellitus (DM) and parameters of electrocardiography (ECG) was limited. Patients with and without DM (NDM) were randomly enrolled in a study to exploit the influence of DM on planar QRS and T vectors derived from the Virtual Holter process.

Methods: A total of 216 (NDM) and 127 DM patients were consecutively and randomly recruited. We selected a 1-minute length of ECG, which was scheduled for analysis at 4 AM. After a series of calculating algorisms, we received the virtual planar vector parameters.

Results: Patients with DM were elderly (65.61 ± 12.08 vs 59.41 ± 16.86 years, P < 0.001); higher morbidity of hypertension (76.38% vs 58.14%, P < 0.001) and coronary artery disease (44.09% vs 32.41%, P = 0.03); thicker interventricular septum (10.92 ± 1.77 vs 10.08 ± 1.96 mm, P < 0.001) and left ventricular posterior wall (9.84 ± 1.38 vs 9.39 ± 1.66 mm, P = 0.03); higher lipid levels and average heart rate (66.67 ± 12.04 vs 61.87 ± 13.36 bpm, P < 0.01); higher angle of horizontal QRS vector (HQRSA, –2.87 ± 48.48 vs –19.00 ± 40.18 degrees, P < 0.01); lower maximal magnitude of horizontal T vector (HTV, 2.33 ± 1.47 vs 2.88 ± 1.89 mm, P = 0.01) and maximal magnitude of right side T vector (2.77 ± 1.55 vs 3.27 ± 1.92 mm, P = 0.03), and no difference in angle of frontal QRS-T vector (FQRSTA, 32.77 ± 54.20 vs 28.39 ± 52.87 degrees, P = 0.74) compared with patients having NDM. After adjusting for confounding factors, DM was significantly effective on FQRSTA (regression coefficient –40.0, 95%CI –66.4 to –13.6, P < 0.01), HQRSA (regression coefficient 22.6, 95%CI 2.5 to 42.8, P = 0.03), and HTV (regression coefficient 0.9, 95%CI 0.2 to 1.7, P = 0.01). Confounding

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factors included: sex, 2-hour postprandial blood glucose, smoking, triglyceride, apolipoprotein A, creatinine, left ventricular ejection fraction, and average heart rate.

Conclusions: The risk factors of DM and lipid metabolism abnormality particularly apolipoprotein A significantly modified parameters of virtual planar QRS and T vector, including frontal QRS-T angle.

There are approximately 40 million people with diabetes mellitus (DM) in China. The abnormal glucose metabolism due to DM may induce cardiomyopathy and lead to changes on the echocardiography (ECG). In previous research, the effects of DM on ECG were concentrated in heart rate variability,[1–6] RR interval,[6] T-wave alternans,[7] QTc interval,[8–10] and ST segment,[11] which are predictive of cardiac mortality and diagnosis of silent myocardial infarction in DM. Recent reports showed that the maximal magnitude of frontal QRS-T angle (FQRSTA) was significantly associated with the prognosis of elderly patients,[12] myocardial infarction,[13–17] heart failure,[17] and chronic dialysis.[18–20]

There was no report about the influence of DM on the virtual planar QRS vector, T vector, and FQRSTA, derived from a Holter monitor. In this study, we randomly enrolled several patients with and without type 2 DM (NDM) in order to exploit the influence of DM on planar QRS and T vector virtually derived from Holter.

MATERIALS AND METHODS

Subjects

All consecutive patients who had gone through 24-hour Holter tests between May 2013 and May 2014 were randomly selected. This population included 216 of NDM and 127 of type 2 DM cases. The diagnosed criteria of type 2 DM was according to standards of medical care in diabetes as follows: HbA1c ≥6.5%, was performed in a laboratory using a method that was NGSP-certified and standardized to the DCCT; fasting plasma glucose ≥7.0 mmol/L and fasting was defined as no caloric intake for at least 8 hours; 2-hour postprandial plasma glucose ≥11.1 mmol/L during OGTT and the test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; for patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥11.1 mmol/L should be performed.[21, 22]

All the data were digitally recorded in a central computerized database. The database included demographics, comprehensive clinical data, diagnoses and findings from all laboratory tests undertaken at a single centralized laboratory of the First Affiliated Hospital of Jinan University. The designs and schemes of this study were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Jinan University. All information pertaining to this population was anonymized and deidentified prior to analysis.

Echocardiographic Measurements

Standard comprehensive two-dimensional and Doppler echocardiographic examinations were performed using commercially available systems. Cardiac chamber quantification by two-dimensional ECG was performed according to guidelines provided by the American Society of Echocardiography. Left ventricle diameters were measured using two-dimensional ECG according to the recommended criteria. Thickness of the interventricular septum and left ventricle posterior wall were measured at end-diastole. Left ventricular ejection fraction was calculated by the following equation: 100 × (end-diastolic volume-end-systolic volume)/end-diastolic volume. For assessing conventional diastolic parameters, left atrial volume was measured by Simpson's biplane method.[23, 24]

Vectorcardiogram Algorisms

ECG Analysis

For the purpose of this study, a 12-lead ECG was recorded in a 24-hour Holter (Biomedical Instruments, Shenzhen, China). In order to avoid the interference of exercise and emotional factors, we selected a 1-minute length of ECG at 4 AM for analysis. All ECG records were automatically analyzed, edited, and manually confirmed. All ectopic beats, interference, and artifacts were detected. After a series of calculating algorisms, we obtained the virtual planar vector parameters.

Figure 1. Wave filtering.

Wave Filtering

By taking three consecutive cardiac beats as the smallest unit of measurement, the baseline drift was corrected and filtered first for each minute ECG before calculating minute mean ECG. The baseline of the three consecutive cardiac beats was straightened by a noninvasive filter in order to remove artifacts, while ensuring QRS waveform distortion. The high frequency signal (>40 Hz) was removed by means of a low-pass filter after baseline drift (Fig. 1).

Rules for Selecting Cardiac Beats

First, abnormal cardiac beats were excluded; these exclusions consisted of ectopic beats, interference, and artifacts. In addition, interference of sinus beats by ectopic beats was excluded in calculations before and after abnormal cardiac beats. (Fig. 2).

Second, differences between RR intervals of candidate sinus beats and mean RR intervals of the minute sinus beats were required to be less than 15%. This was to ensure the consistency in cardiac waveform of median wave in the subsequent calculation.

Calculations of Minute Median Wave

Median wave was computed in each lead; algorisms are as follows: First, waveform data were obtained from the minute ECG after filtering. Each effective cardiac beat served as 350 and 650 ms before and after QRS wave, respectively, meaning that the waveform data length was 1000 ms, so that each waveform data could include complete P, QRS, and T wave. The values of waveforms in the same position were arranged in order, from big to small, or small to big, and then the value of

intermediate position was taken as median wave (Fig. 3). Algorisms are as follows:

beat1: S_{11}, S_{12}, S_{13}, S_{14} ...
beat2: S_{21}, S_{22}, S_{23}, S_{24}, ...

. . .

Median values:

S_{11}, S_{21}, S_{31}, S_{41}, ...-> M_1
S_{12}, S_{22}, S_{32}, S_{42}, ...-> M_2
S_{13}, S_{23}, S_{33}, S_{43}, ...-> M_3
. . . .
Median waveform: M_1, M_2, M_3, ...

Note: S_{ij} represented as the j sample point for the i cardiac beat. M_i was the i sample point of median waveform.

Twelve-Lead ECG Converted into Frank Lead

The 12-lead ECG was converted into three orthogonal ECG, using the following formula:[25,26]

$$X = -0.172V_1 - 0.074V_2 + 0.122V_3 + 0.231V_4$$
$$+ 0.239V_5 + .194V_6 + 0.156I - 0.010II$$

$$Y = 0.057V_1 - 0.019V_2 - 0.016V_3 - 0.022V_4$$
$$+.041V_5 + 0.048V_6 - 0.227I - 0.887II$$

$$Z = -0.229V_1 - 0.310V_2 - 0.246V_3 - 0.063V_4$$
$$+ 0.055V_5 + 0.108V_6 + 0.022I + 0.102II$$

Measurements

The median waveform was measured from X, Y, and Z leads, and the parameters were obtained as follows: starting point, peak and end point of P wave, QRS wave, and T wave (Fig. 4). Then
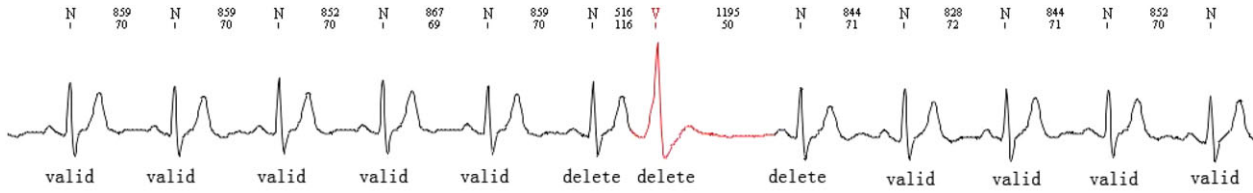
Figure 2. Selecting cardiac beats.
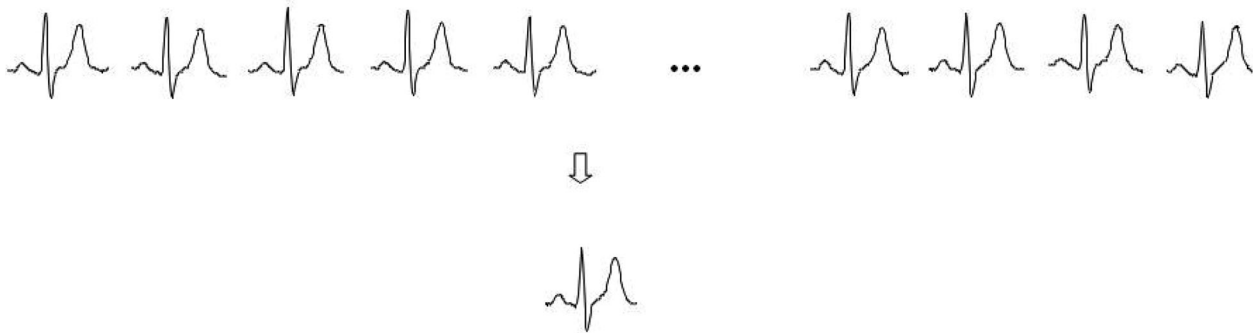
Figure 3. Median wave.
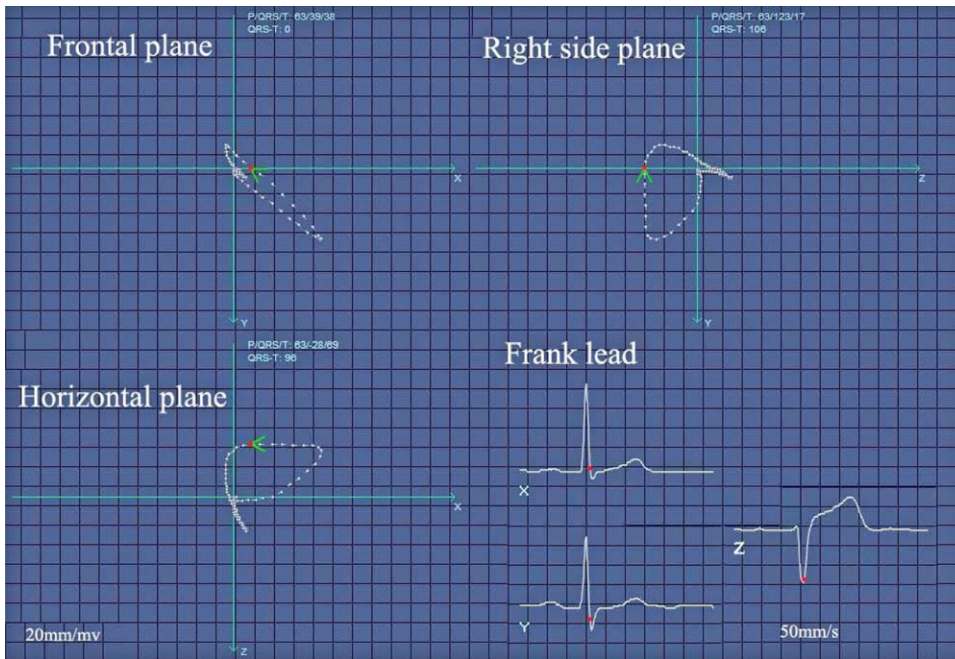
Figure 4. Virtual vectors

the parameters of vector in frontal, horizontal, and right side planes were calculated as positions, maximal magnitudes, and angles of longest axis of P, QRS, and T vectors. In our study, we only analyzed the characters of QRS and T vector. The virtual vectors were converted by Frank leads, and the orientation angles in principal planes were defined as follows: frontal plane, 0° as left, +90° as inferior, −90° as superior and ±180° as right; Horizontal plane, 0° as left, +90° as anterior, −90° as posterior and ±180° as right; Right side plane, 0° as anterior, +90° as inferior, −90° as superior

and ±180° as posterior. Finally, we obtained maximal magnitude of frontal/horizontal/right side QRS vector, which were abbreviated as FQRSV, HQRSV, and RSQRSV; the angles of maximal QRS and T vector in frontal/horizontal/right side planes, which were abbreviated as FQRSTA,HQRSTA, and RSQRSTA; angles of maximal QRS vector and the X-axis in frontal/horizontal/right side planes, such as FQRSA, HQRSA, and RSQRSA; angles of maximal T vector and the X-axis in frontal/horizontal/right side planes, which were abbreviated as FTA, HTA, and RSTA.

STATISTICAL ANALYSIS

Continuous data were expressed as mean ± SD and compared with the two-tailed student's t-test for unpaired data. Categorical data were compared using the chi-square test. Single factor model and basic model were used to screen covariates. Single factor model: Y = C (covariates to be checked) + F (fixed and variables to be adjusted); the factors were put into the model to adjust for covariates, and check the P value. The basic model: Y = X (risk factors) + F (fixed and variables to be adjusted); potential covariates were then added for inspection and replacements were added one by one. Selection criteria: a covariate in the single factor model and the P value <0.20; after adding covariates in the basic model, changes in risk factor regression coefficients were ≥10%. Model 1 was adjusted for sex and age only, while model 2 was adjusted for sex, age, and covariates that had been screened. Relationships between factors and virtual planar parameters were analyzed with multiple regression equations, using the generalized estimating equation with or without the covariates, after sex and age adjustments were fixed. All statistical analyses were performed using Empowerstata software. P values ≤0.05 indicated statistical significance.

RESULTS

Baseline Characteristics

The distributions of clinical characteristics between DM and NDM are shown in Table 1. The male distribution of NDM and DM was not statistically different (49.54% vs 39.37%, P = 0.07). The age of the DM group was significantly older than the NDM (65.61 ± 12.08 vs 59.41 ± 16.86 years, P < 0.001). The morbidity of hypertension in DM was significantly higher than that in NDM (76.38% vs 58.14%, P < 0.001). Compared with NDM, the morbidity of coronary artery disease was obviously higher in DM (32.41% vs 44.09%, P = 0.03). Coronary artery disease diagnosed by coronary arteriography detected that coronary artery stenosis was more than 50%. The 2hBG, HbA1c, triglyceride, and ApoB of DM were significantly higher than those of NDM. The interventricular septum and LVPW of DM were also obviously thicker than those of NDM (IVS: 10.92 ± 1.77 vs 10.08 ± 1.96 mm, P < 0.001; LVPW: 9.84 ± 1.38 vs 9.39 ± 1.66 mm, P = 0.03). The abbreviations in this article are shown in Table 1.

Characteristics of QRS and T Vector

The characteristics of virtual planar QRS and T vector are shown in Table 2. In DM patients, the average heart rate was significantly higher than NDM patients (66.67 ± 12.04 vs 61.87 ± 13.36 bpm, P < 0.01). FQRSTA was not significantly different between DM and NDM (32.77 ± 54.20 vs 28.39 ± 52.87 degrees, P = 0.74). The maximal magnitude of horizontal and right side T vector (HTV and RSTV) of DM was obviously lower, respectively, compared with NDM (HTV: 2.33 ± 1.47 vs 2.88 ± 1.89 mm, P = 0.01; RSTV: 2.77 ± 1.55 vs 3.27 ± 1.92 mm, P = 0.03). It was noted that magnitude of virtual vector = 0.1 mv/mm. Compared with DM, the angle of horizontal QRS vector (HQRSA) of NDM was more negative (−2.87 ± 48.48 vs −19.00 ± 40.18 degrees, P < 0.01). The abbreviations of vector parameters were showed in footnote of Table 2.

DM and Angle of Frontal QRS-T Vector

FQRSTA was chosen as the outcome variable, and DM as the risk factor to be analyzed; sex and age were set as fixed adjustment variables; covariates were screened among the routine factors related to cardiovascular risk, such as coronary artery disease, hypertension, 2hBG, smoking, cerebral vascular disease, cholesterol, HDL, LDL, triglyceride, ApoA, ApoB, Lpa, BUN, Creatinine, Cystatin C, HbA1c, RV, LV, LVPW, LVEF, and average heart rate (abbreviations shown in Table 1). As a result, hypertension, 2hBG, ApoA, Cystatin C, HbA1c, LVPW, and average heart rate were screened as covariates, which were

Table 1. Clinical Characteristics in NDM and DM Populations

Factors	NDM	DM	P Value
Number	216	127	
Males	107 (49.54%)	50 (39.37%)	0.07
Age (years)	59.41 ± 16.86	65.61 ± 12.08	<0.001[a]
Smoking	49 (22.90%)	19 (15.57%)	0.11
Hypertension	125 (58.14%)	97 (76.38%)	<0.001[a]
Coronary artery disease	70 (32.41%)	56 (44.09%)	0.03[a]
Cerebral vascular disease	33 (15.35%)	22 (17.32%)	0.63
History of DM (years)	–	8.0 ± 7.1	–
2-hour postprandial blood glucose (2hBG, mmol/L)	6.84 ± 1.67	14.58 ± 5.27	<0.001[a]
Glycosylated hemoglobin (HbA1c,%)	5.58 ± 0.47	7.05 ± 0.16	<0.001[a]
Cholesterol (mmol/L)	4.48 ± 1.10	4.66 ± 1.26	0.18
Triglyceride (mmol/L)	1.42 ± 0.72	1.95 ± 1.35	<0.001[a]
High density lipoprotein (HDL, mmol/L)	1.22 ± 0.29	1.18 ± 0.25	0.12
Low density lipoprotein (LDL, mmol/L)	2.51 ± 0.86	2.61 ± 1.02	0.33
Apolipoprotein A (Apo A, mmol/L)	1.43 ± 0.28	1.42 ± 0.23	0.77
Apolipoprotein B (Apo B, mmol/L)	0.87 ± 0.24	0.96 ± 0.31	<0.01[a]
Lipoprotein A (Lpa, mmol/L)	274.33 ± 221.15	221.15 ± 245.67	0.17
Blood urine nitrogen (BUN, mmol/L)	5.45 ± 2.31	5.41 ± 2.43	0.87
Creatinine (μmol/L)	80.77 ± 48.16	75.57 ± 63.39	0.40
Cystatin C (mg/L)	1.00 ± 0.51	1.04 ± 0.50	0.56
Aortic diameter (end-diastolic, mm)	28.11 ± 4.71	28.82 ± 3.17	0.20
Left atrium diameter (LA, mm)	36.60 ± 6.80	38.15 ± 7.15	0.09
Pulmonary artery diameter (PA, mm)	21.47 ± 2.18	21.30 ± 2.30	0.57
Interventricular septum (IVS, mm)	10.08 ± 1.96	10.92 ± 1.77	<0.001[a]
Right ventricular outflow tract (RVOT, mm)	27.68 ± 3.63	27.44 ± 3.69	0.63
Right ventricle (RV, mm)	20.70 ± 3.07	20.51 ± 2.75	0.62
Left ventricular posterior wall (LVPW, mm)	9.39 ± 1.66	9.84 ± 1.38	0.03[a]
Left ventricle (LV, mm))	44.49 ± 5.57	43.66 ± 6.50	0.30
Left ventricular ejection fraction (LVEF,%)	61.70 ± 7.71	62.27 ± 8.41	0.59

[a]P < 0.05; DM = diabetes mellitus; NDM = nondiabetes mellitus.

calculated by single factor model and basic model. Analyzing with the multiple regression equation, FQRSTA and DM were selected to be the outcome variable and risk factor. Model 1 was only adjusted for sex and age, while model 2 was adjusted for sex, age, hypertension, 2hBG, ApoA, cystatin C, HbA1c, LVPW, and average heart rate. In model 1, the regression coefficient was 0.9 (95%CI −10.9 to 12.6, P = 0.88). After adjusting for sex, age, and covariates, the regression coefficient of DM was −40.0 (95%CI −66.40 to −13.6, P < 0.01), as shown in Table 3. In the multiple regression equation model, the ApoA level was also significantly effective on FQRSTA, whose regression coefficient was 36.72 (P = 0.04), as shown in Table 4.

DM and Angle of Horizontal QRS Vector

We also analyzed the relationship between DM, the risk factor, and HQRSA, serving as the outcome variable. As mentioned above, we screened the covariates among the routine risk factors, which may enhance the relationship between DM and HQRSA. Finally, the results showed that hypertension, cerebral vascular disease, 2hBG, LDL, triglyceride, ApoB, cystatin C, HbA1c, and the average heart rate were the covariates; this did not include the fixed adjusted factors, sex, and age. In multiple regression equation (Table 5), the regression coefficient of DM in model 1, recently adjusted for sex and age, was 13.9 (95%CI 4.0 to 23.8, P < 0.01). Whereas in model 2, adjusted for sex, age, and the related covariates, the regression coefficient of DM was 22.6 (95%CI 2.5 to 42.8, P = 0.03). During the process of multiple regression analysis (Table 6), the regression coefficient of triglyceride was −7.90 (P = 0.02).

DM and Maximal Magnitude of HTV

HTV was selected to be the outcome variable and DM was still designated as the risk factor to be

Table 2. Parameters of QRS and T Ring in NDM and DM Populations

Parameters	NDM	DM	P Value
Average heart rate (bpm)	61.87 ± 13.36	66.67 ± 12.04	<0.01[a]
FQRSV (mm)	11.56 ± 4.98	10.84 ± 4.39	0.37
FQRSA (degrees)	43.55 ± 30.86	44.21 ± 25.78	0.98
FTV (mm)	3.40 ± 2.15	2.88 ± 1.81	0.06
FTA (degrees)	43.41 ± 50.14	34.82 ± 57.73	0.32
FQRSTA (degrees)	28.39 ± 52.87	32.77 ± 54.20	0.74
HQRSV (mm)	9.05 ± 4.19	8.06 ± 3.65	0.07
HQRSA (degrees)	−19.00 ± 40.18	−2.87 ± 48.48	<0.01[a]
HTV (mm)	2.88 ± 1.89	2.33 ± 1.47	0.01[a]
HTA (degrees)	38.04 ± 41.30	35.56 ± 50.34	0.87
HQRSTA (degrees)	67.46 ± 47.52	65.41 ± 51.10	0.92
RSQRSV (mm)	9.74 ± 4.32	8.68 ± 3.79	0.06
RSQRSA (degrees)	93.98 ± 60.11	86.73 ± 58.47	0.51
RSTV (mm)	3.27 ± 1.92	2.77 ± 1.55	0.03[a]
RSTA (degrees)	53.37 ± 41.06	49.91 ± 58.19	0.79
RSQRSTA (degrees)	63.89 ± 55.51	65.46 ± 59.74	0.97

Magnitude of virtual vector = 0.1 mv/mm.
[a]$P < 0.05$. FQRSV = maximal magnitude of frontal QRS vector; FQRSA = angle of frontal QRS vector; FTV = maximal magnitude of frontal T vector; FTA = angle of frontal T vector; FQRSTA = angle of frontal QRS-T vector; HQRSV = maximal magnitude of horizontal QRS vector; HTV = maximal magnitude of horizontal T vector; HQRSA = angle of horizontal QRS vector; HTA = angle of horizontal T vector; HQRSTA = angle of horizontal QRS-T vector; RSQRSV = maximal magnitude of right side QRS vector; RSTV = maximal magnitude of right side T vector; RSQRSA = angle of right side QRS vector; RSTA = angle of right side T vector; RSQRSTA = angle of right side QRS-T vector; DM = diabetes mellitus; NDM = nondiabetes mellitus.

Table 3. Relationship between DM and FQRSTA

Model	Regression Coefficient	95%CI Upper	95%CI Low	P Value
Model 1	0.9	−10.9	12.6	0.88
Model 2	−40.0	−66.4	−13.6	<0.01[a]

Model 1, adjusted for sex and age; Model 2, adjusted for sex, age, hypertension, 2-hour postprandial blood glucose, apolipoprotein A, cystatin C, glycosylated hemoglobin, left ventricular posterior wall, and average heart rate.
[a]$P < 0.05$. DM = diabetes mellitus.

Table 4. Multiple Regression Analysis between DM and FQRSTA

Factors	Regression Coefficient	Std. Err.	Wald	Pr(>|W|)
(Intercept)	−158.64	53.41	8.82	<0.01[a]
DM	−40.00	13.46	8.84	<0.01[a]
Sex	−1.16	9.97	0.01	0.91
Age	−0.50	0.39	1.61	0.20
Hypertension	14.47	8.62	2.82	0.09
2-hour postprandial blood glucose	2.38	1.62	2.15	0.14
Apolipoprotein A	36.72	17.74	4.29	0.04[a]
Cystatin C	30.88	20.17	2.34	0.13
Glycosylated hemoglobin	572.59	392.94	2.12	0.15
Left ventricular posterior wall	6.25	3.54	3.11	0.08
Average heart rate	0.37	0.38	0.92	0.34

[a]$P < 0.05$. DM = diabetes mellitus.

analyzed; sex and age were set as fixed adjustment variables, and routine risk factors that had been mentioned above were screened as covariates, calculated by single factor model and basic model. Coronary artery disease, hypertension, cerebral vascular disease, 2hBG, smoking, cholesterol, triglyceride, ApoA, ApoB, Lpa, BUN, creatinine, HbA1c, LV, RV, LVEF, LVPW, and average heart rate were chosen as the covariates (Table 7). When put into multiple regression equations of DM as the risk factor and HTV as the outcome variable to be analyzed, the regression coefficient

Table 5. Relationship between DM and HQRSA

Model	Regression Coefficient	95%CI Upper	95%CI Low	P Value
Model 1	13.9	4.0	23.8	<0.01[a]
Model 2	22.6	2.5	42.8	0.03[a]

Model 1, adjusted for sex and age; Model 2, adjusted for sex, age, hypertension, cerebral vascular disease, 2-hour postprandial blood glucose, triglyceride, low density lipoprotein, apolipoprotein B, cystatin C, glycosylated hemoglobin, and average heart rate.
[a]$P < 0.05$. DM = diabetes mellitus.

Table 6. Multiple Regression Analysis between DM and HQRSA

Factors	Regression Coefficient	Std. Err.	Wald	Pr(>|W|)
(Intercept)	−85.97	31.39	7.5	<0.01[a]
DM	22.62	10.28	4.85	0.03[a]
Sex	−1.85	7.68	0.06	0.81
Age	0.52	0.38	1.87	0.17
Hypertension	6.74	9.70	0.48	0.49
Cerebral vascular disease	3.73	13.91	0.07	0.79
2-hour postprandial blood glucose	−1.75	1.07	2.67	0.10
Glycosylated hemoglobin	375.77	254.51	2.18	0.14
Triglyceride	−7.90	3.28	5.79	0.02[a]
Low density lipoprotein	−7.79	12.78	0.37	0.54
Apolipoprotein B	36.32	41.50	0.77	0.38
Cystatin C	−2.03	6.53	0.1	0.76
Average heart rate	0.49	0.34	2.14	0.14

[a]$P < 0.05$. DM = diabetes mellitus; NDM = nondiabetes mellitus.

Table 7. Relationship between DM and HTV

Model	Regression Coefficient	95%CI upper	95%CI low	P Value
Model 1	−0.3	−0.6	0.0	0.10
Model 2	0.9	0.2	1.7	0.01[a]

Magnitude of virtual vector = 0.1 mv/mm. Model 1, adjusted for sex and age; Model 2, adjusted for sex, age, coronary artery disease, hypertension, 2-hour postprandial blood glucose, smoking, cerebral vascular disease, cholesterol, triglyceride, apolipoprotein A, apolipoprotein B, lipoprotein A, blood urine nitrogen, creatinine, glycosylated hemoglobin, left ventricular posterior wall, left ventricle, left ventricular ejection fraction, right ventricle, and average heart rate.
[a]$P < 0.05$. DM = diabetes mellitus.

of DM in model 1 only adjusted for sex and age was −0.3 (95%CI −0.6 to 0.0, P = 0.10), while the regression coefficient of DM in model 2 adjusted for sex, age, and the covariates was 0.9 (95%CI 0.2 to 1.7, P = 0.01). The factors of sex (regression coefficient −0.79, P = 0.03), 2hBG (regression coefficient −0.08, P < 0.01), smoking (regression coefficient 1.22, P < 0.001), ApoA (regression coefficient −2.76, P < 0.001), creatinine (regression coefficient −0.02, P = 0.02), triglyceride (regression coefficient −0.23, P = 0.03), LVEF (regression coefficient 0.06, P = 0.001), and average heart rate (regression coefficient −0.03, P = 0.01) were significantly effective on HTV (Table 8).

DISCUSSION

This study indicated that DM was significantly effective on FQRSTA, HQRSA, and HTV analysis, using 1-minute length of ECG from Holter at 4 AM. After adjustment of confounding factors, DM still significantly decreased FQRSTA by 40 degrees, and increased HQRSA and HTV by 22.6 degrees and 0.09 mv, respectively. Multiple risk factors were involved in the influence between DM and QRS-T vector, especially the lipid metabolism abnormality. ApoA elevated by per 1 mmol/L would significantly increase FQRSTA by 36.72 degrees, after adjustment of other risk factors.

Table 8. Multiple Regression Analysis between DM and HTV

Factors	Regression Coefficient	Std. Err.	Wald	Pr(>|W|)
(Intercept)	5.96	3.59	2.75	0.10
DM	0.93	0.37	6.25	0.01[a]
Age	−0.01	0.01	0.43	0.51
Sex	−0.79	0.37	4.61	0.03[a]
Smoking	1.22	0.35	12.15	<0.001[a]
Coronary artery disease	−0.07	0.22	0.11	0.74
Hypertension	−0.17	0.37	0.2	0.66
Cerebral vascular disease	−0.15	0.32	0.23	0.63
2-hour postprandial blood glucose	−0.08	0.03	6.93	<0.01[a]
Glycosylated hemoglobin	0.76	15.05	0	0.96
Cholesterol	0.69	0.37	3.46	0.06
Triglyceride	−0.23	0.11	4.69	0.03[a]
Apolipoprotein A	−2.76	0.83	11.1	<0.001[a]
Apolipoprotein B	−2.40	1.40	2.95	0.09
Lipoprotein A	−0.001	0.0006	3.39	0.07
Blood urine nitrogen	0.13	0.09	2.24	0.13
Creatinine	−0.02	0.007	5.45	0.02[a]
Left ventricle	−0.01	0.02	0.09	0.77
Left ventricular posterior wall	0.11	0.09	1.44	0.23
Right ventricle	0.02	0.03	0.45	0.50
Left ventricular ejection fraction	0.06	0.02	10.73	0.001[a]
Average heart rate	−0.03	0.01	6.23	0.01[a]

Magnitude of virtual vector = 0.1 mv/mm.
[a]$P < 0.05$. DM = diabetes mellitus.

DM and FQRSTA

Widened spatial QRS-T angle or FQRSTA is not only suggestive of increased divergence between depolarization and repolarization,[27–29] but also altered T wave axis,[30] T wave abnormalities,[31] the likelihood of increased cardiac diseases,[15,32–39] a higher quantity of coronary artery calcification,[40] and higher morbidity of multiple vessel coronary artery disease.[41] FQRSTA is a very powerful predictor of cardiovascular events (e.g., myocardial ischemia),[42] sudden cardiac death,[13–17,43] appropriate ICD therapy,[44,45] all-cause mortality,[15,33–37] increased cardiac-related hospitalizations,[17,35] reduced left ventricular function,[34–36,46] especially in patients with postinfarction,[13–17] acute myocardial infarction with LVEF ≤40%,[47] the elderly,[12] chronic dialysis,[18–20] heart failure with preserved ejection fraction,[17] and ischemic stroke[48] considered stronger than any of the classical cardiovascular risk factors.[16,17] Risk factors leading to an elevation in FQRSTA were related to coronary artery disease, dialysis, poor-controlled hypertension,[49,50] pulmonary arterial hypertension,[51] left/right ventricular hypertrophy,[51–54] dilated left ventricle,[55] lower LVEF,[56] DM,[57,58] smoking,[57–59] and female gender.[57,58] Most researches were focused on QRS-T angle derived from planar traditional ECG or spatial vector. The study related to FQRSTA derived from Holter was limited. To analyze FQRSTA, we eliminated interference from exercise and emotional factors by selecting a 1-minute length of ECG from Holter at 4 AM. FQRSTA was not obviously different between DM and NDM. After making adjustments for the confounding factors, indications were that DM and ApoA were significantly effective on FQRSTA with the regression coefficient of −40.0 (95%CI −66.4 to −13.6, P < 0.01) and 36.72 (P = 0.04), respectively. Thus, we concluded that the risk factor of DM might cause FQRSTA to decrease by 40 degrees, or change toward a more negative trend when compared with NDM. In the sharp contrast with DM, the confounding factor of ApoA elevated by per 1 mmol/L may result in FQRSTA being increased by 36.72 degrees, or change toward a positive direction. This may explain why there was no significant distinction of FQRSTA between DM and NDM before adjustment of the confounding factor or covariates. Thus, the risk factors of DM and ApoA contributed to the influence of FQRSTA, as negative and positive orientations. Compared to previous studies, hemodialyzed patients with extreme QRS-T angle of Holter experienced

major arrhythmic events[60]; Widened QRS-T angle derived from Holter was common and associated with life-threatening ventricular arrhythmia in patients with systemic sclerosis, although this analysis was restricted to 10-second ECG of Holter.[61]

The influence of QRS-T angle on DM was concentrated in planar ECG and spatial vector. In previous studies, compared to NDM, QRS-T angle values of DM were higher by almost two folds (P < 0.001) and independently associated with HbA1c (P = 0.03). Higher spatial or FQRSTA in T2DM was associated with glycemic control, cardiac autonomic neuropathy, left ventricular performance, ventricular hypertrophy, and several markers of preclinical atherosclerotic disease, such as carotid intima-media thickness and coronary artery disease.[62–64] This kind of relationship between QRS-T angle and cardiac autonomic neuropathy may suggest structural, functional, and electrical imbalance.[65] Furthermore, spatial QRS-T angel >45–50 degrees in T2DM increased the risk of incidents of cardiovascular disease by 114% total mortality increase by two folds[33] and the morbidity of silent myocardial infarction by 19%.[66] Although FQRSTA derived from planar ECG and spatial vector may be used to estimate the prognosis and morbidity of cardiac diseases mentioned above; we have not yet analyzed the influence of FQRSTA from Holter on prognosis or diagnosis of cardiac diseases in this study.

DM and Angle of Horizontal QRS Vector

Compared with NDM, patients with DM showed a significant leftward shift of the electrical axis; this was also discovered in the offspring of DM patients.[67] Recent study showed that low QRS magnitude may be associated with an increased risk of mortality in individuals free of apparent cardiovascular disease. This study did not find significant association between QRS magnitude and DM.[68] In our population, HQRSA was higher in DM, compared with NDM. In multiple regression analysis adjusting for confounding factors, the regression coefficient of DM was 22.6 (95%CI 2.5 to 42.8, P = 0.03), suggesting that DM would significantly increase the HQRSA by 22.6 degrees, while triglyceride (increased by per 1mmol/L) reduced HQRSA by 7.9 degrees (regression coefficient −7.9, P = 0.02).

DM and Maximal Magnitude of HTV

In recent years, most studies have concentrated on T-wave alternans of Holter in DM. T-wave alternans are the change of T-wave magnitude from beat to beat. Myocardial infarction with DM or NDM can elevate T-wave alternans.[7] T-wave alternans are a powerful predictor of sudden cardiac death and arrhythmia events in postmyocardial infarction with left ventricular dysfunction[7,69] in DM or NDM populations.[70] There have been no reports associated with DM and T vector, especially derived from Holter. In our study, the HTV of DM was reduced significantly as compared with NDM. After adjustment of the covariates, the regression coefficient of DM was 0.9 (95%CI 0.2 to 1.7, P = 0.01), indicating a positively increased direction. It meant that DM would significantly increase HTV by 0.09 mv. The confounding factors produced a negative trend and reduced the HTV values, such as sex, triglyceride, 2hBG, ApoA, creatinine, and average heart rate. In addition, besides the DM factor, smoking and LVEF factors gave positive HTV effects. Thus, HTV was associated with multiple risk factors.

Underlying Mechanisms of QRS and T Vector Change in DM

Our results showed that after adjusting the confounding factors, FQRSTA was negatively changed, and HQRSA and HTV increased positively and solely by DM. These changes were also attributed to multiple factors, such as lipid level, 2hBG, sex, smoking, average heart rate, and LVEF. As stated above, the long-term history of impaired glycemic control would induce DM cardiomyopathy, which is characterized as DM-related cardiac structural and functional changes that are not caused by coronary atherosclerosis or hypertension. DM cardiomyopathy alone would cause ventricular hypertrophy, myocardial lipo-toxicity, oxidative stress, cellular apoptosis, inter-stitial fibrosis, contraction-relaxation dysfunction, impaired myocardial contractile reserve, mito-chondrial dysfunction, cardiac autonomic disease, adverse dispersion of repolarization, and disorders of myocardial metabolism.[71–73] Several DM populations were usually accompanied with metabolic syndrome, and some of them with complicated silent cardiovascular diseases which induced ventricular repolarization dynamics.[74] In the animal

model of DM, the maximum amplitude of I_{Na} was significantly reduced with less Na^+ influx during contraction and an increased Ca^{2+} load in ventricular cells[75]; resting membrane potential and action potential amplitude were reduced, while the depolarization time and half repolarization time were evidently extended. The lengthening of early-phase repolarization contributed to diminished K^+ currents.[76] Meanwhile, the QRS-T angle depended on heterogeneity and dynamical change of the action potential duration in myocardial cells, and its gradients of transmural, apicobasal, and left-right ventricle.[65] The potentially pathophysiological mechanisms of planar QRS and T vector change were induced by the risks of multiple levels and factors, including DM, lipid metabolism, cardiac electrical disturbance, and smoking, which thus caused adverse cardiac structure, functional and autonomic change, and imbalance.

LIMITATIONS

Our study was a research of small cohort, followed for only a short period of time. Thus, we didn't evaluate whether the change of virtual planar QRS and T vector would affect the cardiac events, for example, the cardiac mortality or all-cause mortality. In process analysis, there may be some cases with invalid HTA value, which would lead to synchronization of HQRSTA and HQRSA. Conversely, there is no comparison between planar QRS and T vector virtually derived from 24-hour Holter, planar ECG, and true planar vectors. Their differences and relationship are still unknown. We need to further exploit which kind of characters of QRS and T vector would be best to evaluate the cardiac events and prognosis. A recent study showed when estimating the QRS-T angle that the personal correlation coefficients between Dower/Kors transformations and true spatial vector were 0.71/0.85 (P < 0.01), suggesting that Kors transformation may be more accurate than Dower transformation.[27] These transformation methods were only applied to traditional 12-lead ECG, not to Holter. Thus, for estimating the QRS vector, T vector and the angle of QRS-T vector in Holter, the method closest to the spatial vector is still unclear. In our retrospective and clinical study, we have not measured the waist circumference and body mass index. However, these indexes were usually positively correlated to lipid levels.

CONCLUSIONS

We analyzed virtual planar QRS and T vector derived from 1-minute ECG of Holter at 4 AM. After adjusting confounding factors, it was indicated that DM significantly reduced FQRSTA by 40 degrees and increased HQRSA and HTV by 22.6 degrees and 0.09 mv, respectively. ApoA would also significantly modify the parameter of FQRSTA. The potentially pathophysiological mechanisms of QRS and T vector changes may be induced by the risks of multiple levels, including DM, lipid metabolism, cardiac electrical disturbance and smoking, which thus caused cardiac structure, functional and autonomic changes and imbalance.

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