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Complex assessment of the Temporal Lability of Repolarization

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Stochastic fluctuations of I_{Ks} in the presence of cell-to-cell uncoupling leads to temporal variability of action potential duration and subsequent early afterdepolarizations, which occur in late phase 2 or phase 3 of the cardiac action potential, could propagate through cardiac tissue and generate ventricular arrhythmias (1;2). However, surface ECG imposes well-recognized limitations for repolarization assessment: dependence on particular ECG lead axis and inaccuracies in the T end detection. In contrast, vectorcardiograms (VCGs) have advantages in their description of repolarization(3). Recently we proposed a novel 3-dimensional (3-D) ECG method to assess temporal repolarization lability(4;5). However, the complexity of spatial T-vector movements over time makes it unlikely that any single method would describe temporal lability of repolarization in full. Therefore, the goal of this study was to develop a comprehensive set of markers of temporal lability of repolarization in a discriminating model.

We conducted age-, gender-, and race- matched Case-Control study. All study participants gave written, informed consent upon entering the study. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology(6). Participants of ongoing prospective observational cohort study of patients with structural heart disease and a primary prevention ICD were included in this analysis (NCT00733590)(5). Healthy subjects participated in the Intercity Digital Electrocardiogram Alliance (IDEAL) study, which was previously described elsewhere(7). Baseline modified Frank surface orthogonal ECGs were recorded at rest for approximately 5 minutes before the implantation of an ICD using a PC ECG machine (Norav Medical Ltd, Thornhill, ON, Canada, sampling frequency 1000 Hz, amplitude resolution of 2.44 μ V) in Cases, and using the SpaceLab-Burdick digital Holter (SpaceLab-Burdick, Inc., Deerfield, WI, sampling frequency 1000 Hz, amplitude resolution of 4.88 μ V) in Controls. Blinded ECG analysis was performed using custom MATLAB (MathWorks, Inc, Natick, MA) software. Recordings in atrial fibrillation, premature ventricular complexes (PVCs) and the subsequent beat were excluded from analysis; only sinus beats were analyzed. Mean spatial TT' angle was calculated as a measure of beat-to-beat spatial T axis variability, as the angle between two consecutive T vectors using the definition of the inner product. The area of the T-loop was calculated using successive triangles along the loop from the peak to the origin

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point. Variability of spatial T vector magnitude and that of spatial T-loop area were measured as their respective variances. Additionally, the ratio of the T peaks cloud volume to the R peaks cloud volume was calculated as previously described(4;5). Normalized T loop area variance (TareaVN) was calculated according to the equation:

$$TareaVN = \log \left[\frac{\text{Variance of spatial T - loop area}}{(\text{Mean spatial T - loop area})^2} \right]$$

Normalized T amplitude variance (TampVN) was calculated according to the equation:

$$TampVN = \log \left[\frac{\text{Variance of spatial T vector amplitude}}{(\text{Mean spatial T vector amplitude})^2} \right]$$

The QT interval was calculated as the time from beginning of Q or R wave (8) to the end of the T-wave (9), averaged over all beats on all leads. QT interval was corrected for heart rate using Bazett's formula. QT variance was calculated as the variance of the QT interval, and QT variability index (QTVI) was calculated(10).

A classification model was implemented to distinguish healthy state of repolarization lability in Cases and Controls. For this purpose, QTVI, mean spatial TT' angle, TampVN, and TareaVN entered the PCA model. The PCA technique was employed to combine the repolarization lability variables and to develop a comprehensive set of repolarization lability markers. Then, a canonical linear discriminant analysis was applied to correlate the differences in repolarization lability of the relevant principal component scores to the health state. The Student's *t*-test was applied to compare the scores of the first principal component of the Cases and Controls. Sensitivity and specificity of the comprehensive repolarization lability score were calculated. The proposed comprehensive repolarization lability score for each study participant was calculated according to the following equation:

$$RL\ score = FW_{TT'} \cdot ZS_{TT'} + FW_{TampVN} \cdot ZS_{TampVN} + FW_{TareaVN} \cdot ZS_{TareaVN} + FW_{QTVI} \cdot ZS_{QTVI},$$

where FW is the scoring coefficient, or optimal regression weight, determined for each variable in the PCA model for the 1st Principal Component, and ZS is the Z-Score of the parameter in our population for each individual subject. For example, the Z-Score for Subject A for TT' angle is calculated as follows:

$$ZS_{TT'} = \frac{\text{Subject A's TT' Angle} - \text{Mean TT' Angle}}{\text{Std Dev of TT' Angle}}$$

Results showed that Cases and Controls were well-matched by age, gender, and race. All study participants were Caucasian. Amongst Cases, two-thirds of patients (n=42, 68%) had non-ischemic cardiomyopathy, and half of the patients (n=31, 50%) had NYHA class III HF. The mean ejection fraction was 22.4±10.3%.

Repolarization lability PCA model included mean spatial TT' angle, QTVI, TampVN, and TareaVN. After extracting the PCA vectors and scores, it was verified that the first two Principal Components represent about 85% of all variance of the dataset (PC1 = 51.4%, PC2 = 34.0%, PC3 = 11.1 %, PC4 = 3.5%). Interestingly, multiple repolarization lability parameters contributed to a similar extent. All studied repolarization lability parameters

correlated with each other. The first factor, PC1, which accounted for the greatest variance at 51.4%, was the most heavily loaded by spatial TT' angle (0.506) and QTVI (0.631). The second factor, PC2, accounting for 34.0% of the variance, was most heavily loaded by TampVN (0.658) and TareaVN (0.580). Repolarization lability score, calculated using the PCA scoring coefficients, showed a remarkable, statistically significant difference for discriminating Cases from Controls (Figure 1). Canonical linear discriminant analysis showed that taking all 4 aforementioned repolarization lability parameters separates Cases from Controls with 100% sensitivity and 98.4% specificity (canonical correlation coefficient 0.969, Eigen-value 15.6; $p < 0.0001$).

Thus, our study showed that patients with structural heart disease and systolic dysfunction are characterized by significantly increased temporal repolarization lability as measured by increased spatial TT' angle, by increased normalized variance of T loop area, and by increased QTVI. The repolarization lability score developed (composed of spatial TT' angle, QTVI, normalized variance of spatial T vector magnitude, and normalized variance of T loop area) nearly perfectly differentiated healthy subjects from patients with structural heart disease and primary prevention ICD (100% sensitivity and 98.4% specificity). Future studies are needed to determine the predictive value of repolarization lability score in different patient populations.

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Figure 1.

Boxplots of 3-dimensional ECG repolarization liability parameters : **A.** Mean spatial TT' angle; **B.** Normalized variance of spatial T vector amplitude; **C.** Normalized variance of T spatial loop area; **D.** Spatial T vector amplitude; **E.** QT interval variance. **F.** Boxplot of the scores of the 1st principal component of the final PCA model (eigenvalue = 2.06; accounted for 51.4% variability) in Cases and Controls. Median (*white horizontal line crossing the box*) and interquartile range [IQR] (*box*) of corresponding variable values. Whiskers specify the adjacent values, defined as the most extreme values within 1.5 IQR of the nearer quartile.

Table 1

Clinical characteristics and ECG parameters in Cases and Controls

Parameter	Cases, n=62	Controls, n=62	P
Age $\pm$ SD, y	46.5 $\pm$ 8.4	45.8 $\pm$ 8.8	0.595
Male Gender, n(%)	33(53)	34(55)	0.857
Systolic BP $\pm$ SD, mmHg	121.4 $\pm$ 22.0	118.9 $\pm$ 11.0	0.421
Diastolic BP $\pm$ SD, mmHg	69.2 $\pm$ 9.65	76.15 $\pm$ 8.46	0.0001
BMI	29.9 $\pm$ 5.5	23.9 $\pm$ 3.1	<0.0001
Smokers, n(%)	36(67)	22(35)	0.001
Mean heart rate, bpm	72.4 $\pm$ 11.9	64.8 $\pm$ 9.8	0.0002
Heart rate variance, ms ²	756.4(322.9–1296.9)	742.3(434.4–1723.0)	0.257
Mean QTc	475.6 $\pm$ 39.0	411.7 $\pm$ 20.3	<0.0001
QT interval variance, ms ²	552.1(326.5–837.3)	203.3(149.7–290.4)	0.0047
QTVI	0.51 $\pm$ 0.52	–2.17 $\pm$ 0.64	<0.0001
Mean spatial T-T' angle, deg	5.5(3.8–8.5)	3.0(2.2–4.2)	<0.0001
	6.9 $\pm$ 5.3	3.4 $\pm$ 1.6	<0.0001
Mean T vector amplitude, mV	0.53 $\pm$ 0.33	0.71 $\pm$ 0.25	0.0007
T vector amplitude variance, mV ²	.001(.0005–.002)	.094(.053–.134)	<0.0001
TampVN	–5.2 $\pm$ 1.3	–1.6 $\pm$ 1.0	<0.0001
Mean T Loop Area, mV ²	55.4(25.3–116.5)	122.6(78.0–175.6)	0.0003
T Loop Area Variance, mV ⁴	80.7(17.6–242.5)	142.6(55.7–288.3)	0.1054
TareaVN	–3.5 $\pm$ 2.1	–4.6 $\pm$ 0.9	0.0004
T/R peaks cloud volume ratio	0.19(0.10–0.34)	0.23(0.15–0.41)	0.107

QTVI=QT variability index; TampVN= Normalized variance of spatial T vector amplitude; TareaVN= normalized variance of spatial T loop area.