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Repolarization lability measured on 10-second ECG by spatial TT' angle: reproducibility and agreement with QT variability

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Abstract

Background—Reproducibility of spatial TT' angle on the 10-second ECG and its agreement with QT variability has not been previously studied.

Methods—We analyzed 2 randomly selected 10-second segments within 3-minute resting orthogonal ECG in 172 healthy IDEAL study participants (age 38.1 ± 15.2 years, 50% male, 94% white). Repolarization lability was measured by the QT variance (QTV), short-term QT variability (STV(QT)), and spatial TT' angle. Bland-Altman analysis was used to assess the agreement between different log-transformed metrics of repolarization lability, and to assess the reproducibility.

Results—The heart rate showed a very high reproducibility (bias 0.14%, Lin's rho_c = 0.99). As expected, noise suppression by averaging improves reproducibility. Agreement between two 10-second LogQTV was poor (bias -0.04; 95% limits of agreement [-1.89; 1.81]), while LogSTV(QT) (0.04[-1.01; 1.10], and especially LogTT' angle (-0.009[-0.84; 0.82]) was better.

Conclusion—TT' angle is a satisfactory reproducible metric of repolarization lability on the 10-second ECG.

Introduction

Cardiovascular mortality is a leading cause of death in the United States, with sudden cardiac death (SCD) proving to be the most common cause of cardiovascular mortality(1). Ventricular arrhythmia causes more than half of SCDs. It has been previously shown(2,3) that increased repolarization lability represents a predisposing electrophysiological substrate that is mechanistically linked to ventricular tachycardia(VT)/fibrillation(VF). Several

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methods to detect QT variability on the surface ECG have been developed(4). Studies showed that short-term QT variability(5), and T wave variability(6) predicted potentially fatal ventricular arrhythmia in heart failure (HF) patients.

However, these methods of quantifying repolarization lability have traditionally required long ECG recordings, at least 30 sec for short-term QT variability(7). Necessity of relatively long ECG recording was motivated by complex relationships between RR' and QT intervals, and an attempt to adjust QT variability by RR' variability. However, adjustment of QT variability by RR' variability did not improve, but rather worsened the predictive value of QT variability(8). In addition, requiring long ECG recordings to assess repolarization lability is associated with increased cost, and therefore, a limited number of clinical studies have investigated clinical utility of repolarization lability for the risk stratification of SCD.

Novel dynamic vectorcardiography (VCG), or three-dimensional ECG, approach for assessment of repolarization lability was developed by Tereshchenko's group(8-12) and showed association with VT/VF(12). Specifically, spatial TT' angle was shown to be virtually independent of RR' interval(11). Therefore, spatial TT' angle enables assessment of repolarization lability on a 10-second ECG recording, routinely available in clinical practice. However, reproducibility of spatial TT' on 10-second ECG has not been previously studied. The goal of this study was: to evaluate reproducibility of spatial TT' angle and agreement with QT variability.

Methods

Study Population

We analyzed data of the Intercity Digital Electrocardiogram Alliance (IDEAL) study(13), provided by the NIH-funded The Telemetric and Holter ECG Warehouse initiative (14). Study design was as previously described(11,13). Only healthy participants 18 years and older were included in this analysis, as confirmed by the absence of a history of any chronic illnesses; normal physical examination, echocardiogram, and stress test; and normal 12-lead ECG in sinus rhythm.

ECG Recording and selection of segments for analysis

High resolution (1000 Hz) modified (5th intercostal space) Frank orthogonal XYZ ECG was recorded by the SpaceLab-Burdick digital Holter recorder (SpaceLab-Burdick, Inc., Deerfield, WI) at rest in the supine position for at least 3 minutes.

Three epochs were selected for repolarization lability analysis. Two non-adjacent 10-second segments of ECG recording were uniformly selected for all ECG recordings. One 10-second segment was selected midway through the recording, and another 10-second segment was selected a third of the way through the recording. An investigator (AF) also inspected the 10-second segments to ensure that there was no large presence of noise distortion or irregular beats in these segments, to avoid skewing statistical results. In addition, repolarization lability was measured on the entirety of the 3-minute ECG recording.

Only sinus beats were included in the analysis. Premature atrial and ventricular contractions were excluded, along with the first subsequent beat. Fiducial points (QRS onset, R-peak, T-peak, and T-end) were automatically detected on each orthogonal lead using custom MATLAB (MathWorks, Inc, Natick, MA) software. All ECGs were reviewed for correct point detection by investigators, as previously described(11). QT interval was measured on each beat and each lead separately, and then averaged across the three ECG leads.

Repolarization liability assessment by QT variance

QT variance (QTV) was calculated as the variance of the average QT duration across three leads. QTV was log-transformed to normalize distribution.

Repolarization liability assessment by Poincaré plots of the QT intervals

As previously described(7), short-term QT variability (STV(QT)) was quantified by the distance between adjacent points on a Poincaré plot of the QT intervals. For a recording with n number of beats, STV(QT) was calculated as:

$$SVT(QT) = \sum_{k=2}^n \left[|QT_k - QT_{k-1}| / (n * \sqrt{2}) \right]$$

Repolarization liability assessment by spatial TT' angle

On orthogonal XYZ ECGs, VCG fiducial points (origin point, peak of spatial QRS vector, and peak of spatial T vector) were detected automatically using custom MATLAB software as previously described(11). The crosspoint between the QRS and T loop was determined first for each beat. Then, all beats were aligned in 3-D space by translocating the crosspoint of each beat to the origin of 3-D space (0,0,0), thus shifting all data points within the beat. This alignment process eliminated effects of baseline wandering and respiration, while preserving the capability to detect repolarization liability. Peaks of spatial QRS and T vectors were defined as the points furthest away from the origin of their respective loops. We calculated the amplitudes of the spatial QRS and T vectors for each beat. Spatial TT' angle was measured for each pair of consecutive beats as an angle between consecutive spatial T vectors (Figure 1). Mean spatial TT' angle was averaged across the duration of the analyzed segment (10-second or 3-minute, accordingly).

Statistical analysis

STATA 13 (StataCorp LP, College Station, TX) was used for statistical analysis. Normally distributed variables are reported as mean and standard deviation (SD). Due to non-normal distribution of repolarization liability parameters, log-transformation was performed as needed for the subsequent inclusion of the variable in the Bland-Altman analysis. Bland-Altman analysis(15) was used for the assessment of agreement between different metrics of repolarization liability, and for the assessment of reproducibility of repolarization liability, measured on random 10-second segments. The degree of agreement was expressed as the mean absolute difference (bias), 95% limits of agreement, and mean relative difference (relative bias, calculated as the mean difference of two measurements divided by their mean value). The correlations strength was measured by the Pearson's correlation coefficient r . In addition, Lin's concordance correlation coefficient ρ_c (rho_c) was calculated(16) to describe the strength of agreement: >0.95 indicates almost perfect agreement; 0.80–0.95, substantial

agreement; 0.70–0.80, moderate agreement; <0.70, poor agreement. The Bradley-Blackwood procedure(17) simultaneously compared the means and variances of the two measurements. To assess the robustness of our findings, we conducted several sensitivity analyses. First, we compared the results after exclusion of study participants on beta-blockers. We also compared the results of Bland-Altman analysis of reproducibility between the first 10-sec interval and 3 min-segment, to the results of reproducibility between the second 10-sec interval and 3-min segment.

Results

Study population

The study population was composed of 172 healthy adult patients. Mean age was 38.1 ± 15.2 years, 50% were male, and 94% were white. Mean height was 169.6 ± 10.4 cm, mean weight was 69.8 ± 15.2 kg, and BMI was 24.2 ± 4.6 cm/kg². Two participants (1.2%) were on beta-blockers.

When comparing a 3-minute to a 10-second ECG recording, the heart rate showed a very high reproducibility, with a bias below 0.2%, and Lin's concordance coefficient greater than 0.95, indicating substantial agreement (Table 1). The Bradley-Blackwood F-test for heart rate was not significant, confirming validity of the Bland-Altman analysis. Correlation and concordance between heart rate in two 10-second recordings was very similar to the correlation and concordance between a 3-minute and 10-second recording (Table 2). However, the range of 95% limits of agreement between two random 10-second segments was wider (about 10 bpm), as compared to 95% limits of agreement range between 10-second and 3-minute segments (about 6 bpm).Uncorrected QT interval showed almost perfect agreement within 95% limits of agreement, up to 10 ms in the 10 sec vs. 3 min recording comparison, and up to 14 ms in the 10 sec vs. 10 sec recording comparison.

Reproducibility of QT variance

As expected, agreement between two measurements of QTV was poor, with the 95% limits of agreement range in the order of 2 to 4 (Tables 1,2). The Bradley-Blackwood F-test was highly significant in the case of comparing 3-minute and 10-second recordings (Figure 2A), indicating that the disagreement between the 3-minute QTV and the 10-second QTV was highly dependent on the value of the QTV. However, this was not the case for the assessment of QTV agreement between two random 10-second segments (Figure 2C). Concordance and correlation between any two measurements of QTV were poor (Figure 2B, 2D). Amongst all three metrics of repolarization lability, QTV showed the worst reproducibility between two random 10-second segments, as well as between 3-minute and 10-second segments (Tables 1 and 2): poor correlation and concordance, high relative bias and disagreement in the order of 3 to 4, which means that for any random 10-second interval, the QTV measured may be raised (or diminished) up to the fourth power of a QTV measured at any other random 10 second interval.

Reproducibility of short-term QT variability

Disagreement between two STV(QT) measurements was less prominent as compared to QTV disagreement; it was in the order of 2. For any random 10-second interval, the STV(QT) measured may be raised (or diminished) up to the second power of a STV(QT) measured at any other random 10 second interval (Figure 3A, 3C). Concordance and correlation between any two measurements of STV(QT) were poor, as well (Figure 3B, 3D). Similarly to QTV behavior, disagreement between the 3-minute STV(QT) and the 10-second STV(QT) increased as STV(QT) value increased.

Reproducibility of spatial TT' angle

Disagreement between two measures of TT' angle was less noticeable. Range of the 95% limits of agreement stayed close to 1. Thus, differences in two TT' angle measurements did not exceed the value of spatial TT' angle itself (Figures 4A, 4C). Correlation and concordance between 2 TT' angle measurements (Figures 4B, 4D) was stronger than correlation and concordance of STV(QT). Similar to STV(QT) agreements, agreement between 3-minute TT' angle and 10-second TT' angle was inconsistent across TT' angle values: the larger the TT' angle the lower the agreement. However, a very strong agreement of TT' angle was observed between two random 10-second measurements (Figure 4A).

Agreement between different repolarization lability metrics

Comparison of QTV with spatial TT' angle clearly showed disagreement (Figure 5A) and absence of concordance (Figure 5B) between the two metrics. At the same time, correlation between QTV and TT' angle was moderately strong (Table 3) and statistically significant ($P < 0.0001$), which underscores the misleading use of correlation for the assessment of agreement between two methods.

Moderate agreement between STV(QT) and TT' angle was present (Figure 5C), and coherence between these two methods was observed as well (Figure 5D). Importantly, the Bradley-Blackwood F-test was not significant, thus agreement between STV(QT) and TT' angle was independent from the values of either metric.

Sensitivity analyses

Reported results of reproducibility analyses did not change significantly after the exclusion of two study participants on beta-blockers during the study. Furthermore, to test the robustness of our findings, we compared reproducibility between the first 10-second and 3-minute recording, with reproducibility between the second 10-second and 3-minute recording. No significant differences were observed.

Discussion

Our study confirmed the well-known fact that any method that suppresses noise by averaging is more reproducible than another method that does not involve noise suppression. This is why TT' angle is concordant with STV(QT), but completely discordant with QTV. In addition, this study showed fundamental differences between 10-second and 3-minute repolarization lability. QT interval variability measured over 3-minute period is largely due

to an adaptation to changing heart rate(18), whereas 10-second ECG segments reflect predominantly stochastic repolarization lability(2,3).

Robust reproducibility of a diagnostic or prognostic method is extremely important for appropriate interpretation and clinical use of a method. Satisfactory reproducibility of TT' angle opens the door for the measurement of repolarization lability on routinely available 12-lead ECG, after its transformation into orthogonal XYZ ECG. The possibility of quantifying repolarization lability on widely available clinical 10-second ECGs will help advance further clinical investigations of repolarization lability in different clinical settings.

Spatial TT' angle and other measures of repolarization lability

Observed differences in reproducibility of QT variance and mean TT' angle were expected. Spatial TT' angle is calculated as a mean, and QT variance is calculated as a variance. Because spatial TT' angle is calculated as a mean, the presence of noise is suppressed by averaging. Meanwhile, because QTV is calculated as the variance of QT intervals, any noise will be emphasized by the variance metric.

By measuring beat-to-beat changes in the spatial position of the T-axis, mean spatial TT' angle is a measure of beat-to-beat changes in cardiac repolarization. In other words, TT' angle is a measure of difference in spatial T vector (or T-axis) position between two consecutive beats. Our study showed that TT' angle is concordant with STV(QT), but discordant with QTV. This is consistent with the methodologies applied: while STV(QT) quantifies absolute differences in repolarization duration between consecutive beats, QTV is a variance of QT interval over a certain time segment. Thus, both TT' angle and STV(QT) attenuates slow variations in repolarization vector (TT' angle) or QT interval (STV(QT)), while accentuating sudden changes in repolarization vector (TT' angle), or QT interval (STV(QT)), which are likely due to intrinsic repolarization lability caused by an increased stochasticity of ion channels gating(2,3). On the other hand, QTV is more sensitive to slow changes in QT due to variation in autonomic tone or respiration(5). Observed in this study differences in repolarization lability methods might reflect previously reported differences in the mechanisms behind distinct repolarization lability metrics. While increased short-term repolarization lability might result from drug-induced I_{Ks} and I_{Kr} block with drug-induced torsade de pointes arrhythmias(19), increased QTV is likely a sign of increased sympathetic tone in the ventricles of the heart (20,21). At the same time, in patients with structural heart disease, both short- and long-term repolarization lability is associated with VT/VF or death(5,22).

In this study, we observed that Bradley-Blackwood F-test was significant for comparison of 10-second with 3-minute repolarization lability metrics, which highlight existence of the relationship between the degrees of repolarization lability with the degree of agreement. However, F-test was not significant for comparison of repolarization lability measured on two random 10-second segments. This is another argument in support of the notion that mechanisms of repolarization lability measured over 3-minute epoch differ from the mechanisms of repolarization lability measured over 10-second. Our recent study showed that abnormal spatial TT' angle, measured on routine resting 10-second ECG, is associated with SCD in the general population of asymptomatic adults, after adjustment for traditional

risk factors and known ECG risk markers of SCD(23). The finding of satisfactory reproducibility of TT' angle will have important implications for the future implementation of the method in clinical practice.

Assessment of reproducibility

In spite of the long history of repolarization lability, this is the first study of its reproducibility, which brought expected findings and confirmed well known fact that any method that suppresses noise by averaging is more reproducible than another method that does not involve noise suppression. Choosing the appropriate method to study reproducibility is important. We used Bland-Altman analysis(15), Bradley-Blackwood test(17), and concordance Lin's coefficient(16). The concordance Lin's coefficient is the product of the measure of precision and accuracy. Lin's coefficient increases in value as a function of the nearness of the data's reduced major axis to the line of perfect concordance (the accuracy of the data) and the tightness of the data about its reduced major axis (the precision of the data). In this study Pearson correlation coefficient between TT' angle and QTV was significant and moderately strong (Figure 5B), whereas concordance between TT' angle and QTV was virtually absent. This study illustrated that statistically significant correlation (measured by Pearson's correlation coefficient) between TT' angle and QTV does not necessarily mean that measured parameters agree, and are concordant. Correlation coefficient measures the strength of the relation between two variables, but not the agreement between them.

The Bradley-Blackwood test is very important for appropriately interpreting the Bland-Altman analysis since it simultaneously compares the means and variances of the two measurements(17). In this study, the Bradley-Blackwood F-test was significant for assessment of reproducibility of 10-second and 3-minute measurements for all repolarization lability parameters: QTV, STV(QT) and TT' angle. Therefore, in such cases, the mean bias did depend on the average magnitude of the measurement and inadequately described the differences between the 10-second and 3-minute repolarization lability ECG measurements. This illustrates fundamental differences between 10-second and 3-minute repolarization lability. QT interval variability measured over 3-minute period is largely due to an adaptation to changing heart rate, whereas 10-second ECG segments reflect predominantly stochastic repolarization lability(2,3), as 10 second interval is much shorter than the physiologic span of QT/RR hysteresis(18). Future clinical studies are needed to compare the clinical significance of repolarization lability measured over a 10-second, as compared to 3-minute time interval. Overall, the smallest absolute and relative bias with a relatively narrow 95% limits of agreement was observed for TT' angle.

Limitations

A number of limitations of this research should be mentioned. We have measured the short-term QT interval variability in a combination of 3 ECG leads, although the lead-to-lead differences have previously been reported. While it is well known that repolarization characteristics in men and women are different, we did not study gender differences in this study. Further clinical studies are needed to determine associations between repolarization lability metrics and clinically meaningful outcomes.

Conclusions

Spatial TT' angle is a metric of repolarization lability, concordant with the measurement of short-term variability of the QT interval. TT' angle is a satisfactory reproducible metric of repolarization lability on clinical 10-second ECG.

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Figure 1.

Measurement of a spatial TT' angle. A. Schematic presentation of QRS and T loops and spatial T vectors of consecutive bats. B. Origin point, peak of spatial QRS vector (green), and peak of spatial T vector (red) detected on each beat. C. Spatial QRS vectors (green) and spatial T vectors (red) of consecutive sinus beats of 3-minute interval. D. All beats are aligned in 3-D space by translocating the crosspoint of each beat to the origin of 3-D space (0,0,0), thus shifting all data points within the beat. Spatial TT' angle is measured as an angle between the pair of two consecutive spatial T vectors, and then averaged over studied time epoch.

Figure 2.

A. Bland-Altman plots demonstrating agreement of log-transformed QT variance (logQTV) measurements at 3-minute and 10-second segments. The scatterplot presents paired differences (Y axis), plotted against pair-wise means (X axis). The reference line indicates the perfect average agreement, $Y=0$. The central dashed line indicates the mean absolute difference between the 2 measurements, or mean bias. Upper and lower lines represent the mean $\pm$ 2 standard deviations, or 95% limits of agreement. B. Concordance scatterplot of the logQTV, measured at 3-minute and 10-second segments. The reduced major axis of the data goes through the intersection of the means and has the slope given by the sign of Pearson's r and the ratio of the standard deviations. The reference line shows the perfect concordance, $Y=X$. C. Bland-Altman plots demonstrating agreement of logQTV measurements at 2 random 10-second segments. D. Concordance scatterplots of logQTV at 2 random 10-second segments.

Figure 3.

A. Bland-Altman plots demonstrating agreement of log-transformed short term QT variability (LogSTV) measurements at 3-minute and 10-second segments. B. Concordance scatterplot of the LogSTV, measured at 3-minute and 10-second segments. C. Bland-Altman plots demonstrating agreement of LogSTV measurements at 2 random 10-second segments. D. Concordance scatterplots of LogSTV at 2 random 10-second segments.

Figure 4.

A. Bland-Altman plots demonstrating agreement of log-transformed TT' angle (Log TT' angle) measurements at 3-minute and 10-second segments. B. Concordance scatterplot of the Log TT' angle, measured at 3-minute and 10-second segments. C. Bland-Altman plots demonstrating agreement of Log TT' angle measurements at 2 random 10-second segments. D. Concordance scatterplots of Log TT' angle at 2 random 10-second segments.

Figure 5.

A. Bland-Altman plots demonstrating disagreement of log-transformed TT' angle (Log TT' angle) and log-transformed QT variance (Log QTV) measurements at 3-minute segments. B. Concordance scatterplot of the Log TT' angle and Log QTV, measured at 3-minute segments. C. Bland-Altman plots demonstrating agreement of Log TT' angle and log-transformed short term QT variability (Log STV) measurements at 3-minute segments. D. Concordance scatterplots of Log TT' angle and Log STV at 3-minute segments.

Table 1
Reproducibility agreement of 3-minute and 10-second ECG measurements (n = 172)

Parameter	ECG 3 min (mean±SD)	ECG 10 sec #2 (mean±SD)	Bias	Relative Bias, %	95% Limits of Agreement	Pearson, <i>r</i>	Lin's, ρ_c [95%CI]	Bradley- Blackwood F (P)
Heart rate, bpm	65.4±10.6	65.5±10.7	-.092	-0.14	[-3.28; 3.09]	0.988	0.99[0.985; 0.992]	0.81(0.446)
QT, ms	425.0±27.9	425.5±28.4	-0.0001	-0.00002	[-4.91; 4.91]	0.996	0.99[0.995; 0.997]	0.134(0.875)
Log QTV	3.18±0.94	2.83±1.19	0.35	11.73	[-1.12; 1.83]	0.77	0.72 [0.65; 0.78]	32.9(<0.0001)
Log STV(QT)	1.18±0.50	1.11±0.61	0.08	7.00	[-0.62; 0.78]	0.813	0.791[0.737;0.844]	13.7(<0.0001)
LogTT' Angle	1.15±0.48	1.11±0.55	0.041	3.62	[-0.542;0.625]	0.843	0.832[0.788;0.877]	7.07(0.0011)

QTB =QT corrected by Bazett; QTF= QT corrected by Fridericia; Log QTV = log-transformed QT variance; Log STV(QT)=log-transformed short-term QT variability; LogTT' angle=log transformed spatial TT' angle.

Table 2
Reproducibility agreement of two 10-second ECG measurements (n = 172)

Parameter	ECG 10 sec #1 (mean±SD)	ECG 10 sec #2 (mean±SD)	Bias	Relative Bias, %	95% Limits of Agreement	Pearson, <i>r</i>	Lin's, ρ_c [95%CI]	Bradley- Blackwood F (P)
Heart rate, bpm	65.5±10.8	65.5±10.7	0.004	0.006	[-5.09; 5.10]	0.97	0.97 [0.96; 0.98]	0.27 (0.76)
QT, ms	425.5±28.4	425.0±28.0	0.465	0.001	[-6.91; 7.84]	0.991	0.99[0.988;0.994]	2.44 (0.090)
Log QTV	2.79±1.20	2.83±1.19	-0.042	15.0	[-1.89; 1.81]	0.69	0.69 [0.61; 0.77]	0.188(0.829)
Log STV(QT)	1.15±0.65	1.11±0.61	0.042	3.72	[-1.01; 1.10]	0.645	0.642[0.554;0.730]	1.06 (0.350)
Log TT* Angle	1.10±0.61	1.11±0.55	-0.009	0.81	[-0.84; 0.82]	0.737	0.733[0.664;0.802]	1.74 (0.178)

Table 3
Agreement of corrected QT interval and repolarization lability measures (n = 172 participants)

Metric #1, (mean ± SD)	Metric #2, (mean ± SD)	Bias	Relative Bias, %	95% Limits of Agreement	Pearson, <i>r</i>	Lin's, ρ_c [95%CI]	Bradley- Blackwood F (P)
Log TT' Angle 1.15 ± 0.48	Log STV(QT) 1.18 ± 0.51	-0.030	-2.60	[-1.036; 0.975]	0.463	0.461 [0.344; 0.579]	0.577 (0.568)
Log TT' Angle 1.15 ± 0.48	Log QTV 3.18 ± 0.94	-2.03	-93.8	[-3.70; -0.36]	0.435	0.075 [0.048; 0.103]	852 (<0.0001)