Published in final edited form as:

J Electrocardiol. 2016 ; 49(3): 417–422. doi:10.1016/j.jelectrocard.2016.01.007.

Beat-to-Beat Determinants of the Beat-to-Beat Temporal and Spatial Variability of Repolarization

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Abstract

Background—The goal of this study was to compare the time series predictors of beat-to-beat variability in repolarization in healthy individuals.

Methods—Spatial QRS- and T-vector amplitudes, spatial QRS-T, RR' and TT' angles, RR' and QT intervals, and QRS- and T-loop roundness were measured on 453 consecutive sinus beats in 168 healthy subjects (mean age 39.8±15.6 y; 50% men; 93% white). Panel time-series regression models were adjusted by age, sex, and race. Appropriate time series of ECG metrics served as predictors and outcomes.

Results—Increase in T-loop roundness index by 0.1 was associated with 1.1° (95%CI 0.9–2.2; P=0.048) increase in corresponding TT' angle. One unit increase in a respiration index was associated with 4 ms (95%CI 0.6–7.0; P=0.021) increase in QT interval.

Conclusions—Spatial TT' angle and beat-to-beat variability in T-loop roundness represent intrinsic measures of repolarization variability. QT interval variability characterizes the effect of respiration and heart rate variability.

Keywords

repolarization variability; spatial TT' angle; repolarization; QT interval

Introduction

Recently, we showed that increased beat-to-beat temporal and spatial variability of repolarization, as measured by spatial TT' angle on a routine 12-lead ECG, is independently associated with sudden cardiac death in a large prospective community-dwelling cohort [1].

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Conflict of interest: none

Also, a novel dynamic vectorcardiographic (VCG) approach for measuring beat-to-beat temporal and spatial variability in the cardiac repolarization has been shown as a valuable tool to identify heart failure patients at risk of ventricular tachyarrhythmia [2–5]. Importantly, the spatial TT' angle appeared to be minimally influenced by heart rate [1; 6], and demonstrates good reproducibility [7].

Experimental and theoretical works showed that the mechanism of temporal and spatial variability in repolarization is associated with stochastic gating of calcium and potassium ion channels, and abnormal late sodium current [8; 9] in the presence of cell-to-cell uncoupling. However, human surface ECG is affected by variety of factors (e.g. respiration, baroreflex, and heart rate variability) which may introduce beat-to-beat variability unrelated to intrinsic beat-to-beat variability in repolarization. It is not entirely clear which ECG metrics truly reflect beat-to-beat variability of repolarization. Previously, [1] only cross-sectional predictors of the ECG measures of beat-to-beat variability have been studied. In cross-sectional analysis, spatial TT' angle averaged across 10 seconds was associated with extrinsic factors (heart rate, QRS axis) averaged across 10 seconds, as well as repolarization characteristics (spatial T vector magnitude, T axis, QTc interval, spatial QRS-T angle) [1]. Cross-sectional analysis has obvious limitations and does not appropriately allow for evaluation of the dynamic nature of beat-to-beat associations. However, predictors of the time series of ECG repolarization metrics have not been previously studied. The goal of this study was to conduct comprehensive evaluation and comparison of the time series predictors of beat-to-beat variability in QT interval, spatial TT' angle, T-loop roundness, and T vector amplitude.

Methods

Study Population and ECG Recording

We analyzed digital ECGs from participants of the Intercity Digital Electrocardiogram Alliance (IDEAL) study [10]. Clinical and demographic characteristics of the study population were previously described [6]. Our analysis only included healthy participants of at least 18 years of age. High resolution (1000 Hz) modified (5th intercostal space) Frank orthogonal XYZ ECGs were recorded at rest in the supine position for at least 3 minutes.

Time Series ECG Analysis

Three minutes recordings of consecutive sinus beats were analyzed. All described below ECG and VCG metrics were measured on each consecutive sinus beat. No beats were excluded from analysis; all ECG recordings contained consecutive sinus beats only. RR' intervals and QT intervals were measured on each X, Y and Z leads and then averaged across 3 leads.

Time Series Dynamic VCG analysis

VCG fiducial points (origin point, peak of spatial QRS vector, and peak of spatial T vector) were detected automatically using custom MATLAB (MathWorks, Inc, Natick, MA) software, as previously described [6]. The amplitudes of the spatial QRS and T vectors were measured. Spatial TT' angle was calculated as the spatial angle between two sequential T

vectors, as previously described [5; 6]. Spatial RR' angle was similarly measured between two sequential QRS vectors. Mean spatial QRS-T angle was measured on each beat, as previously described[11].

T-Loop and QRS-Loop Roundness

Spatial T-loop roundness was quantified via principal component analysis (PCA)[12]. For each T loop, the two most significant components accounted for the length and width of the loop, respectively. A roundness quantification, roundness index, was then created by taking the ratio of the two largest eigenvalues of the covariance matrix of the data points composing the T loop. Thus, a ratio close to 1 represents nearly circular loop geometry. Deviance from 1 means the loop is oval-shaped.

ECG-Derived Respiration index

Respiration was derived using a previously validated approach[13]. The respiration index for each beat was calculated as

$$\text{Respiration index} = \tan^{-1} \left(\frac{\text{QRS Area } X}{\text{QRS Area } Z} \right), \quad (1)$$

where *QRS Area X* and *QRS Area Z* are the areas of the QRS complex on the X and Z leads, respectively.

Frequency-based coherence analysis

Frequency-based correlation between signals was measured using spectral coherence, which quantifies the strength of interaction between two signals as a function of the frequency of their fluctuations[14]. First, the sinus beat time series of analyzed metrics were resampled to 4 Hz using cubic spline interpolation. Linear trends were also removed from the data. Then, the power spectral densities of signals were calculated using the Welch method[15]. The magnitude-squared coherence (C_{xy})[14] between two signals (x and y) was measured by the equation,

$$C_{xy} = \frac{|G_{xy}|^2}{G_{xx}G_{yy}}, \text{ where } \quad (2)$$

G_{xy} is the cross-spectral density between x and y , and G_{xx} and G_{yy} the autospectral density of x and y respectively. Perfect spectral coherence between x and y is indicated by $C_{xy} = 1$; a complete absence of coherence is indicated by $C_{xy} = 0$.

To quantify coherence between signals, the mean of the coherence was taken in the frequency band of 0 to 0.33 Hz, capturing the coherence between signals in the frequency range of significant spectral power, and enabling estimation of the coherence with respiration, as 0.33 Hz is the upper limit of the normal resting respiration rate.

Statistical analysis

To characterize predictors of beat-to-beat changes in QT interval, spatial TT' angle, T-loop roundness, and T vector amplitude, we built panel time-series regression models[16] with a common correlated effects mean group estimator. These models reflect the nature of analyzed data; they emphasize variable nonstationarity, cross-section dependence (due to true unobserved correlations between ECG metrics common to all patients), and heterogeneity in the individual patient-specific slopes over time. Time series of the spatial TT' angle measured between two sequential T vectors (for each pair of beats) served as an outcome in one set of the models. Time series of the QT interval measured on each beat served as an outcome in another set of models. The third and the fourth sets of models were built for the time series of the T-loop roundness and the time series of T-vector amplitude measured on each beat as outcomes, respectively. Age, sex, and race were entered as “fixed” effects predictors, for adjustment. Time series of RR' and QT intervals, spatial QRS and T peak vector amplitudes, mean spatial QRS-T angle, T-loop and QRS-loop roundness, spatial RR' and TT' angles, and respiration index were entered as patient-specific “random” effects predictors. The Pesaran and Smith (1995) mean group (MG) estimators, and the Pesaran (2006) common correlated effects mean group (CCEMG) estimators were calculated. In the CCEMG models the cross-section averages of the dependent and independent variables were included as additional regressors to account for the unobservable latent predictors. STATA 14 (StataCorp LP, College Station, TX) was used for the analysis.

Results

Study population

Data of 168 study participants were analyzed (mean age 39.8 ± 15.6 y; 84 (50%) men; 156 (93%) white). Time series of 453 consecutive sinus beats were included in the analysis. A representative example of the consecutive sinus beats displaying beat-to-beat time series of spatial TT' angle, spatial T vector amplitude, and T-loop roundness in a healthy individual participant of the study is shown in Figure 1.

Patient-specific predictors of beat-to-beat spatial TT' angle

Results of the panel time-series regression models (adjusted by age, sex, and race) are presented in Tables 1a–b. Time series of RR' and QT intervals were inversely associated with time series of spatial TT' angle. Prolongation of QT interval by 100 ms on a certain beat was associated with a decrease in TT' angle by 1.3° on the same beat. Similarly, shortening of RR' interval by 100 ms on a certain beat was associated with an increase in TT' angle by 0.2° on the same beat. Association of spatial TT' angle with QRS-T angle was also inverse. Widening of spatial QRS-T angle by 10° on a certain beat was associated with a decrease in TT' angle by 0.42° on the same beat. Time series of RR' angle were directly associated with time series of TT' angle. Widening of RR' angle by 10° on a certain beat was associated with widening of TT' angle by 2.8° on the same beat. However, the strongest association was observed with T-loop roundness time series. An increase in T-loop roundness index by 0.1 on a certain beat was associated with about 1° increase in TT' angle measured between the same and subsequent beat. Interestingly, observed association faded in a model with the CCEMG estimator, which suggested the presence of time-variant

unobserved factors with heterogeneous impact across study participants (panel members). Time series of QRS or T vector amplitudes, QRS roundness, and respiration were not associated with time series of spatial TT' angle.

Patient-specific predictors of beat-to-beat T-loop roundness

Time series of spatial TT' angle significantly predicted the time series of T-loop roundness. An increase in TT' angle between a particular beat and its subsequent beat was associated with an increase in T-loop roundness on a particular beat (Table 1a). No other time series variable determined the time series of T-loop roundness.

Patient-specific predictors of beat-to-beat QT interval variability

Time series of QT interval were significantly and strongly predicted by respiration index. One unit increase in a respiration index in a certain beat was associated with 4 ms increase in QT interval on the same beat (Table 1b). As expected, RR' interval time series also predicted QT interval time series. An increase in RR' interval by 100 ms was associated with a 1.4 ms increase in the corresponding QT interval. Spatial RR' angle time series were inversely associated with QT interval time series. An increase in RR' angle by 10° on a particular beat was associated with about 1 ms shortening of QT interval. Interestingly, observed association faded in a model with the CCEMG estimator, implying the presence of beat-to-beat variable unobserved factors with heterogeneous impact across study participants.

Patient-specific predictors of beat-to-beat T vector amplitude

Time series of T vector amplitude were predicted by all tested time series, with exception of the time series of TT' angle. Increase in QRS vector amplitude and in T-loop roundness on a particular beat was associated with increase in T vector amplitude on the same beat. Increase in RR' and QT interval, RR' angle, QRS-T angle, QRS roundness and respiration index on a particular beat was associated with decrease in T vector amplitude on the same beat (Table 1a).

Frequency-based coherence

QT interval showed highest coherence with spatial QRS vector amplitude, RR' interval, and respiration (Table 2). This was expected, as QT interval is known to be affected by heart rate and respiration. However, TT' angle, as compared to QT interval, had a lower coherence with all extrinsic factors.

Discussion

Our study employed a sophisticated and robust statistical approach for analysis of person-specific time series of heart beats and elucidated predictors of beat-to-beat variability in ECG metrics. We demonstrated strong association of beat-to-beat variability in spatial TT' angle with T-loop roundness time series. T-loop roundness time series were predicted solely by TT' angle time series, which suggests that beat-to-beat variability of TT' angle and T-loop roundness reflects intrinsic temporal and spatial repolarization variability, and is minimally influenced by extrinsic factors. In contrast, beat-to-beat QT variability time series

were predicted by respiration and RR' interval time series only, suggesting that QT variability reflects QT interval changes in response to respiration and extrinsic factors, but does not characterize repolarization lability. Time series of spatial T vector amplitude were predicted by wide variety of both extrinsic and intrinsic repolarization factors.

Beat-to-beat time series of spatial TT' angle and T-loop roundness reflect intrinsic repolarization variability and are minimally affected by extrinsic factors

While experimental and theoretical electrophysiological studies elucidated mechanisms of beat-to-beat action potential variability and showed mechanistic link between temporal variability in repolarization and life-threatening ventricular arrhythmias [8; 9], translation of this concept into clinical electrophysiology has been challenging. Assessment of repolarization in human ECG is substantially affected by extrinsic factors such as respiration and heart rate variability. Repolarization could be quantified by several metrics on ECG and VCG: QT interval, spatial T vector amplitude and direction, spatial TT' angle, and T-loop roundness. For further clinical studies it is important to select ECG repolarization metric(s), which reflect intrinsic repolarization variability, rather than extrinsic factors.

In this study we showed that beat-to-beat time series of spatial TT' angle and T-loop roundness are not affected by respiration. Moreover, T-loop roundness time series were predicted by TT' angle time series only. In turn, TT' angle time series were predicted by time series of repolarization characteristics (QT interval, QRS-T angle, T-loop roundness), and were only minimally affected by heart rate variability (RR' interval time series). This finding is consistent with previously shown independent association of spatial TT' angle with sudden cardiac death/ventricular arrhythmia in the general population [1] and in heart failure patients [5]. Spatial TT' angle is adequately reproducible on 10-sec ECGs [7] and deserves further clinical evaluation as a mechanistic predictor of sudden cardiac death and ventricular tachyarrhythmias. It is currently unknown whether beat-to-beat variability in T-loop roundness is independently associated with sudden cardiac death. Results of our study suggest that further evaluation of beat-to-beat T-loop roundness variability is needed.

Beat-to-beat time series of QT interval reflect extrinsic factors: respiration and RR' interval dynamics

This study showed that QT interval variability is substantially affected by external factors. In fact, QT variability was predicted by extrinsic factors only: respiration, RR' intervals, and spatial RR' angle. No beat-to-beat time series of repolarization characteristics predicted beat-to-beat QT interval time series. Similarly, the coherence analysis showed strong coherence of QT interval (but not TT' angle) with respiration and RR' interval. This finding helps to explain our previous observation of QT variability index being associated with cardiovascular and all-cause mortality, but not sudden cardiac death [17]. Results of this study clearly showed that QT variability is not a preferential measure of intrinsic repolarization lability. In clinical scenarios when only single channel ECG is available for analysis (and therefore, dynamic VCG assessment of intrinsic repolarization variability is impossible), additional computational approaches are needed to minimize effect of extrinsic factors, and to accentuate effect of intrinsic repolarization factors on QT interval variability, with subsequent re-evaluation in the panel time-series regression analysis.

Patient-specific analysis of the time series

In this study we applied panel time series regression analysis [16]. The strength of a panel data analysis approach is in its patient-specificity, which permits heterogeneity in individual participants' time-series behavior, and appropriately accounts for patient-specific correlations between consecutive beats in beat-to-beat time series. Panel time series regression analysis is widely used in financial statistics, but has not been previously applied for ECG time series analysis. Panel time series regression analysis fits the studied data well, which helps to answer the research question appropriately.

Dynamic repolarization phenomena: T-wave alternans and post extrasystolic T-wave change

Results of this study may have wide applicability and help to explain not only non-alternating repolarization variability, but also other dynamic repolarization phenomena, such as T-wave alternans (TWA) and post extrasystolic T-wave change (PEST). This study showed that temporal variability of spatial T-vector amplitude (alternating form of which is measured as TWA) is affected by both intrinsic and extrinsic factors. It is possible that in some studies' populations TWA were formed in result of true intrinsic repolarization alternans, whereas in other studies' populations appearance of TWA on the surface ECG was influenced by extrinsic factors. This explains controversies in the predictive value of TWA [18; 19]. Possibly, alternans of T-loop roundness or alternans of TT' angle could become more accurate predictors of ventricular arrhythmias and sudden cardiac death than TWA.

Results of our study are consistent with previous reports of the effect of extrinsic factors (e.g. baroreflex) on repolarization, presented as PEST [20]. Further studies of intrinsic and extrinsic predictors of cardiac repolarization in different patient populations are needed.

Limitations

In this study we used ECG-derived respiration, as no recorded respiration signal was available. Though this method has been clinically validated [21], it is indirect and therefore may not account for all effects of respiration on ECG, and especially on VCG signal. Therefore, while respiration index time series did not predict TT' angle and T-loop roundness time series, another study with a directly recorded respiration signal is needed for definitive conclusion about freedom from respiration influence for beat-to-beat TT' angle and T-loop roundness time series.

Further study should be done to explore the potential clinical relevance of the intrinsic nature of repolarization variability metrics. It is important to note that only healthy individuals were studied in this study, and additional work should explore if similar results occur in patients with high risk for SCD. Beat-to-beat predictors of repolarization variability amongst different patient populations may differ and may provide insight regarding the clinical relevance of such metrics.

Conclusions

Spatial TT' angle and beat-to-beat variability in T-loop roundness represent intrinsic measures of beat-to-beat repolarization lability. Beat-to-beat variability in QT interval represent effect of extrinsic factors (respiration and heart rate variability) on ECG.

Acknowledgments

Authors thank Lichy Han, BS, and Sanjoli Sur, BS, for help with the data analysis.

Financial support:

This work was partially supported by the National Institutes of Health (HL118277 to LGT).

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Figure 1.
Representative example of the consecutive sinus beats beat-to-beat time series of spatial TT' angle, spatial T vector amplitude, and T-loop roundness

Table 1a

Patient-specific predictors of T-loop roundness and T vector amplitude time series

Outcome:		T-loop roundness time series		T vector amplitude time series	
Predictor		Coefficient (95%CI)	P	Coefficient(95%CI)	P
RR' interval time series, ms	MG	$1*10^{-4}(-2*10^{-4} \text{ to } 5*10^{-4})$	0.416	$-9*10^{-4}(-5*10^{-4} \text{ to } -1*10^{-3})$	<0.0001
	CCEMG	$2*10^{-4}(-9*10^{-6} \text{ to } 5*10^{-4})$	0.164	$-9*10^{-4}(-5*10^{-4} \text{ to } -1*10^{-3})$	<0.0001
QT interval time series, ms	MG	$-8*10^{-4}(-2*10^{-3} \text{ to } 4*10^{-4})$	0.172	$-6*10^{-3}(-4*10^{-3} \text{ to } -8*10^{-3})$	<0.0001
	CCEMG	$-7*10^{-4}(-2*10^{-3} \text{ to } 4*10^{-4})$	0.255	$-6*10^{-3}(-4*10^{-3} \text{ to } -8*10^{-3})$	<0.0001
Spatial QRS vector amplitude time series	MG	0.16(-0.009 to 0.322)	0.063	0.24(0.19–0.29)	<0.0001
	CCEMG	0.15(-0.10 to 0.31)	0.068	0.23(0.18–0.28)	<0.0001
Spatial T vector amplitude time series	MG	0.05(-0.12 to 0.22)	0.582	N/A	
	CCEMG	0.08(-0.13 to 0.28)	0.459	N/A	
Spatial RR' angle time series	MG	$-2*10^{-4}(-3*10^{-3} \text{ to } 3*10^{-3})$	0.910	$-8*10^{-3}(-1*10^{-2} \text{ to } -2*10^{-3})$	0.010
	CCEMG	$-2*10^{-4}(-3*10^{-3} \text{ to } 3*10^{-3})$	0.911	$-3*10^{-3}(-8*10^{-2} \text{ to } -2*10^{-3})$	0.007
Spatial TT' angle time series	MG	$3*10^{-3}(1*10^{-3} \text{ to } 5*10^{-3})$	0.001	$-4*10^{-3}(-8*10^{-3} \text{ to } -1*10^{-3})$	0.125
	CCEMG	$3*10^{-3}(1*10^{-3} \text{ to } 5*10^{-3})$	0.001	$-3*10^{-3}(-8*10^{-3} \text{ to } -1*10^{-3})$	0.157
QRS-loop roundness time series	MG	0.006(-0.05 to 0.07)	0.840	-0.29(-0.44 to -0.14)	<0.0001
	CCEMG	$-2*10^{-3}(-0.06 \text{ to } 0.06)$	0.995	-0.28(-0.43 to -0.13)	<0.0001
T-loop roundness time series	MG	N/A		0.58(0.10–1.05)	0.018
	CCEMG	N/A		0.59(0.11–1.07)	0.016
Spatial QRS-T angle time series	MG	$4*10^{-4}(-3*10^{-3} \text{ to } 4*10^{-3})$	0.798	-0.002(-0.003 to -0.001)	<0.0001
	CCEMG	$6*10^{-4}(-2*10^{-3} \text{ to } 4*10^{-3})$	0.699	-0.002(-0.002 to -0.001)	<0.0001
Respiration index time series	MG	-0.01(-0.03 to 0.009)	0.266	-0.130(-0.169 to -0.090)	<0.0001
	CCEMG	-0.01(-0.03 to 0.007)	0.214	-0.123(-0.163 to -0.084)	<0.0001

MG=the Pesaran and Smith (1995) mean group estimator; CCEMG=the Pesaran (2006) common correlated effects mean group estimator

Table 1b

Patient-specific predictors of spatial TT, angle and QT interval time series

Outcome: Predictor	TT, angle time series		QT interval time series	
	Coefficient (95%CI)	P	Coefficient(95%CI)	P
RR' interval time series, ms	MG	0.025	0.014(0.009-0.020)	<0.0001
	CCEMG	-0.002(-0.005 to -0.00002)	0.048	0.012(0.006-0.018)
QT interval time series, ms	MG	-0.013(-0.023 to -0.002)	0.022	N/A
	CCEMG	-0.011(-0.022 to -0.0007)	0.037	N/A
Spatial QRS vector amplitude time series	MG	1.62(-9.84 to 13.08)	0.782	6.14(-13.88 to 26.17)
	CCEMG	1.95(-9.56 to 13.46)	0.740	8.51(-5.68 to 22.70)
Spatial T vector amplitude time series	MG	2.80(-8.55 to 14.14)	0.629	-2.56(-43.95 to 38.82)
	CCEMG	4.21(-7.42 to 15.84)	0.478	-3.25(-44.63 to 38.12)
Spatial RR' angle time series	MG	0.28(0.21-0.34)	<0.0001	-0.090(-0.67 to -0.013)
	CCEMG	0.28(0.22-0.34)	<0.0001	-0.080(-0.164 to 0.003)
Spatial TT' angle time series	MG	N/A		-0.023(-0.081 to 0.034)
	CCEMG	N/A		-0.004(-0.064 to 0.057)
QRS-loop roundness time series	MG	3.09(-1.54 to 7.73)	0.191	-13.13(-33.88 to 7.62)
	CCEMG	2.63(-1.79 to 7.05)	0.244	-13.84(-34.17 to 6.48)
T-loop roundness time series	MG	10.79(0.09-21.50)	0.048	-14.63(-55.54 to 26.27)
	CCEMG	9.71(-0.78 to 20.20)	0.070	-13.38(-54.24 to 27.47)
Spatial QRS-T angle time series	MG	-0.042(-0.063 to -0.022)	<0.0001	0.029(-0.053 to 0.111)
	CCEMG	-0.044(-0.064 to -0.024)	<0.0001	0.026(-0.053 to 0.106)
Respiration index time series	MG	-0.20(-1.20 to 0.81)	0.698	3.80(0.56-7.04)
	CCEMG	-0.18(-1.34 to 0.98)	0.759	4.14(0.58-7.71)

MG=the Pesaran and Smith (1995) mean group estimator; CCEMG=the Pesaran (2006) common correlated effects mean group estimator

Table 2

Coherence between repolarization metric and extrinsic factors

Signal	Mean coherence with	
	TT' angle	QT interval
Spatial QRS vector amplitude	0.31±0.11	0.57±0.12
RR' interval	0.30±0.11	0.50±0.13
Spatial mean QRS-T angle	0.32±0.12	0.40±0.12
Spatial T vector amplitude	0.30±0.11	0.45±0.11
T-Loop roundness	0.31±0.13	0.32±0.12
Respiration	0.32±0.12	0.49±0.13