T-Wave Morphology Parameters Based on Principal Component Analysis Reproducibility and Dependence on T—Offset Position

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Background: T-wave morphology parameters based on principal component analysis (PCA) are candidate to better understand the relation between QT prolongation and torsades de pointes. We aimed to assess the repeatability and to determine the influence of T-end position on PCA parameters.

Methods: Digital ECGs recorded from 30 subjects were used to assess short term (5 minutes), circadian and long-term (28 days) repeatability of PCA parameters. The T-end cursor position was moved backward and forward (± 8 ms) from its optimal position. We calculated QRS-T angle, PCA ratio, and T-wave residuum (TWR).

Results: At long-term evaluation, coefficients of variation were 11.3 ± 9.9%, 11.7 ± 7.1%, and 23.0 ± 22.0% for the QRS-T angle, PCA ratio, TWR, respectively. After moving the T-end cursor, repeatability was 0.42 ± 0.2%, 1.00 ± 1.04%, 4.0 ± 4.2% for the same PCA parameters.

Conclusions: T-wave morphology parameters based on PCA are reproducible with the exception of TWR and QRS-T angle. In addition, PCA is robust, showing only little dependence on T-end cursor position. These data should be taken into account for safety pharmacology trials.

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ECG; QT interval; principal component analysis; repeatability

The principal component analysis (PCA) is originally a technique that aims to represent a large number of signals by means of a limited number of fundamental values. When applied to digital ECG tracings, the method determines the "principal components" which represent most of the ECG information. Usually, the first three principal components provide nearly the total energy of the ECG.[1,2] Since the mathematical procedure calculates fundamental orthogonal components, PCA analysis of the ECG signal is a modern approach to the old-fashioned vectocardiography based on orthogonal X, Y, and Z physical leads.[2,3]

Clinical applications of PCA applied to digital ECGs are rapidly increasing. For instance, PCA analysis can compensate for respiration or body position-related ECG morphology changes.[4] The PCA analysis can also enrich the characterization of ventricular repolarization. In particular, it has been shown that PCA analysis of body surface potential maps can identify non-dipolar content.[1,5,6] Lux and De Ambroggi suggested that a complex multipeak distribution of ECG information might reflect regional ventricular repolarization heterogeneity.[1,5]

Subsequently different authors have hypothesized that PCA analysis of the standard digital 12-lead ECG may also reflect regional ventricular repolarization heterogeneities[7,8,9] thus, representing a better ECG marker of arrhythmic risk than the discredited so-called "QT dispersion".[9,10,11] Actually, different T-wave parameters obtained after using PCA analysis, such as the QRS-T angle, PCA ratio, and the T-wave residuum have been shown as promising predictors of cardiovascular[12–14] or total mortality[13,15,16] in population studies.

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Cardiovascular safety of new drug entities is critical.[17–19] Current guidelines on the proarrhythmic potential of a drug are based on QT prolongation,[20] but there is a poor understanding of the relation between QT prolongation and clinical risk of pro-arrhythmia. We lack predictive biomarkers to improve our approach of the pathway leading to torsades de pointes.[18,21] PCA characterization of ventricular repolarization could represent a solution to replace QT duration.

However, before being used in pharmacological studies, any biomarker needs clinical qualification. The repeatability of T-wave morphology parameters based on PCA over time as well as the influence of preprocessing require to be better documented.[22] T-wave morphology parameters based on PCA are believed to be less dependent on precise determination of T wave offset than more traditional analyses,[9,23] although the influence of precise cursor position has not been systematically tested.

The aim of our study was two-fold: (1) to assess the repeatability over time of T-wave morphology parameters based on PCA in the setting of a thorough QT study, (2) to determine the influence of T-end position on the same parameters.

PATIENTS AND METHODS

Study Design

The data reported in the present paper are part of a phase 1 clinical trial designed as a 3-way crossover study. The study was randomized, double blind and placebo-controlled. Only placebo data are reported in the present paper. The study was approved by two independent ethics committees and subjects signed an informed consent form.

The study population included 30 healthy subjects, 15 males, and 15 females. The mean age was 29 ± 5 years.

ECG Recordings and Preprocessing

Digital 12-lead ECGs (MAC5000 GE Medical systems, Milwaukee, USA) were repeatedly recorded in resting supine position and in this trial the healthy subjects were in fed conditions. The electrodes were placed at the same place for each ECG recording. From the ECG data base we selected the following subset for each subject: (1) five ECGs at Day 1 (D1), including three ECGs (5 minutes apart) at 8:00 a.m. time point, a second ECG at 2:00 p.m., and a third one at 8:00 p.m. (2) at Day 14 (D14) and Day 28 (D28) one ECG recorded at 8:00 a.m. That subset was used to assess repeatability of PCA parameters (Fig. 1), the short term (three ECGs 5 minutes apart), the circadian (three ECGs 6 hours apart), and the long term ones, respectively (three ECGs 2 weeks apart).

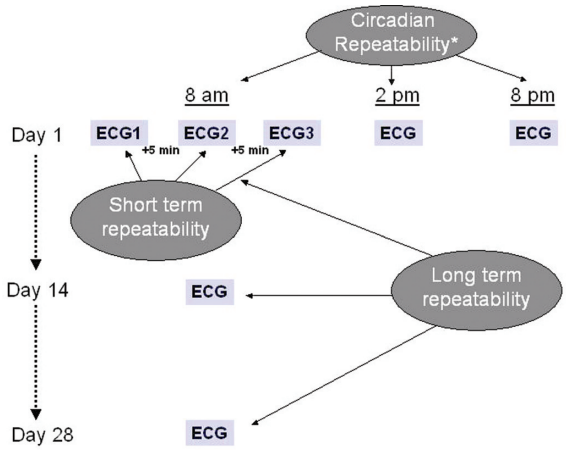

Figure 1. Study design.* The circadian repeatability was assessed at the placebo period.

First electrical cardiac signals from MAC5000 10-second ECG strips were averaged (custom-averaging process based on a sample-to-sample averaging). Then the position of QRS onset, QRS offset, and T-wave end cursors was automatically determined on the averaged ECG waveforms and manually corrected by an expert cardiologist when necessary using the 12-lead overlapped view the ECG (Fig. 2). PCA analysis was performed separately on the area of the QRS complex (QRS onset–QRS offset) and on the T-wave time interval (QRS offset- T-wave offset).

Finally, the position of the T-wave end cursor was shifted from its "optimal" position as defined above on one of the ECG recorded at 8:00 a.m. The cursor position was moved 4 and 8 ms backward and forward. We thus obtained for each ECG five different cursor positions (QT-8 ms, QT-4 ms, QT, QT+4 ms, and QT+8 ms). The corresponding QT intervals were used to assess the influence of the T-wave end position on PCA derived values.

PCA Analysis

PCA analysis was run using a custom dedicated software. Singular value decomposition was applied to the covariance matrix of the raw ECG data

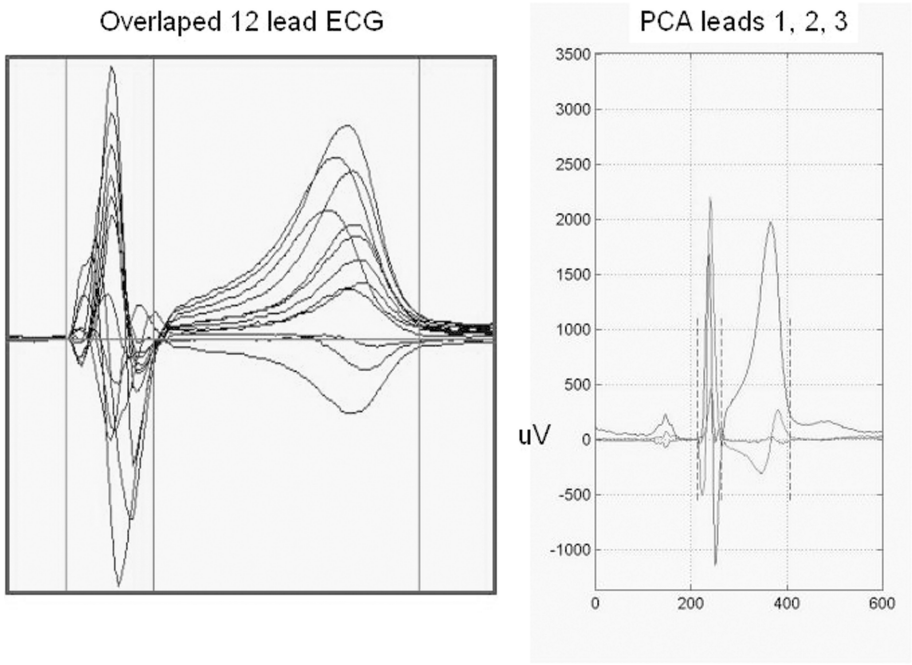

Figure 2. ECG processing Left panel: Cursor position identification on the 12-lead overlapped ECG Right panel: The three first PCA leads.

(amplitude at sampling time × ECG channel) from the eight independent ECG leads. Singular value decomposition was applied to obtain the eigenvectors and the eigenvalues of the QRS complex and of the T wave.[24,25,26]

The orthogonal eigenvectors delineate a eight-dimensional space, whereas the eigenvalues (λ_1, ..., λ_8) represent the energy in each dimension. The first dimension, given by the first eigenvector, contains the maximum energy. The sum of all the eigenvalues represents the total power of the ECG signal. Singular value decomposition was applied independently on QRS complex and T wave to obtain the eigenvectors and the eigenvalues for each part of the signal. The angle θ between QRS and T is defined as the angle between the principal vector of the QRS complex, and the principal vector extracted from the T wave.

The projection of the T wave on the subspace defined by the last five eigenvectors is commonly named the non-dipolar components of the T wave or "T-wave residuum" (TWR). The energy of the TWR is computed by the following formula: $TWR4-8 = 100 - [\sum_{i=4}^{8} \lambda i / \sum_{i=1}^{8} \lambda i)^{*}100]$. Similarly, the proportion of energy remaining after the first two orthogonal leads is calculated by $TWR3-12 = 100 - [(\sum_{i=3}^{8} \lambda i / \sum_{i=1}^{8} \lambda i)^{*}100]$.

In each dimension, the dispersion of the T wave PCA loop is given by sigma (σ_i, expressed in mV) where σ_i is defined as: $\sigma_i = \sqrt{\lambda_i}$, i = 1...8 (Fig. 3).

The ratio of the second to the first σ ($\sigma 2/\sigma 1$) is the so-called PCA ratio and provides an estimate of the roundness of the PCA T-wave loop (Fig. 3).

The percentage of the PCA T-wave loop projected on the plane defined by the two first eigenvectors is defined as: $\%T\_\sigma 1\sigma 2 = (\sum_{i=1}^{2} \sigma i / \sum_{i=1}^{8} \sigma i)^{*}100$. Similarly, $\%T\_\sigma 1\sigma 2\sigma 3 = (\sum_{i=1}^{3} \sigma i / \sum_{i=1}^{8} \sigma i)^{*}100$ represents the percentage of the PCA T-wave loop projected on the space defined by the three first eigenvectors.

Statistical Analysis

Data are presented as mean ± SD. Quantitative data were compared using ANOVA for repeated measures. The coefficient of variation was defined as the intrasubject SD divided by the grand mean, multiplied by 100. In addition, Bland and Altman plots were calculated for the short-term repeatability (10 minutes apart), long-term repeatability (28 days), circadian repeatability (8 a.m. vs 2 p.m.). Bland and Altman method was also used to assess the influence of T-wave end position.

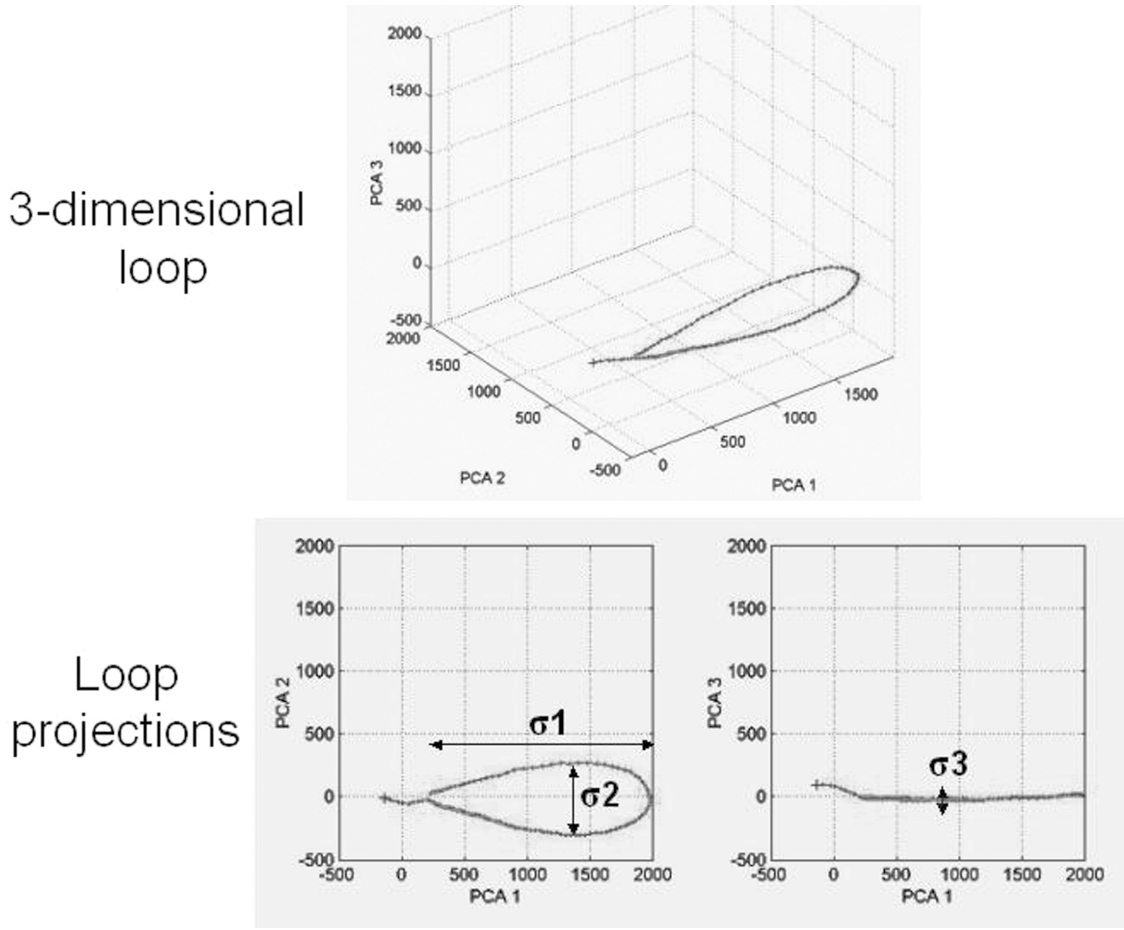

Figure 3. The T-wave loop (upper panel) and its projection onto the PCA1/PCA2 and PCA1/PCA3 preferential planes.

RESULTS

Gender Differences

Table 1 shows the ECG and T-wave morphology parameters based on PCA separately in males and females. Females had a non-significant faster heart rate and prolonged QT/QTc intervals.

More than 90% of the T-wave loop was included in two dimensions (%T˙ $\sigma 1\sigma 2$) and more than 95% in three dimensions (%T˙$\sigma 1\sigma 2\sigma 3$). Both the %T˙$\sigma 1\sigma 2$ and %T˙$\sigma 1\sigma 2\sigma 3$ were significantly higher in males than in females. Accordingly, the T-wave residuum (TWR4–8) was significantly higher females.

The width of the T-wave loop was close to 20% of its length ($\sigma 2/\sigma 1$) without significant difference between genders. The QRS-T angle was around 45–50 degrees.

Repeatability of PCA Parameters over Time

Table 2 shows the actual values of ECG and T-wave morphology parameters for the different time points. The values measured around 8 a.m. (either triplicate ECGs or ECGs across study days) were very close to each other. Oppositely, the variations of both ECG and T-wave morphology parameters from 8 a.m. to 2 p.m. were significant.

The co-efficients of variation together with the Bland and Altman values are shown Table 3 and Figure 4. The repeatability of T-wave morphology parameters slightly decreased from short to long-term evaluation. The circadian repeatability was not as good as the long term one measured at the same time of the day. The TWR showed much higher coefficients of variability than other PCA parameters.

Table 1. T-Wave Morphology Parameters Based on PCA in Male and Female Normal Subjects

	Females	Males
R-R (ms)	1042 ± 103 [870; 1250]	1091 ± 143 [845; 1333]
QT (ms)	403 ± 25 [364; 446]	399 ± 28 [358; 442]
QTc Bazett (ms)	395 ± 19 [349; 418]	383 ± 23 [340; 412]
QRS-T angle	51.9 ± 36 [16.9; 88.9]	45.8 ± 18 [6.9; 67.7]
%T$\dot{\sigma}1\sigma2$	92.6 ± 2.2 [88.9; 95.5]	94.3 ± 1.5* [91.5; 96.4]
%T$\dot{\sigma}1\sigma2\sigma3$	95.7 ± 1.4 [92.6; 97.4]	96.7 ± 0.7* [95.3; 97.8]
TWR 3–8 (%)	0.260 ± 0.179 [0.060; 0.604]	0.161 ± 0.135 [0.037; 0.489]
TWR 4–8 (%)	0.078 ± 0.060 [0.021; 0.209]	0.042 ± 0.020* [0.019; 0.083]
$\sigma2$ / $\sigma1$	0.20 ± 0.07 [0.08; 0.31]	0.23 ± 0.07 [0.12; 0.35]

* $P < 0.05$
Mean ± SD – Numbers in brackets indicate the range

The Role of T-Wave End Cursor Position

Table 4 present the values of PCA parameters after shifting the position of the T-offset cursor. Although statistically significant, the differences observed were rather small (Table 4) and of a lesser magnitude than the differences between triplicate ECG recordings. Correspondingly, the repeatability of the measures was excellent (Table 5 and Fig. 5).

Rate influences

With the exception of the QRS-T angle, T-wave morphology parameters based on PCA were correlated with the R-R interval (Table 6). However, although significant, the correlations were weak (less of 10% of T-wave morphology parameters changes could be explained by R-R changes). In addition, the slope (alpha coefficient) of the relationships were low. For instance, a 100 ms RR interval change would induce a 0.3% absolute change in the %T$\dot{\sigma}1\sigma2\sigma3$ parameter.

DISCUSSION

Main Results

Most of T-wave morphology parameters based on PCA, but not TWR and QRS-T angle display stable results over time in healthy subjects. Another important result is that the position on the T-offset cursor has only little influence on T-wave morphology parameters.

Significance of T-Wave Morphology Parameters Based on PCA

The QRS-T angle is the easiest PCA parameters to be understood intuitively. In the early 1930s, Wilson and coworkers tried to separate between T-wave variations related to changes in the depolarization wave (so-called "secondary" T-wave changes) and those related to the repolarization itself (or "primary" T-waves changes). Wilson therefore introduced the concept of the "ventricular gradient" which is calculated by summing the QRS and the T-wave areas from orthogonal XYZ leads. The calculation of the QRS-T angle using PCA is mathematically related to the ventricular gradient. Accordingly, an increase in QRS-T angle has been demonstrated as a predictor of bad outcome.[14,27]

However, assuming that regional rather than global ventricular heterogeneities are implicated in arrhythmia mechanisms,[28] the QRS-T angle is probably not the best surrogate for arrhythmic risk stratification.

The PCA ratio is an old vectocardiographic parameter that describes the projection of the T-wave loop onto its preferential plane.[3,29] The length of a normal T-wave loop is five times longer than its width, leading to a PCA ratio around 20%. Several data suggest that a malfunctioning ventricular repolarization process is associated with an increase in the PCA ratio (an increase of T-wave loop roundness)[30,31] that in turn is associated with an increased mortality.[12,14,16] The association between an increased T-wave loop roundness and increased mortality is not fully elucidated.

PCA analysis of body surface potential maps clearly demonstrates that after the first three components the remaining energy is associated with the presence of electrical multipeaks.[1,5,6] From 12-lead ECG, the so-called TWR could represent the nondipolar components of the T-wave energy and could reflect regional ventricular repolarization heterogeneities,[7,8] although this link has yet not been fully demonstrated from the standard 12-lead set. As in previous studies, we found that the TWR stands for only a small amount (i.e. less than 1%) of total T-wave energy in normal subjects.[7–9,15]

Table 2. Values of T-Wave Morphology Parameters Based on PCA at Different Times

	Short-Term Repeatability (n = 30)			
	ECG 1	ECG 2	ECG 3	ANOVA
R-R (ms)	1065 ± 126	1042 ± 108	1048 ± 102	NS
QT (ms)	401 ± 23	399 ± 20	399 ± 22	NS
QRS-T angle	49.7 ± 27.6	49.8 ± 26.8	49.2 ± 27.0	NS
%T$\dot{}\sigma 1\sigma 2$	93.5 ± 2.2	92.6 ± 2.4	93.3 ± 2.6	NS
%T$\dot{}\sigma 1\sigma 2\sigma 3$	96.2 ± 1.2	96.3 ± 1.3	96.1 ± 1.5	NS
TWR 3–8(%)	0.207 ± 0.186	0.210 ± 0.213	0.228 ± 0.241	NS
TWR 4–8(%)	0.064 ± 0.054	0.065 ± 0.071	0.073 ± 0.090	NS
$\sigma 2$ / $\sigma 1$	0.21 ± 0.07	0.21 ± 0.07	0.21 ± 0.07	NS
	Long-Term Repeatability (n = 29)			
	D1	D14	D28	ANOVA
R-R (ms)	1064 ± 124	1057 ± 155	1068 ± 126	NS
QT (ms)	400 ± 23	400 ± 30	401 ± 26	NS
QRS-T angle	50.3 ± 27.8	49.2 ± 27.9	48.2 ± 28.4	NS
%T$\dot{}\sigma 1\sigma 2$	93.5 ± 2.3	93.2 ± 2.3	93.5 ± 2.1	NS
%T$\dot{}\sigma 1\sigma 2\sigma 3$	96.2 ± 1.2	96.2 ± 1.1	96.3 ± 1.2	NS
TWR 3–8 (%)	0.206 ± 0.189	0.241 ± 0.258	0.209 ± 0.166	NS
TWR 4–8 (%)	0.064 ± 0.065	0.059 ± 0.041	0.059 ± 0.048	NS
$\sigma 2$ / $\sigma 1$	0.21 ± 0.07	0.20 ± 0.08	0.21 ± 0.07	NS
	Circadian Repeatability (n = 30)			
	8 a.m.	2 p.m.	8 p.m.	ANOVA
R-R (ms)	1043 ± 129	941 ± 129	1045 ± 150	$P < 0.001$
QT (ms)	399 ± 29	388 ± 27	395 ± 28	$P < 0.001$
QRS-T angle	48.5 ± 27.2	52.4 ± 25.5	47.5 ± 27.2	$p < 0.001$
%T$\dot{}\sigma 1\sigma 2$	93.1 ± 2.5	91.8 ± 3.1	93.7 ± 2.0	$P < 0.001$
%T$\dot{}\sigma 1\sigma 2\sigma 3$	96.1 ± 1.2	95.4 ± 1.5	96.4 ± 1.0	$P < 0.001$
TWR 3–8 (%)	0.258 ± 0.316	0.415 ± 0.491	0.189 ± 0.157	$P < 0.001$
TWR 4–8 (%)	0.064 ± 0.053	0.105 ± 0.102	0.049 ± 0.032	$P < 0.001$
$\sigma 2$ / $\sigma 1$	0.21 ± 0.07	0.24 ± 0.11	0.19 ± 0.07	$P < 0.01$

Since it represents energy, the TWR is not a descriptor of the shape of the T-wave loop. The projection of the T-wave loop onto its preferential space ($\sigma 1$-$\sigma 2$-$\sigma 3$) is described by the three eigenvectors. It is well known that 95% of the T-wave loop is projected on the $\sigma 1$-$\sigma 2$-$\sigma 3$ space.[3,30]

Gender and Heart Rate Influences

T-wave morphology parameters based on PCA display relatively large standard deviation due to different modulating factors. Gender modulates T-wave parameters with more complex repolarization feature in females. Indeed, in females a lesser percentage of T-wave loop can be projected in a single plane or space, when compared to males. Females also show a trend to an increased TWR. These results are consistent with those published by Smetana et al.[7] In addition, gender-related differences in ventricular repolarization properties are well documented both at the experimental and clinical levels.[32,33]

More critically, PCA of the T-wave morphology is also dependent on heart rate.[8] To take into account this physiological modulation, Smetana et al. suggest running PCA analysis after heart rate stratification ("binning") from long-term ECG series.[8] In the present study, the slopes of the relationships between heart rate and PCA parameters are small ($\leq 6^{*}10^{-3}$) although significant, explaining only 5–10% of the distribution of the parameters (Table 6). It is smaller than in the reports from Smetana et al.[8] the discrepancy being probably related to the range of heart rate considered. In the report of Smetana

Table 3. Repeatability over Time of ECG and T-Wave Morphology Parameters

	Coefficient of Variation			Bland and Altman		
	10 minute	4 weeks	Circadian	10 minute	4 weeks	Circadian
QT	**1.08 ± 0.74 %**	**2.48 ± 1.75 %**	**2.51 ± 1.45 %**	**1.7 (−11.5; 14.9)**	**−0.4 (−26.8; 26.0)**	**11.7 (−17.0; 44.4)**
QTc	**1.58 ± 0.95 %**	**2.12 ± 1.44 %**	**2.44 ± 1.66 %**	**−1.0 (−19.5; 17.4)**	**0.6 (−20.8; 22.0)**	**−8.8 (−32.9; 15.3)**
QRS-T angle	3.0 ± 2.1 %	11.3 ± 9.9 %	9.0 ± 6.5 %	0.5 (−3.9; 4.8)	2.2 (−13.3; 17.6)	−3.9 (−21; 13)
%T·σ1σ2	0.4 ± 0.4 %	0.9 ± 0.6 %	1.3 ± 0.8 %	0.13 (−1.49; 1.76)	0.0 (−2.1; 2.1)	1.3 (−2.2; 4.8)
%T·σ1σ2σ3	0.3 ± 0.2 %	0.4 ± 0.2 %	0.7 ± 0.4 %	0.08 (−0.89; 1.05)	−0.08 (−1.15; 0.99)	0.8 (−0.9; 2.5)
TWR 3–8 (%)	16.1 ± 18.6 %	36.4 ± 43.9 %	48.6 ± 69.2 %	−0.02 (−0.19; 0.15)	−0.001 (−0.26; 0.25)	−0.16 (−0.81; 0.49)
TWR 4–8 (%)	19.8 ± 30.3 %	23.0 ± 22.0 %	45.5 ± 55.8 %	−0.009 (−0.09; 0.07)	−0.004 (−0.03; 0.04)	−0.04 (−0.18; 0.09)
σ2 / σ1	3.9 ± 2.7 %	11.7 ± 7.1 %	19.1 ± 19.9%	0.003 (−0.02; 0.02)	0.004 (−0.07; 0.08)	−0.03 (0.21; 0.15)

Bland & Altman : bias (± 1.96*SD) - circadian = 8 a.m. versus 2 p.m.

et al. long-term ECG recordings had been obtained, thus providing larger RR ranges than those obtained when recording only short term 10-second resting ECGs. In addition, Smetana et al. showed that T-wave parameters mainly change for RR intervals shorter than 700 ms.[8] Of note, the heart rate influences on T-wave morphology parameters based on PCA are much lesser than observed for the crude QT duration (>10% with $R^2 = 39\%$ in our study). Our data suggest that for RR intervals included between 900 and 1200 ms a correction for heart rate changes is not mandatory for T-wave morphology parameters analysis.

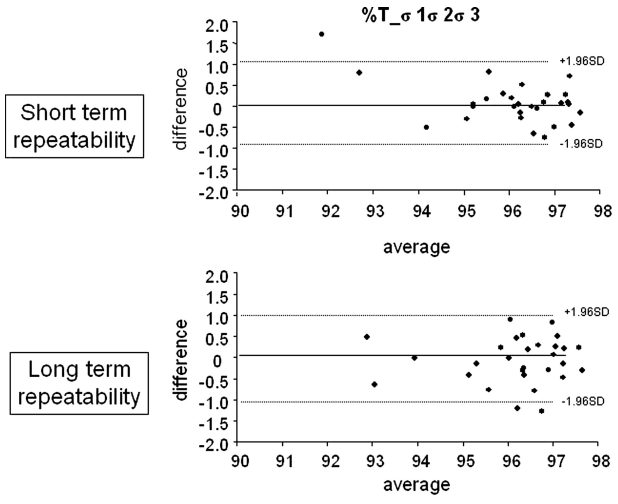

Figure 4. Bland and Altman plots of short and long-term repeatability of %T·σ1σ2σ3.

T-wave Morphology Parameters Based on PCA Repeatability over Time

In our study, the repeatability of PCA measures with the exception of TWR only slightly decreased from short to long-term evaluations. However, the circadian repeatability was not as good as the short or the long term ones. Previous studies have demonstrated autonomic influences on T-wave parameters.[34,35] In this study, the main changes were observed at 2 p.m., that is in postprandial conditions. Thus, the circadian differences in T-wave morphology parameters based on PCA may not be related only to circadian heart rate changes.[36]

The repeatability of the measure of the TWR was lesser than other PCA parameters. Batdorf et al. have already reported that the 1-month reproducibility of TWR is not very high.[22] In their study, the reproducibility of TWR measurement could be enhanced by increasing the number of beats used for QRST averaging.[22] In our experience, the amplitude of the TWR was not correlated with the level of noise (data not shown). Hence, the reduction of TWR variability when increasing the number of beats used for QRST averaging[22] is probably not related to an increase of the signal to noise ratio. Besides, it is not known whether averaging the signal over a long period might mask the non-dipolar

Table 4. Values of T-Wave Morphology Parameters Based on PCA for Different T-End Cursor Positions

	QT-8 ms	QT-4 ms	QT	QT +4 ms	QT +8 ms
R-R (ms)	1055 ± 151	1055 ± 151	1055 ± 151	1055 ± 151	1055 ± 151
QT (ms)	393 ± 29	397 ± 29	401 ± 29	405 ± 29	409 ± 29
QRS-T angle	48.5 ± 27.5	48.6 ± 27.5	48.7 ± 27.6	48.7 ± 27.6	48.8 ± 27.6
%T$\dot{}\sigma 1\sigma 2$	93.3 ± 2.2	93.3 ± 2.2	93.2 ± 2.3	93.2 ± 2.3	93.1 ± 2.3
%T$\dot{}\sigma 1\sigma 2\sigma 3$	96.2 ± 1.03	96.2 ± 1.03	96.2 ± 1.04	96.1 ± 1.04	96.1 ± 1.04
TWR 3–8 (%)	0.234 ± 0.246	0.238 ± 0.251	0.241 ± 0.253	0.243 ± 0.255	0.245 ± 0.255
TWR 4–8 (%)	0.057 ± 0.039	0.058 ± 0.040	0.059 ± 0.040	0.061 ± 0.041	0.062 ± 0.041
$\sigma 2$ / $\sigma 1$	0.203 ± 0.08	0.203 ± 0.08	0.203 ± 0.08	0.203 ± 0.08	0.204 ± 0.08

ANOVA $P < 0.001$ for all PCA parameters except for $\sigma 2$ / $\sigma 1$

component of the T wave. Therefore, further studies are needed to clarify the TWR variability.

The repeatability over time of the T-wave morphology parameters other than the TWR and QRS-T angle can be considered as close to the one of QT/QTc intervals (Table 3) and thus good enough to be used in clinical trials, provided that the time profile of ECG sample is considered.

Robustness

The vectocardiography theory suggests that the loop structure would be not very sensitive to the position of T-wave end cursor. Indeed, the extremities of the T-wave signal only represent a small proportion of samples used to determine the preferential planes.[37] In the present study, we systematically assessed the influence of T-end position by shifting the cursor 4 and 8 ms backward and forward. Our results show that the T-wave morphology parameters based on PCA changes following cursor modification were clinically insignificant. The difficulty of an accurate and reproducible T-wave end assessment has been long recognized.[23] This limitation is even more critical in case of T-wave morphology abnormalities. Therefore, the relative independence of T-wave morphology parameters on terminal samples of the T-wave would simplify the procedures involved in manual measurements of ECG time intervals. Our results give a rationale for the use of automatic T-end assessment for PCA.[7,8] The limited influence of the last millisecond of the T-wave signal is in accordance with experimental data. Previous studies have shown that the degree of repolarization heterogeneity is dependent on cells differential properties within the ventricular wall[38] but not on crude QT interval duration.[39]

Study Limitations

The use of an average beat may have provided different results than the use of a single beat but the averaging process was preferred in order to improve the signal to noise ratio. It should also be acknowledged that it is difficult to compare stability of measurements that have not the same unit or the same scale. In addition, although T-wave morphology parameters based on PCA have been proposed

Table 5. Repeatability of T-Wave Morphology Parameters Based on PCA According to QT Interval Measurement

	Coefficient of Variation		Bland & Altman	
	−4 ms versus +4 ms	−8 ms versus +8 ms	−4 ms versus +4 ms	−8 ms versus +8 ms
QRS-T angle	0.21 ± 0.12%	0.42 ± 0.24%	−0.19 (−0.46; 0.07)	−0.39 (−0.92; 0.14)
%T$\dot{}\sigma 1\sigma 2$	0.05 ± 0.04%	0.10 ± 0.08%	0.09 (−0.08; 0.26)	0.18 (−0.15; 0.51)
%T$\dot{}\sigma 1\sigma 2\sigma 3$	0.04 ± 0.03%	0.07 ± 0.05%	0.07 (−0.04;0.18)	0.12 (−0.07; 0.32)
TWR 3–8	1.4 ± 1.7%	3.0 ± 2.8%	−0.005 (−0.023; 0.013)	−0.011 (−0.05; 0.027)
TWR 4–8	2.2 ± 2.2%	4.0 ± 4.2%	−0.0024 (−0.008; 0.003)	−0.0045 (−0.015; 0.006)
$\sigma 2$ / $\sigma 1$	0.49 ± 0.52%	1.00 ± 1.04%	0.0005 (−0.005; 0.006)	0.0009 (−0.010; 0.012)

Bland & Altman : bias (± 1.96*SD)

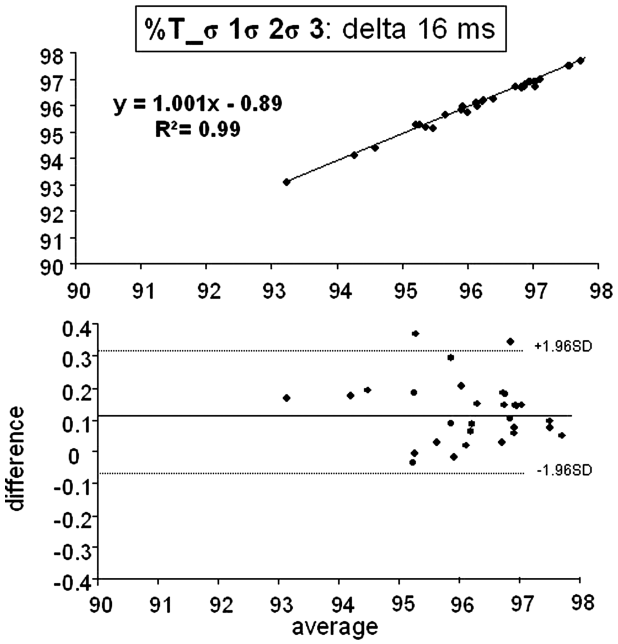

Figure 5. Bland and Altman plots for %T˙σ1σ2σ3 after 16 ms change in QT duration.

to characterize ventricular repolarization complexity their relevance to drug-induced cardiac toxicity has not been so far demonstrated. The present study reports only placebo data of a phase 1 clinical trial, we could thus not investigate the drug-induced changes in PCA parameters. However, the evaluation of drugs' impact on ventricular repolarization is based on placebo-controlled studies. It is therefore important to have some insight on the intrinsic variability of the PCA parameters on baseline conditions.

Table 6. Correlations with R-R Interval

	Alpha Co-efficient	P for Alpha Co-efficient	Bêta Co-Befficient	R^2
QT	0.119	<0.0001	275	0.39
QRS-T angle	NS	NS	NS	NS
%T˙σ1σ2	0.005	<0.0001	87.7	0.09
%T˙σ1σ2σ3	0.003	<0.0001	93.0	0.10
TWR 3–8	−0.001	<0.05	0.610	0.03
TWR 4–8	$-9.5\ 10^{-5}$	<0.01	0.166	0.04
σ2 / σ1	$2.0\ 10^{-4}$	<0.0001	0.01	0.12

NS = not significant

CONCLUSION

The repeatability over time of the T-wave morphology parameters other than the TWR and QRS-T angle can be considered as close to the one of QT/QTc intervals.

The T-wave morphology parameters based on PCA show small heart rate influences in resting conditions. In addition, T-wave morphology parameters are robust, showing only little dependence on the accuracy of T-end determination.

These data should be taken into account for safety pharmacology trials.

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