

Investigating the effect of sotalol on the repolarization intervals in healthy young individuals

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Abstract

Background: The dissociation between a drug-induced increase of the QT interval prolongation and an increased risk for ventricular arrhythmias has been suggested by academic investigators and regulatory agencies. Yet, there are no alternative or complimentary electrocardiographic (ECG) techniques available for assessing the cardiotoxicity of novel compounds. In this study, we investigated a set of novel ECG parameters quantifying the morphology of the T-loop. In a group of healthy individuals exposed to sotalol, we compared their drug-induced changes to the drug-induced prolongations of the QTc, QTc apex and T-peak to T-end intervals.

Methods: We implemented a set of parameters describing the morphology of the T loop in its preferential plane. These parameters measure the time interval needed for the heart vector amplitude to change from its maximum value to a time when its amplitude has been reduced by 30%, 50%, and 70%. These measurements are called *early repolarization duration* (ERD) when they are located before the T-wave apex and *late repolarization duration* (LRD) when measured after the apex. They depend on both the speed of the repolarization process and the morphology of the T loop. Thirty-nine healthy individuals were exposed to sotalol in a crossover-design study. Sixteen ECGs were recorded per day during 3 days. The first day (day 0) was baseline; a single dose of sotalol (160 mg) was given during day 1, and a double dose was given during day 2 (320 mg). The plasma concentration of the drug was measured just before the ECG recordings.

Results: The values of all investigated parameters revealed a dose-dependent effect of sotalol (in average between parameters, $\rho = 0.9$, $P < .001$). Our investigations described profound and statistically significant changes in the morphology of the vectorial T loop for day 1 (peak effect of sotalol: $\Delta\text{ERD}_{50\%} = 23 \pm 6$ msec, $P < .05$; $\Delta\text{LRD}_{50\%} = 8 \pm 3$ msec, $P = .05$) and day 2 (peak effect of sotalol: $\Delta\text{ERD}_{50\%} = 51 \pm 14$ msec, $P < .05$; $\Delta\text{LRD}_{50\%} = 20 \pm 12$ msec, $P = .05$). When investigating the timing of peak drug concentration and peak effect of the drug on the various repolarization parameters, we found asynchrony between ERDs/LRDs (≥ 3.5 hours after dosing) and QTc/QTc apex profiles (< 3.5 hours after dosing), suggesting that the time of maximum prolongation on the repolarization process was not synchronized with the time of maximum drug-induced heterogeneity of repolarization.

Conclusion: This study describes the sotalol-induced changes of the T-loop morphology in healthy individuals based on novel vectocardiographic parameters. These observations might help in improving the next generation of ECG markers for the evaluation of drug cardiotoxicity.

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Keywords:

QT interval; Torsades de pointes; Long QT syndrome; Sotalol; Vectocardiography; ECG

Introduction

While the association of increased arrhythmia risk with QTc prolongation is well established,¹ the association between a rate-corrected QT prolongation and the presence

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of an arrhythmogenic substrate has been strongly questioned. Indeed, the releases of several postmarketing reports have described noncardiac drugs with small QTc prolonging effect associated with significant torsadogenic properties,^{2,3} whereas other drugs that have no history of cardiac events were significantly prolonging the QTc interval.^{4,5} Consequently, one faces a challenging exercise related to the design and validation of a more reliable ECG surrogate marker of drug cardiotoxicity than QTc prolongation.

The mechanisms involved in the triggering of drug-induced arrhythmias remain to be fully elucidated, yet one recognizes the role of the repolarization heterogeneity as a required arrhythmogenic substrate.^{6,7} For instance, the TriAd concept suggests the importance of the combined roles of action potential triangulation, reverse use dependency of the drug, and repolarization instability. An unbalanced contribution of these factors could lead to an increased ventricular heterogeneity and an increased propensity to torsades de pointes (TdPs).⁷ Another concept, mainly based on in vitro experiments, emphasizes the association between ventricular transmural heterogeneity and the promoting role of early after-depolarization as primary factors triggering ventricular tachyarrhythmias.^{8,9}

In the arena of development of novel ECG markers, different techniques are currently investigated; they include T-wave and T-loop morphologies^{10,11} as well as time intervals such as the T-peak to T-end (TpTe) interval. TpTe interval has been suggested to be a predictor of ventricular arrhythmias in an increasing number of studies involving animal and human data.^{12–15} However, its association with transmural dispersion and/or apicobasal ventricular heterogeneity is actively debated. In this work, we will consider the duration of this interval as an index of global ventricular repolarization heterogeneity.^{12,13}

We investigated the effects of dl-sotalol, a class III antiarrhythmic agent with strong I_{Kr} inhibitory properties and associated with numerous cases of TdPs, on the morphology of the T-loop.^{16,17} Our objective was to describe the sotalol-induced changes of QTc and TpTe intervals and compare them with the changes of novel computerized indices quantifying the morphology of the T loop. As noted above, the dissociation between the level of QT/QTc prolongation and the propensity to arrhythmic events may suggest the existence of “malignant” and “benign” QT/QTc prolongations; the level of ventricular heterogeneity may help distinguish them.

Method

Study populations and ECG recordings

A group of 38 healthy individuals were enrolled (28 men; 28 ± 8 years; body mass index, 24.4 ± 3.4 kg/m²) and underwent repeated digital 12-lead ECG recordings during a 3-day protocol. The first day of the experiment was the baseline. During the second day, patients were exposed to a single dose of sotalol (160 mg); and during the third day, a double dose of 320 mg of sotalol was used. All recordings were preceded by a 5-minute resting period in supine position. Standard 12-lead ECGs were recorded for 10 seconds using a

commercial equipment (Mortara Instruments, Milwaukee, WI). Sixteen recordings were done at identical times each day, first during baseline (day 0) and then immediately after the dosing (at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 13, 16, and 22.5 hours after dosing during day 1 and day 2). The recordings were sampled at 500 Hz with a 16-bit amplitude resolution.

Sotalol blood plasma concentration was measured before each ECG. The protocol is described in details elsewhere.¹⁸

The interval measurements: QT, QT apex, and TpTe intervals

In this analysis, the *repolarization interval* (RI) is defined between the J point and the point located 220 milliseconds before the next R peak. Such approach requires that the patients remain at rest during the ECG recording to avoid high heart rates, that is, short RR intervals in which 220 milliseconds before the next R peak would encompass the beginning of the P wave. All measurements of RIs are based on the singular value decomposition (SVD) from the 12-lead signals. The SVD is used to reduce the dimension of the ECG lead systems from 12 leads to 2 leads.¹⁹ We refer to the resulting 2 leads as the *eigenvectors 1* (ev_1) and 2 (ev_2).

We measured the QT, QT apex, and TpTe intervals (TpTe = QT – QT apex) from ev_1 . The software²⁰ was used to automatically measure the QT interval in all available cardiac beats in sinus rhythm. The median values from all measured beats are reported. The apex and the end of the T wave were identified in a fully computerized manner.

ERD and LRD parameters

ERD_% and LRD_% are measurements of interval durations based on the T loop. The starting point of these intervals is the time at which the length (magnitude) of the repolarization vector is maximized (V_{max} in the lower panel of Fig. 1). The ending point of these intervals is identified by a circle of diameter equal to 30% of V_{max} (Fig. 1 illustrates ERD_{30%} and LRD_{30%}). Consequently, these parameters measure the time needed for the repolarization vector to vary from its maximum length to a time point corresponding to a 30% reduction of its maximum length. The LRD_% is a measure toward the end of the RI, and the ERD_% is directed toward the J point (Fig. 1, lower panel). The durations of these intervals increase when the electrical vector slows down or/and the roundness of the T loop increases. Consequently, these parameters measure time interval duration reflecting both the velocity of the repolarization vector and the repolarization heterogeneity.

The SVD and the repolarization measurements were computed in each cardiac beat, and we reported the average values from all beats for a given ECG tracing.

Heart rate correction

All repolarization measurements were heart-rate corrected using a pooled technique. A linear regression analysis was used to model the relationship between repolarization measurements and RR intervals during baseline periods. For a given parameter, we pooled all data from the overall

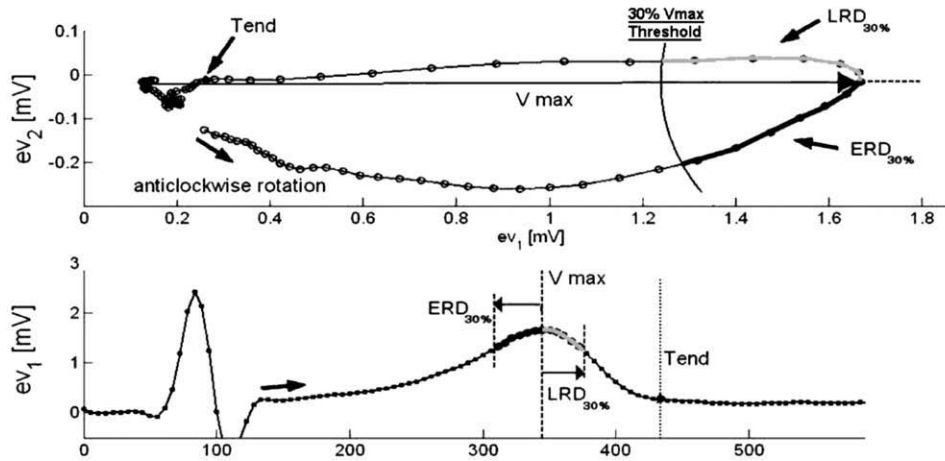


Fig. 1. Illustration of the ERD and LRD (for a detection threshold equal to 30% of Vmax); ERD measures the time needed for the cardiac vector magnitude to be reduced by 30% when following a clockwise rotation (opposite to time direction), whereas LRD is the time needed for the heart vector magnitude to be reduced by 30% when following an anticlockwise rotation (toward the end of the T wave). The ERD and LRD parameters are reported on ev_1 in the lower panel (see text for more detailed description).

population, merging data from and between individuals. The slope (β) characterizing this relationship was used to correct the repolarization measurements such as $QTc = QT + \beta(1 - RR)$. The same heart-rate correction technique was applied to all other measurements.

Statistical analysis

We reported the median values and their 95% confidence intervals for each time point describing the drug effect profile on the repolarization parameters. When comparing 2 parameters at a given time point or when assessing if a drug effect was different from 0, a *t*-test with appropriate testing hypotheses was used. When comparing the profiles of curves describing the evolution of parameters over time, we used the Pearson product moment correlation coefficient (ρ) to measure the degree of linear relationship between the 2 variables. For a 2-tailed test of the correlation, $H_0: \rho = 0$ vs $H_1: \rho \neq 0$, where ρ is the correlation between a pair of variables. For all implemented tests, a *P* value inferior or equal to .05 was considered statistically significant.

Results

Profiles of sotalol-induced prolongation of the QT, QT apex, and TpTe intervals

Fig. 2 describes the profile of the sotalol plasma concentration based on the average value between all individuals at each time point and their 95% confidence interval. It reveals a maximum plasma concentration recorded on average between 2.5 and 3 hours after dosing. Fig. 3 illustrates the profile for the sotalol-induced prolongation of QTc, QTc apex, and TpTe intervals (corrected for heart rate). The upper panel corresponds to changes during day 1 in reference to baseline, and the changes between the second day and baseline are described in the lower panel. Each time point is the median value and its 95% confidence interval across the study population.

The QTc, QTc apex, and TpTe intervals were significantly correlated ($P < .001$) with the sotalol plasma concentration (QTc: $\rho = 0.97$, QTc apex: $\rho = 0.94$, and TpTe: $\rho = 0.89$); but Fig. 3 suggests that the effect of the drug on the repolarization segment is not evenly distributed across the QT interval. First, the profile computed from day 1 reveals that the drug primarily prolongs the QT apex interval (corrected for heart rate). The profiles of the QTc and QTc apex are almost superimposed from hour 0 to hour 2.5. During this period, sotalol does not induce any prolongation of the TpTe interval (nearly equal to 0). During and after 2.5 hours after dosing, one can note that QTc apex has reached a maximum, whereas QTc interval continues to be prolonged by the effect of the drug; this increase is the contribution of the TpTe prolongation to the overall changes of the QTc interval. During day 2, one can note a similar development of the various interval prolongations with a higher contribution of the TpTe interval during the period between 1 and 2.5 hours after the dosing. As a note, there is a

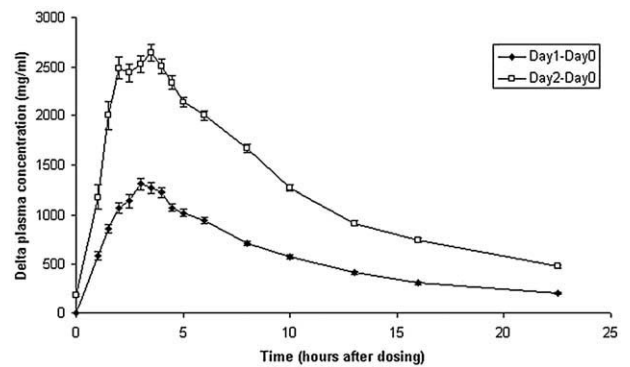


Fig. 2. The curves provide the mean values and corresponding 95% confidence intervals of level of sotalol plasma concentration within the study population for the 2 days of the protocol. A single dose of 160 mg of sotalol was given at time 0 of day 1, and a double dose (320 mg) was given at time 0 of day 2.

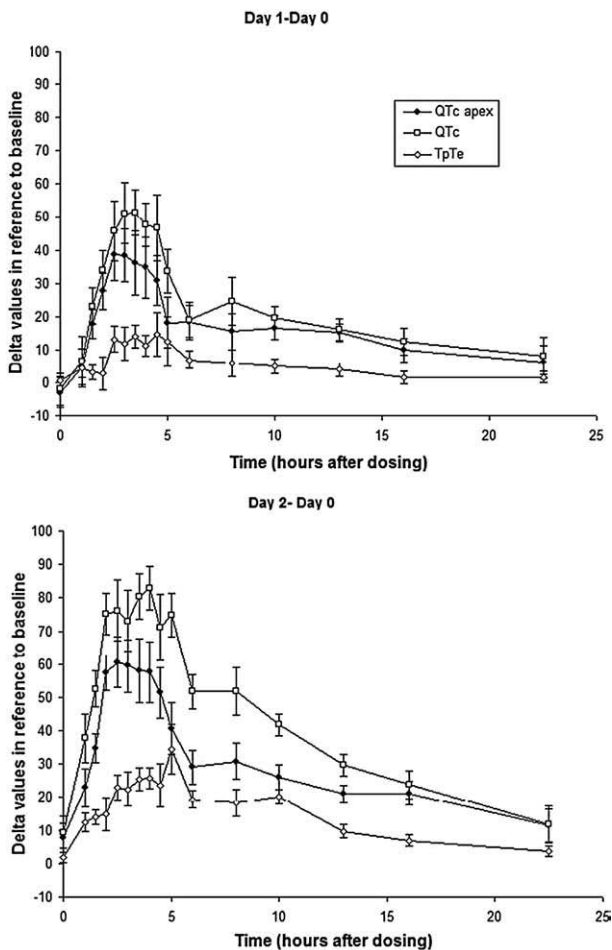


Fig. 3. Sotalol-induced evolution of QTc, QTc apex, and TpTe intervals across time for the 2 days of the study. The upper panel describes these curves for day 1 (single dose), whereas the lower panel is for day 2 (double dose). For each time point, we reported the median values among the population and its 95% confidence interval. These measurements were fully computerized. Apart from the first 3 and the last 3 time points from TpTe interval of day 1, all sotalol-induced changes are significantly different from 0 ($P < .05$).

carryover effect of the drug at the beginning of day 2 (Fig. 2) leading to a slight but significant ($P = .05$) prolongation of the QTc and QTc apex intervals at time 0. This carryover effect might explain the slight contribution of the TpTe interval during the first 2 hours of day 2 that does not exist during day 1.

Profiles of sotalol-induced prolongation of the ERDs and LRDs parameters

The average values of sotalol-induced changes of ERD_{70%} and LRD_{70%} across day 1 and day 2 are presented in Fig. 4. The figure is limited to these 2 parameters (70%) for the clarity of purpose, but all other ERD and LRD parameters (30% and 50%) have similar profiles. The ERD and LRD parameters reflect dose-dependent prolongation during day 1 and day 2. The drug effect profiles of ERDs (ERD_{30%}: $\rho = 0.90$, ERD_{50%}: $\rho = 0.93$, and ERD_{70%}: $\rho = 0.96$) and LRDs (LRD_{30%}: $\rho = 0.79$, LRD_{50%}: $\rho = 0.81$, and LRD_{70%}: $\rho = 0.90$) were highly correlated ($P < .001$ for all).

Comparing the profiles of sotalol-induced prolongation measured by QTc apex and ERDs

Fig. 5 describes the superimposition of the sotalol-induced changes of ERD_{70%} and QTc apex.

During the first 3 hours after dosing, the QTc apex prolongation is fully superimposed with the ERD_{70%}, revealing that all the sotalol-induced prolongation of the QTc apex interval is also captured by the ERD parameter. This state of the repolarization is similar to the one we have observed while studying the effect of moxifloxacin on the ventricular repolarization process.²¹

The portion of the signal encompassed by ERD_{70%} is nested inside the QT apex interval; it is noteworthy that sotalol-induced repolarization prolongation measured by ERD_{70%} continues to increase, whereas the prolongation of the QT apex diminished. Indeed, at 6 hours after dosing, ERD_{70%} measured a prolongation twice that of QTc apex interval during day 2. Based on this observation, one could suggest that the heterogeneity is, in this specific example, dissociated from the sotalol-induced prolongation of the ventricular repolarization process.

Timing of the sotalol-induced changes of the surface repolarization parameter

As shown in Fig. 2, the maximum plasma concentration of sotalol occurred at 2.5 and 3 hours after dosing for day 1

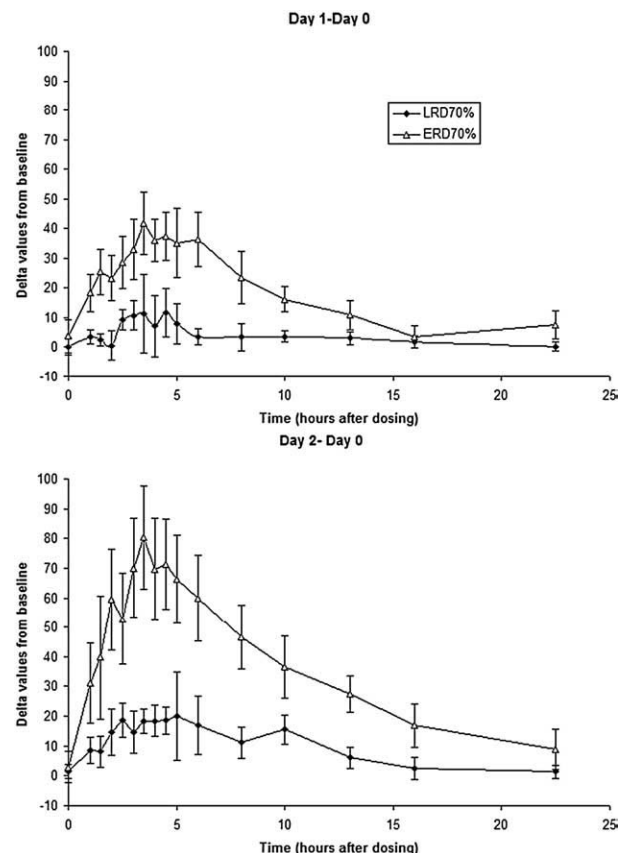


Fig. 4. Profiles of the ERD and LRD parameters (for the 70% threshold) during day 1 (upper panel) and day 2 (lower panel). The figures reveal that the ERD and LRD parameters present a dose-response to sotalol.

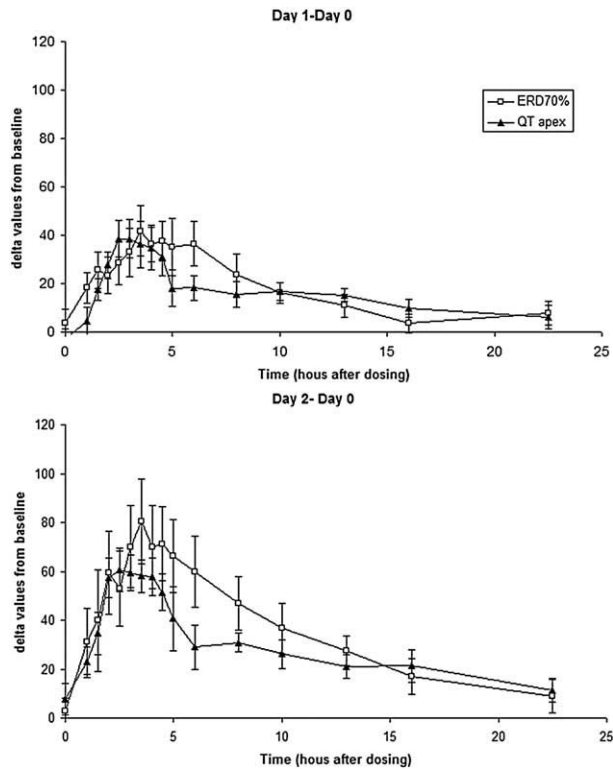


Fig. 5. Differences in the pattern of the profile of sotalol-induced changes of the ventricular repolarization process when quantified using the QTc apex and ERD_{70%} parameters. The 2 curves present different patterns being fully synchronized during hour 0 and hour 2 and showing very different amplitude between hour 3 and hour 10.

and day 2, respectively. Table 1 provides the values of the maximum changes of sotalol on QTc, QTc apex, TpTe, ERD_{30%}, and LRD_{30%} parameters and their associated time of occurrence. The table reveals the presence of time shifting of the peak effects of the drug between the various repolarization parameters. For instance, QTc and QTc apex show a peak effect occurring between 2.5 and 4 hours after dosing, whereas the TpTe, ERDs, and LRDs were, on average, at or beyond 4 hours after dosing.

These results suggest again the presence of an asynchrony between the levels of drug effect on the early and late part of the QT interval.

Interestingly, the sotalol-induced peak prolongation of the QTc apex interval occurs much earlier than the peak

prolongation measured by the ERD parameters suggesting that the morphology of the T-loop still changes while the QT apex stop prolonging.

Discussion

This study describes the sotalol-induced changes of the T-loop morphology in healthy individuals. We compare these changes to the drug-induced prolongation of the QTc, QTc apex, and TpTe intervals. All parameters reveal a dose-dependent effect of sotalol on their values. The study is consistent with the results from the previous report describing the effect of dl-sotalol on the QT measurements realized using different recording and measurement techniques.²²

In addition, the study provides new insights into the sotalol-induced changes of the morphology of the T loop and their timing. Our discussion provides speculative explanations for the dissociation observed between drug-induced interval prolongation and loop morphology changes.

Assessment of abnormal T morphology in the congenital long QT syndrome

The investigation of the T morphology has been primarily used for characterizing individuals with the congenital form of the long QT syndrome (LQTS) in whom specific T-wave morphology has been linked to specific type of genetic mutations.²³⁻²⁹ The pioneering work related to T-wave morphology analysis suggested that symptomatic LQTS patients present a significantly higher percentage of notched T waves than asymptomatic patients (81% vs 19%, respectively).²⁵ Lehman et al²⁴ compared the prevalence of T-wave humps (double-peaked T waves: T2) in 254 members of 13 (diagnosed) LQTS families with 2900 healthy control subjects. In the group of patients with a prolonged QT interval, T2 waves were present in 53% of individuals, but only in 16% of those with borderline QTc. In healthy volunteers, these numbers were less than 1%. Thereafter, quantitative indices capturing T-wave morphology were developed by Padrini et al³⁰ and were successful at discriminating symptomatic patients from age-matched healthy subjects (n = 14). These preliminary works suggest that T morphology brings supplemental information to QTc prolongation in such patients. More recently, our group confirmed these observations; we investigated T morphology as a phenotypic expression of LQTS mutations when

Table 1
Average timing and values and their 95% confidence interval for the repolarization indices

Unit	Peak effect value (day 1 – day 0) (ms)	Peak effect time (day 1 – day 0) (h)	Peak effect value (day 2 – day 0) (ms)	Peak effect time (day 2 – day 0) (h)
QT apex (ev ₁)	38 ± 9	2.5	61 ± 9	2.5
QTc (ev ₁)	52 ± 19	3	83 ± 10	4
TpTe (ev ₁)	15 ± 6	4.5	34 ± 24	5
ERD _{30%}	15 ± 4	5	25 ± 9	5
ERD _{50%}	23 ± 6	4.5	51 ± 14	4
ERD _{70%}	42 ± 10	3.5	80 ± 17	3.5
LRD _{30%}	7 ± 3	4.5	14 ± 8	5
LRD _{50%}	8 ± 3	3.5	20 ± 12	5
LRD _{70%}	12 ± 8	4.5	41 ± 15	5

considering the two most spread forms of the syndrome (whereas the QTc prolongation could not).³¹ Based on Holter technology and relying on an RR bin technique, the repolarization indices based on Principal Components Analysis (PCA), revealed their ability to separate patients carrying KvLQT1 and KCNH2 mutations.^{31,32} All these reports consistently support the role of T morphology as a phenotypic expression of the LQTS mutation by bringing information complementary to the QT/QTc prolongation.

Assessment of abnormal T morphology in the acquired LQTS

In the acquired form of this syndrome or in patients with drug-induced QT prolongation, ERD and LRD parameters were compared with QTc prolongation for detecting the effect of moxifloxacin. This antibiotic compound is a subtle I_{Kr} inhibitor used as a positive control substance in drug safety trial. It can trigger ventricular arrhythmias but at very high dose. Based on logistic models, we tried to separate the ECG tracings “on” vs “off” drug. The ERD_{30%} was selected as the most relevant index to identify the presence of moxifloxacin. Afterward, based on receiver operating characteristic analysis, we compared 3 statistical models: (1) QTc; (2) ERD_{30%}; and (3) ERD_{30%}, QTc apex, and TpTe intervals. First, the results revealed that only the early part of the T wave was prolonged and the TpTe interval was not affected by the drug. Second, the receiver operating characteristic analysis demonstrated that the combination of information about both morphology and QTc prolongation maximized the ability of the logistic method to separate the group of ECGs on and off moxifloxacin.²¹

The role of ERD, LRD, TpTe, and QTc intervals as potential markers of the presence of an arrhythmogenic substrate has been further investigated by comparing their values in 2 groups of cardiac patients with and without a history of drug-induced TdPs.³³ This work revealed that baseline ECGs present specific T-loop morphology and abnormal ERD values characterizing patients with a predisposition to TdPs. The ERD_{30%} and the ERD_{50%} were significantly higher in patients with a history of TdPs in comparison with patients without such history (35 ± 8 vs 44 ± 13 msec, respectively; $P = .03$), yet the QTc apex was not prolonged in these patients (350 ± 19 vs 358 ± 23 msec, $P = .3$). Such observation suggests that the patients with a predisposition to drug-induced TdPs could present higher repolarization heterogeneity at baseline captured by our novel ECG markers (ERDS).

TpTe interval and T-loop morphology

Heterogeneity of ventricular repolarization is known to underlie arrhythmogenesis.^{6,34} The TpTe interval was introduced as a marker of transmural dispersion in the wedge preparation from dog by Watanabe et al¹⁴; and subsequently, it was described as an independent predictor of TdPs in several human studies: Takenaka et al¹³ have shown that, during exercise, ECG tracings from LQT1 patients have a prolonged TpTe interval, whereas the ECGs from LQT2 patients do not. Because LQT1 patients are prone to cardiac events under exercise, this study would support the link between an increased TpTe interval and the presence of an

arrhythmogenic substrate. In addition, clinical observations have emphasized the presence of TpTe prolongation in patients with TdPs³⁵ and have presented the TpTe prolongation as a marker of arrhythmia inducibility.¹⁴ In animal studies, this concept has been strengthened further in experiments involving nontorsadogenic drugs (amiodarone³⁶ and pentobarbital sodium³⁷) prolonging the QTc interval but reducing the transmural dispersion.

Additional studies are needed to better understand the meaning of an abnormal prolongation of the TpTe interval when measured from the surface ECGs. Xia and Yuan¹⁵ and Opthof et al¹² investigated the correlation between TpTe and transmural dispersion in animals (swine and dogs), but they did not find any relation. Clearly, there is a lack of understanding around the respective contributions of transmural dispersion and apicobasal heterogeneity of repolarization to the inscription of the TpTe interval on the body surface ECGs.

Our study compares the dose-response of parameters designed to measure both repolarization prolongation/shortening and heterogeneity from the vectorial loop. First, the results show that the sotalol-induced changes of ERDs are correlated with QTc apex interval during the first 2 hours after dosing but they become dissociated from QTc apex beyond 2 hours after dosing. Because ERD prolongs whereas QT apex (measured from first eigenvector) starts decreasing, one would expect the repolarization changes captured by ERD to be issued from the second eigenvector (defining the second axis of the T loop) and thus to correspond to changes in T-loop morphology reflecting an increased heterogeneity of the ventricular repolarization. Second, the LRD parameters represent the same measurements as ERDs but are located in the late part of the T-wave apex. Interestingly, the LRD parameters are not dissociated with sotalol-induced TpTe prolongation, suggesting that TpTe and LRD might measure the same information. Therefore, our analysis enriches our current effort to better understand how the morphology of the T wave may help us to better separate dangerous from safe QT-prolonging drugs. Based on our current observations, (1) moxifloxacin is associated with ventricular repolarization heterogeneity mainly located in the early portion of the T wave (in healthy individuals),²¹ (2) patients with a history of drug-induced TdPs have longer sotalol-induced QT prolongation than patient without a history of TdPs (in addition, they present more pronounced sotalol-induced changes in the late portion of the T wave [TpTe interval and LRDs]),³³ and (3) we suggest in this study that sotalol produces large QT prolongation and profound increased heterogeneity detected in both the early and late portion of the T wave of healthy individuals; more importantly, (4) the time of peak sotalol-induced QT prolongation was not synchronized with the time of maximum ventricular heterogeneity.

To conclude, one can speculate that non-torsadogenic drugs could provoke smaller ventricular heterogeneity than torsadogenic drugs. In sotalol, the overall T-wave/T-loop morphology is affected (early and late portion of the T wave), whereas in moxifloxacin, only the early portion of the T wave is changed. This observation is consistent with the description of repolarization heterogeneity reported in patients with the

congenital LQTS³⁸ showing large interlead disparity in T-wave morphology (increased repolarization heterogeneity). Such hypothesis about the predominant role of the repolarization morphology in predicting an individual predisposition to ventricular arrhythmias should be challenged by studying torsadogenic drugs with small QT prolongation effect.

Limitations

A prior work investigated the robustness of the T-loop indices to slight shifts of QT interval definition; the authors suggested that such transformation was robust to such variation.³⁹ In our study, we lack such investigation; and the reproducibility and robustness of our repolarization indices should be demonstrated in future works. Second, we opted to use a pooled technique to correct our parameters for heart rate. Such strategy generates an opportunity for a biased estimation of the drug effect on the repolarization indices. Indeed, we used the baseline data to estimate these relationships, although we have shown that sotalol modifies this relationship.²⁰ However, as of today, the authors do not believe there is a more appropriate alternative to such method when using 10-second ECG tracings.

Conclusions

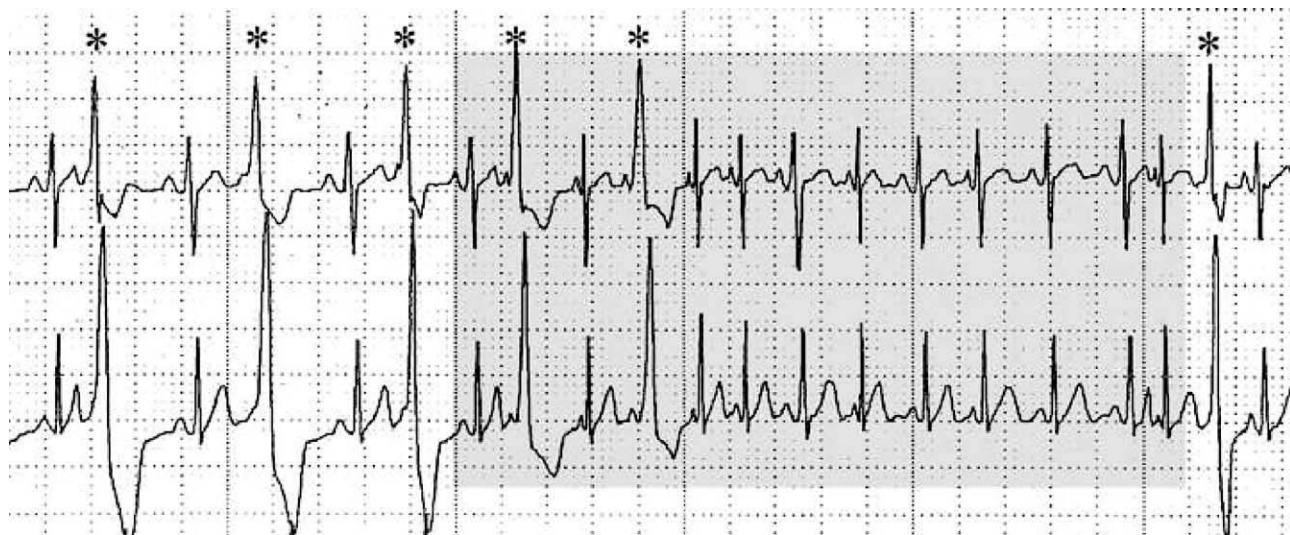
The study presents a description of the effect of sotalol on the T wave and the T loop and the effect of the changes in plasma concentration of the drug on various repolarization quantifiers. The study suggests that the peak plasma concentration is synchronized with its peak effect on QT interval but not with its peak effect on ventricular heterogeneity. These observations require confirmation in a larger set of data; but today, they clearly reveal that drug-induced QT prolongation represents only one aspect of the effect of sotalol to the repolarization intervals from surface ECGs. These observations might help design the next generation of ECG markers for the evaluation of drug cardiotoxicity.

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Paper drag mimicking sinus tachycardia



Two simultaneously recorded rhythm strips are shown. The rhythm begins as normal sinus with ventricular bigeminy, as each sinus-stimulated QRS complex is followed by a premature ventricular complex (asterisks). After the third premature ventricular complex (gray box), the rhythm appears to become more rapid, eventually coming to resemble sinus tachycardia at a ventricular rate close to 200 beats per minute. The premature ventricular complexes are also becoming more narrow than at the beginning of the rhythm strip. Upon careful inspection, some of the PR intervals are clearly measured to be physiologically impossible (some are as short as 40 milliseconds), as are some QT intervals (some are as short as 120 milliseconds); and PR intervals, QRS durations, and QT intervals are varying. Apparent rapid rates which are accompanied by physiologically impossible conduction times and compressed PQRST complexes represent paper drag (in older Holter recordings which employed reel-to-reel tape, tape drag resulted in the same phenomenon.) In this case, the paper drag occurred at the central telemetry write-out unit in the nursing station. Paper drag can be present anywhere that printer paper is used, such as analog electrocardiogram machines and telemetry units.

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