A history of drug-induced Torsades de Pointes is associated with T-wave morphological abnormalities

Bhuiyan, Tanveer Ahmed; Graff, Claus; Kanters, Jørgen K.; Melgaard, Jacob; Toft, Egon; Kääb, Stefan; Struijk, Johannes J.

Published in:
Clinical Pharmacology & Therapeutics

DOI (link to publication from Publisher):
10.1002/cpt.886

Publication date:
2018

Document Version
Accepted author manuscript, peer reviewed version

A history of drug-induced Torsades de Pointes is associated with T-wave morphological abnormalities

Word Count: 2953

Number of Figures: 3

Number of Tables: 3

Number of References: 30

Authors:

Tanveer A. Bhuiyan, PhD[a], Claus Graff, PhD[a], Jørgen K. Kanters, MD[b], Jacob Melgaard, PhD[a], Egon Toft, MD, DMSc[c] , Stefan Kääb, MD, PhD [d], Johannes J. Struijk, PhD[a]

[a] Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[b] Laboratory of Experimental Cardiology, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

[c] College of Medicine, Qatar University, Doha, Qatar

[d] Medizinische Klinik und Poliklinik I, University Hospital Munich, Ludvig Maximilians University, Munich, Germany; German Center for Cardiovascular Research (DZHK), partner site: Munich Heart Alliance, Munich, Germany

Address for Correspondence:

Johannes J Struijk
Fredrik Bajers Vej 7 C1-205
Department of Health Science Technology
Aalborg University, Denmark
Phone: +4599408817
Fax: +4598154008
Email: jjs@hst.aau.dk

Keywords: T-wave morphology, QT interval, Torsades de Pointes, Drug induced repolarization, reduced repolarization reserve, hERG.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/cpt.886

Abstract

The hypothesis of the study is that TdP history can be better identified using T-wave morphology compared to QTcF at baseline. ECGs were recorded at baseline and during sotalol challenge in 20 patients with a history of TdP (+TdP) and 16 patients without previous TdP (-TdP). The Fridericia-corrected QT interval (QTcF) and T-wave morphology combination score (MCS) were calculated. At baseline, there was no significant difference in QTcF between the groups (+TdP: QTcF = 446±9 ms; -TdP: QTcF = 431±9 ms, p = 0.27). In contrast, MCS was significantly different between the groups at baseline (+TdP: MCS = 1.07±0.095; -TdP: MCS = 0.74±0.07, p = 0.012). Both QTcF and MCS could be used to discriminate between +TdP and –TdP after sotalol but only MCS reached statistical significance at baseline. Combining QTcF with MCS provided a significantly larger difference between groups than QTcF alone.

Introduction

Drug-induced repolarization abnormalities put vulnerable patients at risk of torsades de pointes (TdP) and sudden cardiac death (SCD).[1] Drugs that inhibit the rapidly activating component of the delayed rectifier potassium current in the myocardium (I_{Kr}) manifest in the ECG by prolonging the QT interval, which has been associated with drug-induced TdP and SCD.[2] A drug-induced QTc prolongation (QT corrected for changes in heart rate) of less than 5 ms is unlikely to induce TdP whereas prolongations greater than 20 ms are associated with substantially higher risk.[3] In addition, the risk of TdP increases exponentially at a rate of 5% with every 10 ms prolongation of QTc beyond 440 ms.[4]

However, the relation between the prolongation of QTc and proarrhythmic risk is not straightforward. QTc is a mediocre parameter for assessing risk of drug-induced TdP and there are a number of QTc prolonging drugs with very limited or no proarrhythmic history. For instance moxifloxacin,[5-7] tamoxifen,[8] and ranolazine[9] prolong the QTc interval without causing arrhythmia. These observations challenge the QTc-based drug safety screening and recent studies suggest that repolarization abnormalities can be assessed with a higher degree of precision with other electrocardiographic markers.[10-13]

Several markers based on the properties of the T-wave have been proposed. The interval between the peak of the T-wave and the end of the T-wave (TpTe) has received significant attention. The T-wave right slope in lead I was found to improve the detection of patients with history of TdP if used in combination with QTc.[13] A prolonged TpTe interval has been associated with risk of TdP during acquired bradyarrhythmia when notched T-waves are present.[14] However, studies of TpTe as a marker of drug-induced repolarization have shown conflicting results. For example, an increased TpTe was found in patients treated with amiodarone, although amiodarone is antiarrhythmic[15] TpTe also failed to distinguish the symptomatic and asymptomatic patients in congenital long QT syndrome.[16] Moreover, TpTe correlates strongly with QT and thus does not add new information to the QT interval,

the latter remaining the preferred marker.[17] T-wave alternans was also suggested as a proarrhythmic risk marker: It was observed just prior to episodes of TdP.[18] Area based markers of the T-wave, such as Relative T-wave Area (RTA), attained their maxima just before the onset of TdP in dogs treated with sertindole.[19] A systematic quantification of T-wave morphology as defined by Graff *et al.*[10, 11] combines three features of T-wave morphology: Asymmetry, flatness and notch into a composite score named Morphology Combination Score (MCS). MCS was shown to be a robust parameter that may improve drug safety studies, for example in cases where the QT interval and some other T-wave morphology markers show false positive results.[11, 20] Several markers, including MCS parameters, ERD and LRD of the T-wave loop, QRS-T angle, Spatial Ventricular Gradient and Total cosine R-to-T were analysed by Vicente *et al.*[12] in a study using dofetilide, quinidine, ranozil and verapimil. The study showed that the morphological parameters effectively identified pure hERG blocking, whereas interval analyses may reveal additional sodium and calcium channel blocking that might reduce the torsadogenic risk of a drug.

Patients with a history of TdP (+TdP) have altered repolarization and, therefore, respond more to I_{Kr} inhibiting drugs in terms of QTc interval than patients without such history (-TdP).[21] The baseline QTc values in those two groups of patients suggest that abnormal repolarization is normally masked and hence stressing the patients with e.g. sotalol is required to unmask any an existing repolarization disturbance. In this study, we have investigated if the T-wave morphology parameter MCS can be used to identify the +TdP patients and –TdP patients at baseline and after sotalol challenge, with QTc as reference measure.

Results

Study sample

The clinical characteristics of the patients are shown in Table 1. There was no significant difference between the average ages of the +TdP and –TdP groups: +TdP 59±12 and -TdP 62±12 years (p=0.59). The +TdP group consisted of 11 males and 9 females and the -TdP were 5 males and 11 females. Two-way ANOVA tests, at baseline and at the time of maximum response, showed that the results are independent of the different male-female ratios in the groups considering both MCS (Baseline: p=0.24; Maximum response: p=0.84) and QTcF (Baseline: p=0.59; Maximum response: p=0.79) and the interaction between patients' sex and the presence of the history of drug induced TdP was not statistically significant.

QTcF and MCS

The difference in QTcF at baseline between the +TdP and –TdP groups was not statistically significant (Table 2). Five patients had a QTcF duration above a gender specific QTcF threshold for LQTS (QTcF >470 ms in men and QTcF >480 ms in women)[22] which comprised four patients (3 male + 1 female) from the +TdP group and one patient (1 female) from the –TdP group. Table 2 shows the baseline values and sotalol-induced changes in the two groups.

The QTcF value attained its maximum at twenty-minutes after completion of the drug infusion for both groups. The mean difference between the QTcF values for the +TdP and –TdP groups at this time was 51.4 ms (p= 0.0018).

In contrast to QTcF, at baseline the difference (0.33) in MCS between the groups was statistically significant (p=0.01). The maximum values of MCS occurred about 20 minutes after completion of the drug infusion for both groups. The mean difference in MCS between the groups at this time point was 0.38 (p=0.037).

Representative ECGs indicating prominent QT interval prolongation and T-wave changes during the sotalol infusion (0, 5, 10 15 and 20 minutes) from both the +TdP and –TdP groups are shown in Fig. 1. During the drug infusion period of 20 minutes and during about 20 min. after completion of the infusion, the QT interval increased from baseline for both groups. The corresponding changes in the T-wave morphology are associated with increased asymmetry, flatness and notching.

The averages of QTcF and MCS for each five-minute segment during the whole experimental period (up to 20 min after infusion) are presented in Fig. 2, with error bars indicating the 95% confidence intervals (CI). QTcF increased more in patients with a history of TdP as compared with the patients in the –TdP group, ($p<0.017$). In contrast, the change in the T-wave morphology was similar in the two groups ($p=0.73$).

Identification of Patients with a History of TdP

A linear discriminant analysis[23] was used to identify the +TdP and –TdP patients based on QTcF and/or MCS values at baseline and at 20 min after completion of the sotalol infusion. Table 3 shows the sensitivity (Se), specificity (Sp), positive predictivity (PP) and negative predictivity (NP) for the univariate (discriminant analysis based on QTcF and MCS separately) and covariate cases (discriminant analysis considering both QTcF and MCS).

McNemar's test showed that a combined method, using QTcF and MCS, provides a significantly higher accuracy (0.69) of correct identification of patients compared with QTcF-only (accuracy = 0.50) based identification at baseline ($p=0.04$).

Discussion

Administering I_{Kr} inhibiting drugs to the patients with a history of TdP poses substantial risk of arrhythmogenesis as evident from their post dose QTcF values. From the analyses of Kääb *et al*.,[21] and Couderc *et al*.,[24] it is evident that the QTcF at baseline was not significantly different between the +TdP and -TdP groups which corroborates our QTcF finding. After the sotalol infusion, the +TdP group responded with significantly higher QTcF than the –TdP group. Kääb *et al*.[21] reported the higher post-dose QTcF of the +TdP group as compared with the –TdP group as the unmasking of the reduced repolarization reserve of the former group. The repolarization reserve by definition is a defensive mechanism against the triggering of TdP as a result of the interaction of other ion channels.[25] However, the association between drug-induced repolarization changes and the so-called repolarization reserve is not clear. We do not have measures to quantify and relate the repolarization reserve with ECG parameters. Nevertheless, the higher QTcF of the +TdP group can be assumed to reflect their abnormality in repolarization, which agrees with the observations of Sauer et al., that higher baseline QTc was associated with discontinuation of sotalol and dofetilide.[26]

Stress testing has been established as a way to unmask the presence of LQTS.[27] The higher post-dose QTcF of the +TdP group implies the need for a stress test to find patients with latent repolarization disturbance. In contrast, MCS already at baseline identifies repolarization disturbances with similar accuracy as stress testing with QTcF, thus implying that that a combination of QTc and MCS at baseline could eliminate the need for provocative stress testing.

QTcF based correct identification of patients in their respective groups (+TdP or -TdP) increased after drug treatment (baseline: 9 post-dose: 14) as shown in Table 3. However, this accuracy can be already attained at baseline when both the baseline QTcF and MCS were used in the discriminant analysis. On the other hand, there is no significant difference

between the number of correct identifications by MCS at baseline (n=12) and by QTcF after sotalol treatment (n=14). Hence, again it can be inferred that the combination of the baseline values of QTcF and MCS may be used to avoid stress testing.

Other T-wave based parameter e.g. the T-loop morphology analysis by Couderc[24] on the data of similar groups also shows the differences between groups. A difference in early repolarization duration (ERD) between the groups was significant at baseline but not significant after sotalol treatment. On the other hand, late repolarization duration (LRD) showed the exact opposite response - being similar in the two groups at baseline and significantly different after sotalol. This transition of the significance of early and late repolarization duration is interesting although the reason for it is unclear. The TpTe between the groups was not significantly different at baseline although it attained a significant level after the sotalol treatment but with very high standard deviation, which might not be clinically useful for identifying individual vulnerable patients.[24] Also TpTe/QTc was not significantly different between the groups, neither at baseline nor after sotalol.[24] However, some other measures related to the risk of TdP may be investigated in future studies. The Index of Cardio-Electrophysiological Balance (iCEB=QRS/QT)[28,29], QT-instability[30], and the Electro-mechanical window (EMW)[31,32] have shown some potential with respect to QT-prolongation and the risk of TdP, although EMW would require an echocardiography in addition to the ECG.

We found a larger mean QT interval prolongation after sotalol in the +TdP group compared to the -TdP group. This differential QT effect highlights another problem related to potential wrongful labelling of the risk associated with a drug. A QT-based risk assessment of TdP is obtained from a Thorough QT (TQT) study carried out in healthy volunteers. The study is used to assess whether or not a drug will have a QT interval prolonging effect in the target population. However, it has never been demonstrated that QT interval data from TQT

trials in healthy volunteers can be extrapolated to the target population to identify repolarization effects reliably. In fact, our QT results suggest the opposite. Extrapolation to the clinical situation based on QT labelling may, therefore, be inappropriate and wrong. On the other hand, MCS is a stable parameter and the mean baseline MCS of the –TdP patients (0.74) and of the healthy volunteers from another sotalol study by Graff et al. (0.71)[11] are interestingly similar. Furthermore, we emphasize our observation that sotalol had similar effects on T-wave morphology in the +TdP and –TdP groups and propose further studies to be carried out to investigate if T-wave morphology changes are more consistent across different patient populations than QT interval changes.

The results of this study suggest that T-wave morphology is an indicator of risk of TdP and that the standard QT analysis should be enriched with analysis of T-wave morphology in patients with suspected pro-arrhythmic tendencies or for screening of patients to be treated with QT prolonging drugs such as Class III antiarrhytmics.

Methods

Study population

The ECG data were obtained from patients with paroxysmal atrial fibrillation (AF) and was available from the Medical Center of the University of Munich, Germany. The +TdP group (n=20) was defined as patients with a documented history of TdP in association with QT-prolonging drugs. The –TdP group (n=16) consists of patients who were treated with sotalol for their paroxysmal AF and without a history of TdP. All of the patients were informed about the study and gave signed consent for the study, which was approved by the local ethics committee of the university and the procedures were followed accordingly.

Study Protocol

The protocol was described by Kääb et al.[21] In short, all patients rested in supine position for 60-90 min. prior to testing. Tests were performed between 9:00 and 13:00, and dl-sotalol was

infused at a constant rate over a 20-min interval at a dose of 2 mg/kg body weight in both groups. All the patients were closely monitored in the ICU from 1 h before to 24 h after testing. Digital 12-lead ECGs were recorded as nine consecutive five-minute segments while the patients were in a supine position, at baseline (1 ECG segment), during intravenous sotalol infusion of 20 minutes (4 ECG segments) and the 20 minutes steady state phase just after discontinuing sotalol infusion (4 ECG segments).

ECG Analysis

Median Beat Formation

The central three minutes of each of the five-minute ECG segments were used to derive 18 median beats in each lead of the 12-lead 10-second recordings in that three minute period. The MUSE/Interval Editor software (GE Healthcare, Milwaukee. WI, USA) was used to form the median beats. QT-interval and T-wave morphology parameters were calculated from the first principal component of each of the 18 median beats. The resulting 18 values were subsequently averaged for each five-minute segment.

QT and T-wave Morphology Measurement

The QT interval was measured using the tangent method described by Lepeschkin et al.[33] and corrected for heart rate with Fridericia's formula to give QTcF.

The details of the morphology measurement were presented by Graff et al.[11, 20] In brief; the morphology measure is a combination of the measures of T-wave asymmetry, flatness and notching.

Asymmetry was defined as the average squared difference in the slope profiles of the ascending and descending part of the T-wave (see Fig. 3A for a normal symmetric T-wave and 3B for an asymmetric T-wave).

Flatness was calculated as a modified version of the standard kurtosis measure which is used to describe the peakedness of a probability distribution (Fig. 3C has a flatter T-wave than 3A and 3B).

The notch in the T-wave was quantified by the depth of the nadir near the peak of the T-wave. The magnitude of a notch was measured on a unit amplitude T-wave and assigned to 1 of 3 categories: No notch = 0, moderate notch (perceptible bulge) = 0.5 and pronounced notch = 1.0 (distinct protuberance above the apex). Fig. 3D shows a notch in the T-wave.

The morphology measures were linearly combined to yield the Morphology Combination Score (MCS) as a measure of the overall description of the T-wave morphology.

$$MCS = Asymmetry + 1.6 \times Flatness + Notch$$

ECG measurements were calculated before unblinding of data.

Statistical Analysis

As some of the ECG segments were missing at random, a standard method (Expectation Maximization algorithm (EM)[34]) was used to account for the missing values in the statistical analysis. All analyses were done in SPSS (IBM SPSS Statistics 21 Inc). A 2-way ANOVA was used to account for potential bias due to the different male-female ratios between the groups. An independent sample t-test was performed to calculate the significance of the differences at baseline and after sotalol infusion between the groups. Linear discriminant analysis was used as a measure of distinction between +TdP and -TdP. A McNemar test was used for the classification of +TdP and -TdP groups. $P<0.05$ was considered significant. Results are presented as mean±standard error (SE) unless otherwise stated.

Limitations of the study

The sample size in this study was small (n=36), although it contained ample ECG data of

(45 minutes) from each patient. Both groups consisted of patients with paroxysmal AF and according to Hong *et al.*, AF has a shortening effect on the QT interval, which indicates that the results might be different for different heart diseases.[35]

The dosage was a single infusion of sotalol, which does not affect the results at baseline, but with repeated administration of the drug the results may develop differently over time.

The automatic calculation of the QT interval is a possible source of error. To mitigate this problem we have manually evaluated the resulting QRS-start and T-end points on the ECGs without finding errors requiring overreading, although the tangent method as such systematically underestimates the QT interval.

Several interesting parameters have been proposed in the literature. In the current paper we have investigated QTc and MCS only. The results encourage future study with other promising parameters.

Study Highlights

- What is the current knowledge of the topic

Patients with a history of TdP are prone to drug induced repolarization disturbance which can trigger TdP. A latent abnormality in repolarization is primarily measured in the ECG as a prolongation of the QT interval. However, using the QT interval alone it is difficult to identify vulnerable patients without stress testing.

- What question did this study address?

The study investigates if T-wave morphology (MCS) can aid in identifying vulnerable patients at risk of TdP.

- What this study adds to our knowledge

At baseline, without the need for stress testing, T-wave morphology but not QTc can be used to identify vulnerable patients with a history of TdP (+TdP) and patients without such history (-TdP).

- How this might change clinical pharmacology or translational science

T-wave morphology analysis can be used as an adjunct to QTcF measurements to stratify patients for TdP risk without drug challenge

Acknowledgements

This work was supported by the Danish Council for Strategic Research (HEARTSAFE Grant Number: 10-092799).

Disclosures

Claus Graff, Jørgen Kanters, Johannes Struijk and Egon Toft are the authors of T-wave morphology descriptors. A license agreement exists between Aalborg University and GE healthcare. All authors declare no conflict of interests.

Author Contributions

J.J.S., T.A.B., and C.G. wrote the manuscript; S.K. designed the research; T.A.B., J.K.K., J.M., and E.T. performed the research; J.J.S., T.A.B., C.G., J.K.K., J.M., and E.T. analyzed the data.

References

1. Lasser, K.E., Allen, P.D., Woolhandler, S.J., Himmelstein, D.U., Wolfe, S.M. & Bor, D.H. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* **287**, 2215-20 (2002).

2. Haverkamp, W. *et al.* The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. *Cardiovasc. Res.* **47**, 219-33 (2000).

3. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (Center for Drug Evaluation and Research Food and Drug Administration, 2005).

4. Moss, A.J. *et al.* The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation.* **84**, 1136-44 (1991).

5. Badshah, A., Janjua, M., Younas, F., Halabi, A.R. & Cotant, J.F. Moxifloxacin-induced QT prolongation and torsades: an uncommon effect of a common drug. *Am. J. Med. Sci.* **338**, 164-166 (2009).

6. Sherazi, S., DiSalle, M., Daubert, J.P. & Shah, A.H. Moxifloxacin-induced torsades de pointes. *Cardiol. J.* **15**, 71-73 (2008).

7. Altin, T. *et al.* Torsade de pointes associated with moxifloxacin: a rare but potentially fatal adverse event. *Can. J. Cardiol* . **23**, 907-908 (2007).

8. Liu, X.K., Katchman, A., Ebert, S.N. & Woosley, R.L. The antiestrogen tamoxifen blocks the delayed rectifier potassium current, IKr, in rabbit ventricular myocytes. *J. Pharmacol. Exp. Ther.* **287**, 877-883 (1998).

9. Antzelevitch, C. *et al.* Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation.* **110**, 904-910 (2004).

10. Graff, C. *et al.* Covariate Analysis of QTc and T-Wave Morphology: New Possibilities in the Evaluation of Drugs That Affect Cardiac Repolarization. *Clin. Pharmacol. Ther.* **88**, 88-94 (2010).

11. Graff, C. *et al.* Identifying drug-induced repolarization abnormalities from distinct ECG patterns in congenital long QT syndrome: a study of sotalol effects on T-wave morphology. *Drug. Saf.* **32**, 599-611 (2009).

12. Vicente, J. *et al*. Comprehensive T wave Morphology Assessment in a Randomized Clinical Study of Dofetilide, Quinidine, Ranolazine, and Verapamil. *J. Am. Heart Assoc*., **4**, e001615 (2015).

13. Sugrue, A. *et al*. Electrocardiographic Predictors of Torsadogenic Risk During Dofetilide or Sotalol Initiation: Utility of a Novel T Wave Analysis Program. *Cardiovasc. Drugs Ther*. **29**, 433–441 (2015).

14. Topilski, I. *et al.* The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. *J. Am. Coll. Cardiol.* **49**, 320-328 (2007).

15. Smetana, P., Pueyo, E., Hnatkova, K., Batchvarov, V., Camm, A.J. & Malik, M. Effect of amiodarone on the descending limb of the T wave. *Am. J. Cardiol.* **92**, 742-6 (2003).

16. Kanters, J.K. *et al.* T(peak)T(end) interval in long QT syndrome. *J. Electrocardiol.* **41**, 603-608 (2008).

17. Bhuiyan, T.A. *et al.* The T-peak-T-end interval as a marker of repolarization abnormality: a comparison with the QT interval for five different drugs. *Clin. Drug. Investig.* **35**, 717-724 (2015).

18. Pham, Q., Quan, K.J. & Rosenbaum, D.S. T-wave alternans: marker, mechanism, and methodology for predicting sudden cardiac death. *J. Electrocardiol* . **36**, 75-81 (2003).

19. Bhuiyan, T.A., Graff, C., Kanters, J.K., Thomsen, M.B., Struijk, J.J. Flattening of the electrocardiographic T-wave is a sign of proarrhythmic risk and a reflection of action potential triangulation. *Comput. Cardiol.* **40**, 353-356 (2013).

20. Graff, C. *et al.* Quantitative analysis of T-wave morphology increases confidence in drug-induced cardiac repolarization abnormalities: evidence from the investigational IKr inhibitor Lu 35-138. *J. Clin. Pharmacol.* **49**, 1331-1342 (2009).

21. Kääb, S., Hinterseer, M., Näbauer, M. & Steinbeck, G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome--a case-control pilot study using i.v. sotalol. *Eur. Heart. J.* **24**, 649-657 (2003).

22. Drew, B.J. *et al.* Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation.* **121**, 1047-1060 (2010).

23. Hair Jr., J.F., Black, W.C., Babib, B.J. Anderson R.E. & Tatham, R.L. *Multivariate data analysis* (Pearson Prentice Hall: Upper Saddle River, New Jersey, 2006).

24. Couderc, J.P. *et al.* Baseline values and sotalol-induced changes of ventricular repolarization duration, heterogeneity, and instability in patients with a history of drug-induced torsades de pointes. *J. Clin. Pharmacol*. **49**, 6-16 (2009).

25. Roden, D.M. Repolarization reserve: a moving target. *Circulation* **118**, 981-982 (2008).

26. Sauer, A.J. *et al.* Electrocardiographic markers of repolarization heterogeneity during dofetilide or sotalol initiation for paroxysmal atrial fibrillation. *Am J. Cardiol.* **113**, 2030-2035 (2014).

27. Vyas, H., Hejlik, J. & Ackerman, M.J. Epinephrine QT stress testing in the evaluation of congenital Long-QT syndrome: Diagnostic accuracy of the paradoxical QT response. *Circulation.* **113**, 1385-1392 (2006).

28. Lu, H.R., Yan, G.X., & Gallacher, D.J. A new biomarker − index of Cardiac Electrophysiological Balance (iCEB) − plays an important role in drug-induced

cardiac arrhythmias: beyond QT-prolongation and Torsades de Pointes (TdPs). *J. Pharmacol. Toxicol. Meth.* **68**, 250-259 (2013).

29. Robyns, T. *et al.* Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a new biomarker for the identification of patients at increased arrhythmic risk. *Ann. Noninvasive Electrocardiol.* **21**, 294-304 (2016).

30. Linde van der, H.J., *et al.* A new method to calculate the beat-to-beat instability of QT duration in drug-induced long QT in anesthetised dogs. *J. Pharmacol. Toxicol. Meth.* **52**, 168-177 (2005).

31. Linde van der, H.J., Deuren van, B., Somers, Y., Loenders, B., Towart, R., & Gallacher, D.J. The Electro-Mechanical window: a risk marker for Torsade de Pointes in a canine model of drug induced arrhythmias. *Br. J. Pharmacol.* **161**, 1444-1454, (2010).

32. Bekke ter, R.M.A, *et al.* Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk. *Eur. Heart J.* **36**, 179-186 (2015).

33. Lepeschkin, E. & Surawicz, B. The Measurement of the Q-T Interval of the electrocardiogram. *Circulation.* **6**, 378-388 (1952).

34. Little, R.J.A. & Rubin, D.B. *Statistical analysis with missing data* (Wiley: Hoboken, New Jersey, 2002).

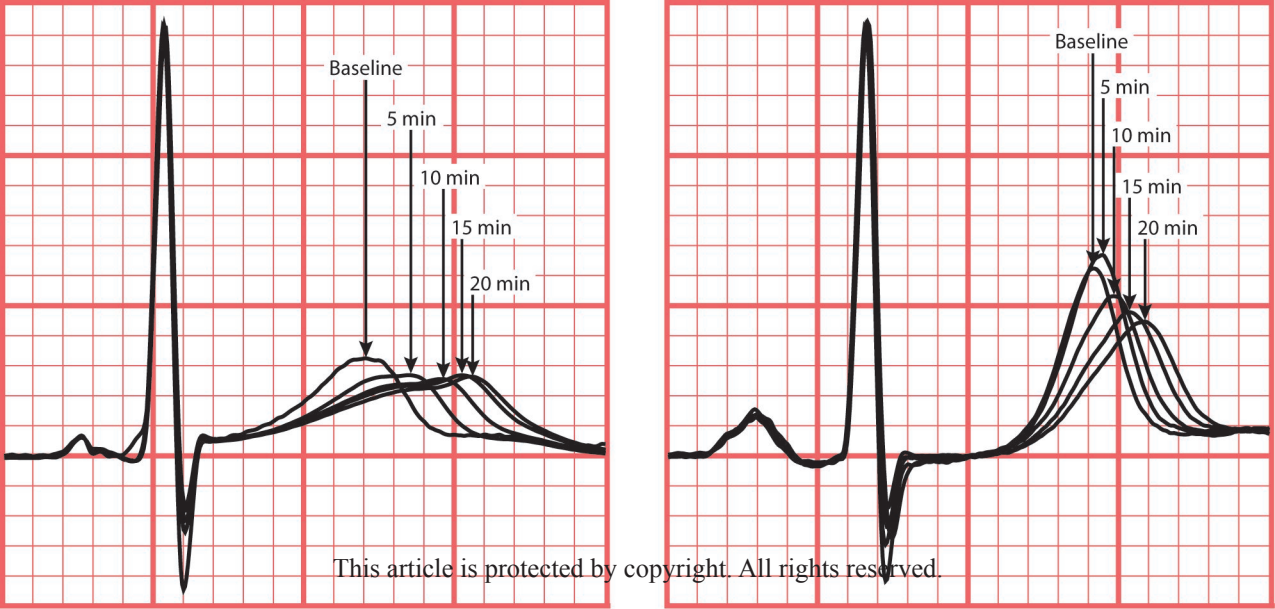
35. Hong, K., Bjerregaard P., Gussak I., Brugada, R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *J. Cardiovasc. Electrophysiol.* **16**, 394-396 (2005).

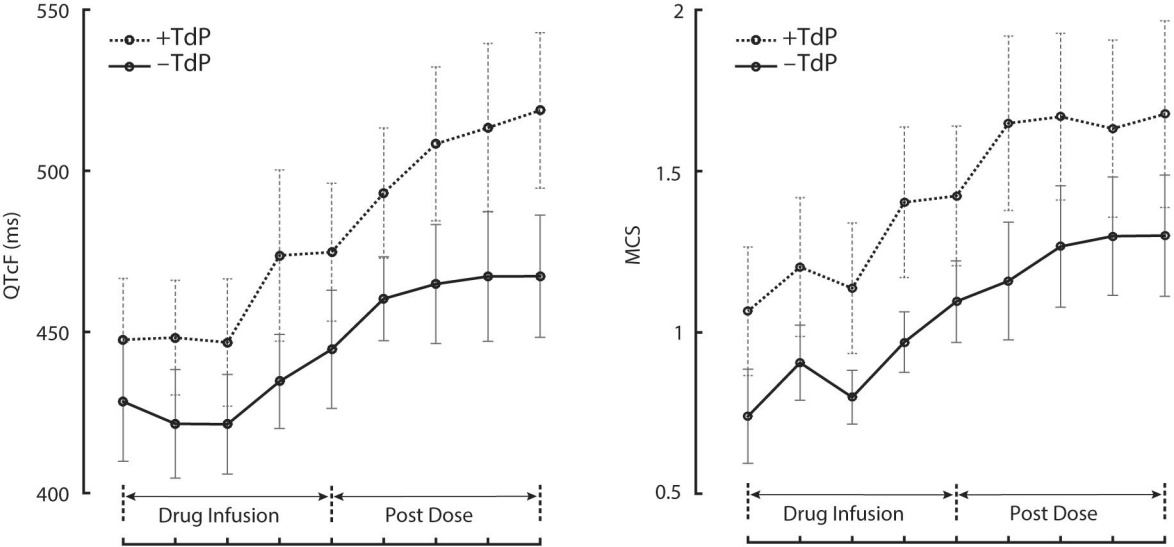
Figure legends

Figure 1. Representative ECGs (first principal components) during sotalol infusion. Left panel: ECG from a patient with a history of TdP (+TdP); Right panel: ECG from a patient with no history of TdP (-TdP).

Figure 2. Development of QTcF and MCS in response to the sotalol infusion. Left panel: The development of QTcF from baseline up to 20 min post dose for the +TdP and –TdP groups. Right panel: MCS values from baseline up to 20 min post dose. Circles and error bars indicate means±95% confidence intervals.

Figure 3. ECGs with different T-wave morphologies. (A) Normal, (B) Asymmetric, (C) Flattened, and (D) Notched T-wave.





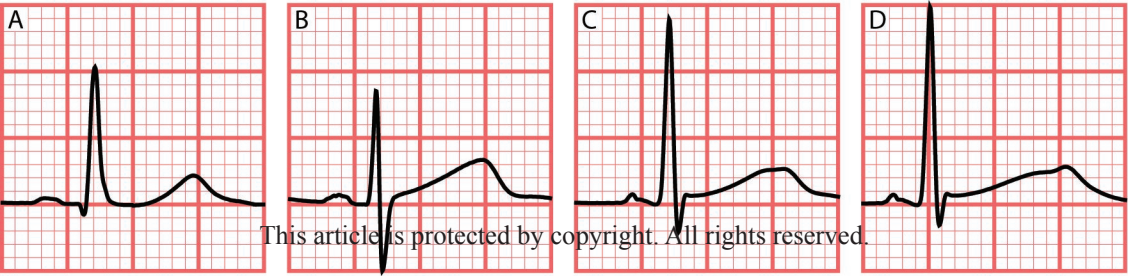


Table 1: Patient Demographics

Age (yrs)	Gender	CAD	MI	HT	AF	LVEF (%)	TdP cause

+TdP: Group with history of TdP							
70	m	yes	yes	no	yes	56	Erythromycin
52	m	no	no	yes	yes	60	n.a.
54	f	no	no	no	yes	56	Sotalol
63	m	no	no	no	yes	29	Sotalol
77	f	yes	yes	yes	yes	45	Sotalol
39	m	no	no	no	no	n.a.	Imipramin
47	f	no	no	yes	yes	n.a.	Diuretic
72	f	no	no	yes	yes	n.a.	Cipramil
75	f	no	no	yes	yes	60	Sotalol,
58	m	no	no	no	yes	60	Sumatriptane
61	f	no	no	no	no	n.a.	Bisacodyl
64	m	no	no	no	yes	30	Sotalol
55	m	yes	yes	yes	yes	30	Amiodarone
72	f	no	no	yes	no	30	n.a.
40	m	no	no	no	no	39	Clarithromycin
65	f	no	no	yes	no	63	n.a.
72	f	no	no	no	no	74	n.a.
45	m	no	no	no	yes	36	n.a.
45	m	no	no	no	yes	36	n.a.
68	m	no	no	yes	no	65	n.a.
-TdP: Group without history of TdP							
60	f	no	no	no	yes	n.a.	
67	f	no	no	yes	yes	70	
70	f	no	no	no	no	60	
61	f	no	no	yes	yes	n.a.	
65	f	no	no	no	yes	n.a.	
70	f	n.a	n.a.	n.a.	n.a.	n.a.	
64	f	no	no	yes	yes	n.a.	
62	f	no	no	yes	yes	80	
82	f	no	no	yes	yes	65	
63	m	yes	no	no	yes	50	
56	m	no	no	no	yes	n.a.	
36	m	no	no	no	no	65	
70	f	yes	no	yes	yes	64	
54	m	yes	no	yes	yes	65	
73	f	no	no	yes	no	66	
37	m	no	no	no	no	70	

CAD - Coronary artery disease; MI - myocardial infarction; HT - Hypertension; AF - history of Atrial Fibrillation; LVEF - Left Ventricular Ejection Fraction; n.a. - information was not available

Table 2: Baseline values and sotalol induced changes (mean ±standard error)

	Baseline Values			Sotalol induced change from baseline		
	-TdP	+TdP	p	-TdP	+TdP	p
Intervals (ms)						
QT	409±7	433±10	0.07	74±13	107±10	0.043†
QTcF	431±9	447±10	0.26	36±10	73±9	0.017†
QTcB	445±12	454±10	0.57	16±14	55±9	0.022†
RR	873±51	924±40	0.42	230±46	207±30	0.67
T-wave Morphology parameters						
MCS	0.74±0.07	1.07±0.09	0.01†	0.56±0.12	0.61±0.097	0.73
Asymmetry	0.096±0.02	0.20±0.04	0.04†	0.12±0.04	0.09±0.02	0.67
Flatness	0.39±0.02	0.47±0.02	0.036†	0.16±0.03	0.17±0.01	0.75
Notch	0.01±0.02	0.11±0.05	0.09	0.18±0.06	0.24±0.07	0.46

† significant

Table 3: Sensitivity (Se), Specificity (Sp), Positive Predictivity (PP) and Negative Predictivity (NP) at baseline and 20 min post dose

	QTcF		MCS		QTcF & MCS	
	Baseline	Post dose	Baseline	Post dose	Baseline	Post dose
Se	0.45	0.70	0.60	0.65	0.70	0.70
Sp	0.56	0.75	0.69	0.75	0.69	0.94
PP	0.56	0.78	0.71	0.76	0.74	0.93
NP	0.50	0.67	0.58	0.63	0.65	0.71