

Flattening of the Electrocardiographic T-wave is a Sign of Proarrhythmic Risk and a Reflection of Action Potential Triangulation

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Abstract

Drug-induced triangulation of the cardiac action potential is associated with increased risk of arrhythmic events. It has been suggested that triangulation causes a flattening of the electrocardiographic T-wave but the relationship between triangulation, T-wave flattening and onset of arrhythmia has not been studied in detail.

In this paper, we have analyzed the simultaneous recordings of 10-lead electrocardiograms and monophasic action potentials (MAP) from the left ventricle of five dogs that were given supratherapeutic doses of the IKr inhibitor sertindole. All dogs developed Torsades de Pointes (TdP) arrhythmia.

We show that MAP triangulation measured as the duration between 30% and 90% repolarization causes flattening of the electrocardiographic T-wave. Triangulation and flattening attain maximum values just before the onset of TdP.

A quantitative measurement of electrocardiographic flatness could present new opportunities in drug trials as a means to distinguish between safe and unsafe drugs.

1. Introduction

Drug-induced repolarization changes of myocardial cells can be the substrate for Torsades de Pointes (TdP) arrhythmia and sudden cardiac death (SCD) in vulnerable patients [1], [2].

Our studies of the electrocardiographic T-wave morphology [3-5] have shown that, compared to the QT interval, the shape of the repolarization segment can be a more sensitive marker for assessing drug-induced repolarization changes.

This is not surprising since the electrophysiological effects that occur with torsadogenic drugs are expected to affect the whole T-wave. For example, it has been

demonstrated that drug torsadogenicity is related to triangulation (increase of the duration of phase-3) of the monophasic action potential (MAP) and not just to the increase of MAP duration and its reflection on the electrocardiographic QT interval [6].

Triangulation of the monophasic action potential can occur differentially across the myocardial wall or in different regions of the heart. Triangulation of the MAP can therefore cause changes in the electrical gradients during repolarization, either transmurally, left-right, or apico-basal.

It is important to quantify the presentation of such drug-induced repolarization changes in the ECG but it is even more important to identify those ECG characteristics that can lead to TdP arrhythmia.

In the present study we have analyzed the effect of an IKr blocker (sertindole) on the triangulation of MAPs and flattening of the electrocardiographic T-wave in dogs that develop TdP.

Sertindole is an antipsychotic drug which is effective in the treatment of schizophrenia [7]. Data has shown an association between sertindole and prolongation of the QT interval, as well as an increased risk of serious arrhythmic events and sudden cardiac death [8]. As a consequence, the drug has been withdrawn from the market.

The increased arrhythmic risk associated with sertindole makes the drug suitable for studying the relationship between triangulation of MAPs and the electrocardiographic T-wave just before the onset of TdP arrhythmia.

In this study we quantify the electrocardiographic changes in T-wave morphology that occur in dogs just before TdP onset and we show a direct relationship to triangulation of the endocardial MAP.

Immediately before TdP onset the duration of phase-3 of the MAPs increases and the electrocardiographic T-waves flatten.

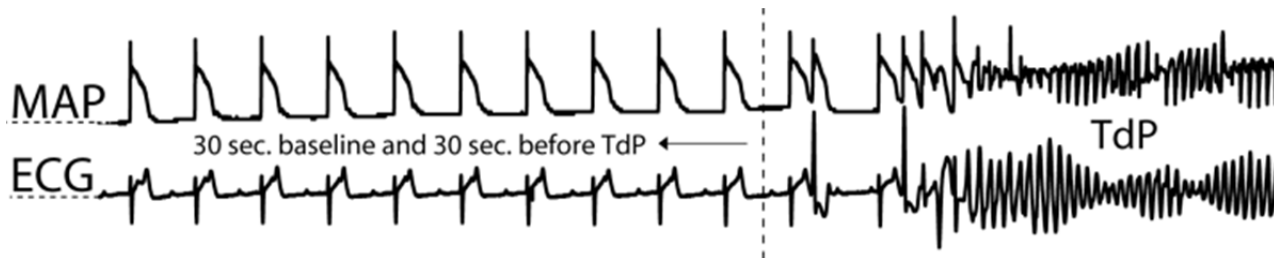


Figure 1. Extraction of MAP and ECG segments at baseline and just before the onset of TdP arrhythmia.

2. Methods

2.1. Study population and design

In this study, 5 dogs were used from a group of 13 healthy dogs where complete AV block was induced by radio frequency ablation as described in [9]. Before the dogs were given sertindole, they went through a TdP-susceptibility test using dofetilide (IKr blocker). Those dogs that showed reproducible TdP on 25 μ g/kg/5min dofetilide were selected for the sertindole study (5 dogs). Details of the protocol have been described [10]. Briefly, sertindole was given at supratherapeutic dose (1mg/kg body weight) at the rate of 6-9 minutes infusion. TdP was seen in all 5 dogs after 7 ± 2 min drug infusion.

2.2. MAP recordings

Endocardial MAPs were continuously recorded from left and right ventricles before sertindole administration (baseline) and during drug infusion until the development of TdP. Left ventricular MAPs were used in this study. Each MAP was normalized with respect to its plateau amplitude in order to remove any time dependent loss of amplitude due to declining contact pressure of the catheter. Baseline wander was reduced by subtracting a baseline estimate found by spline fitting of the isoelectric points [11].

2.3. ECG recordings

Ten lead ECGs (I, II, III, aVR, aVL, aVF, V1, V2, V3, V4) were recorded synchronously with MAP recordings. Noise was eliminated from data by a 15 tap moving average filter. Baseline wander was reduced by subtracting a baseline estimate found by spline fitting of the isoelectric ECG points [11]. Lead V4 was used for T-wave analysis.

2.4. Extraction of data segments

From each dog, three median MAPs and three median ECGs were constructed from 3x10 second consecutive recordings at baseline and 3x10 s recordings just before TdP onset. Figure 1 shows the simultaneous recording of MAPs and ECGs for one dog immediately before the onset of TdP. The medians for each dog were used to calculate one average value for MAP triangulation and ECG flatness at baseline and one average value just before TdP.

2.5. MAP triangulation

IKr inhibiting drugs affect the morphology of MAPs by slowing down the phase-3 repolarization. Hence, triangulation of the action potential can be quantified by the duration of phase-3. Specifically, triangulation is defined by the time interval between 30% repolarization to 90% repolarization on the MAP [12]. Figure 2 shows the calculation of phase-3 duration (D_{30-90}) from a plateau-normalized MAP.

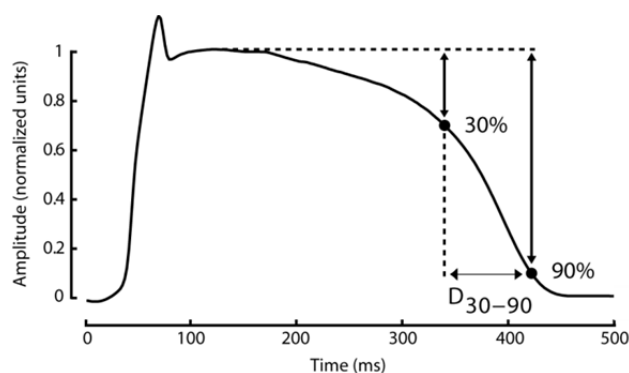


Figure 2. Measurement of triangulation on the MAP.

2.6. T-wave flattening

We have used the area of the T-wave relative to an enclosing rectangle as an indicative parameter of flatness. The flatness measurement is shown in figure 3.

First, T-end was identified by the tangent method. A horizontal line was subsequently drawn and moved back from T-end along the descending T-wave in such a manner that its width (W) touches both the ascending and the descending parts of the T-wave without intercepting the QRS complex. With the current data, the longest horizontal line that could be drawn was 180 ms. The T-wave was then enclosed by a rectangle with horizontal width (W=180 ms) and height (H) between the base of the rectangle and the peak of the T-wave.

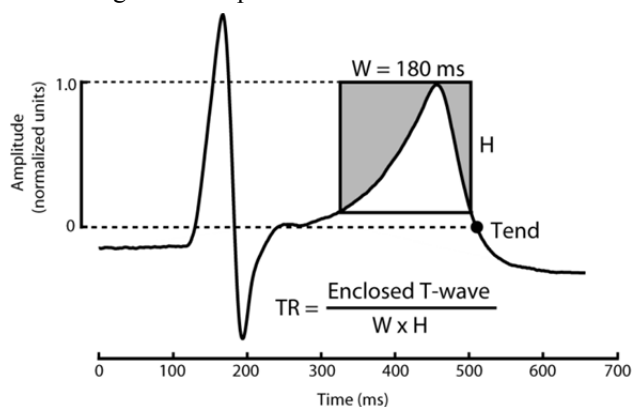


Figure 3. Quantification of T-wave flatness.

The ratio of the area enclosed by the T-wave to the area of the surrounding rectangle (T-wave Ratio, TR) was used as a measure of flatness. The area of the T-wave segment was calculated by numerical integration.

3. Results

Sertindole increased the phase-3 duration of MAPs (D_{30-90}) and flattened the electrocardiographic T-wave (T-wave Ratio, TR), figure 4. The D_{30-90} duration increased from 100.6 ± 12.5 (mean, standard error) to 155.0 ± 28.5 , $p=0.08$. The T-wave ratio increased from 0.44 ± 0.01 to 0.52 ± 0.04 , $p=0.06$.

The MAP triangulation and ECG flattening attained maximum values just before TdP onset.

4. Discussion

In this study we have shown that triangulation of the monophasic action potential and flattening of the electrocardiographic T-wave both occur after a supratherapeutic dose of sertindole was given to dogs.

In a previous study we also showed that the peak changes in T-wave morphology and phase-3 duration of

the MAP occurred at almost the same point in time with low doses of sertindole [13].

Sertindole increases the MAP duration by slowing down the repolarization i.e. prolonging phase-3. The effect of an IKr blocker is prominent mostly in phase-3 and prolongation of phase-3 causes the MAP to appear more triangular compared to its baseline rectangular shape. The triangulation of MAPs manifest on the ECG as a flattened T-wave.

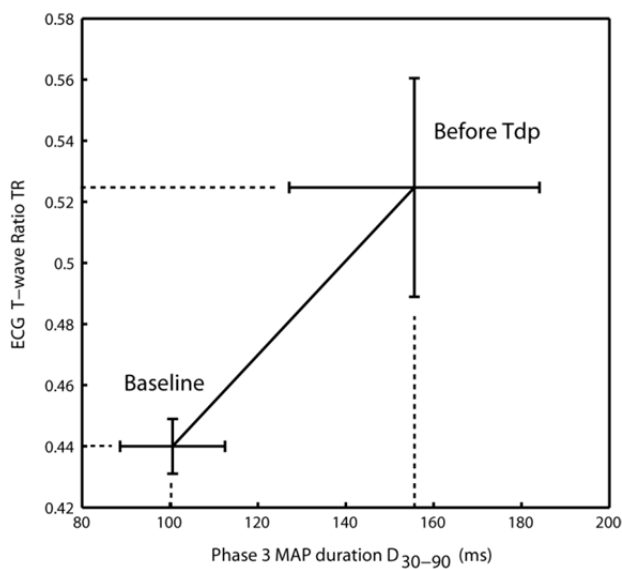


Figure 4. Concurrent MAP triangulation and T-wave flatness on the ECG. I-bars indicate mean values ± 1 standard error.

A flattened T-wave covers a relatively larger area in a rectangle that encloses the T-wave compared to the normal T-wave.

The T-wave ratio (TR) measurement of flatness is robust to noise since area is calculated by numerical integration. The duration of phase-3 is also a robust measurement. Although changes from baseline did not reach statistical significance, due to the low number of dogs, we believe that the observed increase in both parameters before TdP is real and that a true relationship exists between MAP triangulation and T-wave flatness. In other words, the increase of phase 3 duration of MAP is the primary cause of the flatness of T-wave.

This finding indicates that increasing flatness of the T-wave is associated with a higher risk for TdP. However it is uncertain if this is generally true for all IKr blockers or only those which cause triangulation of the MAP.

Animal studies have shown that, TRIaD (Triangulation, Reverse use dependence, Instability and Dispersion) has a good predictive value of TdP. The potential value of TRIaD parameters was verified in about 700 trial drugs [14]. So, the electrocardiographic

measurement of flatness can be of particular significance for drug safety testing since it is the body surface reflection of triangulation.

We believe that measurement of electrocardiographic T-wave flatness can be valuable in thorough QT studies and clinical drug safety testing where MAP data is not available. A measurement of electrocardiographic T-wave flatness in such a setting could be used to distinguish between safe and unsafe drugs.

5. Conclusion

Flattening of the electrocardiographic T-wave is a result of triangulation of the monophasic action potential. The repolarization effects can be observed in dogs following IKr inhibition by sertindole. Peak effects are observed immediately before TdP onset.

Further studies are needed to investigate the relationship between MAP triangulation, T-wave flatness and TdP arrhythmia.

References

- [1] Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287:2215-20.
- [2] Fermini B, Fossa AA. The impact of drug-induced QT interval prolongation on drug discovery and development. *Nat Rev Drug Discov* 2003;2:439-47.
- [3] Graff C, Matz J, Christensen EB, Andersen MP, Kanters JK, Toft E, Pehrson S, Hardahl TB, Nielsen J, Struijk JJ. 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* 2009;49:1331-42.
- [4] Nielsen J, Graff C, Hardahl TB, Andersen MP, Kristoffersen J, Struijk JJ, Toft E, Meyer JM. Sertindole causes distinct electrocardiographic T-wave morphology changes. *Eur Neuropsychopharmacol* 2009;19:702-7.
- [5] Graff C, Andersen MP, Xue JQ, Hardahl TB, Kanters JK, Toft E, Christiansen M, Jensen HK, Struijk JJ. Identifying Drug-Induced repolarization abnormalities from distinct ECG patterns in congenital Long QT Syndrome. *Drug Saf* 2009;32:599-611.
- [6] Hondeghem LM, Carlsson L, Duker G. Instability and triangulation of the action potential predict serious proarrhythmia, but action potential duration prolongation is antiarrhythmic. *Circulation* 2001;103:2004-13.
- [7] Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, Burght MVD, Nielsen MS, Wehnert A. Sertindole improves both the positive and negative symptoms of schizophrenia: Results of a phase III trial. *Int J Psych Clin Pract* 2000;4:55-62.
- [8] Food and Drug Administration: Minutes of the Psychopharmacological Drugs Advisory Committee, 7 Apr 2009.
- [9] Opstal JM, Verduyn SC, Leunissen HD, Groot SH, Wellens HJ, Vos MA. Electrophysiological parameters indicative of sudden cardiac death in the dog with chronic complete AV-block. *Cardiovasc Res* 2001;50:354-61.
- [10] Thomsen MB, Volders PG, Stengl M, Spätjens RL, Beekman JD, Bischoff U, Kall MA, Frederiksen K, Matz J, Vos MA. Electrophysiological safety of sertindole in dogs with normal and remodeled hearts. *J Pharmacol Exp Ther* 2003;307:776-84.
- [11] Badilini F, Moss AJ, Titlebaum EL. Cubic spline baseline estimation in ambulatory ECG recordings for the measurement of ST segment displacements. *Proc Conf IEEE Eng Med Biol Soc* 1991;3:584-5.
- [12] Hondeghem LM, Dujardin K, De Clerck F. Phase 2 prolongation, in the absence of instability and triangulation, antagonizes class III proarrhythmia. *Cardiovasc Res* 2001;50:345-53.
- [13] Bhuiyan TA, Graff C, Thomsen MB, Struijk JJ. Triangulation of the monophasic action potential causes flattening of the electrocardiographic T-wave. *Comput Cardiol* 2012;39:757-60.
- [14] Valentin JP, Hoffmann P, De Clerck F, Hammond TG, Hondeghem LM. Review of the predictive value of the Langendorff heart model (Screenit system) in assessing the proarrhythmic potential of drugs. *J Pharmacol Toxicol Methods* 2004;49:171-81.

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