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Scenarios for Increasing, Decreasing and Stability of Tpe/QT Ratio (Simulation Study)

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Abstract

The objective of this simulation was to study the physiological meaning of the novel index for arrhythmic risk stratification – Tpe/QT ratio (the interval from the peak to the end of the T-wave (Tpe) on electrocardiogram divided by QT interval).

Methods and Results: The role of two factors determining Tpe/QT ratio – action potential duration (APD) and dispersion of repolarization (DOR) – was studied *in silico* at two levels: ventricular wall segment and the whole heart ventricles. The simulations performed in the framework of both the segment and the entire ventricles' models showed that Tpe/QT magnitude reflects the dynamic relationship between the longest and the shortest APD rather than the magnitude of DOR, as interval Tpe does. Tpe/QT ratio remained unchanged even at large DOR, provided that the longer the ventricular APD, the greater the gap between the longest and the shortest of them. The imbalance between the longest and the shortest APD values led to the increased or decreased Tpe/QT.

Conclusion: Simulations showed that Tpe/QT is not just a corrected Tpe interval, but it reflects the balance between the longest and the shortest APD in the heart ventricles.(**International Journal of Biomedicine. 2022;12(4):535-538.**).

Keywords: action potential duration • dispersion of repolarization • arrhythmic risk stratification • electrocardiographic index

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Abbreviations

APD, action potential duration; **DOR**, dispersion of repolarization; **Tpe**, Tpeak-Tend interval.

Introduction

Tpeak-Tend interval (Tpe) has been demonstrated to reflect the magnitude of myocardial dispersion of repolarization (DOR),[1-3] which is considered to be one of the major prerequisites for reentrant arrhythmogenesis. However, despite the solid rationale, Tpe utility as the arrhythmic risk marker is not straightforward. In the general population, the association of Tpe with mortality has not been confirmed[4] or appeared to be U-shaped.[5] These complexities warrant further studies of the ECG predictors of arrhythmic risk.

One of the approaches to this problem may be a search for composite markers since they may reflect the interaction between different arrhythmogenic factors, including DOR manifesting as Tpe and action potential duration (APD) manifesting as QT interval. A Tpe/QT ratio has been proposed as an index of ventricular repolarization, which may be useful for arrhythmic risk stratification.[6,7]

However, the physiological meaning of this novel marker remains unclear. Since Tpe and QT reflect DOR and APD, respectively, the Tpe/QT ratio is thought to provide an estimate of DOR with respect to the total duration of repolarization excluding the confounding effects of heart rate variability and inter-individual variation of the QT interval and emphasizing disproportionate amplification of DOR.[7,8] In turn, the disproportionate amplification of DOR should arise from the abnormal proportion between the shortest and

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the longest APD. APD shortening/lengthening depends on heart rate, drug effects, myocardial pathology, etc., and this dependence may not be the same for the shortest (supposedly epicardial) and longest (supposedly endocardial) APD.

The aim of the present simulation study was to test different ways of APD shortening/lengthening and to find out which one of them is associated with the increase, decrease, or constant magnitude of Tpe/QT ratio.

Material and Methods

Morphology of action potentials

The morphology of ventricular action potentials was simulated using the model of a rabbit ventricular myocyte;[9] for each model cell, the duration of repolarization phase of action potential was scaled according to APD value set for this cell.

The effect of APD lengthening on Tpe/QT ratio was studied using two computer models: ventricular wall segment (the simple model, allowing us to exclude the effects of ventricular geometry and complicated sequences of de- and repolarization) as well as the realistic model of the rabbit heart ventricles.

Model of the heart ventricles

The rabbit ventricular model was a realistically shaped cellular automata model based on experimental data.[3] The model consisted of ≈100,000 discrete elements, with realistic 3D gradients of APD and activation times (transmural, apicobasal, anterior-posterior and left-to-right), reconstructed from experimental epicardial and intramural measurements (Fig. 1).

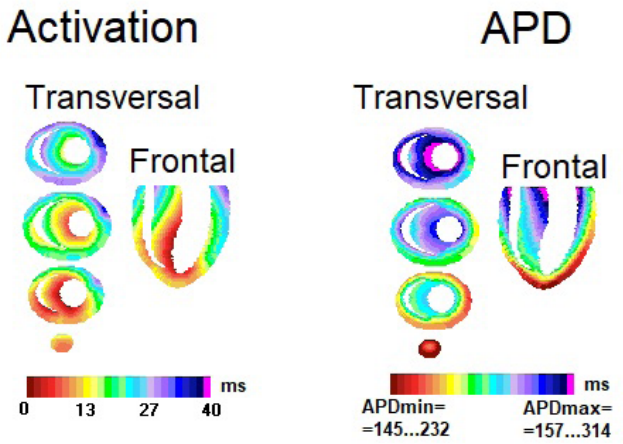

Figure 1. *Realistic activation sequence and APD distribution in the model of the rabbit heart ventricles simulated on the basis of experimental data.*[3]

Ventricular segment model

The segment of the left wall of the rabbit ventricular model consisted of ≈5,000 elements. The difference from the whole ventricular model was that only the transmural gradients of APD and activation times were present (Fig. 2).

APD lengthening

In all simulations, the same initial values of the minimal and maximal APD (APDmin and APDmax, respectively) were used (150 ms and 200 ms for the ventricular segment, 145 ms and 157 ms for the whole ventricle). APDs were prolonged in the following ways (i) proportional changes (i.e., by multiplying all APDs by the same factor), (ii) addition of the same increment to all APDs, (iii) differential changes (by multiplying APDmin and APDmax by different change factors). The change factors for intermediate APD values (neither maximum nor minimum) were calculated by the following:

$$Ki = Kmin + (Kmax–Kmin)*((APDi–APDmin)/(APDmax–APDmin)),$$

where Ki – APD change factor for i-th model element; APDi – initial APD magnitude for i-th model element;

Kmax and Kmin – change factors for APDmax and APDmin, respectively.

The moment of the T-wave peak on the simulated ECGs was determined as the instant of the maximal potential value, the T-wave end – as the point of intersection of the baseline and the tangent to the steepest part of the descending part of the T-wave (tangent method).

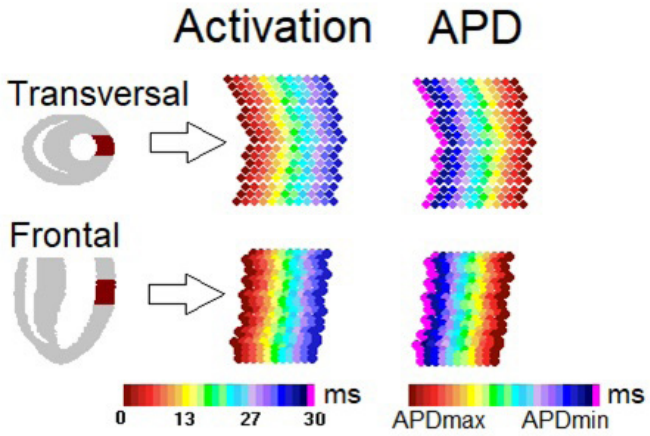

Figure 2. *The simplified activation sequence and APD distribution (only transmural gradients of APD and activation times) in the left ventricular segment of the model of the rabbit heart ventricles.*

Results and Discussion

Segment model: Stable Tpe/QT

The stable Tpe/QT ratio (even at more than twofold increase in APD) was achieved when APDmax was changed 20% less than APDmin (Fig. 3, A), which was accompanied by a moderate increase in the APDmax-APDmin difference and a slight increase in DOR and Tpe. In other words, the stable Tpe/QT ratio required that the longer the APD, the greater the difference between the longest and shortest APDs. And for this, it is necessary that the shortest and the longest APDs change with different rates. These simulation results explain the mechanisms providing a relatively unaltered Tpe/QT ratio in healthy individuals at a wide heart rate range from 60 bpm to 100 bpm.[7]

Segment model: Decreased Tpe/QT

APD prolongation when APDmax-APDmin difference remained constant or decreased was associated with a decrease

in Tpe/QT ratio. These were scenarios where APDmax and APDmin were changed by the same increment (Fig. 3, B), and the scenario where APDmax was prolonging 40% less than APDmin (Fig. 3, C). In scenario B, DOR and Tpe were stable, and the increased QT resulted in the decreased Tpe/QT ratio. In scenario C, the predominant prolongation of APDmin, compared to APDmax, decreased DOR, Tpe, and Tpe/QT ratio. In other words, the decreased Tpe/QT resulted from the less-than-expected difference between the longest and shortest APD in respect to the APD range.

Segment model: Increased Tpe/QT

APD prolongation associated with the steep increase in APDmax-APDmin difference and DOR led to the increase in Tpe/QT ratio (Fig. 3, D-F). This outcome was observed in the scenario with the proportional APDmax and APDmin changing (Fig. 3, D), and in the scenarios with differential APD increase with APDmax being changed 40% (Fig. 3, E) and 20% (Fig. 3, F) more than APDmin.

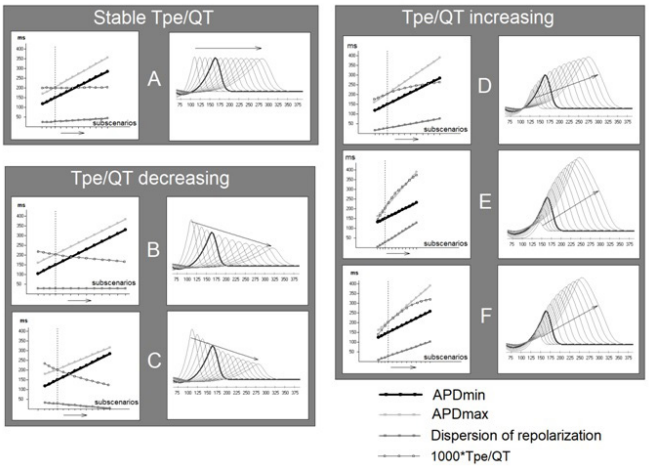

Figure 3. *The changes in morphology of the simulated T-wave and the associated changes in Tpe/QT ratio for different scenarios of APD shortening/prolongation.*

The abscissas show the subscenarios of each scenario, the ordinates – the corresponding values of APDmin, APDmax, DOR and Tpe/QT. For convenience of data presentation, Tpe/QT was scaled by a factor of 1000. The common starting point for all simulation scenarios (APDmin=150 ms, APDmax=205 ms, Tpe/QT=0.2) is indicated by a vertical dotted line, the corresponding "starting" T-wave is highlighted with a thick line.

A – APDmin were changed 20% faster than APDmax; B – APDmax and APDmin were changed by the same increment; C – APDmax was prolonging 40% less than APDmin; D – proportional changes in APDmax and APDmin; E – APDmax were changed 40% faster than APDmin; F – APDmax were changed 20% faster than APDmin.

Whole ventricles' model

The initial APDmin=145 ms and APDmax=157 ms values provided a Tpe/QT ratio of 0.2 in the model of the whole rabbit ventricles (Fig. 4). The stable Tpe/QT ratio was achieved when APDmin was prolonged 40% less than APDmax. The increase in APDmax up to 2 times (from 157 ms to 314 ms) and in APDmin up to 1.6 times (from 145 ms to 232 ms) resulted in an almost threefold increase in DOR (from 46 ms up to 124 ms), while Tpe/QT ratio of the simulated ECG remained constant (Fig.4).

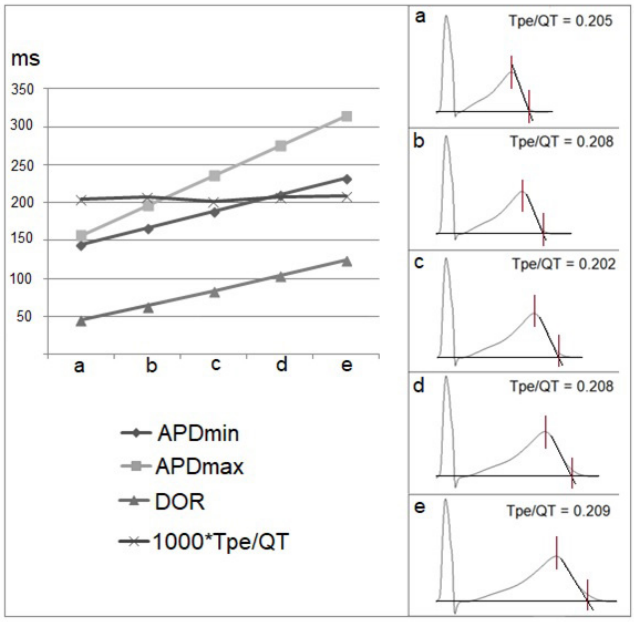

Figure 4. *Progressive APD prolongation in the model of the whole rabbit heart ventricles: APDmax changing 20% faster than APDmin provided stable magnitude of Tpe/QT ratio even at high DOR values.*

*Left panel: APDmax, APDmin, DOR and 1000*Tpe/QT values (for convenience of data presentation, Tpe/QT was scaled by a factor of 1000) in the model. Right panel: the simulated ECGs (lead V2) corresponding to cases a – e on the left panel.*

Both the simplified ventricular segment model and the realistic whole ventricles' model demonstrated that APD prolongation with the moderate increase in the APDmax-APDmin difference due to the different change factors for APDmax and APDmin was associated with the stable Tpe/QT magnitude even at high DOR values.

Experimental confirmation of the simulation results

There are experimental and clinical data that support our simulation findings. In most cases, the increased Tpe/QT is associated with increased Tpe. In this regard, Tpe/QT was considered as an index of DOR.[13] On the other hand, there is clinical evidence that Tpe/QT and Tpe can change differentially. In the febrile period, shortening of QT and Tpe intervals was accompanied by an increase in Tpe/QT ratio.[14] In the patients treated with ziprasidone, Tpe was the same as in the control group, whereas Tpe/QTc was decreased.[15]

The changes of APD and DOR are closely related to each other. However, the contributions of the two variables to arrhythmogenesis can be different. The previous studies from our group[16,17] showed that modification of APD could change the risk of the reentrant arrhythmias independently of DOR. Tpe, QT and Tpe/QT ratio reflecting DOR, APD, and APD range, respectively, may contain independent diagnostic information. Tpe/QT ratio has been demonstrated to have association with clinical outcomes, which was independent of DOR-associated and APD-associated markers. From a large number of ECG

indices (ST-segment elevation/depression, T-wave inversion, presence of Q waves, QT, QTc, QT dispersion, Tpe, Tpe dispersion, Tpe/QT, and QTpeak/QT), it was Tpe/QT ratio that was associated with major adverse cardiovascular events in the acute phase of Takotsubo syndrome.[18]

Limitations of the study

The limitations of the simulations are as follows: (1) The same action potential shape (no epicardial "spikes and domes") was assigned for all ventricular layers; (2) No electrotonic APD flattening and anisotropic fiber architecture was included in the model; (3) The model was based on the nonhuman (rabbit) experimental data, and specific calculated values could not be directly applied in clinical settings. However, the above limitations could hardly affect computation of the Tpe and QT intervals and modify the major findings of the present study.

Conclusion

The present simulation study demonstrates that Tpe/QT ratio reflects rather the relationship between the longest and the shortest APD, than DOR. In conditions of DOR and/or APD changes, the Tpe/QT ratio can be maintained at the same level, if the longest and the shortest APDs change at different rates, and vice versa; Tpe/QT ratio increases or decreases in the cases with a "disbalance" between the longest and the shortest APDs in the heart ventricles. These findings suggest that Tpe/QT ratio might serve as an independent index of arrhythmic risk to be used with other repolarization-related markers, such as Tpe and QT intervals.

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Competing Interests

The authors declare that they have no competing interests.

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