

# Gender Dependency of QT Parameters

Josef Halánek, Pavel Jurák, Pavel Leinveber, Vlastimil Vondra, Jolana Lipoldová

**Abstract**— The gender dependency of QT parameters was tested on data provided by the Telemetric and Holter ECG Warehouse of the University of Rochester (THEW), NY. Data from 62 men and 55 women was analyzed. Three dynamic models of QT/RR were used for the analysis: transfer function model (TRF); exponential weighted model (EXP) and exponential weighted model with direct coupling (EXPDC). Statistically significant differences between men/women exist at QTc and at the time constant of QT adaptation to RR changes. The QT parameters given by different QT/RR models were compared. The QTc does not depend on the model used – the differences are minimal. The levels of other parameters tend to depend on the model used, though a significant correlation exists between similar parameters given by different models. The standardization of the dynamic QT/RR model is undoubtedly an important task for the future. Detailed analysis of the influence of drugs on QT dynamic parameters may explain why cardiac arrhythmias and drug-induced Torsades de Pointes are more prevalent in women. Measurements with significant and defined excitation of RR are the important prerequisite in such analysis.

**Index Terms**—gender dependency, QT/RR dynamic model, QT dynamic parameters

## I. INTRODUCTION

The gender differences of ventricular repolarization have been tested and reported [1-3]. It is well known that the QTc interval is longer in women than in men. Torsades de Pointes associated with long QT syndrome is more common in women, and women have more drug-induced proarrhythmia compared to men. Some other parameters were tested, such as the interval from the peak to the end of the T wave (TpTe) [3], QT interval variability and repolarization in-homogeneity [4], and the morphology of the T wave [5]. An analysis of the gender dependency of dynamic properties of QT/RR coupling is still lacking. Such analysis of the dynamic properties of repolarization may help to better understand why cardiac arrhythmias and drug-induced Torsades de Pointes are more prevalent in women.

## II. METHODS

### A. Data

The gender dependency of QT parameters was tested on data

Josef Halánek, Pavel Jurák, Pavel Leinveber and Vlastimil Vondra are with the Department of Magnetic Resonance and Bioinformatik, Institute of Scientific Instruments of the ASCR, Královopolská 147, 612 64 Brno, Czech Republic. Email for correspondence: josef@isibrno.cz

Jolana Lipoldová is with the St Anne's University Hospital, Pekařská 53, 656 91 Brno, Czech Republic

provided by the Telemetric and Holter ECG Warehouse of the University of Rochester (THEW), NY, the Normal database [<http://thew-project.org/index.htm>]. ECG signals about 30 min. in length were extracted from the database. Two records were extracted for each subject, first a.m. and then p.m. The applied criteria for the extracted records were:

- i) Sufficient RR changes in signal;
- ii) The good quality of the extracted part of the ECG signal to detect the majority of QT intervals.

Singular value decomposition (SVD) was used as preprocessing. The three-dimensional signal from the database was reduced to a one-dimensional signal:

$$S(t) = \sqrt{ev_1^2 + ev_2^2} \quad \text{where } ev_1 \text{ and } ev_2 \text{ are eigenvectors}$$

[6]. The S(t) signal was analyzed with our custom-designed software ScopeWin to obtain a continuous series of RR and QT intervals. The QT interval duration was determined from the onset of the QRS wave to the end of the T wave, defined as the crossing between the isoelectric line and the tangent to the descending T wave. A semiautomatic method of QT detection was used. If there was any doubt about proper detection or if accurate detection was not deemed possible, the ECG was marked with the corresponding regions labeled as non-detectable QT intervals.

### B. Dynamic QT/RR coupling

The dynamic parameters of QT have not yet been standardized. They are based on a supposed QT/RR model and their validity depends on the validity of the model used. Three dynamic models of QT/RR coupling were used:

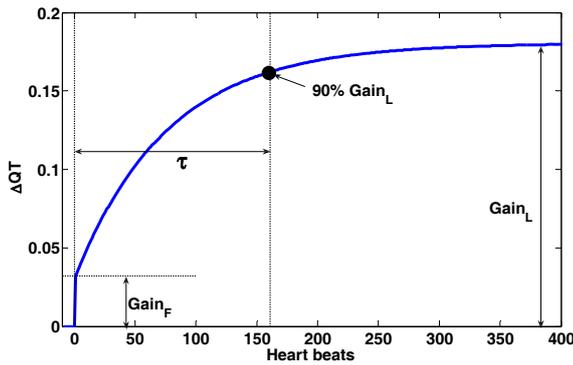
- i) Transfer function model (TRF) [7];
- ii) Exponential weighted model (EXP) [8];
- iii) Exponential weighted model with added direct coupling between QT and RR (EXPDC) [9].

These models have different QT/RR parameters that can be presented in the optimal way on the QT step response, i.e. on supposed QT behavior after step change of RR. The corresponding step responses are shown in Fig. 1. Even though the model parameters are different, some common dynamic QT parameters may be determined:

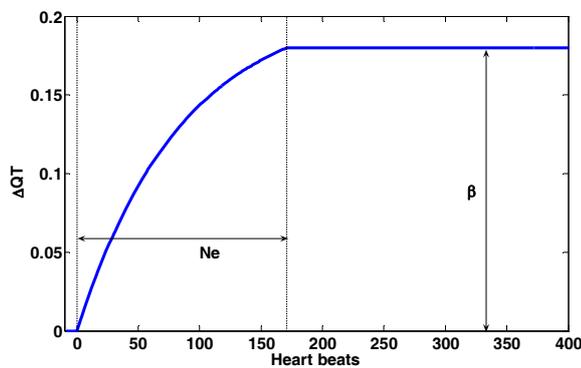
- a) The QT/RR slope ( $\text{Gain}_1$ ), i.e. the gain of QT/RR coupling for low variability of RR. This is the one basic parameter of the TRF model; it corresponds to  $\beta$  in linear regression in the EXP model and is the sum of direct coupling and weight coupling in the EXPDC model.
- b) The time constant of QT adaptation on RR change  $-\tau$ . In the TRF model, the  $\tau$  means the delay after which the step response has achieved 90 % of the change needed to attain the new steady state value. In the EXP and EXPDC models the number of weighted RR coefficients is used – Ne.

III. RESULTS

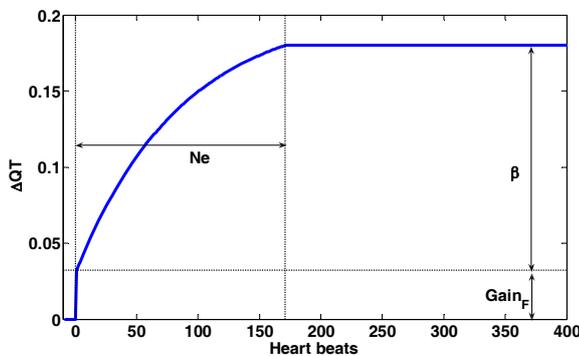
The QT and RR intervals were detected on ECG signals from 62 men and 55 women. The resulting data sets in which the variability of the QT intervals detected was lower than 4 ms were excluded from the final analysis. In such data, the signal to noise ratio is low and the QT variability is given primarily by random QT variability, not coupled with RR. The assessment of QT parameters is inaccurate in such data. As the result, 163 (92/71 men/women) data sets were used in the final analysis. The comparison of QT dynamic parameters for different models is given in Tab. 1.



a) TRF model. The shape of step response is given by optimized parameters of feedback control system.



b) EXP model. The shape of step response is given by assumption that QT depends on exponential weighted average of previous RR intervals. Gain<sub>L</sub> is β, parameter given by linear regression. τ is Ne, the number of weighted coefficients. Gain<sub>F</sub> is missing in this model.



b) EXPDC model. The shape of step response is given by EXP model and added direct coupling between QT and RR. Gain<sub>L</sub> is the sum of β and Gain<sub>F</sub>. τ is Ne, the number of weighted coefficients. Gain<sub>F</sub> is given by direct coupling. Fig. 1. The step responses, i.e. the QT behavior after sudden change of RR in supposed models.

c) The gain of QT/RR coupling for fast variability of RR (Gain<sub>F</sub>). This is a basic parameter in the TRF model and the level of direct coupling in the EXPDC model. Such a parameter is missing from the EXP model.

The QTc and QT variability independent of RR were tested as other parameters. Both parameters were computed from model parameters. The QT variability independent of RR is given as the rms of the differences between model QT and detected QT.

TABLE I

The QT dynamic parameter (mean±STD) in dependency on gender and supposed model. Significant differences between men and women are marked (\* p<0.05, \*\* p<0.01, \*\*\* p<0.001).

		TRF	EXP	EXPDC
QTc [ms]	men	375±19***	373±19***	375±19***
	women	386±21	384±22	386±21
Gain <sub>L</sub>	men	0.179±0.05	0.164±0.05	0.173±0.05
	women	0.183±0.05	0.168±0.05	0.180±0.05
τ[beats]	men	156±84*	150±71*	185±69*
	women	130±58	128±66	160±62
Gain <sub>F</sub>	men	0.031±0.01	-	0.033±0.01
	women	0.033±0.01	-	0.034±0.02
rms [ms]	men	4.7±2.4	5.2±2.2	4.6±2.3
	women	4.7±2.8	5.1±2.6	4.6±2.6

Different QT/RR models give slightly different levels of parameters. This corresponds with the validity of the model and the definition of model parameters. The agreement among parameters for different models is given by the Pearson correlation coefficient (Tab. II) and by paired differences (Tab. III).

TABLE II

The Pearson correlation coefficients between parameters given by different models. The correlation is analyzed over all data sets.

	TRF*EXP	TRF*EXPDC	EXP*EXPDC
QTc	0.981	0.989	0.993
Gain <sub>L</sub>	0.908	0.932	0.954
τ	0.721	0.772	0.883
Gain <sub>F</sub>	-	0.703	-

TABLE III

The paired differences over all data sets (mean±STD) of parameters given by different models.

	TRF-EXP	TRF-EXPDC	EXP-EXPDC
QTc [ms]	2.3±4	0.81±3	-1.5±2.5
Gain <sub>L</sub>	0.013±0.02	0.004±0.02	-0.009±0.02
rms [ms]	-0.47±0.6	0.07±0.4	0.54±0.4
Gain <sub>F</sub>	-	-0.003±0.01	-

IV. DISCUSSION

According to our results, significant gender differences in QT parameters exist in QTc and the time constant of QT adaptation (Tab. I). The QTc gender dependency is well

known; the time constant dependency has yet to be published. The QT/RR slope is higher in women [1, 3], but not statistically significant in our analyzed data.  $Gain_F$  is slightly higher in women, but again not statistically significant.

According to previous analysis based on static parameters, the sex differences in the QT interval are more apparent at slower heart rates owing to the longer QTc in women. At higher heart rates, the differences in QT intervals are minimized owing to the steeper QT/RR slope in women [1]. This is valid at a steady state heart rate, when the QT interval is already adapted on RR. Such analysis cannot explain the higher prevalence of cardiac arrhythmias in women.

It is well known that abrupt arousal or vigorous physical activity are basic triggers of arrhythmias [10]. We hypothesize that significant differences in the QT interval during the onset of an excitation comparable to steady state may assist our understanding of the higher prevalence of arrhythmias. Such dynamic differences of QT intervals are directly proportional to the level of the QT/RR slope and the time constant of QT adaptation, and indirectly proportional to the level of  $Gain_F$ . According to this hypothesis, the higher prevalence of cardiac arrhythmias in women, given by the longer QTc and steeper QT/RR slope, is compensated to some extent by the slightly faster adaptation of QT.

The QT behavior on a sudden change of RR, relative to steady state, is demonstrated in Fig. 2. The QT step response is given by the blue line, the QT steady state level by the black line. The QT difference is given by the red line, and corresponds to the dotted area between the step response and the steady state level of QT. The maximal amplitude of difference is seen at the time of RR change and its level is  $(Gain_L - Gain_F) * \Delta RR$ . The duration of QT difference depends on the time constant  $\tau$ .

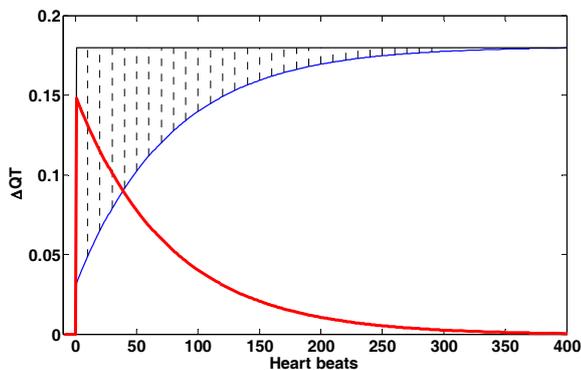


Fig. 2. The QT difference from steady state in sudden change of RR. The QT step response is blue line; the QT steady state level is the black line. The QT difference, given by delayed QT adaptation, is the red line; it corresponds to dotted area between step response and steady state level.

The dynamic portion of the QT coupling describes the behavior of the cardiovascular system at the onset of an excitation; this may assist our understanding of “Torsades de Pointes” initiation, and is hopefully related to the reasons and conditions under which physical activity or stress may trigger a dangerous arrhythmia. The test of drug influence on QT dynamic parameters may explain why women have more drug-induced proarrhythmia than men. The proarrhythmic

influence of drugs may originate in a change of  $Gain_L$  or  $\tau$  without any change in QTc.

The three QT/RR dynamic models were tested. According to rms (the difference between model QT and detected QT) the best model is EXPDC (Tab. III). The rms in the TRF model is nearly the same – the differences are not significant. The EXP model has significantly higher rms, and the QT random variability is overestimated in this model. In the EXP model, the important parameter  $Gain_F$  is lacking, and its step response diverges from the expected time evolution of the QT interval when subjected to sudden changes in heart rate [11-14].

We suppose  $Gain_F$  to be an important parameter as demonstrated in Fig. 2, the amplitude of QT difference on a sudden change of RR is dependent on the  $Gain_F$  level. The peak of QT difference decreased with increased  $Gain_F$ . QT detection can cause some limitation in  $Gain_F$  assessment. Detected QT intervals must be given without averaging, and the errors in QT detection may significantly limit the validity of  $Gain_F$ .

The origin of the TRF model is the control system theory; there is no assumption about the shape of the step response. The shape is the result of analysis and only this model is able to achieve agreement with the Padrini and Franz measurements [12, 13] without certain assumptions.

The origin of the EXP and EXPDC models is a mathematical assumption about the shape of the step response. The shape of the step response is given by assumption; it is not the result of any analysis.

QTc given by different models is nearly equal (Tab. I, III) and significant correlation exists between QTc given by different models (Tab. II). The type of model is not significant in QTc analysis. The similarities between models also exist for other parameters, though the differences are higher and the correlation is lower. In any case, the analysis of QT dynamic parameters supposes the standardization of the QT/RR model and represents an important task for the future.

#### A. Limitation

The analyzed data should include a sufficient change and range of RR intervals given by some form of stress, preferably corresponding to arrhythmia triggers. Others, the signal to noise ratio is low, and the signals corresponding to QT/RR coupling are covered by random QT variability. The assessment of QT parameters is inaccurate in such data.

The type of RR stress should be defined. According to our experience, QT dynamic parameters depend on the type of RR stress [7]. The QT parameter dependency on the type of RR stress has not yet been generally accepted, but only such dependency may explain the gene-specific triggers of arrhythmia [10]. There is no information given about subject activity in the database used, and we may assume that the analyzed data represents various types of RR excitation. The missing information about RR excitation limits the presented analysis of QT gender dependency. Our results are preliminary – exact analysis must be based on data with a defined type of RR excitation. We hypothesize that the gender dependency of QT parameters will be more significant in data

with a defined type of excitation.

## V. CONCLUSION

There is a significant gender difference in QT adaptation time. In our opinion, the proarrhythmic influence of longer QTc and steeper QT/RR slope in women may be compensated to a certain extent by faster adaptation of QT intervals to RR changes in women. We hypothesize that a detailed analysis of drug influence on QT dynamic parameters may explain why cardiac arrhythmias and drug-induced Torsades de Pointes are more prevalent in women.

The standardization of the QT/RR dynamic model and measurement with significant and defined excitation of RR are important prerequisites in analysis of QT dynamic parameters.

## ACKNOWLEDGMENT

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