# Application of novel QT interval correction and QT/RR assessment models to ECG 24-hour recordings in cardiac patients

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**Abstract.** The aim of the study was to apply different novel ventricular repolarization assessment models to clinical 24-hour ECG recordings for identification of patients with high level of myocardial electrical instability (MEI), i.e. those significantly predisposed to development of potentially life-threatening cardiac arrhythmias. In order to explore the ventricular repolarization inhomogeneity, Holter recordings of forty patients, divided into 4 groups according to their maximal Lown grade (Lown 0, 3A, 4A, 4B), were studied using six QT/RR regression models and six heart rate correction formulas. The algorithm developed during the study enables application of these novel models in routinely registered ECG 24-hour recordings in patients with various heart diseases and without overt heart condition. This approach assures heart rate correction optimization for every single person. The QTc deviation values, obtained with the linear correction model, differed significantly in patients with various MEI levels; thus, if further validated, they can be used as a method for arrhythmia risk stratification.

**Key words:** sudden cardiac death, ventricular repolarization inhomogeneity, QT/RR ratio, QT interval correction and variability.

## 1. INTRODUCTION

Sudden cardiac death (SD) is a very frequent cause of death all over the world – its incidence is three times higher than all lung cancer, breast cancer and AIDS deaths combined. To treat SD, it is necessary to take actions in the first 3–4 minutes that is usually impossible. Development of methods to identify risk groups as accurately as possible and provide them timely precautionary treatment is the only possibility to decrease the number of SD cases. Numerous invasive and non-invasive tests for risk stratification are routinely used in clinical practice.

According to one of the current concepts, a large amount of necessary information, required for identification of patients with high level of myocardial electrical instability, i.e. patients significantly predisposed to the development of potentially life-threatening cardiac arrhythmias, can be derived from ECG QT interval, reflecting ventricular repolarization. About 60 different approaches for the analysis of QT and T-wave shape have been developed. Repolarization dynamics and variability are of increasing interest as Holter-derived parameters, reflecting changes in myocardial vulnerability, and which contribute to increased risk of arrhythmic events and SD. Two dynamic properties of VR, the QT interval variability at 24-hour ECG recording (QTV) and QT interval rate-adaptation, have undergone more intensive investigation in recent years in order to assess their utility for high-risk patient identification. Increased QT–RR slopes are frequently observed in patients prone to develop arrhythmic events: post-infarction patients, long QT syndrome patients, patients with ischemic and non-ischemic cardiomyopathy as well as in patients taking drugs, affecting repolariza-tion [1–6]. QT variability reflects beat-to-beat changes in repolarization duration and morphology, and such changes can be quantified using a number of algorithms, which are currently in various phases of development and validation. In the majority of published studies, a method proposed by Berger et al. [1], the assessment of QT variability index, which is calculated for each subject as the logarithm of the ratio of normalized QT variance to heart rate variance, has been applied. The relationship between QT and RR has been frequently simplified to a curvilinear relationship, represented by Bazett or Fridericia QTc correction formulas. However, Holter recordings (HM) demonstrate a varying nature of the QT/RR ratio, frequently described not only by the linear formula but also by other more complicated equations. Thus the slope of linear correlation between QT and RR intervals has showed higher values during day than night, and steeper slope in females than males [7]. As demonstrated in [8], the QT/RR slope is highly individual even in patients without overt heart disease. This subject-specific uniqueness is most likely determined by genotypic variations, basic heart rate, autonomic response, as well as by the structure and function of repolarizing currents in myocardium. The lack of coherence among the previous studies suggests that various formulas have been influenced by the individual differences in QT/RR relation.

The aim of the study was to apply different novel QT/RR regression models and heart rate correction formulas to clinical 24-hour ECG recordings, providing QTc interval values that are independent of corresponding RR interval values, that were developed in healthy patients using short isolated HM strips, and to evaluate the discriminating significance of this approach for patients with different MEI levels assessed by maximal Lown grade of spontaneous ventricular arrhythmias during recording, which has unequivocally demonstrated its independent prognostic value [9].

## 2. METHODS

### 2.1. Patient population and data acquisition

Holter recordings from consecutive 179 patients, exhibiting sinus rhythm during 24 hours, were analysed. Patients, receiving class I and III antiarrhythmic drugs, were excluded from the study. Patients were divided into four groups according to the maximal Lown grade ventricular arrhythmia during Holter monitoring. Patients with various cardiac diseases, such as coronary artery disease, hypertensive heart disease, idiopatic cardiomyopathies, and without apparent heart disease, were distributed almost equally among the groups.

The groups were as follows:

Group 1 – grade 0 ectopy – no ventricular premature beats at 24-hour ECG recording; this group was also taken as the reference group;

Group 2 – grade 3A ectopy – polymorphic ventricular premature beats;

Group 3 – grade 4A ectopy – ventricular couplets;

Group 4 – grade 4B ectopy – ventricular tachycardia of three or more beats.

The recordings were divided into the four above-mentioned groups by an experienced cardiologist. Group 1 included 60 patients (mean age $39\pm19$), Group 2 – 58 patients (mean age $54\pm16$), Group 3 – 32 patients (mean age $59\pm12$) and Group 4 – 29 patients (mean age $57\pm18$). The mean age differences between the groups were statistically relevant except for the Group 1.

ECGs were recorded using a 3-channel, 24-hour ECG recorder (model RZ152, Rozinn Electronics, Inc.), sampling frequency 180 Hz and resolution 10 bits. The full disclosure of 24-hour signal from the same ECG channel (channel 0) for every patient was chosen for further pre-processing and analysis.

### 2.2. Data analysis

Analysis of the 24-hour recordings was performed with the Ecgpuwave algorithm that analyses an ECG signal from the specified record, detecting the QRS complexes and locating the beginning, peak, and end of the P, QRS, and ST-T waveforms [10,11]. Ecgpuwave classifies each T-wave as normal, inverted, positive monophasic, negative monophasic, biphasic negative-positive, or biphasic positive-negative.

In order to study the QT/RR relation, the data of QT and RR intervals of each subject were studied separately. The following six QT/RR regression models were used to test our data [8]:

1) linear model

$$QT = \beta + \alpha \times RR,$$

2) hyperbolic model

$$QT = \beta + \frac{\alpha}{RR},$$

3) parabolic model

$$QT = \beta \times RR^{\alpha},$$

4) logarithmic model

$$QT = \beta + \alpha \times \ln(RR),$$

5) shifted logarithmic model

$$QT = \ln(\beta + \alpha \times RR),$$

6) exponential model

$$QT = \beta + \alpha \times e^{-RR}.$$

For each patient, the six regression models were determined to understand which fitted the QT/RR data in the best way. In this study the main focus was on heart rate correction formulas, presented as follows.

## 2.3. Heart rate correction

Given formulas of the regression models are converted to generic heart rate correction formulas/models:

1) linear model

$$QT_c = QT + \alpha \times (1 - RR),$$

2) hyperbolic model

$$QT_c = QT - \alpha \times \left( \frac{1}{RR - 1} \right),$$

3) parabolic model

$$QT_c = \frac{QT}{RR^{\alpha}},$$

4) logarithmic model

$$QT_c = QT - \alpha \times \ln(RR),$$

5) shifted logarithmic model

$$QT_c = \ln(e^{QT} + \alpha \times (1 - RR)),$$

6) exponential model

$$QT_c = QT + \alpha \times \left( e^{-RR} - \frac{1}{e} \right).$$

The purpose of the heart rate correction formulas is to grant $QT_c$ interval values that are independent of the corresponding RR interval values. For instance, this independence can be tested by computing the correlation coefficients. The "most efficient" heart rate correction formula yields zero correlation. In order to determine the dynamics of the QT interval, analysis only of the RR interval, preceding the measured QT interval, may be inadequate. The QT interval duration of the given beat is influenced by several beats, usually minutes of RR cycles, and heart rate history is only poorly represented by a single RR interval. Therefore to adjust for this time-lag, we decided to investigate QT–RR relationship by

averaging the RR interval. In this study all the results are presented with the RR interval averaged over 60 s. For each of the correction formulas the parameter $\alpha$ was varied from 0 to 1, with a step of 0.001. For each patient the value of $\alpha$ was identified when the correlation between $QT_c$ and RR was zero.

## 3. RESULTS

In order to present the results, 10 patients from each group were chosen. Figures 1 to 5 illustrate the patterns of the $QT_c$/RR scatter diagrams, obtained for different proposed models for one patient from the first group. The figures on the left represent the standard $QT_c$/RR relation and figures on the right show the RR intervals averaged over 60 s. Hyperbolic model is not shown due to the lack of adequate results. As mentioned before, all the parameter $\alpha$ values correspond to the maximum zero correlation and it is shown that depending on the model, they can be different for one patient.

Group 1 (0 ectopy)



**Fig. 1.** Linear model ($\alpha = 0.062$, $\alpha = 0.130$).



**Fig. 2.** Parabolic model ($\alpha = 0.125$, $\alpha = 0.260$).
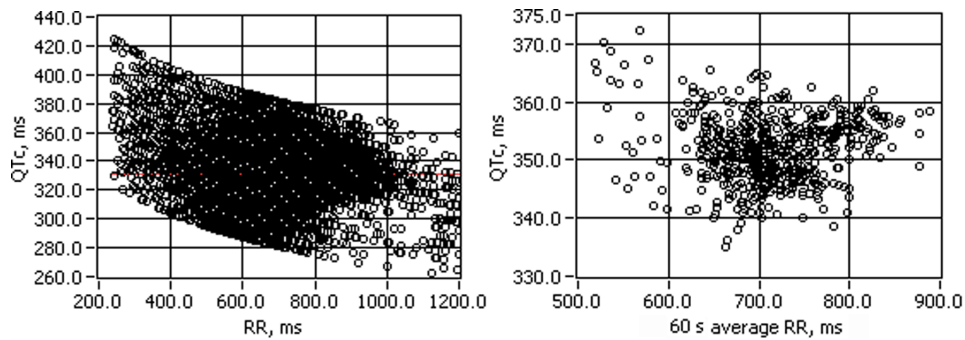
111

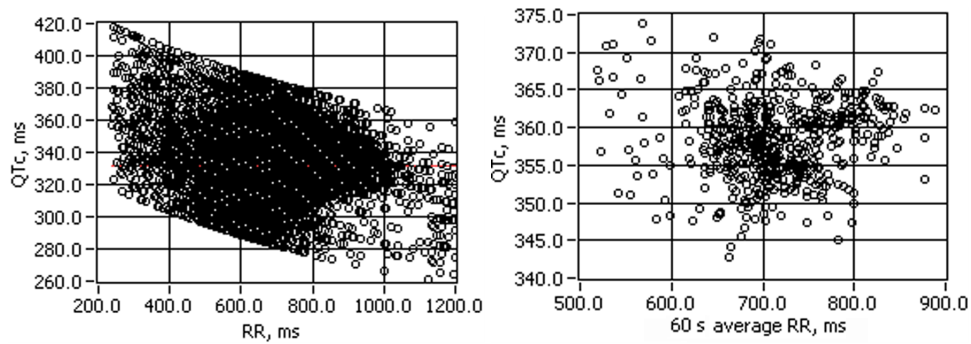**Fig. 3.** Logarithmic model ($\alpha = 0.041$, $\alpha = 0.086$).



**Fig. 4.** Shifted logarithmic model ($\alpha = 0.083$, $\alpha = 0.178$).
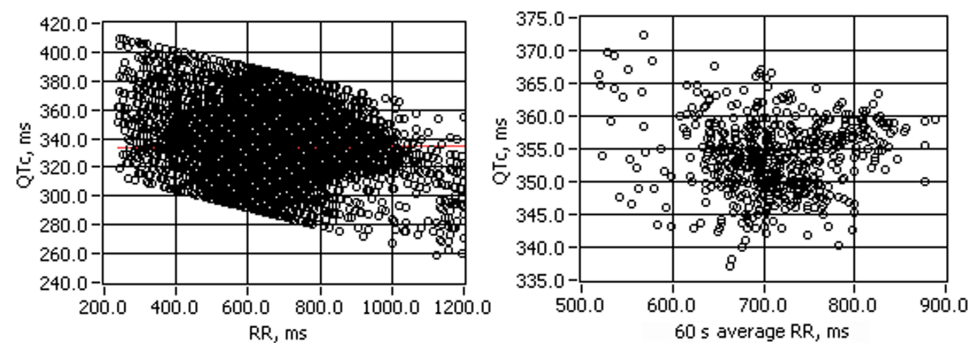


**Fig. 5.** Exponential model ($\alpha = 0.122$, $\alpha = 0.256$).

For the rest of the patients of Groups 2 to 4, only the linear and the parabolic models are demonstrated due to very high similarity with the rest of the models for one single patient (Figs. 6 to 11). The data for one patient of each group is shown. Once more, application of the hyperbolic model gave no reproducible results.

Group 2 (3A ectopy)



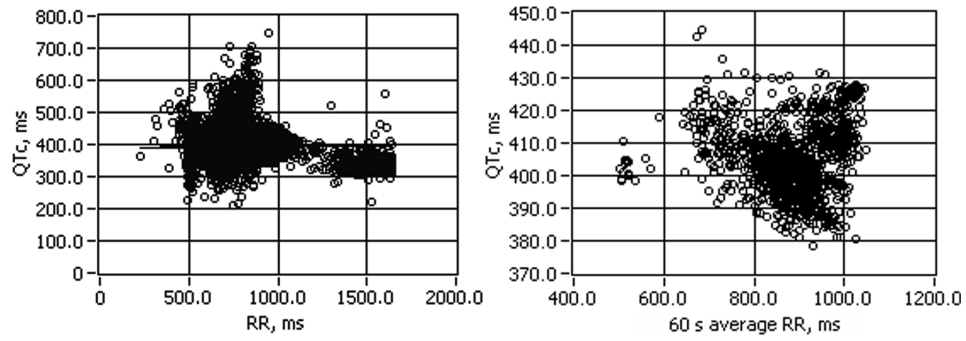**Fig. 6.** Linear model ($\alpha = 0.090$, $\alpha = 0.148$).



**Fig. 7.** Parabolic model ($\alpha = 0.206$, $\alpha = 0.309$).
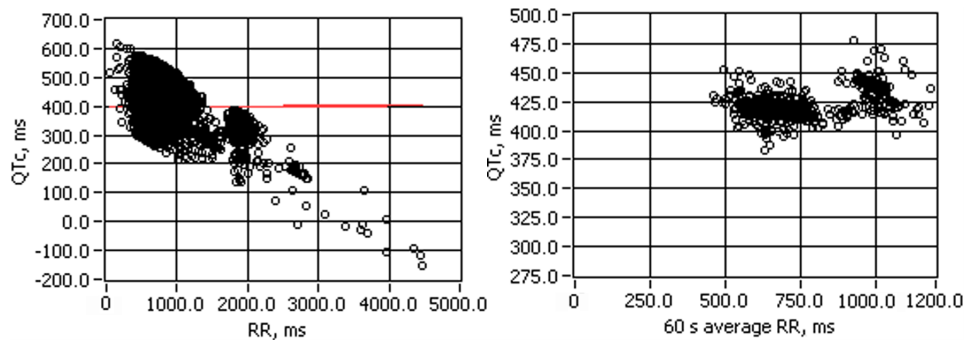
Group 3 (4A ectopy)



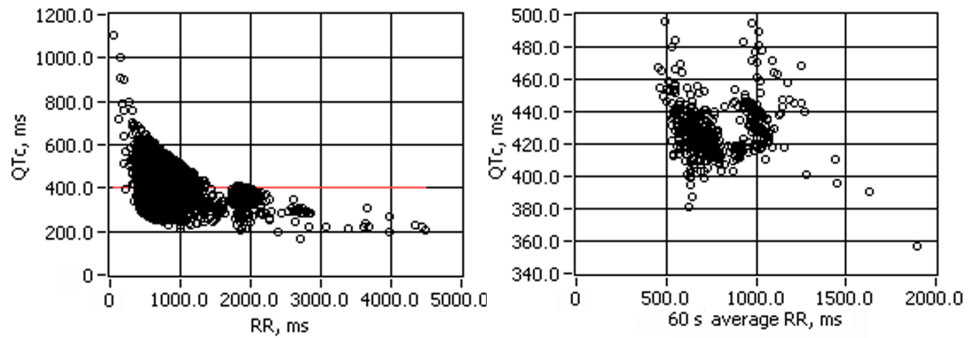**Fig. 8.** Linear model ($\alpha = 0.147$, $\alpha = 0.222$).

**Fig. 9.** Parabolic model ($\alpha = 0.371$, $\alpha = 0.516$).
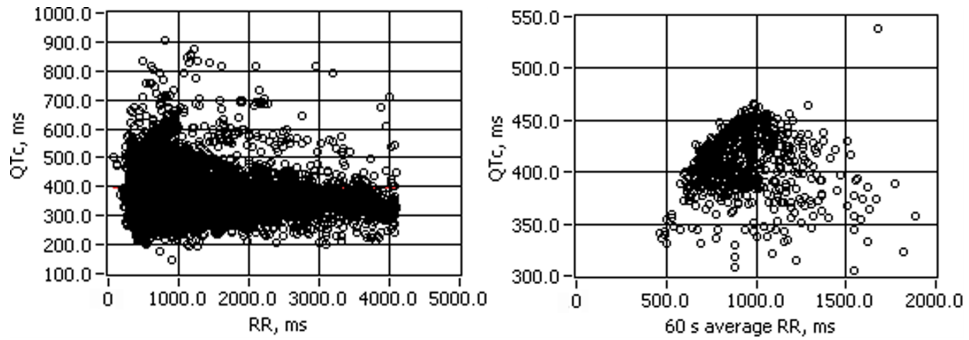
Group 4 (4B ectopy)



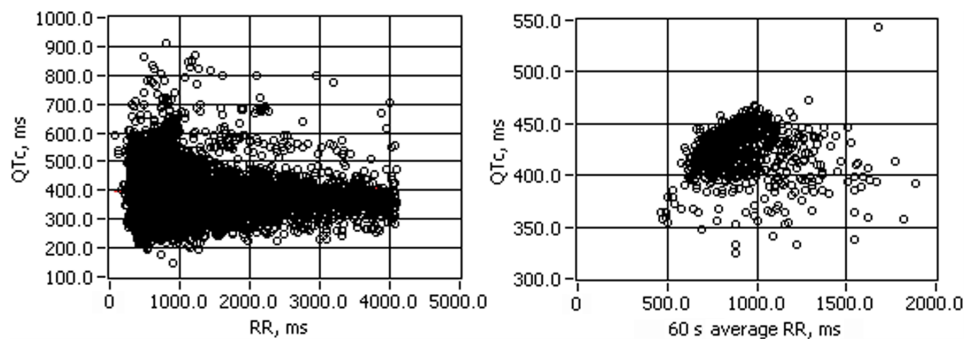**Fig. 10.** Linear model ($\alpha = 0.023$, $\alpha = 0.086$).



**Fig. 11.** Parabolic model ($\alpha = 0.072$, $\alpha = 0.267$).

Visually, it is obvious that adaptation of the QT interval to heart rate changes differed in patients of different groups, but the intersubject differences within one clinical group are remarkable as well, as demonstrated in Figs. 12 to 15.
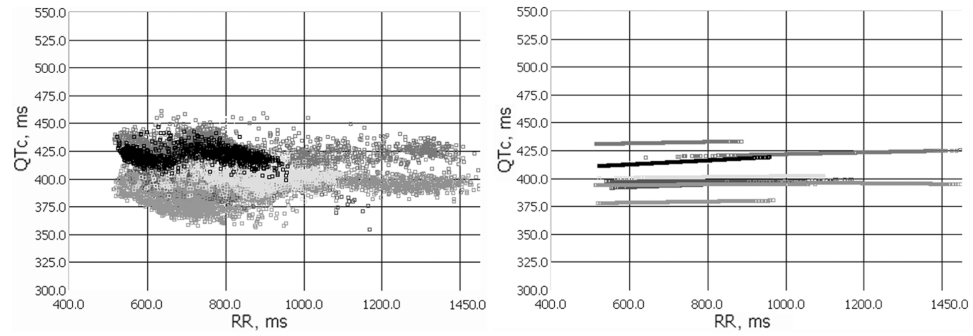
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Linear model, Group 1



**Fig. 12.** Combined scatter diagram for 10 patients in Group 1 (parameter $\alpha$ varied from 0.140 to 0.240).

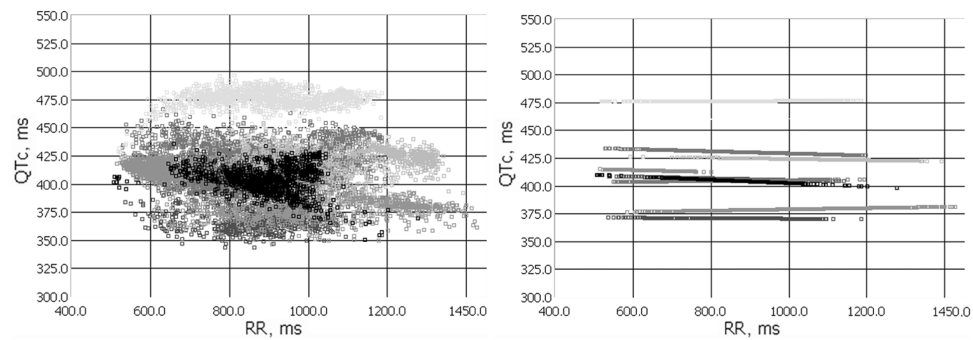Linear model, Group 2



**Fig. 13.** Combined scatter diagram for 10 patients in Group 2 (parameter $\alpha$ varied from 0.100 to 0.200).
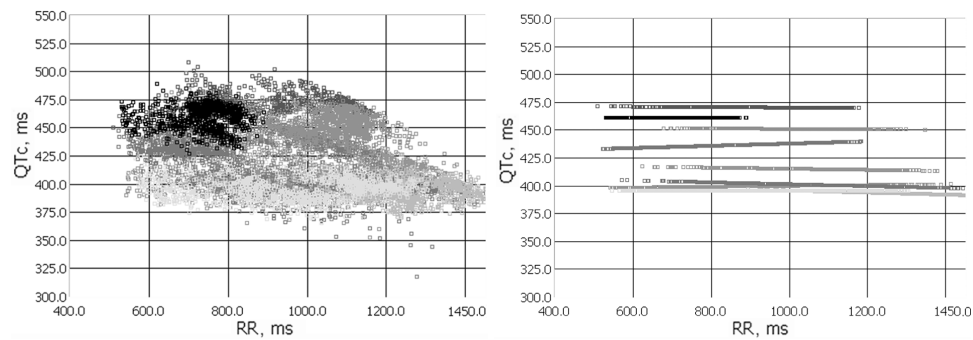
Linear model, Group 3



**Fig. 14.** Combined scatter diagram for 10 patients in Group 3 (parameter $\alpha$ varied from 0.120–0.240).
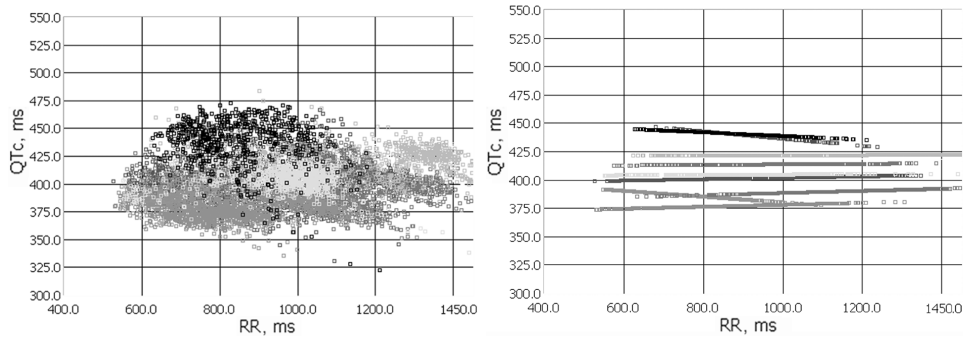
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Linear model, Group 4



**Fig. 15.** Combined scatter diagram for 10 patients in Group 4 (parameter $\alpha$ varied from 0.120–0.180).

Figures 12 to 15 demonstrate the QT/RR relation differences for patients of four groups. Each figure of the scatter diagram contains 10 patients. Figures on the right represent the closeness of fit of regression lines in the scatter diagrams when the correlation was set to zero.

The second part of the study was to evaluate the clinical applicability of novel $QT_c$ correction models for the discrimination of patient groups with different MEI level, assessed by ventricular arrhythmias' maximal Lown grade during ECG 24-hour recordings. As an example we present the results obtained by $QT_c$ variability assessment using the linear model. As seen in Figs. 16 to 18, there is a significant difference in $QT_c$ standard deviation (SD) in Groups 3 and 4 as compared to Group 1 patients. The mean $QT_c$ duration did not differ in Group 3 patients, 409±16, 417±26 and 402±35 ms, respectively, but the difference in standard deviations was significant: 16±1.8, 26±6.4, 35±8.8 ms, respectively ($p$1,3 and $p$1,4 < 0.05). Thus, more significant $QT_c$ variability characterized patients with high level of MEI.
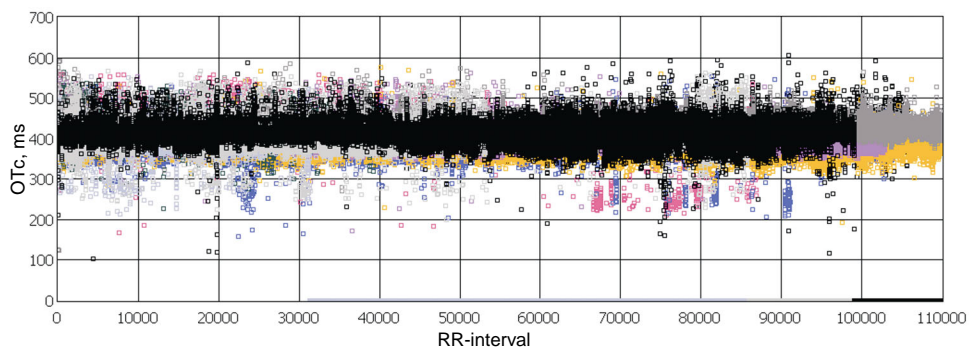
Linear model, Group 1



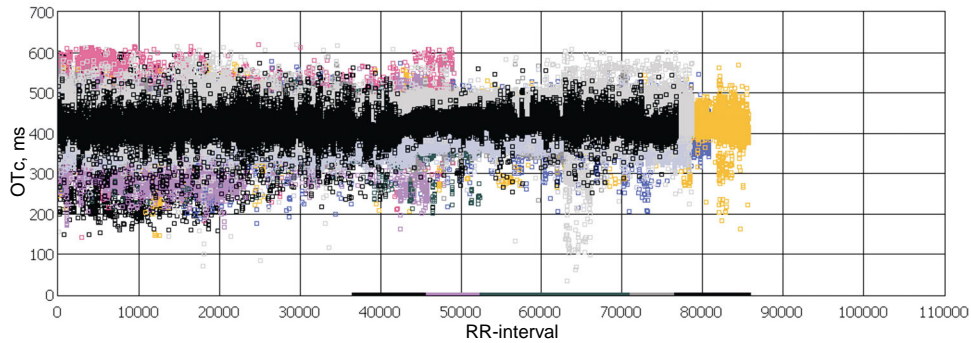**Fig. 16.** $QT_c$ variability assessment.

Linear model, Group 3



**Fig. 17.** QT$_c$ variability assessment.
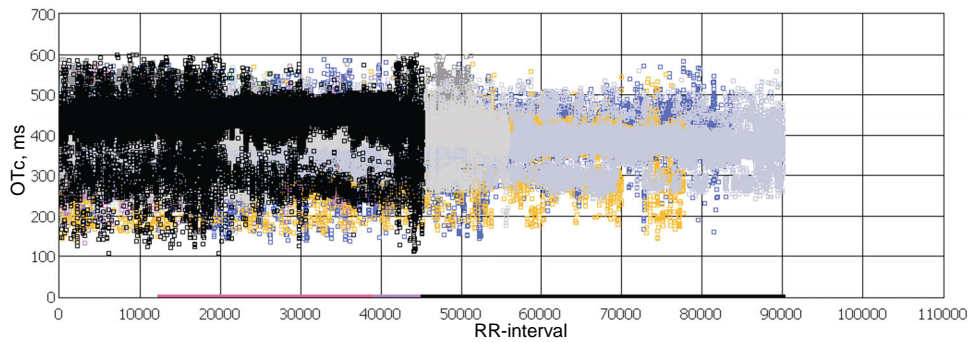
Linear model, Group 4



**Fig. 18.** QT$_c$ variability assessment.

## 4. DISCUSSION

Due to the substantial intra- and intersubject variability of the QT$_c$/RR interval relation, no "universal" mathematical formula can be found to describe this relation correctly in all persons. It is worth mentioning that substantial degree of intrasubject variability found in our study is not a common finding in previous studies (note the parameter $\alpha$ values in Figs. 1 to 5). A mathematical model to describe the QT$_c$/RR relationship can be valid for one patient but not for another. This could result in a subsequent overcorrecting or undercorrecting of the QT interval for a patient. The reason for that may be the fact that although changes in the heart rate and heart rate variability influence changes in QT interval, QT variability cannot be entirely explained by changes in the autonomic nervous system. It is likely that beat-to-beat changes in action potential duration depend on instantaneous changes in the channel activity or in the number of channels involved in the repolarization process. Even with stable RR interval, there is a

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possibility of repolarization changes due to variations in the number of channels involved [10]. Myocardial conditions (ischemia, fibrosis) might alter the number of channels involved in the repolarization process, and changes in cycle length (RR interval) might further potentiate beat-to-beat variability of repolarization.

In order to provide more accurate results for heart rate correction, we have also acknowledged the concept of "ideal correction" when the correlation approaches zero.

It is important to mention the fact that if we had used the Bazett formula, in which the parameter $\alpha$ is considered to be approximately 0.4 [8], we would not have managed to correct the patients' heart rates properly. The use of the general $QT_c$ correction formula for more precise ventricular repolarization assessment, in order to predict SD risk or drug-induced QT interval changes, would always be appropriate and lead to non-reproducible results. As stated before [8], when a precise determination of $QT_c$ interval is needed, the heart rate correction should be optimized for every single person.

## 5. CONCLUSIONS

1. The algorithm, developed during the study, permits application of novel QT interval correction and QT/RR ratio determination models in routinely registered ECG 24-hour recordings for patients with various heart diseases and without overt heart disease.
2. Significant intra- and intersubject variability of $QT_c$ and QT/RR ratio was recorded in patients with different levels of myocardial electrical instability, thus in order to obtain "ideal" correction (zero correlation), individual parameter $\alpha$ values should be applied to every single person.
3. Deviations of the $QT_c$, obtained by the linear correction model, differed significantly for patients with various MEI levels; thus if it is further validated, it could be used as a method for arrhythmia risk stratification.

## ACKNOWLEDGMENTS

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## Uudsete QT-intervalli korrigeerimise ja QT/RR-suhte määramise mudelite rakendamine EKG 24 tunni registreerimisel südamehaigetel

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Uuringu eesmärgiks oli rakendada uudseid vatsakeste repolarisatsioonifaasi analüüsimise mudeleid kliinilistel EKG 24 tunni salvestustel eesmärgiga identifitseerida kõrge müokardi elektrilise ebastabiilsusega (MEE) patsiente. Vatsakeste repolarisatsioonifaasi mittehomogeensuse uurimisel kasutati 40 patsiendi ööpäevaringseid EKG-sid, mis jaotati nelja gruppi vastavalt maksimaalsele Lowni gradatsioonile; EKG-de analüüsimiseks kasutati kuut QT/RR-i regres-

sioonimudelit ja kuut südamerütmi korrigeerimise mudelit. Töö käigus välja töötatud algoritm võimaldas nimetatud mudelite rakendamist rutiinsete Holteri monitooringute analüüsimiseks erinevate südamehaigustega patsientidel. Selline lähenemisviis võimaldab südamerütmi korrigeerimise optimeerimist igal üksikul patsiendil. $QT_c$-intervalli deviatsioonid, mis saadi lineaarse korrektsioonimudeli rakendamisel, erinesid märgatavalt eri MEE tasemega patsientidel. Täiendavate uuringute järel võib see seaduspärasus olla rakendatav kõrge riskiga patsientide väljaselgitamisel.