Cardiac Repolarization Analysis: Immediate Response

Josef Halamek[1], Pavel Jurak[1], Eleonora Tobaldini[2], Nicola Montano[2], Pavel Leinveber[3]

[1]Institute of Scientific Instruments, Czech Academy of Sciences, Brno, Czech Republic
[2]Departiment of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy
[3]St. Anne's University Hospital, ICRC, Brno, Czech Republic

Abstract

The reproducibility of QT parameters was tested on data recorded in subjects undergoing graded head-up tilt. Two QT detection algorithms were tested: D1 - on a beat to beat basis and D2 - on a 10-beats average basis. Relative irreproducibility, defined as STD/mean, in the case of D1 detection was 0.7, 6.3, 10 [%] for QTc, QT/RR slope and QT restitution respectively. With D2 detection it was 0.7, 6.3, and 59 [%] respectively.

Conclusion: QT immediate response, i.e. the QT restitution, is reproducible parameter with D1 detection. D2 detection eliminates any information about QT restitution and does not increase the reproducibility of QT slow properties, as QTc and QT/RR slope.

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1. Introduction

Cardiac repolarization adaptation (represented by variation of QT intervals to RR changes) has two distinct phases: 1) an immediate response (restitution, i.e. the dependence on the preceding RR interval) and 2) a slow adaptation (memory, i.e. the dependence on amount of previous RR intervals). Both these phases are well known since many years ago. The time evolution of the action potential duration after sudden changes of cycle length has been measured by Franz [1]. Padrini [2] measured the adaptation of the QT interval to heart rate changes in an isolated, perfused guinea pig heart. The curve shapes presented by Padrini and Franz are similar. However, the analysis of restitution is mostly neglected, even if this parameter is significantly different between controls and Long-QT syndrome patients [3], it is modified by drugs such as dobutamine [4] and it is important in the analysis of fast short term QT variability. The reason for this lack of consideration is due to the low reproducibility of the measure, which can be related to inappropriate QT detection algorithm. Therefore, we tested the reproducibility of QT parameters using two different algorithms: a) D1 - on a beat to beat basis; b) D2 - on a 10-beats average basis, so called "global QT" [5].

2. Data

Analysis was performed on ECG signals recorded in three healthy volunteers during a graded head-up tilt protocol [6]. The subjects underwent six sessions, with tilt table angles randomly chosen (15, 30, 45, 60, 75, 90°). Each tilt session consisted in rest (7 min), tilt (10 min) and recovery (3 min).

Sampling frequency was 1000 Hz. The ECG lead with the best shape of T waves was used for the analysis. The RR and QT intervals were detected with our custom-designed software ScopeWin (Institute of Scientific Instruments, Brno, Czech Republic). The QT interval duration was determined from the onset of the QRS complex to the end of the T wave, defined as the crossing between the isoelectric line and the tangent to the descending T wave. The detection was visually checked and corrected (for RR intervals) or flagged as no detectable (for QT intervals).

The resulting RR and QT intervals series were used in the case of D1 detection. The moving window, with a length of 10 beats and an overlap of 5 beats, was used in the case of D2 detection. Median value of QT intervals from window was assigned to last QT interval from the window. QT intervals not assigned were set as not defined. The RR series were equal in both detections; QT series in case of D2 detection represent some type of "global QT" detection [5].

3. QT parameters

QT dynamic parameters are not yet standardized and they depend on supposed model of QT-RR coupling; different models have been used [7-12].

Our model is based on transfer function, defined by recursive relation (3 optimized parameters) between QT and RR intervals without mean levels [10, 11]. This model was given by Bayes optimization of the ARMA model, when the optimum between complexity and general parameter validity was analyzed [10]. The QT step response of this

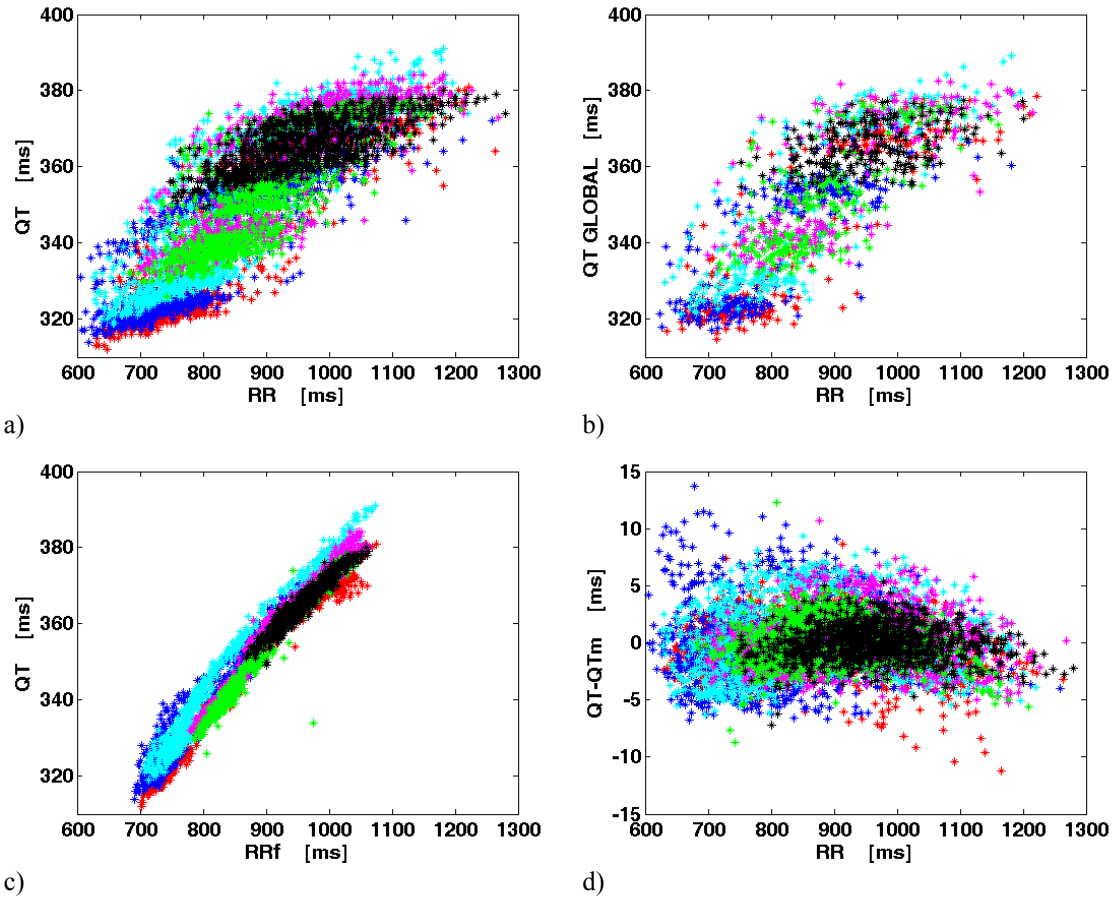

Figure 1. Subject S2, 6 tilt table angles. Order of plotting for different angles of tilt is: 90º, 75º, 60º, 45º, 30º, 15º, and corresponding colors are red, blue, cyan, magenta, and green, black. The successive plotting may overlap preceding plotting; i.e. only the measurement with 15º (black) is fully visible. a) D1 detection; b) D2 detection; c) QT hysteresis elimination according ARX model [11]; c) Error between detected QT (D1 detection) and predicted QT by model.

model, computed from optimized parameters, is always similar to a known QT step response measured in patients with pacemaker or in the isolated heart [1, 2]. This model defines the set of QT parameters for analyzed measurement: i) QTc, i.e., a 60-bpm equivalent QT duration computed from the QT/RR model; ii) the gain of QT-RR coupling for slow variability of RR ($Gain_S$), i.e., QT/RR slope, i.e. the parameter that describes QT memory; iii) the gain of QT-RR coupling for fast variability of RR ($Gain_F$), i.e. restitution, i.e. the parameter that describes the immediate change of QT ; iv) the time constant of QT adaptation to RR changes; v) random QT variability, i.e. QT variability not dependent on RR changes. The parameters are not affected by hysteresis because the ARX model controls for it [11].

4. Results

Graphical results of detected intervals, hysteresis elimination and error between detected QT and QT assessed from model for subject S2 over different tilt table angles are shown in Fig. 1. Mean levels ± STD over 6 angles of tilt for subjects S1 to S3 are reported in Tab. 1 and relative inaccuracy given as STD/mean is reported in Tab. 2. Parameter distribution over different tilt table angles is represented in Fig. 2.

Table 1. Mean levels ± STD over 6 tilt table angles for subjects S1, S2 and S3 and QT detections D1 and D2.

subject/ detection	QTc [ms]	$Gain_S$ ×10	$Gain_F$ ×100
S1/D1	362±2	1.72±0.06	2.4±0.2
S1/D2	362±2	1.71±0.06	0.55±0.36
S2/D1	374±3	1.86±0.14	3.3±0.5
S2/D2	374±3	1.86±0.14	0.68±0.32
S3/D1	369±3	1.71±0.14	3.3±0.2
S3/D2	369±3	1.70±0.14	0.41±0.26

Table 2. Relative inaccuracy (STD/mean × 100) for subjects S1 to S3 and mean inaccuracy over subjects for QT detections D1 and D2

	QTc [%]	$Gain_S$ [%]	$Gain_F$ [%]
S1/D1	0.62	3.3	8.2
S1/D2	0.63	3.4	65.3
S2/D1	0.74	7.3	14.7
S2/D2	0.73	7.3	46.6
S3/D1	0.73	8.2	7.2
S3/D2	0.74	8.0	64.1
mean/D1	0.7	6.3	10.0
mean/D2	0.7	6.3	58.7

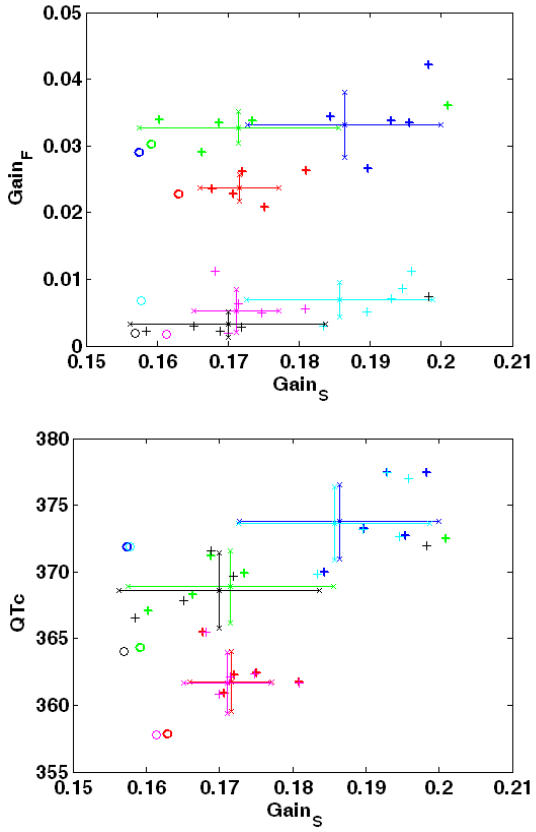

Figure 2. Parameters distribution. Crossing of lines defines mean and lines represent STD for given subject. Marks describe single measurement; 'o' represents tilt with angle 15. Colors define subject and detection. D1 detection: red, blue and green for subject S1, S2 and S3 respectively. With D2 detection corresponding colors are magenta, cyan and black.

5. Theory

D2 detection, based on averaging of ECG or detected QT intervals over few beats is the low pass filter. The fast QT variability is filtered out by this filter. The analyzed frequency responses of QT-RR coupling with D1 detection and D2, together with influence of low pass filter on frequency response with D1 detection are in Fig. 3.

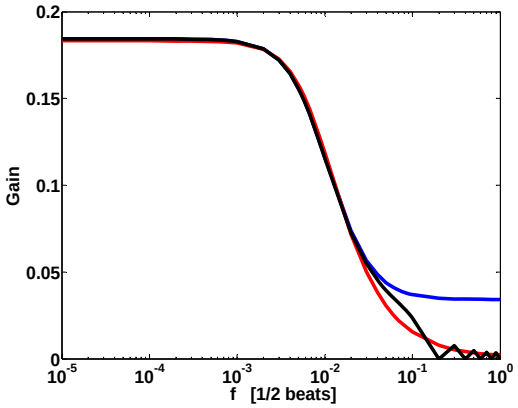

Figure 3. Analyzed frequency responses of QT-RR coupling with D1 detection (blue), D2 (red) and the influence of the low pass filter on response with D1 (black). Order of plotting: blue, red, black. Subject S2, angle 90º.

6. Discussion

The best reproducibility from tested QT parameters is at QTc (inaccuracy 0.7 %). The reproducibility of $Gain_S$ and $Gain_F$ is about order worse but acceptable. Inaccuracy is 6.3 and 10 % respectively.

$Gain_F$ may be analyzed with QT detection beat per beat only. Using D2 detection ("global QT") the $Gain_F$ cannot be analyzed. Averaging ECG signal or detected QT intervals over few beats eliminates fast QT variability and any information about $Gain_F$ is missing (see Fig. 3). However, with D2 detection we cannot speak about reproducibility of $Gain_F$, as such parameter does not exists in analyzed data (see black line in Fig. 3). On the other hand, slow QT parameters (QTc and $Gain_S$) are not affected by type of QT detection (Fig. 2, 3, Tab. 1, 2).

According to our opinion, global QT and D2 detection should not be used anymore. They do not increase the accuracy of slow QT parameters and they eliminate the information about fast QT variability and about fast coupling between QT-RR.

The reproducibility of any parameter depends on signal-to-noise ratio (SNR) of analyzed data. SNR is given by ratio of QT variability corresponding to RR changes and QT variability not determined by RR changes (random QT variability and detection errors). With small RR changes, the majority of variability in detected QT intervals may be related to detections errors and random QT variability and so the minimal SNR of analyzed data is in measurements with tilt table angle of 15º. QT parameters from these measurements have

maximal differences from mean levels (see Fig. 2). Analyzing the reproducibility excluding the 15º angle, the inaccuracy of QT parameters decreased (data not presented).

In the analysis we suppose that QT parameters do not depend on angle of tilt. There may be some physiological dependency, as in [6] and QT parameters depend on excitation [13, 14]. In any case, SNR somehow depend on input data (angle 15º). The value of reproducibility may be increased by longer measurements or/and by increasing RR changes. The presented irreproducibility can be considered maximal, however significantly better reproducibility may be achieved.

7. Conclusion

QT restitution is a reproducible parameter and its analysis may be important in evaluating the prevalence of arrhythmias. This parameter may be analyzed with QT detection beat per beat only. Using global QT, i.e. averaging ECG per few beats, eliminates any information about restitution and such detection is probably the origin of the reported irreproducibility of restitution. Global QT has no contribution in accuracy of slow QT properties (QTc, QT/RR slope) and shouldn't be used anymore.

The reproducibility of QT parameters depends on SNR of analyzed data and the SNR may be increased by longer measurement and increased RR interval changes.

It is time to open more detailed discussion about QT detection, best QT/RR model and best set of QT parameters.

Acknowledgements

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Address for correspondence.

Josef Halamek
Institute of Scientific Instruments, Czech Academy of Sciences
Kralovopolska 147, Brno 612 64
Czech Republic
josef@isibrno.cz