33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Excitation Specificity of Repolarization Parameters

J. Halámek, P. Jurák, V. Vondra, I. Viščor, M. Plachý, and P. Leinveber

Abstract— **The excitation specificity of QT dynamic parameters was tested on three groups of subjects: healthy subjects; non-medicated hypertensive subjects with metabolic syndrome; and subjects with essential hypertension. Four different excitations of RR were used: bicycling exercise; tilt with breathing 0.1 and 0.33 Hz; and deep breathing. Linear dynamic feedback model of QT/RR coupling was supposed at the analysis and next repolarization parameters were tested: QTc; gain of QT/RR coupling for slow and fast RR variability; time constant of QT adaptation; and random QT variability.**

Results: Dynamic repolarization parameters statistically significantly depend on the type of RR excitation. The gain of QT/RR coupling for slow RR variability, the time constant of QT adaptation and QTc are maximal at RR excitation given by the bicycling exercise. The frequency of breathing, i.e. corresponding vagal modulation has no effect on repolarization parameters. The measurements with deep breathing, without any other slow excitation of heart rate, has low signal-to-noise ratio of analyzed data and resulting QT parameters are inaccurate.

Conclusion: The use of heart rate excitation and all measurements conditions should be defined for the exact analysis of the repolarization dynamic parameters.

I. Introduction

The measurement and analysis of ventricular repolarization is still a matter of debate. Some recommendations exist [1], but in all areas – QT detection, QT heart rate correction and repolarization parameters there are many questions that remain unanswered. The attention is mostly concern on QTc but cardiac repolarization has multidimensional characteristics that are not represented by the simple unidimensional duration of the QTc [2]. Different parameters were suggested to describe the dynamic properties of QT intervals [3], some other parameters describe the heterogenity of repolarization [4], but the diagnostic contribution of all suggested parameters is rather limited and still discussed.

The attention is mostly focused on different algorithms of QT analysis and the conditions of ECG measurement are neglected. Previous analyses of QTc were based on steady state parts of ECG signal and nonlinear static correction as Bazett's, Fridericia's or some others were used. In present, individual subject specific correction of QT on heart rate is mostly assumed and a measurement with heart rate changes should be used. The more detailed conditions of measurements are not specified, it is assumed that QT/RR coupling is only subject specific and not excitation specific.

The dependency of QT/RR coupling on the type of RR excitation may be one reason of limited accuracy, reproducibility and diagnostic contribution of used QT parameters. The arrhythmias in long QT subjects are triggered by genotype specific stress [5], different QT/RR slopes exist for the day than for the night [6], and repolarization parameters differ during rest, gravitational and isometric stress [7]. Our aim was to test the dependency of repolarization dynamic parameters on the type of heart rate excitation.

II. Measurements

Three groups of subjects were studied. Healthy subjects (47 subjects, age 41±18, maximal/minimal age 72/22); non-medicated hypertensive subjects with metabolic syndrome (34 subjects, age 46±12, maximal/minimal age 59/22) and subjects with essential hypertension (7 subjects, age 26±5, maximal/minimal age 33/22). All measurements were done in supine position with different excitation of hear rate:

a) Exercise: subject in supine position and breathing normally during three intervals about 5 minutes each according to the sequence: 1) rest, 2) bicycling, 3) rest. The load was about 1 W/kg and the speed of bicycling was constant.

b) Tilt6: subject in supine position for 7 minutes, then tilted by 75° for 10 minutes and supine again for the last 5 minutes; controlled breathing at a frequency of 0.1 Hz, i.e. 6 breaths per minute, in all positions.

c) Tilt20: subject in supine position for 7 minutes, then tilted by 75° for 10 minutes and supine again for the last 5 minutes; controlled breathing at a frequency of 0.33 Hz in all positions.

d) Breath: subject in supine position; controlled deep breathing at a frequency of 0.1 Hz for 5 minutes.

The ECG was recorded with a 3-lead bedside system, model 90308 (SpaceLabs, Inc., Redmond, WA, USA). The analog signals were sampled at 500 Hz and converted in digital form by a 16-bit analog-to-digital Converter. Data were stored in binary files for subsequent analyses. The signal with the maximal T wave was analyzed with our custom-designed software, ScopeWin, to obtain a

This work was supported by the grant KONTAKT No. ME09050 of the Ministry of the Education of the Czech Republic.

Josef Halámek, Pavel Jurák, Vlastimil Vondra, and Ivo Viščor are with Institute of Scientific Instruments, Academy of Sciences, Czech Republic, Kralovopolska 147, 612 64 Brno, Czech Republic (phone + 420-541514311, e-mail: josef@isibrno.cz, jurak@isibrno.cz, vond@isibrno.cz, ivovi@isibrno.cz)

Martin Plachý and Pavel Leinveber are with St. Anne's University Hospital Brno, Pekarska 53, 656 91 Brno, Czech Republic (e-mail: martin.plachy@fnusa.cz, pavel.leinveber@fnusa.cz)

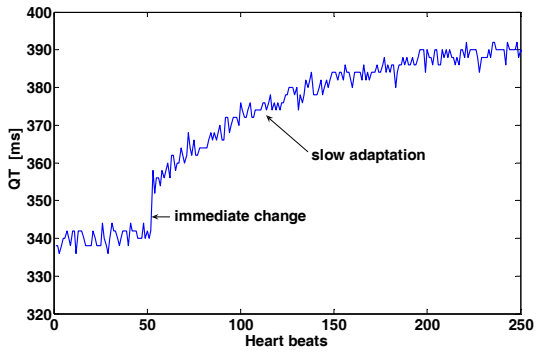
continuous series of RR and QT intervals. The QT interval duration was determined from the onset of the QRS wave to the end of the T wave, defined as the crossing between the isoelectric line and the tangent to the descending T wave. A semiautomatic method of QT detection, with visual control was used. If the T wave was distorted or with low amplitude, the corresponding parts of the QT intervals were marked as nondetectable.

III. QT PARAMETERS

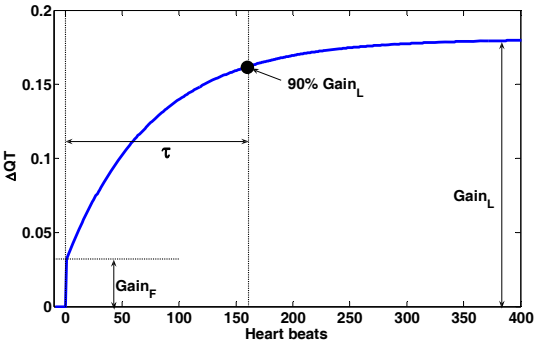
Linear dynamic feedback model (TRF) [8, 9] of QT/RR coupling was supposed at the analysis. TRF model suppose next recursive relation between RR and QT intervals without mean levels, i.e. RRx=RR-mean(RR), QTx=QT-mean(QT):

$$qtxm(i) = b_2 rrx(i-1) + b_3 rrx(i-2) - a_1 qtxm(i-1) \quad (1)$$

where rrx(i) and qtxm(i) are i-th values of variables (RRx, QTxm) and QTxm is model QT without mean level, i.e. QTm=QTxm+mean(QT). a1, b2 and b3 are fitted parameters, which are given by minimizing the residuum between QT and QTm. Resulting minimal residuum (RMS) represents the QT random variability independent on RR. The QT step response is computed from fitted parameters a1, b2 and b3 and the QT parameters $Gain_L$, $Gain_F$, τ are defined from step response, see Fig.1, where the measured QT step response is also, to compare the shapes.



a)



b)

Fig. 1. a) The measured QT step response in a patient with a pacemaker.
b) An example of QT step response at the TRF model and the presentation of QT parameters.

QTc is given by next relation:

$$QTc = mean(QT) + (1000 - mean(RR)) \times GainL \quad (2)$$

The following five QT parameters were analyzed:

- QTc: Computed from model
- $Gain_L$: The gain of QT/RR coupling for slow variability of RR, i.e. the QT/RR slope.
- $Gain_F$: The gain of QT/RR coupling for fast variability of RR, i.e. the relative amplitude of QT change immediately after the change of RR.
- τ: The time constant of QT adaptation, i.e. the number of heart beats after which QT has achieved 90 % of the steady state level.
- RMS: QT random variability, independent on RR.

The analysis of QT/RR coupling and the accuracy of QT parameters are limited by signal-to-noise ratio of analyzed data. The QT intervals are distorted by detection errors and some QT variability independent on RR exist. Moreover QT irregularities, not yet explained, may distort QT intervals [8]. The validated QT parameters may be achieved only when the fast and slow QT variability corresponding to RR excitation is higher than the detection errors and random QT variability. For this reasons, the basic properties of detected RR and QT intervals are presented together with repolarization parameters.

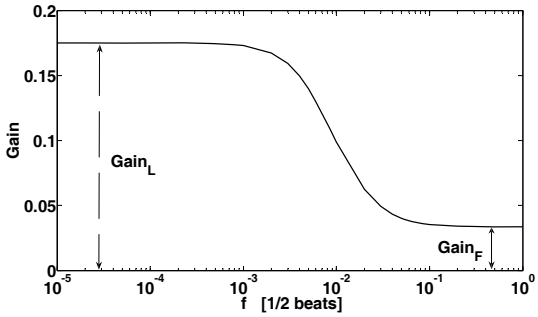


Fig. 2. Example of QT/RR frequency response.

Beats were used as the unit of the sampling frequency in the analysis of QT/RR coupling. The proper unit of sampling frequency is also an open question for the future. Whether the sampling frequency in beats or in seconds guarantees more reproducible results must be tested. Frequency response of QT/RR coupling has a shape similar to Fig. 2. According to this frequency response the slow pass band for QT and RR variability was set from 0.00001 to 0.005 beats and fast pass band from 0.005 to 0.5 beats.

Statistical significant differences between QT parameters corresponding to different excitations were tested by ANOVA and the Bonferroni correction addressing the problem of multiple comparisons was applied.

IV. RESULTS

The basic properties of detected RR and QT intervals for healthy subjects are in Tab. 1. There are mean level and

variability (represented by standard deviation) of RR and QT intervals, correlation between RR and QT, variability of RR and QT in low frequency band and higher frequency band and correlation between filtered RR and QT. The parameters are computed over the entire measurement and in Tab. 1 they are given as a mean level ± standard deviation over subjects. These results are presented for the healthy group only. The influences of excitations are similar in other groups. Resulting repolarization parameters are in Tab. 2.

Statistically significant differences within the healthy group are between exercise and all the other excitations in $Gain_L$ ($P<0.01$) and in τ ($P<0.001$). The significant differences in QTc within the healthy group are between exercise and tilt6 only ($P<0.05$). In subjects with metabolic syndrome, the significant differences are between exercise and both tilts in $Gain_L$ ($P<0.00001$), τ ($P<0.01$), QTc ($P<0.0001$) and $Gain_F$ ($P<0.05$).

The statistically significant differences between groups of subjects were not tested. This is another task; our aim in this study was testing the repolarization parameters dependency on the type of excitation. Different groups of subjects were used to see if the trend of excitation dependency was similar within different groups.

TABLE I

Mean level ± standard deviation over healthy subjects of basic RR and QT parameters. Mean level of RR and QT over entire measurement are mRR and mQT respectively, variability (standard deviation) of RR and QT are vRR and vQT respectively, corr means the correlation between RR and QT. Appendix L at vRR, vQT and corr represents filtered signals RR and QT in pass band from 0.00001 to 0.005 [beats] and appendix H that signals were filtered in pass band from 0.005 to 0.5 [beats]. All parameters, except correlation, are in ms.

	Exercise	Tilt6	Tilt20	Breath
mRR	695±80	812±95	831±91	912±91
mQT	332±22	352±22	363±22	370±24
vRR	148±35	123±47	137±45	103±41
vQT	26±6	16±7	21±7	6±4
corr.	0.88±.06	0.82±0.1	0.91±.06	0.6±0.2
vRRL	142±34	100±41	126±44	5±11
vQTL	25±6	16±7	20±7	0.7±1
corrL	0.90±0.1	0.94±.03	0.96±.02	0.57±0.4
vRRH	43±17	69±34	52±29	101±40
vQTH	3.8±1.3	5±2	3.6±1	5.3±4
corrH	0.37±0.2	0.5±0.2	0.49±0.2	0.59±0.2

V. Discussion

Repolarization parameters depend on the type of heart rate excitation. The most dependent are $Gain_L$ and τ, but QTc is also statistically significant dependent. The dependency of repolarization parameters QT was described in [7], with the conclusion that hypertensive stress increases the dispersion of repolarization and QT interval.

The proper correction of QT on heart rate must be used to prove QT dependency on the type of heart rate excitation. The debatable Bazett's correction is used in [7], but its influence was eliminated by the conditions of measurements. They measured steady state at the same heart rate achieved by two different type of stress. We have analyzed the dynamic measurements, and QT heart rate correction is given by the assumed dynamic model. The validity of correction is given by the validity of the model and may be tested by analyzing agreement between time evolution of detected QT intervals and model QT intervals.

TABLE II

Mean levels ± standard deviation over repolarization parameters of subjects. QTc in ms is computed from the dynamic model. $Gain_L$ and $Gain_F$ are gains of QT/RR coupling for slow and fast RR variability respectively. τ in beats is the number of beats when QT achieves 90% of its steady state. RMS in ms is QT random variability, independent of heart rate.

	Exercise	Tilt6	Tilt20	Breath
	healthy subjects			
QTc	399±30	386±20	395±21	389±61
$Gain_L$	0.21±0.06	0.17±0.04	0.18±0.04	0.14±0.2
$Gain_F$	.036±.013	.033±.012	.034±.013	0.35±.02
τ	162±41	88±30	83±32	84±142
RMS	4.7±1	4.4±2	3.8±1	3.2±2
	subjects with metabolic syndrome			
QTc	430±31	400±27	395±23	359±100
$Gain_L$	0.26±0.06	0.19±0.05	0.18±0.04	0.23±0.2
$Gain_F$	0.06±0.03	0.05±0.02	0.03±.014	0.06±.03
τ	146±28	113±57	98±38	156±100
RMS	6.4±2	4.8±2	4.1±2	3±1
	subjects with essential hypertension			
QTc	391±26	378±27	372±21	384±53
$Gain_L$	0.21±0.04	0.17±0.05	0.16±0.03	0.2±0.16
$Gain_F$	0.04±0.02	0.04±0.01	0.035±.01	0.04±.02
τ	170±23	143±90	75±34	178±150
RMS	4.5±2	5.5±3	4±1	2.5±0.7

Our result of QTc dependency on the type of heart rate excitation corresponds with [7], hypertensive stress increases QTc relative to gravitational stress. QT does not depend on heart rate only, some other parameters such as blood pressure may have impact on its level.

We used four types of heart rate excitation, bicycling exercise, tilt with controlled breathing 6 and 20 times per minute and deep breathing 6 times per minute. Bicycling was used as the stress that may provoke arrhythmias at long QT subjects. The QT adaptation is the slowest with this excitation. The QT parameters from tilt excitation with controlled breathing 6 and 20 times per minute are nearly the same. So we may assume that the deep breathing and corresponding vagal modulation of sinoatrial and atrioventricular node have no effect on QT parameters.

The excitation with deep breathing only is not sufficient to analyze repolarization parameters. The repolarization parameters are inaccurate with this excitation, their standard deviation is maximal. This is valid before all at QTc, $Gain_L$ and τ. All these parameters represent the slow QT/RR coupling. The slow RR excitation is missing with this type

of excitation. See Tab. 1, RR slow variability is about 20 times lower than with other excitation and the QT slow variability is below QT quantization error.

We tested three groups of subjects. Statistically significant dependency of repolarization parameters on excitation exists in all groups and the trend of dependency of repolarization parameters is in all groups similar. We may conclude that the definition of measurement protocol is at QT analysis important and can not be neglected.

VI. Conclusion

The QT analysis should be based on measurement with significant RR excitation in slow and faster frequency bands to achieve good signal to noise ratio of analyzed QT/RR coupling. The excitation of heart rate and all conditions of measurements should be defined, as the QT depends not only on RR but on other parameters as well. The repolarization dynamic parameters depend on the type of RR stress and this may explain different triggers of arrhythmias at long QT subjects.

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