Excitation Specificity of Repolarization Parameters

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Abstract. *QT/RR coupling was analyzed in two groups of subjects (healthy and hypertensive) with two protocols (exercise and tilt). A dynamic model of QT/RR coupling with 3 optimized parameters was used to analyze dynamic properties (memory and restitution) and to eliminate QT hysteresis. Linear and nonlinear models were used to analyze static properties. Parameter reproducibility was tested by a bootstrap methodology. The linear model is better with the tilt test, the nonlinear model is better in hypertensive patients with the exercise test. QT memory differs significantly between the exercise and tilt test in both groups. The QT/RR slope is steeper in the exercise test and QT adaptation faster with the tilt test. The excitation specificity of QT parameters may explain genetic dependent triggers of arrhythmias and QT/RR nonlinearity.*

Keywords: Repolarization analysis; QT/RR slope; QT restitution; Excitation specificity

1. Introduction

The measurement and analysis of ventricular repolarization began in 1920, when Bazett's correction was originated, though it remains a matter of debate. A number of recommendations exist [1], though unanswered questions remain in all areas (analyzed measurement, QT detection, QT-RR model, and QT parameters). The subject specificity of QT-RR coupling is generally accepted [2-7], and corresponding analysis of QT-RR coupling must be based on measurements with sufficient heart rate changes. Discussion of the type of heart rate stress used and the level of heart rate changes needed to obtain reproducible results is mostly neglected, even though it is known that QT-RR coupling is excitation specific [8,9]. QTc, as QT equivalent for 60 bpm, is used as the basic QT parameter. It should be analyzed after QT hysteresis elimination. Various models of QT-RR coupling and various algorithms of hysteresis elimination are used [2-7]. QT hysteresis is given by the dynamic properties of coupling, and physiological parameters – QT restitution and memory – may be analyzed with the proper model [6]. Analysis of QT parameter dependency on the two types of heart rate stress (exercise and tilt) was our aim.

2. Subjects and Methods

Healthy subjects (21 subjects, age 40±17) and non-medicated hypertensive subjects (21 subjects, age 43±11) were studied with two types of heart stress: exercise and a tilt-table test. Exercise: subject in supine position during three intervals of about 5 minutes each according to the sequence: 1) rest, 2) pedalling at a constant speed with a load of about 1 W/kg, 3) rest. Tilt: subject in supine position for 7 minutes, then tilted to 75° for 10 minutes and returned to the supine position for the last 5 minutes. The lead with the maximal T wave was analyzed with our custom-designed ScopeWin software. The end of the T wave was defined as the crossing between the isoelectric line and the tangent to the descending T wave. The results were visually controlled and distorted parts or parts with a low amplitude of the T wave were marked as non-detectable. A dynamic linear model (Eq. 1) was used to analyze dynamic properties of QT-RR coupling and to eliminate QT hysteresis:

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

where rrx(i), qtx(i) and qtxm(i) are i-th values of RR, QT and QTm without mean levels. QTm is model QT and a_1, b_2, b_3 are fitted parameters to achieve the best agreement between QT and QTm.

The parameters a_1, b_2, b_3 define the QT reaction on RR change (Fig. 1a) and the shape of response corresponds extremely well with the known QT response measured in patients with a pacemaker (Fig. 1b). The parameters a_1, b_2, b_3 and mean levels of RR and QT define QT static and dynamic QT parameters. The dynamic parameters are: i) $Gain_S$, i.e. the gain of QT-RR coupling for slow variability of HR, i.e. QT/RR slope; ii) $Gain_F$, i.e. the gain for fast variability of HR, i.e. the QT immediate response, i.e. QT restitution; and τ, i.e. the time constant of QT adaptation. $Gain_S$ and τ describe QT memory, i.e. QT slow adaptation. A more detailed description of the methodology used can be found in [6].

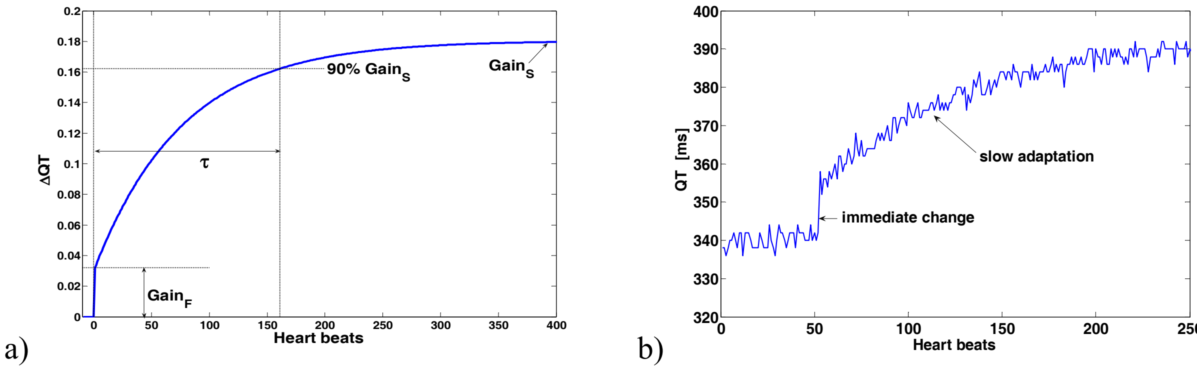

Fig. 1. a) QT response on sudden change of RR according to supposed model. b) QT response measured in patient with a pacemaker as the reaction on sudden change of RR.

Parameters a_1, b_2, b_3 may be used to eliminate QT hysteresis, i.e. dynamic properties of QT-RR coupling [3, 5, 6]. Static QT properties (QTc, QT/RR slope, QT nonlinearity) are analyzed using the RRf (filtered RR) that is given by Eq. 2.

$$RRf = filter(b, a, RR - mean(RR)) / GainS + mean(RR) \quad (2)$$

where *filter* and *mean* are Matlab functions and *b, a* are parameters *a1, b2, b3*. An example of hysteresis elimination is given in Fig. 2. Two models of coupling between QT and RRf were tested. The linear (QTL), Eq. 3a, and nonlinear (QTN), Eq. 3b, presented in [4].

$$QTLm = a0 + a1 \times RRf, \quad (3a)$$

$$QTNm = a0 - (\delta/\gamma) \times (1 - RRf^{\gamma}) \quad (3b)$$

where a0, a1, δ and γ are optimized parameters according to the agreement of QTLm or QTNm with QT. The decision on the linearity/nonlinearity of coupling is mostly based on minimal RMS, though this is not sufficient proof. The RMS of QTNm must always be lower, as this model has 3 optimized parameters, as compared to 2 in QTLm. QTc reproducibility is more important than RMS and we tested this reproducibility with a bootstrap methodology [10].

3. Results

QT hysteresis elimination with a dynamic model is presented in Fig. 2. The QT parameters are shown in Tab. 1. The mean levels and STD, together with the statistical significance of differences between exercise and the tilt test, are given in Tab. 1.

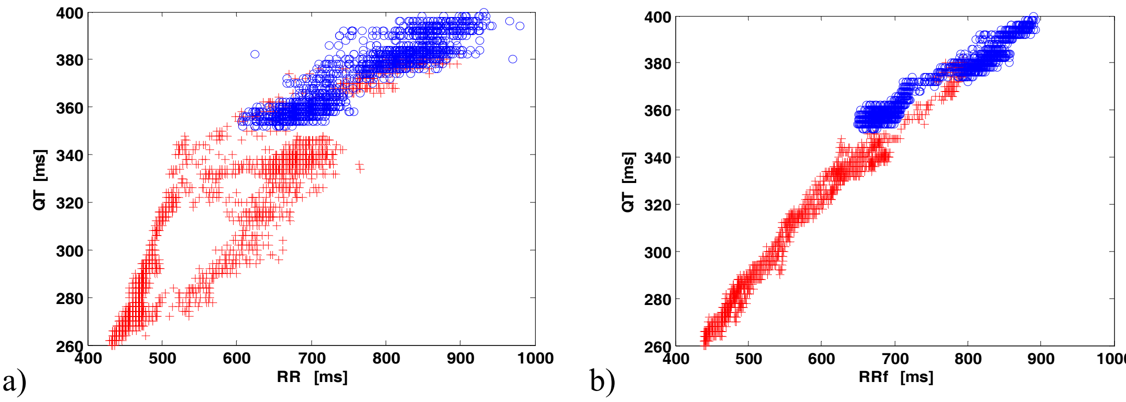

Fig. 2. Healthy subject, red marks '+' exercise test, blue marks 'o' tilt test. a) Raw detected QT and RR intervals. b) Raw QT intervals and filtered RR intervals to eliminate QT hysteresis.

Table 1. Mean levels ± STD. The inaccuracy of parameters, given by a bootstrap methodology and defined as STD/mean in %, is shown after the slash '/'. HY_E, HY_T are hypertensive subjects with exercise and tilt test respectively, CN_E and CN_T are healthy subjects with exercise and tilt test. QTcL and QTcN are QTc given by the linear and nonlinear models respectively, $Gain_S$, $Gain_F$ and τ are QT dynamic parameters, δ/γ is the QT/RR slope of the nonlinear model. The statistical significance of differences between exercise and the tilt test, given by a nonparametric paired t test is: *...P<0.05; **...P<0.01; ***...P<0.001; †...P<0.0001.

	QTcL [ms]	QTcN [ms]	$Gain_S$ [n.u.]	$Gain_F$ [n.u.]	τ [beats]	δ/γ [n.u.]
HY_E	423±30	394±29	0.24±0.06	0.047±0.024	127±41	0.09±0.06
	NS / 0.16 %	NS / 0.14 %	** / 0.93 %	NS / 23 %	* / 6 %	** / 3 %
HY_T	409±35	409±46	0.19±0.06	0.037±0.016	94±57	0.20±0.17
	/ 2.2 %	/ 2.2%	/ 7.2 %	/ 29 %	/ 9 %	/ 9 %
CT_E	395±24	381±20	0.21±0.05	0.040±0.020	161±42	0.12±0.04
	NS / 0.13 %	NS / 0.14 %	*** / 0.8 %	NS / 16 %	† / 4 %	** / 1.6 %
CT_T	386±22	388±23	0.15±0.04	0.032±0.014	75±24	0.17±0.10
	/ 0.06 %	/ 0.4 %	/ 1.2 %	/ 21 %	/ 11 %	/ 8 %

4. Discussion

Two groups of subjects, with two types of heart stress, were analyzed with two QT-RR models. Not all combinations can be discussed. With the tilt test, the QTc does not depend on the model used. With the exercise test, QTcN is shorter than QTcL, P<0.05. This corresponds with the downward shape of the QT-RR curvature and is probably the result of the increased oxygen demand of the working muscles. Some differences, not significant, exist between QTc during tilt and exercise. The sign of the differences depends on the model used. QTcL is longer with exercise, QTcN shorter than with tilt. The increased inaccuracy of QTc with tilt is the result of the lower span of heart rate. The accuracy of QT parameters significantly depends on the level of heart rate changes and on the position of 60 bpm relative to heart rate changes. These results were not presented due to the limited size of the paper.

QT memory, defined by $Gain_S$ and τ, is significantly different in the exercise and tilt tests in both groups. With exercise, the QT/RR slope ($Gain_S$) is significantly steeper and QT adaptation (τ) is significantly longer than with the tilt test. The QT/RR slope given by the nonlinear model (δ/γ) is also significantly different in the exercise and tilt tests, though it is steeper with the tilt test. This is given by definition, as δ/γ defines the slope in the narrow area of 60 bpm and $Gain_S$ defines the slope over the entire span of RR changes.

The excitation specificity of QT parameters may explain different genetic triggers of arrhythmias [8] and QT/RR nonlinearity. The linear model is better with the tilt test; the nonlinear model is better with exercise, where markers corresponding to ischemia occur in some subjects. Dynamic parameters significantly depend on the type of heart rate stress. They define the QT evolution during heart rate changes; they significantly differ between controls and LQT1 subjects [11], and may explain triggers of arrhythmias [8]. On the other hand, insight into the physiological background of QT dynamic parameters, i.e. restitution and memory, together with dependency on type of heart rate stress, is lacking. Extremely well controlled studies with defined provocations will be needed.

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