Contrasting Time and Rate based approaches for the assessment of drug-induced QT changes

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Abstract

We aim to highlight the pitfalls of different validated methods used for the assessment of drugs' effect on QT duration.

Digital 12-lead Holter ECGs were recorded at baseline and after a single dose of sotalol in 39 healthy subjects (age=27.4±8.0). Using both Time and Rate-based approaches we obtained averaged QRS-T complexes every minute ("Time-Bins") and at different RR intervals ("Rate-Bins"). "Time-Bins" were corrected for heart rate using a subject-specific approach.

The individual α coefficients increased from placebo (0.309±0.052) to sotalol (0.454±0.136), $p<0.0001$. When the placebo individual α coefficients were applied to correct the QT interval on sotalol, the changes were >5 ms smaller than those obtained using the ON drug α coefficients. The "Rate" averaging process leads to a complete loss of the time course of drug effect.

In conclusion, the individual correction formula calculated from placebo condition cannot always be used for QT correction on drug.

1. Introduction

Some non-cardiovascular drugs may induce an excess of mortality related to life-threatening ventricular arrhythmias[1]. This pro-arrhythmic effect (mainly Torsades de Pointes) is related to drug-induced ventricular repolarization impairment and is commonly associated with the prolongation of the QT interval on the surface electrocardiogram (ECG)[2-4].

The characterization of drugs' effects on QT interval in pre-approval trials is therefore essential in order to prevent rare although serious adverse events for a drug potentially occurring in more vulnerable individuals in a large population exposed to the drug in postmarketing practice[5]. Accordingly, regulatory agencies issued recommendations concerning the design, the analysis, and the interpretation of clinical studies to assess the potential of a drug on QT/QTc interval duration[6-8].

Thorough QT studies have to deal with complex sources of variations which include heart rate-dependent and –independent factors[9-13]. In this regard, the Critical Pathway initiative launched by the US Food and Drug Administration is an attempt to improve the use of science in drug evaluation[14].

Although heart rate changes are the main source of variation of the QT interval, the management of heart rate influences on QT duration is so far not resolved. Two different approaches are conceivable. Most of the data submitted by pharmaceutical companies normalize the QT duration to a 60 bpm heart rate (HR), and "universal" (Bazett and Fridericia) rate correction are still used instead of the state-of-the-art subject-specific correction formula[15]. The comparison of QT interval at identical HR has recently been proposed to avoid the need for any HR correction formula[16-18].

The debates on these fundamentally different approaches are not only academic discussions[19]. Indeed, thorough QT studies are intended to detect a threshold level of

regulatory concern as low as 5-10 ms[7]. Thus, any potential methodological confounding factor may induce a bias which, although quantitatively small, may have major implications for drug safety.

The aim of this paper is to highlight the relative advantages and disadvantages and potential biases of different validated methods used for the assessment of drugs' effect on QT interval duration. Hence, we evaluated the effect of sotalol, a well known torsadogen drug which also has an effect on heart rate, on QT duration in healthy subjects using the 2 different approaches, the QT correction and the comparison at identical heart rate.

2. Methods

2.1. Study population

The data reported in the present paper are part of an open-label and non-randomized cardiovascular methodology study with sotalol conducted at Pharmacia's Clinical Research Unit (Kalamazoo, MI, USA). The study protocol has been previously described[20]. The study population included 39 healthy subjects, 28 males and 11 females. The mean age was 27.4±8.0 years. All subjects gave written informed consent and the study protocol was approved by the Bronson Methodist Hospital Independent Institutional Review Board in Kalamazoo, MI, USA.

2.2. ECG recording and analysis

We report the results from the analysis of continuous digital 12-lead Holter ECG recordings (H12 recorders, Mortara Instrument Inc, WI, USA; 180 samples per second) obtained at baseline (Day 0) and after a single dose of sotalol 160 mg (Day 1). The on-treatment data were compared to baseline data during a 4-hour time window centered around Tmax (± 2 hours from the plasma Tmax of sotalol) in each subject and the chronologically matching part of the Holter trace at baseline.

ECG recordings were edited (H-Scribe, Mortara Instrument Inc, WI, USA) to ensure that cardiac beats of sinus origin were accurately identified and that non-sinus beats as well as artifacts had been excluded for quantitative analysis. ECG recordings were then transferred to a dedicated software (WinAtrec 8.00, AMPS LLC, NY, USA) used to perform a beat averaging approach that has been called the "Bin" method[17, 21, 22, 23].

Two separate binning/averaging approaches were applied to the 4-hour analysis window. The first is the Time Binning and it is aimed to assess the drug effect on QT interval

duration at different time-points. Within the 4 hours analysis window, one template every minute is constructed, thus generating 240 Time-Bins for each recording.

The QT interval duration obtained in each individual Time-Bin template was corrected using the Bazett's formula ($QTcB=QT/RR^{1/2}$), the Fridericia's formula ($QTcF=QT/RR^{1/3}$), and the subject-specific correction formula based on a power-law (log-log) model ($QTcNi=QT/RR^{\alpha Ni}$), using the one-minute averaged RR interval.

The computation of QTcNi was applied separately on baseline and on sotalol measurements. We will thus refer to QTcNi-OFF to indicate heart rate corrections using power-law best fit from the baseline data and QTcNi-ON to indicate heart rate corrections using the power-law best fit from the sotalol data.

The second averaging method applied was the so-called RR-Bin approach, also commonly referred to as the "Rate Binning". With this method QT duration is evaluated at fixed RR interval levels (the RR Bins), with 10-ms resolution between adjacent RR Bins. Individual cardiac complexes of sinus origin are stratified according to the value of the preceding RR interval (RR-1). The cardiac complexes are subsequently accepted for averaging (i.e. included in the RR bin) only when there are preceded by stable heart rate. HR stability was defined by the following formula:

$$\mathbf{RR\text{-}1 = RR_{[observation\ period]} \pm thr}$$

where $RR_{[observation\ period]}$ is the mean RR interval of the period considered for heart rate stability and thr is a tolerance threshold. In this study, the observation period was fixed to 60 seconds (R60)[24] and the threshold to 20 ms.

Comparisons of QT interval durations at the same heart rate (i.e. from same RR Bins from baseline and sotalol templates), and thus without the implantation of a correction formula were performed. In addition, we also calculated the individual power-law log/log model coefficients at baseline and on sotalol from the Rate Binning data.

As an alternative rate-independent method, ΔQT/ΔRR plots were constructed from the Time Bins series. The intercept (i.e. ΔRR=0) of the linear relationship describing the data was used as the rate-independent point estimate of drug-induced QT change. This approach was performed on both populations (i.e. by pooling all the ΔQT/ΔRR pairs from all the study population) and on an individual basis.

QT measurements on both time and rate bins were blindly performed by a single reader (Pierre Maison-Blanche). The analysis was carried out on a single preferred lead in each subject. The end-points of the study were:

1) the change in QT or QTc interval duration on sotalol versus placebo at identical time-point (ΔQT or ΔQTc) for the Time-Binning approach
2) the change in QT interval duration on sotalol versus placebo at identical heart rate for the Rate Binning approach and the point estimate.

2.3. Statistical analysis

Data are presented as mean ± SD. Comparisons between placebo and sotalol were performed using a 2-tail paired Student's test. A p value <0.05 was considered as significant. Statistical analysis was performed using Statview 5.0 (SAS Institute, Inc, NC).

3. Results

3.1. Sotalol effect on heart rate

As expected, the mean RR interval was significantly longer on sotalol (986.5±129.5 ms versus 848.4±118.0 ms on placebo, $p<0.0001$).

3.2. Sotalol effect on QT duration

3.2.1. Time Bin analysis

The individual α coefficient from power-law best fit analysis significantly increased from placebo (0.309±0.052: range: 0.197 : 0.416) to sotalol (0.454±0.136: range: 0.208 : 0.783), $p<0.0001$ (Table 1).

The time-course of sotalol-induced QTcNi prolongation from the 240 time-points is shown in Figure 1.

In Figure 2, the mean ΔQT, ΔQTc (Bazett, Fridericia), ΔQTcNi (QTcNi-ON) are depicted. The Emax for the effect of sotalol was delayed approximately 60 minutes after the Tmax for sotalol concentration in plasma (Figure 1 and 2). The change in uncorrected QT was overtly larger than the changes in heart rate corrected QT. The smallest ΔQT was observed when using the Bazett's correction formula (Figure 2). Conversely, both Fridericia and the individual correction formulae provided a larger similar significant 30 to 40 ms QT prolongation around Emax (Figure 3 and Table 2). For instance, at T180, ΔQTcB was 21.4 95%IC[12.9; 30.0] and ΔQTcNi 35.0 IC95%[24.7; 45.3].

In Figure 3 the differences between the ΔQTcNi-OFF and the ΔQTcNi-ON are highlighted. When the placebo individual α coefficients were applied to correct the QT interval on sotalol (QTcNi-OFF), the changes were smaller than those obtained using the ON

drug α coefficient (QTcNi-ON). For instance, at T120 the differences was a 6.5 ms decrease and at T180 a 5 ms decrease (Table 2 and Figure 3).

The drug-induced increase in individual α coefficients was not homogeneous after sotalol administration. Indeed, the individual α coefficients calculated from the first 120 ECGs (0 to 2 hours) were significantly higher than the coefficients calculated from the last 120 ECGs (2 to 4 hours) ($p<0.05$ on both placebo and sotalol)(Table 1).

3.2.2. Rate Bin analysis

Figure 4. and Table 3. show the prolonging effect of sotalol on QT interval duration as assessed using the Rate Binning approach and exemplify the reverse rate-dependence of sotalol-induced QT prolongation.

With Rate Binning, the individual α coefficients were not used for heart rate correction since this method allows QT duration comparisons at the same heart rate without using any heart rate correction formula. However, the individual α coefficients were also calculated with this approach. The α coefficients was 0.315±0.049 (range: 0.197; 0.432) on placebo and 0.419±0.097 (range: 0.231 ; 0.718) on sotalol, $p<0.0001$.

3.2.3. The point estimate from ΔQT/ΔRR plots analysis

In Table 4, the intercept of the ΔQT/ΔRR regression analysis (the point estimates), computed from the overall population and from subject-specific basis, and repeated over the entire 4-hour analysis and over 2-hours sub periods are reported.

The point estimate calculated from the 4 hours of the recordings is different from the two 2-hour periods. The point estimate of sotalol-induced QT prolongation was larger over the second time-window.

4. Discussion

Using 24-hour, continuous digital 12-lead Holter ECG recordings, sotalol-induced QT prolongation in healthy subjects was assessed with two complementary methods, one based on standard time averaging (Time Binning) and the other based on heart-rate related averaging (Rate-Binning). Although both approaches provided comparable results our study indicates that each method has intrinsic limitations as well as potential pitfalls that might lead to biased results.

4.1. The Time Binning approach

Thorough QT studies are usually based on the serial recording of 10-second 12-lead surface ECG recordings. The assessment of the time course of drug's effects together with parmakokinetic data is one of the useful tools to evaluate the drug concentration-response. In addition, thorough QT studies need to be placebo controlled[7] and since the duration of the QT interval at baseline has been shown to follow a circadian rhythm[11, 25], serial time-matched measurements are mandatory for any placebo-corrected evaluation. Therefore, all of the thorough QT studies are based on numerous ECG recordings. The ICHE14 document expresses a concern on using data from ambulatory ECG recordings since QT interval durations from Holter ECG might not quantitatively correspond to those from standard ECG[7]. In the present study, we made use of long term ambulatory ECG recordings from which 12-lead ECGs were extracted every minute. This method is referred to as the Time-Bin approach. We could obtain a much larger number of data points that what is normally available from the standard thorough QT design using serial ECG recordings. The sotalol-induced QTc prolongation reported in the present study are very similar to those published on the same

database but using the "conventional" approach based on serial resting 10-second ECG recordings[20].

ECGs recorded at the same time-point in the same subject do not necessarily have the same heart rate, thus requiring the application of heart rate correction formula. Since the relationship between HR and QT duration has been shown to be highly individual, the current best strategy for HR-correction is to use a subject-specific correction formula[15, 26-29]. However, our results seem to indicate that the individual correction formula applied on placebo QT data condition cannot be systematically used for QT data on drug. Indeed, it is well known that blockers of the potassium current change the relationship between HR and QT duration[30]. This effect is well documented with sotalol[31] and the increase in the QT rate-dependence was also evidenced in the present study. Furthermore, we show that using the off-drug instead of the on-drug correction formula led to an "underestimation" of drug-induced QT prolongation. Figure 5 illustrates this phenomenon in the individual subject from our study. Because the QT rate-dependence was less pronounced on placebo, the placebo correction formula led to an incorrect estimation of the sotalol effect. Correction from HR<60 bpm led to an overestimation of QT duration whereas correction from HR>60 bpm to an underestimation. In the present study, the mean RR interval on sotalol was slightly below 1000 ms (HR of 60 bpm) with a distribution close to the normal. Accordingly, more QT intervals have been corrected from faster heart rates than from slower heart rates, thus leading to an "underestimation" of sotalol-induced QT prolongation.

Using the optimum HR-correction strategy (i.e. a different HR correction formula for each subject on placebo and on drug) is associated with different pitfalls. The relationship between HR and QT duration is not only subject-specific, but also shows circadian (day/night) variations[32, 33] where even hourly changes have been reported[25]. In the present study, the QT values derived by the HR-correction formula on placebo were significantly

different between the first 2-hour period versus the subsequent 2-hour period. As a consequence, applying the same HR-correction at different time-points for a given subject may result in bias. Moreover, on top of physiologic variations, pharmacokinetic / pharmacodynamic considerations may also have detrimental consequences in a single dose trial. In our study, the effect of sotalol on ventricular repolarization was not constant through the 4-hour observation period in spite of having defined the period according to pharmacokinetic data. This problem was worsened by a delayed Emax from Tmax. Again, using a unique "on-drug" HR-correction formula while the drug's concentration changes may induce a potential bias.

Repeated assessment of the QT/RR relationship from appropriately short observation periods may overcome these drawbacks. However, narrowing the observation period is associated with a decrease in the number of QT/RR pairs available from each period, leading to a less precise evaluation of the QT/RR relationship. On the same data as reported in the present study, Couderc et al. have shown that a large number of QT/RR pairs together with a wide range of RR intervals are required for a reliable individual correction model[34]. The use of a moving time-window for QT/RR relationship assessment may be a solution to get a better time definition for the α coefficient but again keeping in mind the need for a sufficient range of RR intervals.

In summary, even the best currently known strategies for detecting the time course of drug-induced QT prolongation is inherently associated with an imprecision in the HR-correction process.

4.2. The Rate Binning approach

The Holter-based so-called Rate Bin approach had been originally developed by our group to better characterize the relationship between HR and QT duration[22, 33, 35, 36].

Subsequently, this method has been used as an alternative approach to measure rate-independent estimates of QT interval changes under treatment[17]. The main benefit brought about by this method is to allow direct comparison of ECG samples at identical HR, thus avoiding the need for any QT correction formulae. Therefore, no mathematical models are required and no assumptions on the properties and stability of the QT/RR relationship are necessary. In contrast to the Time Bin approach, the Rate Bin method is not hampered by the potential effect of the drug on the relationship between QT interval and heart rate. Although the calculation of the QT rate-dependence is not required with the Rate Bin approach, it may easily be computed to provide similar results as those obtained with the Time Bin approach. The main advantage of the Rate Bin method is the capability of emphasizing the influence of heart rate on drug's effect. Our data show that the sotalol-induced QT prolongation was more pronounced at slow than at fast HRs. This phenomenon known as the "reverse rate dependent effect" has been long recognized with class III antiarrhythmic drugs[31, 37] and has been demonstrated even with weak IKr blocker such as moxifloxacin using the Rate Bin method[24, 28].

In spite of its conceptual advantages the Rate Bin approach has been criticized[19]. An intrinsic limitation of the method is represented by the impossibility of QT comparisons when there are not overlapped RR intervals. This might be the case with drugs that dramatically change HR, although it is very unlikely provided that the QT comparison might be performed at any heart rate (i.e. not necessarily at RR=1000 ms).

The second, more significant drawback is that the averaging process leads to a complete loss of the time course of drug effect. Consequently, the largest time-matched mean difference between the drug and placebo cannot be assessed.

A potential solution to improve the analysis of the time course of drug's effect on QT prolongation would be to narrow the time window of Rate-Binning. However, a shorter

observation period might result in missing QT measurements at some heart rates (RR Bins), thus making the comparison with placebo data difficult. The Rate Bin approach is therefore not perfect, as while on one side it solves the HR-correction problem on the other the price paid is a loss of at the cost of the precision of temporal assessment.

4.3. The ΔQT/ΔRR plots

The intercept of the linear ΔQT/ΔRR relationship is a standard use of an analysis of covariance that has been proposed as the rate-independent point estimate of drug-induced QT change[17]. Its simplicity has made this method attractive; yet, it has been so far poorly evaluated and seldom used for thorough QT studies. One legitimate issue about this method is whether it should be calculated on a population- or a subject-specific basis. The population based approach includes many ΔQT/ΔRR pairs and thus provides narrow confidence intervals. However, the patho-physiological meaning of such results is difficult to understand whereas the calculation of the mean of individual point estimates is more intuitive. With the individual approach the number of ΔQT/ΔRR pairs is dramatically decreased and the accuracy of each individual point estimate might be questionable. So far, the minimum number of pairs required for a fair estimation of drug effect has not been determined. The present study included ECG data from 240 time-points for each subject, and both population- and subject-specific approaches provided very similar point estimates of sotalol-induced QT prolongation, although their boundaries were quite different.

Because of the very large number of ΔQT/ΔRR pairs available with the population approach, it is easy to narrow the observation period. We could thus confirm with the 2-hour point estimates the heterogeneity of sotalol effect over the 4-hour period observed by using the time bin method. However, further narrowing of the observation period would lead to a loss of accuracy as a consequence of reduction of the number of ΔQT/ΔRR pairs mainly with

the subject-specific approach. Therefore, as with the Rate Bin method, the time course of drug effect is lost by using the point estimate approach.

In addition, the point estimate method represents a mix of drug's effect at various heart rates and cannot always be compared to an effect at the corrected QT interval or at a 1000 ms RR interval.

Finally, the Point Estimate approach combines the disadvantages of the loss of time track of Rate Binning and as with the Time Bin approach, it provides no data on rate influences on drug's effect.

4.4. Study limitations

The main limitation is represented by the potent IKr block effect of sotalol. The magnitude of the potential disadvantages of each method described in the present study may not be the same with weaker potassium current blockers. Nevertheless, the limitations underlined in the present study are inherent to each method.

It should be recognized that some of the method-related discrepancies observed in single dose trials may not be valid for repeated dose trials. Our study does not include a pharmacokinetic/pharmacodynamic model and some of sotalol effects on QT duration as well as QT/RR relationship may be dependent on its concentration. However, our placebo data underline that ventricular repolarization properties change within a few hours independently of drug's concentration. Therefore, similar changes in the QT/RR relationship may be also observed at drug's steady state concentration. In addition, as discussed earlier, with fast changing drug's concentration both the Rate and Time Bins approaches would have been hampered by using short time-windows.

4.5. Conclusion

The evaluation of drugs' influences on QT interval duration is a difficult process due to the complex properties of ventricular repolarization and its modulation by ionic channel blocking drugs. No currently used ECG method can be considered as free of pitfalls. The individual correction formula calculated from placebo condition cannot always be used for QT correction on drug. In the other hand, the Rate Bin approach is characterized by a loss of the precision of temporal assessment. In that respect, the combination of different approaches seems to be a reasonable strategy. The recording of long continuous ECGs as provided by digital 12-lead Holter technology would be appropriate for a primary analysis in the thorough QT study or as a support for additional analyses.

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Figure legends

Figure 1.

Mean QTcNi over the 240 minute observation period on placebo (white triangles) and on sotalol (black triangles). QTcNi on sotalol was calculated using the αNi coefficient calculated on sotalol (QTcNi-ON).

Figure 2. Time binning. Mean sotalol effect

Mean sotalol-induced QT and corrected QT change (ΔQT and ΔQTc) over the 240 minute observation period. QTcB=Bazett correction formula, QTcF=Fridericia correction formula, QTcNi-ON=subject-specific and drug-specific correction formula.

Figure 3. Mean ΔQTcNi over the 240 minute observation period using a separate individual correction formula for placebo and sotalol (ΔQTcNi–ON) and using the placebo individual correction formula to correct the QT interval while on sotalol (ΔQTcNi–OFF).

Figure 4. Rate binning.

Mean±95% Confidence interval of sotalol-induced QT changes at different RR intervals. The sotalol-induced QT prolongation was more pronounced at slow than at fast heart rates.

Figure 5. QT/RR relationship on placebo (gray line) and on sotalol (black line) in a single subject.

The dotted lines represents QT normalization to RR=1000ms according to the placebo QT/RR relationship. Using the placebo correction formula led to an incorrect estimation of sotalol

effect. Correction from RR>1000 ms led to an overestimation of QT duration whereas correction from RR<1000 ms to an underestimation.

Table 1. Correction formulae individual α coefficients – Time Binning approach

	Placebo	Sotalol 160 mg
Subject-specific 0-4 H	0.309±0.052 Range (0.197; 0.416)	0.454±0.136* Range (0.208; 0.783)
Subject-specific 0-2 H	0.293±0.073 Range (0.016; 0.433)	0.349±0.201 Range (0.001; 0.827)
Subject-specific 2-4 H	0.247±0.078† Range (0.046; 0.389)	0.298±0.151† Range (-0.026; 0.515)

Mean±SD

*$p<0.0001$ versus placebo

†$p<0.05$ versus 0-2 H

Table 2. RR and QT changes using the Time Binning approach

		Placebo	**Sotalol 160 mg**	**Delta**
RR	T1	890±114	914±147	23.8 [-32.6; 80.2]
	T60	830±135	1008±117**	178.0 [127.0; 229.0]
	T120	847±111	1030±114**	183.7 [152.7; 214.7]
	T180	819±118	993±135**	173.6 [116.2; 231.0]
	T240	798±108	916±132**	117.6 [73.0; 162.2]
QT	T1	384±22	390±35	6.0 [-4.9; 16.9]
	T60	376±27	417±34**	41.3 [30.3; 52.3]
	T120	374±25	431±35**	57.5 [48.8; 66.2]
	T180	369±27	427±29**	57.8 [45.7; 69.9]
	T240	365±25	407±28**	41.4 [32.2; 50.6]
QTcF	T1	401±18	404±22	2.9 [-2.8; 8.6]
	T60	401±21	416±28**	15.5 [9.0; 22.0]
	T120	396±20	428±32**	32.0 [23.8; 40.2]
	T180	395±18	429±28**	40.0 [31.7; 48.3]
	T240	394±24	413±46*	19.4 [10.2; 28.6]
QTcNi ON	T1	399±16	414±31*	15.1 [6.5; 23.7]
	T60	404±19	424±28**	20.1 [12.2; 28.0]
	T120	401±22	435±30**	34.6 [24.8; 34.4]
	T180	400±22	435±28**	35.0 [24.7; 45.3]
	T240	396±23	428±32**	32.9 [21.1; 44.7]
QTcNi OFF	T1	399±16	403±23	3.4 [-2.8; 9.6]
	T60	404±19	417±28*	13.3 [3.5; 22.1]
	T120	401±22	429±32**	27.7 [12.2; 41.2]
	T180	400±22	429±28**	29.9 [14.8; 45.0]
	T240	396±23	419±28*	23.7 [11.2; 36.2]

Mean ± SD

*p<0.05 **p<0.0001 - paired tests

Numbers in brackets indicate the 95% Confidence Interval

Table 3. QT changes using the Rate Binning approach

	QT placebo	**QT sotalol**	**Delta QT**
RR=700 ms	350.2±17.9	367.6±24.6	21.3±10.0 [14.4; 28.2]
RR=800 ms	368.4±14.2	394.8±22.7	27.3±15.4 [21.1; 33.5]
RR=900 ms	380.9±15.2	412.8±25.1	31.6±14.9 [26.2; 37.0]
RR=1000 ms	393.5±10.6	428.9±20.1	32.6±12.3 [26.6; 38.6]
RR=1100 ms	410.5±11.3	444.1±24.2	27.6±17.1 [14.9; 40.3]

Mean±SD

Numbers in brackets indicate the 95% Confidence Interval

Table 4. Intercept of the ΔQT /ΔRR relationship

	0–4 hour time-window	**0–2 hour time-window**	**2–4 hour time-window**
Population Point Estimate	22.4 IC95%[21.6; 23.1]	12.9 IC95% [12.0; 13.7]	37.6 IC95% [36.3; 38.9]
Subject-specific Point Estimate	23.0±14.2 Range (-9.8; 52.0)	17.3±15.1 Range (-9.0; 55.3)	37.1±18.5 Range (-16.1; 71.9)

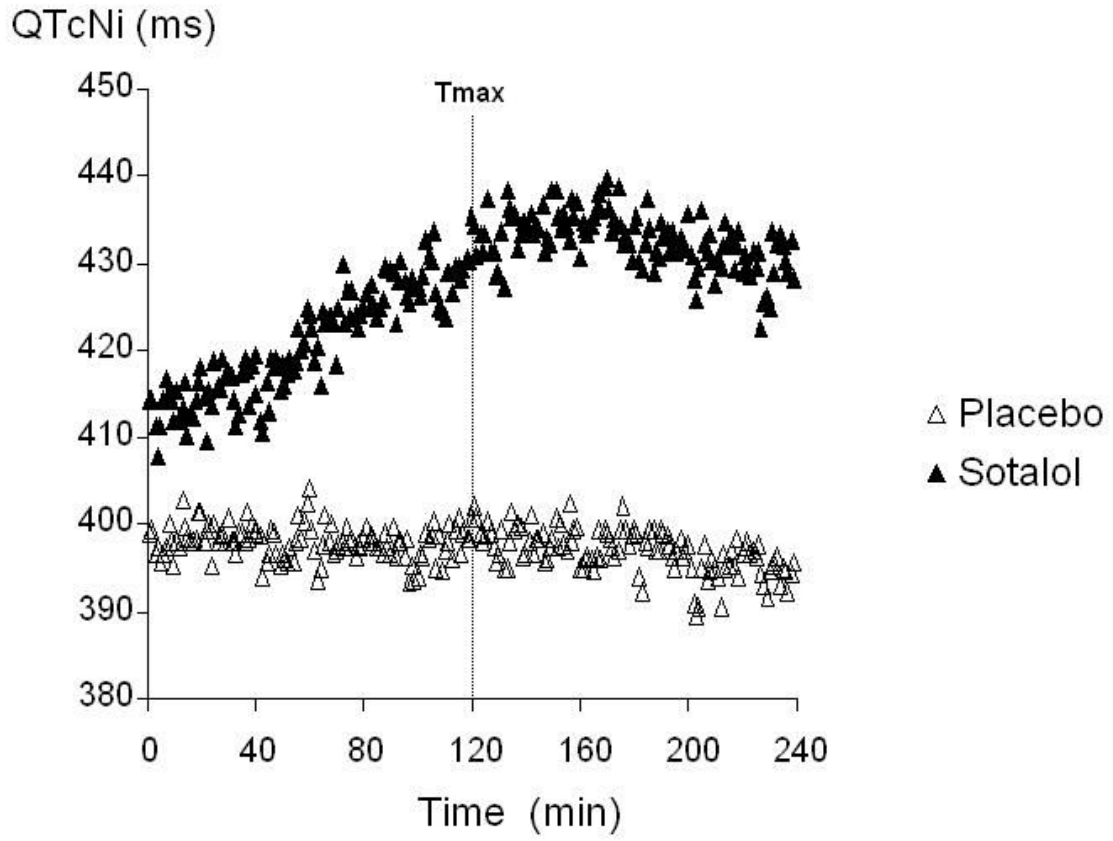

QTcNi (ms)
450
440
430
420
410
400
390
380
Tmax
0
40
80
120
160
200
240
Time (min)
Placebo
Sotalol

Figure 1

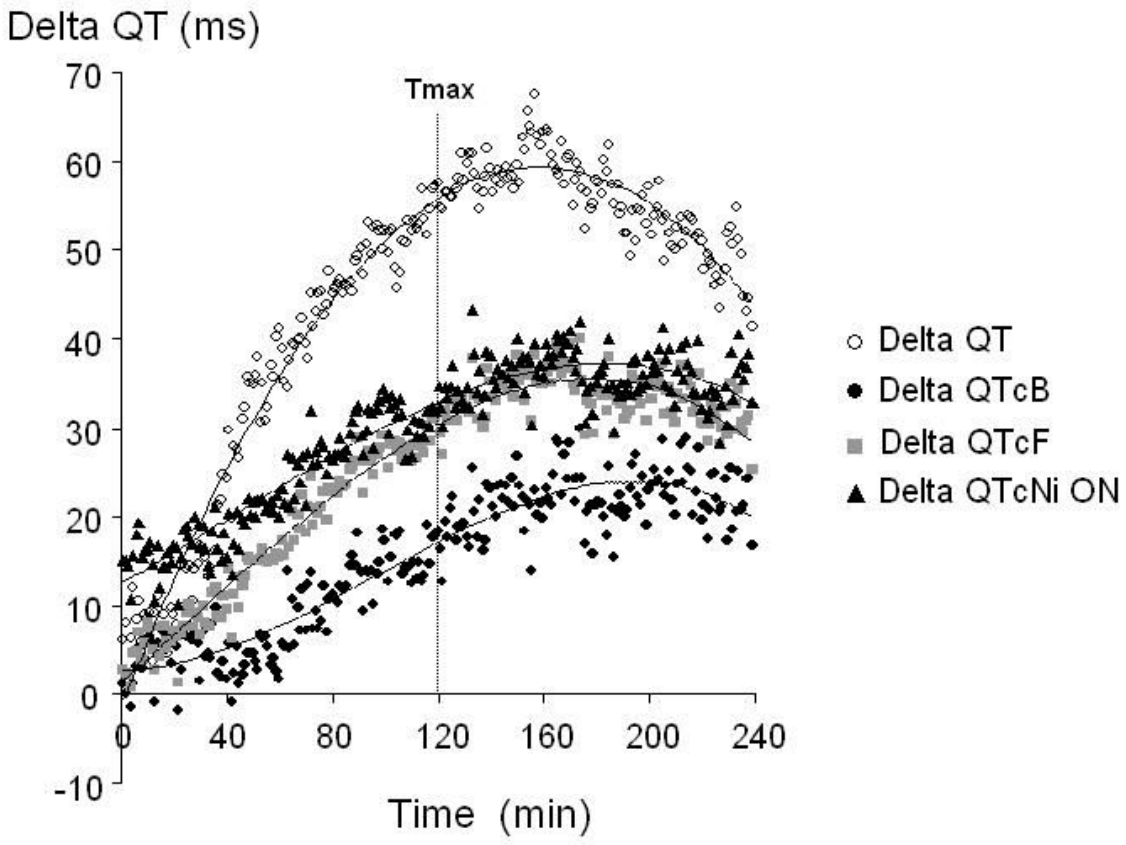

Delta QT (ms)
70
60
50
40
30
20
10
0
-10
Tmax
0
40
80
120
160
200
240
Time (min)
Delta QT
Delta QTcB
Delta QTcF
Delta QTcNi ON

Figure 2.

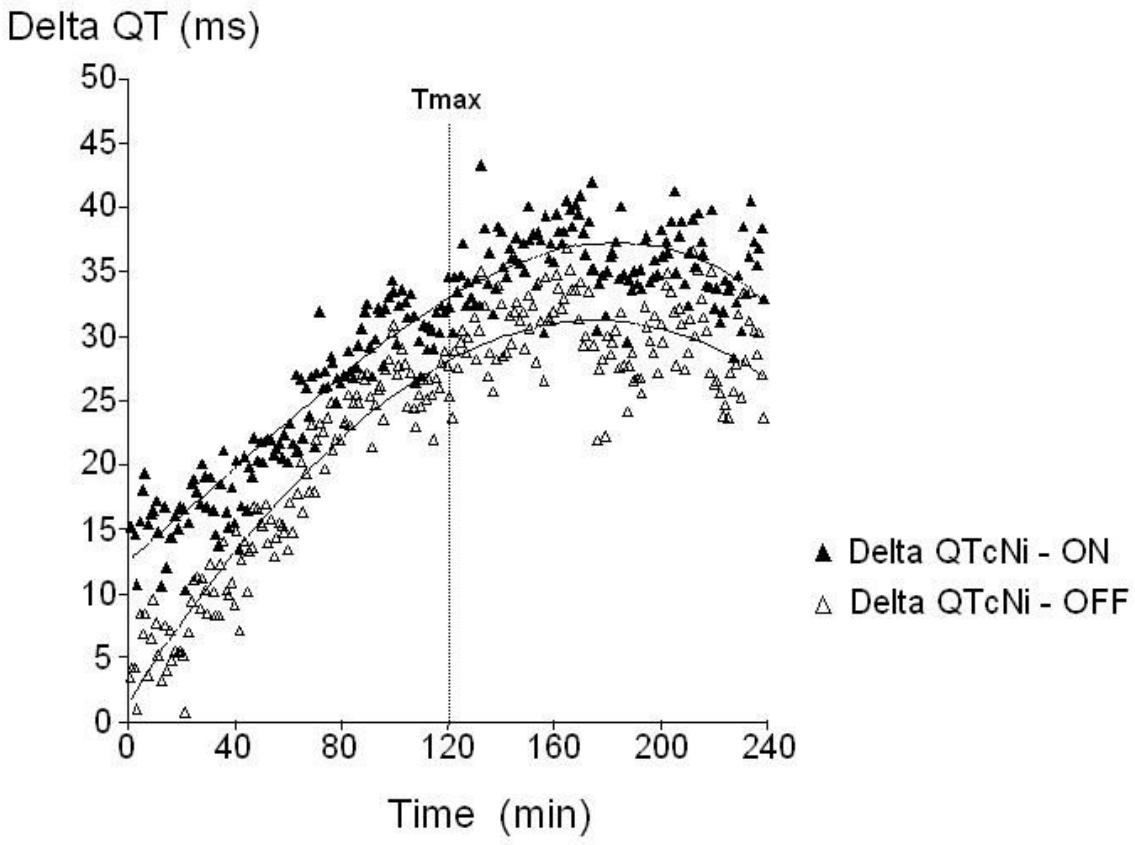

Delta QT (ms)
Tmax
50
45
40
35
30
25
20
15
10
5
0
0
40
80
120
160
200
240
Time (min)
Delta QTcNi - ON
Delta QTcNi - OFF

Figure 3.

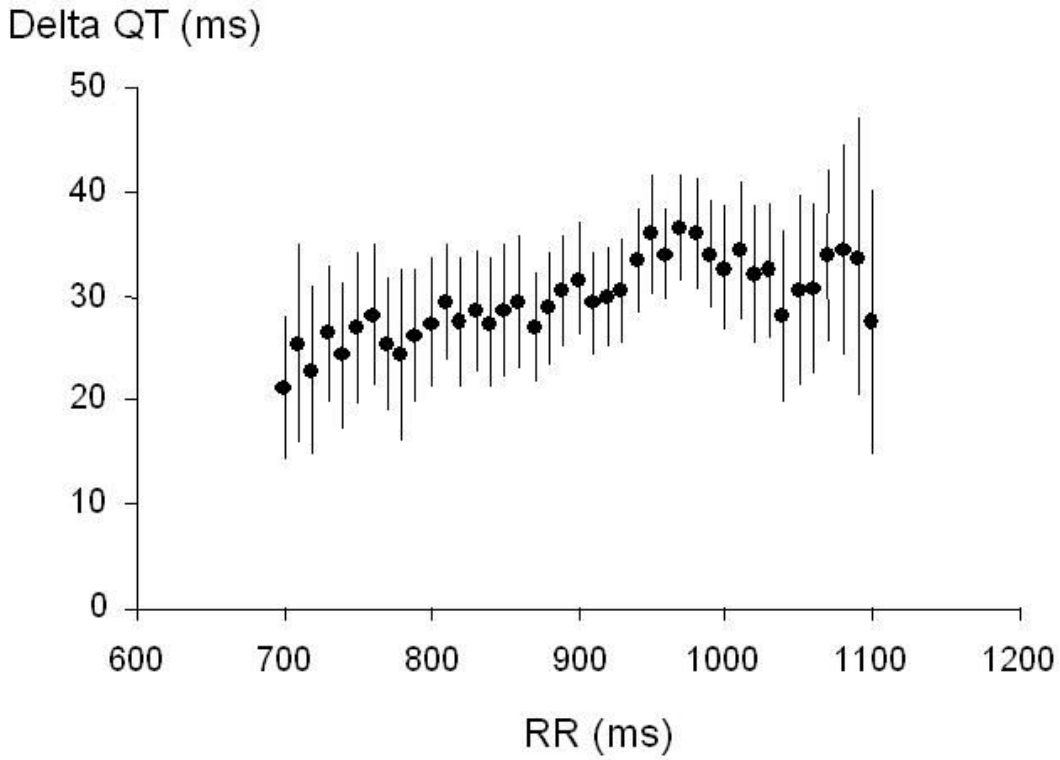


Figure 4.

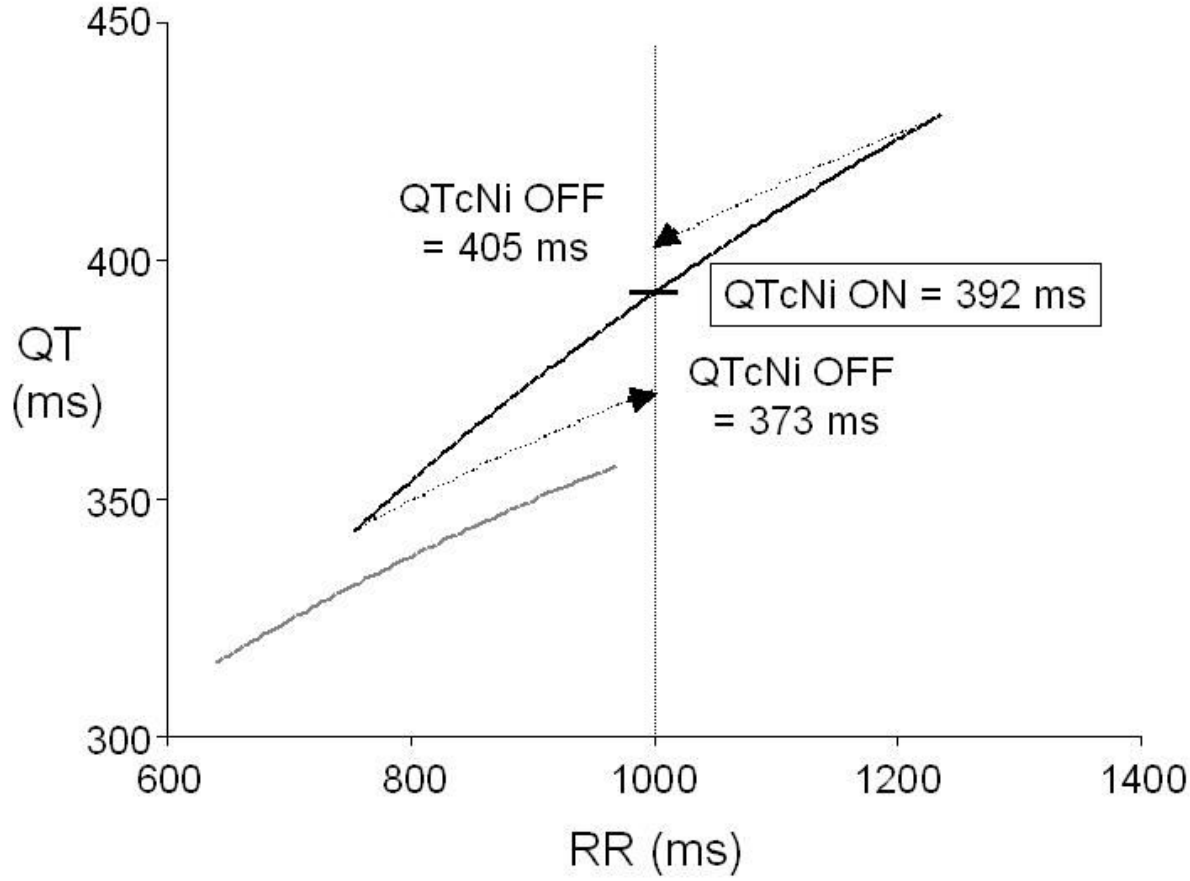
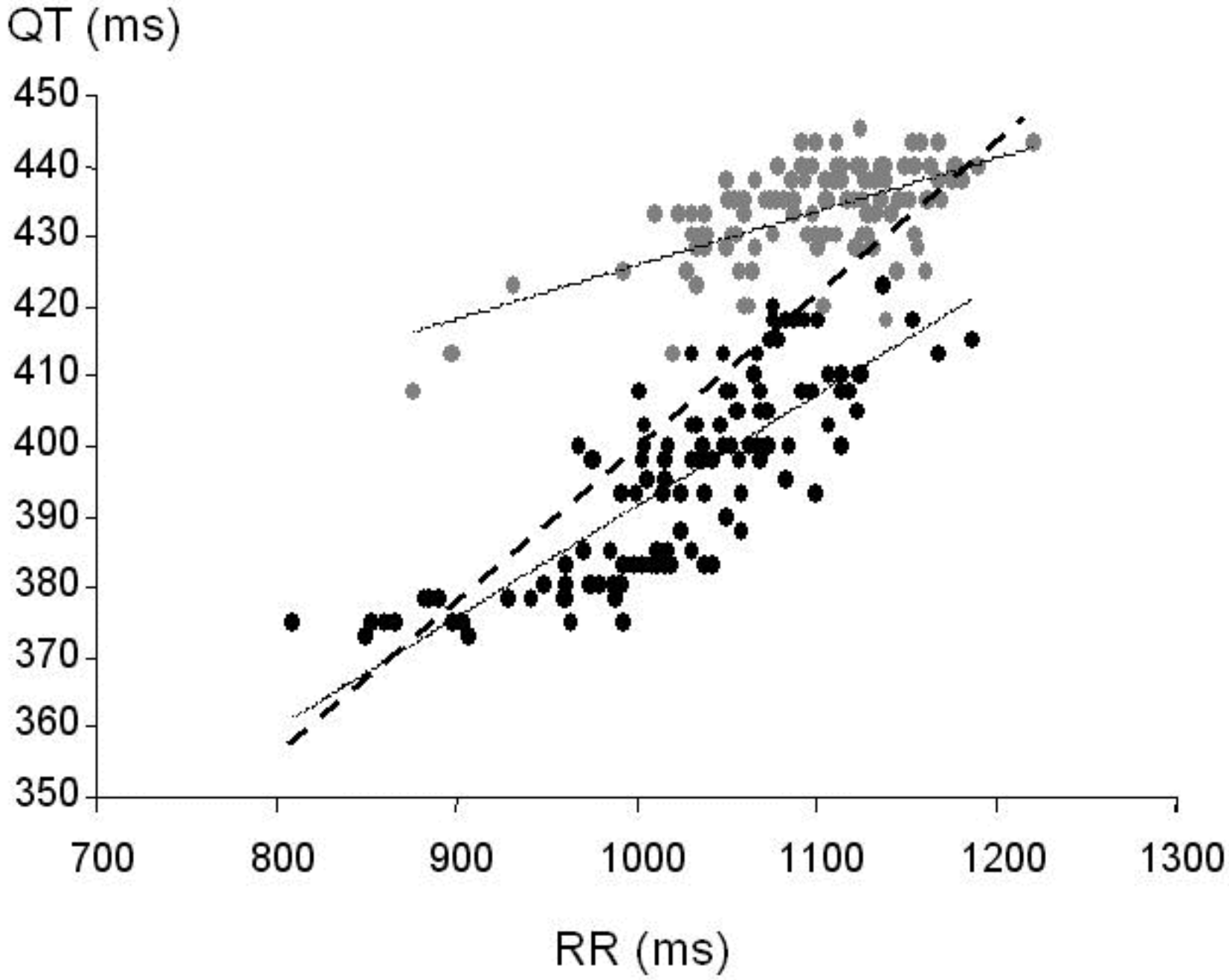
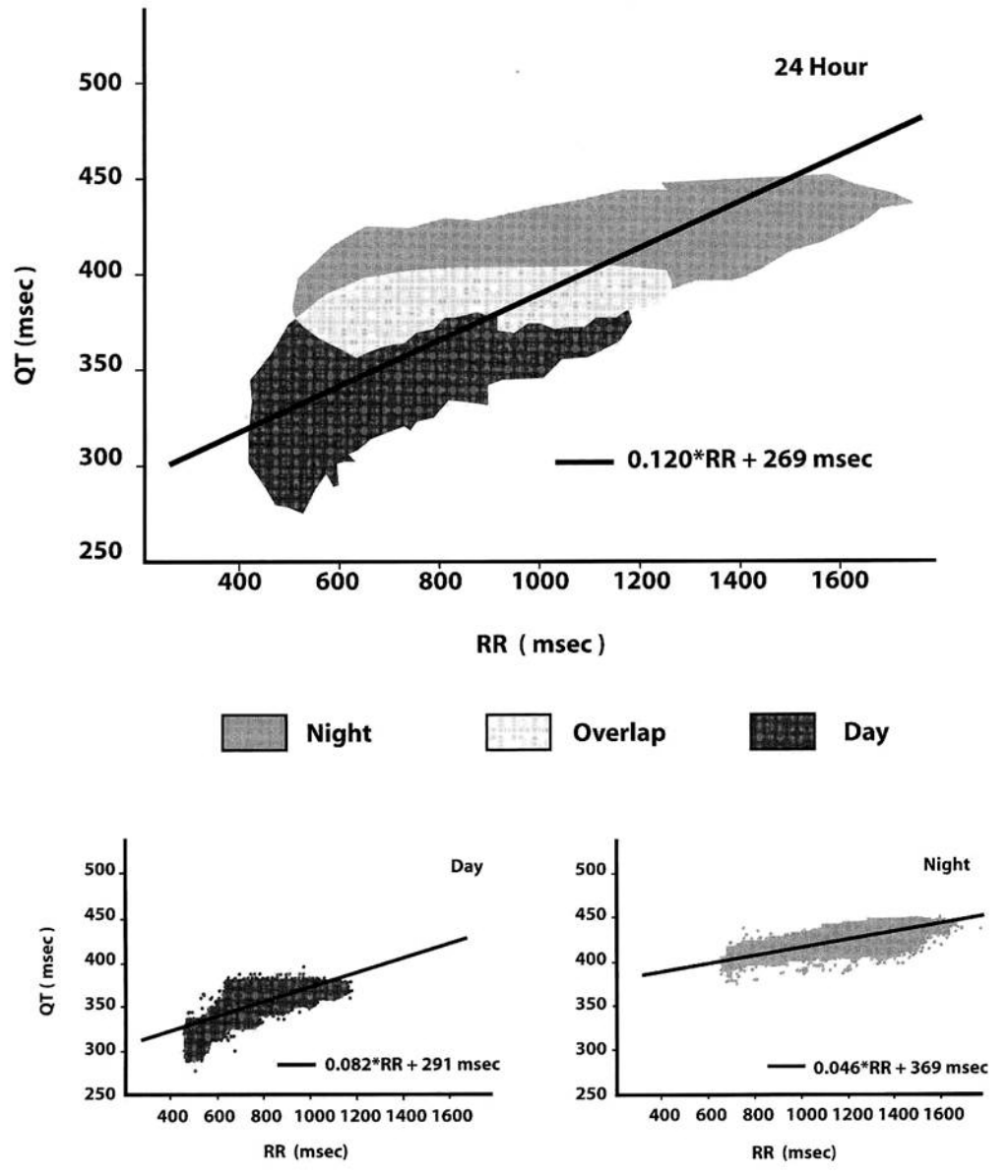

450
400
350
300
QT
(ms)
600
800
1000
1200
1400
RR (ms)
QTcNi OFF
= 405 ms
QTcNi ON = 392 ms
QTcNi OFF
= 373 ms

Figure 5.


QT (ms)
450
440
430
420
410
400
390
380
370
360
350
700
800
900
1000
1100
1200
1300
RR (ms)


24 Hour
QT (msec)
500
450
400
350
300
250
400
600
800
1000
1200
1400
1600
RR (msec)
0.120*RR + 269 msec
Night
Overlap
Day
Day
QT (msec)
0.082*RR + 291 msec
RR (msec)
Night
0.046*RR + 369 msec
RR (msec)