

# Effect of QT Interval Correction during Autonomic Blockade in Combination with Changes in Posture

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## Abstract

*The measurement of QT interval on ECG is a marker for malignant ventricular arrhythmias. When QT is measured, it must be corrected to become independent of heart rate (HR) and become a comparable measure of repolarization between different conditions. The objective of this work was to evaluate different types of QT interval correction (Bazzett, Individual and Hodges) for different QT/RR relations. This was accomplished with selective blockade of sympathetic and vagal autonomic systems by using combinations of postural changes and drugs. When comparing vagal condition (supine) versus sympathetic condition (standing atropine) a significant shortening of 43 ms ( $P < 0.006$ ) was observed. Whereas when comparing sympathetic (standing) versus vagal condition (supine propranolol) a significant lengthening of 23 ms ( $P < 0.005$ ) was observed. The Individual correction method achieved the best uncorrelation between QT and RR interval, making QT more independent of HR and ANS status.*

## 1. Introduction

There was many efforts to find a unified method of QT interval correction [1] useful in a wide range of heart rate (HR) values. The goal of QT interval correction is to convert each measured interval to a standard value ( $QT_c$ ), making differences in  $QT_c$  only due to sympato-vagal status differences and not on HR, making possible inter or intrasubject comparisons. Although this problem is clearly formulated, a satisfactory solution has not been found yet. The precise measurement and correction of QT interval is highly important because it indicates different cardiac abnormalities [2]. Short QT values could happen due to a premature repolarization, in such cases the T wave starts right after QRS complex ends, no ST segment exists in such cases. Otherwise, exists many causes of long QT interval [3]. Clinical mean for this syndrome is highly variable. It can be related to many drugs, like the amiodarone which is an antiarrhythmic. In post infarct patients, long

QT interval may represent a presumable risk factor. In cases of patients with congenital long QT, a high probability to develop malicious ventricular arrhythmias or sudden death has been observed. Also there are studies with drugs which modify QT interval, where the use of a bad correction method may induce erroneous conclusions about the effect of drugs[1]. In this work QT interval was measured when autonomic nervous system (ANS) has been blocked with a combination of drugs and postural changes [4]. Atropine and propranolol were used to block vagal and sympathetic systems respectively, while subjects were in standing and supine position. This pharmacological and postural combination is useful to explore QT interval correction techniques within different ANS status. Three correction techniques were studied simultaneously: Bazzett, Hodges and Individual.

## 2. Methods

### 2.1. Experimental protocol

The database used in this work proceed from a previous work [5] where the regulation mechanism of the autonomic nervous system was studied. Electrocardiogram (ECG) recordings were made on 13 adult subjects (age between 19 and 39, median 21 years). Standard surface ECG activity was filtered for anti aliasing purposes at 180 Hz, and sampled at a frequency of 360 Hz with an amplitude resolution of 8 bits. Those recordings were made during autonomic nervous system blockade by using pharmacological (atropine, propranolol) and postural (supine, standing) combinations. The ECG recordings were made of the following way: a) All subjects were measured in supine control position (SUC) then were moved to the standing control position (STC) and measured after 5 min for hemodynamic equilibration. b) Then all subjects were returned to the supine position and given either atropine (0.03 mg/kg, n=7) or propranolol (0.2 mg/kg, n=6) reaching SUA and SUP condition respectively. Both groups were measured after 10 min for equilibration. c) Finally all subjects were moved to the standing position, and af-

ter 5 min for hemodynamic equilibration STA and STP conditions were reached respectively and measured. The database used in this work contains 52 *ECG* recordings of 7 minutes each.

## 2.2. ECG processing

The measurements of *RR* and *QT* intervals were made automatically with a program developed in our laboratory in R language [6]. First of all, *ECG* recordings were smoothed with a moving average filter ( $Y[n] = \frac{1}{17} \sum_{j=0}^{16} X[n-j]$ , cutoff frequency 10 Hz). Isoelectric baseline movement was removed from the *ECG* signals after interpolating this movement with cubic spline algorithm. First the R wave was detected and then *RR* intervals were calculated for the whole recording. Only those beats that accomplished that  $RR[i] > 450 \text{ ms}$  ( $HR < 133 \text{ bpm}$ ) and  $RR[i] > 0.75 * RR[i-1]$  were analyzed. Before measuring *QT* interval, *Q* peak (*Q*) and the end of *T* wave ( $T_e$ ) were detected. To ease the detection of the  $T_e$  point, a window that is function of the  $RR[i]$  interval was used. The current *RR* interval is defined by:

$$RR[i] = t[i] - t[i-1] \quad (1)$$

Where  $t[i]$  is the current *R* peak time position. The start and the end of the *T* wave window is the defined by:

$$W_{Ton}[i] = t[i] + RR[i] * 0.06 \quad (2)$$

$$W_{Tend}[i] = t[i] + RR[i] * 0.3 \quad (3)$$

The fiducial points were detected analyzing the first and second differentiated *ECG* signal ( $X_{D1}[n]$  and  $X_{D2}[n]$  respectively). To obtain differentiated signals  $H_{D1}[z] = 1 - z^{-12}$  and  $H_{D2}[z] = 1 - z^{-10}$  where applied to the *ECG* signal. Peak locations of monophasic ( $TP1[i]$ ) and biphasic ( $TP1[i]$  and  $TP2[i]$ ) *T* waves were detected with the zero crosses of  $X_{D1}[n]$  that are bounded by the window defined by  $W_{Ton}[i]$  and  $W_{Tend}[i]$ . The  $T_e[i]$  detection window was between the  $TP1[i]$  and  $W_{Tend}[i]$  for monophasic and between  $TP2[i]$  and  $W_{Tend}[i]$  for biphasic. In this window, the maximum absolute value of  $X_{D1}[n]$  ( $X_{D1}^{max}[i]$ ) was sought by detecting zero crosses of  $X_{D2}[n]$ . Then a linear function was:

$$y[n] = X_{D1}^{max}[i] * n + b \quad (4)$$

Where  $b$  is a constant that fits the signal in the point of maximum slope ( $X_{D1}^{max}[i]$ ). Finally the intersection of (4) with the isoelectric line of the *ECG* determines the value of  $T_e[i]$ . The *Q* peak was detected looking for  $X_{D1}[n]$  zero crosses within  $W_{Qon}[i]$  and  $W_{Qend}[i]$ .

$$W_{Qon}[i] = t[i] - RR[i] * 0.2 \quad (5)$$

$$W_{Qend}[i] = t[i] \quad (6)$$

The ascending zero cross closest to  $W_{Qend}[i]$  is assumed as *Q* peak. This *Q* peak point was used as beginning of *QT*

interval due to robustness in automatic *ECG* delineation. This *QT* interval estimation was assumed as equivalent to the standard definition. Then  $QT[i]$  is measured as:

$$QT[i] = T_e[i] - Q[i] \quad (7)$$

For those *T* waves where the algorithm failed the detection of  $T_e$  point, an experimented observer annotated all fiducial points with a software designed for this purpose.

## 2.3. QT interval correction

Once measured *QT* interval, it is corrected by three methods ( $QT_c$ ): Bazzett [7], Individual [8] and Hodges [9]. For Bazzett and Individual corrections, a parabolic function like (8) is used.

$$QT_c[i] = \frac{QT[i]}{RR[i]^\alpha} \quad (8)$$

Bazzett correction is for *RR* in seconds, and  $\alpha = 0.5$ . In the case of Individual correction  $\alpha$  value is calculated for each subject searching for the minimum value of coefficient of determination ( $r^2$ ) between  $QT_c$  and *RR*. Hodges correction can be calculated as:

$$QT_c[i] = QT[i] + \frac{1.75(1 - RR[i])}{1000} \quad (9)$$

## 2.4. Statistical analysis

Paired t test were evaluated between each drug condition (atropine or propranolol) and its control. Values were expressed as  $mean \pm sd$  and values of  $P < 0.05$  were considered significant.

## 3. Results

Tables 1 and 2 shows the results of measuring *RR* interval, and calculating  $QT_c$  by Bazzett ( $QT_{cB}$ ), by Individual correction ( $QT_{cI}$ ) and by Hodges ( $QT_{cH}$ ).  $\Delta QT_c$  stands for the mean of  $QT_c$  in drug minus  $QT_c$  in control condition, so it would indicate the effect of drug supply to the control group. For supine and standing condition the *RR* interval decreased and increased significantly for atropine and propranolol supply respectively. Bazzett's and Individual correction only showed any significant difference in propranolol condition. For standing condition only Hodges correction for atropine condition did not detect significant differences. In table 3 when comparing mainly vagal condition for control group (SUC) versus mainly sympathetic condition in drug (STA) only  $QT_{cI}$  showed significant shortening of 43 ms ( $P < 0.006$ ). Whereas when comparing mainly sympathetic (STC) versus mainly vagal condition (SUP) only Hodges did not show any difference while for Individual a significant lengthening of 23 ms ( $P < 0.005$ ) was observed. The Individual technique achieved better uncorrelation within each recording among correction techniques (Figure 1) being the most suitable to compare conditions.

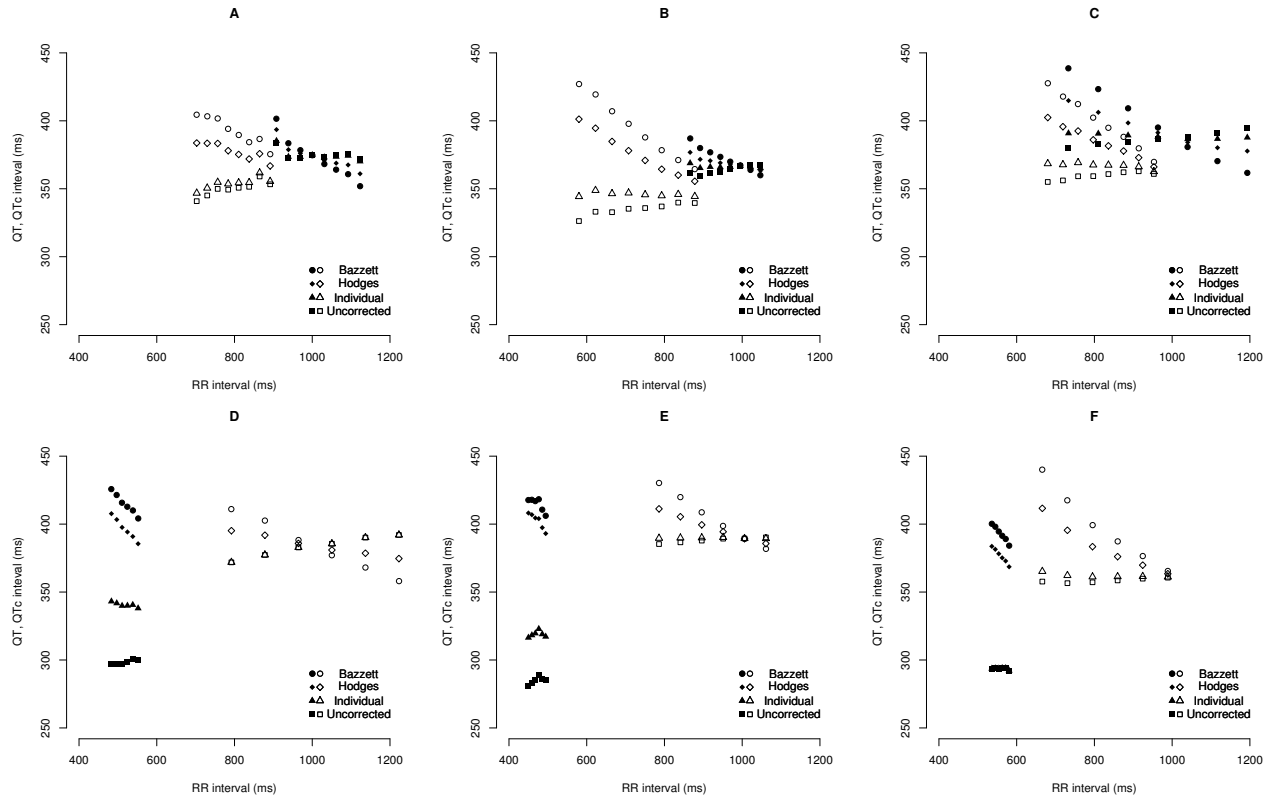


Figure 1. Six  $QT/RR$  patterns from subjects in control (empty fill) and drug (filled) conditions. Points belongs to the mean of  $QT$  and  $QT_c$  by all formulas taken from RR bins ranging from 10 to 50 ms. Panels A, B and C are subjects from STC and SUP group, while D, E and F are from SUC and STA group.

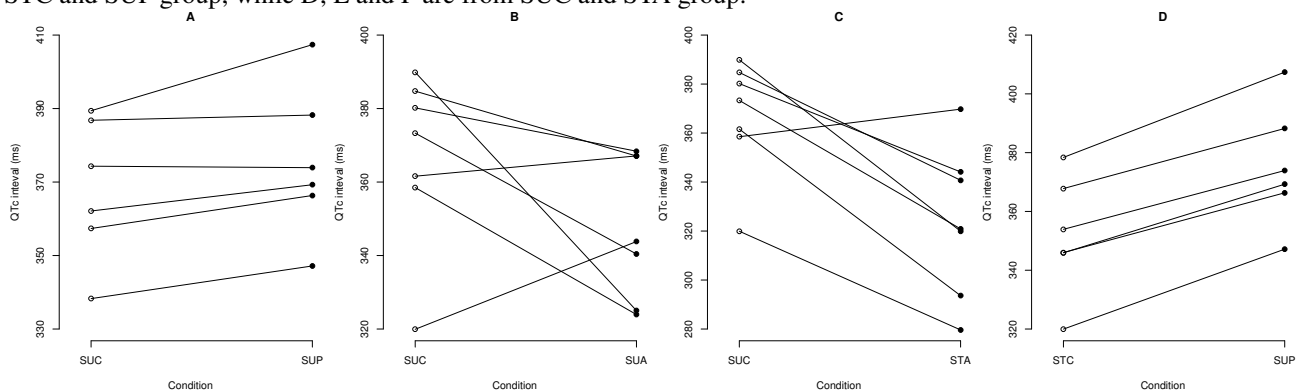


Figure 2. Values for  $QT_{cI}$  before and after drug supply in supine and standing position. In panel A and B atropine and propranolol supply is compared for supine position. Changes from mainly vagal to mainly sympathetic and viceversa are shown in panel C and D respectively.

#### 4. Discussion and conclusions

The  $\beta$ -blockers, like propranolol, are antagonistic of sympathetic system. Studies with the same drugs were performed in [10] where  $QT$  interval was calculated at 6 paced cycle lengths, sympathetic tone did not seem to interfere significantly whereas vagal tone increased intrinsic dependence of  $QT$  interval at increasing cycle length. A recent research work that compares the effect of different correction formulas suggested that  $\beta$ -blockers do not af-

fect  $QT$  interval when it is properly corrected [1]. Moreover other work indicated that  $QT/RR$  patterns exhibits substantial intrasubject stability and intersubject variability (figure 1) making Individual correction convenient [11]. Our results are in concordance with these results (figure 2). In this work we considered only a parabolic regression model in the individual correction situation to fit  $QT/RR$  patterns, this limitation is reflected in many cases where individual correction can not uncorrelate  $QT$  from  $RR$

Table 1. Comparison of control and atropine condition for different postures.  $\Delta QT_c$  is calculated as the mean of  $QT_c$  with drug supply minus  $QT_c$  in control condition. Results in ms as mean  $\pm$  sd.

|                        | SUC           | SUA                        | $\Delta QT_c$ | STC          | STA                       | $\Delta QT_c$ |
|------------------------|---------------|----------------------------|---------------|--------------|---------------------------|---------------|
| <i>RR</i>              | 851 $\pm$ 137 | 604 $\pm$ 139 <sup>‡</sup> | -             | 690 $\pm$ 57 | 502 $\pm$ 57 <sup>‡</sup> | -             |
| <i>QT<sub>cB</sub></i> | 395 $\pm$ 7   | 404 $\pm$ 25               | 9             | 411 $\pm$ 11 | 400 $\pm$ 13*             | -11           |
| <i>QT<sub>cI</sub></i> | 367 $\pm$ 24  | 348 $\pm$ 20               | -18           | 359 $\pm$ 13 | 324 $\pm$ 31*             | -35           |
| <i>QT<sub>cH</sub></i> | 385 $\pm$ 6   | 389 $\pm$ 13               | 5             | 390 $\pm$ 9  | 390 $\pm$ 16              | 8             |

\* ( $P < 0.05$ ); <sup>†</sup> ( $P < 0.005$ ); <sup>‡</sup> ( $P < 0.0005$ )

Table 2. Comparison of control and propranolol group for different postures.  $\Delta QT_c$  is calculated as the mean of  $QT_c$  with drug supply minus  $QT_c$  in control condition. Results in ms as mean  $\pm$  sd.

|                        | SUC          | SUP             | $\Delta QT_c$ | STC           | STP                       | $\Delta QT_c$ |
|------------------------|--------------|-----------------|---------------|---------------|---------------------------|---------------|
| <i>RR</i>              | 911 $\pm$ 73 | 1039 $\pm$ 145* | -             | 796 $\pm$ 105 | 912 $\pm$ 88 <sup>‡</sup> | -             |
| <i>QT<sub>cB</sub></i> | 382 $\pm$ 11 | 371 $\pm$ 16*   | -11           | 387 $\pm$ 9   | 372 $\pm$ 11 <sup>‡</sup> | -15           |
| <i>QT<sub>cI</sub></i> | 368 $\pm$ 19 | 375 $\pm$ 21*   | 7             | 352 $\pm$ 20  | 358 $\pm$ 20*             | 6             |
| <i>QT<sub>cH</sub></i> | 376 $\pm$ 14 | 374 $\pm$ 17    | -1            | 374 $\pm$ 10  | 366 $\pm$ 14*             | -7            |

\* ( $P < 0.05$ ); <sup>†</sup> ( $P < 0.005$ ); <sup>‡</sup> ( $P < 0.0005$ )

interval. Also conditions that involved atropine supply showed concentrated  $QT/RR$  patterns leading to a problem when finding the regression formula for it. Lack of statistically significant difference for *SUA* condition was probably caused by the impossibility of the parabolic regression to fit the  $QT/RR$  pattern for the two subjects that exhibits a lengthening in  $QT$  interval (figure 2). Some recent works, for the individual correction, proposed about 10 regression formulas to fit  $QT/RR$  patterns and could be an improvement for future works [12]. Other improvement for the intrarecording  $QT_c$  decorrelation could be obtained by considering the adaptation delay between  $QT$  and  $RR$  [12]. Our results shows that, accepting the individual correction as valid, differences in  $QT_c$  are much more marked when vagal system is blocked (just sympathetic change: SUC vs. SUP  $\Delta QT_c = 7$  ms; just vagal change: STC vs. STA  $\Delta QT_c = -35$  ms table 1 and 2), suggesting that  $QT_c$  is mainly controlled by the vagal system. When analysing the results from the other corrections this conclusion is not as evident (table 1 and 2). As can be seen in Figure 1, the Individual correction method achieved the best uncorrelation between  $QT_c$  and  $RR$  interval, making  $QT_c$  more independent of  $HR$  and  $ANS$  status.

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Table 3. Comparison of control and drug conditions for extreme  $ANS$  status. Results in ms as mean  $\pm$  sd.

|                        | SUC          | STA          | $\Delta QT_c$ | STC          | SUP          | $\Delta QT_c$    |
|------------------------|--------------|--------------|---------------|--------------|--------------|------------------|
| <i>QT<sub>cB</sub></i> | 395 $\pm$ 7  | 400 $\pm$ 13 | 5             | 387 $\pm$ 9  | 371 $\pm$ 16 | -16 <sup>†</sup> |
| <i>QT<sub>cI</sub></i> | 367 $\pm$ 24 | 324 $\pm$ 31 | -43*          | 352 $\pm$ 20 | 375 $\pm$ 21 | 23 <sup>‡</sup>  |
| <i>QT<sub>cH</sub></i> | 385 $\pm$ 6  | 390 $\pm$ 16 | 5             | 374 $\pm$ 10 | 374 $\pm$ 17 | 1                |

\* ( $P < 0.06$ ); <sup>†</sup> ( $P < 0.005$ ); <sup>‡</sup> ( $P < 0.0005$ )

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