# QT interval analysis on ambulatory electrocardiogram recordings: a selective beat averaging approach

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**Abstract**—*A computerised method for the analysis of QT intervals in ambulatory ECG recordings is presented. This approach is based on selective beat averaging which allows one to process P-QRS-T complexes together with the environment that characterises them. Long-term autonomic nervous system influences are accounted for by separating the analysis over different circadian periods. Effects of QT recovery time are taken into account by requiring a stable heart rate preceding each beat to be averaged. Before averaging, beats are resampled and realigned with respect to the R-wave peak estimated by parabolic interpolation. Averaged ECG templates are then analysed with an algorithm which automatically detects QRS complex and T-wave features. Repolarisation analysis is based on first and second derivatives of lowpass filtered ECG (recursive Butterworth filter). The QT/RR relationship and the circadian QT variation at identical heart rate were analysed in 14 normal individuals. When performed at stable heart rate conditions and when confined to well-defined circadian periods, the QT/RR relationship was strongly linear ($r = 0.95 \pm 0.06$); in addition, the slope of this relation changed between day and night (respectively, $0.197 \pm 0.07$ and $0.139 \pm 0.03$, $p < 0.01$). The range of circadian QT variation at identical heart rate was approximately 20 ms for both males and females.*

**Keywords**—*QT interval, Ambulatory ECG recordings, Selective beat averaging, QT/RR relation*

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## 1 Introduction

THE QT INTERVAL corresponds to the time elapsed between the depolarisation of the first myocardial ventricular cell and the end of the repolarisation of the last ventricular cell. Despite its well-known limitations (MURRAY *et al.*, 1994), manual measurement of QT interval on surface ECG and its rate correction with Bazett formula remains the standard quantitative evaluation of ventricular depolarisation. The recent advent of digitised ECG has originated multiple efforts to obtain alternative and more significant indexes. Today, the measurement of QT interval is becoming available on commercial systems dedicated to resting, exercise and long-term computerised ECG.

Investigation of the repolarisation of each single cardiac beat for long periods of time has made possible the study of many new research topics such as T-wave alternans (ROSENBAUM *et al.*, 1994), QT variability (VISKIN *et al.*, 1996; BERGER *et al.*, 1997) and QT dynamicity (MERRI *et al.*, 1992; LOMBARDI *et al.*, 1996). Yet, a clear methodology on the way to treat the massive information obtainable from 24-hour recording has not been established. Most of the current difficulties are related to the fast acquisition of reliable beat-to-beat measurements. The management of poor quality data typical of beat-to-beat analysis often causes the exclusion of physical activity portions of the tracing (MERRI *et al.*, 1990*b*; LAGUNA *et al.*, 1990; ALGRA *et al.*, 1993) which are generally correlated with noise and which, on the other hand, often reflect relevant cardiovascular information.

One can easily verify that identical RR intervals are responsible for QT values that are longer at night than at daytime (BROWNE *et al.*, 1983). Knowing this, the use of a unique correction formula to study QT rate adaptation does not appear meaningful. Conversely, a complete autonomic blockade would not abolish rate-dependent changes of the QT interval but it may modify them. Thus, an approach to analyse repolarisation in the long term should attempt to take into account both the heart rate and the autonomic nervous system, possibly independently.

The purpose of this work is to present a novel method suited to the automatic analysis of QT interval on ambulatory ECG recordings. This method is based on selective beat averaging (SBA) which is an averaging technique capable of considering the environment preceding each single cardiac complex.

In Section 2 we provide an extensive description of all details of the approach and in Section 3 we display the findings of two experiments performed on a normal group which highlight the advantages offered by this technique. In the first experiment, we show the effect of applying SBA to the rate dependency of QT interval (QT/RR relationship). In the second, we provide quantitative data on the circadian changes of QT intervals as obtained with the new method.

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## 2 Methods

### 2.1 *ECG files and annotation files*

The starting point is to obtain Holter-validated (properly edited) information. Currently, we are interfaced with six commercial systems, some based on analogue and some on digital technology, providing multiple sampling rates and different amplitude resolutions. The next step is to obtain digitised ECG files and relative annotations (beat labels). If, for the former, the only requirement is a knowledge of the digitised ECG binary format, for the latter, proper editing of annotations on the original commercial machine is crucial. Our approach is a trade-off between preserving essential information such as 'interesting' heart rate and heart rate variability periods (even if it is time consuming), and the possibility of tagging the noisy (and not interesting) regions provided by some systems.

When necessary, the annotation file obtained is modified by a smoothing algorithm. This is fundamental for proper functioning of SBA and it is done to impose the maximum regularity on the tachogram (somewhat similarly to what is done in heart rate variability) to obtain reliable running means. In practice, a smoothed annotation list is obtained by interpolating isolated and/or a run of non-sinus episodes. Depending on the duration of the period to be smoothed, the interpolation is a cubic spline (for short periods) or linear spline (for longer periods).

### 2.2 *Selective beat averaging*

Beat averaging is the simplest way to obtain better quality (higher signal-to-noise ratio) templates. In the most general case, beat averaging is applied to *consecutive* sinus beats and is ended by time constraints or when a minimal noise level is obtained. With the exception of some beats that may be excluded for bad quality, this form of averaging may also be referred to as time-averaging.

The averaging procedure becomes *selective* whenever some criteria of beat inclusion is applied. In most cases, the criteria are based on heart rate conditions, which justify the use of a rate-averaging terminology. The concept of selective averaging is not new, and has been applied to study arrhythmia events. Sequences of RR intervals preceding frequent ventricular extrasystoles have been investigated to assess the electrophysiological mechanisms associated with ventricular excitability (ZIMMERMANN *et al.*, 1986; ALBRECHT *et al.*, 1988). The dynamic behaviour of high-resolution body surface ECG recordings was also analysed with a selective beat approach, either using a short–long RR sequence generated by ventricular extrasystole (NARAYANASWAMY *et al.*, 1993), or at different values of cardiac cycle length (ROMBERG *et al.*, 1995). Modes of onset of Torsade de Pointes were also identified by our group; in particular, the presence of oscillatory patterns preceding arrhythmia onset was observed (LOCATI *et al.*, 1995).

In the method presented in this study, selective beat averaging is used to obtain averages of P-QRS-T complexes that are preceded by the same stable heart rate (defined by a specific rule). This philosophy aims to respect the restitution curve of ventricular repolarisation which demonstrates how full adaptation of QT interval to changes in heart rate is achieved only after a time period that can be longer than a minute (FRANZ *et al.*, 1988). Thus, despite an identical RR interval, beats occurring 'in the middle of heart rate changes' may have a different repolarisation shape from those occurring at stable heart rate. Most of all, they will have a different QT duration. Fig. 1 provides an example of this phenomenon. The overlapped QRS complexes are *all* preceded by the same RR interval but by a different heart rate trend: the beats with shorter QT intervals have been taken a few seconds after an increase in RR interval (i.e. the QT interval is under adaptation and it is increasing); conversely, the beats with longer QT intervals have been taken a few seconds after a decrease in RR (the QT interval is adapting towards a shorter value). The beat drawn with a thicker line was preceded by stable heart rate and represents the steady-state morphology for the RR interval considered. All the beats shown in the figure are taken from a 3 h segment of the same subject and some of them actually occurred only a few minutes apart.

The simplest way to define stability automatically is to set up an observation period (say of one minute) and to define stable beats as those preceded by an RR interval (RR_1) equal to the mean RR interval of the observation period (MIN_1). More precisely the definition is the following:

$$RR\_1 \pm th1 = RR\_2 \pm th2 = MIN\_1 \quad (1)$$

where $th1$ and $th2$ are two thresholds, set by default to 15 and 50 ms, and RR_2 is the second preceding RR interval. Alternatively, stability may require the equivalence of RR intervals calculated on more subperiods, such as in eqn. 2:

$$RRP\_1 \pm th1 = RRP\_2 \pm th2 = RRP\_3 \pm th3 = MIN\_1 \quad (2)$$

where *RRP*_1, *RRP*_2 and *RRP*_3 are the mean RR intervals calculated over three equal-length subsegments covering the global observation period. Other definitions of stability may require more stringent conditions and/or impose further criteria of selection based, for instance, on HRV parameters. The definition of stability of eqn. 1 generally provides a large number of individual beats within a template and the results given in this report are based on the application of this formula.

Given a rule of selection and the time frame where to apply it (e.g. the diurnal period), the algorithm determines a family of templates stratified over the range of available RR intervals. The stratification resolution (in milliseconds) is user selectable and can be as small as 10 ms, which is appropriate for systems with high sampling rate. The total number of templates obtained within a family depends on this resolution and on the effective range of heart rates available in the time period analysed.

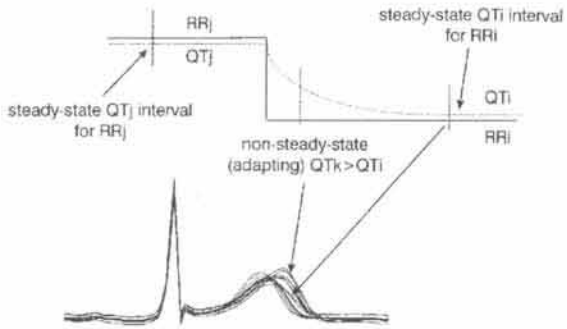



**Fig. 1** *Effect of heart rate on QT interval. Superimposed beats preceded by the same RR interval (RRi) but by a different heart rate trend. The central complex (thicker line) is preceded by a stable rate whereas other complexes are either preceded by an accelerating rate (those with longer QT intervals) or by a decelerating rate (those with shorter QT intervals). In the upper part, a schematic representation of a sudden heart rate acceleration (RR decreases from RRj to RRi) is depicted. Away from steady-state, the QT interval (QTk) has not yet reached full adaptation and is longer than its corresponding steady-state value QTi. A similar scenario (but with shorter non-steady-state QT values) can be drawn for a sudden heart rate deceleration*

### 2.3 *Beat alignment*

Accuracy of QRS fiducial location cannot be assumed in ambulatory recordings. It may depend on the commercial algorithm implemented and on the quality of the ECG analysed. When performing averaging, variability in beat-to-beat QRS alignment causes a jittering effect which could substantially modify the shape of the averaged template (ROS *et al.*, 1981). More critically, a classical approach based on cross-correlation, typical of high-resolution ECG, becomes questionable at lower sampling rates of ambulatory monitoring. To cope with this problem, all individual QRSs to be averaged are oversampled (256 or 512 Hz) and resynchronised with respect to the apex of the R-wave estimated by the peak of the interpolated parabola (MERRI *et al.*, 1990*a*). The formula applied for the resampling is the following:

$$x_r[K] = x_n(kM) = \sum_{n=-0.1/T}^{+0.1/T} x_0[n] \left. \frac{\sin[\pi(t - nT)/T]}{\pi(t - nT)/T} \right|_{t=kM} \tag{3}$$

where $T$ and $M$ are, respectively, the sampling intervals (s) of the original sequence $x_0[n]$ and the resampled sequence $x_r[k]$. This formula is derived from the continuous-time ideal reconstruction filter of sampling theory which permits reconstruction of signal $x_n(t)$ from its discretised sequence $x_0[n]$ by summation of weighted and shifted sinc functions $(\sin(x)/x)$ (OPPENHEIM and SHAFER, 1989). It differs from the ideal reconstruction filter in the sense that extremes of summations cover only 200 ms of the discrete sequence, rather than the ideal $[-\infty, +\infty]$ interval. Of course, an ideal reconstruction filter has many good properties and in particular it avoids the lowpass filtering effect on $n$th-order holding functions (OPPENHEIM and SHAFER, 1989). The newly discretised function $x_r[k]$ is obtained by sampling $x_n(t)$ with interval $M$ and by synchronising it to the parabola peak, i.e. by imposing the estimated peak to be a sample of $x_r[k]$. Fig. 2 shows an example of this technique applied to a QRS complex.

### 2.4 *Template quality control*

Residual template noise level is calculated after the implementation of a highpass frequency domain filter with cutoff of 40 Hz (CHRISTENSON *et al.*, 1989) and is defined as the root mean square value (in microvolts) in a window of 40 ms following the QRS complex. To allow direct control of template quality, the sequence of occurrence of each individual beat is stored and optionally visualised. The user can verify (modify) the location of all QRS alignment points, delete individual beats and/or impose template reconstruction based on his/her modifications. Fig. 3 is an example of this tool for a template obtained by averaging 15 beats.

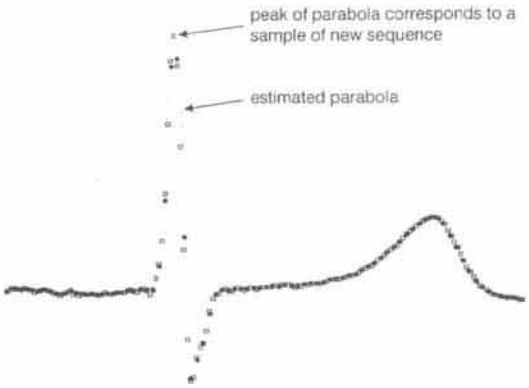



**Fig. 2** *Example of resampling technique. Original (●) and resampled (□) ECG are superimposed. A parabolic interpolation is first performed on the original sequence. Then, the new sequence is reconstructed by imposing the estimated peak to be a sample. Note that samples of new sequence (256 Hz) are closer to one another than those of old sequence (128 Hz)*

### 2.5 *Template analysis*

Quantitative analysis of SBA template families is automatically performed. A minimal default value of 1 μV noise level is required for a single template to be analysed. However, on the basis of visual inspection of template quality, this threshold can be reduced. Template analysis consists of the measurement of many parameters on each of the available leads (i.e. either two or three in standard Holter); in this work we focus on QTm (from QRS onset to T-apex) and QTo (from QRS onset to T-wave offset) intervals which are calculated on each lead after the detection of the following fiducial points.

*QRS onset and offset*: These fiducial points are lead-independent and by default they are determined on the vector magnitude calculated on the three Holter leads. However, the use of a specific lead (which reduces the vector magnitude to the absolute value), or of a combination of two leads is also possible. This flexibility is necessary whenever one lead is either non-recorded, noisy or simply skewed with respect to the other two (typical of some analogue recorders). QRS onset and offset are searched starting from R-apex location (respectively, backwards and forwards) as the return to baseline of the highpass filtered (2nd-order forward difference) QRS shape.

*T peak*: The repolarisation shape (starting at QRS offset) is lowpass filtered (cutoff 20 Hz) with a recursive bidirectional Butterworth 4th-order filter. A T-window is then defined on the basis of heart rate (starting from R-apex, window onset and offset are at 15% and 60% of the preceding RR interval). The first and second derivatives of the (lowpass filtered) repolarisation shape are then considered. In addition, the number and position of all zero crossings, local maxima and minima detected on the first derivative, are also considered (in this regard the frequency characteristics of the Butterworth filter is fundamental as the number of zero crossing can be sensitively larger if the signal is not sufficiently smoothed). All these points represent inflections of the ECG signal (plateaux for zero crossings, maximal ascending and descending slopes for maxima and minima, respectively). In the simplest case (i.e. a monophasic T-wave) there is only one zero crossing which corresponds to the apex of the T-wave (the relative position of local maximum and minimum determines the polarity). In more complicated morphologies (such as biphasic or notched T-waves or in the presence of a U-wave), the number of inflection points increases and the algorithm chooses the location of the T-wave apex as the location of a specific zero crossing in a heuristic way which takes into account the distance between pairs of zero crossings and the relative amplitude of maxima and minima between them. Eventually, the algorithm attempts to identify all possible morphologies and to detect secondary bumps or even U-waves. Finally, the location of the T-wave apex is refined by fitting a parabola in an interval centred around the designated zero crossing and by using the apex of the parabola.

*T-offset and T-onset*: The detection of these points can fall out of the above described T-window (only the T-apex has to fall within). The T-offset search starts at the last significant local first derivative minimum (or maximum), which

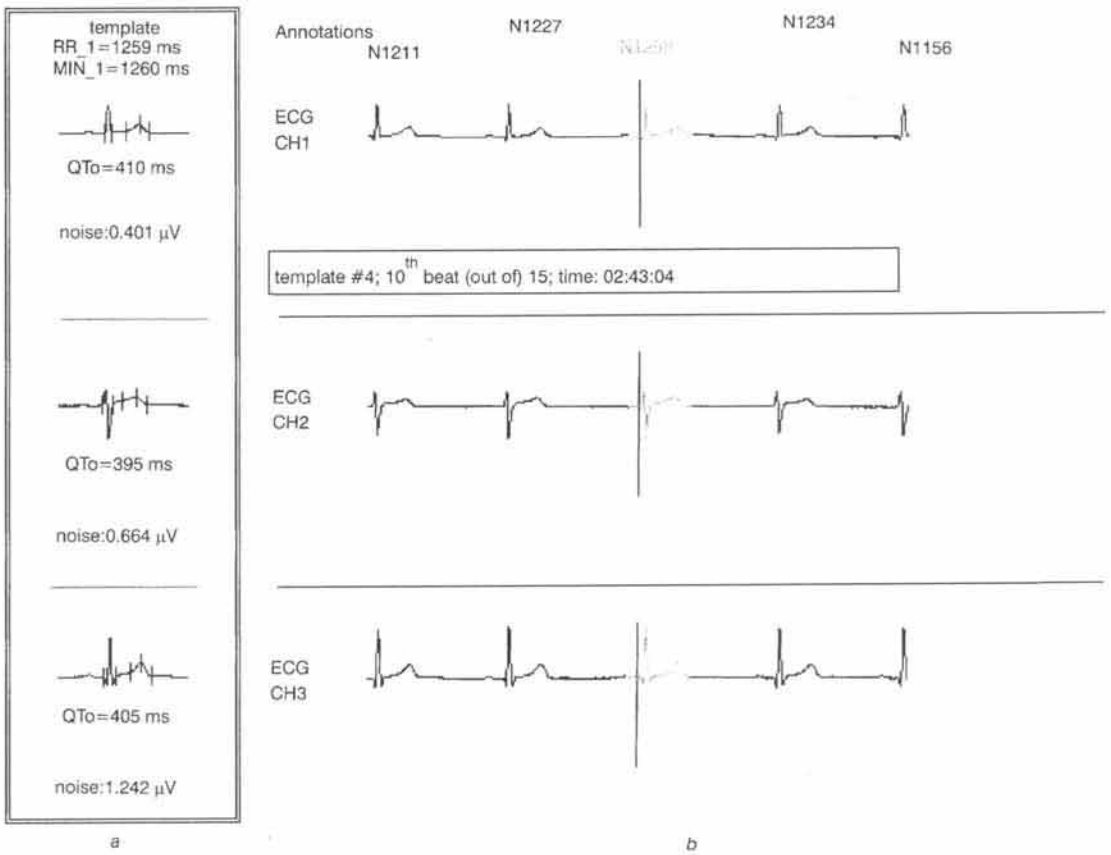



**Fig. 3** *Example of an averaged template visualisation. (a) The averaged template with cursors and noise levels (in microvolts). (b) The 5-second-strip centred on the 10th individual beat is drawn. The preceding interval of the individual beat is 1258 ms, while the average of all preceding intervals is 1259 ms and the average of all preceding minutes is 1260 ms. Large vertical bars mark the alignment point of the individual beat under consideration. Thanks to this tool, the user can review all the beats within a template (15 in the case represented), and ask for template reconstruction on the basis of his/her modifications*

corresponds indeed to the last descending (ascending) T-wave significant inflection. In the presence of a U-wave, a U-apex and U-offset are also searched. The T-offset is defined as the point where the product of the first and second derivative falls below 10% of a threshold defined as the product of the last maximum (minimum) first and second derivatives. Alternatively (on the basis of user selection), the T-offset can be detected using the Surawicz method, i.e. at the intersection between the tangent of the maximum slope and the baseline (LEPESCHKIN and SURAWICZ, 1952). In a similar way, the T-onset is determined before the T-apex (Surawicz option not available). Fig. 4 shows a graphic example of a template on one lead with monophasic T-wave.

### 2.6 *Algorithm validation*

In the case of noisy templates (noise $>1\,\mu V$), the algorithm may fail to detect one or more of the above described fiducials. One such instance is, for example, when too many zero crossings are detected within the T-wave window. In this condition, some of the quantitative measurements will simply by considered as missing and ignored by all subsequent applications. Occasionally, the user will want either to verify some of the strange-looking (or missing) cursors and override (insert) new positions.

Reliability of the algorithm was tested on 40 templates obtained from 20 subjects (10 normal and 10 with repolarisation abnormalities). For each subject, two diurnal and nocturnal periods were randomly chosen, and one stable template was calculated (tuned to the average RR interval of the interval chosen). The 40 templates were subsequently analysed by the automatic algorithm and printed on paper at $25\,mm\,s^{-1}$ with 1 mm grid. An expert physician visually inspected the 40 templates by trying to identify QRS onset, T-wave apex and T-wave offset (by the Surawicz method), whenever possible. Manual and automatic fiducials were considered identical if they were no more than 4 ms apart. Only 32 templates could be measured manually, and in these

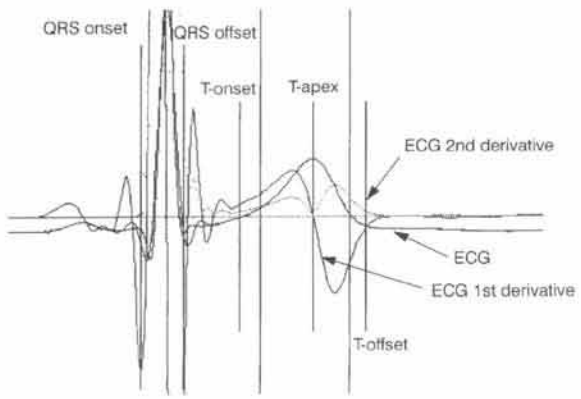



**Fig. 4** *Analysis of one template. This figure displays the signal processing involved in the analysis of one template (lead X is shown). Raw and lowpass filtered ECG can be distinguished only around the QRS complex, where a ringing effect is apparent. The T-wave window for the determination of T-apex is delimited by the two large vertical bars within which all zero crossings of the first-derivative are computed (only one for this example)*

instances automatic and manual measurements were very close; in particular, the T-apex matched in all templates (100%) and the T-offset matched in 29 cases (91%). Automatic analysis of the eight non-manually measurable templates was possible in six cases. When using the method based on first and second derivatives (which was impossible to replicate manually), the T-offset measure was generally shorter than that obtained with the Surawicz method ($8 \pm 5$ ms). However, by visual comparison of different templates, this method tended to be more robust to changes of T-wave amplitude which, in contrast, affected considerably the Surawicz approach (both manual and automatic).

### 2.7 *QT/RR relationship by SBA*

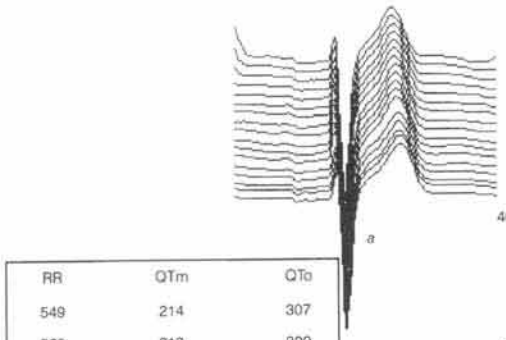
The basic difficulty in studying the physiology of QT and RR relationships is that not only does the QT interval need a time lag to adapt itself to a heart rate change, but both QT and RR intervals are placed under the influence of long-term autonomic balance. When analysed at steady state, the QT/RR relation assesses the gain of the transfer function between RR and QT intervals, which has been shown to be altered during pathological conditions (MERRI *et al.*, 1992; FUNCK-BRENTANO *et al.*, 1991; EXTRAMIANA *et al.*, 1997; NEYROUD *et al.*, 1998). Conversely, during transients (i.e. when heart rate is changing), this relation is actually characterised by hysteresis phenomena (SARMA *et al.*, 1987). It is then fundamental to avoid the combination of transient (unstable) and steady-state (stable) QT/RR pairs. By choosing a selection rule based on stability and a time window characterised by an unchanged long-term autonomic balance, SBA can account for both short-term heart rate changes and long-term autonomic modulation. In practice, SBA is applied separately at day and during night-time and two separate linear regressions are extracted. This is done by selecting the fastest diurnal hours and the slowest nocturnal hours on the basis of the individual frequency table. Fig. 5 is an example of the sequences of stable templates (sorted by increasing RR interval) obtained during the diurnal period (8 hours) of a normal subject.

### 2.8 *Statistical evaluation of QT/RR relationship*

In order to strengthen the statistical relevance of the QT/RR relationship, we systematically apply the method introduced by ALTMAN and GARDNER (1988). This approach allows the determination of confidence intervals (CI) of all parameters involved in the linear relation between two variables. In particular, a slope is considered statistically relevant (i.e. non-flat) only if its 95% CI does not include the zero value (Fig. 5). Comparison between two relations can be determined by calculating the 95% CI of the difference between the two slopes. Again, statistical significance is considered when the 95% CI of the slope difference does not include the zero value. In this way, differences in the QT/RR relations day versus night, stable versus unstable, baseline against drug effect can be assessed. Fig. 6 shows the statistical comparison between the QTo/RR slopes of two families obtained in stable and unstable conditions during the same time window (a 6-hour diurnal segment); indeed, the unstable environment leads to a slope significantly different (smaller) from that obtained in a stable condition (95% CI on the slope difference is always positive). Any other standard method (either beat-to-beat or based on time-related averages) would have somewhat mixed all the beats and provided an intermediate (eventually less linear) kind of dependency.

### 2.9 *QT trends*

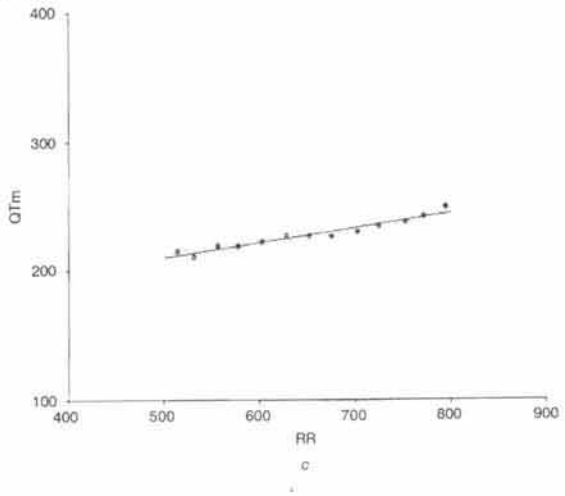
Evaluation of the QT/RR relationship is confined to specific portions of the 24 hours, as imposed by long-term autonomic balance. Conversely, one may be interested in more general



*a*

| RR | QTm | QTo |
|---|---|---|
| 549 | 214 | 307 |
| 569 | 213 | 309 |
| 585 | 219 | 312 |
| 604 | 223 | 316 |
| 623 | 224 | 317 |
| 646 | 231 | 317 |
| 664 | 227 | 320 |
| 685 | 230 | 324 |
| 705 | 231 | 325 |
| 721 | 234 | 328 |
| 745 | 238 | 332 |
| 757 | 246 | 339 |
| 784 | 250 | 340 |

*b*




*c*

**Fig. 5** *Example of diurnal stable family. (a) The family of templates obtained during eight consecutive diurnal hours. (b) The table of QTm and QTo intervals; (c) the QT/RR relationship obtained for this family of templates. QTm = 0.117RR + 152; 95% CI on slope: 0.097 : 0.136; r = 0.94*

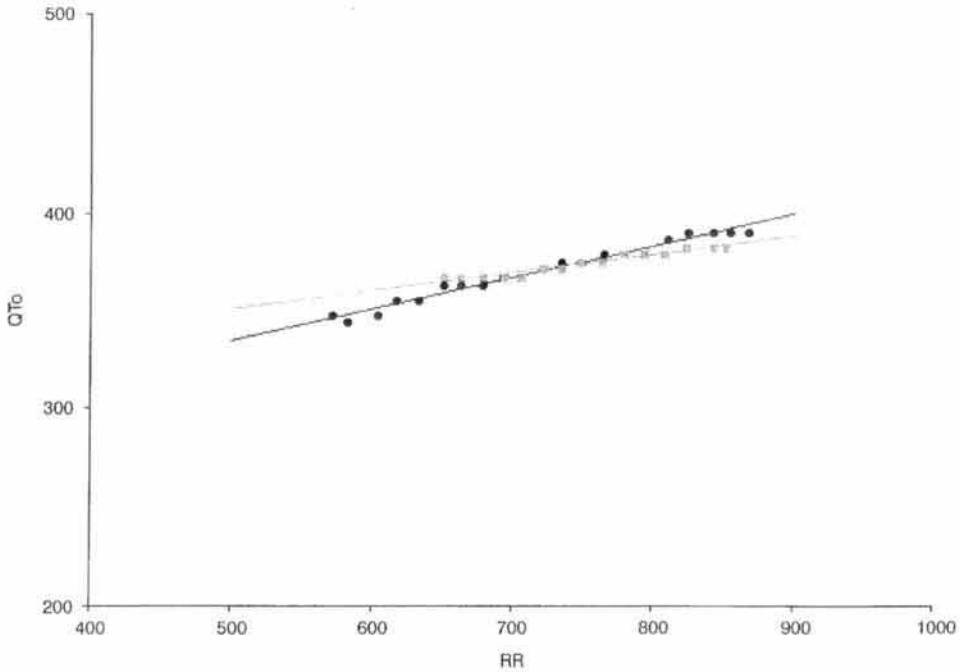



**Fig. 6** *Comparison of QT/RR slopes obtained in stable (●) and unstable (■) conditions. QT/RR relationships estimated over the same circadian period provide higher slopes under stable conditions.* ● *QTo = 0.161RR + 254; r = 0.97.* ■ *QTo = 0.094RR + 304; r = 0.94. 95% CI on slope difference: 0.046 : 0.08; p < 0.0001*

aspects of repolarisation such as the QT interval duration and its circadian behaviour. This task can be fulfilled by simply reducing the time window used for SBA and by considering the whole 24 hours. Fig. 7 shows the kind of results that can be obtained with this generalisation of SBA applied to a representative subject. In this example, the time window used for creation of stable templates was fixed at 2 hours which resulted in 12 separate periods. Within each period, a family of stable templates has been obtained (RR stratification was performed with 20 ms resolution) and automatically analysed. Thus, a series of measurements stratified over heart rate and by time period can be inspected. For some combination of RR/period, the QT interval is actually missing simply due to the absence of beats for that specific time/rate combination. Indeed, it is at slow diurnal and fast nocturnal pairs that QT intervals are missing. By fixing either the RR interval or the time period we obtain slices that provide 'circadian trends at fixed RR intervals' or once again, rate dependency.

This particular application is referred to as QT trends as it allows one to assess the evolution of the QT interval independently of the heart rate (thus avoiding the need for a correction formula). In addition, the intrinsic filtering provided by SBA permits an evaluation of repolarisation considered at full adaptation.

## 3 Results

### 3.1 *QT/RR rate dependency*

To show the power of the SBA approach, we calculated the QT/RR relationship both with 1 minute time-related templates and with SBA stable templates in 14 healthy individuals (7 females, ages between 20 and 31 years), both at day and during night periods. For simplicity, we show only data relative to one of the three recorded leads (orthogonal lead X). Results relative to Pearson linear correlation values are shown in Table 1. When assessed with (rate-related) SBA slopes separately at day and at night, the QT/RR relationship always provided very high correlation coefficients. In particular, rate-related slopes always show a correlation coefficient $r$ larger than 0.7 whereas in 10 circumstances (out of 28), time-related slopes had an $r$ coefficient smaller than 0.5. Finally, when comparing rate-related and time-related slopes, statistical equivalence (i.e. no difference) was achieved in only 12 instances (43% of total test); in the remaining cases the time-related slope was either larger or smaller, probably reflecting the amount of instability in one direction (accelerations) or another (decelerations). When considering mean slopes, both time- and rate-related families show reduced nocturnal slopes (for 1 minute time-related: $0.199 \pm 0.07$ versus $0.143 \pm 0.05$, $p < 0.01$; for rate-related: $0.197 \pm 0.07$ versus $0.139 \pm 0.03$, $p < 0.01$). Fig. 8 shows an example of a QTo/RR relationship where rate-related slope was significantly different (in this case smaller) from the time-related slope.

### 3.2 *QT trends*

QT trends allow one to estimate the amount of circadian variability at fixed rate (i.e. indirectly assessing the amount of error using the Bazett formula at different times of the 24 h). Table 2 summarises the results obtained for the same population as the preceding experiment. Data are again based on measurements on lead X. At two fixed rate values (RR = 600 and 800 ms), both genders show a global change of both QTo and QTm ($\Delta$QTo and $\Delta$QTm) of about 20 ms. This range of variation was consistently due to the day–night differences. More precisely, all subjects showed longer QT intervals (at the same heart rate) during the nocturnal period, in accordance with the nocturnal lengthening phenomenon recently described (BROWNE *et al.*, 1983).

Fig. 9 demonstrates this effect for all three recorded leads. The two templates shown are a diurnal and a nocturnal template obtained from the same recording for the same RR interval. The QT interval is clearly longer in the nocturnal template.

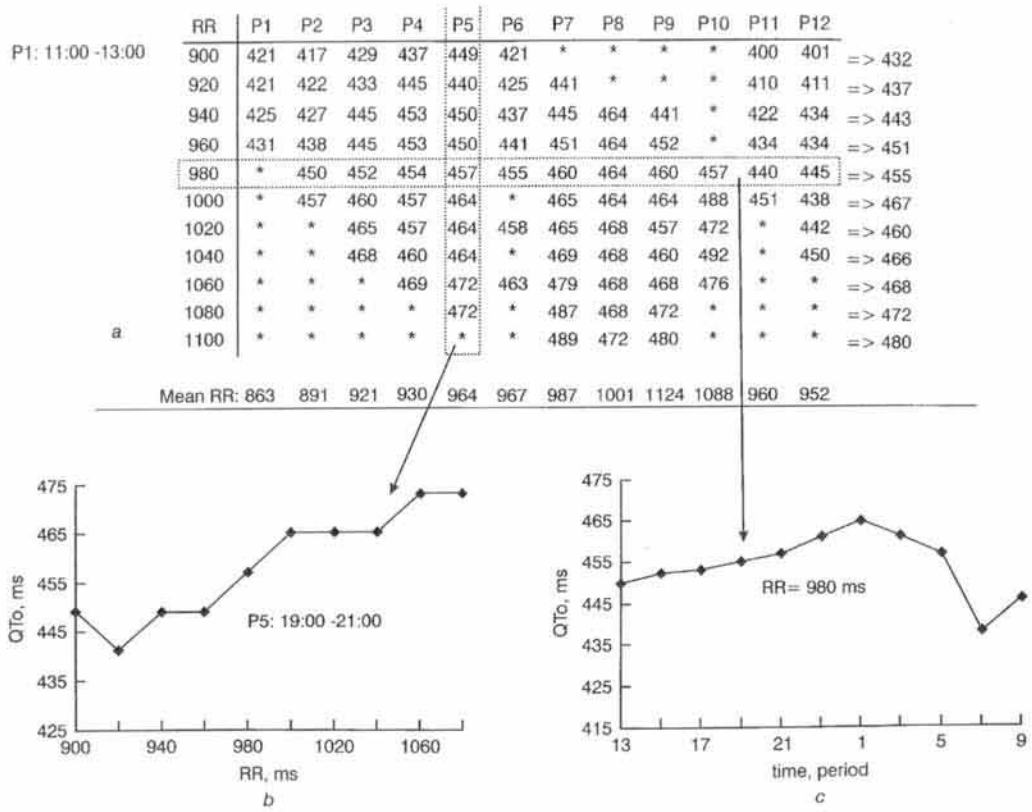



**Fig. 7** *Extract from QT trend analysis for a representative subject. (a) The 24 hours are divided in 12 two-hour periods, within which the QT intervals at increasing stable heart rates are given (b) a slice of the table for a fixed period (thus providing QT/RR relation within the selected period); (c) a slice at a fixed RR interval (thus providing circadian variation at identical RR interval)*

*Table 1 Pearson correlation coefficients in time- and rate-related families*

| QTo | SBA | Time-related | $p$ |
|---|---|---|---|
| Day | $0.96 \pm 0.04$ | $0.72 \pm 0.18$ | $< 0.0001$ |
| Night | $0.92 \pm 0.08$ | $0.50 \pm 0.26$ | $< 0.0001$ |

## 4 Discussion and conclusions

An original and fully computerised method for the analysis of ventricular repolarisation has been presented. This approach accounts for both short-term (rate-adaptation related) and long-term (autonomic nervous system related) influences on ventricular repolarisation and its fundamental basis is the selection (and separation) of cardiac beats preceded by stable and unstable heart rate.

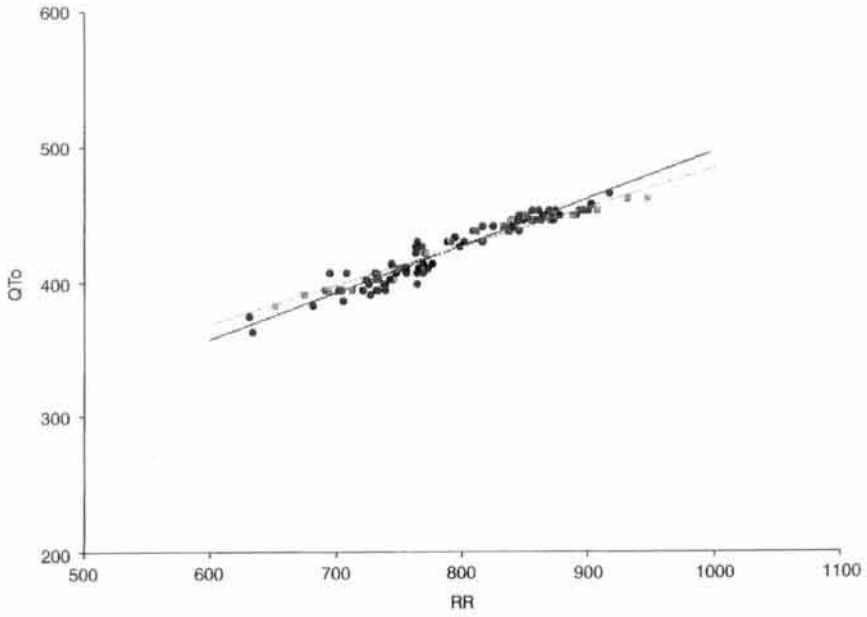



**Fig. 8** *Comparison of QT/RR slopes obtained with SBA rate-related (■) and time-related (●) averaging. Despite a larger number of QT/RR pairs, the correlation coefficient of time-related families is smaller. Furthermore, the two regression lines are statistically different. ●QTo = 0.344RR + 151, r = 0.78. ■ QTo = 0.285RR + 198; r = 0.96. 95% CI on slope difference: 0.02 : 0.10; p = 0.003*

*Table 2 Circadian variation of QT interval*

| | Males | | Females | |
|---|---|---|---|---|
| Parameter | RR = 600 | RR = 1000 | RR = 600 | RR = 1000 |
| QTm | 251 ± 11 | 300 ± 13 | 263 ± 11 | 340 ± 21 |
| QTo | 344 ± 14 | 394 ± 14 | 353 ± 16 | 428 ± 27 |
| ΔQTm | 19 ± 11 | 21 ± 7 | 18 ± 13 | 19 ± 15 |
| ΔQTo | 20 ± 11 | 22 ± 7 | 22 ± 11 | 21 ± 13 |

Data shown are mean ± SD and are expressed in milliseconds

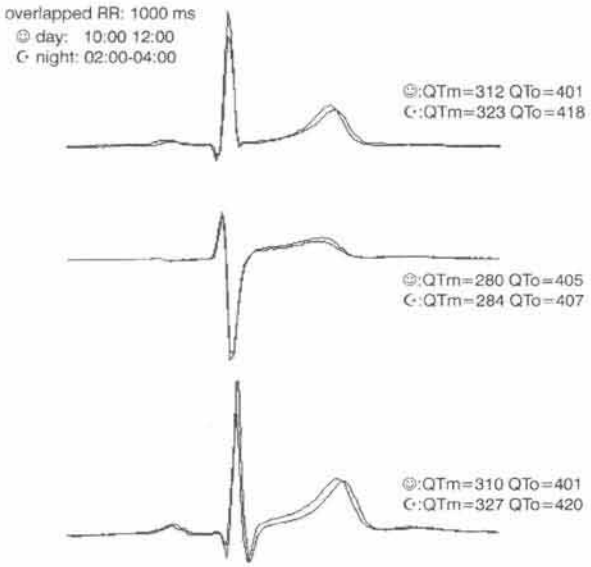



**Fig. 9** *Superposition of diurnal and nocturnal templates. Both complexes shown were obtained under stable heart-rate at the same RR interval. The longer QT intervals of all three leads in the nocturnal template are apparent*

Selective beat averaging selection of stable templates obtained separately in the daytime and during the night exhibit a strongly linear QT/RR relationship. Linear regression analysis on QT/RR pairs performed on the same subjects but with (more standard) 1 min time-related templates provided correlation coefficients sensitively smaller. In several instances (and especially at night), correlation of time-related regressions was low enough to attempt higher-order fits, although the corresponding SBA rate-related regression remained very high. Thus, taking account of the environment, the QT/RR relationship is linear. Whatever the type of averaging, nocturnal slopes show significantly reduced slopes. Thus, the importance of separating the long-term influences of autonomic nervous system is already apparent with standard time-related templates. Most non-invasive classical studies investigating the QT/RR relationship diverge from our approach in two major features. The first is to consider every QT interval against the immediately preceding RR cardiac cycle length (beat-to-beat approach) regardless of mid-term heart rate fluctuations (MERRI *et al.*, 1992; SARMA *et al.*, 1987). The second is to ignore long-term circadian autonomic influences by considering the full 24 hours (MERRI *et al.*, 1992; STRAMBA-BADIALE *et al.*, 1997). An immediate consequence is that correlation coefficients are significantly reduced thus justifying the need for better fits.

Regarding QT interval duration, this study showed that even at the same stable heart rate, and even respecting adaptation, the QT interval shows circadian, sex-independent fluctuations. These variations should be taken into account for proper evaluation of drug or pathologically related conditions. For instance, the magnitude of nocturnal QT lengthening is reduced in patients with coronary artery disease (MURAKAWA *et al.*, 1992) and in patients with diabetes mellitus (BEXTON *et al.*, 1986).

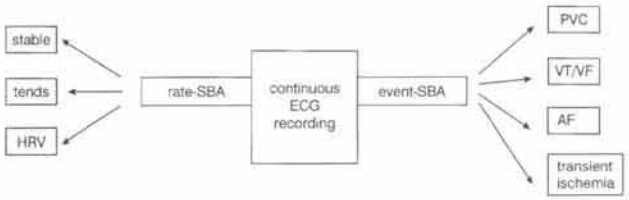



**Fig. 10** *Extension of SBA analysis in continuous ECG recordings*

In this article we have covered in detail one possible approach to the analysis of repolarisation in continuous ECG recordings. This approach is based on the extrapolation of stable heart rate periods at different circadian times and to the acquisition of robust QT/RR relations. A possible generalisation with more thorough physiological implications of selective beat averaging is shown in Fig. 10. For instance, as an extension of the plain day/night separation to take into account long-term influences of the autonomic nervous system, we could also stratify over different physical activity periods with the use of an activity status index (HLATKY *et al.*, 1989; OKA *et al.*, 1996), different sleep conditions (VERRIER *et al.*, 1997) or awakening (TOIVONEN *et al.*, 1997). The support for these deeper stratification criteria requires additional biological sensors, which could be made available, together with continuous ECG recording. These sensors may include body position detectors, a respiratory-rate analyser, EEG and blood pressure recorders and so on.

Dynamic quantitative analysis of QRS complexes and of T-waves can also be provided by SBA based on event-related averaging. Late potentials in the terminal part of the QRS complex before ventricular extrasystole may indicate the presence of a substrate for re-entry (NARAYANASWAMY *et al.*, 1993). Similarly, the amplitude of T-wave changes following short–long sequences is greater in patients prone to lethal ventricular arrhythmias (VISKIN *et al.*, 1996). Finally, selection of ECG segments preceding atrial fibrillation together with QRST substraction, could allow one to identify some specific site of origin of atrial complexes (COUMEL *et al.*, 1987; HAISSAGUERRE *et al.*, 1998).

## 5 Limitations

SBA provides a long-term analysis of repolarisation at steady-state (i.e. at full adaptation). Thus, by definition, all transient phenomena have been ruled out and cannot be taken into account when using this approach.

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