Holter Monitoring for QT: Types of Analyses and Endpoints The RR Bin Method in Depth

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Summary

The chapter describes in details the mathematical background of the so-called Holter bin method with particular emphasis given to the technical aspects of the method both in terms of signal processing and in terms of data management.

The phenomenon of QT hysteresis and the way it is handled by the Holter bin method is described. Finally, a brief overview of the pharmaceutical trials where the method was implemented is given.

1. Background

Many non-cardiovascular drugs have the adverse effect to delay cardiac repolarization, a phenomenon that can be quantified in humans on the surface electrocardiogram (ECG) by the QT interval (1,2). Despite a number of limitations associated with its assessment, the drug-induced prolongation of QT interval is considered an important marker for the risk of life-threatening arrhythmias (torsades de pointe) (3,4).

An additional challenge associated with the measurement of the QT interval is its intrinsic property of being inversely related to heart rate (QT interval shortens as heart rate increases) (5,6), a characteristic that justifies the need for a way to normalize QT interval changes whenever the heart rate also changes. This normalization is more commonly known as QT correction and the never ending debate on which regression formula should be used to define the best model (or formula) to normalize the QT interval is far from being resolved.

While waiting for more reliable and more reproducible markers of drug-induced delayed repolarization, we thus need to define methodologies capable to reliably capture changes in the QT intervals while minimizing the risks associated with correction formula or regression models.

The so-called Holter bin approach (also known as the RR bin method) is one of the methods that have been proposed in the pharmaceutical arena.

In this chapter, the technical characteristics of the Holter bin method used to assess drug-related changes in both the QRS and the QT intervals (7, 8), will be described in details. The method presented is part of a larger research package called WinAtrec designed to cover various aspects in continuous ECG monitoring analysis.

2. The Holter bin method

2.1 General concepts

2.1.1 Interfacing with commercial systems

WinAtrec entry point is validated Holter data. This means that all beat validation and editing (positioning and labeling) are assumed to be correctly performed beforehand, on the commercial system environment. In general, commercial systems store ECG waveform and the validated annotation information on disk files with proprietary (and sometimes compressed) data formats.

The interface between WinAtrec and these commercial systems depends on data organization; some systems include tools for the export of ECG and annotations information into public domain formats (such as ISHNE or MIT) which are directly supported by WinAtrec. Others simply provide the format description of their internal file structures and authorize the usage. In general, the first step is thus to perform a reformatting form the original formats of ECGs and annotation files (different for each separate vendor) to an unique internal format used by WinAtrec which, for the ECG waveforms, is that proposed by the ISHNE society (9).

2.1.2 Smoothing of annotation files

Proper implementation of the RR Holter bin approach requires a correct computation of the continuous (beat-to-beat) averaged heart rate need to compensate for non-sinus events, noise, intermittent data and similar conditions typical of Holter recordings. To handle these situations, WinAtrec computes a so-called smoothed annotation file, where the original (raw) sequence of beat labels is replaced by a new interpolated sequence. The portions of the raw annotation file where interpolation is applied can be based on one or more user-selectable set of events (for example sequences of ventricular and/or supraventricular beats, pauses, and short RR intervals). The position of beat labels to be inserted is then computed using a cubic-spline interpolation technique by considering the last and first three valid RR interval before and after the portion to be smoothed.

The result of this procedure is to obtain an interpolated annotation sequence characterized by inserted beat labels not associated with real beats (and thus not used for analysis) but only used for the computation of the correct rate beat-to-beat averaged heart rate. Figure 1 is an example of the interpolation of an isolated ventricular beat. Please note that an L (interpolation) label has been placed on the normal beat after the PVC. This is to avoid the post-PVC beat to be subsequently used by the Holter bin method, but only for the computation of the beat-to-beat averaged RR interval.

2.1.3 Selective Beat Averaging: the substrate of Holter bin

The RR Holter bin is a beat averaging approach. In general, beat averaging is applied to *consecutive* sinus beats within a time window and it is used to obtain low noise level templates (the noise content decreases by a factor of $1/\sqrt{n}$ when we average n beats). The averaging technique used in the Holter bin approach employs a more complex selection model to group the individual beats to be average which is called selective beat averaging.

The concept of selective beat averaging is not new as it was 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 (10,11). Dynamic behavior of high resolution body surface ECG recordings was also analyzed with a selective beat approach, either using short-long RR sequence generated by ventricular extrasystole (12), or at different values of cardiac cycle length (13). Modes of onset of Torsade de Pointes were also identified with a selective beat averaging model that identified the presence of oscillatory patterns preceding the arrhythmia onset (14).

In WinAtrec, selective beat averaging is used to group (average) individual P-QRS-T complexes preceded by the same stable heart rate as computed over an observation period preceding each of the beats to be averaged. The observation period can be reduced to a single beat (the "RR-1 only" model) where all the beats will be considered for analysis regardless of the stability conditions preceding them. The philosophy behind the concept of imposing stability aims to respect

the restitution curve of ventricular repolarization which demonstrates how full adaptation of QT interval to changes in heart rate is only achieved after a time period that can be longer than a minute (15). Thus, despite an identical RR interval, beats occurring "in the middle of heart rate changes" may have a different repolarization shape than those occurring at stable heart rate. Most of all, they will have a different QT duration. This phenomenon, known as hytesresis will be covered in details in Section 3.

One simple way to define stability is to impose the averaged RR interval computed over the observation period (RR_{Per}) to match with the immediately preceding RR interval (RR_{-1}):

$$RR_{-1} = RR_{Per} \pm th1 \qquad (1)$$

where th1 is a user-selectable threshold set by default to 15 msec. Alternatively, stability may require the equivalence of RR intervals calculated over more subperiods, or imply the usage of other variables such for example heart rate variability parameters (16). Recently, more sophisticated definitions based on the usage of the best fit model applied on a per-case basis have been proposed (17).

Given a rule of selection and the time period where to apply it (for example a circadian period or a the peak concentration of a compound), the algorithm used in the Holter bin determines a family of averaged templates, one per class of RR intervals (from here the terminology RR bins). The stratification (bin) resolution is user selectable and can be as small as 10 milliseconds which is appropriate for systems with high sampling rate. The total number of templates obtained within a family depends on bin resolution and on the effective range of heart rates available in the time period analyzed. Figure 2 summarizes the process of beat/selection allocation of Holter bin method: starting from the RR interval measurements, individual beats are allocated (averaged) in the bin whenever they meet the selection criterion imposed. At the end of the process, a single QT interval

(or other quantitative parameter) is measured on the averaged waveform. Figure 3 shows a cascade display of a family of templates together with the associated histograms of RR bins

2.1.4 Correcting the trigger jitter of annotation files

Commercial Holter systems implement proprietary algorithms and mathematical definitions for QRS fiducial markers (for example the center of mass or maximum velocity in the QRS). Because of these differences, consistency in the positioning of QRS fiducials cannot be assumed a-priori. Even worse, a so-called trigger jitter effect, which can be defined as an inconsistent positioning of the fiducial QRS markers (even between a beat and the next), is known to affect many systems. Trigger jitter would typically produce larger (longer) and smaller (less amplitude) QRS complexes. In addition, even the RR bin assignment would be affected as the sequence of RR intervals would also be modified by a wrongly positioned fiducial point.

All methods that implement some form of beat averaging, thus including Holter bin, should include proper signal pre-processing to avoid (or to correct for) trigger jittering. In WinAtrec, the correction algorithm is based on a complete re-analysis of the QRSs positions and on the application of a parabolic interpolation to reliably define the apex of the QRS complex of each beat (16,18). Figure 4 is a real-case example where trigger jitter is overtly seen within a few seconds of data; the strip in the upper part is extracted before the correction and the lower strip after the correction. Figure 5 shows the effect of trigger jittering in an extreme case: the two overlaid templates are the averages of QRS complexes from the same time window before (light pen) and after (black pan) trigger jitter correction (from the same ECG subject of Figure 4). The before-correction template is clearly affected by BOTH a distorted QRS (smaller amplitude plus an artifact S wave) and even a T wave alteration. The importance of applying proper trigger jitter correction is apparent.

2.1.5 Proper beat alignment

Most commercial systems produce digital ECGs at a relatively low sampling rate (in the range of 200 Hz). When performing beat averaging single beats need to be aligned (superimposed) on the top of each other. This process, even when the effect of trigger jitter has been compensated, can still determine small distortions in the averaged complexes, due to the random positioning of the alignment (fiducial) markers associated with sampling rate.

To cope with this problem all individual beats to be averaged are oversampled (at 400 Hz) and resynchronized with respect to the apex of the R-wave as estimated by the peak of the fitted parabola (16,18). More details on the mathematic model used to perform this realignment can be found in the original article that introduced selective beat averaging (16).

Of note, this resampling procedure is not applied with the aim to increase or to add information (a purely utopian goal) but only with the intent to produce better alignment of individual beats before averaging. To give a quantitative ballpark, on a commercial system with a sampling rate in the range of 200Hz (i.e. digital samples 5 msec apart) an averaged complex obtained without realignment can produce QRS complexes from 3 to 8 msec longer than that of the individual beats used for the averaging (data extrapolated from WinAtrec validation documentation).

2.1.6 Measurements on averaged waveforms versus beat-to-beat measurements.

Even after reducing the variability linked with heart rate variations (using bin stratification), hysteresis (imposing stability) or autonomic factors (focusing on well-defined circadian periods), some residual variability related to other factors (on for all the short-term respiratory related variations) will still characterize the individual beats used for averaging. It is thus legitimate to question how representative a measurement performed on an averaged waveform can be with respect to the population of measurements from the individual beats used to obtained the averaged waveform.

WinAtrec validation addressed this specific issue on both real and on simulated data and we will report three significant examples. In Figure 6a, results from a real case example are reported: the distribution of beat-to-beat QT measurements is displayed together with the single-value QT measurement (vertical line) obtained on the waveform derived averaging all the individual beats from a 8-hour time window (12:00-20:00; RR interval range: 610-1230). In both cases (i.e. on beat-to-beat and on the averaged waveform) the QT interval was measured by the same algorithm implemented in WinAtrec used in fully-automatic (no user overreading) mode. In this algorithm, the T wave offset definition is based on first derivative adaptive threshold (16).

Of note, the averaged waveform of this experiment was intentionally derived without using any selection criteria (no RR bin stratification, no stability imposed), and thus maximizing all sources of variability. Indeed, the range of QT intervals is fairly large and also contains the algorithm "mistakes" (in the small tail of the left hand of the distribution, and above 500 msec on the right hand). The range of beat-to-beat QT intervals typically seen with RR bin is of course much smaller and reduced to only few milliseconds, particularly when a stable model is imposed.

The beat-to-beat distribution of Figure 6a is not symmetric and it has faster descend at QT intervals higher than then mean value (423 msec) and with a small tail centred around 300 msec. The median and the mode (most frequent) values were respectively 420 and 411 msec. The measurement derived from the averaged waveform was 410 msec thus reflecting the mode (most frequent value) of the distribution.

The same behaviour is confirmed on simulated data. In Figure 6b and 6c, the distribution of individual QT intervals was predetermined to have respectively a rectangular and a triangular shape centred at 400 msec and covering the 350-450 msec range. Like in the real case example, the QT interval measured on the averaged template matched with the mode of the distribution (which for these two simulations also correspond the mean and median values).

These results indicate that from a pure mathematical standpoint, and at least with respect to the measurement algorithm implemented in WinAtrec, measurements performed on the averaged

waveform reflect the most frequent values of the measurements from the individual beats used for the averaging, and thus are not biased by extremes values from the individual beat population.

2.2 Audit Trail of RR Holter bin

One of the big concerns with the implementation of Holter bin approach in clinical trials is that of a proper audit trail on the individual beats used (averaged). For each period analyzed, WinAtrec automatically generates a log file where a beat-to-beat report is stored. The log file includes an header where user selectable options chosen are reported (for example the length of the observation period, bin resolution, span of RR interval considered). The header is followed by a beat-to-beat table where time of occurrence, beat label, RR interval, and bin allocation of each individual beat in the analyzed period is reported. This table allows a-posteriori verification of proper bin allocation and verification of proper beat exclusion (based on either beat labeling or on stability criteria). The table is followed by a summary where basic statistics (total number of included/excluded beats) and number of individual beats averaged in each bin are reported. Figure 7 is an extract of the Holter bin beat-to-beat report from a real case.

3. The hysteresis dilemma

Repolarization duration does not respond instantaneously to sudden heart rate changes and the QT interval takes time to adapt to heart rate changes. This phenomenon is well known and has been observed and described since many years (15). During exercise, hysteresis is very easily seen in the QT/RR plane as the state map curves follow two completely separate patterns during the exercise and the recovery phases (19). The most critical consequences of this phenomenon is that using the preceding RR interval, either for correcting or even, as in our case, to decide bin allocation, may be quite dangerous. In Figure 8, an ideal model for hysteresis is shown on the QT/RR plane (each circle identifying a singe beat): in the centre we have a steady-state (QT_1, RR_1) pair. If we imagine an ideal step increase in heart rate (i.e. a sudden acceleration) the RR interval will jump from RR_1 to

RR_3 ($RR_3 < RR_1$) while the QT interval will take time to reach the new steady state value QT_3. During the adaptation phase QT intervals are **longer** than at steady state value QT_3. Conversely, an ideal step decrease in HR (a sudden deceleration), will trigger a jump increase in RR ($RR_2 > RR_1$), and an adaptation phase with observed QT intervals shorter that the new steady state QT interval (QT_2). These shorter/longer QT intervals during adaptation times will have two major consequences:

1) During adaptation, for a fixed RR interval we would observe several different values of QT with a consequent altered correction mechanism (if we correct the QT interval). In the context of an averaging approach such as the Holter bin, individual beats with different QT intervals would be included in the same RR bin.
2) ANY QT/RR regression model fitted to all observed data would produce altered results with weaker (less steep) slopes observed when keeping all (stable and unstable) observations.

The model of Figure 8 is purely ideal, as we do not have sudden step changes in a daily standard scenario (the closest we can get would be using pacemakers or running an exercise-test protocol). On the other hand, the hypotheses derived can be verified on real data. Figure 8 has been obtained from a normal subject with substantial physical activity during the recording. The averaged RR interval in the period analyzed in the example was 700 msec (see the histogram in upper right corner of the Figure). The superimposed waveforms shown in Figure 8 were obtained respectively averaging all the beats with a preceding RR interval of 630 msec (dark pen waveform), and only averaging the beats preceded by a stable heart rate (light pen waveform). Thus, the RR bin shown (RR=630), corresponds to an heart rate faster than the mean heart rate of the explored period, and potentially includes both steady-state values (for the RR=630 level) and adapting periods that we could assume to be acceleration sequences. The “ALL” beat (unstable) waveform overtly shows

a longer QT interval than the stable waveform, confirming the hypotheses of the model. Of note, the number of averaged beats in the stable waveform is significantly smaller than that in the unstable waveform (70 versus 151).

The example shown in Figure 9 was taken intentionally as an extreme case with "a lot" of hysteresis (a normal subject which was active during the period analyzed). However, the same type of results (observing shorter QT intervals whenever the heart rate is below the averaged heart rate and longer QT intervals in heart rate ranges above the mean heart rate), can be confirmed in general, although in many cases (particularly when the subject analyzed was forced to keep resting condition by the clinical protocol) the differences between the stable and unstable model were minimal.

Ideally, the amount of hysteresis should be quantified on a case by case basis and a stable model should be imposed anytime the hysteresis would cross a certain threshold. Certainly, a good way to minimize the problem would be to carefully define protocols aimed to minimize a-priori the presence of hysteresis (for example limiting physical activity and make sure the ECGs analyzed would be taken only after stable heart rate conditions).

What needs to be clear is that hysteresis is not a methodological pitfall of an approach more than another, but rather a physiologic phenomenon that can affect the data on a case-by-case magnitude. We strongly believe that the Holter bin method, through the intrinsic concept of selective beat averaging, is actually one of the existing methods that better control the presence of hysteresis. Clearly the price paid to take this into account can be that of excluding a significant amount of beats that, depending on the definition of stability imposed, can become a big percentage of total available data.

Table 1 reports the results from a real case example that help us to understand the price of hysteresis. Data from the table are taken from a normal subject and are based on a 2-hour time period (16:00-18:00),with an averaged heart rate of 60 beats per minute (RR=1000). The RR Holter bin algorithm was run using a "RR-1 only" model (i.e. no control of hysteresis or all beats included)

and using the stability criteria from section 2.1.3 with a progressively increasing observation period (10, 20, 30 and 60 seconds). In the second column of the table the QT interval from the RR bin at the averaged RR of the considered period (RR_{1000}) is reported with (in parenthesis) the number of individual beats averaged. Last columns also report the QT interval associated with two RR bins away from the averaged RR, respectively RR_{1050} and RR_{950}.

Model	QT_{RR1000} (n)	QT_{1050} (n)	QT_{950} (n)
RR-1 only	345 (1406)	358 (318)	345 (213)
10 seconds	345 (1048)	360 (152)	345 (124)
20 seconds	345 (988)	360 (122)	343 (87)
30 seconds	345 (982)	362 (105)	343 (84)
60 seconds	345 (967)	362 (79)	340 (49)

Table I: The price of hysteresis

The price "paid" to impose stability is apparent. Even with a short observation period (10 seconds), the "loss" of beats is already significant, although more important (in percent) away from the averaged RR (in the RR_{1000} bin the number of included beats changed from 1406 to 1048, a 25% loss; in the RR_{1050} bin it changed from 318 to 152 beats, a 52% loss). This loss of beats progressively augmented by increasing the length of the observation, although it was less pronounced in the central RR bin. With 60 seconds observation period, the loss was 31%, 75%, and 77% respectively for the RR_{1000}, RR_{950} and RR_{1050} bins, with an overall total loss of 842 beats out of 1937 initially available (43%). In the central (averaged RR) bin, the QT interval did not change with the imposed stability whereas it progressively increased and decreased in the RR_{1050} and RR_{950} bins. This observation is perfectly in line with the ideal model previously described, i.e. without hysteresis control the QT interval is longer at faster heart rates (shorter RR intervals) and shorter at lower heart rates (longer RR intervals).

In the Alfusozin study, the study that gave the visibility of this technology to the pharmaceutical world, the Holter bin method was applied using the "only RR-1" model, i.e. without

using the stable model and hysteresis was intentionally minimized at the protocol level (8). This decision (whose discussion is beyond the scope of this chapter) led to some confusion and criticisms which created the misconception that the Holter bin approach cannot correct hysteresis or (even worse) that hysteresis is a problem specific to this method. All the arguments reported should have clarified that this is definitely not the case.

4. QT/RR relation with the holter bin method

An intrinsic feature of the Holter bin method is that only a single QT interval will be derived from a given RR interval. In the QT/RR plane this characteristics leads to a plot with a limited number of QT/RR pairs (one per each bin). A thorough discussions on the advantages and problems of this is beyond the scope of this chapter and has been exhaustively covered in literature. Actually, the method itself was initially developed with the purpose of better assessing QT dynamicity, and in particular the QT/RR relationship. The most important and well-accepted findings can be summarized as follows:

- When the inspected period (i.e. the period where the method is applied) is well defined from an autonomic nervous system perspective (for example avoiding to mix day and night) the QT/RR relationship is strongly linear with high correlation coefficients (16,20,21,22)
- The relationship is stronger (i.e. steeper) if we focus on stable heart rate conditions. In other words mixing stable heart rate and hysteresis periods lead to a different QT/RR relationship (18). Figure 10 show the QT/RR plot from a real case example and are extracted from a 4 hour period. In Figure 10a all the beats (n=19846) were included whereas in Figure 10b a 60 seconds stability period was imposed (n=7412, i.e. almost 2/3 of total beats were excluded). While remaining in both cases highly linear (r = 0.96), the slope of the stable model was significantly steeper (again in perfect line with the model of Figure 7).

Assessment of QT dynamicity has been one of the initial focuses of WinAtrec and several works confirming the above statements have been published on the matter, both on healthy subjects (20,23) and in pathological populations (21,22).

5. Working with RR bin templates: the serial approach

One of the strongest and most practical opportunities offered by the Holter bin approach is certainly its intrinsic orientation toward serial analysis, i.e. toward the comparison of records taken at different time points.

Indeed, the fact of sorting all the analyzed periods by heart rate and to obtain a single reference waveform for each RR interval bin facilitates the superimposition and quantitative comparison of templates obtained under different conditions during the same recording (for example day versus night or comparison between periods with different drug concentrations), or across recordings taken at separate time-matched periods (e.g. baseline versus drug). It is thus possible to compare parameters and measurements from ECG waveforms from different periods (the so-called comparison at identical heart rate), without the need to normalize or correct the observations (e.g. the QT intervals) for heart rate changes.

An example of this serial analysis comparison at identical heart rate is shown in Figure 11 where ALL the templates (i.e. from all the families) of a given RR bin are overlaid. The user can make direct assessment of the QT changes throughout the periods at the same heart rate.

In the example of the Figure, there are five separate time matched periods and the overlapped templates are those associated to the bin RR = 970 (which is common to all five periods). User can jump to the next or previous RR bin by using the arrow buttons in the upper right part of the screen.

The output of this comparison at identical heart rate is a serial table where each measurement variable chosen for the analysis is repeated (columns) over each RR bin (rows). This worksheet organization enables easy derivation of statistics (e.g. delta of variables when comparing)

6. Limitations of Holter bin method and possible evolution

From a pharmacological point of view, the most relevant limitation of the Holter bin approach is that long-enough period of stable conditions (in particular, plasma concentrations) are required to populate an acceptable number of bins. This may become a problem with compounds characterized by a fast response where important periods to be captured (such as the peak concentration period) would be just too short to apply the method. Under these circumstances, a more standard beat-to-beat approach, or even a time-based averaging applied over short durations may be more suitable. WinAtrec can already generate time-based templates and apply the same type of comparative analysis (in particular the serial approach described in section 5) available form the Hotler RR bin method.

The architecture of the method facilitates the extension toward other selection criterion models. For example, the selection of bins could be based on different physical activity periods with the use of an activity status index, considering different sleep conditions (25) or focusing over awakening periods (26). The support for these more sophisticated stratification criteria would require additional biomedical sensors that could become available with continuous ECG recording. Alternatively, selection could be driven by the occurrence of specific events, such as arrhythmias or ischemia. As a future direction it may also be interesting to take into account, in addition to the dependence of the actual QT value on a certain number of previous RR intervals, also the action of inputs capable to modify QT interval independently of RR interval changes (27).

Last, the Holter bin approach should not be seen as a method limited to the analysis of repolarization but rather as a technique suited for the quantitative analysis of electrocardiograms in the broad sense. Interestingly enough, the first application of the method in a pharmaceutical clinical trial was for the analysis of QRS intervals (see next section).

7. Holter bin method usage in pharmaceutical trials

7.1 Usage of Holter bin method for assessment of drug-induced QT prolongation in class III antiarrhytmic agent.

The objective of this study was to study the influence of heart rate on dofetilide-induced QT prolongation among healthy volunteers (24). Ten healthy volunteers underwent two 24-hour ECG recordings, one in the absence of dofetilide and the other after a single oral dose of 0.5 mg dofetilide. Two 4-hour periods were defined during the second recording: Dh, which corresponded to stable high concentration of the drug, and D1, which corresponded to low concentration of the drug. Corresponding baseline recording periods, Ch and C1, matched by time with Dh and D1 were selected from the control ECG recording in the absence of dofetilide. Rate-independent changes in QT duration were analyzed using the Holter bin method with a 60 seconds stable model. The serial comparison approach described on section 5 was used both to compare in-between recordings (comparison between different concentration periods) and across recordings (baseline versus drug).

During Dh, dofetilide induced a mean 12% lengthening of ventricular repolarization. Dynamic ECG analysis showed that this prolongation increased as RR intervals became longer, a phenomenon known as reverse rate dependence. However, QT prolongation persisted at the shortest (600 ms) RR intervals that could be analyzed. More interestingly, during D1, dynamic ECG analysis showed a persistent, although small, effect of dofetilide on both QT prolongation (3%) and reverse rate dependence of this effect. The study concluded that Dofetilide prolongs QT duration, and this class III effect is influenced by heart rate. The Holter bin method was shown to be sensitive to detect small changes during low concentration periods.

7.2 Usage of Holter bin method for QRS interval changes assessment: the flecainide extended release study.

This study was conducted in the Lariboisiere Hospital between 1999 and 2002 (7,28). The goal of this trial was to inspect pharmacodynamic equivalence of flecainide acetate immediate-release (IR) and controlled-release (CR) formulations as assessed from QRS duration in patients previously treated with the IR formulation (ref). Patients were blindly randomized to the IR group (100 mg b.i.d, n = 25) and to the CR group (200 mg o.d, n = 23) and ECG parameters were measured at baseline and at Week 8 from 24-hour Holter.

The Holter bin approach was used to derive QRS interval durations at different classes of constant RR intervals (bin resolution: 10 msec; stability period: 1 minute) over the entire 24 hours. Using Hodges-Lehmann estimates of the difference between IR and CR groups for percent change in QRS duration between baseline and Week 8 was 1.6% [-0.1; 3.7], indicating that both formulations were pharmacodynamically equivalent. Median QRS values (102 ms *versus* 100.1 ms at baseline; 103.15 ms *versus* 99 ms at week 8) as well as first and third quartiles were very similar in both groups (Table II). The correlation between QRS duration and RR classes at baseline was highly significant ($p < 0.0001$). The study conclusion was in favour of pharmacologic equivalence between the two different concentration formulations.

	Flecainide IR (N = 25)	**Flecainide CR** (N = 23)
Baseline (ms)		
Median (ms)	**102.00**	**100.10**
Q1; Q3 (ms)	98.00; 110.38	95.43; 109.92
Week 8		
Median (ms)	**103.15**	**99.00**
Q1; Q3 (ms)	98.00; 109.00	94.24; 105.36
% change between baseline and Week 8		
Median	**0.04**	**-0.5**
Q1; Q3	-0.88; 2.74	-2.33; 0.92
Hodges-Lehman estimate [95% CI]	**0.9** [-0.4; 2.2]	**-0.7** [-2.7; 0.2]
Hodges-Lehman estimate of IR - CR [95% CI]	**1.6 [-0.1; 3.7]**	

Q1; Q3: First and third quartiles. IR: Immediate-release formulation. CR: Controlled-release formulation. 95% CI: 95% confidence interval.

Table II: Results for the flecainide extended release study

7.3 Usage of Holter bin method for QT interval changes assessment: the Alfusozin study

This crossover study included two single doses of the α_1-adrenergic receptor blocker alfuzosin, placebo and a QT-positive control arm (moxifloxacin 400 mg) in 48 healthy subjects (8). Bazett, Fridericia, population-specific (QTcN) and subject-specific (QTcNi) correction formulae were applied to 12-lead ECG recording data. QT1000 intervals (QT at RR=1000 msec) were obtained from Holter recordings using custom software to perform time-matched, subject-specific, rate-independent QT analysis.

The Holter bin approached was applied to analyze a 4-hour period centred around the peak concentration of alfusozin. At the therapeutic dose (10 mg), alfuzosin did not induce any significant change in the QT1000 (+0.1 msec 95%CI[-2.5;2.6]), QTcN (+0.5 msec 95%CI[-2.0;3.0]) or QTcNi intervals (+0.5 msec 95%CI[-2.0;2.9]). Alfuzosin at a supra maximal dose 40 mg induced a small but significant QT1000 increase of 2.9 msec 95%CI[0.3;5.5]. This increase was lower than that induced by moxifloxacin at the therapeutic dose (+7.0 msec 95%CI[4.4;9.6]). Alfuzosin 40 mg increased heart rate by 3.7 bpm, concordant with the greater increase observed with the Bazett formula. The direct Holter-based QT interval measurement method is sensitive to detect small drug-induced QT changes. Alfuzosin produced a slight non significative increase in heart rate and did not significantly prolong QT interval at the therapeutic dose. Alfuzosin's effect on QT interval at 4 times the therapeutic dose was less than 5 msec.

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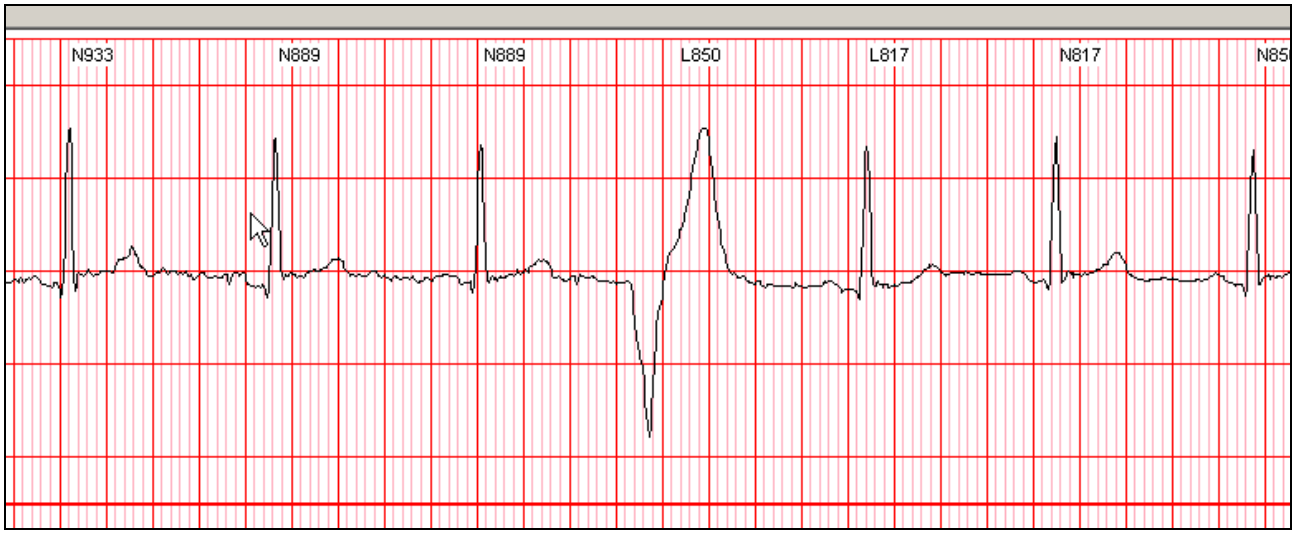


Figure 1: Example of interpolation: The two L-labelled beats will not be used by the RR bin method but only for the computation of the beat-to-beat averaged heart rate.

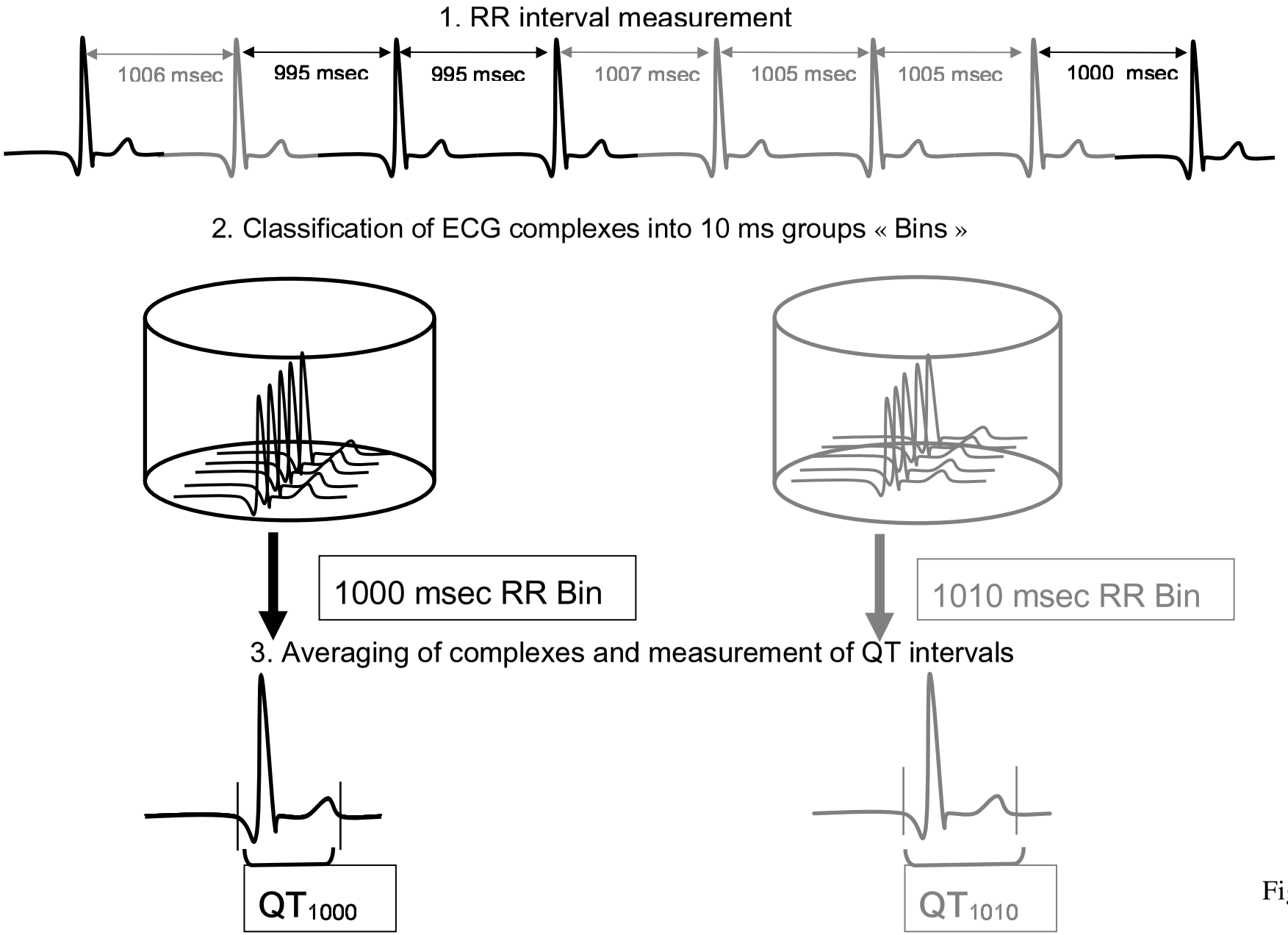

1. RR interval measurement
1006 msec
995 msec
995 msec
1007 msec
1005 msec
1005 msec
1000 msec
2. Classification of ECG complexes into 10 ms groups « Bins »
1000 msec RR Bin
1010 msec RR Bin
3. Averaging of complexes and measurement of QT intervals
QT1000
QT1010

Figure 2

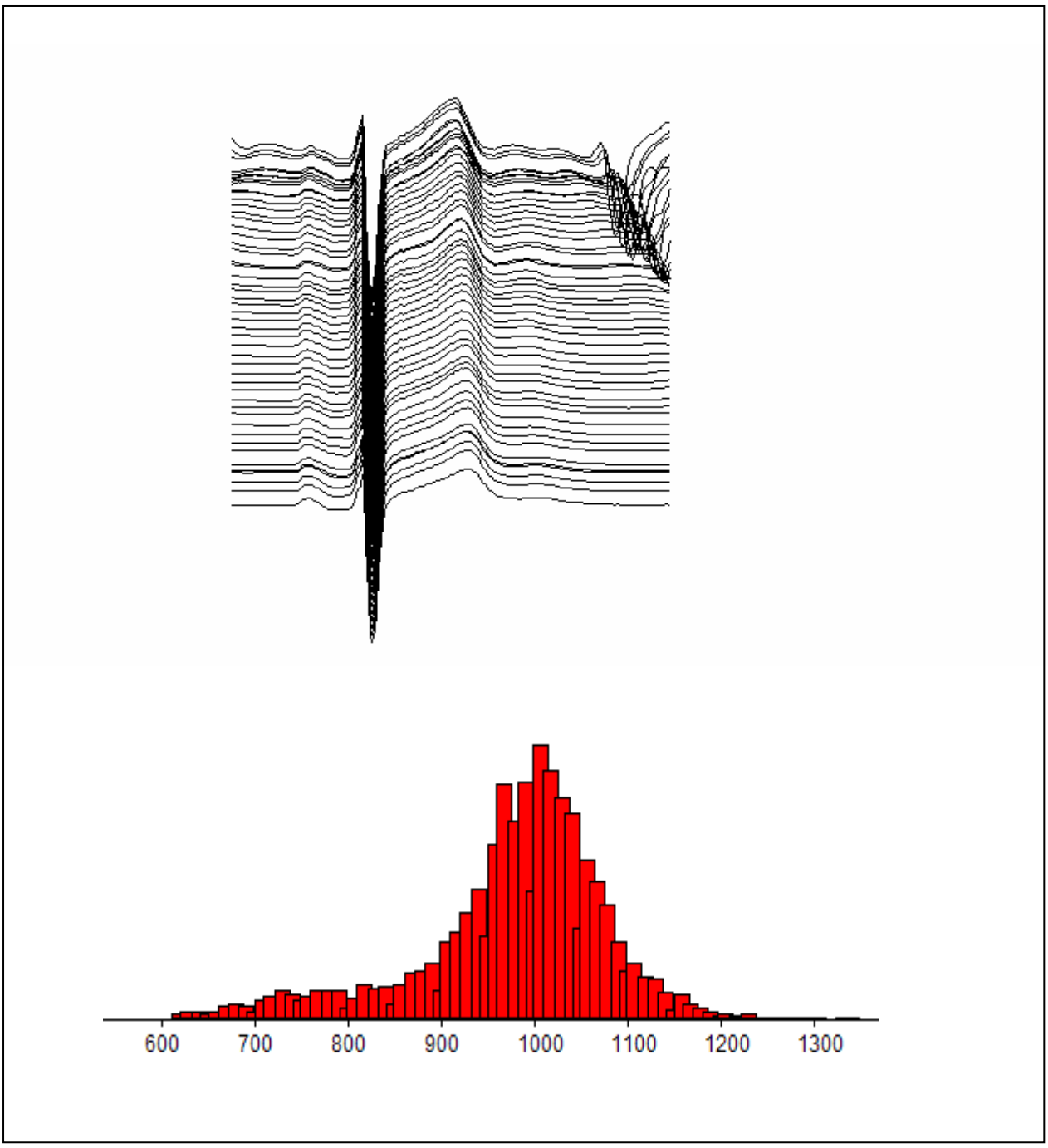


Figure 3: Cascade display of a family of RR bin templates with the associated histogram

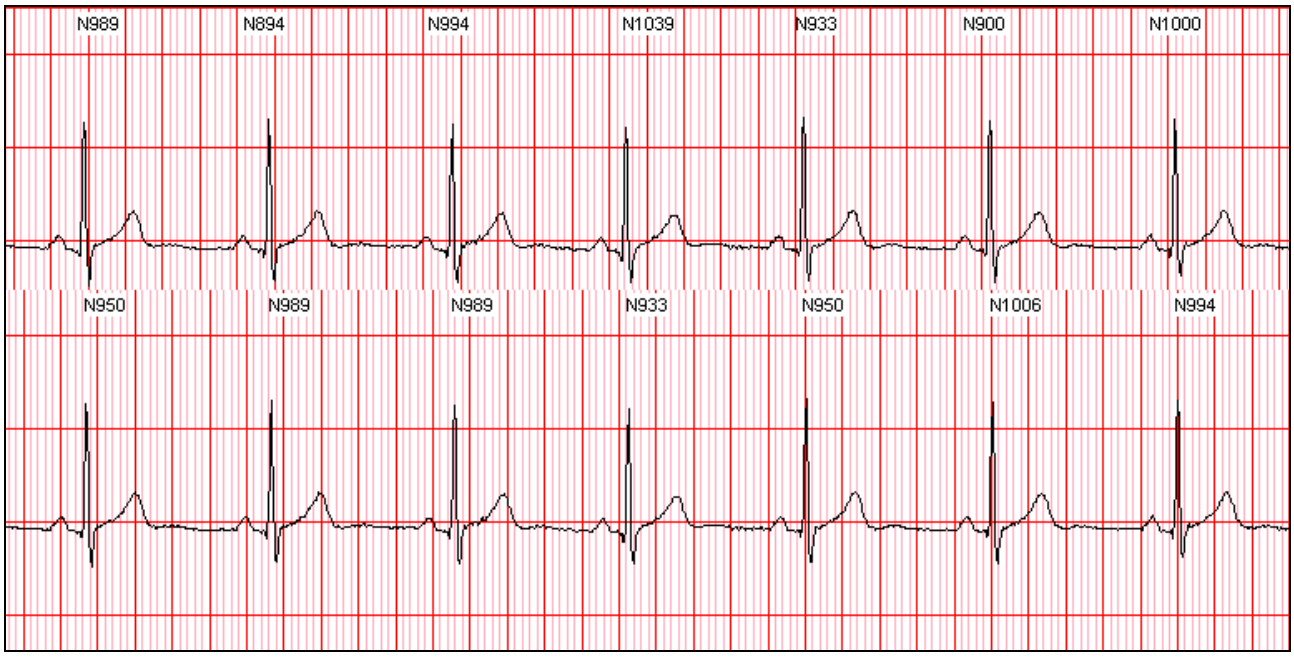


Figure 4: ECG strip shown before (upper panel) and after (lower panel) jitter correction. Before correction, the positioning of beat labels fluctuates form one beat to another whereas after correction they are stabilized. Even the RR interval sequence is seriously affected with changes up to 100 msec long.

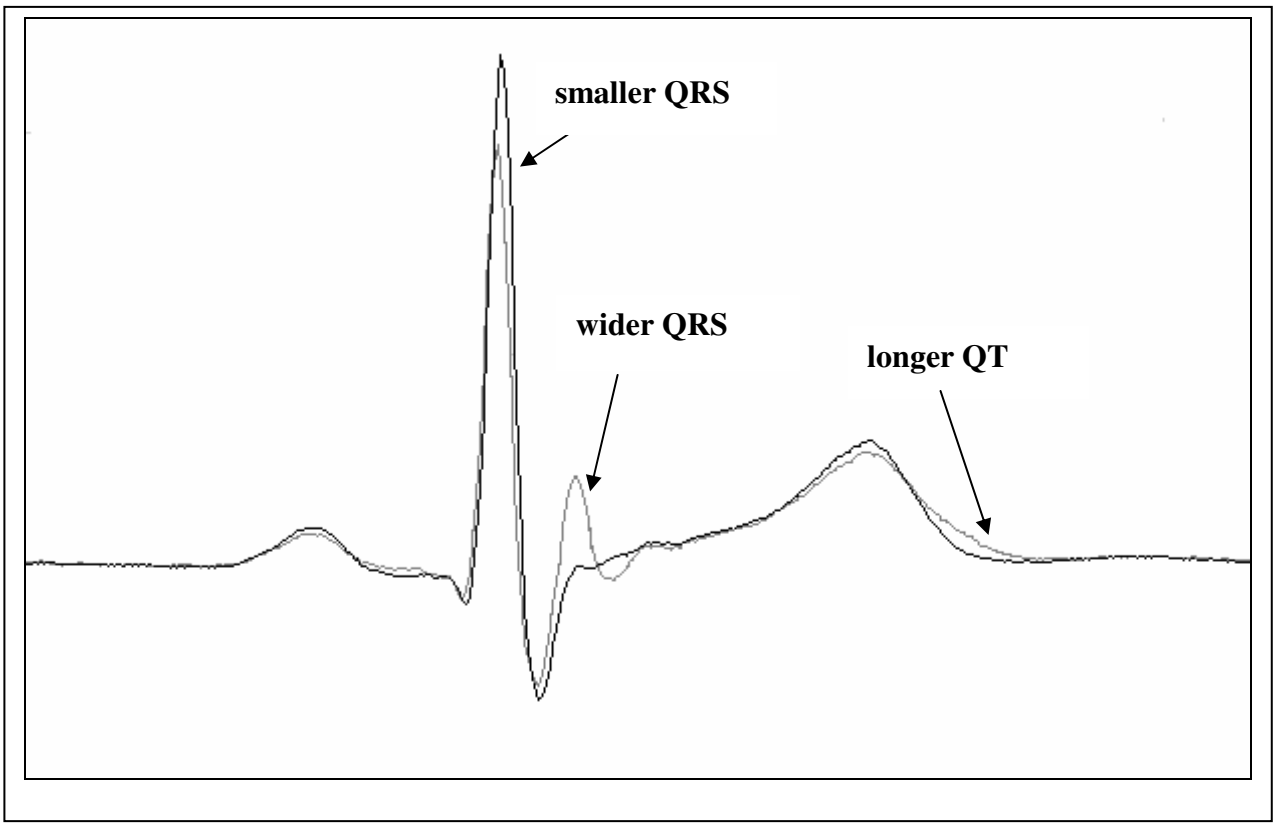
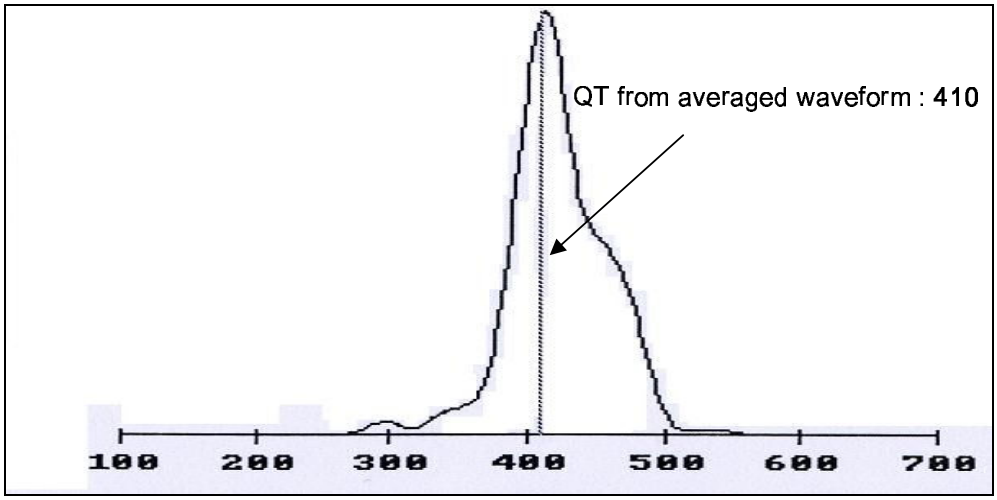
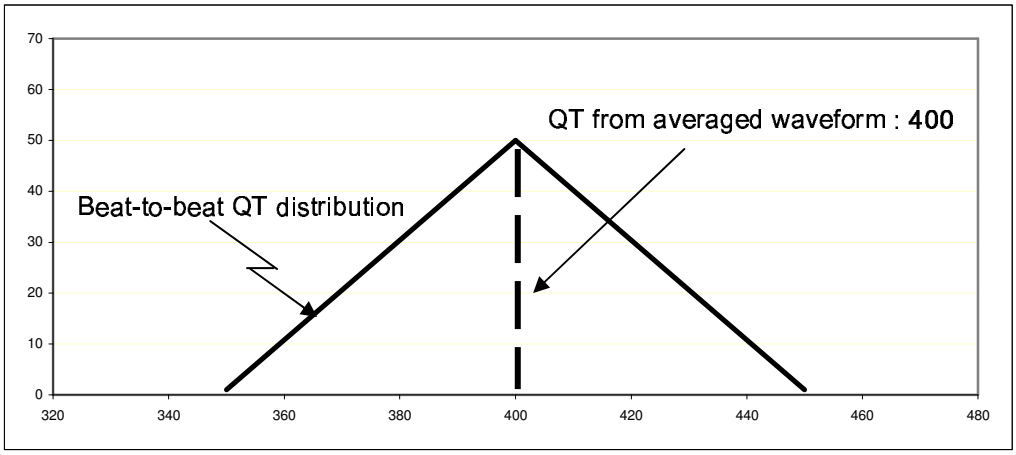


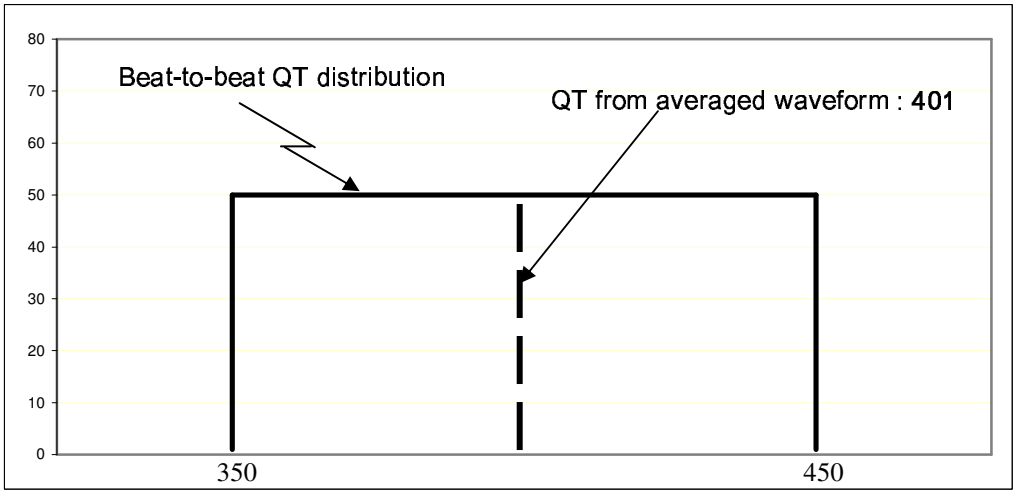
Figure 5: averaged complexes from the ECG of Figure X-1. The waveform in light is that obtained averaging beats before jitter correction; the bold waveform is the that obtained averaging the same beats after correction. The distortions (resulting is a smaller and wider QRS and in a longer QT intervals) are apparent.



A



B



C

Figure 6: Comparison between beat-to-beat distributions and single-value (from the averaged waveform) of QT intervals from a real case example (panel A) and from two simulation experiments based on triangular (panel B) and rectangular (panel C) beat-to-beat distributions.

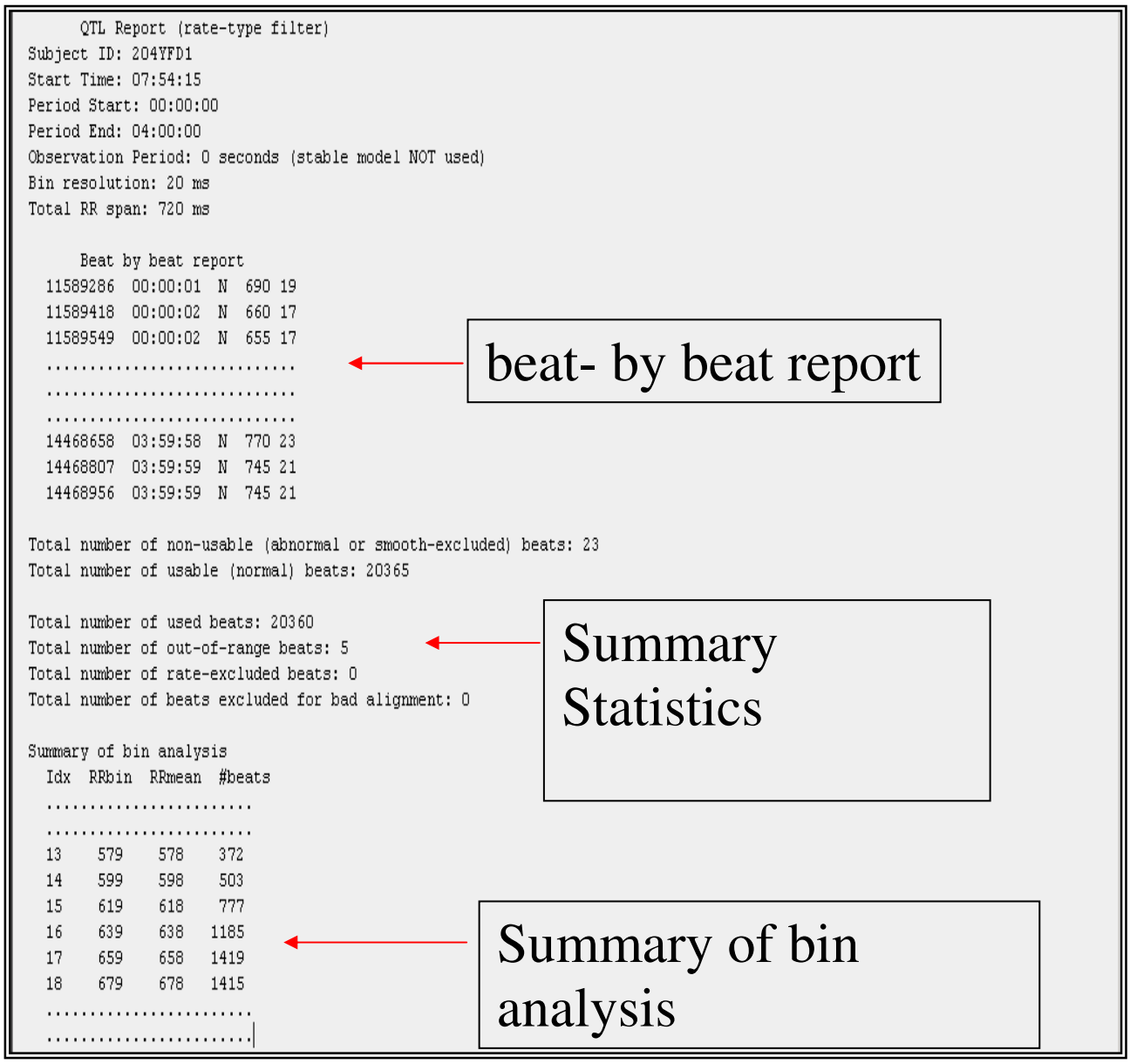


Figure 7: Extract of Holter bin beat-to-beat report

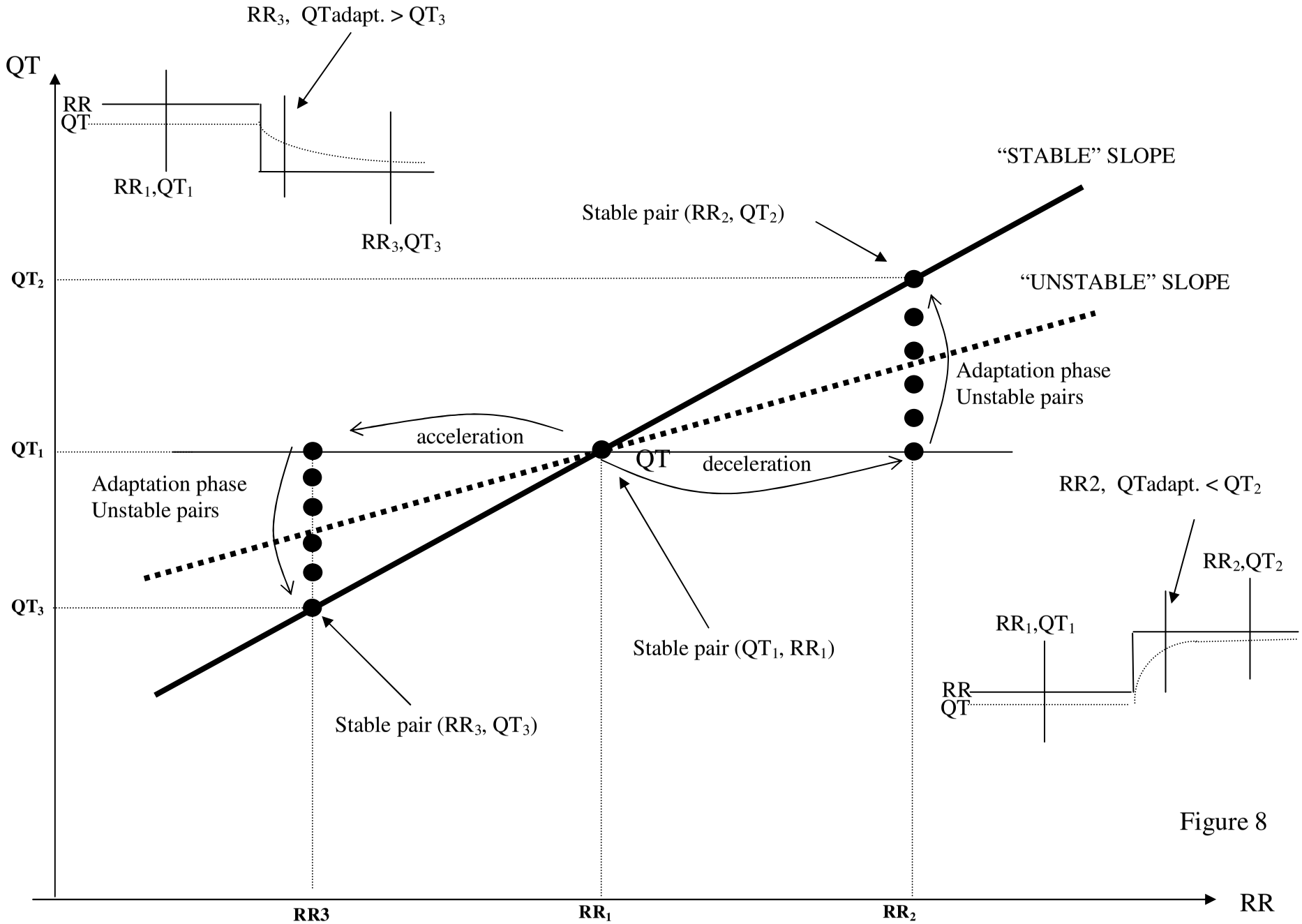
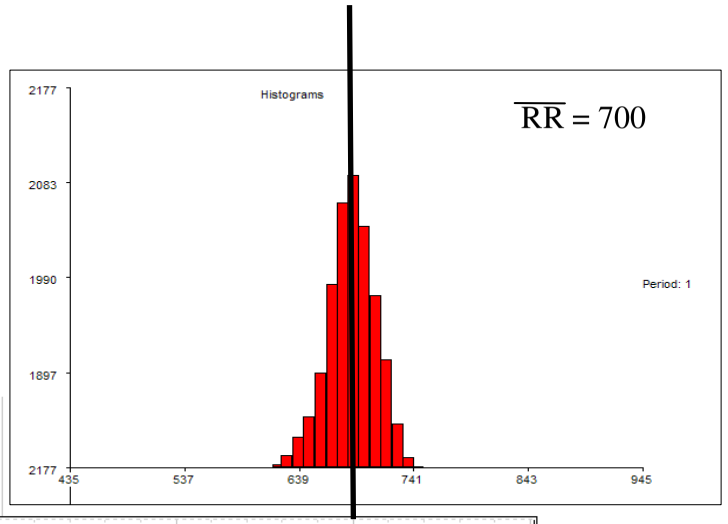

RR3, QTadapt. > QT3
QT
RR
QT
RR1,QT1
RR3,QT3
"STABLE" SLOPE
Stable pair (RR2, QT2)
QT2
"UNSTABLE" SLOPE
Adaptation phase
Unstable pairs
acceleration
QT1
QT
deceleration
Adaptation phase
Unstable pairs
RR2, QTadapt. < QT2
RR2,QT2
RR1,QT1
RR
QT
QT3
Stable pair (QT1, RR1)
Stable pair (RR3, QT3)
RR3
RR1
RR2
RR

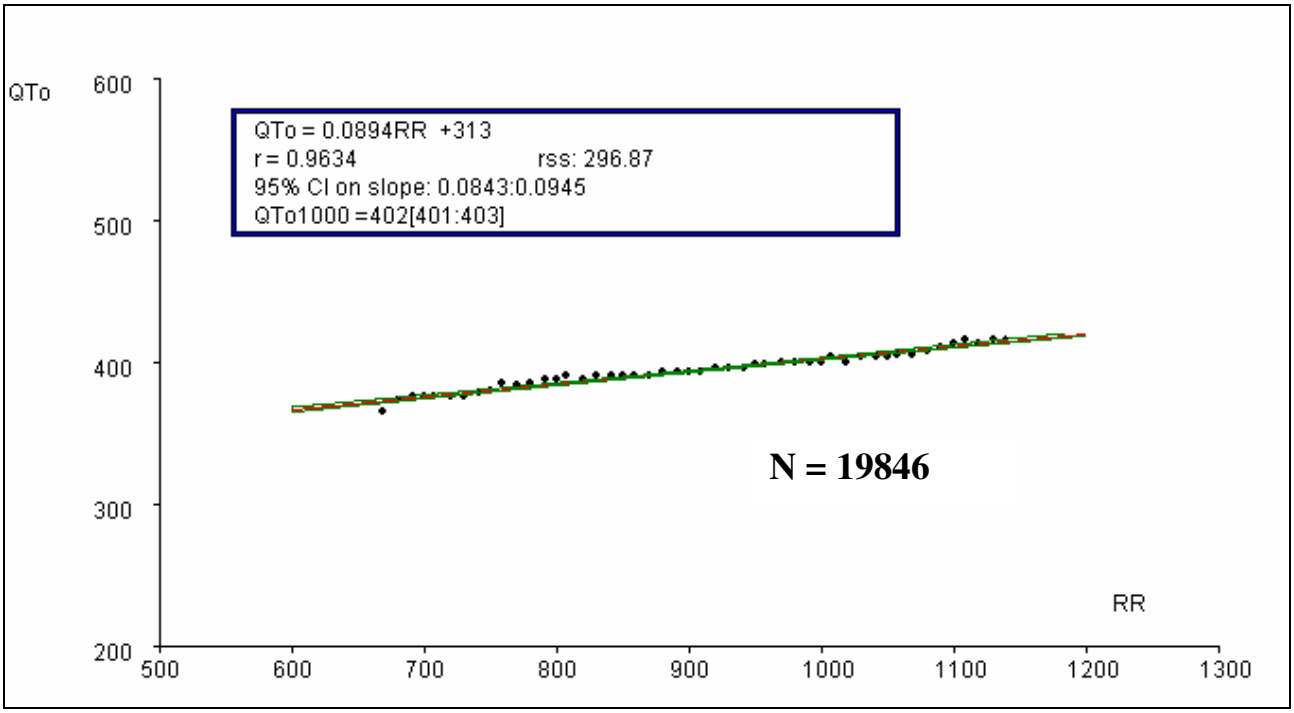
Figure 8

Same ECG, same time period,
Only difference in usage of stable model



Period: 14:00 -16:00

Figure 9



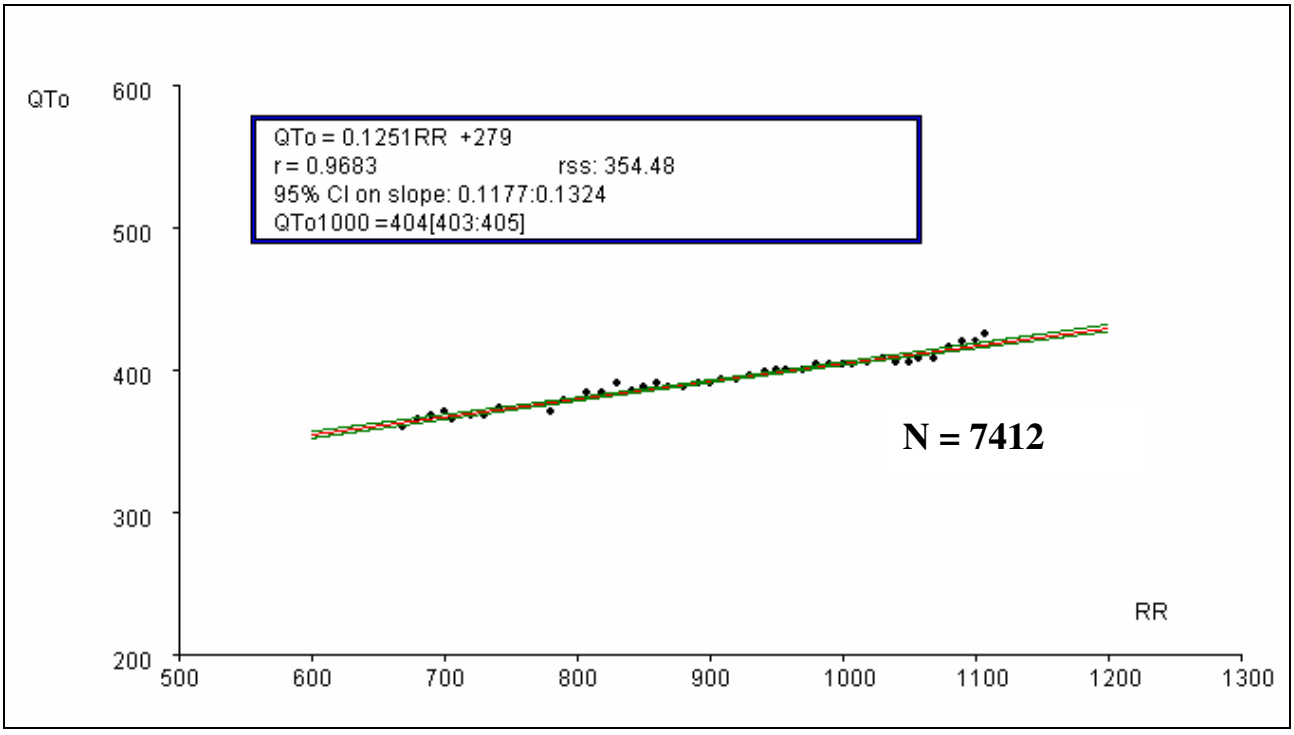


Figure 10: QT/RR plots using the "RR-1 only" model with all beats included (panel A), and using 60 second stable model (panel B)

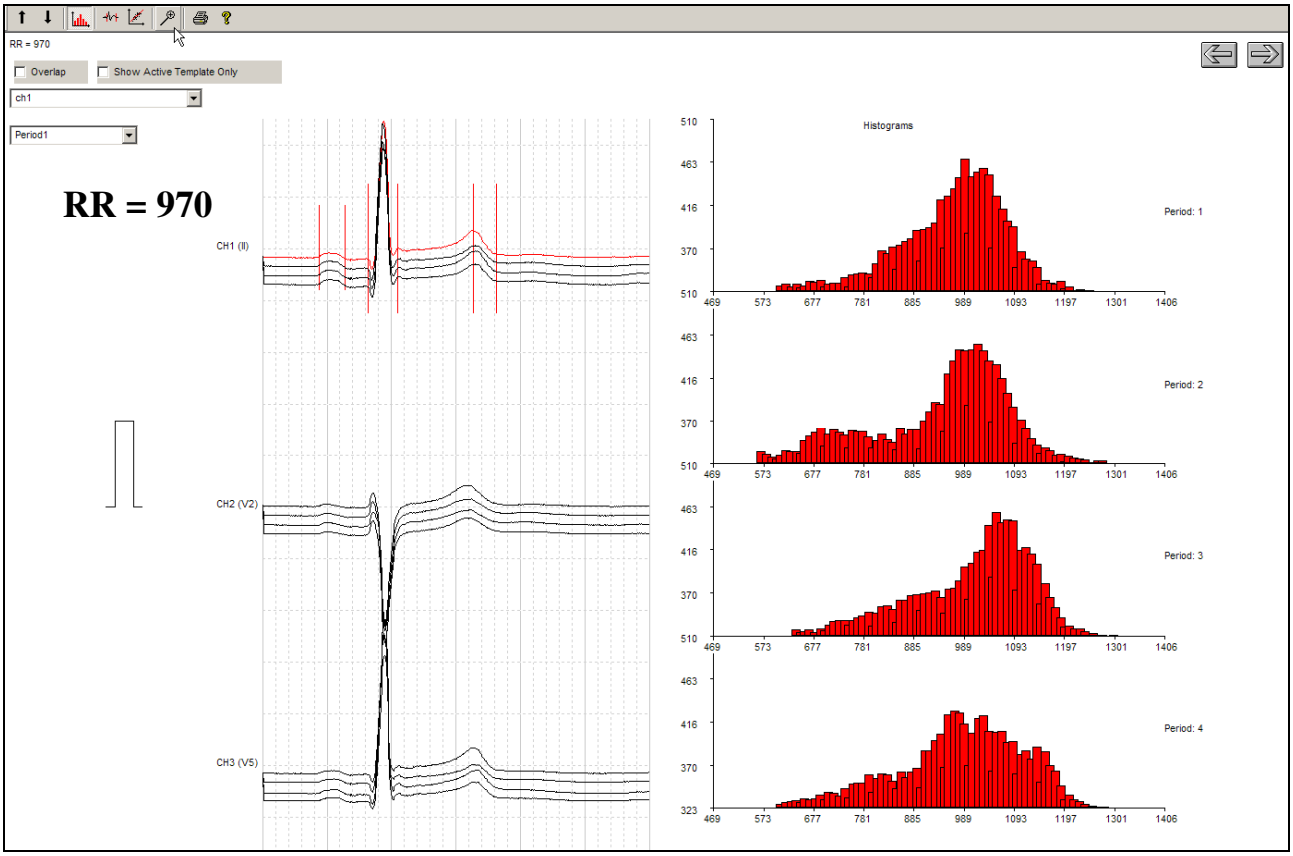


Figure 11 : Example of serial analysis: the five templates overlaid are from five different Holter systems and come from time-matched 4-hour periods (12:00-16:00)