AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

At present nobody really knows for sure which methodology is the optimal one in regard to QT correction for drugs with a substantial effect on heart rate or autonomic tone. To this end, AMPS is happy to announce that Dr Fabio Badilini is collaborating with a panel of experts, including FDA officials, to write a white paper summarizing the current consensus regarding reasonable approaches to the problem. The panel has chosen to describe methods which are believed will improve this assessment and encourage further research in this area. The title of the paper is: "QT/QTc Evaluation for Drugs with Autonomic Effects" and it will be published in 2010 by the Cardiovascular Safety Research Consortium (CSRC). The CSRC is a public-private partnership developed to foster collaboration among academia, industry, and regulatory agencies with a focus on cardiac safety issues regarding drugs in development. We will keep you posted on progress and the publication date.

In this last issue of 2009, we welcome a contribution from Dr Fabrice Extramiana MD, PhD, Assistant Professor at the University Paris 7, he is a member of the cardiology department of the Lariboisière Hospital in Paris and the author of many relevant publications. Dr Extramiana is probably one of the most enthusiastic, and most intensive, users of the well known Holter Bin method. The Lariboisière hospital is in fact the very cradle of this technology and the place where the WinAtrec code (the AMPS product implementing Holter Bin) was written, as he explains in his contribution and where it is used daily for patient's diagnosis. Dr Extramiana's research work speaks for itself, and his constant flow of ideas and suggestions concerning how to improve the algorithm have been invaluable both to AMPS and to the research community in general. We are positive that you will find his contribution very stimulating.

Please accept our best wishes for a very happy end of year holiday, and all the best for 2010!

The AMPS Team.

A Noteworthy Contribution:

The added value of using selective beat averaging approach for Holter-based QT evaluation.

By Fabrice Extramiana, MD, PhD, Lariboisière Hospital, Paris.

Although the surface ECG QT interval duration corresponds to both ventricular depolarization and repolarization times, analyzing ventricular repolarization from surface ECG is not an easy task. Reasons for such a difficulty have been long identified. A crude cause is the difficulty in defining the "true" QT duration and measuring it accurately and reproducibly. Determination of the end of the T-wave had been standardized by Lepeschkin and Surawicz for manual measurements (1) and more recently automatic measurements on digital recordings have made measurements highly reproducible. However, the main difficulties are related to the complexity of ventricular repolarization properties.

We are going here to discuss briefly some of these ventricular repolarization properties that need to be taken into account and to describe the software solutions we used to deal with them.

A software solution

The Winatrec software has been developed by Fabio Badilini in our department during his stay at Lariboisière hospital in Paris and afterward with AMPS. Winatrec is the windows based evolution of the old Atrec (for "Analyse des Troubles du Rythme par ElectroCardiogramme") program launched by Professor Philippe Coumel during the eighties. Winatrec provides solutions for analyses of

QT interval obtained from Holter recordings and taking into account fundamental properties of ventricular repolarization.

Winatrec is based on a selective beat averaging approach (3) tailored to allow the users to select the averaging method according to a specific repolarization property or to different research goals. The selective beat averaging process may be also adjusted by adding additional averaging filters. For instance, a noise filter can be set in order to reject noisy QRS-T complexes and the minimal number of QRS-T complexes defining a template may also be selected to improve the signal to noise ratio. Some examples and results obtained with Winatrec are described below.

Rate-dependence of QT interval duration

Ventricular repolarization duration displays the fundamental physiological property of being dependent on cardiac cycle length. This rate-dependency has been long recognized and documented in both experimental and clinical settings (4, 5). Conceptually, the easiest way to take into account this effect is to measure QT duration at each of the different heat rates. This may be done by averaging QRS-T complexes by RR interval, an approach called the Rate-Bin method.

The Rate-Bin method may serve as the first step to define the QT rate dependence from Holter recordings. QT rate-dependence itself is a specific property of ventricular repolarization. And this method has been successfully applied to demonstrate ventricular repolarization malfunction observed in the long QT syndrome, short QT syndrome as well as after myocardial infarction (6).

This method has also proved useful for the evaluation of drug-induced QT changes. Initial strategies to account for heart rate influences on QT duration have been to correct the QT using "universal" and population-specific correction formulae. However, since the relationship between heart rate (HR) and QT duration has been shown to be highly individual (7), the current best strategy for HR-correction is to use a subject-specific correction formula based on the subject-specific QT/RR relationship.

Using the subject-specific QT/RR relationship it has also been possible to demonstrate that QT-prolonging drugs may change the QT/RR relationship, showing in patients a reverse use dependent effect that was already demonstrated at the cellular level. As a consequence, the extent of drug-induced QT prolongation is dependent on the heart rate considered (i.e. with larger prolongation at slow than at fast heart rates). In addition, we could show that using the same subject-specific correction formula before and after drug dosing could introduce a systematic bias in QT correction (8).

The Rate-Binning may also be used for direct QT duration comparisons at identical heart rates. We could demonstrate the sensitivity of this method (9) which main benefit is to avoid the need for any QT correction formulae. Thus, no mathematical models are required and no assumptions on the properties and stability of the QT/RR relationship are necessary.

Hysteresis of QT duration adaptation after heart rate changes

The physiological relationship between heart rate and ventricular repolarization duration is complex. Following an abrupt change in heart rate, the QT adaptation is not immediate but achieved within a 3-minute time frame although most QT adaptation occurs over the first minute (5).

As a consequence, QT interval measurement performed just after a sudden HR change would lead to a potential instability in the estimation of QT duration (i.e. under-estimation after HR deceleration and over-estimation after HR acceleration) when compared to stable heart rate conditions. Mathematical models have been proposed to correct for this hysteresis phenomenon (10).

Using the Rate-Binning method, it is possible to select QRS-T complexes not only on their preceding RR interval but also according to heart rate stability during a predefined preceding period, thus excluding abrupt RR interval changes from the analysis. Such tools may be of interest since we have shown that the exclusion of rapid heart rate changes slightly influences the results of the magnitude of drug-induced QT changes in healthy subjects (11).

Time-dependence of effects on QT duration

Rate-Binning derived methods (i.e. subject-specific correction or comparison at identical heart rate) are associated with a better management of the complex interplay between heart rate and QT duration. However, its intrinsic limitation is the loss of time track. Indeed, the Rate-Bin method is accurate only if it is used over a relatively long period with a relatively wide range of heart rates. If drugs effects are evaluated, their plasma concentration and as a consequence their pharmacological effects may vary during the evaluation period. The assessment of the time course of drug's effects together with pharmakokinetic data is one of the useful tools to

evaluate the drug concentration-response. In addition, thorough QT studies need to be placebo controlled and since the duration of the QT interval at baseline has been shown to follow a circadian rhythm, serial time-matched measurements are mandatory for any placebo-corrected evaluation.

The selective beat averaging process may be set to average consecutive QRS-T complexes of sinus origin during 1 minute (for instance), thus allowing exact time-matched comparisons between recordings. This method is referred to as the Time-Bin approach.

However, ECGs recorded at the same time-point in the same subject do not necessarily have the same heart rate, thus requiring the application of heart rate correction formula. The current best strategy is to use subject- and condition-specific correction formulae. The Rate-Binning approach keeps track of time-dependent effect while minimizing the imprecision in the heart rate correction process.

Other applications

The selective beat averaging approach may be used when evaluating other ventricular parameters. We used a Rate-Binning approach to evaluate rate influences on T-wave morphology parameters in LQTS patients or after IKr blockade (see reference 6 for examples). In Brugada syndrome, the Rate-Binning approach was used to demonstrate the rate-dependency of ST segment elevation (12) while using a Time-Binning approach we have been able to quantify the Brugada type 1 burden over a 24 hour period (submitted data).

Conceptually, any time-dependent or rate-dependent ECG parameter may be analyzed by using a selective averaging approach which settings may be chosen by the user. Another binning strategy based on user defined "events" (i.e. PVC, abrupt changes in heart rate, short-long-short sequences…) would probably open new areas for the analysis of long-term ECG recordings.

Conclusions

Software solutions for post processing of long term ECG signal have paved the road for quantitative electrocardiography analyzes based on the best available understanding of ventricular repolarisation patho-physiology. The Winatrec software has made possible to demonstrate the reality of fundamental ventricular repolarisation properties in humans, to improve the evaluation of drug-induced QT changes, to describe ventricular repolarisation abnormalities associated with different diseases, and to propose arrhythmic risk stratification tools. These achievements could not have existed without a strong collaboration between engineers, scientists and physicians. Such a partnership should definitely be continued.

References

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Products News

Latest Releases

In the last quarter this major update has been released:

- HeartScope v2: redesign of the old HeartScope tool for a complete Advanced Analysis of Cardiovascular Signals.

Looking forward

In January AMPS is planning to release updates of the following tools:

- Antares v.2.5.x: automatic generation of Representative Beats of the extracted 10 s, 12-leads snapshot, using our automatic algorithm.
- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- CalECG v.3: totally redesigned graphical interface, with new display on ECG signal in predefined format, such as 3 X 4, 6 X 2. Enhanced automatic algorithm for annotation measurements with abnormal beat classification. If desired CalECG v.3 will also include a diagnostic algorithm, embedded in the tool thanks to the cooperation with Glasgow University.
- TrialPerfect v.2: enhanced ECG management, new role definitions, fully compatibility with CalECG v.3 and Fat-QT .

FAT-QT

As announced in the last issue a new product will be part of the AMPS portfolio in the coming weeks: FAT-QT (Fully Automatic Thorough-QT). FAT-QT is a fully automated tool that combining features of two successful and confirmed AMPS tools, namely CalECG and the FDAEcg Suite, will provide in one single tool the capability to perform a fully automated analysis of 12-lead ECG. ECGs will be automatically annotated with the new and improved algorithm of CalECGv3 and, using different scoring-metrics selected by the user, FAT-QT will classify the measured ECGs in different categories. At the end of the process, minutes later, high quality classified ECGs would not require any further review, thus greatly reducing the need for manual review analysis on a small subset of ECGs. FAT-QT will be officially released in January 2010.

AMPS people

Gil Gates, BS

We continue our round of staff introductions with Gil Gates.

Gil received his *Bachelor of Science*s from Louisiana State University in 1988. He joined AMPS in 2006 as Software Development Manager and in this capacity he is leading the team of engineers developing all the AMPS tools, as well as the planning and the design of new applications. In addition to his managerial role Gil also still enjoys hands-on work, he is in fact the head of the TrialPerfect project, the AMPS back-end database that completes the well-know CalECG product providing a complete solution for clinical trials.

Before joining AMPS; Gil has worked in the IT world both in Italy and in the United States, including large companies such as America Online.

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