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

In this last 2013 issue of our magazine we are very pleased to publish a contribution by Dr Pierre Maison-Blanche. Probably most of our readers know Dr Maison-Blanche personally, given the relevance of his work and his proactive role in the world of cardiac safety. Those who have not yet had the privilege of meeting him should know that for the past 30 years Dr. Maison-Blanche has been extensively involved in clinical cardiology and research as a staff member of the Cardiology Division, Lariboisière Hospital (Paris, France), a leading European academic center in this field of medicine, under the leadership of Philippe Coumel, a pioneer in the field of modern Cardiac Electrophysiology. Incidentally, Dr Fabio Badilini met Pierre in Coumel's office for the first time in 1994 when he started his post-doc work in Lariboisière.

Dr. Maison-Blanche is an internationally recognized expert in non-invasive cardiac electrophysiology and has extensive experience in the scientific, clinical and regulatory aspects of electrocardiography in clinical trials. In 1998, he established the Centralized ECG Services Department for MDS Pharma Services and chaired the MDS ECG Advisory Board from 2002 to 2006. From 2006 to 2012, Dr. Maison-Blanche was appointed Chief Medical Officer of Biomedical Systems. He has participated in several meetings with the Food and Drug Administration (FDA) and currently serves as an adviser on ECG issues to many pharmaceutical companies. Since 2012 Dr. Maison-Blanche is a Cardiology Consultant at the Bichat Hospital (Paris, France) and Chief Medical Officer of CardiaBase (Nancy, France).

Dr Maison-Blanche was also an invited speaker at the AMPS-Mortara Regulatory Review of Continuous ECGs Workshop that was held on December 11 in Washington, DC. You will find a full report on the workshop later in these pages.

From the AMPS Team please accept our best wishes for a successful 2014!

A Noteworthy Contribution:

Editing of continuous ECG data: a clinician perspective

Pierre Maison-Blanche, MD, Hôpital Bichat, Paris, France.

Introduction

ECG recording is a cornerstone in Cardiac Safety assessment of new chemical entities (NCE) and this is true as well in preclinical stages (ECG telemetry in dogs is one of the core battery tests from the ICH S7B Guidance), Clinical Pharmacology (Phase 1) trials and later stages of development. Typically, an ECG is collected in resting conditions and modern digital ECG machines offer high quality data from both high sampling rates and high amplitude resolutions. A so called resting ECG includes 12 views of the cardiac electrical activity from the skin electrodes at the body surface and it prints time on the horizontal axis (usually 10 seconds) and voltage on its vertical axis. The ECG was invented by Wilhelm Einthoven in Leiden, Netherlands, in the early years of the 20th Century and strikingly more than one century later, the invention remains widely used in Cardiac Safety evaluation. This is because many abnormalities can be detected by a resting ECG (cardiac rate irregularity, enlargement of a cardiac chamber, block of the electrical impulse ...) at a reasonable cost.

After resting ECG, many other ECG tests were introduced for routine evaluation of cardiac patients, such as Exercise ECG, 24-hour Ambulatory ECG (invented by Norman Holter), High Resolution ECG … Common to these techniques, the ECG acquisition is continuous for a period of time much longer than 10 seconds, and often the patient is not lying in bed but undertaking physical activities. With rapid improvements of software and hardware in the last twenty years, there is actually no more technical limit regarding the duration of continuous digital ECG recordings that can reach up to weeks.

<u>Figure 1A: continuous ECG recording matrix of annotations</u>
The software detects the peaks of the R waves, stores their times of occurrence, and classifies the R waves either as Normal (N) or Ventricular (V). Some systems alternatively will label non normal beats as Abnormal (A). The matrix of annotations is the time distance in milliseconds between R peaks (R-R intervals, than can be N-N, N-V, V-N …). The ECG strip in Figure 1A shows isolated abnormal beats and a run of 3 consecutive abnormal beats. From the matrix, the algorithm can state "VPB, CI 540 msec" for N-V annotation with a distance of 540 msec, or "VRun of 3 beats" for a N-V-V-V annotation. The R-R intervals are multiple of 5 msec because the sampling rate is 200 Hz.

06:24:33	785	N		
06:24:34	785	N		
06:24:35	780	N		
06:24:36	785	N		
06:24:36	795	N		
06:24:37	795	N		
06:24:38	810	N		
06:24:39	820	N		
06:24:40	830	N		
06:24:40	835	N		
06:24:41	840	N		
06:24:42	840	N		
06:24:43	855	N		
06:24:44	740	N		
06:24:44	410	N	PR	SV Run(4) MaxHR : 179 bpm
06:24:44	325	N	PR	
06:24:45	345	N	PR	
06:24:45	410	N	PR	
06:24:46	945	N	CP	
06:24:47	845	N		
06:24:48	840	N		
06:24:49	840	N		
06:24:50	840	N		
06:24:50	820	N		
06:24:51	815	N		
06:24:52	820	N		
06:24:53	820	N		
06:24:54	805	N		
06:24:54	795	N		
06:24:55	765	N		
06:24:56	765	N		
06:24:57	755	N		
06:24:57	765	N		
06:24:58	775	N		
06:24:59	795	N		
06:25:00	805	N		
06:25:01	840	N		
06:25:02	850	N		

<u>Figure 1B: continuous ECG recording matrix of annotations</u>
The matrix of annotations can be exported electronically. It shows an example of a short segment of the electronic matrix at 06h24 AM. The left column is the time of occurrence for each consecutive cardiac beat, the second one is the R-R interval value in milliseconds and the third column corresponds to the beat lables. At that time, the patient had a run of 4 beats with N labels but with short R-R intervals. The algorithm states (right columns) that it is supraventricular run of 4 beats "SVRun(4)". PR: premature beat (with respect to previous heart rate) 410, 325,345 and 410 msec;
CP: compensatory pause (945 msec).

Continuous ECG recordings: the challenge of editing

High quality resting ECG data are automatically processed by algorithms that first filter the raw digital signal, and then detect the successive waves of the cardiac electrical activity, first the P wave (atria) followed by the Q, R and S waves (QRS complex, ventricles) and finally the T waves related the recovery of the ventricles. The outcome is for a single cardiac beat a "matrix" of annotations, i.e tabulated data for amplitude and time of each single ECG wave. It is a single beat because the individual beats available during the 10 seconds are averaged to enhance the signal-to-noise ratio therefore improving delineation of small electrical waves such as the P and Q waves. Manual editing of that high quality averaged cardiac beat only takes few seconds, keeping in mind that the ECG data of Regulatory concern are so far limited to 3 measures, PR, QRS and QT intervals (that requires editing of 4 pre-positioned electrical cursors). In contrast, the use of continuously acquired ECG data in clinical trials faces many key challenges. The quality of the ECG signal is often poor during daily physical activities and continuous ECG recordings may have significant

amount of missing data due to those poor quality segments. Actually, it is probably meaningful to reject noisy regions to obtain better detection and classification of cardiac events and faster scanning of records. Another critical step is how to correctly edit hundreds of thousands of consecutive cardiac beats? Most of the commercial solutions that perform automated analysis of such continuous ECG data are "Holter" Systems (Holter as a link to the family name of the inventor, Normal Holter) that have been developed in the 1980s or the 1990s and the technical specifications are much lower than for high quality, resting, 10 second ECGs, still often limited to 200 samples per seconds (5 msec) and a 10 microvolts resolution.
Given the frequent electrical artifacts related to body movements, the small amplitude electrical waves (P, Q and S waves) cannot be accurately detected and the algorithms have been designed to only recognize the peak of the high amplitude R wave within the QRS complex. Very basic R waveform analysis is then performed, for the reasons reported above.
At the end, the outcome is a basic two-fold matrix, R wave time of occurrence on one hand, together with a rough distinction between normal and abnormal R waveforms on the other (Figure 1A and 1B) …. But the matrix includes hundreds of thousands of occurrences over the 24-hours! From that matrix, Holter Systems faces the challenge of implementation of user friendly editing tools and computation of summary reports.

Editing Tools for continuous ECG acquisition

Given the sparse source data limited to normal/abnormal cardiac beats labels (or "templates") and time of occurrences (R peak to R peak time distance or "RR intervals") the editing tools are designed to:

1. Adjudicate cardiac beats templates (Figure 2) with re-labeling functions (N to V, V to N …).
2. Adjudicate short RR and long RR intervals (Figure 3) with "insert beat" and "remove beat" functions in case of under or over R peak detection, respectively.
3. Adjudicate selected ECG strips representative of main cardiac arrhythmias within the recording.

Editing can be time consuming when spontaneous cardiac arrhythmias are many in a given recording, or when the quality of the tracing is poor, leading to mislabeling, and frequent under and over detections. It is also important to review the noisy regions that have been rejected to check the absence of any cardiac event, such as compressed full disclosure screen display of the ECG with scrolling functions.
Other tools are graphs of heart rates to review fast and slow heart rate occurrences, trends of abnormal cardiac occurrences, by length, by rate, interactive Tables. All the editing tools have in common a very simple rule: the user interface should be friendly, minimizing the number of "clicks" for the Cardiac Technician or the Cardiologist. The presentation of each screen has to be optimized in order to supply with essential information to make a diagnosis easy and adjudicate the cardiac rhythm events.
As stated in by the AHA/ACC Guidelines (1) "*Ambulatory electrocardiography has the potential for producing a substantial amount of invalid data because of technical problems inherent in the recording and analytic processes. The ambulatory state is not stable in most cases. Noise interference from numerous sources that may occur over a 24-h recording period is a major cause for computer inaccuracies in both arrhythmia and ST-segment shift recognition and analysis. Many of the potential sources of error in the computer analysis systems are quite complex, and expertise in the technical aspects of AECGs requires an understanding not only of computer algorithms for the detection of QRS complexes and their classification but also of the problems associated with editing the computer analysis results. Physicians who interpret AECGs should have the knowledge base to assess all potential technical failings*".

Annotations and Holter Reports

From the edited matrix of annotations, a huge amount of ECG data is available during the period of recording and the final Holter Summary Report shows the diagnostically important information in a reliable, clinically understandable, easy and quick-to-read format. A report should include quantitative as well as qualitative information:

- Duration of recording, duration of time analyzed (which can be less than 24 hours when the noisy regions are many).
- Total number of beats, average, maximal and minimal heart rates.
- Trends in heart rate, pauses, arrhythmias, and ischemic episodes.
- Hourly summary table.
- Frequency of atrial arrhythmias (isolated extrasystoles, couplets, runs, tachycardia).
- Frequency of ventricular arrhythmias (isolated extrasystoles, couplets, runs, tachycardia).

As said above, it is important to have the knowledge to assess all potential technical shortcomings.

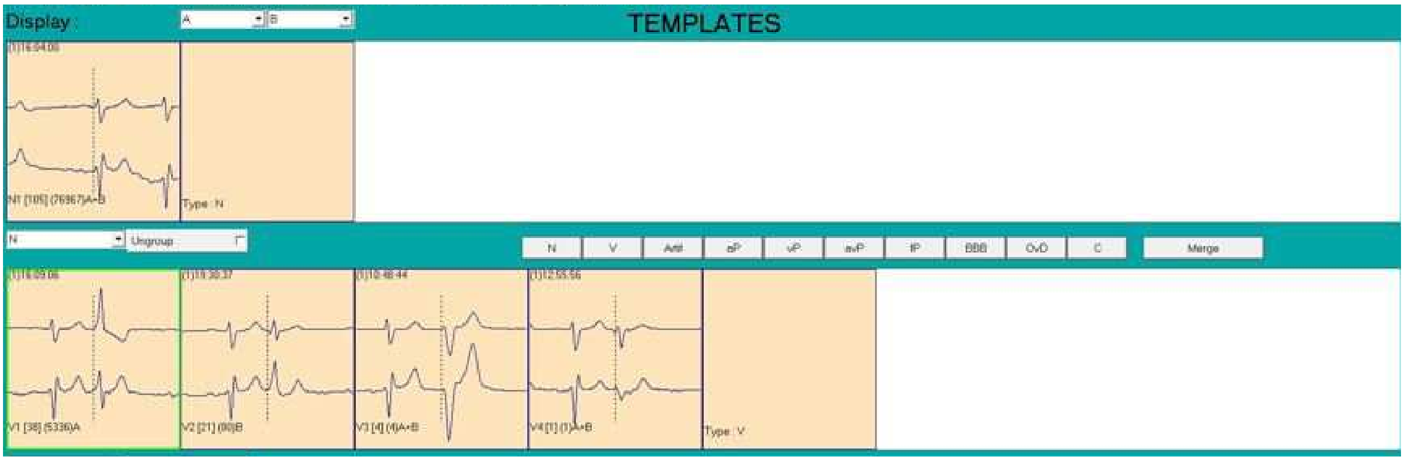

Figure 2: Editing, Adjudication of Template Morphology
After re-labelling misclassified templates, the matrix annotations will include 1) 76,967 annotations as N, 5421 annotations as V, including 5336 V1 annotations and 80 V2 annotations. Other labels available could be P for paced beats, Artif for electrical artifacts, C for calibration pulses.

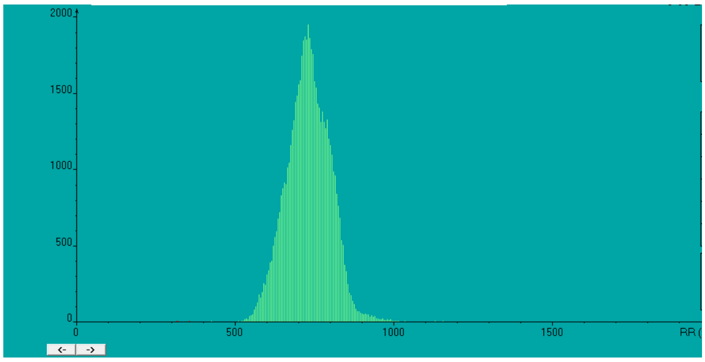

Figure 3A: Editing, Short and Long RR intervals adjudication
The Figure shows a "histogram" of all RR intervals, with the R-R interval duration on the horizontal axis in milliseconds, and the number of occurrences on the vertical axis. Using such a tool, the user can scroll from the longest to the shortest R-R intervals, and vice versa.

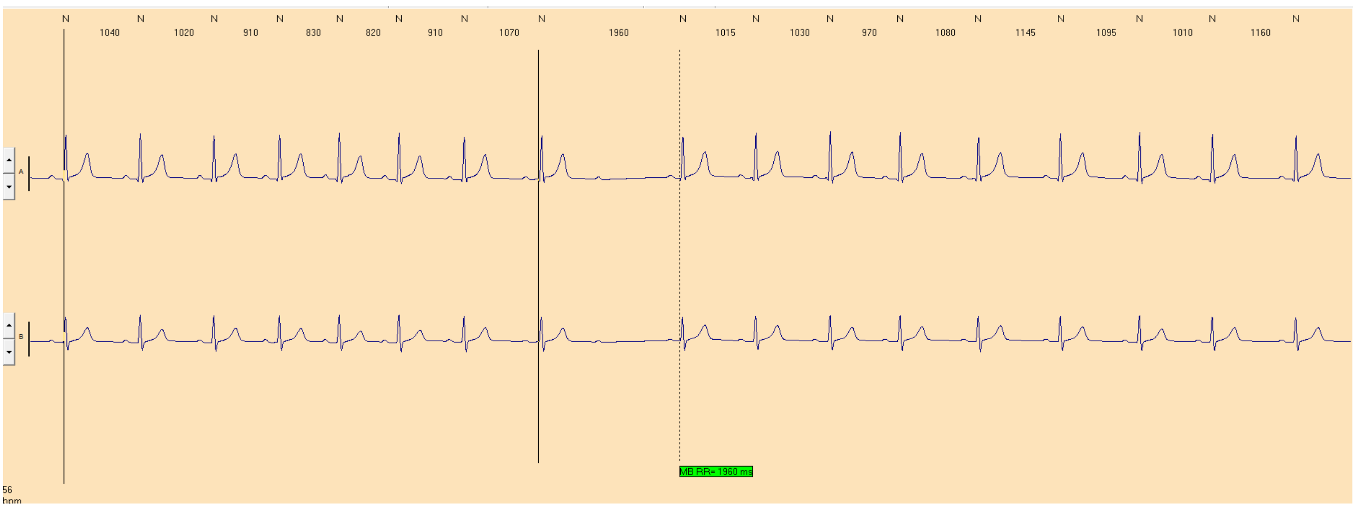

Figure 3B: Editing, Short and Long RR intervals adjudication
With a single click on RR intervals histogram as shown in Figure 3A, the software displays the corresponding ECG strip. In this patient, the longest R-R interval was 1960 msec. The long R-R interval is related to the occurrence of a second degree atrio-ventricular block (AVB). Since the small R waves are not detected, the only possibility to detect AVB on Holter recordings is to adjudicate long RR intervals or RR intervals that are around twice the previous ones (RR to RR ratio).

The P waves being ignored, automatic detection of atrial arrhythmias is only based on the so called "prematurity index" for cardiac beats labeled as N within the annotation stream. Any "N" beat will become a supraventricular extrasystole only if it occurs prematurely in comparison to previous average heart rate (Figure 1B). The default value for this prematurity index is often set at 25%, but it healthy volunteers with large respiratory sinus arrhythmia that can provide false positive atrial extrasystole annotations.

Regarding ventricular arrhythmias, the 2006 AHA/ACC Guidelines recommended some definitions that could be provided in the Summary Report from in depth evaluation of the annotations. The coding schemes could be as follows:

- Non sustained ventricular tachycardia (VT): three or more beats in duration, terminating spontaneously in less than 30 seconds: N-V-V-V…. -V annotations, up to 30 seconds adding all consecutive V-V intervals (Figure 4).
- Ventricular tachycardia is a cardiac arrhythmia of 3 or more consecutive complexes in duration at a rate of greater than 100 bpm: the average V-V cycle length should be less than 600 msec.
- Monomorphic non sustained VT with a single QRS morphology: a single V template within the VT duration
- Polymorphic non sustained VT with a changing QRS morphology: > a single V templates, V1 V2 and V3 within the VT duration.
- Sustained VT: VT greater than 30 seconds in duration: the sum of all consecutive V-V intervals is > 30 seconds.

Annotations and Clinical Research

Holter annotations have been used for Clinical Research as soon as Holter commercial systems have been widely available for routine management of cardiac patient. Bernard Lown in the 1970s reported that ventricular premature beats (VPBs) are present in 85% of patients with coronary heart disease. He presented his well-known Holter classification of VPBs based on frequency (> 30 VPB/hour), morphology (monomorphic or polymorphic), repetitive pattern (isolated, couplets, runs), and degree of prematurity (short coupling interval) as a tool identify patients at high risk of sudden death (4).

Another classic use of Holter annotation is to identify some specific cardiac rate pattern before the onset of spontaneous atrial or ventricular arrhythmias (5-8). Bradycardia and decrease in heart rate (long R-R intervals) suggest an increase in the parasympathetic tone whereas oppositely tachycardia and increase in heart rate (short R-R intervals) is related to sympathetic activation. In particular, those studies have consistently demonstrated that Torsade de Pointes onset (TdP) is associated with a low heart rate environment together with a short-long-short pattern of cardiac cycle length. Increase in ectopy before the onset is interpreted as the critical role of some cardiac or pulmonary artery firing sites (or "triggers") in the genesis of cardiac arrhythmias. Both changes in heart rate and changes in ectopy have been found to be linked in this setting.

A landmark in the clinical value of Holter beat to beat annotations was the report from the Post Infarction Study Group showing that reduced beat to beat heart rate variability (HRV) as assessed by the standard deviation of all N-N intervals was associated with a high risk of sudden cardiac death during follow up (9). This study was also a technical breakthrough. Retrieving annotations from commercial Holter systems was not easy until the era of computerized systems. The engineers from Marquette Electronics in Milwaukee, Wisconsin, under the leadership of Paul Schluter developed a Holter platform that digitized analog 24-hour recordings and stored the beat to beat annotations after editing. Only availability of the ~ 100,000 N-N intervals in electronic format made HRV calculation realistic. Today, all commercial systems include such option to export Holter annotations electronic file.

Annotations and Clinical Trials

Holter recordings are commonly used in Clinical Trials to evaluate cardiac arrhythmia frequency before and after dosing of the NCE, both in Phase II and Phase III trials. Continuous ECG recordings (two leads or three ECG leads only) are implemented in the Study Flow Chart according to some preclinical signal (cardiac arrhythmias observed in the Telemetered dog studies, for instance) or in some specific patient populations such as Heart Failure, Myocardial Infarction, Chronic Obstructive Pulmonary Disease. The basis for the use of Holter recordings can also be the drug class when other compounds from the same class have been associated with Cardiac safety issues.

The classic way to report Holter findings in those trials is Tabulated data showing the total number over the 24-hour at baseline and during the trial. For instance, reporting the changes in the total number of isolated ventricular extrasystoles, and making conclusion about a "safe" profile (decrease in number) or a "safety concern" (increase in number). However, it has been repeatedly shown that there is a large spontaneous variation in arrhythmia occurrence, and the trends in a placebo group are often required for an accurate conclusion, in particular when the

<u>Figure 4: Non Sustained Ventricular Tachycardia</u>
The annotation sequence is "N-V-V-V-V-V-V", leading to a statement of "VRun(6)".
The Holter software only provide a single V template and to better characterize the run, the Cardiac Technician should manually adjudicate this ventricular run as "dimorphic" since there are two different V templates. The correct annotations should therefore be "N-V1-V2-V1-V1-V1-V1".

time between two consecutive Holter records is long (more than one month). The edited annotation matrix could provide improved markers of Cardiac Safety, beyond the total number of episodes, such as:

- Trend in longer and faster cardiac arrhythmias.
- Trend in longer cardiac pause.
- Trend in more complex ventricular arrhythmias, using the Lown criteria, such as shorter coupling intervals, polymorphic versus monomorphic events,…
- In addition hourly breakdowns do not fit with some sharp pharmacokinetic profile and a more narrow segmentation can be computed from the annotations.

Continuous digital 12-Lead ECG acquisition in Clinical Trials is now commonly implemented in Thorough QT Studies as well as in Early Phase 1 Trials (First in Man, Single and Multiple Ascending Dose studies). The continuous mode of acquisition is only a tool to decrease the workload for the bedside staff, since in such healthy volunteers there is no relevant cardiac arrhythmia. The edited annotations however are once again central for extraction of 12lead ECGs within the time window. Customized algorithms make use of the Holter annotation to select (together with a noise criterion) ECG strips after a segment with stable heart rate (i.e low variations in N-N-N intervals). Off line reappraisal of the selection process within the time window, if any, could only be based on the edited annotation data.
Of note, assuming a total number of 15 ECG time points in a Phase 1 trial, the sum of all time windows will be 15x 10 = 150 minutes over the 24 hours, i.e. grossly 10% of the ECG data will be reviewed. Some simple recommendations from a cardiac electrophysiologist stand point can be made to explore the edited annotation in those Phase 1 trials. Thorough QT studies have revealed that drugs may also adversely affect other cardiac electrophysiology ECG parameters, such as PR (atrio-ventricular conduction) and QRS (intra-ventricular conduction) intervals. Experts under the auspices of the Cardiac Safety Research Consortium (CSRC) have therefore produced a white paper providing recommendations for assessing PR and QRS intervals from ECG recordings (10). The white paper reminds us that the block of cardiac calcium and cardiac sodium current is a use-dependent block (greater blockade of current at faster vs. slower heart rates) in contrast with the block of the hERG current which is a reverse use dependent block (greater blockade at slow heart rates). Rather than focusing only on ECG collected in resting conditions, one could filter the annotation stream to extract ECG segments at high heart rates (short N-N-N intervals) and then manually adjudicate PR and QRS intervals. Relevant information that could also be extracted from the annotations is a list of all long N-N intervals, sorted by length. Given the absence of P wave analysis, there is no automated diagnosis of second degree AV block and visual adjudication of the long N-N interval to check presence or absence of a non-conducted P wave is required (Figure 3B).

Closing remarks

Editing continuous ECG data is challenging, and so far there are many shortcomings from commercial Holter systems used in Clinical Trials. Enhanced noise rejection, waveform analysis performed on all 12 leads, detection of P waves, selection of ECG strips by time and by rate are important features that should be implemented in the next generation of Holter Software.

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AMPS Views on:

A quick overview of the "AMPS-Mortara Regulatory Review of Continuous ECGs" workshop

Fabio Badilini, AMPS llc.

The workshop held on Dec 11th in Washington DC, organized and held by Mortara and AMPS, offered a unique opportunity to focus on the status of ECG warehouse with special emphasis on the changes needed to handle continuous ECG data using the aECG v2 data structure. All speakers were from the two organizing companies, with the notable exceptions of Dr. Pierre Maison-Blanche from Paris, who gave a detailed overview of the Holter world from a cardiologist standpoint (see his article on this issue) and Dr. Norman Stockbridge from the FDA, who introduced the workshop and participated in the debate and an intense panel. Two industry representatives, Dr. Robert Kleinman from ERT and Dr. Corina Dota from Astra Zeneca, also contributed sharing their experience with the early submission of continuous ECG data into the ECG warehouse.

Despite a highly technical context, the full day meeting concentrated on many facets of ECG continuous data collection and management, covering for example historical aspects of Holter analysis and the differences on how this data is collected and analyzed within the clinical and regulatory contexts.

The key concept of beat annotations was reinforced as a cornerstone of any analysis based on continuous ECG (whether it is research or regulatory) which requires an accurate and validated list of cardiac beats of the processed/annotated segments (i.e. exact position and type of all the beats captured in the continuously collected data).

The role of different organizations dealing with ECG data was reviewed, spanning from research laboratories that through the years have collected and validated clinically relevant repositories, to public and private organizations such as THEW and CSRC. In this context, it was emphasized that the role of the ECG warehouse is mainly that of a repository of regulatory data, i.e. of ECG waveforms where all measurements relevant to the conduction of a clinical trial with a specific methodology can be adequately stored. This can be the case of studies employing the timepoints-based ICH paradigm, where segments of ECG data used to select/generate the ECG extractions can be now uploaded into the ECG warehouse, but also of new and/or alternative methods that make a more comprehensive use of the continuous ECG, such as Hoter-bin or any beat-to-beat related method.

Two dedicated sessions covered the structure of the aECG concept, with a review of the basics of XML and HL7, followed by a more comprehensive description of the aECG version2, and by an extensive overview of the Mortara set of tools used by the FDA reviewers to inspect the submitted segments of continuous data.

In a dedicated how-to-do-it session, practical examples using AMPS technology (using the software platform provided by Pollux), were given to demonstrate how to submit continuous ECG data under different study scenarios. These included for example the approaches described in the CSRC white paper on the methods to deal with a heart-rate effect [1], as well as examples of non-QT type of analyses such as heart rate variability approaches and T-wave alternans.

In the last session, showcase examples of continuous data from retrospective studies recently successfully submitted to the ECG warehouse were provided. These included examples of extraction-based TQT data, a subset of optimized vs. non-optimized ECG extractions and two variants of beat-to-beat analyses, one that limited analysis of short (a few minutes long) segments and the other which was instead a truly 24-hour beat-to-beat.

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Products News

Latest Releases

AMPS offered to all participant of the Holter aECG Workshop the first Beta version of our AMPS Viewer for annotated ECG of continuous ECG Data.

Looking forward

In Q1 of 2014 AMPS is planning to release:

- The first version of our beat-to-beat continuous-ECG solution, as anticipated on issue 16 of this newsletter, which is in the same class of solutions as WinAtrec, the AMPS software package including the Holter-bin approach.

  Our beat-to-beat Holter solution provides a set of interactive graphical display tools to edit and review individual-beat annotations, including QT and RR time trends and QT/RR clouds.

  For each individual beat, noise level and preceding heart-rate stability are also computed, so that beat-to-beat measurements can be filtered based on the ECG beat quality and preceding heart rate.
- The first official version of AMPS Viewer for annotated ECG of continuous ECG data.

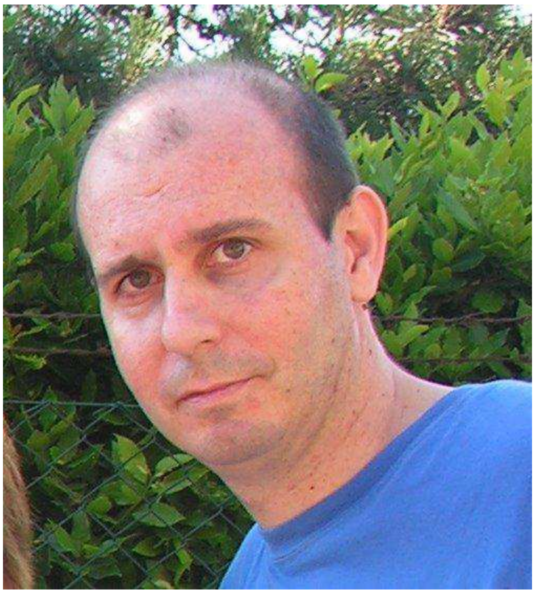
AMPS Notebook

As anticipated in the Editorial, AMPS organized, together with Mortara Instrument, a full-day seminar on the new Holter aECG format and Holter submission to the FDA Warehouse. The Seminar was held on December 11th in Washington DC.

Fabio Badilini has also attended the **American Heart Association**, Scientific Session held from November 16th to 20th in Dallas, Texas.

He also attended **CSRC Annual Meeting**, held in Washington DC on December 12th and 13th.

Fabio has coauthored an interesting paper on T-wave axis deviation and left ventricular hypertrophy, published in the November issue of the Journal of Electrocardiology. This paper can be downloaded from our website in the Documents->Publications page.



Our friend and colleague Umberto Spagnoli sadly passed away on November 21st after a long illness.
He was a talented consultant and was instrumental in shaping the company's culture and direction during its early formative years. His professionalism, optimism and friendship will forever be cherished and remembered by all of us. He is survived by his wife and two children.