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

Consensus is growing in the Cardiac Safety industry about the need to look at more than the traditional 10 seconds ECG traces in order to assess the effects of drugs during pharmaceutical trials. It is a fact that nowadays there are more and more devices allowing to collect more than the usual 10 seconds at basically the same price of the traditional electrocardiographs, computer memory has become extremely cheap, allowing to store large quantities of data at very low costs, and many phase-one centers are already equipped to do so. As you have read in the last AMPS-QT issue the FDA is gearing up to store continuous recordings in the warehouse, one of the reasons being that "it will increase the efficiency of thorough QT studies and allow for the evaluation of new biomarkers for cardiovascular safety". In this context we received, and very gladly publish, an article on this subject by one of the most well known cardiologist worldwide: Dr Jay Mason. Nowadays Dr. Mason is an independent consultant in the cardiac safety of pharmaceuticals. He also serves, in a consultative role, as Chief Medical Officer of Spaulding Clinical Research. Most recently he was Medical Director and Director of R&D at Covance Cardiac Safety Services. He became Chief of Cardiology at the University of Utah in 1983, In 1999 he was appointed Chairman of the Department of Medicine at the University of Kentucky. His clinical, teaching and research emphasis is in cardiac arrhythmias and electrophysiology, and is author of over 400 publications. As usual, enjoy!

A Noteworthy Contribution:

The Five-Minute Electrocardiogram

Jay W. Mason, MD, Professor of Medicine, University of Utah, Chief Medical Officer, Spaulding Clinical Research

The standard electrocardiogram (ECG) is a 10-second recording, most often displayed in a 3 by 4 format, which provides 2.5 seconds of waveform data for each lead. Given the considerable biological variability of every aspect of the ECG, which occurs on a beat-to-beat basis and over longer cycle times, and the often more striking variability associated with acquisition and processing of the body-surface signal, it is clear that the standard ECG cannot represent the true "electrocardiographic state" of the patient. A five minute recording, if effectively analyzed and displayed, may be a reasonable compromise between the need to complete the test quickly and the need for accuracy. The purpose of this article is to consider advantages and disadvantages of the 5-minute recording, based upon my recent experience with recording and analysis of 5-minute long 12-lead ECG recordings.

How is a 5-minute recording done?

Most modern 12-lead diagnostic electrocardiographs can, in fact, make 5-minute recordings, or long recording of various durations. All that is required is adequate electronic storage and on/off functionality intended for longer data capture. And, of course, numerous devices are available that perform multi-lead recordings up to several days in duration for the purpose of arrhythmia and ischemia monitoring. However, few diagnostic electrocardiographs provide a means for using the extended data to enhance 12-lead ECG diagnostic statement capabilities. (I am aware of only one such device in current clinical use.)

How is a 5-minute recording analyzed?

The discussion below describes the analyses performed by the device I have recent experience with. Of course, other analytical approaches are possible and anticipated.

The Summary ECG is a simulated 10-second ECG that we derive from the 5-minute ECG recording. A median or representative beat is created by averaging the PQRST waveforms of all normal, noise-free beats recorded during the 5-minute period, separately for each of the 12 leads.

These medians are than linked together with an inter-beat cycle length equal to the average heart rate during the recording. This results in a very clean looking ECG with the beats within each lead looking identical. The summary ECG is then used to make interval measurements, either by a computer algorithm, or by manual annotation, or both.

Is this better than a standard ECG based on 10 seconds of data? In many ways it is, though there are some potential drawbacks. These pros and cons will be discussed later.

Assessment of Arrhythmias is made possible by longer recordings. Arrhythmias are identified and quantified using existing diagnostic and beat-categorization software, or the recordings can be reviewed by hand at a variety of speeds and time compressions.

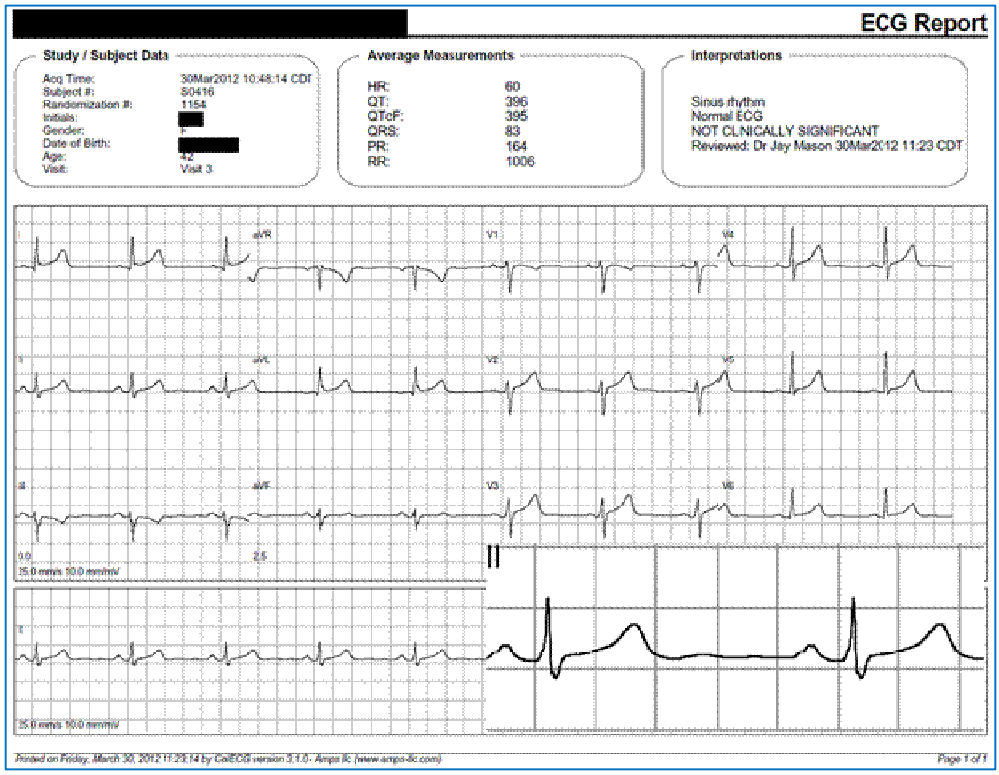
Variability Assessments are performed on the roughly 300 beats recorded over 5 minutes. Simple descriptive statistics for RR, PR, QRS, QT and QTc include mean, median, standard deviation, minimum and maximum. Heart rate variability (HRV) is commonly evaluated either over 24 hour or over 5 minutes. The 5-minute representation of HRV has been shown to correlate fairly well with day-long HRV results, though the ultra-low frequency band cannot be assessed. Variability of QTc is also calculated using indices that have been tested for their prognostic value. We measure variability of T-wave morphology using direct algorithmic amplitude and duration measurements and eigenvector-based analyses of wave shape change.

Other Assessments that we currently perform include a listing of all diagnostic statements derived from each of the thirty 10-second ECG segments captured over 5 minutes (see Figure 5 and Figure 6) and signal averaging for measurement of QRS duration and late potentials. Many other possibilities exist.

Advantages of the 5-minute recording

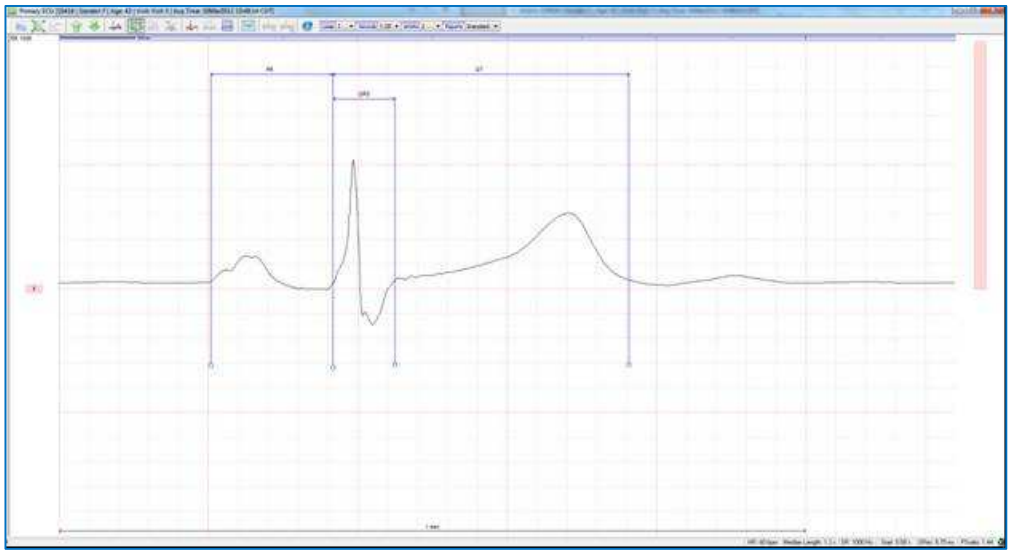
The Summary ECG: Figure 1 shows an example of a Summary ECG.

Figure 1: Example of a Summary ECG. The higher magnification inset at lower right shows that the waveforms in lead 2 are clean and identical.



As you would expect, the tracing is very clear, the inter-beat cycle length is precisely consistent and the PQRST waveforms are identical in each lead. This type of ECG display is extremely easy to view and interpret. The clean waveform is especially suited for high-resolution annotation, as shown in Figure 2.

Figure 2: Lead 2 median beat from subject above viewed in CalECG (AMPS, LLC) for interval measurements



In addition to the clarity of the ECG, the ease of viewing it and the ability to annotate it more accurately, the waveform is based on more real data, and is therefore more robust and reliable. In essence, the representative beat is constructed from about 300 beats rather than the usual 10 beats.

Assessment of Arrhythmias

Even when frequent, arrhythmias are usually not captured on the 10-second ECG. This is probably the greatest shortcoming of routine electrocardiography today. The 5-minute recording greatly increases the opportunity to detect arrhythmias. Figure 3 provides an example of ventricular ectopy that was missed during the initial 10 seconds of the recording, but clearly present during the long recording (Figure 4).

Figure 3: Summary ECG showing no ventricular ectopy.

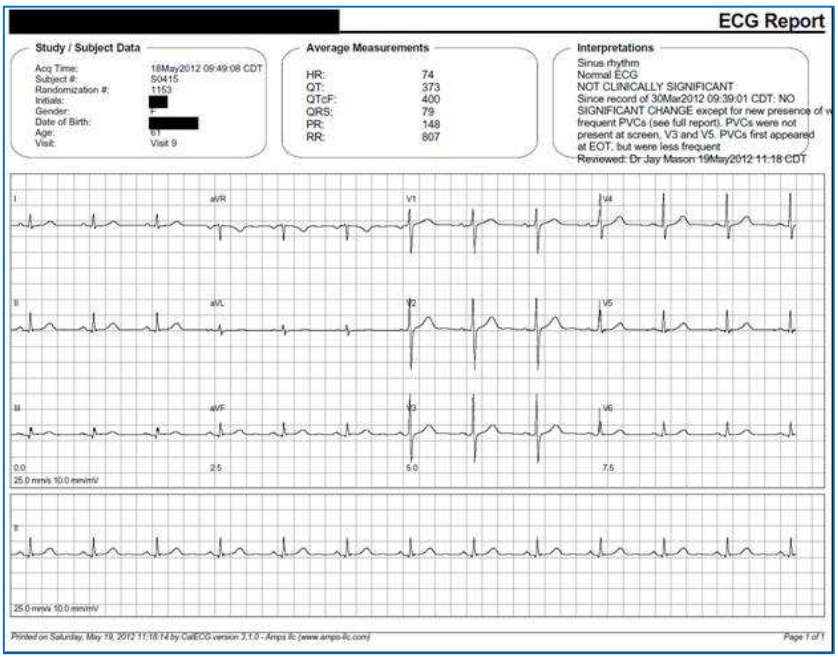
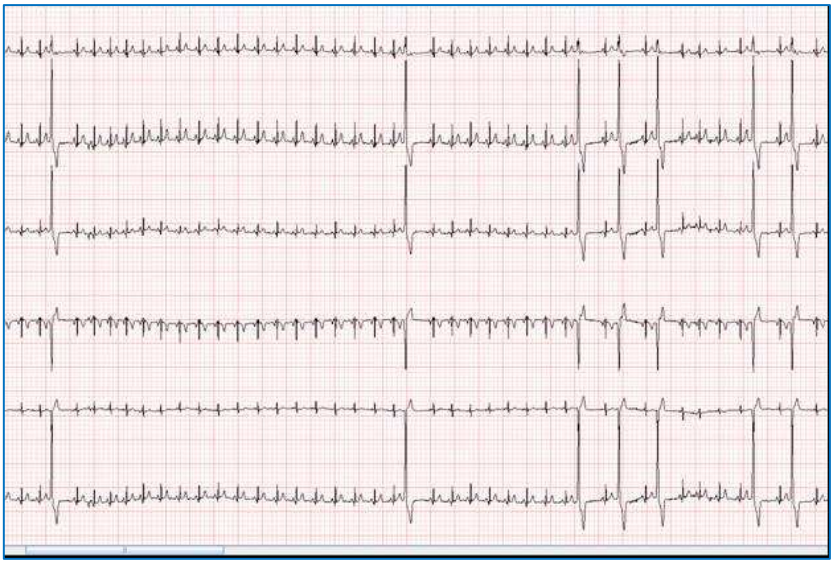


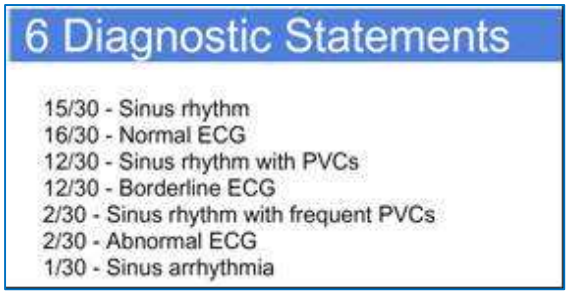
Figure 4: Ventricular ectopic beats detected by the 5-minute recording.



The full report of the 5-minute recording includes a listing of diagnostic statements and their frequency of occurrence during each consecutive 10-second ECG (Figure 5). Note that one PVC was present on 12 of the 30 consecutive 10-second periods ("Sinus rhythm with PVCs") and on 2/30 more than one PVC was present ("Sinus rhythm with frequent PVCs"). Thus, there would have been less than a 50% chance (14/30) of detecting PVC's in this patient with a single 10-second ECG randomly recorded during the 5-minute period. Note, further that, if these recordings had been done by Holter and ECGs had been extracted at this 5-minute time point using a selection strategy that identifies, for example, the three 10-second periods with the most regular rhythm and preceding rate stability, there would have been no chance of detecting the ectopy.

In our limited experience with the 5-minute ECG to date, we have detected many arrhythmias that were not captured on the isolated 10-second ECG, including ventricular ectopy, ventricular tachycardia, supraventricular ectopy, supraventricular tachycardia, sinus pauses and second-degree AV block.

Figure 5: Diagnostic statement list for the subject with PVCs above.



Variability Assessments

Clinical studies have demonstrated that heart rate variability, QTc variability and T-wave morphological variability are risk indicators for cardiovascular and sudden death. These three forms of variability can be measured on 5-minute recordings, yielding a prognostic profile that cannot be reliably derived from a 10-second recording.

Other Assessments

We also use the 5-minute record to detect late potentials using signal averaging. This further contributes to the risk profile. One of the most useful analyses is the Diagnostic Statements listing, illustrated in Figure 5 and Figure 6. This listing can be used to detect evanescent diagnostic criteria

and to assess their importance. Figure 6 illustrates a case in which the computer algorithm (Glasgow) diagnosed definite inferior infarction on one 10 second ECG and possible inferior infarction on 23. No infarct was diagnosed on the remaining six 10-second ECGs. Varying inferior Q-wave presence and amplitude is a well-known ECG problem, well-illustrated in this case. The limb lead recordings during some periods showed clear diagnostic Q waves in leads 2, 3 and aVF, while during other periods the Q-wave was preceded by a small, variable R-wave (Figure 7).

Figure 6: Diagnostic statements listing showing variable criteria for inferior infarction.

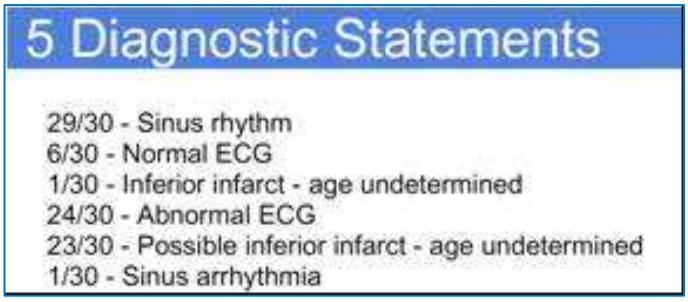
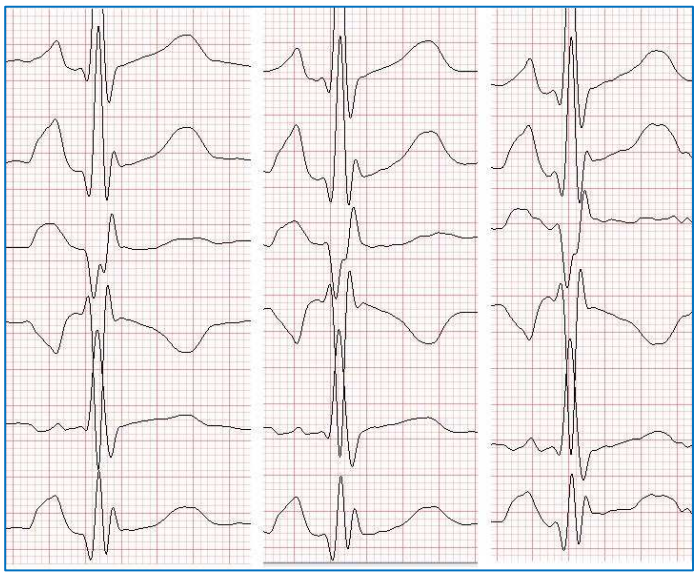


Figure 7: Varying inferior Q-wave criteria in the subject above. Leads 1, 2, 3, aVL, and aVF are displayed from top to bottom in the three panels. The lefthand panel show clearr Q-waves in leads 2, 3 and aVF. The middle and righthand panels show preceding R-waves of varying amplitude.



In this case, the Summary ECG showed diagnostic Q-waves; the averaging process had virtually eliminated the preceding R-wave. The Summary ECG approach may be helpful in

determining the "truth" when diagnostic criteria vacillate. This particular patient had a past history of myocardial infarction.

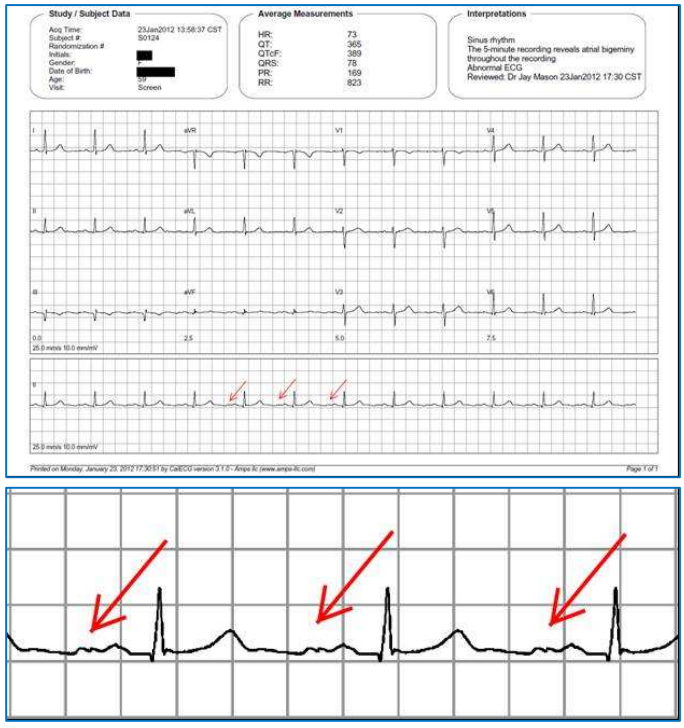
Triplicate ECGs

The recording (or extraction) of triplicate or higher multiples of ECGs at discrete time points has become a commonplace method to reduce the influence of biological and methodological variability of the ECG in pharmaceutical trials. Analyzed properly, the 5-minute ECG eliminates the need for recording triplicates. It is the equivalent of 10 times as many individual recordings, and it reduces the influence of outlier data more substantially than just three recordings.

Disadvantages of the 5-minute recording

The Summary ECG has some disadvantages. By definition, it is based upon normal beats. Thus, it does not itself provide any arrhythmia information. In fact, it may obscure the presence of arrhythmia that would have been detected by the single 10-second ECG. The Summary ECG shown in Figure 8 provides an example. The ECG appears to show normal sinus rhythm. However, lead 2 and several other leads contained an odd artifact preceding each P-wave (see red arrows in Figure 8).

Figure 8: Summary ECG in a subject with persistent atrial bigeminy. The lower panel is a detail from lead 2. Red arrows point to telltale artifact.



A selected 10-second ECG extracted using AMPS Antares software shows the arrhythmia responsible for this artifact (Figure 9) because it was present throughout the 5-minute recording (Figure 10). Comparison of that tracing to the Summary ECG also serves to illustrate the noise-reduction

associated with the Summary ECG method (see, especially, the inferior leads).

Figure 9: Antares-selected 10-second ECG in subject above.

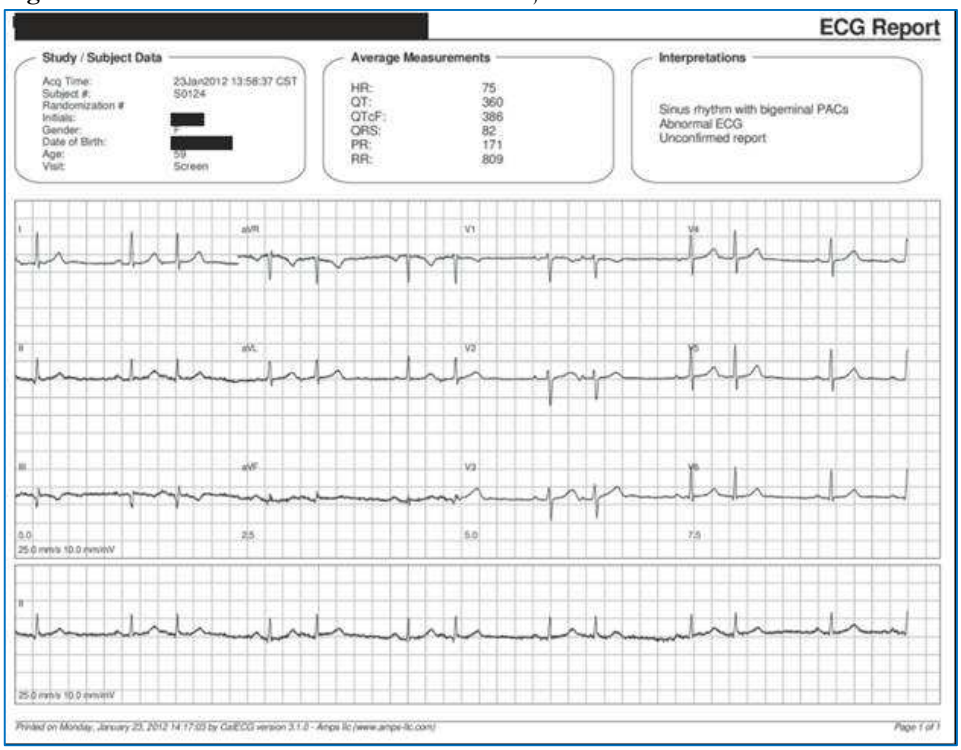
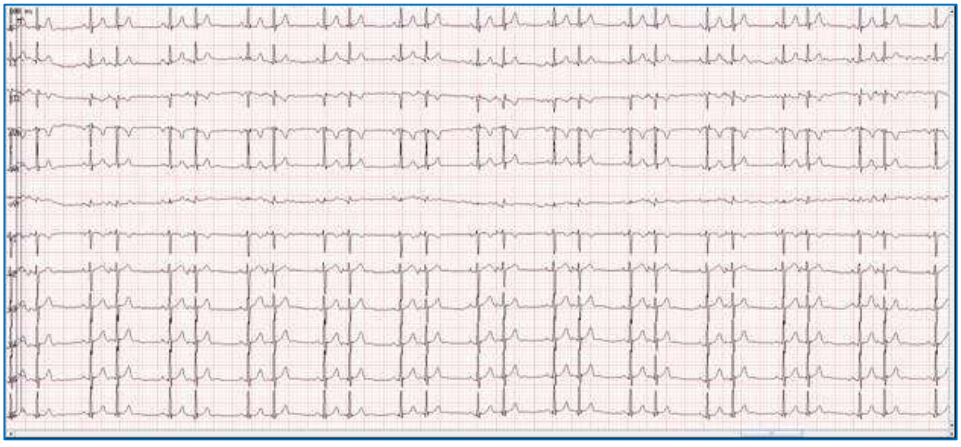


Figure 10: 20-second segment from the 5-minute recording of the subject above.



Other telltale artifacts of this sort seen in this case have been observed in other recordings that included very frequent arrhythmias. This example makes clear the need to check the diagnosis list for arrhythmias not seen on the Summary ECG, and, in some cases to review the full recording.

Other diagnoses that might have been made with isolated 10-second ECGs theoretically could be masked on the Summary ECG. For example, varying normal and abnormal PR duration or intraventricular conduction delay could be averaged to a normal value on the Summary ECG. Of course, in these cases, the single 10-second ECG would be equally misleading, showing either a normal or abnormal value rather than an average value.

Variability Assessment

The variability analyses described above have obvious potential for deriving richer clinical information from the ECG. However, in the cases of QTc and T-wave morphology variability, we do not have sufficient clinical experience to establish normal ranges for normal individuals or patients with various disease states. As time passes and sufficient data is collected, these measures will become more valuable.

Other Disadvantages

The 5-minute ECG cannot be performed in many circumstances. Infants and young children cannot stay still for a full recording. Long recordings are also impossible in some critically ill patients or those undergoing procedures that cannot be interrupted for 5 minutes.

The 5-minute ECG may take longer to perform than a standard ECG, though the method we use reduces or eliminates many procedural steps in the acquisition and storage of the ECG, making the work effort less than that associated with standard recordings.

The 5-minute record unequivocally takes longer to review and interpret. Some of this extra burden can be reduced by using cleaver workflow, prompting and other software aids for the reader.

The 5-minute ECG requires more electronic storage space than a standard ECG. On the other hand, the full file is small enough that its transfer over the internet is essentially instantaneous over the usual bandwidths used in medical practice and research.

Finally, the Summary ECG is not equivalent to the standard 10-second ECG. While it makes sense to use existing normative ranges in interpreting the Summary ECG, eventually new normal values need to be established for the Summary ECG. The bright side of this requirement is that, when established, the new normative

range is certain to be diagnostically more reliable because it will be based upon more robust data.

Recommendation

I don't think it makes sense to continue using isolated 10-second ECGs in medical practice or research. Cardiac rhythm and other physiological manifestations captured by the ECG are too variable to be properly portrayed by a 10-second sample. Just as one would never use a single blood pressure measurement to determine if antihypertensive therapy is needed, one should not rely on a 10-second ECG recording to make critical clinical or research decisions. We have the technology and knowledge to use electrocardiography more rationally that it is used today.

Products News

Looking forward

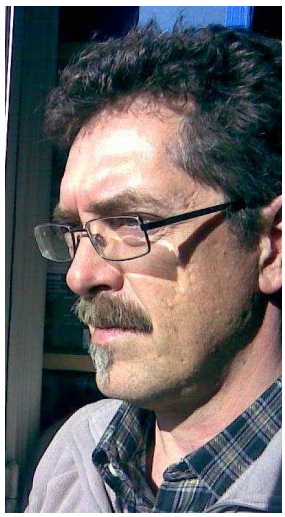
In Q3 of 2012 AMPS is planning to release:

- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.

AMPS Notebook

We are glad to announce the publication of the White Paper written collaboratively by members of the Cardiac Safety Research Consortium from academia, industry, and regulatory agencies, which discusses different methods to characterize the QT effects for drugs that have a substantial direct or indirect effect on heart rate. AMPS Chief Scientist Fabio Badilini is one if the co-authors of the White Paper and has been responsible to describe the Holter bin application, which have been discussed in previous issues of AMPS-QT. Most of the techniques described in the White Paper are optimally performed using continuous electrocardiogram data obtained in clinical studies designed to characterize a drug's effect on the QT interval and in particular require the collection of drug-free data over a wide range of heart rates, particularly at baseline. We believe that the release of this publication will favour am increased usage of secondary methods to assess drug-induced QT interval changes. *Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects (Am Heart J 2012;163:912-30.)*

AMPS People



We complete our round of staff introductions with Daniele Bovio. Graduated in physics from the University of Milan in 1984, Daniele worked until 1990 at the Institute of Cosmic Physics of the National Research Council (CNR) in Italy. He then moved to Paris at the European Academic Research Network office to provide engineering support to the countries connected to EARN, soon was appointed chairman of the Network Operations Group and became the office Director. At EARN, among other things, he contributed to the design and implementation of EBONE, the first European Internet backbone in 1992. In 1995 he left the research world and joined America Online, Inc. as Operations Manager for Europe. At AOL in over 13 years he covered a number of tasks, including the set-up and launch of the European networks, the contracting and provisioning of transatlantic and pan-European telecommunication circuits, and the management of a number of datacenters and of the European Network Operation center. More recently Daniele joined AMPS and took over responsibilities for the Marketing and Sales departments. His e-mail address is: bovio@amps-llc.com