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 2014 AMPS-QT last issue we host an article from Dr. Mirko de Melis, Senior Scientist at the Medtronic Bakken Research Center, which underlines the remarkable potential of Insertable Loop Recorders (ILRs) and their usefulness in a large variety of applications, from unexplained syncope diagnosis to atrial fibrillation detection and management. Medtronic has taken the leadership in this industry thanks to Reveal, possibly the most popular ILR device currently on the market, and AMPS has been working in cooperation with Medtronic and Pharma industries to develop tools adapted to the analysis of single vector ECGs. Dr De Melis's research in the field of physiological signals analysis and development of new sensors for cardiovascular signals monitoring is remarkable and we are positive our readers will appreciate his contribution. As is tradition in the AMPS-QT fourth quarter issue the AMPS team wishes to all our readers all the best for a successful new year!

A Noteworthy Contribution:

The continuous ECG monitoring: established indications and future opportunities.

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Introduction

Arrhythmia and syncope are two important conditions that should be optimally managed (1, 2). In the case of AF, it is the fact that many recurrences of AF do not lead to symptoms but still represent a threat to the patient due to the risk of cerebral and systemic embolism which not only applies to patients on drug therapy but also to those after catheter ablation. The detection of asymptomatic AF influences further treatment strategies especially with regard to anticoagulation. Both patients with AF and those with syncope have to be monitored. The effectiveness of monitoring in detecting events depends on its continuity and duration (3, 4).The adverse effects related to tele-Holters and the lack of acceptance by patients limit the duration of monitoring to a few weeks at most. Besides, it is difficult to make such monitoring continuously (5). This can be avoided by the use of ILRs, which have recently been called insertable cardiac monitors (ICMs). These are small devices that are implanted subcutaneously without the need of any electrode, thus securing full comfort during an examination.

Most of the ICMs evaluated so far require visits to a hospital to have the recording analyzed. Current devices allow monitoring up to 3 years, to register at any time (during symptoms or when the patient or physician wishes so), to register automatically incidents of asystole, bradycardia, ventricular and supraventricular tachycardia or AF, and finally, to transmit data to the tele-centre when the patient or the physician wishes so (6). The introduction of those devices brought the application in practice of specific signal processing techniques for arrhythmias detection and for the discrimination of comorbidities to support a timely medical decision.

I - An established application: Atrial Fibrillation detection in a single vector ECG

Unlike pacemakers and implantable cardioverter-defibrillators, these subcutaneous devices cannot sense endocardial atrial activity, and an analysis of consecutive RR intervals is used for the diagnosis of AF. The irregularity of the RR interval is now a proved parameter for AF detection (7, 8). In a Lorenz plot, each RR interval is plotted against the previous value of the RR interval, and this can be displayed graphically and used to discriminate between AF and sinus rhythm. (see Figure 1).

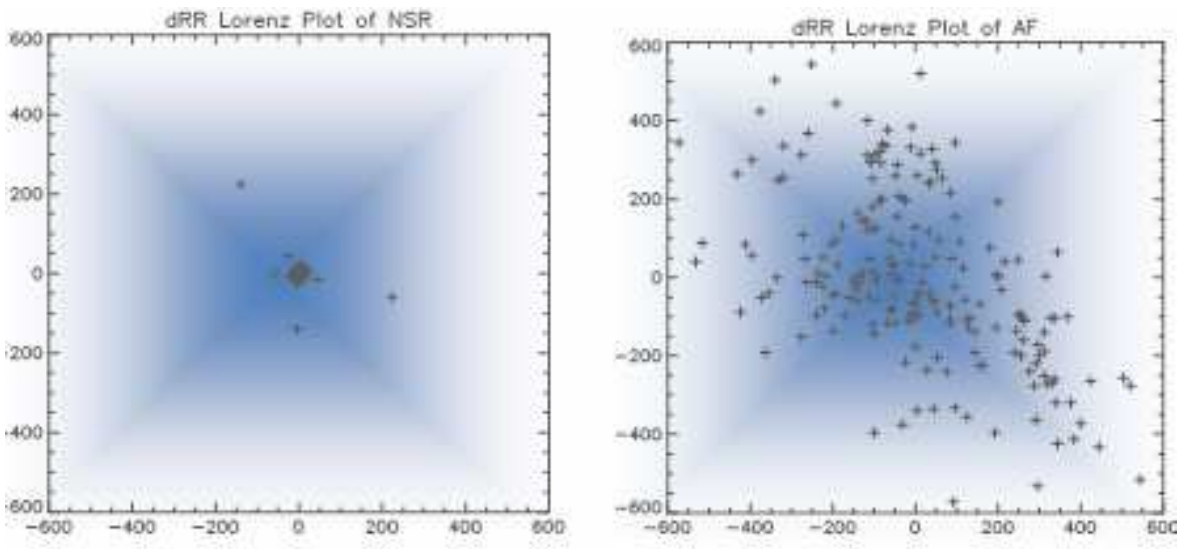

Figure 1: in the left panel the Lorentz plot shows the RR behavior when a patient is in normal sinus rhythm (NSR) while in the right one AF pattern is depicted.

A recent validation study, the Reveal XT Performance Trial (XPECT), showed that a subcutaneous monitoring device equipped with an algorithm for AF detection can accurately measure AF burden (98.5%) and is very sensitive (96.4%) to identify patients with AF, independently of symptoms (9).

II - A future application: the assessment of AFR

The assessment of AFR behavior at initiation and during the first hours of spontaneous AF episodes in patients with paroxysmal AF using time-frequency analysis might be crucial to define a specific strategy to improve treatment success. The ECG signals are preprocessed, including baseline filtering, beat detection, and cross-correlation–based beat classification. Spatiotemporal QRST-cancellation (13), in which an amplitude and morphology adjusted average beat is subtracted from each beat in the signal, is then used. Individual beat averages were used for beats belonging to different beat classes. The resulting residual ECG containing mainly the atrial activity is analyzed using sequential atrial signal characterization, which performs time-frequency analysis using overlapping windows of short duration (2.56 seconds long, 1 window per second) to provide second by second trends of the atrial fibrillation rate. With this method, the signal structure of each window is continuously analyzed by means of its harmonic frequency pattern to assure that the corresponding signal contains an oscillatory atrial signal. Atrial fibrillatory rate beyond the initial 3 hours can be considered stable and may be evaluated for prediction of intervention effect (10).

III - Bridge application: seizures sources discrimination

Transient loss of consciousness (TLOC) can be due to syncope, epilepsy or psychogenic causes. Patients with TLOC are unable to describe their blackout, a witness may be unavailable. Cardiac and neurological investigations may not help. ECG monitoring with ILR allows symptom/ECG correlation in TLOC, but conventional ECG appearance may not be diagnostic (11). The analysis of sympathovagal balance using heart rate variability (HRV) could define distinct "signatures" for syncope, epilepsy and psychogenic disturbance. In 20 patients with TLOC and implanted with an ILR, beat-to-beat RR intervals were extracted from the ECG signals. Marginal RR intervals (reflecting cardiac hyper-excitability) were analyzed using a statistical assessment of the RR values outside a confidence interval (window size of 40 beats). HRV was assessed with a parametric spectral estimation using a sliding analysis window of 60-240s, shifted with 5-20s increments. The sympatho-vagal balance was computed as the ratio of the low frequency components (LF: 0.04 Hz-0.15Hz, mainly sympathetic activity) to high frequency components (HF: 0.15-0.4 Hz, parasympathetic activity).

Arrhythmia patients showed low marginal intervals (<4%), and changes in HRV (mostly sympathetic), Reflex Syncope patients showed low marginal intervals (<4%), and lowering of sympatho-vagal balance before the faint, Epileptic Seizure patients showed increased marginality (10-35%) and increased sympatho-vagal balance, Non-Epileptic Attack Disorder (NEAD) patients showed high

marginal intervals (up to >50%), high sympatho-vagal balance (10-40), high parasympathetic and high sympathetic activity.

The pattern of sympatho-vagal balance derived from the RR variability of the ECG observed during reflex syncope, in tachycardia, and in other arrhythmias is very different from that seen prior to epileptic seizures. Distinct patterns may also help distinguish epilepsy from psychogenic TLOC, but this requires clarification on a larger group of cases. Further work in progress will help define specific sympatho-vagal signatures to help distinguish the causes of TLOC (12).

Conclusion

The concept of ECG continuous monitoring translated into ILRs together with the possibility to take advantage of the signal processing research in the last decades. This has seen the development of several clinical applications, like AF detection and management or unexplained syncope diagnosis. Moreover it offers the possibility to explore new directions, for example the TLOC discrimination, where to find the balance between heart and brain still remains challenging.

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Products News

Latest Releases

In Q4 2014 we have released:

- Version 1.3.0 of AMPS CER-S (Continuous ECG Recordings Suite) with the addition of re-sampling and re-scaling functionalities to the new platform for Holter format conversion.

- Version 1.0.0 of B2B, AMPS beat-to-beat continuous ECG solution.
  The software allows to annotate, in a fully automated way, each ECG beat of a continuous 12-lead ECG recording in ISHNE format, providing PR, QRS, QTpeak, TpeakTend and QT intervals, on each lead and on the Vector Magnitude lead. B2B Includes a dedicated user graphic interface allowing the reviewing and editing of the measured annotations and tools for identifying outliers (time trends as well as QT/RR, QRS/RR and QTpeak/RR plots). In addition the user can flag measurements according to the level of the quality metrics, thus permitting a comprehensive assessment based on noise and heart-rate stability criteria.

Here a summary of 2014 major software releases:

- Antares v. 2.11.0 – v. 2.15.0.
- B2B v. 1.0.0.
- CER-S v. 1.0.0 – v. 1.3.0.
- ECGScan v. 3.3.0, compatible with Windows 7, 8 and 8.1 OS.
- TrialPerfect v. 2.10.0.

Looking forward

In Q1 of 2015 AMPS is planning to release:

- A new major version of CER-S including the following platforms:
  - Continuous ECG beat detection and classification
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia editor

AMPS Notebook

Fabio Badilini attended the **American Heart Association**, Scientific Session held from November 15th to 19th in Chicago, Illinois and the **CSRC Annual Meeting**, held in Washington DC on December 11th and 12th.

Fabio will be attending the **CSRC Annual Meeting** which will be held in Washington DC on February 19, 2015.