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

Since it has been defined for the first time, at the end of the XIX century, and later perfected, the electrocardiogram has helped saving countless lives. Almost 100 years later, in 1992, Pedro and Josep Brugada showed that the classic 10 seconds ECG can still be used to discover new clinical entities in cardiology (the 'Brugada Syndrome' is the commonest cause of sudden cardiac death in individuals aged under 50 years in South Asia). More recently, with the advent of wireless data transmission, the ECG of patients can be transmitted from ambulance to the cardiologist's smart-phone and the clinicians can make immediate decisions to redirect patients to the appropriate lab, saving time in transfers between hospital departments. In spite of its age the ECG is therefore still in very good health, nobody can really tell how much more we could learn from it, and nowadays cardiologists are looking at it from all different angles (e.g. as Dr Jay Mason showed in the last issue of AMPS-QT). In this issue, thanks to the contribution of Professor Paul Kligfield MD F.A.C.C., we offer our readers yet another relevant point of view of how and if the ECG should and could be used for the screening in asymptomatic subjects. Prof. Kligfield does not really need to be introduced, as we are certain that our readers are familiar with his outstanding contribution to the cardiac safety and have read many of his countless articles and books (just in case you can find the full list here: http://weill.cornell.edu/research/researcher/pkligfield/publications.html). As usual Enjoy!

A Noteworthy Contribution:

Use of the ECG in Asymptomatic Adults

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The use of the 12-lead electrocardiogram (ECG) is under scrutiny. Like drugs, diagnostic tests are subject to evaluation of efficacy and safety, and cost-effectiveness of testing has become a major issue in health care management. This is not simply a matter of cost containment. Routine testing may result in unintended consequences when false positive findings lead to further testing or to unnecessary interventions that have risk. As a consequence, recent documents have discouraged the routine use of the resting ECG as a screening test for coronary artery disease in adults with a low risk for CHD events, and recommendations for or against routine ECG screening in asymptomatic subjects at even intermediate and high risk are mixed. (1,2)

Further clouding recommendations for routine use of the ECG in asymptomatic subjects is the rather strict criticism that even where it has useful independent predictive value for future coronary events, there have been no prospective randomized trials that prove that intervention based on abnormal ECG findings favorably alters clinical outcomes in a cost-effective manner. On the surface, these challenges seem to contradict sensible clinical practice, but it is important to consider the context and implications of these recommendations a bit further. The discussion is also an opportunity to consider why the ECG may be useful for other purposes in seemingly asymptomatic or in minimally symptomatic people.

The United States Preventive Services Task Force (USPSTF) report and the ACCF/AHA guideline for assessment of cardiovascular risk recommend against routinely obtaining an ECG to screen asymptomatic adults at very low risk for heart disease for the presence of severe coronary artery disease or for the prediction of coronary events. The recommendations are based on expert consensus from available data that low sensitivity and imperfect specificity of the ECG in general populations leads to the identification of more false positive than true positive cases. The recent USPSTF update highlights a continued absence of clinical trials to prove that

intervention after ECG (as well as exercise ECG) detection of coronary risk has clinical value.

This perspective is reasonable for populations of entirely asymptomatic adults with no risk factors, and it is consistent with recent trends that base test applicability on the incremental relation of post-test to pre-test likelihoods of disease. The Bayesian argument against routine ECG testing of truly asymptomatic people at low risk is arithmetically sound: by definition, very low risk of obstructive coronary disease and very low risk of future coronary events means that the predictive value of tests with imperfect specificity will indeed be very low. A corollary is that false positive tests often lead to further testing that increases health care costs and occasionally to unnecessary interventions that provide no benefit but confer multiple risks. These are valid points, but many of these considerations can be argued, and the evidence may change in the future as these issues continue to be re-addressed.

Most cardiologists would agree that these focused recommendations should not be extrapolated beyond their very precise conditions to people with symptoms or with important risk factors who are referred for specialty diagnosis, even though false positive tests will occur. Populations are made up of individuals for whom outcomes are not fractional. It seems useful in principle to identify occult coronary disease because primary and secondary prevention measures seem to work. Asymptomatic adults with risk factors such as diabetes, hyperlipidemia, hypertension, and the metabolic syndrome are known to benefit from preventive measures. The prevalence of silent myocardial infarction is substantial in these higher risk patients, especially those with diabetes, and secondary prevention can only be effected in some situations after surveillance ECGs are compared with a baseline or prior tracing. How else can silent infarction be recognized? Absence of prospective, randomized data demonstrating useful effect of ECG findings on ultimate clinical outcomes should be a stimulus to ongoing study rather than a definition of test inappropriateness. While it remains to be established that early detection of increased coronary risk by ECG actually reduces adverse outcomes, this certainly is plausible.

Even so, ECGs are performed in asymptomatic patients for a wide variety of clinical indications that are unrelated to screening for anatomically and prognostically severe coronary disease. The ECG in asymptomatic subjects is routinely used to document cardiac rhythm and can provide evidence of unsuspected congenital structural heart disease, such as atrial septal defect and hypertrophic cardiomyopathy, an expanding list of inherited cardiac channelopathies, such as the various long QT syndromes and the Brugada syndrome, pre-symptomatic Wolff-Parkinson-White syndrome, and hypertrophy in untreated hypertension, among other diagnoses with clinical consequences.

In practice, a major purpose of the "routine" ECG in patient care is for future comparison with an ECG taken during a new and unpredicted symptomatic event. This may assist in the evaluation of acute chest pain syndromes, where examination of prior waveform morphology can reduce false positive and false negative diagnoses of ischemia. Similarly, routine pre-operative ECGs in asymptomatic individuals serve not only as a screen for recent infarction but have more relevant value for evaluation of non-specific syndromes in the post-operative period. Clearly, this cannot happen if testing is not done in asymptomatic people. In these situations, care of individuals must be distinguished from population screening statistics, and in my opinion, it is unfortunate that a "baseline" ECG as part of a general patient profile is not recommended for all. It can be argued that the potential harm from a resting ECG can be minimized, but how often the baseline would need to be re-established as individuals age requires study. And it is clear that easy retrievability of prior tracings is a necessary factor in their usefulness, which is not the case with digitally stored data when ECG formatting is proprietary.

Of course, recommendations against ECG screening in asymptomatic low risk subjects by definition does not address the use of the ECG in symptomatic people with chest pain, shortness of breath, palpitations, syncope, and a variety of other complaints. Nearly all (if not all) patients that are seen by cardiologists have some cluster of risk factors or some presenting or elicited symptoms that under current guidelines justify getting an ECG. This is good, because it is hard to believe that a cardiac evaluation could be considered complete without one. I am aware of no large, randomized, prospective study that provides evidence-based proof of beneficial clinical consequences of the stethoscope, but we all know why we use it. From the viewpoint of a cardiologist, evaluation of a patient without an ECG would be like examination of the patient without listening to the heart.

References:

1. Chou R, Arora B, Dana T, Fu R, Walker, M, Humphrey L. Screening asymptomatic adults with resting or exercise electrocardiography: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2011; 155(6):375-85.

2. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American

College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010; 56(25):e50-103.

Products News

Latest Releases

Last June we announced the release of the FDAEcg Suite v2 This new version introduces several major enhancements to version 1 and, among other new features, includes:

- The compatibility with the AMPS Bravo algorithm, which is now used to compute automatic scores.
- No limitation to the number of ECG files that may be loaded, scored and validated in a session.
- Scoring metrics totally revised and redesigned.
- New graphic capabilities.

The FDAEcg Suite v2 is also compatible with Windows 7.

Looking forward

In Q4 of 2012 AMPS is planning to release:

- CalECG v. 3.5.0, with updated BRAVO algorithm;
- Fat-QT v. 1.2.0, with updated BRAVO algorithm.

AMPS Notebook

AMPS has recently taken part in the **Computing in Cardiology** Conference, held in Krakow, Poland from September 9th to 12-th.

Fabio Badilini will be attending the **American Heart Association**, Scientific Session held from November 3rd to 7th in Los Angeles, California.

AMPS Recommends

With this 15th issue we are introducing this new column, with the aim of bringing to the attention of our readers interesting articles appearing on non-conventional (e.g. non-pharma) publications. The main focus will be on technically-oriented reports that we believe of interest for our readers.

We start by recommending an interesting internet article from Baumer, Starc and Porta published on PLOSE One, a peer-reviewed open access journal (www.plosone.org) in all areas of science and medicine. In this paper, Baumer and colleagues compare three different algorithms to assess the beat-to-beat variability of the QT interval from both simulated ECG data and from a group of Holter recordings in patients under Sotalol from the THEW repository. The three compared methods employ different approaches for computerized measurement of the QT interval (conventional derivative-based, template stretching and template time shifting) and exhibit interesting differences in the presences of broadband noise, baseline wander and T-wave amplitude modulation. Not surprisingly, template-based algorithms provide an overall better performance, particularly in the presence of noise, although it can also be concluded that conventional methods are far from being outscored and in certain conditions (specifically under baseline wander) are as good as the novel methods. Enjoy the reading.

Baumert M, Starc V, Porta A (2012) Conventional QT Variability Measurement vs. Template Matching Techniques: Comparison of Performance Using Simulated and Real ECG. PLoS ONE 7(7): e41920. doi:10.1371/journal.pone.0041920.

Full article can be downloaded at:
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0041920

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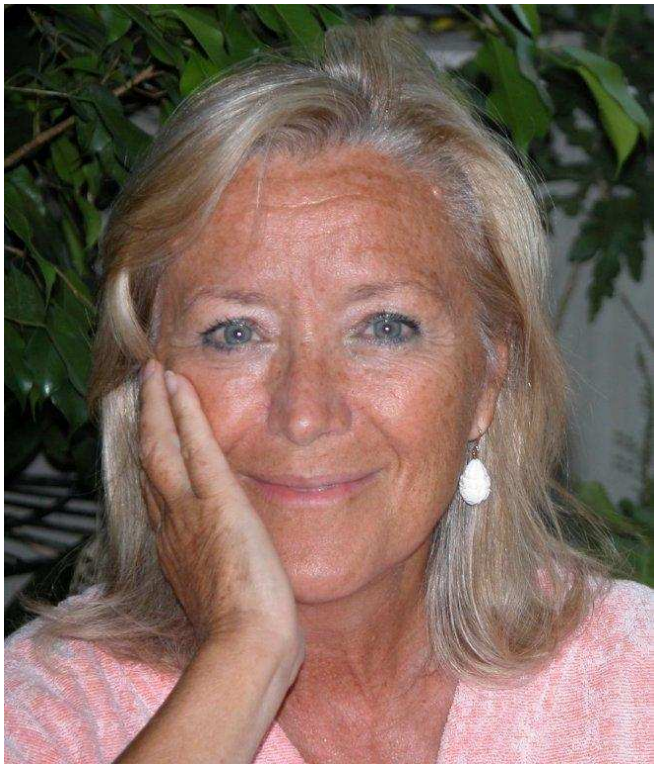
AMPS People

We complete our round of staff introductions with Franca Medioli.



Graduated in Microbiology from the University of Rome, Franca gained most of her professional experience in the Pharmaceutical industry, in particular in GlaxoSmithKline,

where she worked for about 20 years covering roles of responsibilities in Quality Assurance areas, particularly for ensuring and promoting Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP) and Good Clinical Practices (GCP) compliance and Quality Improvement

She started in GSK Parma manufacturing factory as Head of the Microbiological Laboratory in the Quality Assurance dept, with the responsibility for monitoring sterile products manufacturing. In this position she was involved in several Regulatory Authorities inspections , including FDA inspections.

She then moved to GSK Verona Research Center , where she was appointed Head of Microbiology Control Unit in the R&D Pharmaceutical Development arena, with the responsibility of providing scientific support for sterile new drug product development and technology, from early development stages up to product launch.

She ultimately served as Project Manager in the R&D Regulatory Compliance dept, with the responsibility of ensuring GLP and GCP compliance for pre-clinical studies.

More recently, Franca started her collaboration with AMPS as primary QA dept consultant.

She is now assisting AMPS in upgrading and optimizing the existing Quality system, precisely addressing regulatory requirements.

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