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 the last issue of AMPS-QT, we had shared that during the CSRC (Cardiac Safety Research Consortium) annual meeting which was focused on the CiPA (Comprehensive *In Vitro* ProArrhythmia Assay) advancements, the FDA team announced the release of the open source code with the recently published algorithms used for the computation of the ECG parameters (JTp, TpTe). At the end of the meeting, most of the attendees turned towards AMPS' Chief Scientist Fabio Badilini, and were keen to know if we had plans to implement these new developments and advances into our tools. The answer was pretty simple: absolutely! Now, 3 months later, as promised, we dedicate this AMPS-QT issue to the topic and are glad to share with our readers and subscribers interesting updates on the work and the progress made by AMPS. This issue also includes the valuable contribution of Dr. José Vicente, Visiting Scientist, of the Center for Drug Evaluation and Research of the US FDA.

A Noteworthy Contribution:

FDA Releases Automated Algorithm for T-wave Delineation and Clinical Data Used in the Algorithm Development

By José Vicente, PhD, Division of Cardiovascular and Renal Products, ODEI/OND/CDER/FDA, Silver Spring, MD.

The Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative is developing and validating a new paradigm for cardiac safety evaluation of drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential of drugs. Ion channel effects of drugs will be assessed *in vitro* and results will be integrated in an *in silico* model of the human ventricular myocyte to compute a proarrhythmia score. Predicted responses will be verified in human stem cell derived cardiomyocytes and ion channel effects will be confirmed using ECG data in phase 1 clinical studies [1]. Therefore, ECG biomarkers are needed to determine drug-induced ion channel effects in humans.

The CiPA ECG biomarker group was established to identify new ECG biomarkers that would add information beyond PR, QRS and QTc. New ECG biomarkers (i) should be able to differentiate multichannel effects during repolarization; (ii) can be corrected for heart rate; (iii) have sufficient power to detect changes in small sample sizes; and (iv) be available for wide spread use.

An analysis of 12 ECG biomarkers showed that the heart rate corrected J-Tpeak (J-Tpeakc) interval, defined from the junction point of the QRS complex with the ST segment (J point) to the peak of the T-wave (Tpeak), was the best biomarker for differentiating drugs with predominant hERG potassium channel block from drugs with hERG and late sodium and/or calcium current block. This analysis included a retrospective analysis of 34 drugs

using data from thorough QT (TQT) studies and two FDA-sponsored prospective clinical trials [2-5].

In these analyses Tpeak-Tend was measured globally on the vector magnitude derived lead, which is likely more consistent than measuring Tpeak-Tend in a single lead in the presence of complex T-wave patterns. The vector cardiogram leads were derived from the standard 12 leads using Guldenring's transformation matrix [6]. The vector magnitude lead was computed as the square root of the sum of the squares of the vector cardiogram leads ($VCGMAG = \sqrt[2]{X^2 + Y^2 + Z^2}$).

Tpeak was defined as the sample point with maximum vector magnitude in the retrospective analysis. The heart rate dependency of J-Tpeak was also assessed in this analysis and a population based correction factor was computed using an exponential model. The heart rate corrected J-Tpeak (J-Tpeakc) was computed as follows [2]:

$$J - Tpeakc = J - Tpeak/RR^{0.58}$$

In the two FDA-sponsored studies, Tpeak was defined as the maximum of the parabola fitted to the maximum of the T-wave and Tend was determined using the tangent method in the vector magnitude lead (Figure 1).

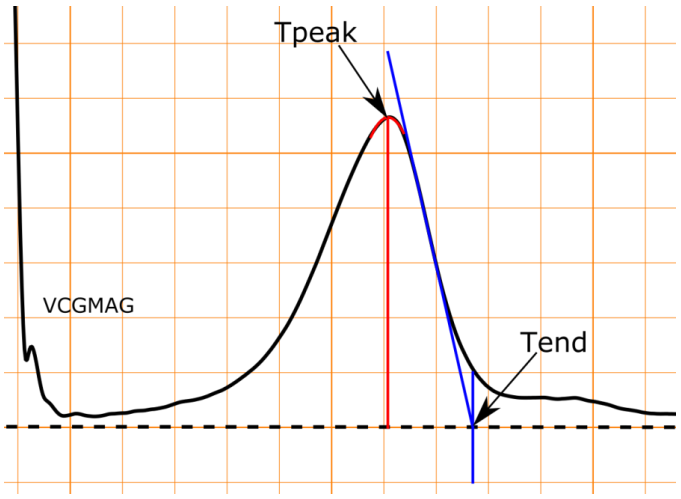


Figure 1: Tpeak and Tend annotations in vector magnitude lead (black). Red lines show the parabola fit around the peak of the T-wave and the Tpeak location. Blue lines show the tangent to the descending part of the T-wave and Tend location where the tangent crosses the isoelectric line.

Some of these automatic annotations were adjusted by the ECG reviewers during the ECG review process. Most of these adjustments were done because the automatic methods were not accurate in presence of flat, low amplitude or notched T-waves (Figure 2).

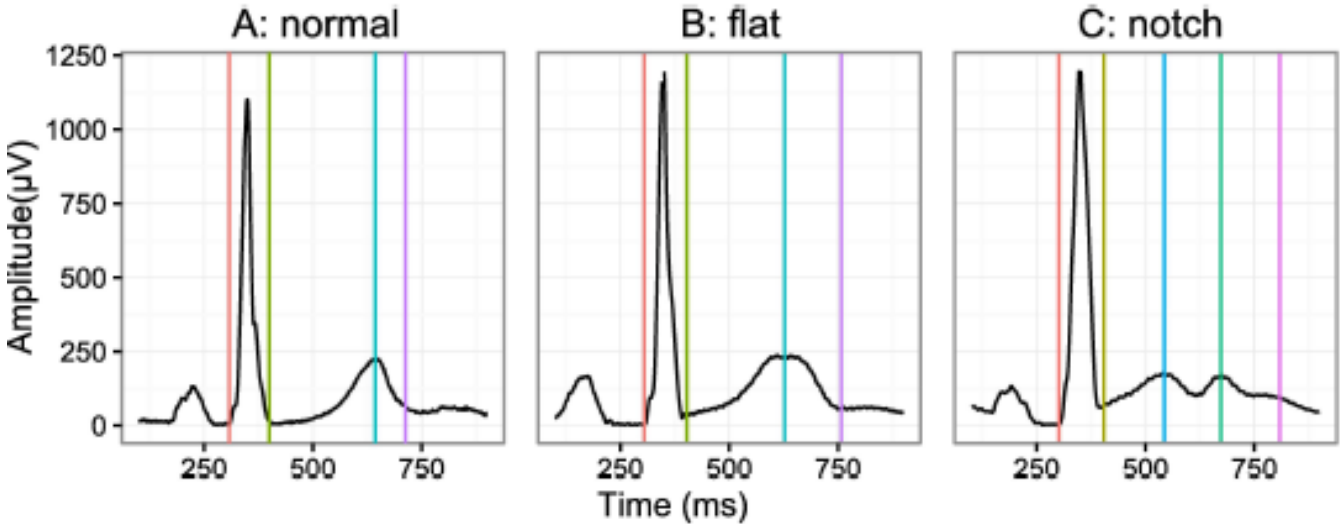


Figure 2: Examples of vector magnitude lead for normal, flat and notched T-waves. Reproduced from Johannesen et al [2].

FDA recently published an automated algorithm for Tpeak and Tend assessment that reproduces the semi-automated measurements in these two FDA-sponsored clinical studies (mean difference in changes from baseline < 1 ms) [2]. This algorithm uses a different approach to the one described above and

was developed using machine learning techniques. The algorithm extracts multiple features from the ECG signal and then applies a set of rules through a decision tree (J48 algorithm) to determine Tpeak and Tend in the vector magnitude lead. The algorithm was trained and validated using ECGs from FDA Study 1 and FDA Study 2 respectively.

While the automated algorithm reproduced the results from the two FDA clinical studies, it is important to recognize that in presence of extreme T-wave morphology changes the assessment of Tpeak and Tend can be challenging. Moreover, in previous studies lead II was the most commonly used lead to measure QT and QRS intervals, but Tpeak-Tend was most commonly assessed on V5. In addition to lead selection, there are differences in the definition of Tpeak that are of particular importance in presence of notched or flat T-waves. Thus, to allow others to compare results obtained using different methods and to foster research and testing of the J-Tpeak interval, FDA released an open source C++ version of the automated algorithm (https://github.com/FDA/ecglib). The clinical data and annotated ECG waveforms of the two clinical studies used in the algorithm development were also released by FDA (FDA Study 1 doi: 10.13026/C2HP45, FDA Study 2 doi: 10.13026/C2D016).

The International Society for Computerized Electrocardiology (ISCE) organized a special session around the J-Tpeak measure for its upcoming annual meeting. Results from private and academic investigators with their proprietary or non-proprietary methods in ECGs from FDA Study 1 will be presented in the J-Tpeak initiative sessions. Results will include J-Tpeak measures in the vector magnitude lead but also in other leads.

In addition, FDA is conducting a retrospective analysis of drug effects on QTc and J-Tpeakc in a large number of thorough QT studies. The J-Tpeak is being automatically assessed using FDA's algorithm on the ECG waveforms previously submitted by the sponsors to the FDA ECG warehouse. Results of this analysis include 80+ drugs and will be presented at ISCE 2017.

FDA is sponsoring the CiPA Phase 1 ECG Biomarker Validation Study, which started on March 2017 (https://www.clinicaltrials.gov/ct2/show/NCT03070470). This prospective clinical study will assess whether exposure response analysis of the QTc and J-Tpeakc intervals in Phase 1 clinical pharmacology studies can be used to confirm that drugs that predominantly block the potassium channel encoded by the human *ether-à-go-go-related* gene (hERG) with approximately equipotent late sodium and/or calcium block ("balanced ion channel" drugs) do not cause J-Tpeakc prolongation and that drugs that predominantly block hERG without late sodium or L-type calcium current block ("predominant hERG" drugs) cause QTc prolongation. Sixty healthy subjects will participate in this study. The study design is similar to single or multiple ascending dose (SAD/MAD) studies, with six drugs (ranolazine, verapamil, lopinavir+ritonavir, chloroquine, dofetilide and diltiazem) and placebo dosed during three consecutive days to achieve low and high exposure levels on days 1 and 3 respectively.

An automated algorithm to assess Tpeak and Tend in the vector magnitude lead was developed by FDA. A C++ version of the algorithm was released as open source to allow others to compare results obtained using different methods and to foster research and testing of the J-Tpeak interval. The CiPA ECG Biomarker Validation Study will assess whether a combined analysis of QTc and J-Tpeakc can differentiate predominant hERG blocking drugs from balanced ion channel drugs using exposure response models in a small sample size. Results of this prospective clinical study are expected in late 2017.

Disclaimer

No official support or endorsement by FDA is intended nor should be inferred. Use of FDA open source code in no way implies endorsement by the FDA or confers any advantage in regulatory decisions. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

References

[1] Colatsky T, et al. **The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative - Update on progress**. *J Pharmacol Toxicol Methods* 2016; 81:15-20.

[2] Johannesen L, et al. **Improving the assessment of heart toxicity for all new drugs through translational regulatory science**. *Clin Pharmacol Ther* 2014; 95(5):501-508.

[3] Johannesen L, et al. **Late sodium current block for drug-induced long QT syndrome: Results from a prospective clinical trial**. *Clin Pharmacol Ther* 2016; 99(2):214-223.

[4] Johannesen L, et al. **Differentiating drug-induced multichannel block on the electrocardiogram: randomized study of dofetilide, quinidine, ranolazine, and verapamil**. *Clin Pharmacol Ther* 2014; 95(5):549-558.

[5] Vincente J, et al. **Electrocardiographic Biomarkers for Detection of Drug-Induced Late Sodium Current Block**. *Plos One* 2016; 11(12):e0163619.

[6] Guldenring D, et al. **Transformation of the Mason-Likar 12-lead electrocardiogram to the Frank vectorcardiogram**. *Conf Proc IEEE Eng Med Biol Soc* 2012; 2012:677-680.

AMPS Views on:

CalECG and Implementation of the Public Domain Code

By Fabio Badilini, PhD, FACC, AMPS llc

One of the critical missions at AMPS has always been to deliver flexible and open technology solutions. CalECG, our resting ECG software solution, is one of the best examples of this. While it still embeds our proprietary keystone components (such as Bravo, our measuring algorithm), CalECG offers on one hand an open architecture capable of supporting a large variety of input/output formats, while on the other it allows the flexibility of complex customization to suit each user's specific needs by embedding external components.

When the FDA announced the release of an open source library in 2016, we committed ourselves to incorporate these changes into our technology in a timely manner. And we have made it happen! After about three months of its release by the FDA (described in José Vicente article), the open source library is now officially available directly as part of CalECG platform!

A detailed technical description on how this implementation has been brought about, and how the embedded library can be used is beyond the scope of this newsletter. However, please stay tuned for dedicated literature that we will soon send out to our customers and contacts. In particular, a webinar entirely dedicated to this topic has been organized (see the advertisement with the link for registration in the last page).

We are excited to share that the process was a fairly simple "plug-and-play" and at this point would like to provide a quick overview and more importantly a few important statements, mainly to avoid potential confusion.

- The open source library is an algorithmic package and does not provide a graphic interface. Once implemented, it returns numbers (like the position of the Tpeak caliper) and it is the responsibility of the hosting environment (in our case the CalECG GUI core) to eventually display the output received. Figure 3 shows an example of a CalECG screenshot showing the superimposed median beats and the related vector magnitude of an ECG (in green) with some of the calipers (Tpeak and Tend) that have been computed with the embedded open source library.
- The library requires the input ECG signal to be expressed in millivolts and sampled at 1000Hz.
- The library input must be the vector of a single cardiac beat which should preferably be a vector magnitude Lead (like the green lead in the Figure 3 example), i.e. an "envelope" of all standard Leads.
- The library requires the input vector to be adequately low-pass filtered and to include the Global RR interval and some pre-position/pre-computed markers, namely Qon, Rpeak and Qoff, and the returned output are the newly placed calipers on T-wave peak and on T-wave offset (Tpeak and Tend).

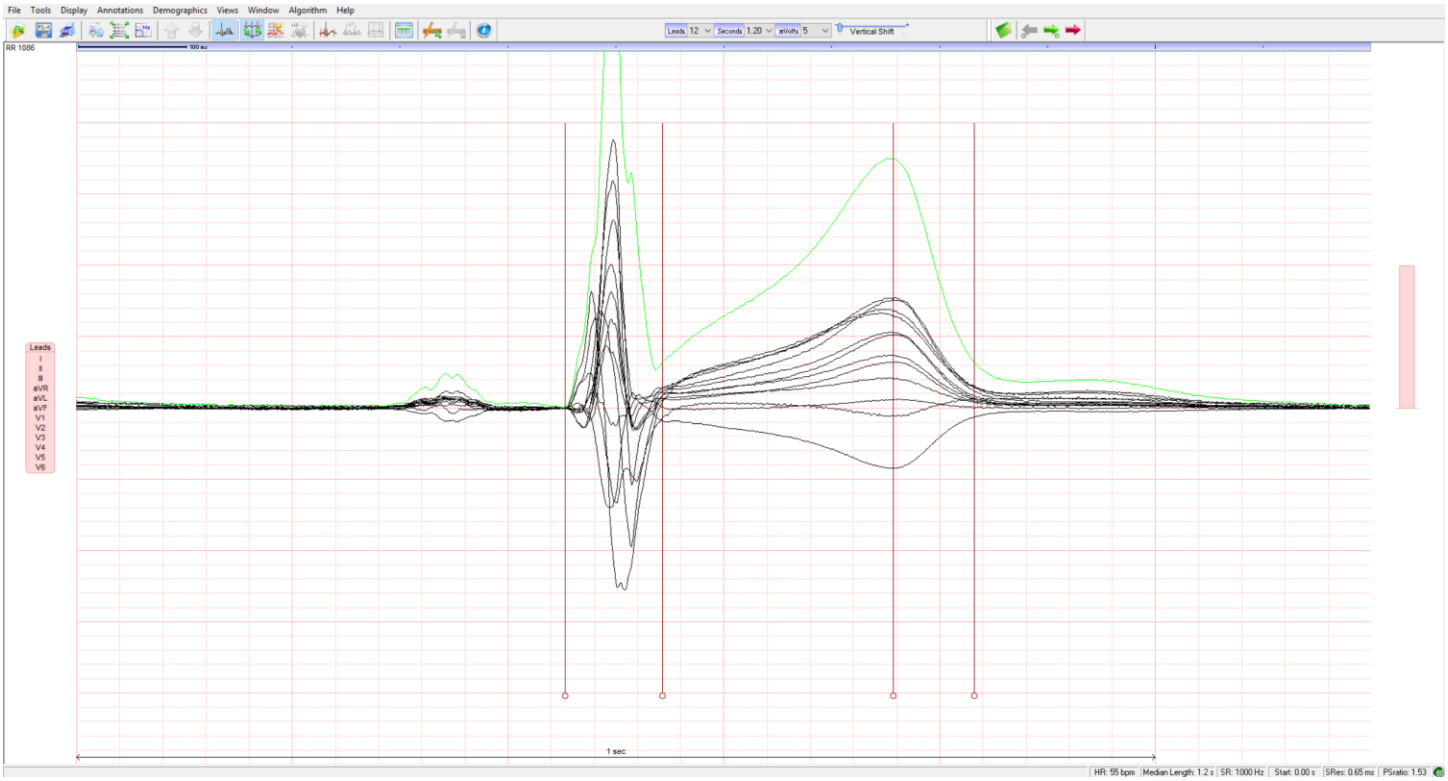


Figure 3: Representative Beats displayed in CalECG. QRS onset and offset markers are computed from BRAVO algorithm whereas the T-wave peak and T-wave offset are from the FDA open source library.

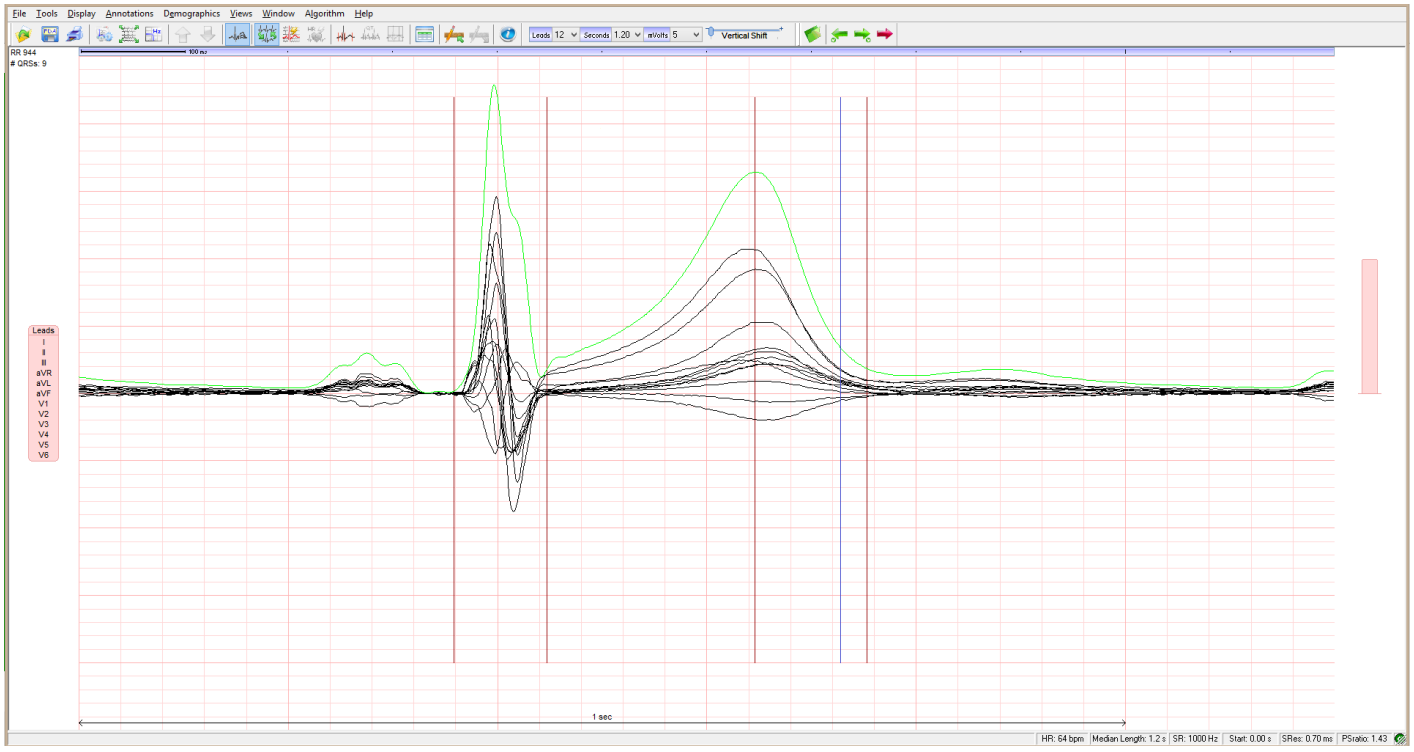
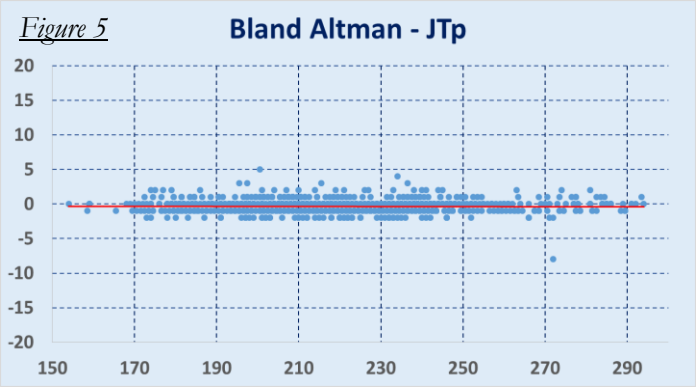


Figure 4: Comparison of ECG calipers from BRAVO (in red) and FDA open source algorithms (in blue). Of note, the T-wave peak caliper was detected in the very same position by both algorithms.

Example (with Results and Discussion)

As an example of potential usage of the embedded library, we report some preliminary results obtained comparing the JTp and TpTe intervals as automatically computed by Bravo, and by the embedded FDA library on a subset (N=1015) of 12-lead 10-seconds ECGs (1000Hz) randomly selected from AMPS internal library. Please take note that the two sets of intervals were obtained within a single execution run of CalECG where the vector magnitude lead was computed and fed to the two independent built-in algorithms. As expected, results enhanced some differences, particularly with respect to the Toffset fiducial markers. Figure 4 is a representative example: while the Tpeak markers are exactly the same (the two calipers are totally overlapped), the Toffset caliper from the open source library (blue marker) is 25msec earlier than the one detected by Bravo (in red).

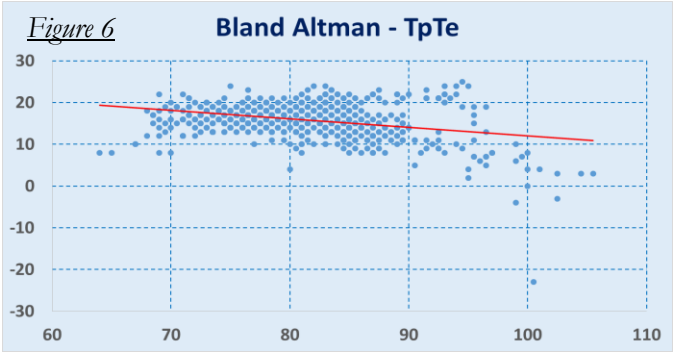
Figure 5



The agreement on the Tpeak marker position is also clear in the Bland-Altman plot of the JTpeak interval as shown in Figure 5 (the J point was the same and thus, differences on the JTpeak intervals are solely related to differences in the Tpeak marker detection). The averaged difference (i.e. the bias) was 0.3±0.9ms, and a non-significant trend (the tendency line in red is perfectly horizontal) was observed.

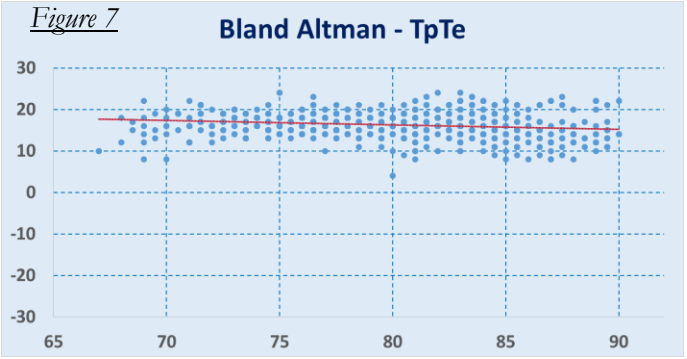
On the contrary, the TpTe interval enhanced a significant bias, with an averaged difference of 16±4ms and a negative slope of 0.202 (i.e. the difference between the TpTe of the two algorithms is larger for shorter TpTe intervals and is reduced by 2 msec for every 10 msec of average change).

Figure 6



These plots reflect a totally automated analysis which for some Toffest data points was affected by outliers that could determine the observed bias, as clearly noticeable in Figure 6. For example, by removing the 50 largest outliers in terms of noise (less than 5% of the data), the overall bias remained unchanged at about 16 msec; however the tendency line was drastically reduced to 0.101, representing a 1 msec reduction for every 10 msec of average change (Figure 7).

Figure 7



Conclusions

The reported data is just a basic example of a comparative analysis and should not be further extrapolated. Yet, we have demonstrated how by using the CalECG embedded platform from AMPS, the open source code distributed by the FDA could be easily implemented and made available for further analysis.

Products News

Latest Releases

In Q1 2017 we have released:

- A new version of CER-S (v. 2.4.0), including the following revised platforms:
  - Continuous ECG beat detection and classification
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia editor
- A new version of Fat-QT (v. 1.4.0), including the latest version BRAVO algorithm allowing the measurement of QTp, TpTe and Pdur intervals and ST amplitude and the computation of several new advanced quality scoring metrics.
- A new version of ViewECGWeb (v. 1.1.0) fully compatible with MS IE10 web browser and mobile devices.
- a new version of CSPER (v. 2.2.0) including the new Annotator platform for ECG measurements, the capability of filtering ECG waveforms and compatibility with Windows 10 and Windows Server 2016.

Looking forward

In Q2 2017 AMPS is planning to release:

- A new version of CalECG (v. 3.9.0), Fat-QT (v. 1.5.0) and TrialPerfect (v. 3.0.0) with the latest version of BRAVO algorithm, including JTp annotation.
- A fully revised version of CER-S (v. 3.0.0.), including the following optimized platforms:
  - Continuous ECG beat detection and classification, including fully renewed algorithm
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia editor

  and with the addition of measuring capability of time intervals, amplitudes and ST elevation both on beat-to-beat basis and averaged time-templates.

AMPS Notebook

Fabio Badilini attended the FDA-ISCE Trustees Meeting held on the FDA CAMPUS in Silver Spring, MD on Friday March 10th.

Fabio will attend the **42nd ISCE Annual Conference** that will be held between April 19th and 23rd in St. Simons Island, GA, where will give a presentation on the JTpeak initiative (Session III). Dr. Roberto Sassi will provide an updated perspective and present new data on the PDF-ECG project (Session V).

AMPS Webinar

AMPS Technology & Regulatory aspects

Overview of how AMPS solutions relate (and not relate) to regulatory aspects:
Continuous ECG submission and the implementation of JTp/TpTe intervals in clinical trials

Wednesday May 3rd 12 PM EDT, 9 AM PDT, 6 PM CEST

Presented by:

Fabio Badilini, PhD, FACC; Chief Scientist AMPS llc

Here the link to register: https://attendee.gotowebinar.com/register/2622884270458281730