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 first issue AMPS QT 2nd decade, we are very honored to host a great friend and inspiring researcher: Dr. Robert Lux, PhD, a Professor Emeritus of Medicine at the University of Utah School of Medicine.

Following his graduate studies in Electrical Engineering at the University of Vermont, Dr. Lux moved to Utah where he was appointed to the faculty at the Cardiovascular Research and Training Institute, a laboratory that focused on clinical and experimental studies of cardiac electrophysiology. His research interests include electrocardiographic mapping, ECG lead systems, and development of cardiac electrophysiologic measurements for assessing heart disease and arrhythmogenic risk. Although "retired" he remains active on research grants at the University and continues to review grants and manuscripts for the NIH and medical journals.

He has been an active ISCE participant since the "2nd Engineering Foundation" meeting (parent meeting of ISCE) in 1976 and chaired the 2003 meeting at Snowbird, Utah. He is ISCE's Immediate-Past President.

Dr. Lux is a world-recognized expert in the analysis of repolarization and his contribution on our bulletin is a great summary of his long-lasting experience in this field.

A warm thank to Bob and, as always, we hope all will enjoy this issue of AMPS-QT.

A Noteworthy Contribution:

The Ubiquitous Yet Elusive T Wave -

Novel ECG Estimates of Ventricular Electrophysiology

By Robert Lux, PhD, Professor Emeritus of Medicine at the University of Utah School of Medicine, Salt Lake City, UT, USA.

During my career of entrepreneur working in the field of biomedical waveform-based signals processing, I have been faced and coped with many different facets of unresolved clinical issues. Nurse alarm fatigue from the intensive bedside monitoring is certainly one of the most fascinating problems I have ever encountered, and where I believe research and innovation are highly needed.

The ECG T wave has been around for a very long time and the short story is that we still don't know everything about it. Since Einthoven first named the deflection in 1895, clinicians and scientists have peered at it, measured its amplitude and duration, catalogued its morphology, and linked it to all manner of cardiac diseases and conditions. In spite of this lengthy history, there remains much to learn and utilize from this tantalizing signal. Part of the challenge relates to the spectrum of factors influencing the T wave that include rate dependency, ventricular depolarization sequence, action potential duration distribution, local versus global abnormalities, pharmacological and neural effects, and genetic factors.

The single T wave measurement that has dominated clinical electrocardiology is the QT interval, the time between the earliest deflection of the QRS and "end" of the T wave in any ECG lead. Abnormal QT duration, after correction for heart rate, has long been recognized as a significant diagnostic marker for life threatening cardiac conditions and diseases, including ischemia, infarction, cardiomyopathy, genetic mutations, pharmacological, neurological or electrolyte imbalance. Nevertheless, there are many issues that complicate interpretation and use of the QT interval. It is non-specific, does not differentiate local from global cardiac conditions, rate correction is imperfect, and although QRS onset is reasonably well defined, end of the T wave (end of ventricular repolarization) is poorly delineated thus introducing uncertainty in the measurement.

This very brief monograph discusses some of the significant, recent research that has focused on quantitating T wave features that can be linked more directly to underlying myocardial cellular electrophysiology and that might be a prelude to improving the specificity of T wave-based diagnoses. The ECG results from the complex sequence of ionic currents from each of the billions of myocyte action potentials (APs) that sum to generate the body surface potential distributions. Established long ago were the facts that the QRS is generated by transmembrane currents during Phases 0 and 1, the ST segment by Phase 2 currents, and the T wave by Phase 3 currents. Crucial to the morphologies of QRS and T waves are the sequences of depolarization (timing of Phase 0, AP upstrokes) and repolarization (timing of Phase 3). Importantly, the repolarization time (RT) of each cell is determined by its depolarization or activation time (AT) plus its action potential duration (APD). **Figure 1** is a cartoon showing a distribution of action potentials having differing depolarization and repolarization times, and differing APDs. This cartoon illustrates important points that are not emphasized in the interpretation of the ECG in general and specifically the T wave:

- The ECG QRS is produced by the summation of all cellular Phase 0, AP upstrokes
- Repolarization begins just after the first cells depolarize (QRS onset)
- The ST segment reflects summation of currents during Phase 2 (AP plateaus)
- The T wave is dominated by all cellular Phase 3 currents (AP downstrokes)
- There is significant overlap of Phases 2 and 3 currents, so "T onset" is a poorly defined transition between Phases 2 and 3.

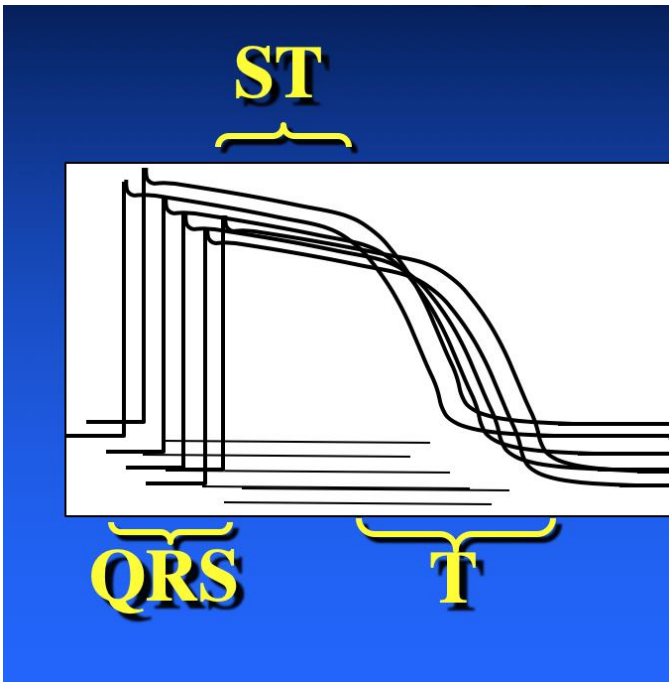

Figure 1: distribution of action potentials having differing depolarization and repolarization times and differing its action potential durations.

These points help to illustrate the directions of current research that focus on repolarization features of the ECG that that could potentially improve specific diagnoses. These include measurement and investigation of the J-T_{peak} and T_{peak}-T_{end} intervals in the assessment of drug safety. However, these, too, have not been shown to reflect underlying electrophysiology. While the J point does reflect the *end* of ventricular *depolarization*, it is not the *beginning* of ventricular *repolarization*. Thus J-T_{peak} does not have a clear meaning. Likewise, in spite of the many published papers that T_{peak}-T_{end} of the ECG reflects transmural dispersion of repolarization, there are no publications validating this in intact human or animal hearts!

Another research direction focuses on T wave morphology based on the long, established history of the utility of T waveforms in detecting and stratifying

disease, genetic mutations (LQT) and abnormal pharmacological effects or electrolyte disorders. The unusual peaked or bimodal T waves in Long QT syndromes have been observed for decades. Related to these mostly subjective morphology assessments, is the so-called "complexity" analysis which implements a principle components-based analysis to quantify abnormality of T waveforms as an index of arrhythmia vulnerability [1]. These measures suggest methods to detect abnormality of the repolarization process, e.g. local regions of abnormal APDs or AP waveform.

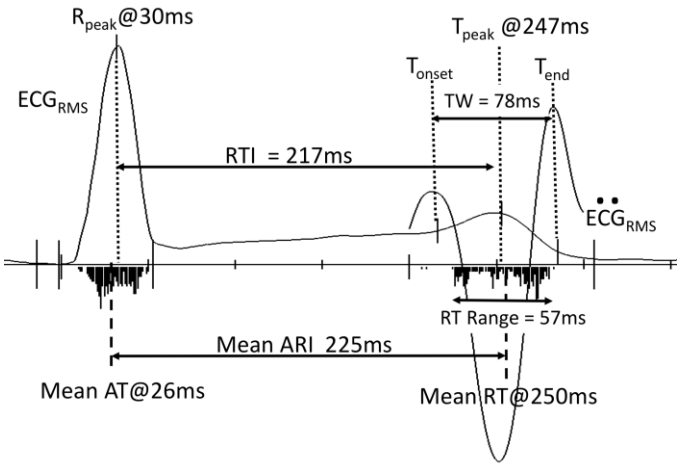

Figure 2. The data show the RMS EG (the signal) and superimposed histograms of ATs and RTs measured from 64 epicardial EGs and 190 EGs from nineteen 10-pole transmural plunge electrodes distributed to on both right and left ventricles [2].

Finally, and to the main point of this monograph, there exist ECG measurements that have been experimentally documented in large animal studies that can be tied specifically to the distributions of cardiac action potential characteristics and timing. This work was based on *activation-recovery interval* (ARI) methodology in which direct mapping of ventricular electrograms (EGs) provide the key features of local depolarization and repolarization times [3, 4]. From cardiac electrograms, recorded from small, unipolar electrodes directly in contact with the myocardium, one may determine the time at which the propagating depolarization wave passes the electrode--the depolarization or activation time (AT). This was verified by simultaneously recording EGs and monophasic action potentials (MAPs) from nearby (<1mm) floating glass microelectrodes. The time of steepest MAP upstrokes (Phase 0) corresponded within a millisecond or two of the time of steepest EG downstroke. Likewise, the time of steepest MAP downstroke (~50% repolarization) was measured as the time of steepest T wave upstroke in the EG. Thus, from simultaneous recording of hundreds of ventricular EGs, one may plot the sequences of ventricular depolarization and repolarization as well as the distribution of action potential durations.

Figure 2 shows data from an experiment that helped to quantitate the relation between easily measured ECG features and the underlying direct measures at the myocardium.

Significant findings include:

- Mean AT and time of RMS Rpeak are within 4 milliseconds
- Mean RT and time of RMS Tpeak are within 3 milliseconds
- Differences between mean AT and RT times and Rpeak and Tpeak times are within 8 milliseconds
- Tonset and Tend times, delineated by peaks of second derivative of the RMS T wave, appear to reflect times of earliest and latest repolarization times, respectively
- Range of RTs appear to have a close approximation by the Tonset and Tend interval--T width (TW)

Similar findings were reported by Opthof et al [5].

These findings and observations suggest that analysis of the RMS signal of the 12-Lead ECG can provide reasonable estimates of times of mean ventricular depolarization, repolarization, action potential duration and repolarization time dispersion. Furthermore, the conflation of directly measured AT and RT histograms with the RMS ECG R and T waves conjures up the concept of the RMS QRS T waves being probabilistic distributions of ATs and RTs. Additionally, given the knowledge that RMS T_{peak} is an estimate of mean 50% AP repolarization time, one might surmise that the T_{onset} - T_{peak} interval reflects *early* Phase 3 repolarization and the T_{peak} - T_{end}

interval reflects *late* Phase 3 repolarization. This dissection of the T wave into early and late aspects of Phase 3 may be useful in quantifying observed imbalances of T wave symmetry observed in abnormal T waves in the presence of disease or abnormal electrophysiology.

In summary, this brief summary suggests the likelihood that novel ECG measurements may provide more direct estimates of underlying cellular electrophysiology.

References

[1] Al-Zaiti S, Sejdić E, Nemec J, Callaway C, Soman P, Lux R: Spatial indices of repolarization correlate with non-ST elevation myocardial ischemia in patients with chest pain. Med Biol Eng Comput. 2018 Jan;56(1):1-12.

[2] Lux RL: Basis and ECG measurement of global ventricular repolarization. J Electrocardiol. 2017 Nov-Dec;50(6):792-797.

[3] Millar CK, Lux RL and Kralios FA: Close correlation between refractory periods and recovery intervals from electrograms. Circulation 66-II:78, 1982.

[4] Haws CW and Lux RL: Correlation between in vivo transmembrane action potential durations and activation-recovery intervals from electrograms. Effects of interventions that alter repolarization time. Circulation 81:281-8, 1990.

[5] Opthof T, Janse MJ, Meijborg VM, Cinca J, Rosen MR, Coronel R. Dispersion in ventricular repolarization in the human, canine and porcine heart. Prog Biophys Mol Biol. 2016 Jan;120(1-3):222-35.

Products News

Latest Releases

In Q1 2019 we have released:

- A new version of *Antares* (v. 2.19.0) now allowing to extract 10 minutes long optimized ECG extractions.
- A new version of *ECGScan* (v. 3.4.0) with revised graphical display and optimized ECG digitization.

Looking forward

In Q2 we are going to release two new versions of CER-S (v.3.2.0 & v.4.0.0), including the following revised platforms:

- Continuous ECG beat detection and classification, including the fully renewed ABILE algorithm, with new long analysis capability, up to 30 days.
- ECG beat editor
- Arrhythmia detection and Arrhythmia editor
- ECG Beat Measure, for measuring averaged time-templates ECG complexes, including ST-displacement assessment.
- Report generation.

In Q2 we are going to proceed with CER-S "CE" and "510K" certification processes.

AMPS Notebook

Fabio Badilini attended the FDA-ISCE Trustees Meeting held on the FDA CAMPUS in Silver Spring, MD in February.

Fabio will attend the **44th ISCE Annual Conference** that will be held between April 10th and 14th in Atlantic Beach, Florida.

The following month, Fabio will attend the **40th** Annual **Heart Rhythm** Scientific Sessions that will be held between May 8th and 11th in San Francisco, California.