AMPS-QT

The AMPS Quarterly - Issue n.44 - 4Q2019 Editors: Fabio Badilini PhD, FACC and Martino Vaglio MS

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

We are honored to host two great friends and inspiring researchers: Dr. Jorgen Kanters, MD, an Associate Professor from the Department of Biomedical Sciences at the University of Copenhagen and Dr. Claus Graff, PhD, an Associate Professor from the department of Health Science and Technology at Aalborg University. And we also thank Jonas Isaksen, also from the University of Copenhagen for his contribution to this newsletter.

Dr. Kanters and Dr. Graff are historical ISCE and CinC participants and represent perfect examples of researchers inspired by all aspects of cardiology, always capable to find the right balance between the medical background to address a clinical problem and the engineering solutions employed for its solution.

But more importantly, our guest writers can be considered pioneers of many of the recent ECG challenges, and specifically the characterization and quantitative description of the morphology of the T wave, which is a topic of great interest in clinical research.

We asked them for a review of their work on the subject, and we are proud to present it in our quarterly bulletin.

A warm welcome and thank you to Jorgen, Claus and Jonas and, as always, we hope our readers will enjoy this issue of AMPS-QT.

A Noteworthy Contribution:

T-Wave Morphology

Jorgen K. Kanters MD[1], Jonas Isaksen MScEng[1], Claus Graff PhD[2]

[1]Laboratory of Experimental Cardiology, University of Copenhagen, Denmark.

[2]Department of Health Science and Technology, Aalborg University, Denmark.

The term *"T-wave morphology"* is used to describe the shape of the T wave both qualitatively as e.g. deep inverted T waves as seen in acute pulmonary embolism, or quantitatively with the use of specialized computer algorithms. A normal T wave has a bell-shaped form where the downslope normally is steeper than the upslope. Most commonly the T wave is positive (like a left skewed normal distribution), although negative T waves may be normal in lead V1, V2 (and rarely in lead V3) and III.

Repolarization is orchestrated by a fine balance of mainly potassium, sodium, and calcium currents. Alteration of these currents may lead to sudden cardiac death as seen in Short- and Long QT syndrome as well as Brugada syndrome [1,2]. The HERG channel Kv11.1 encoded by the *KCNH2* gene is of major interest for the pharmaceutical industry, since HERG is the target for most drugs prolonging the QT interval with a few exceptions. In the 1990s, it became clear that QT prolongation may cause lethal arrhythmias and several drugs were withdrawn from the market due to their effect on the HERG channel.

Hence, detection of HERG blockade became of uttermost interest in all drug studies to prevent fatalities, and thorough QT studies were introduced where new drugs were tested against placebo and a positive moxifloxacin arm. A rule of thumb says that the risk of arrhythmias increases with 5-7% per 10 ms increase in QTc [3]. In reality, the overall risk of drug induced Torsades de Pointes (TdP) is very low and has been estimated to be around 2-4 cases per million person years [4]. Even in congenital Long QT syndrome patients, a recent study showed that QT prolonging drugs are often prescribed after the diagnosis likely due to the physician's unawareness of the HERG blocking properties [5]. Although congenital Long QT syndrome patients are at high risk for development of TdP in general, we could not show increased risk with the use of QT prolonging drugs [5].
Since the introduction of the preclinical ICH S7B and clinical ICH E14 guidelines in 2005, no drugs have been withdrawn from the market [6]. However, one may worry that new drugs with potential to benefit patients were wrongly stopped due to fear of HERG block even when the benefits outweigh the risks.

The T wave represents cardiac potential differences during ventricular repolarization. Most ventricular action potentials will be canceled out in the ECG by each other, but due to regional differences (epicardial/endocardial – right/left ventricle – apical/basal – anterior/posterior wall) repolarization gradients will exist. In the beginning of phase 2 of the action potential these differences will be small (corresponding to the initial ST segment), but as more and more cardiomyocytes begin phase 3, the upslope of the T wave will form. The peak of the T wave will then correspond to the time of the largest repolarization potential difference. As more and more cardiomyocytes enter phase 3, the gradient will decrease thereby forming the downslope of the T wave. So, the T wave is a marker of repolarization dispersion, and since dispersion can lead to reentrant arrhythmias, quantification of T wave morphology may be of major clinical and pharmacological interest.

The QT interval has been used for a century to characterize repolarization, measured from the beginning of the Q wave to the end of the T wave. However, the measurement and interpretation are not always straightforward. The end of the T wave is not always easy to identify, especially with the presence of a U-wave (which may/may not represent a notched T wave). Furthermore, the QT interval is heart rate dependent, and the standard correction method Bazett's is well known to be a bad correction (but simple).

In the seminal paper of Moss [7], he showed that the T wave had characteristic shapes depending on the genetic background of the Long QT Syndrome. Patients with reduction of the I_{Ks} current (*KCNQ1* mutations) had broad based high-amplitude T waves, patients with reduced I_{Kr} current (*KCNH2*/*HERG* mutations) had flat notched T waves and patients with reduced I_{Na} current (SCN5A mutations) had late-appearing T waves with long flat ST segments. This inspired the idea that it may be possible to quantify the T wave morphology to express changes in the different cardiac action potential currents [8]. The initial approach was to fit the T wave integral to a Hill equation [8] (known from enzyme kinetics). With this method, we were able to distinguish between Long QT syndrome patients with *KCNQ1* and *KCNH2* mutations despite having similar QT intervals [8]. Since block of the HERG channel is the cause of >95% of all drug-induced QT prolongation we further refined T wave morphology analysis to quantify the HERG channel function. The Morphology Combination Score (MCS), licensed to GE Healthcare, was designed to evaluate three distinct features seen in Long QT syndrome patients with *KCNH2* mutations: Notches, flatness and asymmetry of the T wave (Fig 1.) [9]. Compared to many variants of T wave morphology, MCS has the advantage of being tested in a broad range of publications also outside the inventor's research groups [10,12].

In short, for calculation of MCS, a principal component analysis is performed on the ECG. Principal component analysis has the advantage that it is robust to electrode misplacement and anatomical variations. The first principal component is used for calculation of the three features in MCS: Asymmetry,

Flatness, and Notches. Asymmetry is calculated as the difference in slopes of the ascending and descending parts of the T wave. Mirroring the one side of the T wave around the peak, asymmetry is defined as the average squared difference between the ascending and descending slope segments [9].

Flatness compares the T wave with the normal distribution. A higher value of flatness corresponds to a flatter T wave [9]. T wave flatness is calculated by normalizing the standard kurtosis measure (fourth central moment) by the standard deviation to the fourth power and subtracting this value from one.

The Notch score evaluates the presence and magnitude of humps in the T wave, a well-known risk marker in the Long QT Syndrome and can be either 0 with no notch, 0.5 with a moderate notch, or 1 with a pronounced notch. A notch is identified from the curvature signal given by the first and second derivatives of the T wave [9,13].

These three subcomponents: Asymmetry, Flatness, and Notches can either be used individually which have received a 510K approval by FDA, or in combination as MCS where

$$MCS=Asymmetry+Notch+1.6*Flatness$$

Like the QT interval, MCS is slightly heart rate dependent ($r^2=0.15$) but not as much as QT ($r^2=0.58$). Furthermore, the intraindividual variation is negligible [14]. Flatness and asymmetry are similar in their ability to detect HERG block whereas notching occurs at higher levels of HERG block.

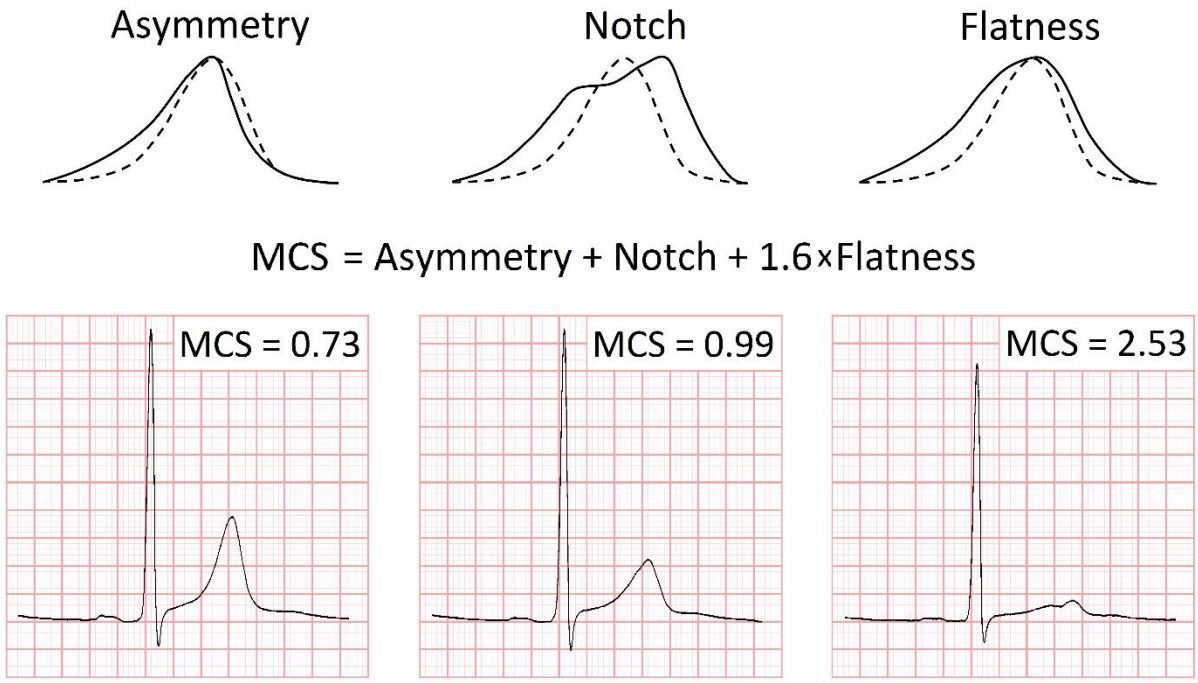

Figure 1. (Upper lane) Gray dashed line represents a normal T wave. The full line represents a T wave from left to right which are more asymmetric, notched, or flat, respectively. Lower lane shows three ECGs with a normal (left) (asymmetry = 0.063, flatness = 0.42, notch = 0), moderately increased (middle) (asymmetry = 0.22, flatness = 0.48, notch = 0) and strongly increased (right) Morphology Combination Score (asymmetry = 0.558, flatness = 0.61, notch = 1). A normal T-wave has an MCS of 0.70 ± 0.16. Reproduced with permission [15].

Other descriptors have been used to described T wave morphology. TpeakTend in combination with JTpeak have been suggested to distinguish between pure HERG block (with prolongation of both TpeakTend and JTpeak) and HERG block with concomitant calcium or late sodium channel block (with diminished or abolished JTpeak prolongation). TpeakTend is widely used, and is proposed in the new CiPA initiative [6] to distinguish between "safe" QT prolongation and "risky" QT prolongation [11]. However, measurement of TpeakTend is not straightforward with flat T waves, and the selection of lead or transformation to for example the vector magnitude ECG to measure TpeakTend has a large influence. Furthermore, the "safe" QT prolongation seen with Ranolazine (with combined late sodium and HERG block) has been questioned after a study found that Ranolazine had higher risk than Dofetilide in a patient cohort with QT prolongation [16]. Ranolazine is also on the CredibleMeds list of drugs which should be avoided in Long QT syndrome. Other methods of quantifying T wave morphology have been published like T wave Vector magnitude [17], T wave morphology restitution [18] have also been suggested, but these methods are characterized by only been used by the inventing groups.

The ability of MCS to identify HERG block of the I_{Kr} current has been demonstrated in several studies [9,13,19] including studies performed by the FDA group [11]. When compared to QTc in a Sotalol thorough QT study [13], MCS detected I_{Kr} block better than QT indicating that MCS is more sensitive than QT for repolarization abnormalities. MCS has also been used to verify the absence of I_{Kr} block in a study with Bilastine, a highly selective non-sedating antihistamine [20]. In the FDA study, the three subcomponents of MCS increased mostly during Quinidine and Dofetilide treatment, with a modest increase with Ranolazine, and an absent response with verapamil [11]. In a study where patients with previous drug-induced TdP undergoing rechallenge with Sotalol [19] (the most torsadogenic drug) both QT and MCS distinguished between patients with earlier TdP and matched controls during Sotalol challenge, but only MCS was able to identify TdP patients at baseline where no drug was given. That indicates that MCS and not QT can identify the arrhythmia substrate without the need for drug challenge. In a yet unpublished study (Isaksen, personal communication (submitted)), MCS predicted all-cause mortality as well as cardiovascular mortality in a large population of primary care patients (n=270,039) independent of the QT interval and significantly better.

In conclusion, MCS is a robust T wave descriptor including several features of T wave morphology to detect HERG block better than QTc. Promising results suggest that MCS may also be used in risk stratification, but further studies are warranted before MCS may be used as a personalized tool for drug prescription. Researchers and companies interested in analyzing ECGs for scientific purpose are welcome to contact us at jkanters@sund.ku.dk.

References

[1] Hedley PL, Jorgensen P, Schlamowitz S, Wangari R, Moolman-Smook J, Brink PA, Kanters JK, Corfield VA and Christiansen M. The genetic basis of long QT and short QT syndromes: a mutation update. Hum Mutat. 2009;30:1486-1511.

[2] Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA and Christiansen M. The genetic basis of Brugada syndrome: A mutation update. Hum Mutat. 2009;30:1256-1266.

[3] Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM and Zareba W. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2010;121:1047-1060.

[4] Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E and Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. Europace. 2014;16:101-8.

[5] Weeke PE, Kellemann JS, Jespersen CB, Theilade J, Kanters JK, Hansen MS, Christiansen M, Marstrand P, Gislason GH, Torp-Pedersen C, Bundgaard H, Jensen HK and Tfelt-Hansen J. Long-term proarrhythmic pharmacotherapy among patients with congenital long QT

syndrome and risk of arrhythmia and mortality. Eur Heart J. 2019;40:3110-3117.

[6] Wallis R, Benson C, Darpo B, Gintant G, Kanda Y, Prasad K, Strauss DG and Valentin JP. CiPA challenges and opportunities from a non-clinical, clinical and regulatory perspectives. An overview of the safety pharmacology scientific discussion. J Pharmacol Toxicol Methods. 2018;93:15-25.

[7] Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA, Vincent GM and Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation. 1995;92:2929-34.

[8] Kanters JK, Fanoe S, Larsen LA, Thomsen PEB, Toft E and Christiansen M. T wave morphology analysis distinguishes between KvLQT1 and HERG mutations in long QT syndrome. Heart Rhythm. 2004;1:285-292.

[9] Graff C, Matz J, Christensen EB, Andersen MP, Kanters JK, Toft E, Pehrson S, Hardahl TB, Nielsen J and Struijk JJ. Quantitative analysis of T-wave morphology increases confidence in drug-induced cardiac repolarization abnormalities: evidence from the investigational IKr inhibitor Lu 35-138. J Clin Pharmacol. 2009;49:1331-1342.

[10] Porta-Sanchez A, Spillane DR, Harris L, Xue J, Dorsey P, Care M, Chauhan V, Gollob MH and Spears DA. T-Wave Morphology Analysis in Congenital Long QT Syndrome Discriminates Patients From Healthy Individuals. JACC Clin Electrophysiol. 2017;3:374-381.

[11] Vicente J, Johannesen L, Mason JW, Crumb WJ, Pueyo E, Stockbridge N and Strauss DG. Comprehensive T wave Morphology Assessment in a Randomized Clinical Study of Dofetilide, Quinidine, Ranolazine, and Verapamil. J Am Heart Assoc. 2015;4.

[12] Hermans BJM, Stoks J, Bennis FC, Vink AS, Garde A, Wilde AAM, Pison L, Postema PG and Delhaas T. Support vector machine-based assessment of the T-wave morphology improves long QT syndrome diagnosis. Europace. 2018;20:iii113-iii119.

[13] Graff C, Andersen MP, Xue JQ, Hardahl TB, Kanters JK, Toft E, Christiansen M, Jensen HK and Struijk JJ. Identifying Drug-Induced Repolarization Abnormalities from Distinct ECG Patterns in Congenital Long QT Syndrome: A Study of Sotalol Effects on T-Wave Morphology. Drug Safety. 2009;32:599-611.

[14] Andersen MP, Xue JQ, Graff C, Kanters JK, Toft E and Struijk JJ. New descriptors of T-wave morphology are independent of heart rate. J Electrocardiol. 2008;41:557-561.

[15] Vedel-Larsen E, Iepsen EW, Lundgren J, Graff C, Struijk JJ, Hansen T, Holst JJ, Madsbad S, Torekov S and Kanters JK. Major rapid weight loss induces changes in cardiac repolarization. J Electrocardiol. 2016;49:467-72.

[16] Romero J, Baldinger SH, Goodman-Meza D, Engstrom K, Valencia CR, Golive A, Medrano F, Rangasamy S, Makkiya M, Fisher JD, Gross J, Krumerman A, Kim S, Garcia MJ, Di Biase L and Ferrick KJ. Drug-induced torsades de pointes in an underserved urban population. Methadone: is there therapeutic equipoise? J Interv Card Electrophysiol. 2016;45:37-45.

[17] Cortez D, Zareba W, McNitt S, Polonsky B, Rosero SZ and Platonov PG. Quantitative T-wave morphology assessment from surface ECG is linked with cardiac events risk in genotype-positive KCNH2 mutation carriers with normal QTc values. J Cardiovasc Electrophysiol. 2019;30:2907-2913.

[18] Ramirez J, van Duijvenboden S, Aung N, Laguna P, Pueyo E, Tinker A, Lambiase PD, Orini M and Munroe PB. Cardiovascular Predictive Value and Genetic Basis of Ventricular Repolarization Dynamics. Circ Arrhythm Electrophysiol. 2019;12:e007549.

[19] Bhuiyan TA, Graff C, Kanters JK, Melgaard J, Toft E, Kaab S and Struijk JJ. A History of Drug-Induced Torsades de Pointes Is Associated With T-wave Morphological Abnormalities. Clin Pharmacol Ther. 2018;103:1100-1106.

[20] Graff C, Struijk JJ, Kanters JK, Andersen MP, Toft E and Tyl B. Effects of Bilastine on T-wave Morphology and the QTc Interval: A Randomized, Double-Blind, Placebo-Controlled, Thorough QTc Study. Clin Drug Investig. 2012.

Products News

AMPS LLC, announces that it has received Conformité Européene (CE) Mark approval for CER-S. The CE marking confirms that CER-S meets the requirements of the European Medical Devices Directive, which now allows AMPS and CardioCalm, its Italian subsidiary, to commercialize CER-S across

the European Union and other CE Mark geographies for the usage in the health-care market.

Fabio Badilini, President and Chief Scientist of AMPS stated, "We are very pleased to report CE Mark approval for CER-S, our modular software program for the analysis and interpretation of continuous ECG recordings. CER-S marks an important leap forward for both AMPS and CardioCalm, as we are bringing to market a powerful and highly sophisticated tool for the analysis of continuous ECG traces (aka Holter) that we are confident will benefit both healthcare providers and patients by bringing the latest advances in ECG analysis technology both for traditional 12 lead Holter equipment and newly developed wearables devices".

Fabio Badilini further stated: "Given the leading-edge technology CER-S brings to manufacturers of continuous electrocardiograph devices, we are confident that our ability to enter the European market will help deliver improved outcomes for the monitoring of cardiovascular pathologies".

For more information on CER-S, please contact us at: info@amps-llc.com.

CER-S Celebration cake at the annual AMPS Christmas dinner.
(In Italian **C'E'** means: "**Is There**")