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

This month's contribution, from Richard L. Verrier, Ph.D., makes us at AMPS particularly proud because it shows clearly how two of our products, namely ECGScan and CalECG, can be used to boost research and empower scientists to explore data that would not be otherwise exploitable. ECGScan in particular enables the use of existing large databases, making available a virtual gold mine of data that can help to address the challenge of ECG-based CAD detection. Dr. Verrier is currently Associate Professor in the Department of Medicine at Harvard Medical School. His research concentrates on the major public health problem of sudden cardiac death, which claims approximately 325,000 lives per year in the United States alone and occurs without prodromes in at least 30% of cases. His work emphasizes both elucidation of pathophysiologic mechanisms and translation from bench to bedside. His patented, FDA-approved diagnostic risk assessment technology is now in use in clinics and hospitals worldwide.

A Noteworthy Contribution:

T-Wave Heterogeneity for Detection of Coronary Artery Disease: Tapping the Gold Mine of Stored ECG Paper Recordings

By Richard L. Verrier, Ph.D., and Bruce D. Nearing, Ph.D Harvard Medical School, Beth Israel Deaconess Medical Center, Boston MA, USA.

Introduction

Noninvasive detection of coronary artery disease (CAD) persists as a daily diagnostic challenge in contemporary cardiology. Provocative testing protocols with exercise tolerance testing (ETT) and pharmacological stress procedure with or without echocardiography or nuclear imaging testing are the standard procedure. Induction of ST-segment depression in conjunction with symptoms is the most widely employed ECG sign of CAD.

Despite decades of experience, it is widely recognized that these tests as currently employed yield an excess percentage of both false positive and false negative tests when compared to the "gold standard" of diagnostic coronary angiography (1). Other ECG parameters have been proposed to improve the diagnostic yield of stress testing, such as ST/heart rate slope or index and ST/heart rate recovery loop (2, 3), but have not resulted in significant advances. Accurate ETT-based detection of CAD with ST-segment measurement has proved to be particularly challenging in women as the false positive rate is 25% to 50% (4).

A new approach for detection of coronary artery stenosis is proposed, namely analyzing the interlead splay of T waves in precordial leads about a mean waveform as the central axis. This index, termed "T-wave heterogeneity" (TWH), has been shown in the experimental laboratory to be highly accurate in detecting arrhythmia susceptibility during acute myocardial ischemia (5-7). In the 5600-subject Health Survey 2000 study, which was designed to provide a cross-section of the entire Finnish population, ECG

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heterogeneity was found to predict cardiac mortality and sudden cardiac death with odds ratios of 3.2 to 3.5 (8). As myocardial ischemia is a prevalent substrate for lethal cardiac arrhythmias, we investigated the potential of TWH to detect obstructive and nonobstructive coronary artery disease.

The goals of the present brief review are to introduce the method and supporting scientific data for second central moment analysis of TWH and to discuss what is known about its clinical utility in detecting CAD.

Method for tracking interlead ECG heterogeneity by second central moment analysis

The "second central moment" technique draws on Newtonian mechanics to track ECG heterogeneity, which is fundamentally related to conduction abnormalities and reentrant arrhythmias. The technique is illustrated in Figure 1. Basically, the method involves generating mean morphologies (the "first moment") of the QRS intervals and T waves from separate precordial leads. Then, the ECGs are superimposed with aligned QRS complexes, and the splay or heterogeneity in morphology about this mean axis (referred to as "the second moment") is calculated in microvolts by taking the square root of the variance. As a result, the approach assesses the shape of the entire waveform rather than merely the duration of the intervals, and the measurement is not unduly weighted by protracted termination or inflections in the T wave, biphasic forms, ST segment changes, or the presence of U waves, features that limit measurement of dispersion of repolarization by conventional QT-interval analysis. The templates of QRS complex-aligned ECGs permit visualization of the splay in morphology and verification of microvolt determinations.

The TWH measurement can be analyzed from paper tracings by utilizing the imaging processing software ECGScan (AMPS-LLC, New York NY) and active contour modelling technique CalECG (AMPS-LLC) of Badilini and coworkers (Figure 2) (9-11).

Early Studies

The second central moment technique for monitoring interlead heterogeneity of morphology has been studied in detail in large animal models since its introduction in 2003 (12). TWH was shown during acute myocardial ischemia to exhibit a crescendo in amplitude, heralding the onset of ventricular fibrillation. An orderly progression in TWH preceded low and high levels of T-wave alternans (TWA) followed by discordant TWA and ultimately ventricular tachycardia and fibrillation. This finding is consistent with the well-established integral relationship between TWH and TWA. Elevated levels of TWH were also found in preclinical studies in response to profibrillatory conditions including partial coronary artery stenosis with and without adrenergic stimulation (5-7).

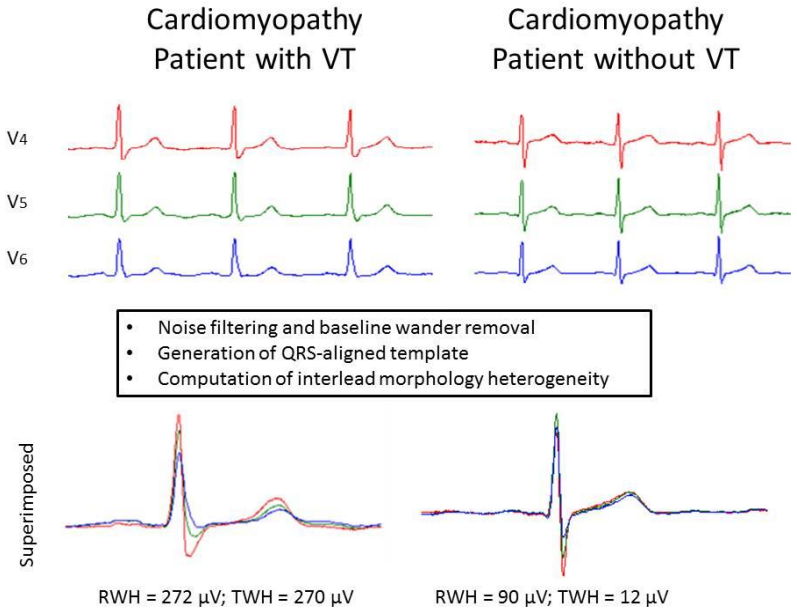

Figure 1: Flowchart of signal processing and computing of the second central moment calculation of R-wave heterogeneity (RWH) and T-wave heterogeneity (TWH) in a representative patient with cardiomyopathy with ventricular tachycardia (VT) (left panel), who exhibited greater splay (heterogeneity) than did the patient with cardiomyopathy without VT (right panel). Electrocardiograms were simultaneously obtained from precordial leads V4, V5, and V6. Reproduced with permission from Heart Rhythm Society from Verrier and Huikuri (14).

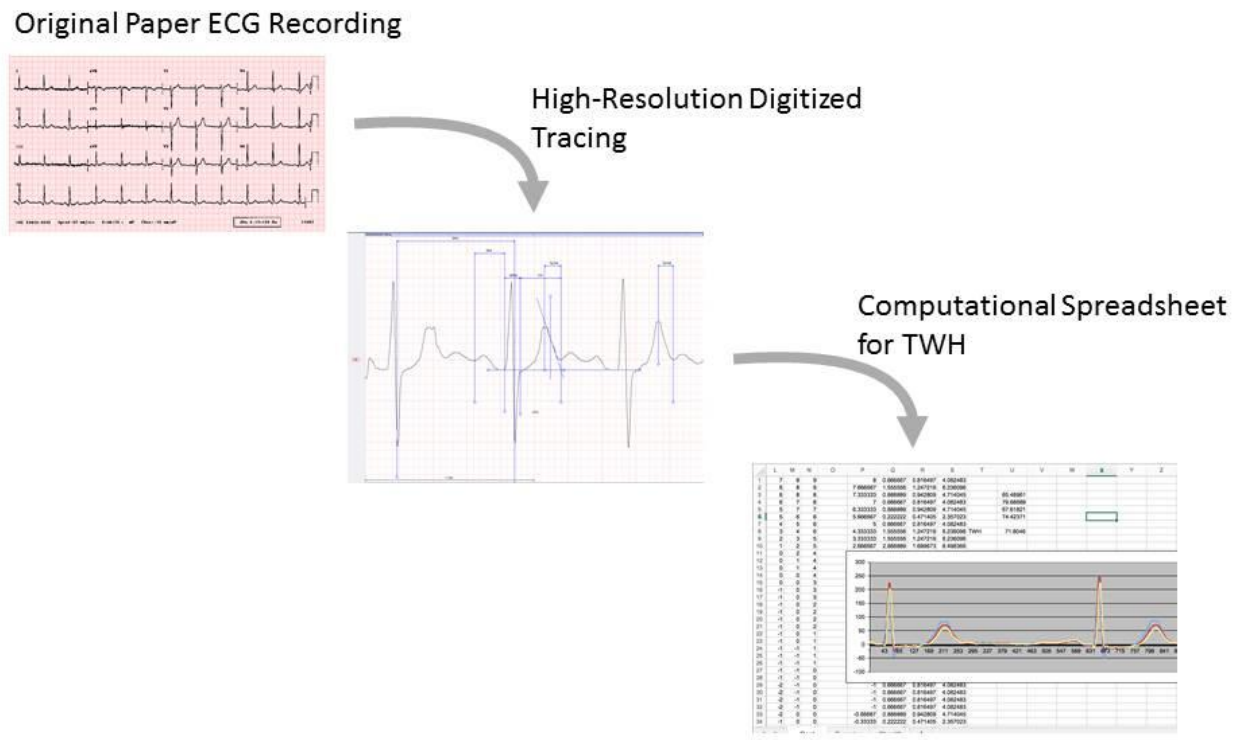

Figure 2: Standard 12-lead analog ECGs for all cases (25 mm/s, 10 mV/mm) and controls (50 mm/s, 20 mV/mm) were scanned with a high-resolution scanner. Image processing software, "ECGScan" (AMPS-LLC, New York, NY), was then used to extrapolate the ECG waveforms using an active contour modeling technique (Badilini, Erdem, Zareba, Moss, 2005). The resulting digital waveforms were converted into .txt files that could be imported into spreadsheets for subsequent analysis. Reproduced with permission from Wiley Periodicals from Stocco et al (10).

In the first clinical study of ECG heterogeneity, patients with decompensated heart failure showed a crescendo in R-wave heterogeneity (RWH) and TWH before TWA and ventricular tachycardia (13), indicating that TWH could constitute a premonitory marker of impending TWA and malignant ventricular arrhythmia (14).

Clinical Studies

Exercise-induced TWH in symptomatic diabetic patients with nonflow-limiting coronary stenosis

A key premise in risk stratification is that a stimulus such as exercise, which perturbs the supply-demand relationship and increases adrenergic drive, can expose latent vulnerability to arrhythmias although myocardial substrate abnormalities may not be evident at rest. Recently, the capacity of second central moment analysis to detect latent cardiac electrical instability was evaluated, prompted by growing awareness that symptomatic diabetic patients with non–flow-limiting coronary stenosis are vulnerable to SCD (10). Cases were patients with ECG recordings during both rest and ETT who were enrolled in the Effects of Ranolazine on Coronary Flow Reserve in Symptomatic Patients with Diabetes and Suspected or Known Coronary Artery Disease (RAND-CFR) study (NCT01754259). Control subjects were nondiabetic patients who underwent ETT and had functional flow reserve >0.8, a range not associated with inducible ischemia. TWH was analyzed from precordial leads V4, V5, and V6 during the pre-randomization phase by second central moment analysis. During exercise to similar rate-pressure products (p=0.31), RAND-CFR patients exhibited a 49% increase in TWH during exercise

(rest: 49±5 μV; exercise: 73±8 μV, p=0.003). By comparison, in control subjects, TWH was not significantly altered (rest: 52±11 μV; ETT: 38±5 μV, p=0.19).

There was a relatively high incidence of false positive ST-segment determinations, as five (56%) controls had ST-segment depression >1 mm despite FFR >0.8, indicating the absence of inducible ischemia (1). Of these five control subjects, four were female, consistent with the high rate of false-positive results in women (4). In these four female control subjects, TWH was unchanged during exercise, consistent with FFR in the normal range. By comparison, among cases with impaired CFR, there was a marked increase in TWH in response to exercise (Figure 3).

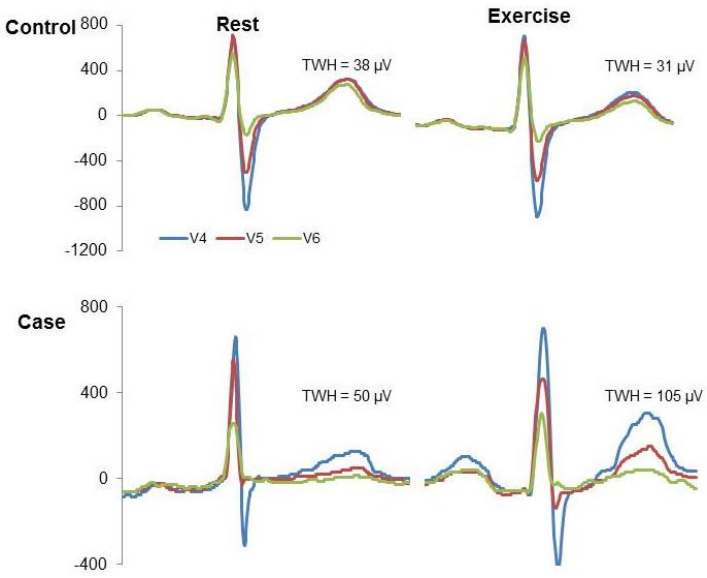

Figure 3: Digitized ECG tracings illustrating T-wave heterogeneity as interlead splay in repolarization morphology during rest and exercise in a representative control subject (upper panels) and representative case (lower panels). Reproduced with permission from Wiley Periodicals from Stocco et al (10).

The precise factors that may have contributed to the increase in TWH during exercise in the cohort of symptomatic patients with diabetes are likely multifold, given the complexity of this disease condition. Among the most prominent are the presence of coronary microvascular dysfunction, diffuse atherosclerosis, changes in myocardial structure including myofibrillar disarray induced by recurrent ischemic episodes, and altered autonomic function (15,16). That structural abnormalities are present in diabetic patients is supported by findings that QT dispersion, an indicator of heterogeneity of repolarization, is elevated during rest (17). Di Carli et al (15) and Carnethon and colleagues (18) reported evidence of significant autonomic dysfunction in patients with diabetes, with predominance in sympathetic tone.

Exercise and pharmacologic stress-induced T-wave heterogeneity for detection of large epicardial coronary artery stenosis

Recently, we analyzed the potential of interlead TWH to improve detection of large epicardial coronary artery stenosis (19). Stress ECG recordings from all 96 patients at our institution who underwent diagnostic coronary angiography within 0 to 5 days after ETT (N=62) or intravenous (IV) dipyridamole infusion (N=34) in 2016 were analyzed. Cases (N=62) had angiographically significant stenosis (≥50% of left main or ≥70% of an epicardial coronary artery ≥2 mm in diameter); controls (N=34) did not. TWH was assessed from precordial leads by investigators blinded to clinicians' records of angiographic and ST-segment results. At rest, TWH levels were similar in cases and controls. In cases, ETT and dipyridamole stress testing induced significant increases in TWH (30%, p<0.0001; 26%, p<0.001, respectively) (Figure 4). In controls, TWH did not change. Area under the receiver-operator characteristic curve (AUC) for TWH increase for any flow-limiting coronary artery stenosis was 0.73 for ETT (p=0.003) and 0.88 for dipyridamole stress testing (p=0.0001). ST-segment changes with either exercise or dipyridamole did not differentiate cases from controls (AUC=0.56 for both tests, NS). TWH generated significantly improved AUC's over ST-segment in subgroup analyses of men, women, diabetics, and nondiabetics during dipyridamole stress testing and in women during ETT. Based on these observations, we concluded that TWH improves the diagnostic accuracy of ETT and dipyridamole stress testing for detection of large epicardial coronary artery stenosis.

The improvement in detection of stenosis by dipyridamole stress over ETT is likely to be due to technical factors as well as conceptual considerations.

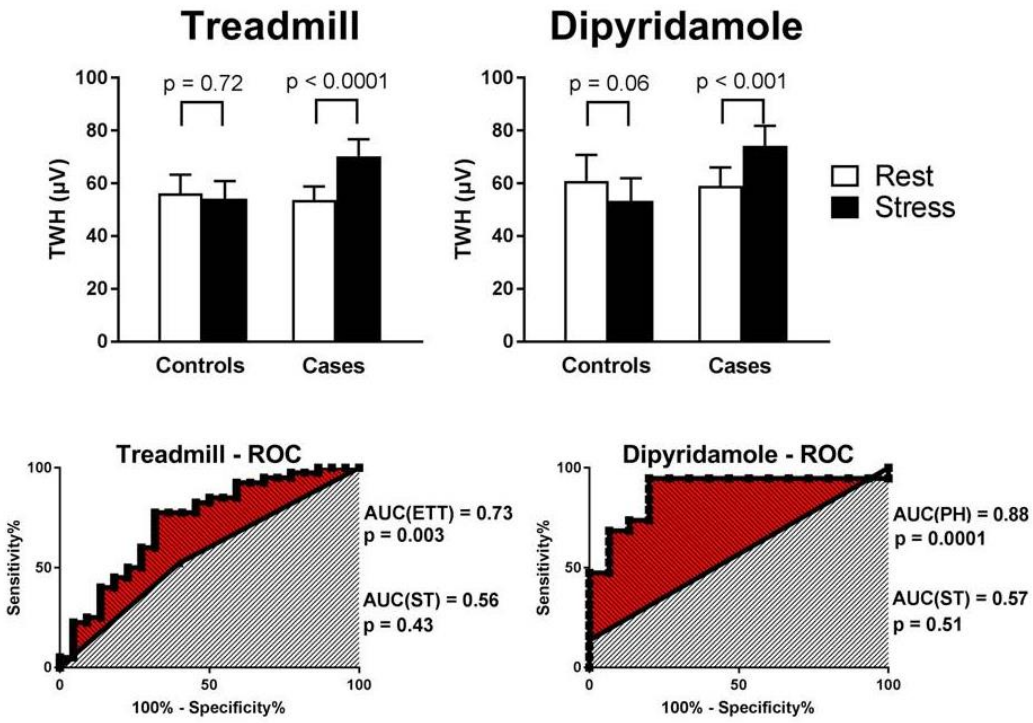

Figure 2: Top panel: At rest, TWH levels, measured in microvolts, were similar for cases and controls. ETT and dipyridamole testing induced significant TWH increases (30%, p<0.0001; 26%, p<0.001, respectively) in cases. In controls, TWH did not change. Bottom panel: Area (AUC) under the receiver-operator curve (ROC) for TWH increase for any flow-limiting coronary artery stenosis (grey plus red areas) was 0.73 for ETT (p=0.003) and 0.88 for dipyridamole (p=0.0001). ST-segment changes with either ETT or dipyridamole (grey areas only) did not discriminate cases from controls (AUC=0.56, p=0.43 for ETT, and AUC=0.57, p=0.51, for dipyridamole). Reproduced with permission from the American College of Cardiology from Silva et al (19).

The rationale for ETT is the imposition of a workload on the heart, which is achieved by increasing heart rate and systemic arterial pressure, resulting in a challenge between supply and demand as well as an increase in cardiac sympathetic drive. The ETT test relies on patient motivation and physical capacity to exercise and is affected by factors that can impair chronotropic response such as bradycardia-inducing medications including beta-blockers and calcium channel antagonists. In pharmacologic stress testing, subjects are resting quietly and the movement artifacts associated with walking and running on the treadmill are avoided, potentially improving the accuracy of the ECG waveform measurements. Dipyridamole testing is based on inducing inhomogeneous perfusion through steal of coronary blood flow from diseased to normal zones (20). Notably, dipyridamole induced increased TWH without a significant effect on ST-segment. Thus, pharmacologic stress testing is inherently suited for the detection of flow-limiting coronary artery stenosis with TWH.

Conclusions

TWH is a promising new tool for detecting CAD during ETT and pharmacologic stress testing. Side-by-side comparison with ST-segment shows the clear superiority of TWH. An important new finding is that TWH can be employed in conjunction with pharmacologic stress testing, which helps to extend the patient population to individuals who are unable to perform a standard ETT. In order for the test to gain widespread use clinically, sizeable databases will need to be analyzed. The fact that the TWH can be measured from paper records digitized with high-resolution scanning techniques such as ECGScan enables the use of existing large databases, making available a virtual gold mine of data that can help to address the challenge of ECG-based CAD detection.

Acknowledgements

The T-wave heterogeneity methodology reported in this article is protected by United States patents assigned to Beth Israel Deaconess Medical Center.

We are grateful to Fabio Badilini, Ph.D., and his team for making available the image processing software, "ECGScan," and "CalECG" (AMPS-LLC, New York, NY) for use in the studies discussed in this article (10,11,19).

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Paper on automated comparisons published on AHJ

In early February 2018, the manuscript titled "Comparison of Automated Interval Measurements by Widely Used Algorithms in Digital Electrocardiographs" has been formally accepted for publication on the American Heart Journal [1]. This achievement was conducted under the auspices of the Cardiac Safety Research Consortium (CSRC) and completes a two-year tremendous effort that have involved seven algorithm companies (including AMPS LLC) and several academic leaders, starting from the manuscript first author Dr. Paul Kligfield from Weill Cornell Medical College, NY. The study is a follow-up of a similar project, which was published on the same Journal in 2014 [2], and focuses on the comparisons of computer-based measurements of electrocardiographic intervals from normals, from subjects receiving moxifloxacin and from patients affected by genetically proved long QT syndrome, provided through an ongoing collaboration between the CSRC and the French long QT registry, and in particular with Dr. Pierre Maison-Blanche. While based on a totally different set of ECGs, the study confirmed the presence of small but statistically significant differences between ECG interval measurements by individual algorithms, which were more pronounced in long QT interval subjects than in normal subjects, thus indicating that comparisons of population study norms should be aware of small systematic differences in interval measurements due to different algorithm methodologies.

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Products News

Latest Releases

In Q1 2018 we have released:

- A new version of CER-S (v. 3.1.0), including the following revised platforms:
  - Continuous ECG beat detection and classification
  - ECG beat editor with new ABILE algorithm
  - Arrhythmia detection and Arrhythmia editor
  - ECG Beat Measure, for measuring both on beat-to-beat basis and averaged time-templates.
- A new version of ECGSolve (v. 2.4.0), formerly CSPER, including the capability of filtering ECG waveforms when converting ECG formats.
- A new version of ECGScan (v. 3.4.0) with revised graphical display and optimized ECG digitization.

Looking forward

In Q2 2018 AMPS is planning to release:

- A new version of CalECG (v. 4.1.0), Fat-QT (v. 2.1.0) and ECGSolve (v. 2.5.0) with the latest version of BRAVO algorithm (v. 4.7.0) and the new vectorized PDF ECG report.

- A new version of CER-S (v. 3.2.0.), including the following revised platforms:
  - Continuous ECG beat detection and classification, including fully renewed algorithm
  - ECG beat editor with new ABILE algorithm
  - Arrhythmia detection and Arrhythmia editor
  - ECG Beat Measure, for measuring 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 February 13th.

Fabio will attend the **43rd ISCE Annual Conference** that will be held between April 25th and 29th in Park City, Utah, where he will chair the last session of the conference "Session X: Update on International Initiatives and Standards" and give the presentation "Exchange of digital ECGs: do we have enough formats?".

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