T Wave and QRS Complex Alternans During Standard Diagnostic Stress ECG Test

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Abstract

The aim of the present work was to study and analyse the presence of both T wave and QRS complex alternans (TWA&QRSA) during diagnostic stress ECG test using principal component analysis, and wave amplitude computation on a combined lead. We studied 57 patients at a mean age of 65 ± 12 y, 44% males. 28 of the patients had angiographically significant coronary artery disease (AS_CAD ≥ 50% stenosis of at least 1 epicardial coronary artery).

The results showed that patients with positive stress ECG test had significantly higher TWA&QRSA values compared to patients with negative stress test (2.32 versus 1.66, p < 0.001 for TWA and 1.77 versus 1.11, p = 0.003, for QRS). Patients with AS_CAD had significantly higher QRSA, but not TWA, values (1.6 and 1.1, respectively; p = 0.017).

1. Introduction

Microvolt T wave and QRS complex alternans (TWA&QRSA) is an electrophysiological phenomenon associated with the change in the shape of the T wave and QRS complex, appearing in alternation on an every other beat basis, that are not apparent to the naked eye. Microvolt TWA has the ability to identify patients at high risk for sudden cardiac death. In studies in animals [1] and humans [2-4], TWA is strongly associated with an increased risk of reentrant ventricular tachyarrhythmias and sudden cardiac death.

T-wave alternans is a heart rate-dependent measure of repolarization [5]. Previously, TWA induced with atrial pacing was shown to predict ventricular arrhythmias in patients undergoing electro-physiologic study [6]. Subsequently, techniques were developed to allow assessment of alternans noninvasively with exercise. There is a high concordance between exercise-induced and pacing-induced TWA [7].

Electrical alternans of the QRS complex is an electrocardiographic phenomenon seen in different clinical situation – mainly supraventricular and ventricular tachycardias [8,9]. The clinical significance of QRSA however is less well studied. There is some data that this electrocardiographic (ECG) parameter may be of some value in determining the risk of sudden cardiac death and the need for device therapy in selected patients [10] although other clinical trials do not confirm these results [8]. QRSA has not yet been studied and described in the context of stress ECG test.

A variety of algorithms for detecting and quantifying TWA have been proposed, employing techniques as spectral analysis, complex demodulation, zero-crossings counting in a series of correlation coefficients, Karhunen-Loève transform, low-pass Capon filtering, Poincaré mapping, periodicity transforms, statistical tests, modified moving average, Laplacian likelihood ratio, etc.

A review by Martínez and Olmos [11] highlights the need for methodological systematization effort in characterization and comparison of the different methods.

PhysioNet and Computers in Cardiology organized a challenge in 2008: Detecting and quantifying T-wave alternans [12]. A set of 100 freely available ECGs with reference rankings of TWA content was specially compiled and posted. Thirty of them contained artificial TWA in calibrated amounts [13]. The artificial TWA was created by modulating the T-wave loop of the synthetic vectorcardiogram (VCG), then projecting the VCG onto 12 scalar ECG leads. In this way, the artificial TWA is distributed across the scalar ECG leads. The TWA amplitudes were defined as the maximum vector difference between the forms of the T-wave loop in the VCG and varied from 2 to 60 microvolts.

The aim of this study is determine the possibility of simultaneous measurement of TWA&QRSA during stress ECG test and to evaluate the clinical significance of the presence of these electrophysiological abnormalities.

2. Methods

2.1. Study group

We studied 59 patients (anamnesis, physical examination, clinical and laboratory data, stress ECG test and ECG analysis). From the initial group of 59 patients we have excluded 2 patients with a history of sustained or non-sustained ventricular tachycardia, since it is a well known fact that such patients have increased values for TWA and QRSA. None of the other 57 patients had a positive anamnesis for ventricular tachycardia.

Demographic characteristics, risk factors distribution and other clinical data for the group of 57 patients are presented in Table 1.

Ethics: Signing an inform consent was a prerequisite for inclusion in the study. The study protocol was approved by the local ethical committee and complied with the Declaration of Helsinki.

Table 1. Demographic characteristics and risk factor distribution for the whole group of patients

Clinical variable	Distribution n = 57
Age – mean ± SD	64.5 ± 11.5
Male – n (%)	25 (44%)
BMI (body mass index) – mean ± SD	28.7 ± 4.9
Arterial hypertension – n (%)	53 (93%)
Diabetes mellitus – n (%)	14 (25%)
Dyslipidemia – n (%)	45 (79%)
Total cholesterol – mean ± SD	4.99 ± 1.12
Triglicerides – mean ± SD	1.52 ± 0.87
Family history of CAD – n (%)	(7%)
Present smokers – n (%)	6 (11%)
Ex-smokers – n (%)	22 (39%)
Angina pectoris – n (%)	48 (86%)
History of myocardial infarction – n (%)	11 (19%)
Positive stress ECG test – n (%)	13 (23%)
Angiographically significant CAD – n (%)	28 (49%)
Percutaneous coronary interv. – n (%)	23 (40%)
Coronary artery bypass grafting – n (%)	5 (9%)

SD – standard deviation; n – number; CAD – coronary artery disease

Patients were included regardless of their sex or age. Patients referred to our department for stress ECG test evaluation of inducible myocardial ischemia were considered eligible. Exclusion criteria were left ventricular systolic dysfunction with ejection fraction < 40%, haemodinamically significant valvular heart disease, heart rhythm other than sinus, patient unable to perform the stress ECG test or unwilling to sign the inform consent.

2.2. Stress ECG test

All patients performed a stress ECG test using veloergometer (GE Marquette Stress PC ECG Application Version 4.312, Medset Medizintechnik GmbH). The protocol we used consisted of 2-min stages with 25W incremental workload. Digital 12-lead electrocardiograms (ECG) were acquired during the whole stress ECG test. The test was considered positive in the setting of ≥ 1 mm horizontal or downward-sloping ST depression 80 msec after J-point.

2.3. TWA&QRSA detection

Some of the authors of the current material successfully participated in the Physionet/Computers in Cardiology Challenge, 2008 for detection and quantification of T wave alternans [14]. Their method for T wave alternans quantification [15], which will be partially retell in the present article, has been effectively expanded towards QRS complex alternans detection and quantification.

The ECG signals were preprocessed to eliminate or suppress the powerline interference, the drift [16] and the electromyographic noise [17]. QRS detection was applied [18], onsets and offsets of the QRS complex and T wave were automatically delineated [19] and their amplitudes were calculated, in a combined lead (CL) simulating the spatial vector [16].

The proposed approach takes into consideration three aspects of the TWA&QRSA detection task: the parameter selection, the interval selection and the classification.

In selecting the more appropriate parameter for TWA classification, the multi-lead approach has been followed, in order to extract a single index from the entire ECG record. Two parameters were chosen, considering the temporal domain: 1) the amplitude and 2) the complexity index of T waves. In the first case the combined lead was used in which T wave onset and offset delineations were performed, and the amplitude were computed.

The second parameter for TWA&QRSA discrimination considers the use of Principal Component Analysis (PCA) for quantifying the complexity index of the T waves. PCA has been applied to the intervals of QRS complexes and T waves. The complexity index is characterized by the ratio 2nd/1st eigenvalues.

In the interval selection two methods were applied: Global and Local (see Figure 1) In the global method, the entire ECG recording was processed, producing a unique time series, which feed the detection block. The local method considers a set of variable length windows of RR intervals, and performing the parameter extraction in each of them. In particular this method considers a window of 128 RR intervals, shifting it in the entire ECG recording.

The detection block performs first, the separation of the parameters from odd and even RR intervals, and then the two series was compared in order to discover the presence of significative differences with the statistical analysis performed by the non parametric paired-sampled Wilcoxon signed rank test.

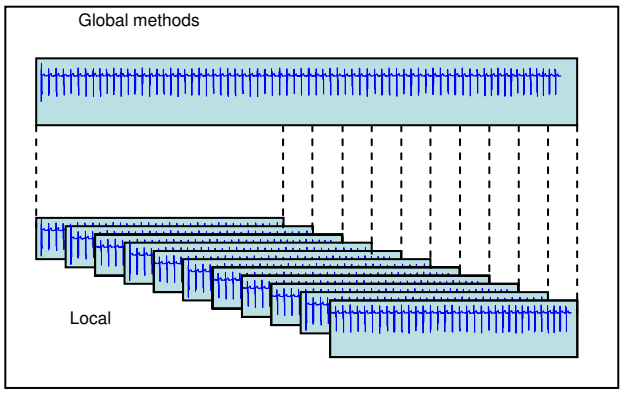

Fig.1. Methods for the interval selection for the detection of TWA: global (entire record) and local (a set of windows)

In the case of Global methods, the statistical test produces a single binary index (1 or 0), which represents the presence or absence of TWA&QRSA. In the case of Local methods, this process is repeated for every interval, producing a set of binary indices, and the number of intervals with positive indices is considered. In case there is at least one Local interval with positive index, it produces a presence indice (1) of TWA/QRSA for the method, otherwise the result will be 0.

All the RR intervals were analyzed, independently by the presence of noise or artifact. In addition, the heart rate was not considered for the determination of the presence/absence of TWA&QRSA.

2.4. TWA&QRSA quantification

The quantification of TWA&QRSA is determined by adding the four binary terms described in the previous section, and, in addition, defining 3 classes. For example, the TWA index is determined adding: 1) global index of T amplitude, 2) global index of PCA of T wave, 3) local index of T amplitude and 4) local index of PCA of T wave, obtaining values in the range [0,4]. The three classes were defined as: negative (TWA index <2), borderline (TWA = 2), and positive (TWA >2).

The QRSA index was similarly considered.

2.5. Statistics

We tested the distribution of data within groups using the Kolmogorov Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD), whereas non-normally distributed data – as median and inter-quartile range (the difference between the 25th and 75th percentile). We compared the results using an independent samples t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables, presented in percentage terms, were compared with Chi square test. To compare mean values between multiple groups we used one-way analysis of variance (ANOVA) test. A two-tailed p value < 0.05 was considered significant. All tests were performed with SPSS 13.0 for Windows.

3. Results

Patients with positive stress ECG test demonstrated significantly higher values for TWA and QRSA than patients with negative test (2.32 versus 1.66, $p < 0.001$ and 1.77 versus 1.11, $p = 0.003$, for TWA and QRSA respectively).

An interesting fact is that there were no patients with TWA < 2 whose stress test result was positive and that almost all patients with TWA > 2 had positive tests. Regarding QRSA: values < 2 resulted in a predominance of negative stress tests, while patients with values > 2 almost always had a positive ECG test (Table 2).

Table 2. Results for TWA and QRSA

	Number of patients	Stress test pos.	Stress test neg.	Signifi-cance
TWA				
< 2	13	0	13	$p < 0.001$
2	37	16	21	n.s.
> 2	7	6	1	$p < 0.001$
QRSA				
< 2	30	6	24	$p < 0.05$
2	23	13	10	n.s.
> 2	4	3	1	$p < 0.05$

Presence of angina pectoris or a history of myocardial infarction (MI) did not result in a significant change of the value of the analyzed ECG parameters, although this was probably influenced by the relatively small number of patients without chest pain or with MI (9 and 11 respectively)

Patients with angiographically significant (> 50% stenosis of at least one epicardial coronary artery) CAD (AS_CAD) had significantly higher values for QRSA (1.6 and 1.1, respectively; $p = 0.017$) compared to patients without advanced coronary atherosclerosis, while patients with percutaneous coronary intervention demonstrated a significant increase in TWA values ($p = 0.37$) compared to those without invasive coronary procedures.

Dividing the patients in subgroups according to their

TWA&QRSA values and performing ANOVA we found the following: 1. age, gender distribution, body mass index (BMI), presence of arterial hypertension (AH), serum cholesterol and serum glucose levels, history of MI, smoking history, family history of premature CAD, angina pectoris and coronary revascularization procedures were evenly distributed between different groups; 2. Patients with TWA > 2 and QRSA > 2 had significantly higher triglycerides values; 3. Higher QRSA values were associated with significantly higher prevalence of diabetes mellitus (DM); 4. The prevalence of AS_CAD was associated with higher QRSA values.

4. Discussion and conclusions

In the present study we have evaluated the performance of principal component analysis and wave amplitude computation on a combined lead for TWA&QRSA detection during stress ECG test in a group of 57 patients. We found that patients with positive stress ECG test demonstrated higher values for both TWA and QRSA compared to patients with negative stress test. We have also observed that TWA&QRSA values in a specific range could be connected with a specific response during stress ECG test, e.g. with values < 2 almost all patients had a negative stress test, while values > 2 were associated with a prevalence of positive tests. Another interesting finding in our study was that QRSA, but not TWA values were higher in patients with AS_CAD.

In this study we have shown that QRSA is present in almost the same patient population in which TWA is detected except for one important but still unclear to us fact: values of QRSA, but not TWA, were significantly higher in patients with AS_CAD.

As a limitation of this study we should consider that patients were not followed-up prospectively in order to estimate the occurrence of major untoward cardiovascular complications, and that our study group was relatively small.

This is a preliminary study. We plan further to expand our group, to include RR variability, signal averaged ECG, and to follow the patients prospectively for at least 12 months in order to evaluate the prognostic power of these different ECG parameters to predict the future incidence of untoward cardiovascular events and in particular, ventricular tachyarrhythmia and sudden cardiac death.

In conclusion: TWA&QRSA values are higher in patients with positive stress test. Patients with AS_CAD had significantly higher QRSA, but not TWA, values.

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