Influence of Diabetes Mellitus on T wave and QRS Complex Alternans During Stress ECG Testing

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Abstract

The aim of the study is to evaluate the influence of diabetes mellitus (DM) on T-wave and QRS-complex alternans (TWA&QRSA) during stress ECG testing. Principal component analysis, combined with wave amplitude computation was used for TWA&QRSA quantification. We studied 77 patients (64±11 years, 44% male). DM was present in 43% and angiographically significant coronary artery disease (AS_CAD) in 51%..

Patients with DM had higher QRSA compared to non-diabetics (p=0.026); TWA did not differ significantly. Patients with positive stress ECG tests had higher TWA&QRSA compared to those with negative stress tests (p<0.001 for TWA and p=0.001 for QRSA), no matter of the presence or absence of DM. In the subgroup of patients with negative stress test, diabetics had higher TWA values (p=0.001). With positive stress test this difference was no longer present.

1. Introduction

Microvolt T wave and QRS complex alternans (TWA&QRSA) is an electrophysiological phenomenon associated with change in the shape of T wave and QRS complex, appearing in alternation on an every other beat basis, that is 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.

Previously, TWA was measured mainly during electrophysiologic studies (EPS), where its induction was shown to predict ventricular arrhythmias [5]. Subsequently, techniques were developed to allow assessment of alternans noninvasively with exercise. There is a high concordance between exercise-induced and pacing-induced TWA [6].

Electrical alternans of the QRS complex is an electrocardiographic (ECG) phenomenon seen in different clinical situation – mainly supraventricular and ventricular tachycardias [7, 8]. The clinical significance of QRSA however is less well studied. There is some data that this ECG parameter may be of some value determining the risk of sudden cardiac death and the need for device therapy in selected patients [9] although other clinical trials do not confirm these results [7]. A recent study has shown that QRSA is increased in patients with positive stress ECG test and in patients with angiographically significant coronary artery disease (AS_CAD) [10].

Diabetes mellitus (DM) is a well recognized cardiovascular risk factor, associated with adverse clinical outcomes. Some studies have found that prevalence of TWA during stress ECG test is higher in diabetic patients compared to controls [11] while others have not found such a relationship [12]. We were not able to find any studies evaluating the relationship between stress ECG test-induced QRSA and DM.

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 [13] 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 [14]. 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 [15]. 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 to determine the influence of the presence of DM on wave alternans (TWA&QRSA) during stress ECG test.

2. Methods

2.1. Study group

We studied 77 patients (anamnesis, physical examination, clinical and laboratory data, stress ECG test and ECG analysis). Demographic characteristics, risk factors distribution and other clinical data for this group of 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 = 77
Age – mean ± SD	64.1 ± 11.1
Male – n (%)	34 (44%)
BMI – mean ± SD	28.7 ± 4.5
AH – n (%)	73 (95%)
DM – n (%)	33 (43%)
Dyslipidemia – n (%)	63 (82%)
Total cholesterol – mean ± SD	5.03 ± 1.14
Triglicerides – mean ± SD	2.09 ± 2
Family history of CAD – n (%)	10 (13%)
Present smokers – n (%)	10 (13%)
Ex-smokers – n (%)	19 (25%)
Angina pectoris – n (%)	61 (79%)
History of MI – n (%)	16 (21%)
Positive stress ECG test – n (%)	28 (36%)
AS_CAD – n (%)	39 (51%)
PCI – n (%)	33 (43%)
Coronary artery bypass grafting – n (%)	8 (10%)

SD – standard deviation; BMI – body mass index; AH – arterial hypertension; MI – myocardial infarction; PCI – percutaneous coronary intervention; n - number

Patients were included regardless of their sex or age. Exclusion criteria were left ventricular systolic dysfunction with ejection fraction <40%, haemodinamically significant valvular heart disease, history of ventricular tachycardia, 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 ECG was acquired during the whole study. 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

The method for TWA detection successfully participated in the Physionet/Computers in Cardiology Challenge, 2008, [16] [17], and it was expanded for QRSA detection and quantification.

The ECG signals were preprocessed to eliminate or suppress the powerline interference, the drift [18] and the electromyographic noise [19]. QRS detection was applied [20], onsets and offsets of the QRS complex and T wave were automatically delineated [21] and their amplitudes were calculated, in a combined lead (CL) simulating the spatial vector [18].

The proposed TWA&QRSA detection algorithm considers three aspects: the parameter selection, the interval selection and the classification.

Multi-lead approach has been followed, in order to extract a single index from the entire ECG record. Two parameters in the temporal domain were chosen: 1) the amplitude and 2) the complexity index. In the first case a combined lead was used, and the amplitude were computed in the QRS or T wave intervals.

The second parameter for TWA&QRSA discrimination considers the use of Principal Component Analysis (PCA) for quantifying the complexity index. 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 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 two variable length windows of 128 and 60 RR intervals, and performing the parameter extraction in each of them.

The detection block performs the separation of the parameters from odd and even RR intervals and the consequent statistical analysis on the two series with the non parametric paired-sampled Wilcoxon signed rank test.

In the case of Global methods, the binary index produced by the statistical test represents the presence or absence of TWA&QRSA.

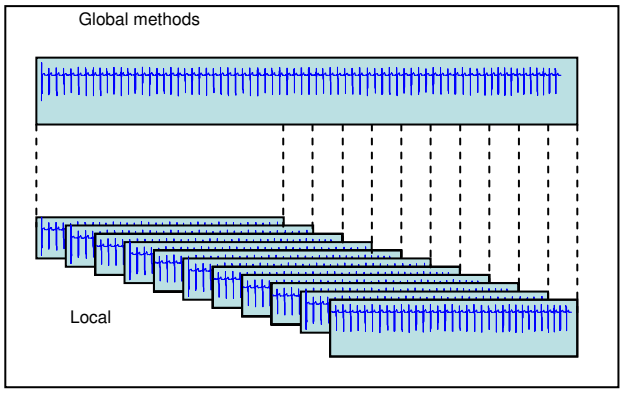

Figure.1. Methods for the interval selection for the detection of TWA: global (entire record) and local (a set of windows)

In the case of Local methods, this process is repeated for every interval, producing a set of binary indices, and in case there is at least one positive index, it signifies the presence of TWA or QRSA.

All the RR intervals were analyzed, independently of the presence of noise or artifact, and the heart rate was not considered.

2.4. TWA&QRSA quantification

The four binary terms described in the previous section allow the quantification of QRSA and TWA. For example adding the two global and the two local indices based on QRS wave amplitude and PCA indices, a parameter in the range 0÷4 is obtained. Then three classes have been defined: negative (QRSA or TWA <2), borderline (QRSA or TWA =2) and positive (QRSA or TWA >2)

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 25^{th} and 75^{th} 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. A two-tailed p value < 0.05 was considered significant. All tests were performed with SPSS 13.0 for Windows.

3. Results

TWA and QRSA measured with 60 RR interval window (TWA_60 and QRSA_60) were significantly higher (i.e. more sensitive) than those measured with 128 RR interval window (TWA_128 and QRSA_128): 1.9 ± 0.8 vs 1.49 ± 0.87 for TWA and 1.44 ± 0.98 vs 1.13 ± 0.91 for QRSA, p < 0.001 for both.

We divided the whole group of patients into two subgroups – patients with DM (33 patients – 43%) and without DM (44 patients – 57%). Diabetics had similar demographic and clinical characteristics compared to non-diabetics, the only exception being higher values for blood glucose (9 vs 5.4, p < 0.001) and triglycerides (3 vs 1.3, p = 0.006) in the group with DM.

Patients with DM had higher TWA and QRSA values compared with non-diabetics, only when wave alternans was evaluated using 60 RR interval window: 2.02 vs 1.73, p = 0.05 for TWA and 1.76 vs 1.2, p = 0.02 for QRSA. Wave analysis with 128 RR interval window did not confer any difference between these groups of patients.

Patients with AS_CAD have higher TWA (2.18 vs 1.61, p < 0.001) and QRSA values (1.82 vs 1.05, p < 0.001) compared to patients without AS_CAD. Neither the presence of DM, nor the method used for wave alternans measurement (60 or 128 RR interval window) made any significant difference to these results.

Patients with PCI during this or previous hospitalizations had higher TWA (2.24 vs 1.64, p = 0.001) and QRSA (1.82 vs 1.16, p= 0.003). In the subgroup of diabetic patients, however, this relationship lost its statistical significance.

Patients with positive stress ECG test had higher TWA (2.39 vs 1.61, p < 0.001) and QRSA values (1.79 vs 1.24, p = 0.019), compared to patients with negative stress test, regardless of the method used for wave alternans measurement (60 or 128 RR interval window). Diabetics with positive stress ECG test also demonstrate higher values for TWA (2.46 vs 1.25, p < 0.001) and QRSA (2.31 vs 1.4, p = 0.01) when compared to diabetics with negative stress ECG test. In the non-diabetic subgroup, however, patients with positive stress ECG test differ only in higher TWA_60 values from those with negative stress test (2.33 vs 1.86, p = 0.024).

4. Discussion and conclusions

In the present study we evaluated the influence of DM on TWA and QRSA during stress ECG testing in a group of 77 patients. We used principal component analysis and wave amplitude computation on a combined lead for TWA&QRSA detection during stress ECG test performing the analysis with 60 and 128 RR interval windows.

Our findings could be summarized as follows: 1. TWA and QRSA values measured with 60 RR interval window were significantly higher than those measured with 128 RR interval window, suggesting that the former method was more sensitive for wave alternans detection; 2. Diabetics had higher TWA and QRSA values than non-

diabetics, but only if the measurement implies 60 RR interval window (the more sensitive methodology); 3. Patients with AS_CAD, PCI or a positive stress ECG test had significantly higher TWA and QRSA values compared to patients without such conditions, regardless of the method used for wave alternans measurement.

Studies considering the influence of DM on TWA [11, 12] give conflicting results. Information about the interaction of DM on QRSA is lacking. The present study is the 1st to demonstrate that patients with DM have higher QRSA than non-diabetics. Our results could also light on the contradictory finding of previous studies: in the presence of DM, which is supposed to induce more subtle changes in wave alternans, a more sensitive method for TWA and QRSA detection should be used (e.g. evaluation with 60 RR interval window). Supporting this hypothesis is the fact that patients with AS_CAD, PCI or a positive stress ECG test (factors with a well-known and studied effect on wave alternans) TWA and QRSA values are higher compared to patients without such conditions, regardless of the method used for wave alternans measurement.

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.

In conclusion: Sensitivity of wave alternans evaluation differs with different measurement algorhythms. TWA and QRSA values during stress ECG test are higher in patients with DM compared to non-diabetics only when a sensitive algorhythm for wave alternans detection is used.

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