T-Wave Alternans Identification in Routine Exercise ECG Tracings: Comparison of Methods

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Abstract

T-wave alternans (TWA) is often measured in special exercise ECGs specifically made for TWA testing in order to minimize the noise level. Still, TWA utility in clinical evaluation would be magnified by the possibility of measuring it in routine standard exercise ECGs, usually affected by a high level of noise. Thus, aim of the present study was to evaluate the performances of 3 automatic TWA identification methods, namely the spectral (SM), the modified-moving-average (MMAM) and the adaptive-match-filter (AMFM) methods, on routine exercise ECGs with increasing heart rate (HR) of 46 implanted-cardiac-defibrillator patients (ICDP). TWA amplitude (TWAA) was measured in 1-min windows during the minimum (MinHR=83±12 bpm) and maximum (MaxHR=123±19 bpm) HR. At MinHR and MaxHR, the SM identified TWA in 12 and 23 ICDP, respectively (median TWAA: 4 µV and 29 µV, respectively; $P<10^{-3}$), whereas the MMAM and AMFM identified TWA in all ICDP but the former method provided much higher median TWAA estimates (MinHR: 1507 µV, MaxHR: 1602 µV; P=0.5258) than the latter (MinHR: 22 µV, MaxHR: 38 µV; $P<10^{-4}$). Eventually, only the SM and AMFM detected the expected significant TWAA increment at MaxHR. Thus, the AMFM appeared the most reliable method for TWA identification in routine exercise ECG recordings.

1. Introduction

T-wave alternans (TWA) is an electrophysiological phenomenon consisting in an every-other-beat fluctuation of the electrocardiographic (ECG) T-wave amplitude and/or shape at stable heart rate (HR) and during sinus rhythm. Visible TWA is a rare phenomenon, whereas microvolt TWA is much more common but requires specifically designed algorithms for its automatic identification [1,2]. At the present time automatically detected microvolt TWA is widely recognized as one of the most promising noninvasive index for risk stratification [3,4].

It is well known that TWA amplitude tends to increase with HR [5,6] so that TWA is often measured from ECG tracings recorded during pacing [6] or exercise tests specifically designed for TWA evaluation in order to reduce the noise level. For example, special TWA electrodes (the Micro-V Alternans Sensors proposed by the Cambridge Heart) are usually used for TWA studies performed by means of the standardized spectral method [7]. Besides increasing TWA amplitude (and thus the signal-to-noise ratio), fast heart rates also reduce HR variability [8]. Both conditions (high signal-to-noise ratio and low HR variability) have been found to be fundamental for a reliable TWA identification by means of any automatic method [9].

As long as TWA requires special exercise-test settings for its detection, its clinical importance is destined to be quite limited. In order to significantly extend TWA usefulness in clinical evaluation there must exist the possibility of measuring TWA on a broad variety of routine standard ECG recordings. In particular, TWA identification from routine standard exercise ECG tracings is particularly challenging because, if on one hand these ECGs imply high HRs and, thus, higher (compared to rest) amplitude TWA, on the other hand they are usually affected by a high level of noise to which the used automatic TWA identification method needs to be particularly robust.

This study investigated the possibility of using three popular techniques, namely the spectral method (SM) [7], the modified-moving-average method (MMAM) [10] and the HR-adaptive-match-filter method (AMFM) [11], to automatically identify TWA from routine standard exercise ECG recordings. More specifically ECG tracings recorded in 46 patients with an implanted-cardiac-defibrillator (ICD) during an ergometer biking test with increasing workload (and thus with increasing HR) were used. The same 1-min ECG windows extracted during the lowest and the highest heart rates reached during the exercise test were submitted to the three automatic TWA identification methods after preprocessing for noise removal in order to allow an evaluation and a comparison of the methods performances.

2. Methods

2.1. Clinical data

Our clinical data consisted of 46 exercise ECG recordings of patients with an implanted cardiac defibrillator (ICD) for primary prevention because of a depressed (<35%) left ventricular ejection fraction. All data belong to the Leiden University Medical Center (The Netherlands) database. The exercise test consisted of an approximately 10-min long bicycle ergometer test with increasing workload from zero to the patient's maximal capacity. Load-increments of 10% of the expected maximal capacity were applied every minute. During the test, ECG recordings were obtained using a CASE 8000 stress test recorder (GE Healthcare, Freiburg, Germany; sampling frequency: 500 Hz; resolution: 4.88 µV/LSB).

2.2. TWA amplitude quantification

TWA amplitude (TWAA) quantification was performed in ECG windows of 64 consecutive beats extracted from the exercise ECG in correspondence of the minimum (MinHR) and maximum (MaxHR) heart rates (i.e. in correspondence of the minimum and maximum workloads, respectively). Before being independently submitted to the automatic TWA identification methods, all selected ECG windows underwent the same preprocessing (Fig. 1) [1,9,12] consisting of noise removal (by means of 0.5-35 Hz band-pass filter), baseline subtraction (by means of a 3rd-order spline interpolation) [1,12], and artefacts and ectopic beats replacement [9,12]. Only windows characterized by stable HR (i.e. by an RR standard deviation greater than 10% of mean RR) and by a limited number of replaced beats (i.e. no more than 5 replaced beats) were considered eligible for a reliable TWA identification by means of the three automatic methods described below.

To quantify TWAA, MATLAB implementations of the three methods algorithms provided by the academic spinoff B.M.E.D. SRL (Bio-Medical Engineering Development, Department of Information Engineering, Polytechnic University of Marche, Ancona, Italy, www.bmed-bioengineering.com) were used.

2.2.1. Spectral method

After having aligned the 64 ECG complexes, a power spectrum is computed for each sequence of corresponding JT-segment samples. All obtained power spectra are then summed to obtain the cumulative power spectrum whose amplitude at 0.5 cycles per beat is called 'alternans peak'. TWAA can be estimated as square root of the alternans peak, after normalization for the number of samples in the

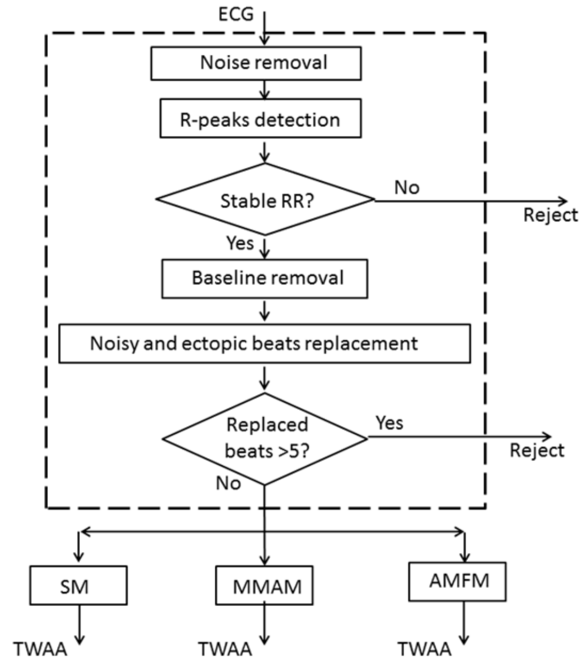

Figure 1. ECG preprocessing steps to be performed before independent automatic TWA identification by spectral method (SM), modified moving average method (MMAM) and heart-rate adaptive match filter method (AMFM).

JT segment [7]. Such measure is considered reliable if the alternans ratio, a signal-to-noise ratio between the alternans peak and the spectral noise level measured in a predefined spectral window, is greater than 3 [7].

2.2.2. Modified moving average method

The MAMM involves computation of even (A) and odd (B) modified moving average beats. During such computation some amplitude constrains were applied to limit the effect of noise on the averaging procedure. TWAA is eventually estimated as the maximum difference between even and odd modified moving average beats along the JT segment.

2.2.3. Heart-rate adaptive match filter method

Ideally, at a fixed heart rate, TWA is characterized by a single frequency by definition equal to half HR (f_{TWA}). In real data, some physiological HR variability is always present so that TWA results characterized by a small frequency band centered in f_{TWA}. On this basis, the AMF was conceived as a HR (and, thus, f_{TWA}) adaptive narrow-band passing filter with its passing band centered in f_{TWA}. When fed with an ECG tracing, the AMF filters out every

ECG components but those relative to TWA. The output of the AMF is the TWA signal, an amplitude-modulated sinusoidal signal whose amplitude is a direct measure of TWAA. TWAA estimation is considered reliable if the TWA signal maxima and minima fall within the JT intervals.

2.3. Statistics

Comparison between clinical and/or TWA parameters relative to the ICD patients during the MinHR and the MaxHR were performed using parametric and non-parametric tests for normal and non-normal distributions, respectively. Normality of a parameter distribution was tested using the Lilliefors test. Comparisons between continuous and normally distributed parameters were performed using the paired t-test for equal means (results were reported in terms of mean±std values). Instead, comparisons between continuous and not-normally distributed parameters were performed using the Wilcoxon rank-sum test for equal medians (results were reported in terms of median values). Eventually, differences in the binary parameters distributions between the two groups were evaluated using the chi-square test. The statistical significance level was set at 5%.

3. Results

The significant increment of HR (identifiable a shortening of the RR interval), which occurred simultaneously to the increment of the workload during the exercise test, had the effect of a significant decrement of HR variability (RR standard deviation). In correspondence of both MinHR and MaxHR, and thus in correspondence of maximum and minimum HR variability, respectively (Table 1), the three TWA identification methods performed differently. In the specific, the SM was able to identify TWA in only few ICD patients (12 and 23 during MinHR and Max HR, respectively; Table 2). Nevertheless, it registered the expected increment of TWAA at high HR (from 4 μV to 29 μV; Table 2). The MMAM detected TWA in all ICD patients (Table 3), but the TWAA values measured at MinHR did not significantly differ from those measured at MaxHR (Table 3). In addition, the MMAM values were always significantly higher than the corresponding ones measured by the other two techniques (of the order of thousands μV the former ones, and tens μV the latter; Tables 1 to 3). Eventually the AMFM was able to identify TWA in all ICD patients in both HR conditions, and TWAA levels measured at MaxHR were significantly higher than those measured at MinHR.

Table 1. RR interval and its variability measured in the 46 ICD patients in correspondence of the minimum (MinHR) and maximum (MinHR) heart rates.

	MinHR	MaxHR	P
RR (ms)	743±103	503±67	$<10^{-21}$
RR sd (ms)	239±13	134±8	$<10^{-5}$

RR: mean RR interval
RRsd: RR interval standard deviation

Table 2. TWA identification by the spectral method in correspondence of the minimum (MinHR) and maximum (MinHR) heart rates.

	MinHR	MaxHR	P
N	12 (25%)	23 (50%)	<0.05
TWAA (μV)	4	29	$<10^{-3}$

N: number of ICD patients with detected TWA
TWAA: TWA amplitude

Table 3. TWA identification by the modified moving average method in correspondence of the minimum (MinHR) and maximum (MinHR) heart rates..

	MinHR	MaxHR	P
N	46 (100%)	46 (100%)	NS
TWAA (μV)	1507	1602	NS

N: number of ICD patients with detected TWA
TWAA: TWA amplitude

Table 4. TWA identification by the heart rate adaptive match filter method in correspondence of the minimum (MinHR) and maximum (MinHR) heart rates.

	MinHR	MaxHR	P
N	46 (100%)	46 (100%)	NS
TWAA (μV)	22	38	$<10^{-4}$

N: number of ICD patients with detected TWA
TWAA: TWA amplitude

4. Discussion

This paper compared the performances of three popular methods for automatic TWA identification, namely the SM, the MMAM and the AMFM, when applied to routine exercise ECG recordings. To reduce the level of noise and to warrantee a certain HR stability, the ECG data underwent the same preprocessing steps before being independently analyzed for TWA evaluation. Thus, possible differences in the methods' performances have to be attributed solely to the their different robustness to interferences necessarily surviving real preprocessing and to the different theoretical hypothesis underlying each technique.

The SM was not able to detect TWA in several ICD patients (75% during MinHR and 50% during MaxHR) because the required condition on the alternans ratio was often not satisfied. This can occur in the presence of noise but also in case of not perfectly aligned T waves [9]. Indeed, in the presence of a certain level of HR variability, beats, which are aligned according to the R peak, may show some misalignment along the T wave that compromises the power spectrum evaluation. This would explain why the number of ICD patients in which TWA was detected was significantly lower for the MinHR phase of the exercise test, during which heart-rate variability was higher, than for MaxHR, during which heart-rate variability was lower. Eventually, this also explain why the SM is usually used in TWA studies performed under controlled HR conditions, often invasively reached through pacing [6]. Eventually, when provided, TWA measures by the SM appear reliable, since showed a significant increment with HR and were characterized by a realistic order of magnitude.

The MMAM identified TWA in all 46 ICD patients in both MinHR and MaxHR conditions. However, levels of recorded TWA were much higher than expected (thousands of µV) and, most of all, they did not increase from MinHR to MaxHR. This finding suggests that the MMAM does not provided reliable TWA measurements, likely because too sensible to noise and poor T-wave alignment, as observed in previous studies [9].

The AMFM was able to provide TWA measurements for all 46 ICD patients in all HR conditions. Moreover, the magnitude of such measurements were consistent with what previously observed [5,6,13] and significantly increased with HR. Thus, among the three analyzed methods, the AMFM appears as the most reliable one to analyze TWA in ECG tracings recorded in routine exercise tests. TWA levels provided by the SM and the AMFM were comparable (same order of magnitude). The small observed differences in TWA quantification are to be addressed to a different definition of TWA amplitude underlying the two techniques, which are the root mean square and the average alternans amplitude over the repolarization segment for the SM and the AMFM, respectively [13].

5. Conclusions

Among the three analyzed popular methods for automatic TWA identification, namely the SM, the MMAM and the AMFM, the latter one appeared as the most reliable for analyzing TWA in routine standard ECG recordings of ICD patients. Such result is due to a greater robustness of the AMFM to the presence of physiological HR variability and noise surviving real preprocessing.

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