T-Wave Alternans Rate of Change with Exercise for Cardiac Risk Assessment

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Abstract

T-wave alternans (TWA) amplitude is an index of risk for arrhythmic events. It increases with heart rate (HR) so that its evaluation is often performed under exercise. This study aims to investigate if TWA rate of change with HR can be also used for risk assessment. Our HR adaptive match filter for automatic TWA identification was applied to exercise ECG recordings of 266 ICD patients, 76 of which developed ventricular arrhythmias during the 4-year follow-up (ICD_Cases), and 190 did not (ICD_Controls). TWA amplitude was measured at 80 bpm (TWA80) and at 115 bpm (TWA115). Instead, TWA rate of change was evaluated as the ratio (TWAratio) and difference (TWAdiff) between TWA115 and TWA80. TWA predictive power was quantified as the area under the receiver operating curve (AUC) when discriminating the two ICD groups. Compared to ICD_Controls, ICD_Cases showed significantly higher TWA80 (22 μV vs. 16 μV) but not TWA115 (24 μV vs. 30 μV vs). The latter group also showed significantly lower TWAratio (1.05 vs. 1.63) and TWAdiff (1 μV vs. 11 μV). TWAratio showed the highest AUC (0.6914) followed by TWAdiff (0.6816), TWA80 (0.6414) and TWA115 (0.4547). Thus, TWA rate of change with HR provided better risk assessment for the occurrence of ventricular arrhythmias than TWA amplitude at both fast (115 bpm) and slow (80 bpm) HRs.

1. Introduction

Microvolt T-wave alternans (TWA), consisting in a subtle every-other-beat fluctuation of the electrocardiographic (ECG) T-wave amplitude at stable heart rate (HR) during sinus rhythm, is universally recognized as a promising non-invasive index to predict the occurrence of malignant ventricular arrhythmias and sudden cardiac death [1-6]. It is well-known that TWA amplitude increases with HR [7,8]. Thus, even though it has been also observed in resting conditions [9,10], TWA analysis is often performed at fast HRs, often reached through exercise [1,5,6,7,11-14].

It can be hypothesized that, besides TWA amplitude, its rate of increment with HR is also related to cardiovascular risk. Under this assumption, the present study aims to investigate if TWA rate of change with HR can be used to assess the risk of malignant ventricular arrhythmias. To this aim our HR adaptive match filter for automatic TWA identification was applied to exercise ECG recordings of 266 patients with implanted cardio-defibrillator, 76 of which developed ventricular arrhythmias during the 4-year follow-up (ICD_Cases), and 190 did not (ICD_Controls). TWA amplitude was measured at 80 bpm and at 115 bpm, and the rate of change of TWA with exercise (and thus with HR) was evaluated by computing the ratio and the difference between the TWA amplitudes at these two HRs, respectively. Eventually, the predictive power for the occurrence of ventricular arrhythmias of the TWA parameters relative to the rate of change with HR was computed and compared to that relative to the TWA amplitude.

2. Method

2.1. Study populations and clinical data

The collection (from August 2006 and September 2010) of routine clinical data from 266 patients with an implanted cardio-defibrillator (ICD) for primary prevention because of a depressed left ventricular ejection fraction (LVEF<35%), constituting the Leiden (The Netherlands) University Medical Center database of exercise ECGs in heart failure patients with ICDs, was retrospectively selected for the present observational study on TWA. All patients underwent a bicycle ergometer test consisting of an approximately 10-minute bicycle test during which the workload was incremented from zero to the patient's maximal exercise capacity by applying load-increments of 10% of the expected maximal exercise capacity every minute. During the bicycle ergometer 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). Eventually, at the end of a 4-year follow-up, 76 patients were classified as ICD_Cases because they had developed ventricular tachycardia or ventricular fibrillation (VT/VF), while the remaining 190 were classified as ICD_Controls.

The clinical ECG data consisted of the six precordial ECG leads (V1 to V6) recorded during the exercise test. Each lead was pre-processed for noise removal (0.5-35 Hz band-pass filter) and baseline subtraction by means of a 3rd-order spline interpolation [15]. Subsequently, single-lead sliding ECG windows including 64 consecutive beats were extracted every 2 s from the entire recording and preprocessed for artifacts and ectopic beats replacement [15,16]. ECG windows characterized by unstable HR (NN standard deviation greater than 10% of mean NN) or by a number of replaced beats greater than 4 were rejected. Eventually, only ECG windows characterized by HR equal to 80±2.5 bpm or 115±2.5 bpm were further processed for TWA evaluation.

2.2. T-wave alternans identification

TWA was identified using our HR adaptive match filter (AMF) based method [15] which assumes TWA to be characterized by a small frequency band centered in half mean HR (by definition the TWA frequency, fTWA), and conceives the AMF as a HR (and, thus, fTWA) adaptive narrow-band passing filter (ideally a match filter) with its passing band cantered in fTWA. The AMF implementation consists of a 6th-order bidirectional Butterworth band-pass filter characterized by a 0.12 Hz wide passing band around in fTWA, and is obtained as a cascade of a low-pass filter (LPF; cut-off frequency fLPF=fTWA+dfTWA, with dfTWA=0.06 Hz) and a high-pass filter (HPF; cut-off frequency fHPF=fTWA-dfTWA) [15,17,18]. Each time the AMF is fed with an ECG lead, it first computes HR, fTWA and its passing-band. Then, it filters out every ECG components but TWA. The output of the AMF is an amplitude-modulated sinusoidal signal, called the TWA signal, that has the same length of the input ECG and is characterized by a frequency which matches fTWA. If really pertaining to TWA (and not to noise with components at fTWA), the TWA signal maxima and minima have to fall inside the JT intervals. The mean amplitude of the TWA signal provides a direct measure of the TWA amplitude for the ECG tracing at the input of the AMF.

TWA identification in our clinical ECG data was performed in a completely automatic way from individuals who were blinded to outcomes, using the B.M.E.D. (Bio-Medical Engineering Development, SRL, Ancona, Italy, www.bmed-bioengineering.com) software implementation of the AMF technique. TWA was identified in each one of the six precordial leads independently by submitting each single-lead 64-beat ECG tracing to the AMF. Eventually, a TWA characterization at 80 bpm and at 115 bpm was provided in terms of maximum TWA amplitude value over the six precordial leads (TWA80 and TWA115, respectively; μV). The rate of change of TWA amplitude with HR was evaluated as the ratio (TWAratio; adimentional) and the difference (TWAdiff; μV) between TWA115 and TWA80.

2.3. Patient inclusion criteria

Inclusion criteria were applied to the ICD patients to warrant a comparable clinical profile of the two ICD groups and a reliable TWA identification. More specifically, patients belonging to ICD_Cases and ICD_Controls groups were considered eligible for the present study if satisfying the following:

- Criterion 1. To rule out very young patients, age at the time of the exercise test had to be over 30 years.
- Criterion 2. To rule out patients with extreme BMI, BMI value at the time of the exercise test had to be between 18 and 35 kg/m^2.
- Criterion 3. At least one of the two TWA80 or TWA115 measures had to be available. This criterion implies that a different number of patients may be involved in the characterization of TWA80 and TWA115.
- Criterion 4. Evaluation of TWAratio and TWAdiff was computed only for those ICD patients for which TWA80 and TWA115 measures were both available.

2.4. Statistics

Normality of a parameter distribution was tested using the Lilliefors test. Comparison between continuous and not-normally distributed parameters (reported in terms of median [25th and 75th percentiles]) were performed using the Wilcoxon rank-sum test for equal medians. To evaluate the TWA predictive power for the occurrence of ventricular arrhythmias, the receiver operating characteristic (ROC) and its area under the curve (AUC) were used. The statistical significance level was set at 5% in all cases.

3. Results

Inclusion criteria 1 and 2 caused rejection of 4 ICD_Cases (5.3%) and 14 ICD_Controls (7.4%). Subsequent application of criteria 3 and 4 caused a further significant decrement of the number of patient involved in the study so that, eventually, TWA80 and TWA115 were measured in 38 and 40 ICD_Cases, respectively, and in 40 and 117 ICD_Controls, respectively, whereas both TWAratio and TWAdiff were measured in 20 ICD_Cases and 64 ICD_Controls.

Compared to the ICD_Controls, the ICD_Cases showed significantly higher TWA80 (median: 22 μV vs. 16 μV; P<0.01; Table 1) but not TWA115 bpm (median: 24 μV vs. 30 μV vs; P=0.4032; Table 1), which resulted comparable. Only the ICD_Controls showed a significant increment of the TWA amplitude when raising HR from 80 bpm to 115 bpm (Table 1).

Table 1. TWA characterization for both ICD groups (ICD_Cases and ICD_Controls, respectively) provided in terms of maximum TWA values (median [25th 75th percentiles]) over the six precordial leads at 80 bpm (TWA80) and 115 bpm (TWA115).

	ICD_Cases	ICD_Controls	P_1
TWA80 (μV)	22 [14 32]	16 [12 24]	$<10^{-2}$
TWA115 (μV)	24 [16 46]	30 [19 48]	NS
P_2	NS	$<10^{-4}$	-

-: not applicable.
NS: not statistically significant.
P_1: P-value when comparing a TWA parameter in ICD_Cases vs. ICD_Controls.
P_2: P-value when comparing TWA80 vs. TWA115 within each ICD group.

Analysis of the rate of change of TWA amplitude with HR showed that, compared to the ICD_Controls, the ICD_Cases showed significantly lower TWAratio (median: 1.05 vs. 1.63; P<0.05; Table 2) and TWAdiff (median: 1 μV vs. 11 μV; P<0.05; Table 2.

Table 2. TWA rate of change for both ICD groups (ICD_Cases and ICD_Controls, respectively) provided in terms of maximum TWAratio and TWAdiff (median [25th 75th percentiles]).

	ICD_Cases	ICD_Controls	P
TWAratio	1.05 [0.76 1.58]	1.63 [1.13 2.72]	<0.05
TWAdiff (μV)	1 [-10 16]	11 [2 25]	<0.05

P: P-value when comparing a TWA parameter in ICD_Cases vs. ICD_Controls.

Eventually, when evaluating each parameter predictive power for the occurrence of ventricular arrhythmias, TWAratio showed the highest AUC (0.6914) followed by TWAdiff (0.6816), and TWA80 (0.6414). TWA115 was not predictive (AUC=0.4547).

4. Discussion and conclusion

This retrospective, observational study on standard clinical data investigated if, beside TWA amplitude, TWA rate of change with HR can be also used to assess the risk of malignant ventricular arrhythmias. To this aim, 266 exercise HR-increasing ECG tracings from ICD patients were used. This population was constituted by 76 patients who developed VT/VF during the 4-year follow-up (ICD_Cases) and 190 patients who did not develop major ventricular arrhythmias (ICD_Controls), and thus was particularly suitable for risk assessment. TWA identification was performed using the AMF-based method [16-20], particularly suitable for analysis of ECG tracings characterized by small variations in the cardiac period in the analyzed ECG. Indeed, instead of hypothesizing TWA as characterized by a single frequency, by definition equal to half HR, this technique supposes TWA to be characterized by a small frequency band centered around half mean HR and designs the AMF as a narrow-band passing frequency instead of a single frequency match filter. Eventually, risk evaluation was performed for TWA amplitude measured at 80 bpm (TWA80), HR which is close to the resting one, and at 115 bpm (TWA115), and for parameters measuring the TWA rate of change with HR computed as TWA115-TWA80 ratio (TWAratio) and difference (TWAdiff).

Due to the requirement criteria, the number of patients used to compute each TWA parameter was significantly lower than that present in the enrolled Leiden University Medical Center database. With very few exceptions, the rejections were mainly due to criteria 3 and 4 relative to the possibility of measuring TWA parameters, and were thus associable to the kind of used data. Indeed, TWA is defined as an every-other-beat alternation of the T-wave morphology during stable sinus rhythm, so that TWA cannot (and should not) be identified in ECG tracings with too high HR variability or too much noise.

TWA80, but not TWA115, was found to be statistically higher in the ICD_Cases than in the ICD_Controls indicating, as also confirmed by the corresponding AUC values, that TWA amplitude predictive power for the occurrence of VT/VF was higher at 80 bpm (AUC=0.6414) than at 115 bpm (AUC=0.4547). Moreover, in the 80-115 bpm range, the ICD_Cases showed almost constant TWA amplitude values, which instead resulted significantly increased in the ICD_Controls, in agreement with previous reported observations that indicate a tendency of TWA to increase its amplitude with HR [7,21]. Thus, the two ICD groups showed a different trend of TWA amplitude in the HR range considered here. Consequently, differences between the ICD_Cases and the ICD_Controls were better highlighted by the way TWA amplitude increased with HR, rather than by the TWA amplitude values. Indeed, both TWAratio and TWAdiff parameters were found to

be significantly different in the two ICD groups. More specifically, their values were significantly lower for the ICD_Cases that for the ICD_Controls, indicating a highest TWA amplitude increment in the latter group than in the former. Risk assessment evaluation showed that both parameters showed higher AUC values than TWA80, and indicated TWAratio (AUC=0.6914) as the best parameter to predict the occurrence of VT/VF, immediately followed by TWAdiff (AUC=0.6816).

The small TWA-amplitude increment observed in the ICD_Controls may relate to the considered HR range, and in particular to the choice of selecting 115 bpm as the upper limit. Such HR was chosen because sufficiently fast and reached by an acceptable number of patients during the exercise. However, it is lower than 120 bpm, HR at which TWA is supposed to be trigged in both healthy and pathological subjects [7]. TWA amplitude evaluation at 120 bpm in both ICD groups, but especially in the ICD_Cases, will be matter of future evaluations.

In conclusion, TWA rate of change with HR, quantified by the TWAratio and TWAdiff parameters, provided better risk assessment for the occurrence of ventricular arrhythmias than TWA amplitude measured at both fast (115 bpm) and slow (80 bpm) HRs.

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