Dependency of T-Wave Alternans Predictive Power for the Occurrence of Ventricular Arrhythmias on Heart Rate

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Abstract

T-wave alternans (TWA), a promising index of cardiac electrical instability, is known to increase its amplitude (TWAA) with heart rate. Still, the effect of heart rate on the TWA predictive power for the occurrence of ventricular arrhythmias remains unclear. Thus, aim of the present study was to evaluate if fast heart rates, besides inducing higher amplitude TWA, also enhances TWA ability to discriminate patients at increased risk of major cardiac events. To this aim, our heart-rate adaptive match filter was used to measure TWA at 80 bpm and at 120 bpm in exercise ECGs of 266 ICD patients, 76 of which developed ventricular tachycardia or fibrillation during the 4-year follow-up (ICD_Cases), and 190 did not (ICD_Controls). TWA ability to discriminate ICD_Cases from ICD_Controls was evaluated using the area under the receiver operating characteristic (AUC). At 80 bpm TWAA was significantly higher in the ICD_Cases than the ICD_Controls (median: 23 μV vs. 16 μV, P=0.0018; AUC=0.672), whereas at 120 bpm TWAA was comparable in the two groups (median: 36 μV for both the ICD_ Cases and ICD_Controls; AUC=0.487). Thus, in our ICD populations, TWA predictive power for the occurrence of ventricular arrhythmias was higher at 80 bpm, when TWAA was smaller, than at 120 bpm, when TWAA was higher.

1. Introduction

Microvolt T-wave alternans (TWA) is an electrophysiological phenomenon consisting in subtle every-other-beat fluctuations of the amplitude and/or shape of the electrocardiographic (ECG) T wave at stable heart rate and during sinus rhythm. At the present time TWA is considered a promising noninvasive index for risk stratification [1-6]. Even though it has been also observed in resting conditions [7,8], TWA analysis is often performed under physical exercise conditions [1,5,6,9-13] since TWA amplitude has been observed to increase with heart rate [9,14]. Beside increasing TWA amplitude (and, thus, the signal-to-noise ratio), fast heart rates also reduce heart-rate variability [15] making TWA identification more reliable [16]. Still, the effect of heart rate on the TWA predictive power for the occurrence of ventricular arrhythmias remains unknown. Thus, the aim of the present study was to evaluate if fast heart rates, besides inducing higher amplitude TWA, also enhance TWA ability to discriminate patients at increased risk for malignant ventricular arrhythmias. To this aim, exercise ECG tracings of implanted cardioverter-defibrillator (ICD) patients were analyzed. More specifically, two populations of ICD patients were considered, respectively developing (ICD_Cases) and not developing (ICD_Controls) ventricular tachycardia or ventricular fibrillation during the 4-year follow-up. TWA was evaluated at 80 bpm and at 120 bpm to identify which heart rate better allows discrimination of the two ICD groups.

2. Clinical data and methods

2.1. Study population and clinical data

Our study population consisted of exercise ECG recordings 266 patients (Leiden University Medical Center, The Netherlands) with an ICD for primary prevention because of a depressed left ventricular ejection fraction (LVEF<35%). All patients underwent an exercise test which consisted of an approximately 10-min bicycle ergometer test during which the workload was incremented from zero to the patient's maximal capacity by applying load-increments of 10% of the expected maximal capacity every minute. During the bicycle ergometer test, 6 precordial leads (V1 to V6) ECG recordings were obtained using a CASE 8000 stress test recorder (GE Healthcare, sampling rate: 500 Hz; resolution: 4.88 μV/LSB). After the exercise test, all patients underwent a 4-year follow-up at the end of the which they were classified as either ICD_Cases (76 patients) if, during the follow-up, they had developed ventricular tachycardia or ventricular fibrillation (treated with anti-tachycardia pacing and/or shock therapy), or

ICD_Controls (190 patients) otherwise.

2.2. ECG preprocessing

All ECG tracings were preprocessed for noise removal (0.5-35 Hz band-pass filter) and baseline subtraction (by means of a 3rd-order spline interpolation) [17]. Subsequently, sliding ECG windows including 64 consecutive beats were recursively (every 2 s) extracted from the entire ECG recording and underwent artefacts and ectopic beats replacement [16,17]. ECG windows characterized by unstable heart rate (NN standard deviation greater than 10% of mean NN) or by a number of replaced beats greater than 5 were rejected. Eventually, only ECG windows characterized by a stable heart rate, a low number (≤5) of replaced beats and a heart rate of 80 bpm or 120 bpm underwent TWA evaluation (see below).

2.3. T-wave alternans identification

All the 64-beat ECG windows (characterized by 6 leads each) found to be suitable for TWA analysis went through our heart-rate adaptive match filter (AMF) procedure [18] for automatic TWA identification. The AMF was previously validated in both simulated settings [16,17,19] and clinical data [7,8,18,20-22]. TWA was independently identified in each one of the six precordial leads.

Ideally, at a fixed heart rate, TWA is characterized by a single frequency by definition equal to half heart rate. In our clinical 64-beat ECG windows some heart-rate variations do occur. Consequently, TWA was supposed to be characterized by a small frequency band cantered in half mean (over the 64 beats) heart rate (f_{TWA}). On this basis, our AMF was conceived as a heart-rate (and, thus, f_{TWA}) adaptive narrow-band passing filter (ideally a match filter) with its passing band cantered in f_{TWA}. In our implementation, the AMF is a 6th-order bidirectional Butterworth band-pass filter characterized by a 0.12 Hz wide passing band centered in f_{TWA}, and consisted of a cascade of a low-pass filter (LPF; cut-off frequency $f_{LPF}=f_{TWA}+df_{TWA}$, with $df_{TWA}=0.06$ Hz) and a high-pass filter (HPF; cut-off frequency $f_{HPF}=f_{TWA}-df_{TWA}$) [17,19]. The squared module of the AMF is expressed by the following equation:

$$\left|H_{AMF}(f)\right|^2 = \left|H_{LPF}(f)\right|^2 \cdot \left|H_{HPF}(f)\right|^2 = \\ = \frac{1}{1+\left(\frac{f}{f_{LPF}}\right)^6} \cdot \frac{\left(\frac{f}{f_{HPF}}\right)^6}{1+\left(\frac{f}{f_{HPF}}\right)^6} \qquad (1)$$

Each time the AMF is fed with an ECG window suitable for TWA analysis, it computes the ECG heart rate and the corresponding f_{TWA}, and then filters out all ECG components, including those relative to noise, but not those relative to TWA. Thus, the output of the AMF is an amplitude-modulated sinusoidal signal, termed the TWA signal, which has the same length of the input ECG and is characterized by a frequency narrow-band around f_{TWA}. If really pertaining to TWA (and not, for example, to QRS or noise oscillations at f_{TWA}), the TWA signal maxima and minima have to fall inside the JT intervals. The TWA-signal amplitude provides a direct estimated of the TWA amplitude (TWAA, μV) characterizing a specific ECG window.

Maximum TWAA value computed over the 6 precordial leads was chosen as representative of the ECG window. When more than a suitable ECG window was available within a specific heart rate, TWA measurements from all suitable windows were averaged.

The MATLAB implementation of the AMF algorithm used to evaluated TWA was 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).

2.4. Statistics

Normality of a parameter distribution was tested using the Lilliefors test. Comparison between non-normal parameters distributions relative to the two ICD groups measured at 80 bpm and 120 bmp was performed using the Wilcoxon rank-sum test for equal medians (relative distributions were characterized in terms of 50th [25th,75th] percentiles. Differences in the binary parameters distributions between the two ICD groups were evaluated using the chi-square test (relative distributions were characterized in terms of number of occurrences). Evaluation of the TWA predictive power for the occurrence of ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation) was performed using the area under the curve (AUC) of the receiver operating characteristic (ROC). The statistical significance level was set at 5%.

3. Results

Due to the lack of heart-rate stability, only a fraction (51-58%) of our ICD patients were found to be suitable for TWA analysis at each specific heart rate (80 bpm and 120 bpm; Table 1).

At 80 bpm TWAA was significantly higher among the ICD_Cases than the ICD_Controls (median values: 23 μV vs. 16 μV; P=0.0018), and the AUC was 0.6718. As expected, when heart rate reached 120 bpm, with a

Table 1. Number of patients within each ICD group who were found to be suitable for TWA evaluation at each specific heart rate (HR).

HR (bpm)	ICD_Cases (76)	ICD_Controls (190)	P_1
80	39 (51%)	100 (53%)	NS
120	42 (55%)	110 (58%)	NS
P_2	NS	NS	

P_1: P-value for ICD_Cases vs. ICD_Controls.
P_2: P-value for 80 bpm vs. 120 bpm.

Table 2. TWA amplitude 50th [25th,75th] percentiles and area under the receiver operating characteristic (AUC).

HR (bpm)	ICD_Cases (76)	ICD_Controls (190)	AUC	P_1
80	23 [15,33]	16 [12,24]	0.6718	0.0018*
120	36 [23,59]	36 [27,57]	0.4872	0.8528
P_2	0.0028	$<10^{-16}$	-	-

HR: heart rate
P_1: P-value for ICD_Cases vs. ICD_Controls.
P_2: P-value for 80 bpm vs. 120 bpm
-: not applicable

significant increment in comparison to 80 bpm, TWAA also significantly increased (median values: 36 μV for both the ICD_Cases and ICD_Controls). However, at this heart rate, TWAA was not longer statistically different between the two ICD groups and the AUC decreased to 0.487 (Table 2; Fig.1).

4. Discussion

The present study investigated if faster heart rates reached through exercise, beside increasing TWA amplitude, also enhance the TWA predictive power for the occurrence of ventricular arrhythmias. To this aim, the Leiden University Medical Center database of exercise ECGs in 266 heart failure patients with ICDs, grouped in 76 ICD_Cases (i.e. patients who developed ventricular tachycardia or ventricular fibrillation during follow-up) and 190 ICD_Controls (i.e. patients who did not develop ventricular arrhythmias during follow-up), was employed. Several ICD patients (42-49%) were not found to be suitable for TWA evaluation at 80 bpm and/or 120 bpm. Indeed, being TWA a phenomenon defined at stable and sinus rhythm, for being considered suitable for TWA evaluation, ECG windows had to be characterized by an approximately stable heart rate (NN standard deviation less that 10% NN mean value, see Methods) [16,19]. Such condition, however, was often not satisfied because, during the exercise test, the heart rate was constantly increasing in response to the increasing workload. Thus, if on one hand the exercise test of this study allowed TWA evaluation at different heart rates without the need

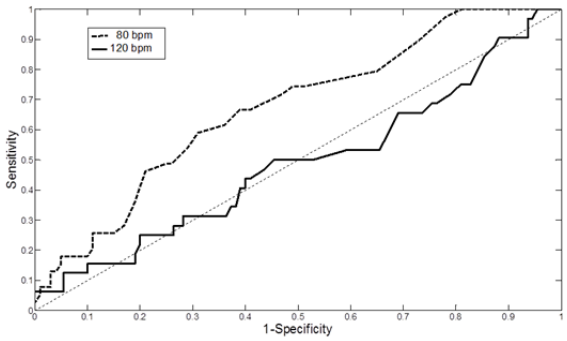

Figure 1. Receiver operating characteristic curves at 80 bpm (AUC=0.672) and 120 bpm (AUC=0.487).

of pacing, on the other hand it caused the rejection of several patients whose heart rate could not be approximated as stable in the observed ECG windows. Once the heart-rate range that optimizes the TWA predictive power for the occurrence of ventricular arrhythmias has been identified, exercise tests characterized by stable rather than increasing heart rate should be considered preferable for TWA evaluation, since they will minimize the number of rejected patients.

Although the ECG tracings of the enrolled patients underwent preprocessing for noise filtering and baseline subtraction and were found to be suitable for TWA analysis, a small heart-rate variability and a low level of noise could still affect them. Consequently, automatic TWA identification was performed using our AMF method which, compared to several other techniques, proved to be particularly robust to the presence of such interferences surviving preprocessing [16]. AMF robustness to noise is due to the fact that it assumes TWA to be characterized by a narrow frequency band around f_{TWA} rather than by solely f_{TWA}, as the other popular techniques do [16,19].

At both 80 bpm and 120 bpm TWA was found to be characterized by a quite low amplitude (few tens of μV). Moreover, at 80 bpm it was significantly higher in the ICD_Cases than in the ICD_Controls. As expected, when heart rate reached 120 bpm, TWA amplitude significantly increased in both ICD groups, confirming the well-known dependency of TWA amplitude on heart rate [9]. However, when comparing ICD_Cases vs. ICD_Controls at this fast heart rate, no statistically significant difference was found and TWA ability to discriminate the two ICD groups was practically negligible (AUC=0.4872). Such results were similar to those previously found in [23] on the same population in which TWA evaluated at rest was found to be more predictive than exercise TWA in correspondence of the maximum workload.

5. Conclusion

In our ICD patients, AMF-derived TWA ability to

discriminate patients at risk for malignant ventricular arrhythmias was higher at 80 bpm, when TWA amplitude was smaller, than at 120 bpm, when TWA amplitude was higher.

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