T-Wave Alternans Hysteresis on Heart Rate

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Abstract

Microvolt T-wave alternans (TWA) increases with heart rate (HR). Thus, TWA is usually analyzed during exercise. However, since TWA during recovery is usually not analyzed, it is not clear if TWA and HR are linked by a one-to-one correspondence, or if it does exist a TWA hysteresis on HR. To investigate such issue TWA was identified in ECG recordings of 266 patients with implanted cardio-defibrillator acquired during a bicycle ergometer test, which included a HR-increasing exercise and a HR-decreasing recovery, both characterized by a HR from 80 to 125 bpm. TWA was always found to have a positive association with HR but, at each HR, exercise TWA was typically different from recovery TWA. Specifically, TWA increased exponentially during exercise (fitting-exponential-curve correlation: ρ=0.99, $P<10^{-7}$) while decreased linearly during recovery (fitting-line correlation: ρ=0.94, $P<10^{-4}$). The two fitting curves crossed at about 115 bpm, so that for lower HRs (80-110 bpm) exercise TWA was significantly lower than recovery TWA (16-21 µV vs. 22-27 µV; P<0.01), while for higher HRs (120-125 bpm) exercise TWA was significantly higher than recovery TWA (41-51µV vs. 28 µV; $P<10^{-6}$). Thus, it does exist a TWA hysteresis on HR since TWA does not depend only on the actual value of HR but also on such value being reached during exercise or recovery.

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 [1-5]. It is well-known that TWA depends on HR. Specifically, it has been observed that TWA tends to increase with increasing HR [6-9] so that, even though it has also been observed in resting conditions [10-13], TWA analysis is often performed at accelerated HRs reached through exercise [1,4-9,14,15]. Since TWA is usually evaluated during the exercise phase of a test, when HR is increasing, and not during the recovery phase, when HR is decreasing, it is not clear yet if there exists a HR-TWA one-to-one correspondence or if it does exist a TWA hysteresis on HR (i.e. TWA amplitude depends on how such HR was reached). Thus, the aims of the present study were: 1- to investigate the dependency of TWA from HR during both phases of test, which are the HR-increasing exercise and the HR-decreasing recovery; and 2- to compare TWA values observed at the same HR during the two test phases.

2. Methods

2.1. Study population

The Leiden (The Netherlands) University Medical Center database of ECG tracings in 266 heart failure patients with an implanted cardio-defibrillator (ICD) for primary prevention because of a depressed (<35%) left ventricular ejection fraction (LVEF) was retrospectively selected for the present observational study on TWA. All patients underwent a bicycle ergometer test during which an ECG was recorded. The test included two phases: exercise and recovery. The exercise phase consisted of an approximately 8-10-min 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. The recovery phase lasted approximately 3-5 min: at first the workload was gradually but quickly decremented to 20 W within 1 min; then, the patient was asked to cycle for other 1-2 min, and eventually had to wait on the bike until his/her HR was close to the HR at the begin of the test.

2.2. Clinical data

During the bicycle ergometer test, 8-lead (I, II, V1-V6) ECG recordings were obtained by means of a CASE 8000 stress test recorder (GE Healthcare, Freiburg, Germany; sampling frequency: 500 Hz; resolution: 4.88 µV/LSB). Such ECG tracings were characterized by an increasing HR during the exercise phase of the test, while during recovery they showed a decreasing HR. The maximum HR was used to discriminate the exact instant when exercise ended and recovery started.

Only the six precordial leads were used in this study because previously found to be optimal to characterize our ICD population in terms of TWA [16]. 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) [17,18]. Subsequently, single-lead sliding ECG windows including 64 consecutive heart beats were extracted every 2 s from the entire ECG recording and were preprocessed for artifacts and ectopic beats replacement [16,17]. 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, all suitable ECG windows were classified according to test phase and HR. More specifically, for each test phase (exercise and recovery), ten different HR classes were considered, from 80 bpm to 125 bpm with and increment of 5 bpm. A HR was considered to belong to the HRi class if $HR_i-2.5$ bpm$\leq HR<HR_i+2.5$ bpm, with HR_i=80, 85...125 bpm.

2.3. Adaptive match filter for T-wave alternans identification

TWA was identified using our HR adaptive match filter (AMF) based method [19], which assumes TWA to be characterized by a small frequency band centered in half mean HR (by definition the TWA frequency, fTWA). The AMF is conceived 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 6^{th}-order bidirectional Butterworth band-pass filter characterized by a 0.12 Hz wide passing band around in fTWA.

Each time the AMF is fed with an ECG tracing, 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 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.

In our clinical ECG data TWA identification 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 independently identified in each one of the six precordial leads by submitting each single-lead 64-beat ECG window to the AMF. Eventually, a TWA characterization in correspondence of each HR was provided in terms of maximum TWA amplitude value over the six precordial leads for each phase of the test.

2.4. Statistics

TWA dependency on HR was investigated by assuming two possible trends, linear (Eq.1) and exponential (Eq.2):

$$TWA = m \cdot HR + q \tag{1}$$

$$TWA = a_1 + e^{\frac{HR - a_2}{a_3}} \tag{2}$$

The coefficients m and q of the line, and a_1, a_2 and a_3 of the exponential curve were determined by finding the best fit in the least-squares sense. Goodness of the fitting curve was quantified by computing the its correlation (ρ) with the experimental data.

Normality of a TWA-amplitude distribution at a specific HR during a phase test was tested using the Lilliefors' test. Comparison between continuous and not-normally distributed TWA parameters (reported in terms of median [25th-75th percentiles]) were performed using the Wilcoxon rank-sum test for equal medians.

Statistical significance level was set at 5% in all cases.

3. Results

In our ICD patients, TWA was found to increase with increasing HR during the exercise phase of the test, and to decrease with decreasing HR during recovery (Fig.1). Still, its value at a specific HR depended on the test phase. Evaluation of the TWA dependency on HR by means of correlation with linear and exponential fitting curves shows that TWA increased exponentially during the HR-increasing exercise (ρ=0.989, $P<10^{-7}$; Table 1) while decreased linearly during recovery (ρ=0.944, $P<10^{-4}$; Table 1). TWA correlation with exponential during recovery was comparable (Table 1), but coefficients were such that exponential could be approximated by a line in HR range of interest.

The exercise fitting exponential curve and the recovery fitting line crossed at about 115 bpm (Fig.1) so that for lower HRs (80-110 bpm) exercise TWA was significantly lower than recovery TWA, while for higher HRs (120-125 bpm) exercise TWA was significantly higher than recovery TWA (Table 2).

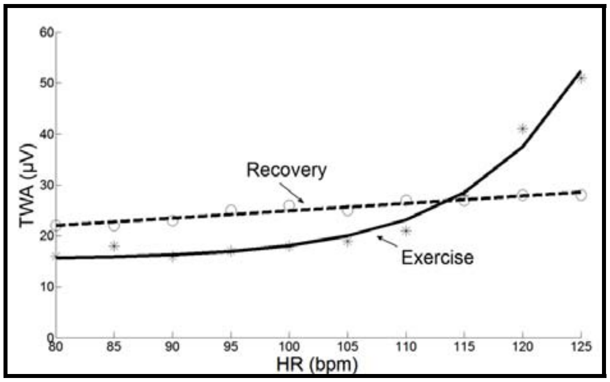

Figure 1. Experimental TWA data during the exercise (*) and the recovery (o) phases of the bicycle ergometer test, and relative optimal (in the least-squares sense) fitting lines, exponential (solid line) for the exercise, and linear (dotted line) for the recovery.

During both the exercise and recovery phases of the test, the number of patients with available TWA measurements at each HR was variable (83-217). Still, the number of patients at a specific HR was usually of the same order of magnitude in the two phases, so that a statistically significant comparison between them was still possible.

4. Discussion

This retrospective, observational study on standard clinical ECG data investigated the dependency of TWA on HR during both phases of a bicycle ergometer test, namely exercise and recovery. To this aim, TWA was identified in ECG tracings of 266 ICD patients, with exercise/recovery HRs ranging from 80 bmp to 125 bpm. TWA was identified using the AMF method [19], particularly suitable for analysis of ECGs characterized by low levels of HR variability [18,21,22]. Indeed, instead of hypothesizing TWA as characterized by a single frequency, fTWA, by definition equal to half HR, this technique supposes TWA to be characterized by a narrow frequency band centered around fTWA and, thus, designs the AMF as a passing band filter.

Although the entire Leiden University Medical Center database of ECG tracings in ICD patients was used, the number of subjects for which a measure of TWA amplitude was available at a specific HR for a specific test phase was typically lower than 266 (Table 2). This was mainly due to the presence of noise, artefacts and/or ectopic beats, or to too high levels of HR variability (see Methods), but also to different subject-dependent HR at the beginning and at the end of the exercise and recovery phases of the ergometer test.

Table 1. Evaluation of TWA dependency on HR during the exercise and the recovery phases or the bicycle ergometer test, quantified as correlation (ρ) between TWA experimental data and fitting curves (m,q: parameters of the linear fitting line; a1, a2,a3: parameters of the exponential fitting curve).

	Linear Fitting	Exponential Fitting
	ρ (m,q)	ρ (a_1, a_2,a_3)
Exercise	0.835* (0.7,-44.3)	0.989*** (15.3,90.1,9.7)
Recovery	0.944** (0.1,10.5)	0.943** (-60.3,-2539.9, 593.9)

*,**,***: statistical significance <0.01, $<10^{-4}$ and $<10^{-7}$, respectively, when correlating experimental TWA values against a fitting curve.

Table 2. TWA amplitude values (50th [25th-75th] percentiles) at various heart rate (HR) during the exercise and recovery phases of the bicycle ergometer test.

	Exercise		Recovery		
HR (bpm)	TWA (μV)	N	TWA (μV)	N	P
80	16 [12- 25]	137	22 [15-32]	83	<0.01
85	18 [12-25]	169	22 [14-35]	99	<0.01
90	16 [12-23]	201	23 [14-41]	120	$<10^{-5}$
95	17 [12-25]	209	25 [16-37]	147	$<10^{-6}$
100	18 [12-26]	217	26 [18-41]	181	$<10^{-8}$
105	19 [13-29]	211	25 [17-42]	180	$<10^{-5}$
110	21 [14-35]	181	27 [18-42]	148	$<10^{-3}$
115	28 [18-50]	153	27 [17-42]	127	NS
120	41 [27-69]	137	28 [20-40]	113	$<10^{-6}$
125	51 [32-81]	113	28 [20-38]	94	$<10^{-8}$

N: number of patients

P: statistical significance when comparing TWA at a specific HR during exercise vs. recovery.

As expected, in our ICD patients, TWA had, overall, a positive dependency from HR (i.e. it increased with increasing HR and decreased with decreasing HR). However, such TWA changes with HR did not occur symmetrically in the two HR-variation directions so that, at a specific HR, exercise TWA was usually significantly different from recovery TWA (TWA hysteresis on HR).

More specifically, during exercise TWA exponentially increased whereas during recovery TWA linearly decreased so that TWA was lower during the exercise than during the recovery at low HRs (<115 bpm), and vice versa at high HRs (>115 bpm).

The TWA hysteresis on HR showed here was never observed before. Results suggest than, when considering TWA at a specific HR, for example for risk stratification, the way such HR has been reached should be taken into account. Moreover, future research will investigate if recovery TWA can improve predictive power for the occurrence of major cardiac events actually observed in resting [10-13] and exercise [1,4-9,14,15] conditions.

6. Conclusions

In our ICD patients, TWA increased with increasing HR during exercise, and decreased with decreasing HR during recovery. Such changes did not occur symmetrically, but TWA amplitude values were lower during exercise than recovery at low HRs (HR<115 bpm), and vice versa at high HRs (>115 bpm). Thus, there is not a HR-TWA amplitude one-to-one correspondence but rather, it seems to exist a TWA hysteresis on HR.

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