Exercise-Induced Repolarization Alternans Heterogeneity in Patients with an Implanted Cardiac Defibrillator

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Abstract

Repolarization alternans (RA), generally recognized as a promising noninvasive index for risk stratification, is often measured under exercise conditions, since RA increases its amplitude with heart rate. Instead, the effect of exercise on the RA location along the JT interval is still unknown. Aim of the present study was to evaluate exercise-induced RA heterogeneity in terms of both amplitude and location. To this aim, we analyzed the ECG precordial leads of 36 patients with an implanted cardiac defibrillator (ICD) who underwent a bicycle ergometer test during which the working load was increased from zero (NoWL) to the patient's maximum capacity (MaxWL). RA was analyzed using our heart-rate adaptive match filter method, which provides an RA parameterization in terms of its amplitude (RAA, μV) and location, the latter measured as time-delay (RAD, ms) with respect to the T-wave apex, so that positive values of RAD indicate RA occurring in the T-wave right side and vice versa. According to our results, during MaxWL, RAA was higher than during NoWL (34±21 μV vs. 16±10 μV; $P<10^{-5}$), whereas RAD was shorter (26±29 ms vs. 69±45 ms; $P<10^{-4}$). Thus, in ICD patients, exercise not only induced a significant increment of RA amplitude, but also caused RA location to move from very late in the repolarization segment toward the T-wave apex.

1. Introduction

Repolarization alternans (RA) is an electrophysiological phenomenon consisting in every-other-beat subtle fluctuations of either amplitude and/or shape of the electrocardiographic (ECG) JT segment at fixed heart rate. Macroscopic RA is quite rare and has been recognized as a harbinger of malignant ventricular arrhythmias [1]. Instead, microvolt RA is much more common, requires specifically designed algorithms for its automatic identification [2-3] and is also generally recognized as a promising noninvasive index for risk stratification [4-10]. Although characterized by its amplitude and time-instant of occurrence along the JT segment, RA is usually described by providing only its amplitude. Still, heterogeneity in the temporal location of RA along the JT segment has recently became a matter of major interest, and the identification of an association between RA location along the JT segment with diseases has been attempted [11-15].

Even though microvolt RA has been also observed in resting conditions [11, 16], it is well known that its amplitude increases at higher heart rates [17] so that RA is often detected from exercise ECG recordings [4, 17]. Instead, the effect of heart rate on the RA location along the JT interval is still unknown. Thus, aim of the present study was to analyze exercise ECG recordings from patients with an implanted cardio-defibrillator to evaluate the effect of heart rate on RA heterogeneity in terms of both its amplitude and location.

2. Methods

2.1. Study population and clinical data

Our study population consisted of 36 subjects from the Leiden University Medical Center (The Netherlands) collection of routine clinical data from patients with an implanted cardio defibrillator (ICD) for primary prevention because of a depressed left ventricular ejection fraction (LVEF<0.35). Each patient underwent a bicycle ergometer test, during which the working load was increased from zero (NoWL) to the patient's maximal capacity (MaxWL), by applying load-increments of 10% of the expected maximal capacity every minute. Thus, each exercise test was approximately 10 minutes long. During the bicycle ergometer test, the ECG precordial leads (V1 to V6) were obtained using a CASE 8000 stress test recorder (GE Healthcare, Freiburg, Germany; sampling frequency: 500 Hz; resolution: 4.88 μV/LSB). After the exercise test, the patients underwent a 4-years follow-up during which they all developed ventricular tachycardia or fibrillation (VT/VF).

2.2. RA characterization by heart-rate adaptive match filter

RA was identified and characterized using our heart-rate adaptive match filter (AMF) method [18], a technique previously tested and prospectively validated in both clinical [11, 16] and simulated settings [2, 19]. More specifically, two windows of 64 consecutive beats were extracted from each lead of the ECG tracing during the NoWL and the MaxWL phases of the exercise test, respectively. For a patient to be enrolled in the study, both NoWL and MaxWL ECG windows had to be characterized by stable heart-rate (NN standard deviation, in s, less than 10% of mean NN, in s). Each one of these windows was then analyzed independently.

After being preprocessed for noise and baseline removal, and for noisy and ectopic beats replacement (patients whose ECG leads showed five or more replaced beats were rejected), each ECG window was submitted to our AMF for RA identification and characterization. At first, the typical RA frequency (f_{RA}) was estimated as half the mean heart rate. Then, the filter was designed as a 6^{th} order bidirectional Butterworth band-pass filter (0.12 Hz wide passing band centered in f_{RA}) and implemented as a cascade of a low-pass filter (LPF; cut-off frequency $f_{LPF}=f_{RA}+df_{RA}$, with $df_{RA}=0.06$ Hz) and a high-pass filter (HPF; cut-off frequency $f_{HPF}=f_{RA}-df_{RA}$). The squared module of the AMF is expressed by the following equation:

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

Thus, the AMF was expected to detect RA by filtering out noise and any other ECG component but the RA typical one. Indeed, the output of the AMF was the RA signal, an amplitude-modulated sinusoidal signal, whose frequency is f_{RA} and characterized by the same length of the input ECG. The RA signal maxima and minima had to fall inside the JT intervals to pertain to RA (Fig. 1). The local amplitude of the RA signal (i.e. its absolute amplitude in correspondence of a maximum or a minimum; Fig.1) provided a measure of the RA amplitude (RAA, in μV) characterizing the corresponding beat [11]. Instead, the time occurrence of a RA signal maximum or minimum represented the center of mass of the alternations, and thus provided information about RA localization along repolarization in the beat [11] (Fig. 1). More specifically, after having identified a reference point (T_{ref}) inside the repolarization segment as the T-wave apex for monophasic T waves, or as the amplitude-weighted mean point between T apexes for biphasic T waves, the RA delay (RAD, in ms) parameter was defined as the signed time interval between the instant at which T_{ref} occurred and the instant at which the RA signal maximum or minimum occurred. Thus, a negative value of RAD indicated the presence of an RA occurring before the T-wave apex (i.e. along the ST segment or the T-wave left side), whereas a positive value of RAD indicated an RA occurring late in the repolarization segment (T-wave right side). Eventually, a RAD equal to zero indicated that the T-wave apex was alternating.

In the case of an ECG tracing not affected by RA, the RA signal at the output of the AMF reduced to a zero constant signal. Consequently, the values of RAA were equal to zero whereas the values of RAD remained undetermined.

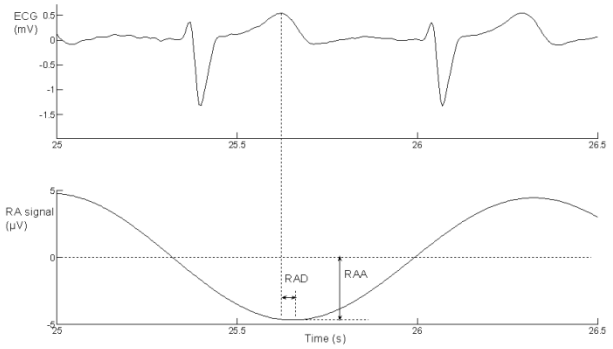

Figure 1. ECG signal (upper panel) and relative RA signal (lower panel) at the output of the AMF from which the RA amplitude (RAA) and delay (RAD) parameters are estimated.

The RAA and RAD values computed from each T wave were averaged over the 64 analyzed beats to provide a characterization of each ECG window. The RAA and RAD values measured in the six precordial leads were then averaged (mean RAA and mean RAD) to provide an overall lead-independent characterization of the RA phenomenon during the NoWL and the MaxWL phases of the bicycle test.

2.3. Statistics

To be independent of normal distributions, non-parametric tests were used to perform comparisons among quantities. More specifically, comparisons between the distributions of the heart rate, and single as well as mean RAA and RAD parameters measured from the NoWL and MaxWL ECG windows were performed using the Wilcoxon rank sum test for equal medians. The statistical significance level was set at 5%.

3. Results

Going from the NoWL to the MaxWL phases of the bicycle test, heart rate increased from 81±10 bpm to 121±13 bpm ($P<10^{-12}$). Accordingly, mean RAA significantly increased in all leads but V6 (Table 1), whereas RAD significantly decreased in all leads (Table 2). Analogously, an increment of mean RAA and a decrement of mean RAD were observed (Table 1, Table 2 and Fig. 2).

Table 1. RAA values (mean±sd over the ICD population) during the NoWL and MaxWL phases of the bicycle test.

Lead	MaxWL (μV)	NoWL (μV)	p
V1	19±9	12±7	$<10^{-3}$
V2	30±20	19±15	<0.01
V3	35±35	18±15	<0.01
V4	35±30	17±13	<0.01
V5	39±23	19±13	$<10^{-3}$
V6	37±28	17±13	NS
Mean V1-V6	34±21	16±10	$<10^{-5}$

Table 2. RAD values (mean±sd over the ICD population) during the NoWL and MaxWL phases of the bicycle test.

Lead	MaxWL (ms)	NoWL (ms)	p
V1	33±31	80±54	<0.01
V2	29±34	56±61	<0.05
V3	22±31	70±52	$<10^{-3}$
V4	21±28	57±55	<0.01
V5	19±38	77±40	$<10^{-3}$
V6	6±27	43±49	<0.05
Mean V1-V6	26±29	69±45	$<10^{-4}$

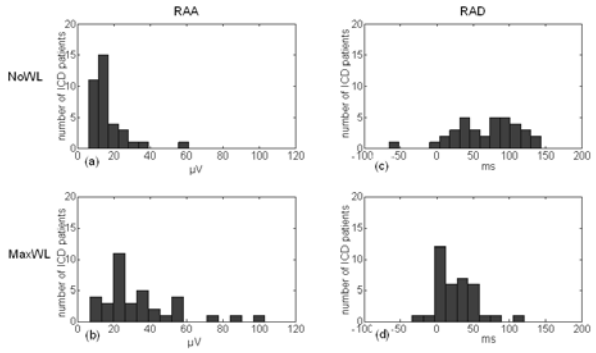

Figure 2. Histograms of mean RAA (panels a and b) and mean RAD (panels c and d) distributions during the NoWL (panels a and c) and the MaxWL (panels b and d) phases of the bicycle test.

4. Discussion

The present study represents, as far as we know, the first attempt to evaluate the effect of high heart rate, reached through exercise, on the RA localization along the JT interval. To this aim ECG tracings of 36 ICD patients, recorded during the NoWL and MaxWL phases of a bicycle test, were analyzed by means of our AMF method. Compared to other RA identification techniques proposed in the literature, the AMF, although requiring a certain heart-rate stability, is more robust to small heart-rate variations [19] which are likely to occur during an exercise test with increasing workload. This properties is due to the fact that the AMF assumes RA to be characterized not only by a single frequency, f_{RA}, defined as half heart rate but, rather, by a small frequency band (0.12 Hz) centered in f_{RA}. In addition, the AMF provides an RA characterization in terms of both amplitude (RAA) and localization, the latter defined as the signed time-delay with respect to the T-wave apex (RAD). Only the six precordial ECG leads were analyzed, since they were previously found to provide analogous information of the twelve standard leads in these kind of patients [20].

As expected, both heart rate and mean RAA were significantly higher during MaxWL than during NoWL (heart rate: 121 bpm vs. 81 bpm; mean RAA: 16 μV vs. 34 μV), confirming the well known dependency of RA amplitude on heart rate [17]. Of major interest, because more innovative, are the results relative to the RA location. The ICD patients were characterized by an RA generally distributed late in the repolarization segment (over the T-wave right hand side, as indicated by positive values of RAD) during both NoWL and MaxWL. This kind of RA is the one that Narayan [13] indicates as the most specific for inducible ventricular tachycardia, which is in agreement with the fact that all ICD patients developed VT/VF during the 4-year follow-up. During MaxWL, however, mean RAD was found to be significantly lower than during NoWL (26 ms vs. 69 ms). Such difference should not be attributed to the shortening of the ECG beat due to the increased heart rate, since RA location is identified with respect to the T-wave peak and not R peak, as in other techniques [12]. This finding rather indicates that the heart-rate increment caused an anticipation of the RA occurrence, which moved from the very late portion of the repolarization segment toward the T-wave apex, as graphically represented in Fig. 3.

5. Conclusion

In our ICD patients RA was generally localized late in the repolarization segment (T-wave right hand side). The exercise induced increment of heart rate caused RA to move toward the T-wave apex, beside increasing its amplitude.

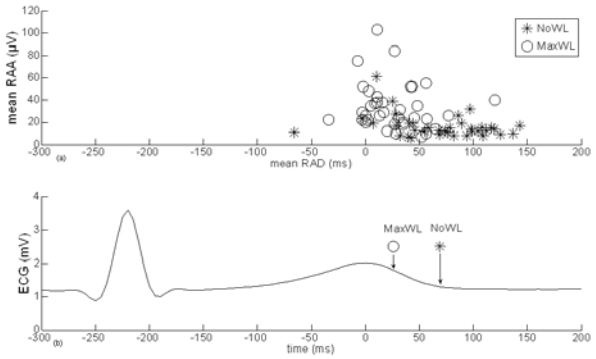

Figure 3. Mean (over the V1-V6 leads) RAD vs. mean RAD observed in the ICD population during NoWL and MaxWL (panel a), and their averaged value (over the 36 ICD patients) indicating the RA center of mass along repolarization (panel b).

References

[1] Raeder EA, Rosenbaum DS, Bhasin R, Cohen RJ. Alternating morphology of the QRST complex preceding sudden death. The New England journal of medicine 1992; 326:271-272.

[2] Burattini L, Bini S, Burattini R. Comparative analysis of methods for automatic detection and quantification of microvolt T-wave alternans. Medical Engineering & Physics 2009; 31:1290-1298.

[3] Martínez JP, Olmos S. Methodological principles of T wave alternans analysis: a unified framework. IEEE Transactions on Bio-Medical Engineering 2005; 52:599-613.

[4] Leino J, Minkkinen M, Nieminen T, Lehtimäki T, Viik J, Lehtinen R, Nikus K, Kööbi T, Turjanmaa V, Verrier RL, Kähönen M. Combined assessment of heart rate recovery and T-wave alternans during routine exercise testing improves prediction of total and cardiovascular mortality: the Finnish Cardiovascular Study. Heart Rhythm 2009; 6:1765-1771.

[5] Maeda S, Nishizaki M, Yamawake N, Ashikaga T, Shimada H, Asano M, Ihara K, Murai T, Suzuki H, Fujii H, Sakurada H, Hiraoka M, Isobe M. Ambulatory ECG-based T-wave alternans and heart rate turbulence predict high risk of arrhythmic events in patients with old myocardial infarction. Circulation Journal 2009; 73:2223-2228.

[6] Sakaki K, Ikeda T, Miwa Y, Miyakoshi M, Abe A, Tsukada T, Ishiguro H, Mera H, Yusu S, Yoshino H. Time-domain T-wave alternans measured from Holter electrocardiograms predicts cardiac mortality in patients with left ventricular dysfunction: a prospective study. Heart Rhythm 2009; 6:332-337.

[7] Hohnloser SH. T-wave alternans: a pathophysiological link to human ventricular tachyarrhythmias. Heart Rhythm 2008; 5:677-678.

[8] Narayan SM. T-wave alternans and the susceptibility to ventricular arrhythmias. Journal of the American College of Cardiology 2006; 47:269-281.

[9] Ikeda T, Yoshino H, Sugi K, Tanno K, Shimizu H, Watanabe J, Kasamaki Y, Yoshida A, Kato T. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study. Journal of the American College of Cardiology 2006; 48:2268-2274.

[10] Klingenheben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. Lancet 2000; 356:651-652.

[11] Burattini L, Bini S, Burattini R. Repolarization alternans heterogeneity in healthy subjects and acute myocardial infarction patients. Medical Engineering & Physics 2012; 34:305-312;

[12] Martínez JP, Olmos S, Wagner G, Laguna P. Characterization of repolarization alternans during ischemia: time-course and spatial analysis. IEEE Transactions on Bio-Medical Engineering 2006; 53:701-711.

[13] Narayan SM, Smith JM. Differing rate dependence and temporal distribution of repolarization alternans in patients with and without ventricular tachycardia. Journal of cardiovascular electrophysiology 1999; 10:61-71.

[14] Nearing BD, Oesterle SN, Verrier RL. Quantification of ischaemia induced vulnerability by precordial T wave alternans analysis in dog and human. Cardiovascular research 1994; 28:1440-1449.

[15] Selvaraj RJ, Picton P, Nanthakumar K, Mak S, Chauhan VS. Endocardial and epicardial repolarization alternans in human cardiomyopathy: evidence for spatiotemporal heterogeneity and correlation with body surface T-wave alternans. Journal of the American College of Cardiology 2007; 49:338-346.

[16] Burattini L, Zareba W, R Burattini. Assessment of physiological amplitude, duration and magnitude of ECG T-wave alternans. Annals of Noninvasive Electrocardiology 2009; 14:366-374.

[17] Bloomfield DM, Hohnloser SH, Cohen RJ. Interpretation and classification of microvolt T-wave alternans tests. Journal of cardiovascular electrophysiology 2002;13:502–512.

[18] Burattini L, Zareba W, Burattini R. Adaptive match filter based method for time vs. amplitude characterization of microvolt ECG T-wave alternans. Annals of Biomedical Engineering 2008; 36:1558-1564.

[19] Burattini L, Bini S, Burattini R. Automatic microvolt T-wave alternans identification in relation to ECG interferences surviving preprocessing. Medical Engineering & Physics 2011; 17-30.

[20] Burattini L, Man S, Burattini R, Swenne CA. Comparison of standard vs. orthogonal ECG leads for T-wave alternans identification. Annals of Noninvasive Electrocardiology 2012; 17:130-140.

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