Identification of Repolarization-Alternans Time Occurrence Improves Discrimination of Abnormal Cases

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Abstract

Repolarization alternans (RA) is characterized by its amplitude and instant of occurrence along the JT segment, but only the amplitude is generally used to discriminate abnormal cases. The role of RA timing was focused in the present study. ECGs from 201 coronary-artery-disease (CAD) patients and 167 control-healthy (CH) subjects were analyzed by our heart-rate adaptive match filter (AMF) method to parameterize RA in terms of amplitude (RAA; μV) and time distance (RAD; ms) from the T-wave apex, and to identify an RA normality region out of which abnormal cases (RA+) are expected to fall. Compared to our CH subjects, the CAD patients showed significant higher mean RAA (19±9 μV vs. 17±15 μV) and RAD variability (-33±37 ms vs. -27±23 ms). Especially, RA+ cases occurring abnormally early (RAD<-82 ms) or late (RAD>28 ms) were, overall, 29, more than twice of those (11) characterized by an abnormally high RAA (RAA>35μV) .

1. Introduction

Repolarization alternans (RA), an electrophysiologic phenomenon manifesting as an alternation of the electrocardiographic (ECG) repolarization segment unaccompanied by gross changes in the heart-cycle length, is generally recognized as a promising predictor of sudden cardiac arrest [1-2]. Visible (macroscopic) RA is quite rare. Instead, microvolt (invisible to the unaided eye) RA, automatically detected by means of specifically designed techniques [3-4] has been found to be present in several diseases [5-9] and linked to inducible [2, 10] as well as spontaneous [1, 8, 11] ventricular arrhythmias.

Although RA is characterized by its amplitude and time-instant of occurrence along the JT segment, only the amplitude is generally used to describe this phenomena and to discriminate abnormal (RA+) cases [12]. Moreover, the few previous studies [13-16] on RA localization report controversial conclusions when an association between RA heterogeneity along the JT segment with diseases was attempted. The aim of the present study was to quantify RA heterogeneity in the coronary artery disease, in terms of both the traditional RA amplitude and a new temporal parameter, RAD, which allows RA localization along the JT segment as the time distance from the T-wave apex. The role of RAD in discriminating RA+ cases was then focused.

2. Methods

2.1. Study populations

Our clinical data consisted of a 20-minute, pseudo-orthogonal (X, Y, Z) lead configuration digital Holter ECG recordings from 201 coronary artery disease (CAD; 166 men) patients and 167 control-healthy (CH; 86 men) subjects. All ECG tracings, recorded in supine and resting conditions making use of Burdick recorders (Burdick Inc., Milton, WI; sampling frequency: 200 Hz, resolution: 10 μV), belong to the Intercity Digital Electrocardiology Alliance (IDEAL) Study databases, which are available at the Telemetric and Holter ECG Warehouse database (http://thew-project.org).

2.2. RA characterization

Repolarization alternans (RA) was identified in the first 5 minutes of each ECG recording. More specifically, ECG segments of 16 consecutive heart beats were recursively (every 2 s) submitted to a preprocessing stage, including noise removal, R-peak detection, baseline removal and identification and replacement of ectopic or noisy beats [4, 17], before being submitted to our heart-rate adaptive match filter (AMF) for RA identification. Only 16-beat ECG strings characterized by a stable heart rate (RR-interval standard deviation less than 10% mean RR interval) and by the presence of at most 1 noisy or ectopic beat were considered eligible for the subsequent RA analysis.

In the presence of a fixed heart rate (and, thus, of a constant time-interval RR between two consecutive sinus beats), RA is, by definition, characterized by a specific frequency of half heart rate: f_{RA}=0.5 cycles per beat, or f_{RA}= 1/(2×RR) Hz. In clinical cases in which heart rate may be considered stable but some physiological

variation might occur, the RA phenomenon can be assumed to be characterized by a narrow frequency band centered around f_{RA}= 1/(2×meanRR) [17-18]. On this basis, our AMF is designed as a pass-band filter with its passing band centered in f_{RA}. Technically, the AMF is implemented as a 6th order bidirectional Butterworth band-pass filter having the passing band $2\times df_{RA}$=0.12 Hz wide and centered at a frequency that adapts to mean RR interval. More specifically, our AMF is a cascade of a low-pass filter (LPF) with cut-off frequency $f_{LPF}= f_{RA}+ df_{RA}$, and a high-pass filter (HPF) with a cut-off frequency $f_{HPF}= f_{RA}-df_{RA}$. The squared module of the AMF transfer function is expressed by the following equation:

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

Being the AMF applied in a bidirectional fashion, no group delay occurs. Thus, the AMF is expected to detect RA by filtering out noise as well as any other ECG component but the RA typical one.

The input signal of the AMF is the 16-beat ECG tracing over which f_{RA} has been computed. In the absence of RA, the output of the AMF, called RA signal, is a zero constant signal. Instead, in the presence of RA, the RA signal is a sinusoidal signal, possibly amplitude-modulated, characterized by the same length of the ECG and by a frequency equal to f_{RA}.

The time occurrences of the sinusoid maxima or minima, which are expected to fall inside the JT intervals when pertaining to RA, provide the center of mass of the alternations in each beat, and, thus, a localization of the alternans inside repolarization (Fig. 1). 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, an RA delay (RAD, in ms) parameter is defined, for each beat, as the difference between the instant at which T_{ref} occurs and the instant at which the sinusoidal RA signal maximum or minimum occurs. Thus, a negative RAD indicates the presence of early repolarization, which mostly involves the ST segment or the first half of the T wave. Instead, a value of the RAD close to zero indicates the presence of central RA, which mostly occurs over the T-wave apex. Eventually, a positive value of the RAD indicates the presence of late RA, characterized by the alternation of the final portion of the T wave. Within the same beat, the amplitude value of the sinusoidal RA signal provides an estimate of the RA amplitude (RAA, in μV).

In the present study, RA analysis was initially performed in each ECG lead individually. More specifically, RAD and RAA values were first averaged over the 16 beats of each single-lead ECG segment. The

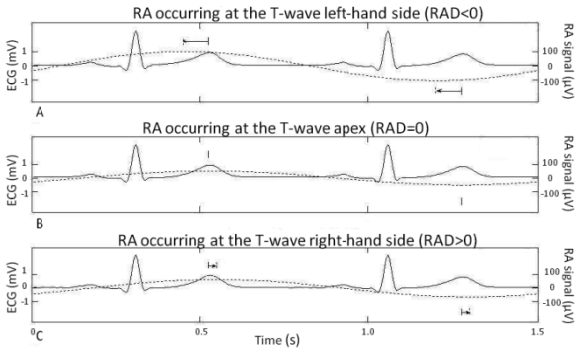

Figure 1. ECG tracing (solid lines) and relative RA signal (dotted lines) at the output of the heart-rate adaptive match filter (AMF) in the presence of early (panel A), central (panel B) and late (panel C) RA.

obtained values were then averaged over the entire 5 minutes of each single-lead recording (M5m_RAD_X and M5m_RAA_X, M5m_RAD_Y and M5m_RAA_Y, and M5m_RAD_Z and M5m_RAA_Z for leads X, Y, and Z, respectively). Eventually, the latter values were averaged over the three leads (M5m_RAD and M5m_RAA) for a comprehensive RA evaluation relative to a single patient.

2.3. Definition of an RA normality region

The M5m_RAD and M5m_RAA distributions over the CH population were used to identify an RA normality region delimited by three thresholds, two (THR_RADmin and THR_RADmax) for the M5m_RAD parameter, respectively defined as the 0.5th and the 99.5th percentiles of the M5m_RAD distribution, and one (THR_RAA) for the non-negative M5m_RAA parameter, defined as the 99.5th percentile of the M5m_RAA distribution. A subject, independently of the belonging population, was classified as characterized by normal levels of RA if the following conditions resulted simultaneously satisfied:

$$\begin{cases} \text{M5m\_RAD} \geq \text{THR\_RADmin} \\ \text{M5m\_RAD} \leq \text{THR\_RADmax} \\ \text{M5m\_RAA} \leq \text{THR\_RAA} \end{cases} \quad (2)$$

If at least one of such conditions was not satisfied, a subject was considered affected by abnormal levels of RA and indicated as RA+.

3. Results

Some levels of RA were detected in CAD patients and CH subjects. However, the CAD population showed RA episodes characterized by higher amplitude and comparable delay (Table 1). Moreover, the CAD patients showed higher RA heterogeneity along the JT segment, as indicated by the standard deviation values of M5m_RAD and M5m_RAA (Table 1). Indeed, as shown in Fig 2, CH

RA cases are mostly localized over the first half of the T-wave, and only occasionally overcome the T-wave apex. Instead, CAD RA cases are distributed along the entire repolarization segment (ST/T wave), with several of them occurring over the ST segment or over the T-wave right-hand side.

The definition of an RA normality region (Fig. 2) delimited by THR_RADmin=-82 ms, THR_RADmax=28 ms and THR_RAA=35 μV, allowed the identification of 36 (17.9%) RA+ CAD patients. Specifically, 22 (10.9%) had M5m_RAD lower than THR_RADmin, 7 (3.5%) had M5m_RAD greater than THR_RADmax, and 11 (5.5%) had M5m_RAA greater THR_RAA. Four RA+ CAD patients characterized by abnormally high M5m_RAA were simultaneously characterized by abnormally low M5m_RAD. By contrast, only 3 (1.8%) cases were at the verge of abnormal condition among the CH subjects.

4. Discussion and conclusion

Our study focused on RA heterogeneity in the coronary artery disease (CAD) in terms of the traditional RA amplitude combined with a new RAD parameter (see Methods) that allows quantification of RA occurrence along the JT segment. Our RAD definition differs from temporal localization parameters defined in previous studies which focused on the time-interval between the R peak and the RA instant of occurrence [14-16], or on the definition of three windows of half JT duration (located at the repolarization beginning, middle and end, respectively) with subsequent identification of the one more affected by RA [13]. Because of the physiological variability of the RR interval and JT duration, these previous RA timing definitions do not allow precise identification of the phase of repolarization more involved in the alternation. This may explain why apparently controversial results have been provided. Indeed, in [13] RA has been found to be more specific for inducible ventricular tachycardia when distributed late, rather than elsewhere, throughout the JT segment. In other studies [14-15] RA has been found to be located within the ST segment and the first half of the T wave in patients undergoing left anterior descending artery occlusion (LAD) and left circumflex artery occlusion (LCX), and to occur a little further on along the JT segment in patients undergoing right coronary artery occlusion (RCA). Eventually, RA heterogeneity along the entire JT segment has been observed in patients with cardiomyopathy [16].

Table 1. Clinical and ECG parameters relative to the CAD patients and the CH subjects.

	CAD patients (201)	CH subjects (167)
M5m_RAD (ms)	-33±37	-27±23
M5m_RAA (μV)	19±9*	17±15

*P<0.05 according to the Wilcoxon rank sum test

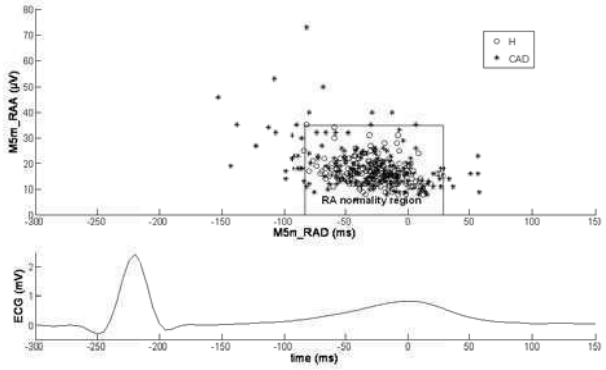

Figure 2. Representation of RA cases relative to the CAD patients and CH subjects and identification of the RA normality region in the M5m_RAD vs. M5m_RAA plane.

Our AMF-based approach [3,17-20] measured RA localization by means of the "delay" (RAD) of the alternans with respect to the T-wave apex, so that large negative values of RAD are necessarily due to RA occurring along the ST segment and the T-wave left-hand side. Instead, RAD values close to zero indicate the presence of RA mainly localized over the T wave, while positive values of RAD indicate alternation of the T-wave right-hand side. Since each portion of the JT segment pertains to a specific phase of the ventricular repolarization, our AMF-based method is expected to provide a more accurate identification of the ventricular repolarization phase involved in the alternation.

Our AMF-based method has the further peculiarity of allowing determination of an RA normality region useful for discrimination of abnormal RA (RA+) cases, potentially at risk of cardiac instability. In the present study the RA normality region was delimited by three thresholds (THR_RADmin, THR_RADmax, THR_RAA, respectively), computed from the RA parameters distribution over the CH population [18-20]. More specifically, THR_RADmin and THR_RADmax were defined as the 0.05^{th} and 99.5^{th} percentiles of the M5m_RAD distribution, whereas only one threshold was defined as the 99.5^{th} percentile over the THR_RAA distribution, being it a non-negative parameter. Such thresholds definition strongly optimizes specificity rather than sensitivity. The rationale for this choice is that RA was initially supposed not be present in healthy conditions [12] so that the number of positive detections among the healthy subjects was forced to be negligible. Because our recent studies support the hypothesis that RA is a phenomenon characterized by an amplitude continuously changing from physiological to pathological conditions [19-20], identification of thresholds levels at 0.05^{th} and 99.5^{th} percentile may result too restrictive, and probably does not represent the best choice for an optimal identification of abnormal RA cases. In spite of that, the

greater RA heterogeneity observed in our CAD patients compared with CH subjects allowed discrimination of 36 of RA+ cases. Since 11 of them could be discriminated by abnormal RA amplitude (irrespective of the simultaneous presence of abnormal RAD in 4 of them), 25 more RA+ cases were detected thanks to an abnormal RAD in the absence of RAA abnormality. Thus, RAD plays a relevant role in RA+ cases discrimination. Moreover, the 29 RA+ CAD patients characterized by abnormal RAD were either characterized by early RA occurrence (M5m_RAD < THR_RADmin; 22 cases) or by late RA occurrence (M5m_RAD > THR_RADmax; 7 cases). This discrimination is to be considered in the association of RA heterogeneity with diseases. Indeed, according to Narayan et al.[13], RA occurring late is mainly associated to ventricular tachycardia.

In conclusion, our quantitative investigation of RA heterogeneity in CAD patients showed that, compared to the CH subjects, the former population shows higher RA amplitude and greater variability of RA localization along the JT segment, as quantified by RAD. RA localization plays an important role in discriminating RA+ cases, given that RA+ cases occurring abnormally early (RAD<-82 ms) or late (RAD>28 ms) were 29, more than twice of those (11) characterized by an abnormally high RAA(RAA>35μV).

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