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Characterization of Repolarization Alternans in the Coronary Artery Disease

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1. Introduction

Repolarization alternans (RA), an electrophysiologic phenomenon consisting on every-other-beat changes of the repolarization morphology (amplitude, shape, and, sometimes, polarity) unaccompanied by gross changes in the heart-cycle length, is generally recognized as a promising electrocardiographic (ECG) predictor of sudden cardiac arrest (SCA; Bloomfield et al., 2006, Chow et al. 2006, Ikeda et al., 2006, Klingenheben et al., 2000, Leino et al., 2009, Maeda et al., 2009, Narayan, 2006, Rosenbaum et al., 1994, Sakaki et al., 2009, Salerno-Uriarte et al., 2007, Stein et al., 2008), that is one of the leading causes of death in developed countries (over 300,000 lives per year in the U.S.; Montagnana et al., 2008, Zheng et al., 2001). On the ECG tracing, RA consists of an alternation of either the ST-segment (Nearing et al., 1991, Rosenbaum et al., 1994), or the T-wave, or even the U-wave (Habbab & el-Sherif, 1992). Macroscopic and, thus, visible RA (like that reported in Fig. 1) is quite rare. After being first reported by Hering in the early 1900s (Hering, 1909), RA has later on been occasionally observed in patients affected by various diseases, among which ischemia (Kleinfeld & Rozanski, 1977), long QT syndrome (Schwartz & Malliani, 1975, Zareba et al., 1994) and ventricular arrhythmias (Verrier et al., 2003). Recent investigations on RA rely on automatic detection of microvolt RA from the digital ECG signal by means of specifically designed techniques, among which the spectral method (implemented in the commercial ECG machine CH2000 and Heartwave, Cambridge Heart Inc., Bedford, MA; Smith et al., 1988, Rosenbaum et al., 1994, Rosenbaum et al., 1996), the complex demodulation method (Nearing et al., 1991, Nearing & Verrier, 1993), the modified moving average method (implemented in the commercial ECG machine CASE-8000, GE Medical Systems, Milwaukee, WI; Nearing & Verrier, 2002), the Laplacian likelihood ratio method (Martínez & Olmos, 2005, Martínez et al., 2006), our adaptive match filter method (Burattini et al., 2008, Burattini et al., 2009b) and others (Burattini et al., 1999, Martínez & Olmos, 2005). Microvolt RA has been found to be much more common than visible RA (Adachi et al., 1999, Chow et al., 2007, Ikeda et al., 2006, Klingenheben et al., 2000, Narayan et al., 2006, Narayan et al., 2007, Reddy et al., 1984) and linked to inducible (Narayan and Smith, 2000, Rosenbaum et al., 1994, Smith et al., 1988) as well as spontaneous (Bloomfield et al., 2006, Klingenheben et al., 2000, Maeda et al., 2009, Narayan, 2006, Verrier et al., 2003) ventricular arrhythmias.

The pathophysiology underlying microvolt RA in humans has not been delineated yet. Several experimental settings have shown that RA may reflect spatial (Banville & Gray, 2002, Chinushi et al., 1998, Narayan, 2006) or temporal (Narayan, 2006, Pastore et al., 1999) dispersion of repolarization, both preceding ventricular fibrillation (Weiss et al., 1999, Smith & Cohen, 1984). Indeed, spatial variations in repolarization (action potential duration, APD) or conduction velocity may prevent depolarization in myocytes that are still repolarizing from their last cycle, causing the typical 2:1 behavior (Banville & Gray, 2002, Chinushi et al., 1998). RA may also result from an alternation of the APD (temporal dispersion of repolarization), which can occur when the relationship of the APD to its preceding diastolic interval (i.e. the APD restitution curve) has a slope greater than one. Under these conditions, mainly occurring in the presence of fast heart rates, small changes of the diastolic interval may cause large APD fluctuations that facilitate alternans (Pastore et al., 1999).

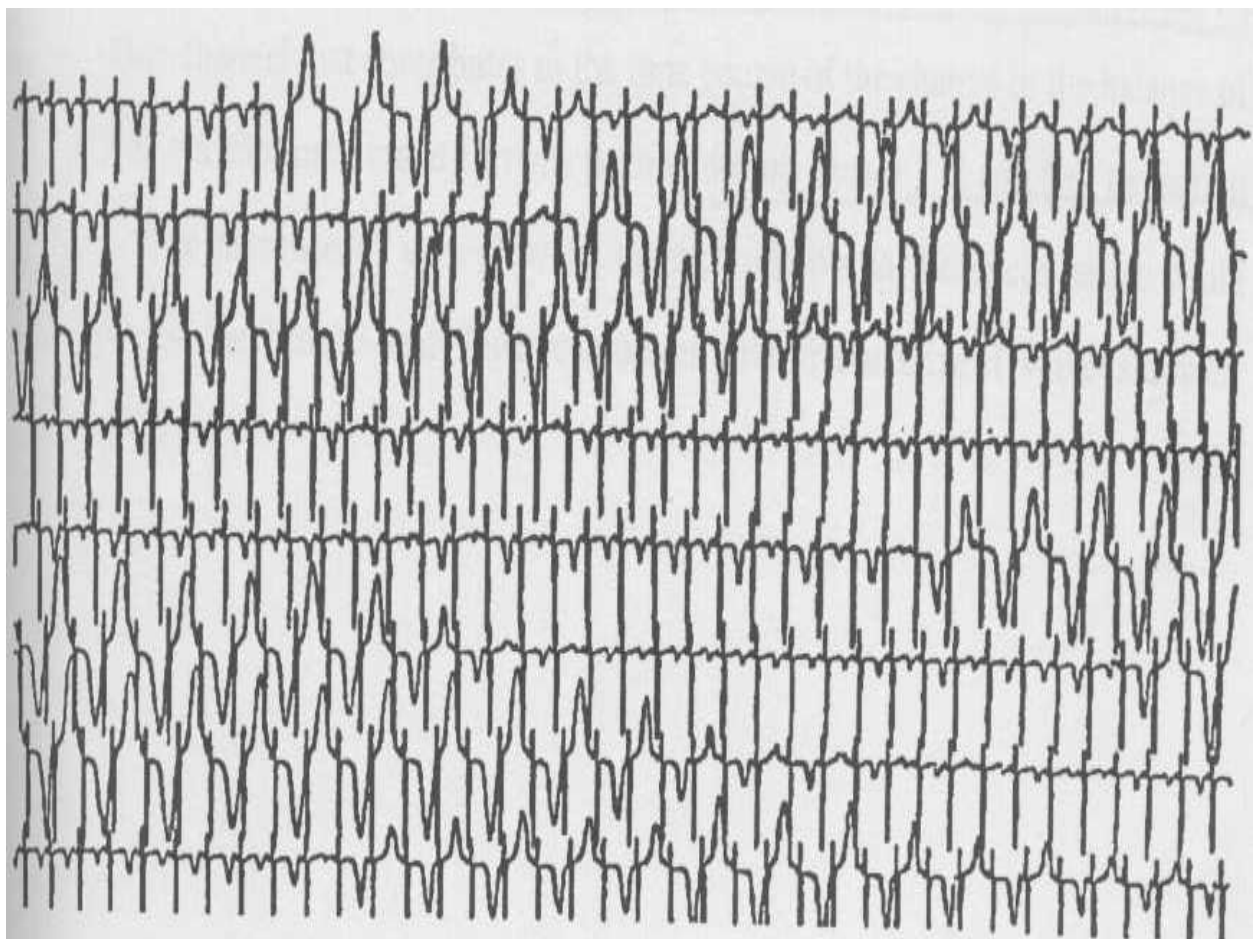


Fig. 1. ECG tracing affected by macroscopic RA.

Alternans derived from the cardiac spatial and temporal dispersion of repolarization projects onto body-surface ECG RA, which shows (Selvaraj et al., 2007) an heterogeneous temporal location along the JT segment, constituted by the ST-segment and T-wave complex. Characterization of this heterogeneity is a matter of major interest, since controversial results have been reported after attempting to identify an association of RA to different diseases. According to Narayan & Smith (Narayan & Smith, 1999) 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 (Martínez et al., 2006, Nearing et al., 1994) 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 (Selvaraj et al., 2007). To the best of our knowledge, quantitative investigations on RA location along the repolarization segment in the coronary artery disease have not been reported yet. Such an investigation was the aim of the present study.

Considering that our adaptive match filter (AMF) based method has been successfully used in previous clinical (Burattini et al., 2008, Burattini et al., 2009a, Burattini et al., 2010) and simulation (Burattini et al., 2006, Burattini et al., 2009b, Burattini et al., 2011) studies for characterization of T-wave alternans (which can be considered a special case of RA limited to the T-wave), this method was applied in the present study to Holter ECGs recordings from coronary artery disease (CAD) patients and control healthy (CH) subjects in order to: A) automatically identify and quantitatively characterize RA in terms of both amplitude and location with respect to the T-wave apex; and B) define a physiological RA region which allows discrimination of abnormal (RA+) from normal RA cases.

2. Methods

2.1 Study populations and clinical data

Our clinical data belong to the Intercity Digital Electrocardiology Alliance (IDEAL) Study databases, available at the Telemetric and Holter ECG Warehouse database (<http://thew-project.org>). The IDEAL protocol was approved by the Research Subject Review Board of the University of Rochester (Rochester, NY) and the study was conducted following required rules for human subjects' research principles, according to the Declaration of Helsinki, as well as to Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Two populations were considered, which consist of 201 coronary artery disease (CAD; 166 men) patients and 167 control-healthy (CH; 86 men) subjects, respectively. Namely, a patient was classified as belonging to the CAD-group if:

1. having positive angiogram (at least one vessel with critical narrowing >75%) with either exercise induced ischemia on ECG or evidence of previous myocardial infarction;
2. being in stable phase of the ischemic heart disease with digital ECG recordings performed on an outpatients basis. Stable post-MI patients should be enrolled at least 2 month after the index event;
3. not having evidence of congenital heart failure. Patients with clinical or echocardiographic evidence for congestive heart failure (LVD >60 mm, EF <40%) were excluded;
4. being in sinus rhythm (no atrial flutter/fibrillation, no pacemaker rhythm, no atrioventricular block, no sick sinus syndrome);
5. not having dilated cardiomyopathy (left ventricular diameter >60 mm and ejection fraction <40%);
6. not having coronary instability (unstable angina requiring hospitalization with evolving ischemic changes in standard ECG);

7. not having congestive heart failure (left ventricular diameter >60 mm and ejection fraction <40%);
8. not having had coronary artery bypass surgery (CABG) in the past. Patients with a history of non-CABG coronary revascularization (percutaneous transluminal coronary angioplasty, stent, atherectomy) were eligible to be enrolled;
9. not having major comorbidity such as malignancy, severe hepatic, renal or cerebral disease.

Instead, a subject was classified as belonging to the CH-group when fulfilling the following criteria:

1. not having overt cardiovascular disease or history of cardiovascular disorders (including stroke, transient ischemic attack, and peripheral vascular disease);
2. not having history of high blood pressure (>150/90 mmHg);
3. not taking medication;
4. not being affected by other chronic illness (e.g. diabetes, asthma, chronic obstructive pulmonary disease, etc.);
5. being diagnosed as being healthy if evaluated by a physician for cardiovascular-related syndrome (chest pain, palpitation, syncope);
6. having normal physical examination;
7. having sinus rhythm in 12-lead ECG without any suspicious abnormalities (e.g. signs of ventricular hypertrophy, inverted T-wave, intraventricular conduction disturbances);
8. having normal echo and normal ECG exercise testing in presence of suspicious ECG changes;
9. not being pregnant.

Clinical parameters such as age, body mass index (BMI), systolic (SAP) and diastolic (DAP) arterial pressure were measured in each subject, whereas the ventricular ejection fraction (LVEF, in %) was determined only for the CAD patients. Therapeutic treatments were also reported. In addition, a 20-minute, 3-lead (pseudo-orthogonal configuration, with bipolar leads X, Y, Z corresponding to limb lead I, augmented limb lead aVF, and precordial lead V3, respectively) digital Holter ECG recording was obtained from each individual in supine and resting conditions, making use of Burdick recorders (Burdick Inc., Milton, WI; sampling frequency: 200 Hz, resolution: 10 μ V). ECG tracings were used to determine the heart rate (mRR; computed as the mean time interval RR between two consecutive sinus beats in a 5-min window) and heart-rate variability (sdRR; determined as the standard deviation of the RR intervals in a 5-min window) as well as RA parameters (see below).

2.2 RA identification and characterization

Repolarization alternans (RA) was identified in the first 5 minutes of each ECG recording. More specifically, ECG segments consisting of 16 consecutive heart beats were recursively (every 2 s) submitted to a preprocessing stage performing noise removal, R-peak detection, baseline removal and identification, and replacement of ectopic or noisy beats (Burattini et al., 2006, Martínez. & Olmos, 2005), before being processed by our heart-rate adaptive match filter for RA identification (see below). 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 a low level of noise or ectopic beats (no more than 1 replaced beats in each ECG string) 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 $f_{RA}=1/(2 \times RR)$ Hz. In clinical cases in which heart rate may be considered stable but presenting some physiological variation, the RA phenomenon is assumed to be characterized by a narrow frequency band, $2 \times df_{RA}$ wide, centered around $f_{RA}=1/(2 \times \text{meanRR})$ (Fig. 2; Burattini et al., 2006, Burattini et al., 2008, Burattini et al., 2009a, Burattini et al., 2010). On this basis, our AMF is designed as a pass-band filter with its passing band centered in f_{RA} (Burattini et al., 2006, Burattini et al., 2008).

Technically, the AMF is implemented as a 6th order bidirectional Butterworth band-pass filter having the passing band 0.12 Hz wide (i.e. $df_{RA}=0.06$ Hz) 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:

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

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 every 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 (Fig. 2), 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 the repolarization (Fig. 3). 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 was computed, 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 value indicates the presence of early repolarization, which mostly involves the ST segment or the first half of the T wave. Instead, an RAD value close to zero indicates the presence of central RA, which mostly occurs over the T-wave apex. Eventually, a positive RAD value 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).

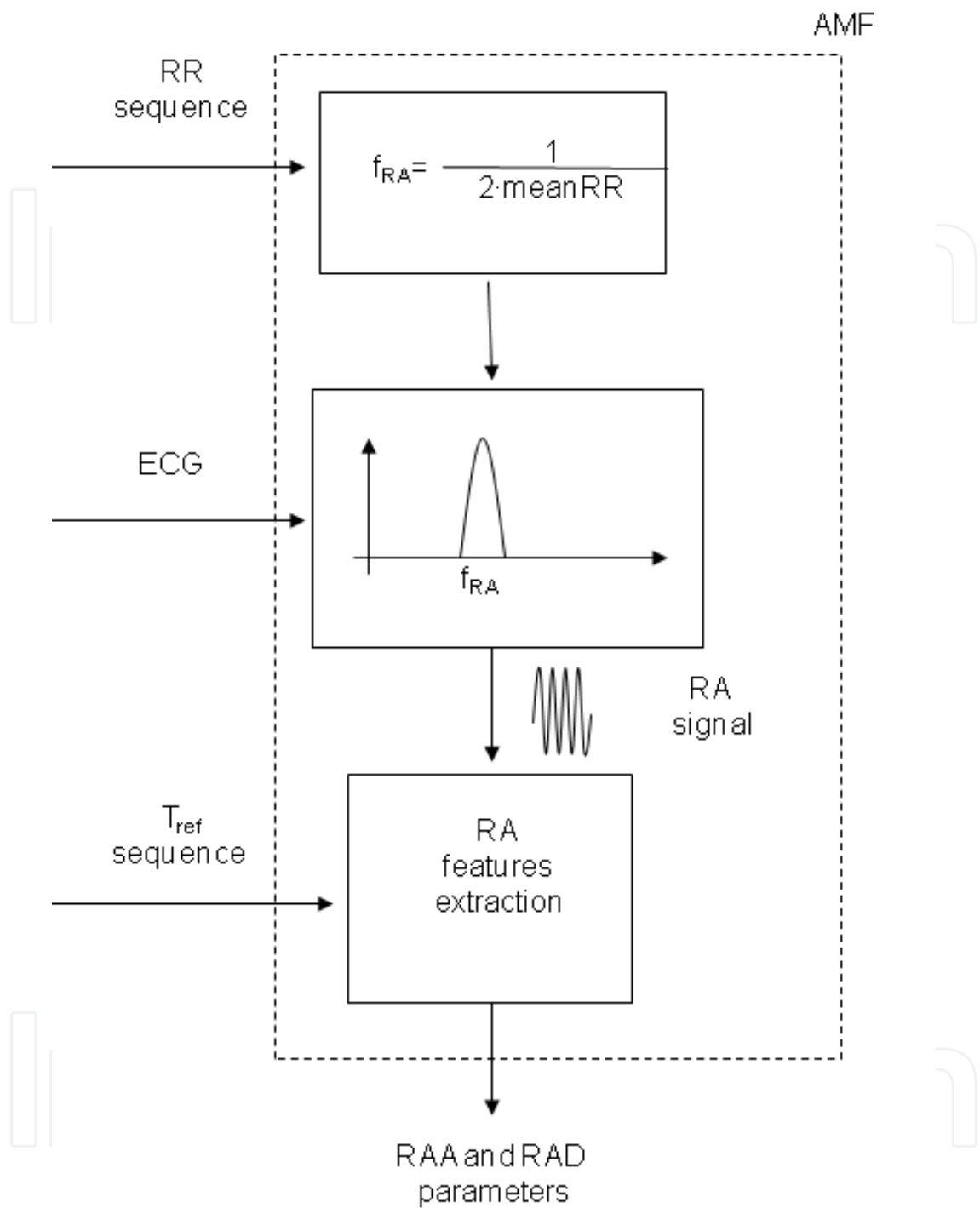


Fig. 2. Block diagram describing the AMF-based procedure for characterization of RA in terms of RAA and RAD parameters.

In the present study, RA analysis was initially performed in each ECG lead as follows. RAD and RAA values were first averaged over the 16 beats of each single-lead ECG segment (M16b_RAD_X and M16b_RAA_X, M16b_RAD_Y and M16b_RAA_Y, and M16b_RAD_Z and M16b_RAA_Z for leads X, Y, and Z, respectively); the resulting 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 characterization relative to a single patient.

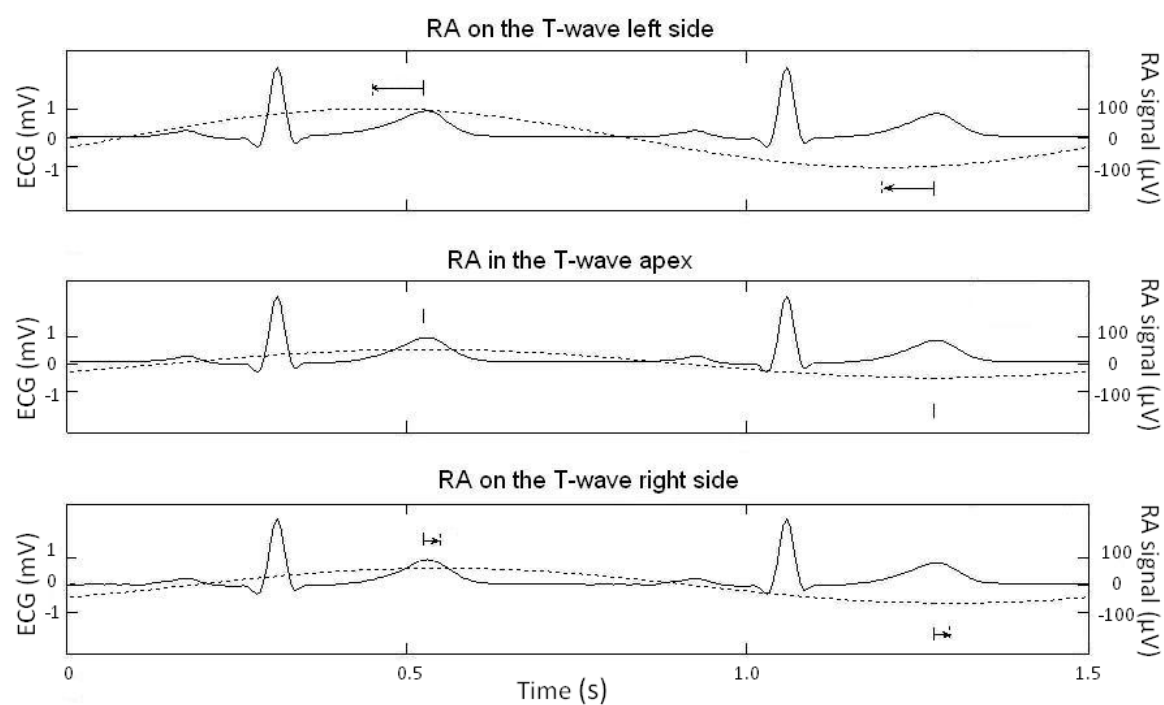


Fig. 3. Simulated ECG tracing (solid lines) and relative RA signal (dotted lines) at the output of the heart-rate adaptive match filter (AMF) in the presence of early (panel A), central (panel B), and late (panel C) repolarization alternans.

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 of them (THR_RADmin and THR_RADmax) were defined for the M5m_RAD parameter as the 0.5th and the 99.5th percentiles of the M5m_RAD distribution, respectively. The third one (THR_RAA) was defined for the non-negative M5m_RAA parameter as the 99.5th percentile of the M5m_RAA distribution. A subject, independently of the belonging population, was classified as characterized by normal RA levels if the following conditions were simultaneously satisfied:

$$\begin{cases} M5m_RAD \geq THR_RADmin \\ M5m_RAD \leq THR_RADmax \\ M5m_RAA \leq THR_RAA \end{cases} \tag{2}$$

These conditions define a physiologic RA region in the M5m_RAD vs. M5m_RAA plane (Fig. 4). Thus, no satisfaction of at least one condition denotes an abnormal RA case (RA+).

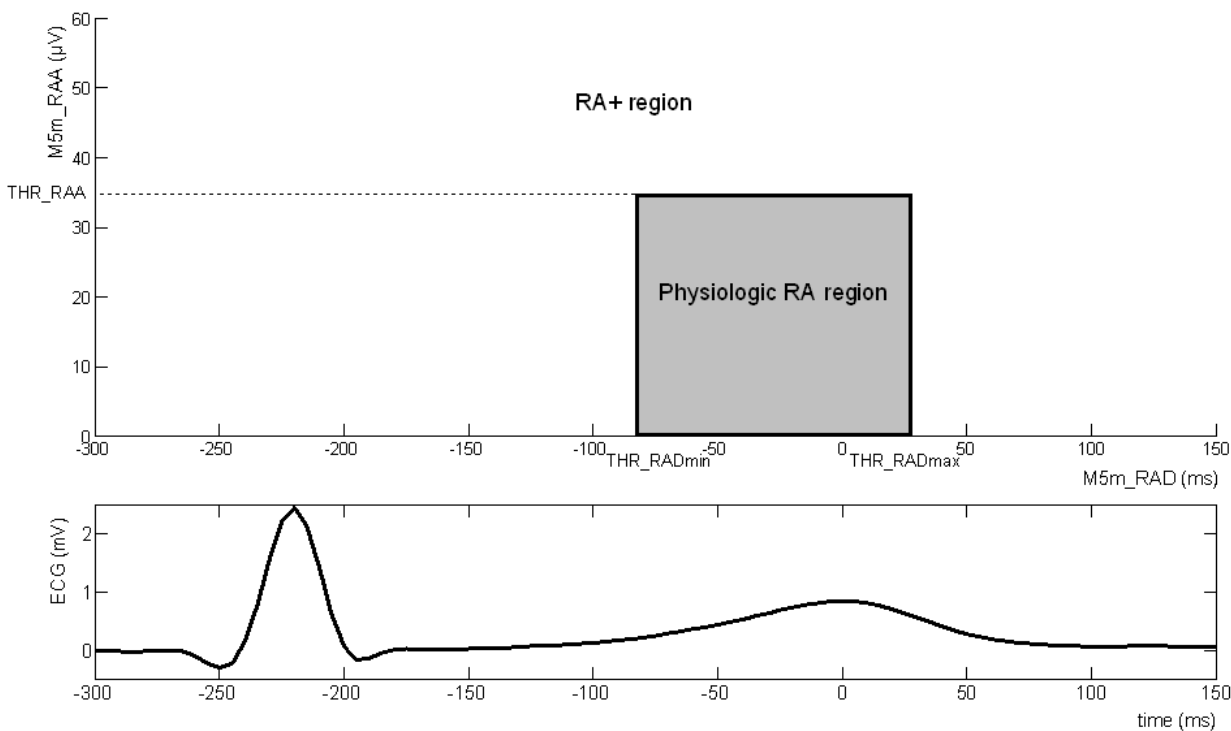


Fig. 4. Definition of a physiologic RA region in the M5m_RAD vs. M5m_RAA plane (shaded area in the upper panel). RA cases falling outside the physiologic RA region are considered abnormal RA cases (RA+). The ECG beat in the lower panel shows RA location along the JT interval.

2.4 Statistics

To be independent of normal distributions, non-parametric tests were used to perform comparisons among quantities. In the specific, comparisons between the distributions of the clinical and ECG parameters over the two populations (CAD vs. CH) were performed using the Wilcoxon rank sum test for equal medians. The Kruskal-Wallis test was used to perform the one-way ANOVA test to evaluate if, in a population, the RA parameters distributions over the three ECG leads were characterized by the same median value. Information about which pairs of leads had different median values was obtained using the multiple comparison procedure. The χ^2 test was used to compare number of treated subjects between the two populations. Eventually, the existence of a possible relationship of the RA parameters with the clinical or the other ECG parameters was evaluated computing the correlation coefficient ρ . Statistical significance level was set at 5%.

3. Results

A summary of the clinical and ECG parameter values characterizing the CAD and the CH populations are reported in Table 1, where pharmaceutical treatments are also specified. Compared to the CH subjects, the CAD patients were significantly older and characterized by significantly higher BMI, SAP, and DAP, and by significantly lower heart rate (longer mRR) and heart-rate variability (lower sdRR).

	CAD patients (201)	CH subjects (167)	P value
Clinical parameters:			
Age (years)	58±11	38±15	<10 ⁻³²
BMI (kg/m ²)	27±4	24±5	<10 ⁻¹³
SAP (mmHg)	129±18	118±12	<10 ⁻¹¹
DAP (mmHg)	79±10	75±8	<10 ⁻³
LVEF	58±11	NA	-
Treatments:			
Beta blocker	150	0	<0.005
Digoxin	0	0	NS
Diuretic	11	0	<0.01
ACE inhibitor	57	0	<0.005
Antiarrhythmic	6	0	NS
ECG parameters:			
mRR (ms)	960±155	904±140	<10 ⁻³
sdRR (ms)	37±40	43±24	<10 ⁻⁶
M5m_RAD_X (ms)	-29±52	-25±29	NS
M5m_RAA_X (μV)	17±10	15±5	NS
M5m_RAD_Y (ms)	-34±51	-24±30	NS
M5m_RAA_Y (μV)	21±12	20±8	NS
M5m_RAD_Z (ms)	-38±44	-32±31	NS
M5m_RAA_Z (μV)	18±9	15±5	<10 ⁻³
M5m_RAD(ms)	-33±37	-27±23	NS
M5m_RAA (μV)	19±9	17±15	<0.05

Table 1. Clinical parameters, therapeutic treatments and ECG parameters relative to the CAD patients and the CH subjects. NA: not available; - : not applicable; NS: not significant.

Some levels of RA were detected in all 201 CAD patients and 167 CH subjects. In both populations, RA amplitude values were significantly greater in lead Y (CAD: M5m_RAA_Y=21±12 μV; CH: M5m_RAA_Y=20±8 μV) than in leads X and Z (CAD: M5m_RAA_X=17±10 μV, M5m_RAA_Z=18±9 μV, P<10⁻⁵; CH: M5m_RAA_X=15±5 μV, M5m_RAA_Z=15±5 μV, P<10⁻⁹). Instead, comparable values of RA delay were measured over the leads in the CAD patients (M5m_RAD_X=-29±52 ms, M5m_RAD_Y=-34±51 ms, M5m_RAD_Z=-38±44 ms), while the CH subjects were characterized by a significantly lower RA delay value in lead Z (M5m_RAD_Z=-32±31 ms) compared to both lead X and Y (M5m_RAD_X=-25±29 ms, M5m_RAD_Y=-24±30 ms, P<0.01). Although RA amplitude appears systematically higher for the CAD patients than for the CH subjects in all leads, statistically significant differences were observed only in correspondence of lead Z (M5m_RAA_Z). No significant differences were found between the two populations in terms of RAD parameters, independently of the lead.

A comprehensive description of the RA phenomenon in the two populations was provided by M5m_RAA and M5m_RAD parameters. In the specific, the CAD population showed RA episodes characterized by higher amplitude (CAD M5m_RAA: $19\pm9\text{ }\mu\text{V}$, CH M5m_RAA: $17\pm5\text{ }\mu\text{V}$, $P<0.05$; Table 1) and comparable delay (CAD M5m_RAD: $-33\pm37\text{ ms}$, CH M5m_RAD: $-27\pm23\text{ ms}$; Table 1). Still, M5m_RAD and M5m_RAA standard deviation values (Table 1) as well as the their distribution histograms (Fig. 5) indicate a greater M5m_RAD and M5m_RAA variability among the CAD patients than the CH subjects. According to these results, RA is localized over the first half of the T wave in most cases of the CH population, and only occasionally overcomes the T-wave apex. Instead, among the CAD patients, RA is distributed along the entire repolarization segment (ST/T wave), with several cases occurring over the ST segment or over the T-wave right-hand side.

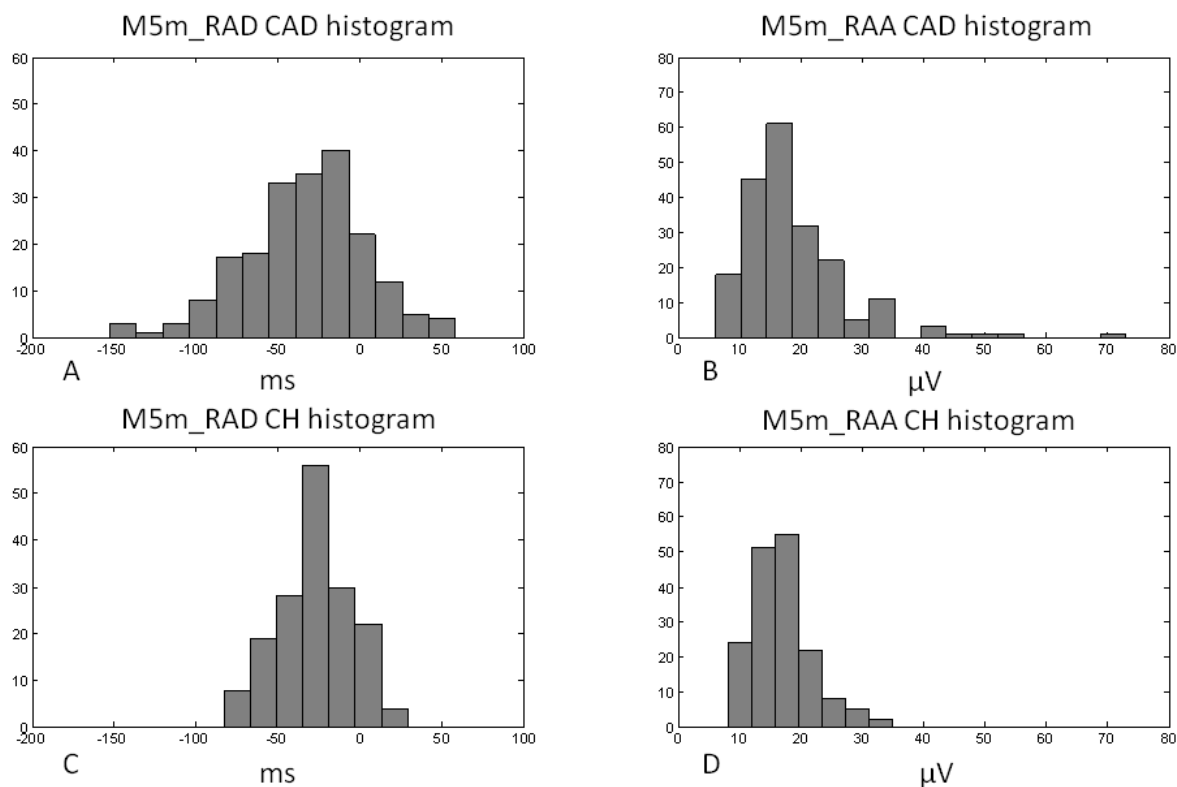


Fig. 5. Histograms of M5m_RAD and M5m_RAA distributions for the CAD (panels A and B) and CH (panels C and D) populations showing a greater M5m_RAD and M5m_RAA variability among the CAD patients than the CH subjects.

The definition of an RA normality region (Fig. 6) delimited by $\text{THR_RADmin}=-82\text{ ms}$, $\text{THR_RADmax}=28\text{ ms}$, and $\text{THR_RAA}=35\text{ }\mu\text{V}$ (as defined in Methods) allowed the identification of 29 (14.4%) RA+ CAD patients with abnormal M5m_RAD. Specifically, 22 (10.9%) had abnormally low M5m_RAD ($\text{M5m_RAD}<\text{THR_RADmin}$) while the remaining 7 (3.5%) had abnormally high M5m_RAD ($\text{M5m_RAD}>\text{THR_RADmax}$). RA+ CAD patients characterized by abnormally high M5m_RAA ($\text{M5m_RAA}>\text{THR_RAA}$) were 11 (5.5%). Among these, 4 were also characterized by abnormally low M5m_RAD. Thus, altogether, 36 (17.9%) RA+ cases were identified among the CAD patients. By contrast, only 3 (1.8%) cases at the verge of abnormal condition were identified among the CH subjects (Fig. 6).

Correlative analysis showed that, in both CAD and CH populations, RA parameters distributions were not significantly linked to the other clinical and ECG ($|\rho| \leq 0.44$; Table 2) parameters distributions. Moreover, CAD patients under pharmaceutical treatments showed RA levels comparable to those characterizing not-treated patients (Table 3).

	CAD patients (201)		CH subjects (167)	
	M5m_RAD (ms)	M5m_RAA (μ V)	M5m_RAD (ms)	M5m_RAA (μ V)
Clinical parameters:				
Age (years)	0.11	-0.01	0.20*	-0.28*
BMI (kg/m ²)	0.19*	-0.10	-0.09	-0.30*
SAP (mmHg)	0.11	-0.08	-0.06	-0.11
DAP (mmHg)	0.16*	-0.07	-0.11	-0.16*
LVEF	-0.17*	0.01	-	-
ECG parameters:				
mRR (ms)	-0.44*	0.29*	-0.42*	0.20*
sdRR (ms)	0.00	0.10	-0.35*	0.39*

Table 2. Correlation coefficient values linking RA parameters with the other clinical and ECG parameters. - : not applicable; *: statistically significant ($P < 0.05$).

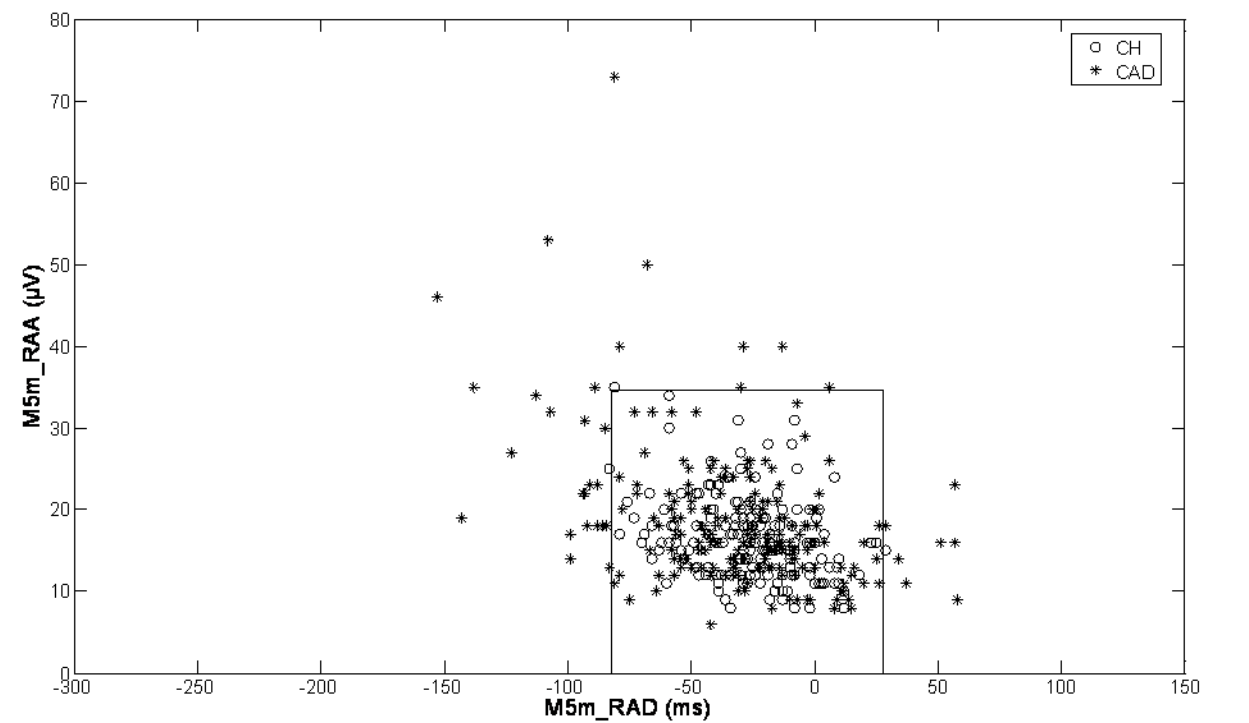


Fig. 6. Representation of the RA cases for CH subjects (o) and the CAD patients (*) in relation to the RA normality region (internal solid-line square) in the M5m_RAD vs. M5m_RAA plane.

	Beta blocker		Diuretic		ACE inhibitor		Anti-arrhythmic	
	Treated (N=150)	Not Treated (N=51)	Treated (N=11)	Not Treated (N=190)	Treated (N=57)	Not Treated (N=144)	Treated (N=6)	Not Treated (N=195)
Clinical parameters:								
Age (years)	58±10	59±12	65±11	58±11	59±10	58±11	54±13	58±11
BMI (kg/m ²)	27±4	27±4	28±5	27±3	27±3	27±4	29±3	27±4
SAP (mmHg)	130±18	127±16	130±14	129±18	134±21	127±16	133±14	129±18
DAP (mmHg)	80±10	76±10	76±9	79±10	81±12	78±9	82±12	79±10
LVEF	58±11	58±10	49±12*	59±10	58±12	58±10	51±11	58±10
ECG parameters:								
mRR (ms)	979±156*	903±137	924±158	962±155	943±143	967±159	865±122	963±155
sdRR (ms)	37±41	35±35	71±72	35±36	42±39	35±40	30±31	37±40
M5m_RAD (ms)	-34±39	-33±32	-19±41	-34±37	-30±31	-35±39	-13±23	-34±37
M5m_RAA (μV)	19±7	19±11	20±7	19±9	19±9	19±8	21±8	19±9

Table 3. Comparison of clinical and ECG parameters between CAD patients under vs. not under pharmaceutical treatment. *: statistical significance (P<0.05) when comparing treated vs. not treated CAD patients groups.

4. Discussion

Our study represents the first attempt to quantify RA heterogeneity in the coronary artery disease (CAD) in terms of the traditional RA amplitude as it combines with a temporal parameter that allows RA localization along the JT segment as a delay from the T-wave apex. This characterization was accomplished by analyzing RA in 5-minute resting ECG recordings by means of our AMF-based technique, previously tested for T-wave alternans detection and quantification in both simulated and clinical settings (Burattini et al., 2006, Burattini et al., 2008, Burattini et al., 2009a, Burattini et al., 2009b, Burattini et al., 2010, Burattini et al., 2011).

Previous studies reported by others identified temporal RA localization in cases other than CAD, either by computing the time-interval from the R peak to the RA instant of occurrence (Martínez et al., 2006, Nearing et al., 1994, Selvaraj et al., 2007) or by identifying three windows of half JT duration (localized at the beginning, at the middle and at the end of repolarization, respectively) and, subsequently, determining which of these was more affected by RA (Narayan & Smith, 1999). The former approach has the major limitation of not taking into account the physiological variability of the RR interval and the JT duration, so that the same time interval localizing RA can be associated to different alternating portions of the JT segment. The latter approach tries to overcome this limitation by use of three windows half-overlapped. However, because of the large variability characterizing the ST segment in clinical cases, the middle window does not necessarily include the T-wave apex, as it is expected to do. Our AMF-based approach resolves these limitations by measuring 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.

Besides RA heterogeneity characterization, our AMF-based method has the further peculiarity of relying on the RA continuity hypothesis. Other techniques, such as the spectral method, the RA identification technique most commonly used in clinics (Smith et al., 1988, Rosenbaum et al., 1994, Rosenbaum et al., 1996), and the Laplacian likelihood ratio method (Martínez & Olmos, 2005, Martínez et al., 2006) ascribe to noise the low-TWA levels, not associated with cardiac instability, which are even detected under physiological conditions. This methodological approach aroused from the early hypothesis that RA could be an on-off phenomenon, usually not present in health (Bloomfield et al., 2002). After the recent experimental study by Pruvot et al. (Pruvot et al., 2004) who demonstrated the possibility of inducing various levels of RA, some of which not necessarily associated to cardiac instability, the hypothesis that RA is a phenomenon characterized by a continuously changing amplitude and/or location from physiological to pathological condition has gained increasing consideration. This assumption requires the set up of methods, like our AMF-based one, that allow identification of an RA normality region to improve reliability in the discrimination of non-physiological or abnormal RA (RA+) levels 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 (Burattini et al., 2008, Burattini et al., 2009a). More specifically, THR_RADmin and THR_RADmax were defined as the 0.5th and 99.5th percentiles of the M5m_RAD distribution, whereas one other threshold was defined as the 99.5th percentile over the THR_RAA distribution, being it a non-negative parameter. Use of percentiles, rather than mean and SD, makes the procedure independent of the assumption of normal distribution for parameter estimates. These threshold definitions strongly optimize specificity rather than sensitivity. The rationale for our choice is that, as mentioned above, RA was initially supposed not be present in healthy conditions (Bloomfield, 2002), so that the number of positive detections among healthy subjects was forced to be negligible (Burattini et al., 2008). Due to our recent studies highlighting the hypothesis that RA is a phenomenon characterized by an amplitude continuously changing from physiological to abnormal conditions (Burattini et al., 2009a, Burattini et al., 2010), identification of thresholds levels at 0.5th and 99.5th percentile may be too restrictive and, thus, not appropriate for an optimal identification of abnormal RA cases. Optimization of thresholds for RA+ identification in relation to risk stratification, however, is beyond the scope of this work, which is mainly focused on RA characterization in the coronary artery disease.

With this aim, our AMF-based technique was applied to ECG tracings from CAD patients, who, compared to CH subjects, are known to show increased levels of T-wave alternans (Bigger & Bloomfield, 2007, Bloomfield et al., 2006, Burattini et al., 2009a, Burattini et al., 2010, Ikeda et al., 2006, Zacks et al., 2007) and to be prone to experience major cardiac events related to it (Narayan et al., 2006). Our results indicate that, in agreement with what previously found (Burattini et al., 2008, Burattini et al., 2009a, Burattini et al., 2010), RA affects all subjects, either diseased or healthy, with different characteristics though. First of all, the CAD patients were, on average, characterized by higher RA amplitude than the CH subjects (CAD: 19 ± 9 μ V, CH: 17 ± 15 μ V; $P < 0.05$). The most interesting results, however, concern the RA localization, which was distributed all over the entire JT segment (ST segment, or T-wave left-hand side, or T-wave right-hand side) in the CAD patients, whereas it occurred mainly over the T-wave left-hand side, and occasionally in correspondence of the T-wave apex, among the CH subjects. Similarly to our CAD patients, RA was found to be distributed all along the JT segment also in the cardiomyopathy (Selvaraj et al., 2007). In spite of the fact that our choice of the threshold values delimiting the RA normality region tends to minimize the number of RA+ cases, the greater RA heterogeneity observed in our CAD patients compared with CH subjects allowed discrimination of a relevant percentage (17.9%) of RA+ cases in the coronary artery disease (Fig. 6). In these abnormal cases RA was characterized by high amplitude (5.5%), as previously reported in other studies on the CAD (Narayan et al., 2006), or occurred either early (11.0%), as in other diseased states (Martínez et al., 2006, Nearing et al., 1994), or late (3.5%) along the JT segment. According to Narayan & Smith (1999), RA occurring late is mainly associated to ventricular tachycardia. Thus, the characterization of RA in terms of both RA amplitude (generally used to discriminate RA+ cases in most studies using other techniques) and RA delay (a parameters which instead is a peculiarity of our AMF-based method) allowed a significant increment in the identification of RA+ cases among the CAD patients, which raised from 11 (identified when using only the RA amplitude parameter) to 36.

According to our results, increased RA heterogeneity observed in the CAD population was not associated to other clinical factors (age, BMI, SAP, DAP and LVEF) or pharmaceutical treatments (beta blocker, digoxin, diuretic, and ACE inhibitor), with the only exception of heart rate. Indeed, a significant, though low ($-0.44 \leq \rho \leq -0.42$; $P < 0.05$), correlation was found between M5m_RAD and RR in both populations, indicating that early RA tends to characterize patients with prolonged RR. Instead, a negligible correlation ($0.20 \leq \rho \leq 0.29$, $P < 0.05$) was found between M5m_RAA and RR distributions. This result is complementary and not in contradiction with the findings from several other studies, which have previously related RA amplitude to heart rate (Bloomfield et al., 2002, Narayan & Smith, 1999, Narayan & Smith, 2000, Smith et al., 1988). Such studies have indeed demonstrated that, within a subject, RA increases when heart rate is forced to increase (by pacing, exercise or drug) over 90 beats/min (Bloomfield et al., 2002). Identification of RA at rest, as in the present study, was often neglected because it requires sophisticated RA identification methods, such as our AMF-based one (Burattini et al., 2011), suitable to detect low levels of RA even in the presence of physiological levels of heart-rate variability (heart-rate variability is indeed strongly reduced at high heart rates).

5. Conclusion

Our quantitative investigation of RA heterogeneity in CAD patients yields the conclusion that, compared to the CH subjects, the former population shows higher RA amplitude and greater variability of RA localization along the JT segment. Especially, in the coronary artery disease, the RA occurs not only over the left-hand side of the T wave, as it is generally observed in health, but also along the ST segment (early repolarization) or along the T-wave right-hand side (late repolarization). Identification of patients characterized by RA occurring in early or late repolarization is relevant since in the literature these kinds of RA phenomena are associated to an increased risk of ventricular arrhythmias. Thus, our AMF-based method appears as a useful tool to identify RA characteristics that help enhancing pathophysiological interpretation and, with it, the ability to discriminate patients at increased risk of sudden cardiac death, who might be appropriately treated before they experience a major cardiac event.

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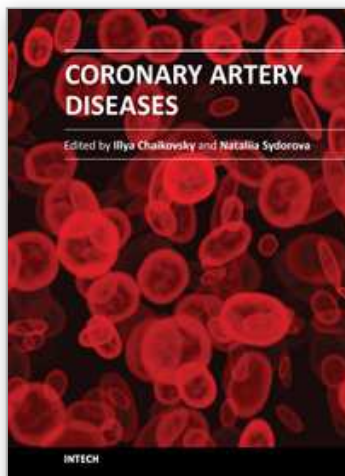
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This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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