Assessment of Physiological Amplitude, Duration, and Magnitude of ECG T-Wave Alternans

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Background: An association between T-wave alternans (TWA) and malignant ventricular arrhythmias is generally recognized. Because relatively low levels of TWA have also been observed in healthy (H) subjects, the question arises as to whether these are ascribable to noise and artifacts, or can be given the relevance of a physiological phenomenon characterizing a preclinical condition.

Methods: To answer this question, in the present study 20-minute not noisy, sinus ECG recordings, from 138 H-subjects and 148 coronary artery diseased (CAD) patients, were submitted to our adaptive match filter (AMF) procedure to identify and parameterize TWA in terms of duration (TWAD), amplitude (TWAA), and magnitude (TWAM, defined as the product of TWAD times TWAA). The 99.5th percentiles of mean values of TWAA, TWAD, and TWAM over 20-minute ECGs were used to define three threshold levels (THRD, THRA, and THRM), which allow discrimination of abnormal TWA levels.

Results: Nonstationary TWA was found in all our H-subjects and CAD-patients. TWAD, TWAA, and TWAM levels were classified as being physiological in 99% of H-subjects and 87% of CAD-patients. A linear correlation ($r = -0.52$, $P < 0.001$) was found between TWAA and RR interval in the H-population.

Conclusions: Our results support the hypothesis of the existence of physiological TWA levels, which are to be considered in the effort to improve reliability of nonphysiological TWA levels discrimination.

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Sudden cardiac death (SCD) from malignant ventricular arrhythmias is one of the leading causes of death in developed countries.^{1,2} A promising electrocardiographic (ECG) predictor of SCD is T-wave alternans (TWA), an electrophysiological phenomenon consisting of a beat-to-beat fluctuation of T-wave amplitude or shape.^{3–7}

TWA has been associated to a broad variety of pathologies, such as long QT syndrome,^{8–10} myocardial infarction,^{11–13} congestive heart failure,¹⁴ dilated cardiomyopathy,¹⁵ coronary artery disease,^{8,16,17} and others.^{4,18–21} A few studies involving control groups of healthy subjects (H-groups) in TWA investigation^{8,13,16,20} reported some TWA

level in H-groups, even though lower than in populations of patients affected by myocardial infarction,¹³ coronary artery disease,^{8,16} and long QT syndrome,⁸ or having low left ventricular ejection fraction.²¹ From these findings, the question arises as to whether small levels of TWA detected in H-subjects are ascribable to noise and artifacts, or can be given the relevance of a physiological phenomenon characterizing a preclinical condition. If the latter is the case, a careful identification and parameterization of TWA in H-subjects is desirable to characterize physiological levels of TWA and determine a threshold level, at the verge of abnormal conditions. TWA parameterization in terms

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of duration, amplitude, and magnitude (a combination of the previous two), and consequent definition of their threshold levels at the verge of abnormal conditions, can be accomplished by our adaptive match filter (AMF) method.^{16,22}

Based on these considerations, in the present study, our AMF algorithm was applied to a population of 138 H-subjects in order to identify and characterize a TWA normality region, in the amplitude versus duration plane, which can constitute a reference mark for future assessment of TWA-related risk factors of malignant ventricular arrhythmias. For a better assessment of TWA in health, TWA features detected from H-subjects were compared to those detected from a population of 148 coronary artery diseased (CAD) patients.

Since, in pathological conditions, TWA is known to be a time-varying phenomenon,^{10,13,23,24} we investigated TWA in 20-minute ECG recordings, rather than in short 128-beat recordings used in most of the reported studies.²⁵ Indeed, 20-minute ECG length, automatically analyzed with our AMF-based technique, improves reliability of nonstationary TWA identification with acceptable computational efforts.²⁶

METHODS

Clinical Data

Our study involved 138 H-subjects and 148 CAD-patients from Intercity Digital Electrocardiology Alliance (IDEAL) Study. The H-subjects had no history of diabetes, hypertension, and cardiovascular diseases. IDEAL protocol was approved by the Research Subject Review Board of the University of Rochester 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.

Clinical parameters such as age, body max index (BMI), systolic (SAP), and diastolic (DAP) arterial pressure were measured in each subject. In addition, a 20-minute, 3-lead (X, Y, Z) digital Holter ECG recording was obtained from each individual in resting conditions, making use of Burdick recorders (Burdick Inc., Milton, WI, USA). Sampling rate was 200 samples per second.

Mean RR interval (MRR_20M) and standard deviation of RR intervals (SDRR_20M) were computed over 20-minute ECG recordings to provide a measure of heart rate and heart-rate variability (HRV).

To control for noise as possible cause of TWA, extraction of 128-beat ECG segments every 10 seconds, throughout each 20-minute recording, was performed in each subject.²⁶ Presence of noisy and nonsinus beats was evaluated using a correlative approach.²⁷ Namely, every beat was correlated against a template (median beat over the 128 available) and was required to show a correlation higher than 0.85 to be considered as a sinus one. A 128-beat ECG segment showing noisy and nonsinus beats, the sum of which exceeded 10, was discarded. The total number of discarded ECG segments was not allowed to exceed 5 minutes recording, such that, at least 15-minute ECG recording could be further on processed for TWA classification. Thus, only subjects whose 20-minute ECG recording satisfied these criteria were considered eligible for the study.

AMF for TWA Quantification

Our AMF method, specifically designed to detect TWA,^{16,22} was applied to ECG series of 128 heart beats. After defining MRR_128B as the mean of RR intervals over such time window, the TWA phenomenon can be characterized by a specific frequency (in Hz) of half-mean heart rate

$$f_{TWA} = \frac{1}{2 \cdot MRR_{128B}} \quad (1)$$

To account for physiological variations of the RR interval, a narrow-frequency band, rather than a single frequency, was assumed to characterize the TWA phenomenon. On this basis, our AMF was designed as a band-pass filter with its passing band centred in f_{TWA} . Technically, the AMF was implemented as a 6th order bidirectional Butterworth band-pass filter, with passing band 0.12 Hz wide (value experimentally found) and centered at a frequency (f_{TWA}) that adapts to MRR_128B. In particular, our AMF was designed as a cascade of a low-pass filter (LPF) with cut-off frequency $f_{LPF} = f_{TWA} + df_{TWA}$, and a high-pass filter (HPF) with a cut-off frequency $f_{HPF} = f_{TWA} - df_{TWA}$ ($df_{TWA} = 0.06$ Hz). The squared module of the AMF transfer function is expressed by the following equation:

$$|H_{AMF}(\omega)|^2 = |H_{LPF}(\omega)|^2 \cdot |H_{HPF}(\omega)|^2$$

$$= \frac{1}{1 + \left(\frac{\omega}{\omega_{LPF}}\right)^{2n}} \cdot \frac{\left(\frac{\omega}{\omega_{HPF}}\right)^{2n}}{1 + \left(\frac{\omega}{\omega_{HPF}}\right)^{2n}} \quad (2)$$

where $n = 3$ (half of AMF order), $\omega_{LPF} = 2\pi f_{LPF}$, and $\omega_{HPF} = 2\pi f_{HPF}$. Being the AMF applied in a bidirectional fashion, no phase delay occurs.

The input of our AMF is a 128-beat ECG tracing, potentially affected by TWA. Every ECG frequency component, other than TWA, is filtered out, such that a sinusoid is provided as output. This sinusoidal wave, which can be referred to as "TWA signal," reduces to a zero constant if TWA is not present.

The TWA signal provided by the AMF is a time domain, constant phase and, possibly, amplitude-modulated sinusoid with its maxima and minima over the T waves. A local estimate of TWA amplitude (A_{TWA}), associated to each single beat, is directly given by the sinusoid amplitude in correspondence of the T-wave apexes. If the T wave of a beat is alternating, its A_{TWA} is greater than zero. In our procedure, all local A_{TWA} values are used to compute global (i.e., relative to all 128 beats of the ECG series) estimates of TWA characteristic parameters. In particular, the following global parameters were determined: TWA duration (TWAD, beats; defined as the total number of beats with alternating T waves), TWAA amplitude (TWAA, μV ; defined as the mean A_{TWA} over all alternating T waves), and TWA magnitude (TWAM, μV beats; defined as the product of TWAA times TWAD). Thus, the AMF allows characterization of nonstationary (i.e., time-varying) characteristics of the TWA signal, when present.

Values of TWAD, TWAA, and TWAM parameters were computed for each available lead. To characterize TWA in each 128-beat ECG, the means of TWAD, TWAA, and TWAM over the three leads (X,Y,Z) were, subsequently, computed to determine a single set of parameters.

Repeated application of our AMF technique 128-beats ECG extracted every 10 seconds over each 20-minute ECG, yielded TWA parameter time-series [i.e., (TWAD(t_k), TWAA(t_k), and TWAM(t_k), $k = 1, 2, \dots$], which provide a description of TWA dynamics during this time frame.²⁶ Mean (MTWAD_20M, MTWAA_20M, and MTWAM_20M) and standard deviation

(SDTWAD_20M, SDTWAA_20M, and SDTWAM_20M) of these time-series were used to characterize TWA variability. The mean values were also used for definition of TWA normality region (see below).

Definition of a TWA Normality Region

Identification of a TWA normality (or physiological) region was performed by computing three thresholds (THRD, THRA, and THRM), one for each TWA parameter, as the 99.5th percentiles of these mean TWA parameters (MTWAD_20M, MTWAA_20M, and MTWAM_20M) over the H-population. The normality region was, then, defined by the following inequalities:

$$\begin{cases} MTWAD_{20M} \leq THRD \\ MTWAA_{20M} \leq THRA \\ MTWAM_{20M} \leq THRM \end{cases} \quad (3)$$

Because TWAM has been defined as the product of TWAA and TWAD, the threshold line defined by THRM in the TWAA-TWAD plane is a segment of hyperbola.

Cases characterized by at least one TWA parameter exceeding the corresponding threshold are considered out of normal range, and thus potentially at increased risk of development of malignant arrhythmias (TWA+).

Statistics

Student's *t*-test was used to compare 13 corresponding parameters (SAP, DAP, BMI, AGE, MALE, MRR_20M, SDRR_20M, MTWAD_20M, MTWAA_20M, MTWAM_20M, SDTWAD_20M, SDTWAA_20M, SDTWAM_20M) of the two populations. According to Bonferroni's method,²⁸ statistical significance at 5% of this multiple-comparison problem required $P < 0.0038$ (i.e., $P < 0.05/13$).

Statistical significance for linear correlation (*r*) between two different parameters of the same population was set at 5% level ($P < 0.05$).

RESULTS

Ten-second ECG segments relative to one H-subject and one CAD-patient, together with the corresponding TWA signals, obtained using our AMF-based technique, are shown in Figure 1 (panels a to d). In both cases, the TWA signals are represented by time-modulated sinusoids, indicating that, even

Figure 1. ECG tracings from (A) one H-subject and (B) one CAD-patient and (C,D) corresponding TWA signals obtained using our adaptive match filter (AMF).

in a 10-second window, TWA appears as a nonstationary phenomenon.

Some levels of TWA were identified in all our H-subjects and CAD-patients. A representative time course of TWA variability, expressed by $TWAD(t_k)$, $TWAA(t_k)$, and $TWAM(t_k)$, in one H-subject, is displayed in Figure 2 (panels a to c).

Values of clinical and TWA parameters relative to the two populations are reported in Table 1. As expected, compared to CAD-patients, H-subjects showed significantly lower SAP, DAP, and BMI. In addition, H-subjects were characterized by a significantly shorter mean RR than CAD. $MTWAD_{20M}$ and $MTWAM_{20M}$ were significantly lower in the H- than in the CAD-population, who also showed a significantly increased $SDTWAA_{20M}$.

Results of correlation analysis of TWA versus age, BMI, SAP, DAP, MRR_{20M} , and $SDRR_{20M}$ are reported in Table 2 for the H-subjects, and Table 3 for the CAD-patients. Both populations were characterized by a significant correlation between $MTWAD_{20M}$ and MRR_{20M} (H: $r = -0.52$, $P < 0.001$; CAD: $r = -0.24$, $P < 0.01$), $MTWAA_{20M}$ and $SDRR_{20M}$ (H: $r = 0.24$, $P < 0.01$; CAD: $r = 0.20$, $P < 0.05$), and $SDT-$

WAA_{20M} and $SDRR_{20M}$ (H: $r = 0.55$, $P < 0.001$; CAD: $r = 0.30$, $P < 0.001$). Other significant correlations, observed in one or the other population,

Figure 2. Time series of (A) TWA duration [$TWAD(t_k)$]; (B) amplitude [$TWAA(t_k)$]; and (C) magnitude [$TWAM(t_k)$] from one healthy subject.

Table 1. Clinical and TWA Parameters (Mean $\pm$ Standard Deviation) Values of 138 H-Subjects and 148 CAD-Patients. P Values Refer to *t*-test of H-Subjects versus CAD-Patients ($P < 0.0038$ for Statistical Significance)

	H-Subjects (138)	CAD-Patients (148)	P Value
SAP (mmHg)	108 $\pm$ 36	128 $\pm$ 17	$P < 0.0001$
DAP (mmHg)	69 $\pm$ 23	78 $\pm$ 10	$P < 0.0001$
BMI (Kg/m ²)	24 $\pm$ 5	27 $\pm$ 4	$P < 0.0001$
Age (years)	38 $\pm$ 15	56 $\pm$ 16	$P < 0.0001$
Male	74	127	$P < 0.0001$
MRR_20M (msec)	880 $\pm$ 134	932 $\pm$ 142	$P < 0.002$
SDRR_20M (msec)	50 $\pm$ 21	43 $\pm$ 25	$P < 0.05$
MTWAD_20M (beats)	59 $\pm$ 14	64 $\pm$ 16	$P < 0.003$
MTWAA_20M (μ V)	35 $\pm$ 12	40 $\pm$ 22	$P < 0.05$
MTWAM_20M (beats/ μ V)	2108 $\pm$ 895	2566 $\pm$ 1518	$P < 0.003$
SDTWAD_20M (beats)	9 $\pm$ 3	10 $\pm$ 4	$P > 0.05$
SDTWAA_20M (μ V)	6 $\pm$ 4	8 $\pm$ 8	$P < 0.002$
SDTWAM_20M (beats/ μ V)	520 $\pm$ 290	701 $\pm$ 684	$P = 0.004$

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; BMI = body mass index; MRR_20M = mean RR interval over 20 minutes (measure of mean heart rate, HR); SDRR_20M = standard deviation of RR intervals over 20 minutes (measure of heart-rate variability, HRV); MTWAD_20M = mean of T-wave alternans duration over 20 minutes; MTWAA_20M = mean of T-wave alternans amplitude over 20 minutes; MTWAM_20M = mean of T-wave alternans magnitude over 20 minutes; SDTWAD_20M = standard deviation of T-wave alternans duration over 20 minutes (measure of TWA variability); SDTWAA_20M = standard deviation of T-wave alternans amplitude over 20 minutes (measure of TWA variability); SDTWAM_20M = standard deviation of T-wave alternans magnitude over 20 minutes (measure of TWA variability).

were found between clinical parameters and TWA parameters, as shown in Tables 2 and 3.

Threshold values identifying a TWA normality region were THRD = 92 beats, THRA = 67 μ V, and THRM = 5029 μ V beats (Fig. 3). According to this criterion, 136 (99%) of the H-subjects were classified as having physiological levels of TWA, while the remaining two H-subjects fell at the verge of abnormal conditions. On the other hand, 129 (87%) of the CAD-patients showed TWA levels comparable with those of H-subjects, while the remaining 19 patients showed decidedly higher levels of TWAD and/or TWAA (Fig. 3), such that they fell in the TWA+ region.

DISCUSSION

An association between TWA and malignant ventricular arrhythmias^{5-7,12-14} and SCD^{3,4,8,10-19,21} is generally recognized. The present study is the first devoted to the aim of testing the hypothesis that a low level of TWA is a physiological phenomenon characterized by "normal" duration and amplitude, which may, in some circumstances, reach levels of nonphysiological condition, potentially at risk of malignant ventricular arrhythmias. Assessment of TWA in health was accomplished by analyzing a population of healthy subjects compared with a population of CAD-patients. In the effort to rule out

Table 2. Correlation of TWA to Clinical Factors for the H-Population

	Age (Years)	BMI (Kg/m ²)	SAP (mmHg)	DAP (mmHg)	MRR_20M (msec)	SDRR_20M (msec)
MTWAD_20M (beats)	0.31 [^]	-0.01	0.07	-0.13	-0.52 [^]	-0.18 [*]
MTWAA_20M (μ V)	-0.34 [^]	-0.28 [^]	-0.07	-0.16	-0.02	0.24 [°]
MTWAM_20M (beats $\cdot \mu$ V)	-0.15	-0.24 [°]	-0.04	-0.21 [*]	-0.28 [^]	-0.05
SDTWAD_20M (beats)	-0.07	-0.01	-0.04	0.13	0.20 [*]	0.18 [*]
SDTWAA_20M (μ V)	-0.17 [*]	-0.09	-0.05	-0.08	0.09	0.55 [^]
SDTWAM_20M (beats $\cdot \mu$ V)	-0.18 [*]	-0.16	-0.07	-0.11	0.01	0.44 [^]

* $P < 0.05$; ° $P < 0.01$; ^ $P < 0.001$.

Meaning of abbreviations is as given in Table 1.

Table 3. Correlation of TWA to Clinical Factors for the CAD-Population

	Age (Years)	BMI (Kg/m ²)	SAP (mmHg)	DAP (mmHg)	MRR_20M (msec)	SDRR_20M (msec)
MTWAD_20M (beats)	0.04	0.02	-0.07	-0.12	-0.24 [°]	-0.16
MTWAA_20M (μ V)	0.13	-0.01	-0.08	-0.00	0.20*	0.20*
MTWAM_20M (beats $\cdot \mu$ V)	0.12	0.02	-0.10	-0.05	0.10	0.10
SDTWAD_20M (beats)	-0.05	-0.07	0.08	0.10	0.04	0.14
SDTWAA_20M (μ V)	0.11	-0.01	-0.01	0.04	0.06	0.30 [^]
SDTWAM_20M (beats $\cdot \mu$ V)	0.11	-0.01	-0.11	-0.06	0.07	0.14

*P < 0.05; [°]P < 0.01; [^]P < 0.001.

Meaning of abbreviations is as given in Table 1.

noise effects on our assessment of a "physiologic" TWA, 20-minute ECG tracings from each subject were submitted to rigorous noise-control criteria, as described in Methods. Subjects of both H and CAD populations who satisfied these criteria were 286 over 524 (138 over 248 H and 148 over 276 CAD).

TWA levels measured in our recruited population of 138 H-subjects were comparable with those measured in most (87%) of our recruited population of 148 CAD-patients. This result supports our hypothesis of the existence of physiological levels of TWA. A correlation ($r = -0.52$, $P < 0.001$) between MTWAD_20M and MRR_20M gives further

support to this conclusion. Relatively low value of r is explained by the fact that the RR range in our investigation is limited to resting conditions. Such correlation is made more evident in reported studies where heart rate is increased by artificial pacing^{6,20} or by recording the ECG under physical exercise.^{29,30} Spectral method for TWA detection used in these reported studies, however, does not allow discrimination between TWAD and TWAA, while our time-domain AMF does. Our results indicate that TWAD, rather than TWAA, increases when RR decreases (Table 2). One could expect a lower TWA in the CAD-patients due to longer RR (Table 1). Our results, however, indicate that this

Figure 3. Region of physiological TWA (normality region) delimited by threshold lines of TWA duration (THRD), amplitude (THRA), and magnitude (THRM). H-subjects and CAD-patients are represented with dots (●) and open circles (○), respectively.

is not the case (Table 1), suggesting that the underlying mechanism generating TWA in the CAD-patients is different from the one generating TWA in H.

Significant differences between clinical parameters, such as age, BMI, SAP, and DAP require consideration as to the possible effect of these parameters on TWA predictive information. Results of correlation analysis between such parameters and TWA, as reported in Tables 2 and 3, showed no significant correlation or poor correlation ($P < 0.0038$, but $|r|$, ranging from 0.17 to 0.34). As expected, males were largely prevalent (86%) within our CAD group, while our H-group counted about 50% of both genders. Comparative analysis of TWA parameters between males and females, within our H-group, showed no significant difference, thus suggesting no effect of gender on physiological TWA level.

Once the existence of a physiological level of TWA is accepted, there is a need to discuss the reliability of a threshold criterion that allows discrimination of abnormal TWA levels potentially at risk of malignant ventricular arrhythmias.

Definition of a TWA normality region based on these thresholds is strongly related to the adopted protocol (length of ECG tracing and algorithm for TWA identification). The protocol proposed here assumes a 20-minute resting ECG recording analyzed by means of our time-domain AMF-based technique. The spectral technique,⁶ that is at the present time one of the most commonly used techniques to measure TWA, was not an appropriate tool for this study, since it makes the assumption of a stationary TWA, whereas in healthy subjects TWA is likely to be non stationary with short duration and low amplitude. Thus, the employment of a time-domain technique is necessary, given the nonstationary nature of TWA in pathological¹³ and physiological (present results) conditions. Compared to the other proposed time-domain methods to detect TWA, such as the modified moving average³¹ and Laplacian likelihood ratio³² ones, our AMF-based technique has the further advantage of not requiring preprocessing of the digital ECG, such as T-wave windowing and synchronization. Advantage of straight-forward TWA detection by our AMF is easily inferred from the example displayed in Figure 1b and d, where the presence of a TWA signal characterized by relatively high amplitude is detected. One can argue that some variability of the T wave is visible in the ECG tracing,

however, such variability is not fully ascribable to TWA because some respiratory modulation is overlapped. Because respiratory signal is characterized by a different main frequency component than TWA, it is filtered out by our AMF-based detection method without requiring, and then without being affected by, a preprocessing step.²²

Compared to the present study, our previous studies^{16,26} suffered from the limitations that (a) TWA, in H-subjects, was ascribed to noise and artifacts, and (b) our identification procedure consisted of one threshold applied to TWA detected from 20-minute ECG recordings, or three thresholds applied to TWA detected from 128-beat ECG recordings.

Use of ECG tracings longer than the traditional 128 consecutive beats²⁵ is suitable to improve reliability of TWA identification in the presence of time varying TWA features. However, analysis of too long tracings (24-h ECG, for instance⁷) requires large computational efforts, long running time, and may result impractical. Combination of 20-minute ECGs with our AMF appears a good compromise between TWA identification reliability, and computational efforts.²⁶

Our definition of three thresholds is based on the observation of time-dependent characteristics of TWA [10, 13, 16, 23, 24, 26, and present study]. Under physiological conditions, this is characterized by low amplitude (under THRA), low duration (under THRD), and low magnitude (under THRM). On the other hand, risky TWA can be either sustained or transient.^{13,16} Threshold on TWAD (THRD) allows identification of sustained (long duration) TWA, even though characterized by very low amplitude. Threshold on TWAA (THRA) allows identification of quickly transient (very few beats) TWA, if characterized by a sufficiently high amplitude. A further threshold, THRM, on TWAM allows identification of TWA with intermediate amplitude and duration. All thresholds are overcome in the presence of sustained, high amplitude TWA.

Even though it is well known that TWA is heart-rate dependent,^{6,20,29–31} we made the choice to analyze ECG tracings recorded in resting conditions. This choice, indeed, is justified by the fact that TWA will have a great impact on the problem of SCD if it allows identification of subjects at increased risk, before they experience a major arrhythmic event, during a routine ECG testing, that is more frequently performed in resting conditions.

Our AMF-based analysis of TWA has a limitation in that its predicting value has not yet been tested against follow-up clinical outcomes in terms of cardiovascular mortality. Nevertheless, some association between TWA and arrhythmic events has been previously observed, after our time versus amplitude characterization of microvolt TWA.¹⁶ Further tests might involve TWA provocative testing (physical and mental activity, pacing, exercise, etc.), which is usually considered to make this phenomenon more predictive.³ Indeed, there are no theoretical limitations to the applicability of our AMF method to these ambulatory conditions. Assessment of the predictive value of our method is beyond the scope of the present work, which is, rather, finalized to the assessment, for the first time, of a normality zone of TWA duration and amplitude. Physiological levels of TWA are to be considered in the effort to improve reliability of nonphysiological TWA levels discrimination.

Conclusions

This study constitutes the first attempt to assess the existence, in humans, of relatively low levels of TWA that may be given the relevance of a physiological phenomenon. To this aim, our AMF-based technique was recursively (every 10 seconds) applied to 128 consecutive beats of 20-minute ECG recordings taken from a population of 138 H-subjects and a population of 148 CAD-patients. A region of physiological levels of TWA was defined with the aid of (a) parameterization of TWA in terms of TWAD, TWAA, and TWAM and (b) definition of parameter thresholds THRD, THRA, and THRM. Our finding of comparable TWA levels in all H-subjects and in 87% of CAD-subjects supports the conclusion that a physiological level of TWA exists. Definition of such normality region helps in discriminating TWA levels pertaining to a nonphysiological condition, potentially at risk of malignant ventricular arrhythmias. Reliability of our AMF plus thresholding procedure in discriminating region of abnormal TWA (TWA+ region) is supported by the fact that 19 over 148 CAD-patients could be classified as TWA+, while only 2 over 138 H-subjects were at the verge of abnormality.

Assessment of the predictive value of our method is beyond the scope of the present work, which is, rather, finalized to the assessment, for the first time, of a normality zone of TWA duration and

amplitude. Physiological levels of TWA are to be considered in the effort to improve reliability of nonphysiological TWA levels discrimination.

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