# IDENTIFICATION OF TIME-VARYING T-WAVE ALTERNANS FROM 20-MINUTE ECG RECORDINGS

## *Issues Related to TWA Magnitude Threshold and Length of ECG Time Series*

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Abstract: Aim of this study was the assessment of a T-wave alternans (TWA) identification procedure based on application of an adaptive match filter (AMF) method, recently developed by ourselves, to a 20-minute digital ECG recording (ECG20). Three-lead ECG20 tracings from 35 patients who survived an acute myocardial infarction (AMI-group) and 35 healthy subjects (H-group) were analysed. The AMI-group showed, on average, increased levels of TWA ($P<0.01$). Considering that noise may cause false positive TWA detection, a threshold ($THR_{TWA}$) was defined for TWA magnitude (TWAM) as the mean TWAM +2SD over the H-group. TWAM exceeding this threshold identified a TWA-positive (TWA+) subject as one at increased risk of sudden cardiac death. Fifteen (43%) AMI-patients vs. zero H-subjects were detected as TWA+. This result meets clinical expectation. TWA manifested as a non stationary phenomenon that could even be missed in all TWA+ subjects if our AMF (as well as any other technique) was applied to a single short-term 128-beat ECG series, as usually done in previous reports. In conclusion, our AMF-based TWA identification technique, applied to 20-minute ECG recordings, yields a good compromise between reliability of time-varying TWA identification and computational efforts.

## 1 INTRODUCTION

T-wave alternans (TWA) is an electrophysiological phenomenon which consists of two-to-one beat-to-beat changes in the morphology (amplitude, shape and, sometimes, polarity) of the electrocardiografic (ECG) T wave. According to the literature, visible and non-visible (microvolt) forms of TWA in ECG recordings play an important role in the arrhythmogenesis of failing myocardium (Schwartz and Malliani, 1975; Zareba et al., 1994; Adam et al., 1984; Smith et al., 1988; Rosembaum et al., 1994; Kusmirek and Gold, 2007; Klingenheben and Ptaszynski, 2007; Narayan, 2007). Visible forms of TWA are infrequent. Non-visible TWA requires computerized analysis of digital ECG recordings to be recognized and parameterized in terms of amplitude and duration. Thus, in the effort to assess a clinically useful marker of sudden cardiac death, development of methods for non-invasive automatic detection of microvolt TWA has been a major challenge in the last two decades (Rosenbaum et al., 1996; Klingenheben et al., 2000; Ikeda et al., 2002; Tapanainen et al., 2001; Bigger and Bloomfield, 2007; Ikeda et al., 2006). Factors that may prevent a reliable TWA quantification must be controlled by


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signal preprocessing, such as high frequency noise filtering, detection of R peaks, RR stability testing, and removal of baseline deviation from the isoelectric line.

Recently, we developed a new adapting match filter (AMF; Burattini et al., 2006) method for automatic TWA detection, which, differently from other reported techniques, does not require any pre-processing of the ECG tracing, with the only exception of R-peak detection. Making use of simulated (Burattini et al., 2006) and experimental (Burattini et al., 2007) data, we showed that this method yields an improvement in reliability of TWA detection over a previously reported correlation method (Burattini,1998; Burattini et al., 1999).

Like any other TWA detection technique, our AMF needs to be applied to ECG tracings with no significant heart-rate variability and with a low noise level. As a consequence, these techniques have traditionally been applied to short-term ECG series, typically consisting of 128 consecutive heart beats. This rises the issue as to whether 128 beats portray sufficient information on the presence of TWA. To address this issue, in the present study we analyzed 3-lead (X,Y,Z) 20-minute digital ECG recordings (ECG20). Our goal was to demonstrate that repeated applications of our AMF-based method to several tracings of 128 heart beats, within an ECG20, yields a good compromise between reliability of TWA identification and computational efforts. Our analysis was performed on Holter ECG recordings from patients who survived a myocardial infarction since these are known to show increased levels of TWA, compared to healthy subjects (Ikeda et al., 2002; Pelicano et al., 2006; Ikeda et al., 2000; Puletti et al., 1980).

# 2 METHODS

## 2.1 Clinical Data

Our study involved 35 healthy subjects (H-group; RR=0.93±0.17 s) and 35 patients who survived an acute myocardial infarction (AMI-group; RR=0.88±0.14 s). For a better traceability during the analysis, healthy subjects were identified as H01, H02, … H35. Analogously, AMI patients were identified as AMI01, AMI02, … AMI35.

A twenty-minute, three-lead (X,Y,Z) digital Holter recording was obtained from each individual in resting conditions, making use of Burdick recorders (Burdick Inc., Milton, WI). Sampling rate was 200 samples per sec. Series of 128 consecutive cardiac beats were extracted every 10 seconds from each tracing. Each series underwent our TWA identification procedure as described below. Because extraction of 128 cardiac beats every 10 s causes a data overlap (on average 109 s for the H-group, and 103 s for the AMI-group) between two consecutive series, effects of this overlapping were tested vs. an extraction procedure (data selection every 128 beats) that avoids data overlapping.

## 2.2 T-Wave Alternans Detection by Adaptive Match Filter

Our adaptive match filter method (AMF), specifically designed to detect TWA (Burattini et al., 2006 and 2007), was applied to each ECG series of 128 heart beats.

To avoid cases where TWA could be driven by heart-rate variability (Adam et al., 1984; Rosembaum et al., 1994; Burattini, 1998; Burattini et al., 1999), an ECG time series has to be characterized by a stable heart rate to be eligible for TWA analysis. Specifically, we required that:

$$SDRR < 0.1 \cdot MRR \quad (1)$$

where MRR and SDRR are mean and standard deviation of RR intervals (in s).

Under this condition, the TWA phenomenon is assumed to be characterized by a specific frequency of half heart rate: $f_{TWA}$=0.5 cycles per beat, or $f_{TWA}$= 1/(2*MRR) Hz. To account for physiological variations of the RR interval, a narrow frequency band, instead of a single frequency, was assumed here to characterize the TWA phenomenon. On this basis, our AMF was designed as a passband filter with its passing band centred in $f_{TWA}$. Technically, the AMF was implemented as a $6^{th}$ order bidirectional Butterworth band-pass filter, having the passing band $2 \cdot df_{TWA}$=0.12 Hz wide (value experimentally found) and centred at a frequency that adapts to mean RR interval. 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 $f_{HPF}= f_{TWA}-df_{TWA}$. The squared module of the AMF transfer function is expressed by the following equation:

$$\left|H_{AMF}(w)\right|^2 = \left|H_{LPF}(w)\right|^2 \cdot \left|H_{HPF}(w)\right|^2 = \frac{1}{1+\left(\frac{w}{w_{LPF}}\right)^{2n}} \cdot \frac{\left(\frac{w}{w_{HPF}}\right)^{2n}}{1+\left(\frac{w}{w_{HPF}}\right)^{2n}} \quad (2)$$

were n=3 (half of AMF order), $w_{LPF}=2\pi f_{LPF}$, and $w_{HPF}=2\pi f_{HPF}$. Being the AMF applied in a bidirectional fashion, no phase delay occurs. Thus, the AMF is expected to detect the TWA signal by filtering out not only noise and baseline wandering, but also any other ECG component but the TWA.

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, beat; defined as the total number of beats with alternating T-waves), TWA amplitude (TWAA, μV; defined as the mean $A_{TWA}$ over all alternating T-waves), and TWA magnitude (TWAM, beat·μV; defined as the product of TWAA times TWAD). TWAM is used to detect the presence of TWA, since it includes information about both TWAA and TWAD. Moreover, TWAM allows identification of different TWA episodes (such as those short in time and high in amplitude, or long in time and low in amplitude), which would not be detected if only TWAD or TWAA, respectively, were used. Thus, the AMF allows characterization of non-stationary (i.e. time varying) characteristics of the TWA signal, when present.

TWAD, TWAA and TWAM parameter values are determined in each available lead. Corresponding values from the three different leads (X,Y,Z) are then averaged for final TWA characterization relative to a specific 128-beat series. The series with the highest TWAM is assumed as the most representative of the entire 20-minute recording.

## 2.3 Identification of TWA-Positive Subjects

Considering that noise and artefacts may be detected as TWA episodes, once TWA is identified and parameterized, there is a need to define the TWA level that characterizes a TWA-positive subject as one at increased risk of sudden cardiac death. Taking advantage of the H-group involved in our study, the mean+2SD value of the TWAM distribution over this group was assumed as the normality threshold ($THR_{TWA}$) of TWA magnitude. Thus, subjects with TWAM greater than $THR_{TWA}$ were considered as TWA positive (TWA+).

## 2.4 Statistical Analysis

Lilliefors test (Lilliefors, 1967), was used to evaluate the hypothesis that each data vector or parameter vector had a normal distribution (significance was set at 5% level) and could be expressed as mean ± SD. Comparisons between two groups of normally distributed samples were performed with two-tailed, non-paired Student's t-test (statistically significant difference was assumed at $P<0.05$).

# 3 RESULTS

Application of our AMF method to an entire 20-minute ECG recording (ECG20), with 128 beat ECG series selected every 10 s, yielded normally distributed TWA parameters with mean±SD for H-group and AMI-group as given in Table 1. The AMI-group was found to be characterized by having significantly higher TWAD, TWAA, and TWAM. The threshold value ($THR_{TWA}$), as defined in Methods, was 4176 beat·μV (that is, 2730+2×723). With this threshold, fifteen patients of the AMI-group (i.e. 43%) were classified as TWA+. No subject of the H-group showed relevant TWA.

Extraction of ECG time series every 128 beats (no overlap between two consecutive series) provided a lower number of TWA+ among AMI-patients (eleven cases, i.e. 31%), and significantly lower estimates of TWA duration, amplitude and magnitude parameters, with respect to the extraction procedure performed every 10 s (Table 2).

Application of our AMF method to 128-beat series taken in proximity of minutes 0 ($t_0$), 5 ($t_5$), 10 ($t_{10}$), 15 ($t_{15}$), and 20 ($t_{20}$), yielded even lower numbers of TWA+ patients associated with significant reduction of mean TWAM, compared to ECG20 with ECG time series extracted every 10 s (Table 3). Eight (23%) out of the 15 (43%) patients identified as TWA+ when analyzing ECG20 (namely, AMI02, AMI10, AMI11, AMI15, AMI18, AMI19, AMI22 and AMI24), were never detected as TWA+ when using single 128-beat series. Four (11%) patients were detected as TWA+ at time $t_0$ and $t_{15}$, two (6%) at $t_{10}$, and only one (3%) at $t_5$ and $t_{20}$.

A representative example of the time course of TWAD, TWAA and TWAM parameters averaged over the three leads in our AMI01 patient is

displayed in Fig. 1a to c. Panel c clearly shows that TWAM, which has been assumed as a marker of the presence of TWA, crosses the $THR_{TWA}$ value at different time instants. Under-threshold values of TWAM are due to a simultaneous decrement of both TWAD and TWAA (panels a and b).

Because TWAM shows fluctuations with threshold-crossing within ECG20, TWA could even be missed in all TWA+ subjects if our AMF was applied to a single, short-term 128-beat ECG series. Confirmation of this statement is found in Fig. 2, where TWAM waves from all fifteen TWA+ patients are displayed. Arrow pointers in proximity of the eleventh minute mark 128-beat ECG series with under-threshold TWAM which would miss all TWA+ cases.

# 4 DISCUSSION

To satisfy the requirement of heart-rate stability for reliable TWA detection, short-term ECG series have been considered for TWA identification in most reported studies. Indeed, spectral analysis has been the first technique proposed in the literature for automatically detecting TWA (Adam et al., 1984). ECG series of 128-consecutive beats were considered for its application because this is the minimal requirement to guarantee reliable spectral analysis. Since then, ECG time series of 128-consecutive beats have been traditionally used for TWA quantification. Thus, the issue arises as to the reliability of using a single 128 beat sequence to detect TWA+ cases. The present study was designed to address this issue by applying our AMF-based method for TWA detection (Burattini et al., 2006). Comparison was performed among the results obtained from 128 beat ECG series selected 1) every 10 s (data overlap), 2) every 128 beats (no data overlap), 3) every 5 minutes, in a time frame of 20 minutes. For this technical investigation, we considered a population of 35 AMI-patients compared with a population of 35 H-subjects. The H-population was used as reference to define a threshold ($THR_{TWA}$) for TWAM parameter provided by our method as a marker to identify a remarkable level of TWA.

A novel finding of our analysis was that, based on the defined threshold, the use of a unique 128 beat ECG series is unsuitable to unmask and detect TWA. An explanation of this shortcoming is found in that TWA is a transient phenomenon characterized by time-varying TWAD, TWAA and TWAM parameters (Fig. 1). As shown in Fig. 2, under-threshold values of TWAM, assumed as marker of TWA, would miss TWA+ patients if a unique 128-beat ECG series in proximity of the eleventh minute was used.

Table 1: Comparison between TWA duration (TWAD), amplitude (TWAA), and magnitude (TWAM) distributions (mean±SD) in the H-group and AMI-group. Data refer to 20-minute ECG recordings (ECG20) with 128 beat time series extracted every 10 s.

| | H-group | AMI-group | t-test |
|---|---|---|---|
| TWAD (beat) | 75±13 | 87±11 | P<0.01 |
| TWAA (μV) | 43±14 | 56±22 | P<0.01 |
| TWAM (beat*μV) | 2730±723 | 3982±1386 | P<0.001 |

Table 2: Comparison between TWA duration (TWAD), amplitude (TWAA), and magnitude (TWAM) distributions (mean±SD) in AMI-group. Data refer to 20-minute ECG recordings with 128 beat time series extracted every 10 s (ECG20 overlap) or every 128 beats (ECG20 no overlap).

| AMI-group | ECG20 overlap | ECG20 no overlap | t-test |
|---|---|---|---|
| TWA+ | 15 | 11 | |
| TWAD (beat) | 87±11 | 81±11 | P<0.001 |
| TWAA (μV) | 56±22 | 50±21 | P<0.001 |
| TWAM (beat*μV) | 3982±1386 | 3453±1253 | P<0.001 |

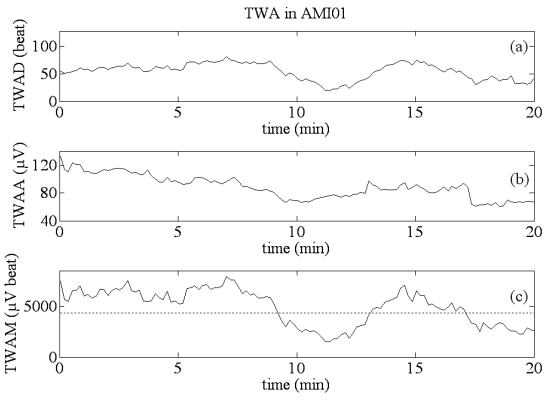


Figure 1: TWA in the AMI01 patient. Panels a, b, and c: respectively, TWA duration (TWAD), TWA amplitude (TWAA), and TWA magnitude (TWAM) as functions of time. In panel c the normality threshold is represented with a dotted line.

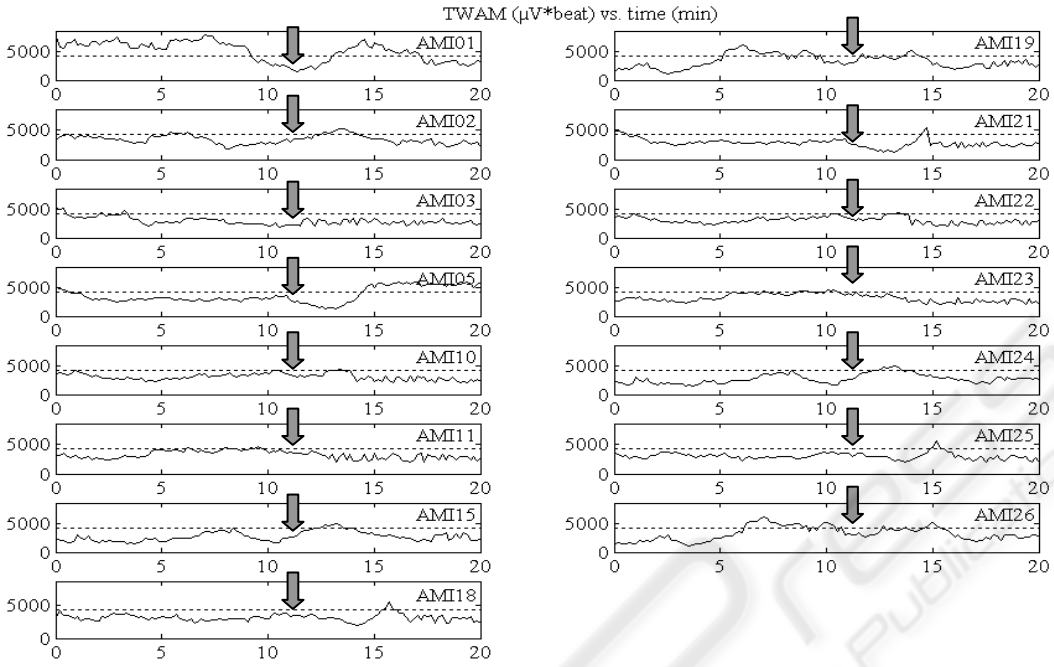


Figure 2: TWAM waves from our TWA+ patients. All them would not be recognised as TWA+ if a single 128 beat series about the eleventh minute (arrows) was used, since TWAM is under threshold (dot line) about this time.

Table 3: TWA+ patients of AMI-group identified by our AMF method applied to the entire 20-minute ECG recording with 128 beats series extracted every 10 s (ECG 20 overlap), and to a single 128-beat series taken in proximity of minutes 0 ($t_0$), 5 ($t_5$), 10 ($t_{10}$), 15 ($t_{15}$), and 20 ($t_{20}$). TWAM: TWA magnitude; TWA+: TWA positive patient. Student's t-test is used to compare the mean TWAM value over each considered 128-beat series ($t_0$, $t_5$, ..,$t_{20}$) with mean TWAM over ECG 20.

| AMI-group | ECG 20 overlap | $t_0$ | $t_5$ | $t_{10}$ | $t_{15}$ | $t_{20}$ |
|---|---|---|---|---|---|---|
| TWA+ individual patients | AMI01 | AMI01 | AMI1 | - | AMI01 | - |
| | AMI02 | - | - | - | - | - |
| | AMI03 | AMI03 | - | - | - | - |
| | AMI05 | AMI05 | - | - | AMI05 | AMI05 |
| | AMI10 | - | - | - | - | - |
| | AMI11 | - | - | - | - | - |
| | AMI15 | - | - | - | - | - |
| | AMI18 | - | - | - | - | - |
| | AMI19 | - | - | - | - | - |
| | AMI21 | AMI21 | - | - | - | - |
| | AMI22 | - | - | - | - | - |
| | AMI23 | - | - | AMI23 | - | - |
| | AMI24 | - | - | - | - | - |
| | AMI25 | - | - | - | AMI25 | - |
| | AMI26 | - | - | AMI26 | AMI26 | - |
| Total TWA+ | 15 (43%) | 4 (11%) | 1 (3%) | 2 (6%) | 4 (11%) | 1 (3%) |
| TWAM (beat*μV) | 3982±1386 | 2708±1324 | 2352±974 | 2330±1030 | 2494±1298 | 2397±1178 |
| t-test | | P<0.001 | P<0.001 | P<0.001 | P<0.001 | P<0.001 |

We identified in 3-lead (X, Y, Z) 20-minute digital ECG recordings a time frame that achieves a good compromise between reliability of TWA identification and computational efforts. Moreover, a 20-minute time frame is short enough to be possibly obtained in controlled conditions, so that noise and heart-rate variability due to emotional or physical factors may not interfere significantly.

The definition of a threshold for TWAM is a critical issue. The value identified here as mean TWAM+2SD over our H-group yielded no presence of TWA in this population, since the under-threshold level of TWA is considered as background noise. Our finding of no TWA in H-subjects is consistent with what is commonly recognised in clinics. Nevertheless, further studies on populations of clinical relevance are desirable to define an optimal normality threshold.

Several techniques have been proposed in the literature for TWA detection (Adam et al., 1984; Nearing et al., 1991; Burattini et al., 1999; Burattini et al., 2006). Among these, the spectral method, pioneered by Adam et al. (1984), is the most widely used in clinics. However, being TWA a transient (i.e. non-stationary) phenomenon (Kusmirek and Gold, 2007; Cox et al., 2007; Richter et al., 2005; and present study), a time-domain approach, as our AMF method, appears, from a theoretical point of view, more appropriate since it provides local (i.e. relative to the single beat) as well as global (i.e. relative to the entire ECG series under analysis) TWA parameterization. Moreover, it is able to discriminate between TWA phenomena sustained-in-time (minutes) but low-in-amplitude and short-in-time (few beats) but large-in-amplitude. Because these two different kinds of TWA could potentially have different clinical implications (statement to be confirmed by future clinical studies), it appears worthwhile to have a TWA detection method, which allows discrimination between them. Such a discrimination is not allowed by the spectral method, which works, by definition, under the hypothesis of stationary signal, and provides TWA measurements that are averaged over the entire ECG time series under analysis (128 beats). As a consequence, no local (at the beat level) parameterization is possible with the spectral method.

Two more TWA detection techniques proposed in the literature are the correlation method (Burattini et al., 1999) and the complex demodulation (Nearing et al., 1991), which operate in the time domain. Compared to the correlation method, our AMF improves TWA detection in the presence of baseline wanderings (Burattini et al., 2006). Complex demodulation is computationally very heavy and has never been used for practical purposes. In addition, compared to any other TWA detection algorithm, our AMF does not require pre-processing of the ECG tracing, because noise and ECG frequency components other than $f_{TWA}$, are simultaneously filtered out.

Our study suggests to analyse 20 minute ECG recordings by applying our AMF to 128 beat ECG time series selected every 10 seconds within a 20-minute time frame. As a consequence, the TWA global parameters (TWA duration, amplitude and magnitude) associated to a time instant are the result of an integration procedure over a 128 beats window, corresponding (see Methods), on average, to 119 s for the H-group, and 113 s for the AMI-group. This, of course, results in a significant overlap of data sets. A certain degree of overlap, however, is necessary. In fact TWA episodes could be divided into shorter ones during the windowing procedure for 128 ECG time series extraction, and this operation could prevent a correct TWA detection and quantification. In addition, to be eligible for TWA analysis, a 128 beat ECG is required to satisfy the heart-rate stability condition (eq. 1). The presence of local arrhythmic or noise conditions, including ventricular premature beats, artefacts, as well as false-positive and false-negative beat detections, may cause rejection of a 128 beat ECG. If no overlap among ECG time series is present, all information on TWA in the time frame belonging to the rejected ECG series is lost. Rather, if a certain degree of overlap is allowed, some information on TWA can be recovered from a close ECG time series not affected by the local noise factor. The time resolution recovering, consisting of the transition from the global (relative to the entire ECG series) domain to the local (relative to the single beat) domain, is possible only with time-domain TWA detection methods, through the availability local TWA amplitude measure ($A_{TWA}$).

Computational efforts limit the frequency of time series extraction from an ECG20. Results of the present study indicate that application of our AMF-based method to 128 beat series extracted every 10 s is a good compromise between reliability of non stationary, transient TWA identification and computational efforts. This kind of analysis, in fact, can be routinely performed in real time in a clinic or doctor's office using a standard personal computer.

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