Average T-wave Alternans Activity in Ambulatory ECGs

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Abstract

T-wave alternans (TWA) is considered as an index of susceptibility of sudden cardiac death (SCD). The utility of TWA testing during ambulatory monitoring is being increasingly studied. A common approach for ambulatory TWA testing is to quantify the maximum amplitude of TWA in an ECG record, which requires visual verification of the results to discard erroneous measurements due to noise or artifacts in the ECG. This work presents a fully-automated method to quantify the average TWA activity in ambulatory ECGs. Our results indicate that quantifying the average TWA activity instead of the maximum TWA amplitude allows the prediction of SCD in in patients with chronic heart failure (CHF).

1. Introduction

T-wave alternans (TWA) is a consistent beat-to-beat alternation in the morphology of the ST segment and/or the T wave, reflecting temporal and spatial heterogeneity of repolarization [1, 2]. In recent years, different works have studied the potentiality of performing TWA tests during ambulatory ECG monitoring [1]. For instance, the maximum amplitude of TWA has been quantified in 24-hour Holter recordings using the Modified Moving Average method MMAM [3]. The maximum amplitude, after visual verification, was compared to a cut point to decide whether such TWA amplitude should be considered normal (positive test) or abnormal (negative test). This binary TWA index based on maximum TWA amplitude has been found to be a strong predictor of arrhythmic events and cardiac mortality in different populations [1]. In the last years, quantitative analysis of TWA amplitude as a continuous variable has also been shown to indicate an increasing cardiac risk [4].

The MMAM measures the local TWA activity at each analysis point using the powerful noise-rejection principle of recursive averaging [3]. However, as only one TWA measurement is usually chosen to characterize an ambulatory record, it is essential that this measurement corresponds to real TWA and that it is not caused by artifacts in the signal. Therefore, the visual verification of TWA measurements after MMA processing becomes indispensable.

One possible way to circumvent this limitation is to extend the averaging approach to longer periods. Long-term averaging of ECG measurements allows the quantification of subtle phenomena such as heart rate turbulence [5], deceleration capacity [6] or baroreflex sensitivity [7]. The hypothesis of this study is that the application of long-term averaging to TWA quantification will produce reliable measurements of the average TWA activity over long periods, and that these measurements, being less sensitive to noise, will make it possible to perform TWA analysis for risk assessment in a fully-automated way.

We present in this work a fully-automated method to analyze TWA in ambulatory records, and propose a quantitative continuous index to predict the risk of sudden cardiac death (SCD) in a population of patients with chronic heart failure (CHF).

2. Study population

Our study population consists on patients with mild to moderate (II-III NYHA class) congestive heart failure enrolled into the prospective multicenter MUSIC study (Muerte Súbita en Insuficiencia Cardiaca, Sudden Death in Heart Failure) [8]. Twenty-four-hour ambulatory ECG recordings were performed using SpiderView recorders (ELA Medical, Sorin Group, Paris, France). XYZ orthogonal leads were recorded at 200 Hz sampling rate. The study protocol was approved by institutional investigation committees, and all patients signed informed consent.

Due to requirements for TWA calculation, only patients with sinus rhythm were included in the study. The clinical characteristics of studied patients as well as medication are summarized in Table 1, in which data are presented as mean ± standard deviation for continuous variables, and number and percentage for categorical variables. No medications were withdrawn during Holter monitoring.

Patients were followed up for a median of 48 months, with total mortality as a primary end point, and cardiac

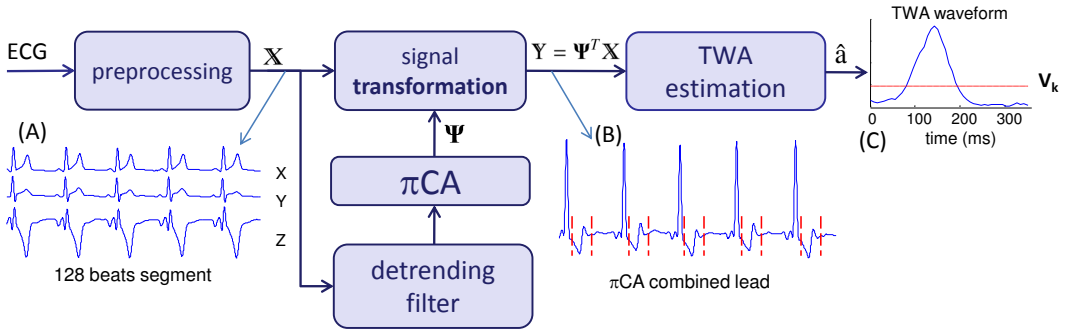

Figure 1. Block diagram of the TWA amplitude estimation method. An ECG segment selected for automatic analysis after low-pass filtering and baseline cancellation is labelled as (A). The new combined lead, computed with πCA is labelled as (B). Finally, the TWA waveform estimated with the Laplacian likelihood ratio method is shown with the label (C). V_k is then computed as the mean of the estimated waveform.

death (CD) and sudden cardiac death (SCD) as secondary end points. Definitions of CD and SCD by the MUSIC Study Endpoint Committee were reported in previous works [8]. During the follow-up period, there were 119 cardiac deaths (18.3% of the population) and 52 sudden cardiac deaths (8%).

3. Methods

Ambulatory records were preprocessed as follows: heart beats were detected and labeled as normal or abnormal by the ECG analysis software Aristotle [9], and a cubic-spline interpolation technique was used for baseline wander cancellation. Then, TWA analysis was performed automatically on every ECG recording. TWA analysis consisted of three steps: 1) selection of signal segments suitable for automatic analysis, 2) estimation of TWA amplitude in those segments, and 3) computation of indices which reflect the general TWA activity through the whole record. These steps are summarized below.

Each Holter ECG recording was segmented in blocks of 128 beats with a 50% overlap. An ECG segment was deemed suitable for automatic TWA analysis if 1) the difference between the maximum and the minimum instantaneous heart rate during the segment was $\leq$ 20 beats per minute (bpm), and 2) at least 80% of the beats in the segment were normal. A beat was considered normal if (a) it was labeled as a normal beat by the Aristotle software, (b) the difference between the RR interval of that beat and the previous RR interval was $\leq$ 150 ms, and (c) the difference between the baseline voltage measured at the PQ segment in that beat and the one measured in the preceding beat was $\leq 300\ \mu$V.

In all ECG segments suitable for analysis according to the previous criteria, the amplitude of TWA was estimated (denoted as V_k for the $k-$th segment) by using the following multilead scheme, which combines the technique of periodic component analysis (πCA) with the Laplacian Likelihood Ratio method (LLRM) [10] (see Fig.1). First, the three leads of the ECG segment were low-pass filtered at 15 Hz to eliminate high-frequency components that could affect the estimation of TWA amplitude. Then, the three orthogonal leads were linearly combined to obtain a new lead in which the visibility of TWA over noise was maximized. The coefficients of the optimal linear combination were computed by means of the πCA technique, which maximizes the desired periodicity in the combined lead. The optimal combination was computed for each segment, and depends on how the alternant components are distributed among the three ECG leads. As we have shown in a previous work [10], the use of πCA allows detection of TWA episodes embedded in noise which remain undetectable if leads are analyzed separately. Finally, TWA amplitude was measured in the new optimal lead. In each beat, an interval of 350 ms after the end of the QRS was selected (ST-T complex). The median TWA waveform, defined as the difference between the ST-T complexes of even and odd beats, was estimated by using the LLRM. In this way, an estimation of the median TWA waveform in the ECG segment was obtained. Finally, the TWA amplitude in the segment, denoted as V_k, was computed as the absolute mean value of the estimated TWA waveform.

After having measured the TWA amplitude in all the suitable segments of an ambulatory recording, two sets of indices were computed: average alternans indices (AAI_x)

and maximum alternan indices (MAI_X).

Average Alternans Indices (AAI_X) were computed as the average of TWA amplitude values V_k measured in segments whose average heart rate (HR) is between X-10 bpm and X bpm, with X= {70, 80, 90, 100, 110}. Thus, AAI_{90} reflects the average TWA activity present in the 24-hour period at heart rates between 80 and 90 bpm. Maximum Alternans Indices (MAI), were computed as the maximum of the TWA amplitude values V_k measured in segments whose average heart rate is between X-10 bpm and X bpm, with X= {70, 80, 90, 100, 110}. Thus, MAI_{90} corresponds to the maximum TWA amplitude measured at heart rates between 80 and 90 bpm in the 24-hour period.

Two-tailed Mann-Whitney test was used for comparison of quantitative variables and Cox proportional hazards analyses were performed to determine the prognostic value of TWA indices in predicting the end points. A p value < 0.05 was considered statistically significant. Data were analyzed using SPSS software (version 15.0; SPSS Inc. Chicago, IL).

4. Results

The mean values of AAI_x are shown un Table 2. Note that not all ECGs presented a HR spanning from 60 to 110 bpm; also, in some recordings, all segments within a certain HR range were discarded for TWA analysis (according to the suitability criteria described in the Methods section). Therefore, not every AAI_x could be computed for every patient. The percentages of indeterminate values for the entire population were 18.1% for AAI_{70}, 9.1% for AAI_{80}, 13.4% for AAI_{90}, 26.1% for AAI_{100}, and 47.2% for AAI_{110}.

As it can be observed, the mean values of AAI_x increased with HR, and there were significant differences between indices from all adjacent HR intervals (see Table 2).

Table 2 also shows the mean values of the maximum alternans indices MAI_x. Although a slight increase in the average MAI_x can be noticed when HR increases, differences between adjacent HR intervals are only significant between the intervals 60-70 bpm and 70-80 bpm.

Univariate Cox analysis was performed for all AAI_x and MAI_x, taken as continuous variables. The average alternans index AAI_{90} was found to be associated with SCD, but not with all-cause mortality or non-cardiac mortality (Table 3). The MAI_x indices were not significantly associated to any of the end points according to Cox analysis.

Table 1. Characteristics of patients. NYHA = New York Heart Association; LVEF = Left ventricular ejection fraction; ARB = Angiotensin receptor blocker; ACE = Angiotensin-converting enzyme.

Age (yrs)	63 ± 12
Sex (men)	462 (71.1%)
NYHA class III	117 (18.0%)
LVEF = 35	356 (54.8%)
Diabetes	245 (37.7%)
Beta-blockers	454 (69.8%)
Amiodarone	59 (9.1%)
ARB or ACE inhibitors	573 (88.2%)
Average HR (bpm)	75 ± 12
Maximum HR (bpm)	122 ± 26

Table 2. Average alternans indices (AAI_X) and maximum alternans indices (MAI_X) computed in intervals with heart rate in the range of X-10 to X bpm. Values are given as mean ± standard deviation. Significant differences between each range of heart rate and the previous one are indicated by *(p<0.05) and **(p<0.001).

X (range of HR)	% rec	AAI_X (μV)	MAI_X (μV)
70 (60-70 bpm)	81.9	2.8±1.9	16.1±13.1
80 (70-80 bpm)	90.9	3.3±2.3**	17.2±10.6**
90 (80-90 bpm)	86.6	3.9±2.4**	17.5±12.1
100 (90-100 bpm)	73.9	5.0±3.1**	19.7±12.1
110 (100-110 bpm)	52.8	6.1±5.5*	20.6±22.6

Table 3. Association of AAI_{90} as a continuous variable with mortality. 95% confidence interval reported in brackets.

End point	Hazard ratio	p
all cause death	1.04 (0.99 − 1.10)	0.150
CD	1.05 (1.00 − 1.11)	0.051
SCD	1.07 (1.01 − 1.15)	**0.041**

5. Discussion and conclusions

In the last years, the prognostic value of quantitative TWA has been increasingly studied [4]. In this work, we have found that the quantitative index AAI_{90} is a significant predictor of SCD in a population of patients with mild-to-moderate congestive heart failure. When measured at moderate heart rates, higher magnitudes of TWA are known to predict a greater risk of serious outcomes. For TWA to predict cardiovascular events, maximum HR limits ranging from 100 to 125 bpm are usually considered. In this study, we found that the average TWA activity was associated to SCD when measured at lower rates, between 80 and 90 bpm (AAI_{90}). A possible explanation for this difference is that heart failure might be lowering the HR threshold to elicit TWA [11]. It is also possible that the long-term averaging strategy used to compute the AAI indices is allowing to measure subtle TWA which would not be measurable when analyzed in a short time.

On the contrary, maximum TWA amplitudes in the whole 24-hour recording, measured by MAI_x indices, did not predict cardiac risk. The maximum amplitudes obtained were indeed comparable to maximum TWA amplitudes reported in the literature (between 30 and 60 μV), but no significant association was found between the MAI_x and risk of SCD. This was not unexpected, since the maximum TWA amplitude on a long-term recording is very sensitive to noise and artifacts, and thus can lead to inaccurate results if the signal is not visually or automatically checked for validity [12].

Recently, the maximum TWA amplitude has been measured in several studies with the MMAM in ambulatory ECG, either in the whole record or in segments below a maximum HR [1]. In those studies, the maximum TWA amplitude was obtained after visual inspection of the signals to discard erroneous TWA measurements caused by noise and artifacts. This study suggests that quantifying the average TWA activity (AAI) instead of the maximum amplitude (MAI) eliminates the necessity of visually discarding erroneous measurements, and allows the prediction of SCD in in patients with CHF. However, additional prospective evaluation is still required and it would be premature to extend these observations to other groups.

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