Average T-wave alternans activity in ambulatory ECG records predicts sudden cardiac death in patients with chronic heart failure

Violeta Monasterio, PhD,*† Pablo Laguna, PhD,*† Iwona Cygankiewicz, MD, PhD,‡§ Rafael Vázquez, MD, PhD,¶ Antoni Bayés-Genís, MD, PhD,‖ Antoni Bayés de Luna, MD, PhD,§ Juan Pablo Martínez, PhD*†

*From the *CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Zaragoza, Aragon, Spain; †Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Aragon, Spain; ‡Department of Electrocardiology, Medical University of Lodz, Lodz, Poland; §Institut Català de Ciències Cardiovasculars, Barcelona, Catalonia, Spain; ¶Servicio de Cardiología, Hospital Universitario Puerta del Mar, Cádiz, Andalusia, Spain; ‖Cardiology Service, Hospital Universitari Germans Trias i Pujol, Badalona, Spain.*

BACKGROUND T-wave alternans (TWA) is a well-documented noninvasive electrocardiographic (ECG) method useful for identifying patients at risk for sudden cardiac death (SCD).

OBJECTIVE The purpose of this study was to evaluate whether the long-term average TWA activity on Holter monitoring provides prognostic information in patients with chronic heart failure.

METHODS Twenty-four-hour Holter ECGs from 650 ambulatory patients with mild-to-moderate chronic heart failure were analyzed in the study. Average TWA activity was measured by using a fully automated multilead technique, and 2 indices were proposed to quantify TWA: an index quantifying the average TWA activity in the whole recording (IAA), which was used to define a positive/negative TWA test, and an index quantifying the average TWA activity at heart rates between 80 and 90 beats/min (IAA_{90}).

RESULTS Patients were divided into TWA positive (TWA+) and TWA negative (TWA–) groups by setting a cut point of 3.7 μV for IAA, corresponding to the 75th percentile of the distribution of IAA in the population. After a median follow-up of 48 months, the survival rate was significantly higher in the TWA– group for cardiac death and SCD ($p = .017$ and $p = .001$, respectively). Multivariate Cox proportional hazards analysis revealed that both TWA+ and IAA_{90} were associated with SCD with hazard rates of 2.29 ($p = .004$) and 1.07 per μV ($p = .046$), respectively.

CONCLUSION The average TWA activity measured automatically from Holter ECGs predicted SCD in patients with mild-to-moderate chronic heart failure.

KEYWORDS T-wave alternans; Multilead technique; Holter ECGs; Chronic heart failure; Sudden cardiac death

ABBREVIATIONS **CD** = cardiac death; **CI** = confidence interval; **CHF** = chronic heart failure; **HR** = heart rate; **IAA** = index of average alternans; **IMA** = index of maximum alternans; **NYHA** = New York Heart Association; **SCD** = sudden cardiac death; **TWA** = T-wave alternans

(Heart Rhythm 2012;9:383–389)

Introduction

Sudden cardiac death (SCD) remains an important cause of mortality in patients with mild-to-moderate heart failure (New York Heart Association [NYHA] classes II and III). Although previous studies have shown the benefit of implantable cardioverter-defibrillators in this type of population,[1] the cost-effectiveness of the therapy is low, as only a minority of patients with implantable cardioverter-defibrillators benefitted from this therapy during the follow-up period.[2] Therefore, finding effective techniques for risk stratification remains a clinical problem.

T-wave alternans (TWA) is a beat-to-beat alternation in the morphology of the ST segment and the T wave which reflects the temporal and spatial heterogeneity of repolarization.[3] The utility of TWA testing during ambulatory monitoring has been subject to intense investigation in recent years.[4,5] In ambulatory recordings, the maximum amplitude of TWA has been semiautomatically quantified by using the modified moving average method[4] and then compared with a cut point to decide whether such TWA level should be considered normal or abnormal. This binary TWA index is a strong predictor of arrhythmic events and cardiac mortality in different populations.[5] In the past years, the quantitative analysis of TWA amplitude as a continuous

This work was supported by CIBER de Bioingeniería, Biomateriales y Nanomedicina through Instituto de Salud Carlos III and Fondo Europeo de Desarrollo Regional and by Projects TEC2010-21703-C03-02 of Ministerio de Ciencia e Innovación and GTC T-30 from DGA (Spain). **Address reprint requests and correspondence:** Dr Violeta Monasterio, Department of Electronic Engineering and Communications, María de Luna, 1. 50018 Zaragoza, Spain. E-mail address: violeta@unizar.es.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.10.027

Table 1 Characteristics of patients

	Overall population (n = 650)	TWA− (n = 493)	TWA+ (n = 157)	*p* value
Age (y)	63 ± 12	63 ± 11	64 ± 13	.091
Gender (men)	462 (71.1%)	350 (71.0%)	112 (71.3%)	.999
NYHA class III	117 (18.0%)	87 (17.6%)	30 (19.1%)	.721
LVEF ≤ 35%	356 (54.8%)	262 (53.1%)	94 (59.9%)	.142
Diabetes	245 (37.7%)	190 (38.5%)	55 (35.0%)	.451
Beta-blockers	454 (69.8%)	350 (71.0%)	104 (66.2%)	.273
Amiodarone	59 (9.1%)	43 (8.7%)	16 (10.2%)	.632
ARB or ACE inhibitors	573 (88.2%)	441 (89.4%)	132 (84.1%)	.088
Average heart rate (beats/min)	75 ± 12	76 ± 12	75 ± 12	.581
Maximum heart rate (beats/min)	122 ± 26	123 ± 27	119 ± 25	.100
Heart rate range (beats/min)	65 ± 28	63 ± 27	66 ± 28	.204
QRS > 120 ms	294 (45.2%)	206 (41.8%)	88 (56.1%)	**.002**
Nonsustained ventricular tachycardia and > 240 ventricular premature beats in 24 h	164 (25.2%)	102 (20.7%)	62 (39.5%)	**<.001**

Data are presented as absolute frequencies and percentages and as mean ± standard deviation.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TWA+ = T-wave alternans positive group; TWA− = T-wave alternans negative group; Significant differences between TWA+ and TWA− are indicated in bold.

variable has also been shown to indicate an increasing cardiac risk.[6,7]

In this work, we present a fully automated method to analyze TWA in ambulatory records and demonstrate that the average TWA activity in a 24-hour period is an independent predictor of SCD and cardiac death (CD) in patients with chronic heart failure (CHF). Following the approaches of existing studies,[6–8] we propose 2 risk indices: a binary index which defines a positive/negative TWA test, and a quantitative continuous index which reflects an increasing degree of cardiac risk.

Methods

Study population

Consecutive patients with symptomatic CHF corresponding to NYHA classes II and III were enrolled in the MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, a prospective, multicenter study designed to assess risk predictors for cardiovascular mortality in ambulatory patients with CHF.[9] The study protocol was approved by institutional investigation committees, and all patients signed informed consent. The Holter recordings of 650 patients with sinus rhythm were available for the present study.

The collection of clinical data for this population was reported in previous studies.[9,10] The clinical characteristics of studied patients and medications are listed in Table 1. No medications were withdrawn during Holter monitoring.

Follow-up and end points

Patients were followed up every 6 months for a median of 48 months, with total mortality as a primary end point and CD and SCD as secondary end points. Information about end points was obtained from medical records, patients' physicians, and family members. *Cardiac death* was defined as death from cardiac causes, but excluding such vascular causes as pulmonary embolism, aortic aneurysm dissection/aneurysm, or stroke. *Sudden cardiac death* was defined as (1) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than cardiac failure was obvious, (2) an unwitnessed death (<24 hours) in the absence of preexisting progressive circulatory failure or other causes of death, or (3) death during attempted resuscitation. End points were reviewed and classified by the MUSIC Study Endpoint Committee. Table 2 summarizes the number of deaths in the study population during the median 48-month period.

Measurement of TWA

Twenty-four-hour ambulatory electrocardiography (ECG) recordings (XYZ orthogonal leads, 200-Hz sampling rate) were performed by using SpiderView recorders (ELA Med-

Table 2 Events during follow-up

	Overall population (n = 650)	TWA− (n = 493)	TWA+ (n = 157)	*p* value
Total mortality	146 (22.5%)	99 (20.1%)	47 (30.0%)	**.012**
CD	119 (18.3%)	81 (16.4%)	38 (24.2%)	**.033**
SCD	52 (8.0%)	30 (6.1%)	22 (14.0%)	**.003**

Data are expressed as absolute frequencies and percentages.

CD = cardiac death; SCD = sudden cardiac death; TWA+ = T-wave alternans positive group; TWA− = T-wave alternans negative group. Significant differences between TWA+ and TWA- are indicated in bold.

ical, Sorin Group, Paris, France). Heart beats were detected and labeled with the Aristotle ECG analysis software.[11] Baseline wander was canceled with cubic spline technique.[12] Automatic TWA analysis was performed on every ECG recording in 3 steps: (1) selection of signal segments that were suitable for automatic analysis, (2) estimation of the TWA amplitude in those segments, and (3) computation of indices reflecting the general TWA activity through the record.

Selection of segments

ECGs were analyzed in segments of 128 beats with a 50% overlap between adjacent segments. Each segment was included in automatic TWA analysis if (1) the difference between the maximum and the minimum instantaneous heart rate (HR) during the segment was ≤20 beats/min and (2) at least 80% of the beats fulfilled the following conditions: (a) it was labeled as normal sinus beat, (b) the difference between the RR interval of that beat and the previous RR interval was ≤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 ≤300 μV.

Estimation of TWA amplitude

If an ECG segment (denoted as the kth segment) was suitable for analysis, the TWA amplitude in that segment (denoted as V_k) was computed with a multilead scheme that combines a technique called periodic component analysis with the Laplacian likelihood ratio method for TWA analysis.[13]

First, the ECG segment was low-pass filtered at 15 Hz to eliminate noise that could affect the estimation of TWA amplitudes. Figure 1A shows an example of an ECG signal with TWA after baseline cancellation and low-pass filtering.

Then, the 3 leads of the ECG segment were linearly combined to obtain a new lead in which the visibility of TWA over noise was maximized (Figure 1B). This combination can be expressed as follows:

$$\text{combined lead} = a \text{ lead } X + b \text{ lead } Y + c \text{ lead } Z$$

where coefficients a, b, and $c \in \mathrm{R}$ were specifically computed for each segment with periodic component analysis and depended on how the periodic components of the signal were distributed among the ECG leads. Using periodic component analysis for TWA analysis reveals TWA episodes embedded in noise that can be undetectable if leads are analyzed separately.[14]

Finally, TWA amplitude was measured in the new combined lead as follows. In each beat, an interval of 350 ms after the end of the QRS was selected (ST–T complex, marked with dashed lines in Figure 1B). The median difference between ST–T complexes of even and odd beats was computed with the Laplacian likelihood ratio method,[13] obtaining an estimation of the median TWA waveform in the segment (Figure 1C). The amplitude of TWA in the segment (V_k) was finally measured as the absolute value of the mean of the estimated TWA waveform (Figure 1C).

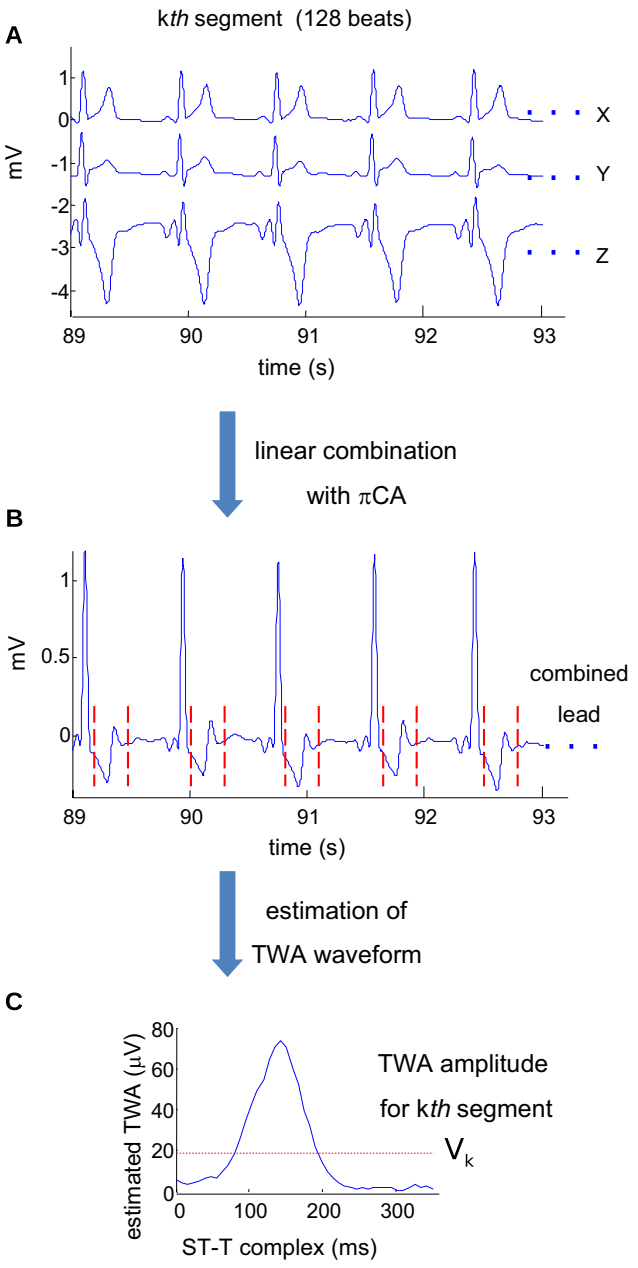

Figure 1 Example of T-wave alternans (TWA) amplitude estimation. **A:** Electrocardiographic segment selected for automatic analysis after low-pass filtering and baseline cancellation. **B:** Combined lead, computed with periodic component analysis (πCA). **C:** Median TWA waveform in the segment, estimated with the Laplacian likelihood ratio method, and absolute TWA amplitude in the segment V_k = 18.5 μV.

Computation of TWA indices

Two sets of indices were computed. The first set reflected the average amplitude of TWA, and the second set quantified the maximum TWA amplitude in the segments under study.

The first set consisted of the index of average alternans (IAA) and the heart rate–restricted indices of average alternans (IAA_X). IAA was computed as the average of all V_k in the ECG and reflected the average TWA activity during the 24-hour period. Note that, for instance, a 24-hour ECG that

presented TWA only during 5% of the time with an amplitude of 60 μV would have an IAA = 3 μV, which means that the IAA cannot be interpreted as a direct measurement of the TWA amplitude at any single point. IAA_X were computed as the average of only those V_k measured in segments with average HR ranging from X − 10 to X beats/min, with X = {70, 80, 90, 100, 110}. For instance, IAA_{90} would reflect the average TWA activity at HR between 80 and 90 beats/min in 24 hours.

The second set consisted of the index of maximum alternans (IMA) and the restricted indices of maximum alternans (IMA_X). IMA was computed as the maximum of all V_k in the ECG. IMA_X were computed as the maximum of the V_k measured in segments with average HR ranging from X − 10 to X beats/min, with X = {70, 80, 90, 100, 110}. For instance, IMA_{90} would represent the maximum TWA amplitude at HR between 80 and 90 beats/min in 24 hours.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Two-tailed Mann–Whitney and Fisher exact tests were used for univariate comparison of quantitative and categorical data, respectively. Survival probability was estimated by using Kaplan–Meier methods with a comparison of cumulative events by using log-rank tests. The prognostic value of TWA indices in predicting the end points was determined with univariate and multivariate Cox proportional hazards analyses. Cox regression models were built considering a significance of ≤.05 as the criterion for entry into a model. Correlation between quantitative TWA indices and HR was evaluated with Spearman's correlation coefficient. A p value of <.05 was considered statistically significant. Data were analyzed by using SPSS software (version 15.0; SPSS Inc, Chicago, IL).

Results

The mean value of IAA in the study population was 3.3 ± 2.1 μV, and the 25th, 50th, and 75th percentiles were 2.4, 2.9, and 3.7 μV, respectively (Figure 2). The IAA 75th percentile varied by <1 μV for different subgroups such as NYHA class II vs class III patients (3.64 μV vs 3.76 μV, respectively) and patients with vs without SCD (4.38 μV vs 3.61 μV, respectively). A weak negative correlation was found between IAA and the average HR in the Holter recording (ρ = −.083; p = .035). However, the correlation between IAA and the average HR of those ECG segments included in automatic analysis was not significant (ρ = .054; p = .169).

The mean values of IAA_X were IAA_{70} = 2.8 ± 1.9 μV, IAA_{80} = 3.3 ± 2.3 μV, IAA_{90} = 3.9 ± 2.4 μV, IAA_{100} = 5.0 ± 3.1 μV, and IAA_{110} = 6.1 ± 5.5 μV. The mean values of IAA_X increased with local HR, and there were significant differences between indices from all adjacent HR intervals (Figure 2). Not all ECGs presented an HR span from 60 to 110 beats/min; also, all segments within a certain HR range were discarded for TWA analysis in some recordings (according to the inclusion rules described in the "Methods" section). Therefore, not every IAA_X could be computed for every patient. The percentages of indeterminate values for the entire population are shown in Figure 2. The correlation between IAA_{90} and the average HR in the Holter recording was ρ = −.474 (p <.001).

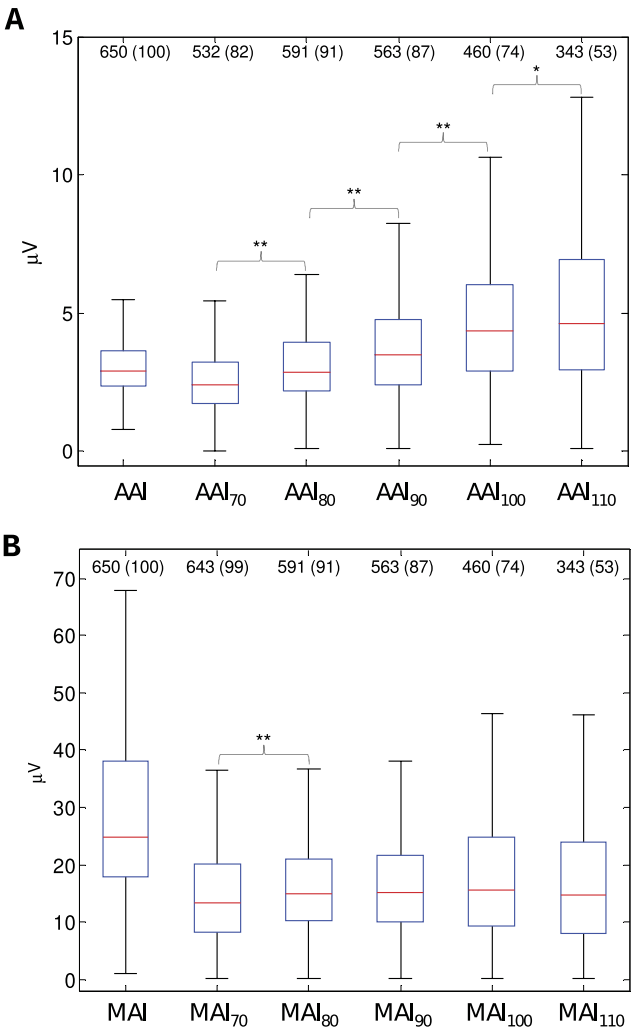

Figure 2 **A:** Boxplot of the indices of average alternans (IAA) computed in 24 hours and in intervals with heart rate in the range of X − 10 to X beats/min (IAA_X). **B:** Boxplot of the indices of maximum alternans (IMA) computed in 24 hours and in intervals with heart rate in the range of X − 10 to X beats/min (IMA_X). The number (percentage) of records in which indices could be computed is indicated above the boxes. Significant differences between the medians of adjacent IAA_X and IMA_X boxes are indicated by * (p <.05) and ** (p <.001).

Patients were divided into TWA positive (TWA+) and negative (TWA–) groups by setting a cut point of 3.7 μV for IAA, corresponding to the 75th percentile of the distribution of IAA in the population. Of the 650 patients studied, 493 (75.8%) were included in the TWA– group (IAA ≤ 3.7 μV) and 157 (24.2%) in the TWA+ group (IAA > 3.7 μV).

Upon comparison of clinical variables between TWA+ and TWA– groups (Table 1), significant differences were found for nonsustained ventricular tachycardia and frequent ventricular premature beats as well as for wide QRS. Pa-

Table 3 Association of T-wave alternans indices with mortality

	Univariate		Multivariate 1*		Multivariate 2†	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Total mortality						
IAA > 3.7 μV	**1.62** (1.15–2.29)	**.006**	**1.54** (1.09–2.19)	**.015**	**1.48** (1.04–2.10)	**.030**
IAA_{90}	1.04 (0.99–1.10)	.150	1.05 (0.98–1.11)	.140	1.04 (0.98–1.11)	.172
CD						
IAA > 3.7 μV	**1.60** (1.09–2.35)	**.017**	**1.54** (1.04–2.26)	**.030**	1.44 (0.97–2.13)	.068
IAA_{90}	1.05 (1.00–1.11)	.051	**1.06** (1.00–1.13)	**.038**	1.06 (1.00–1.13)	.051
SCD						
IAA > 3.7 μV	**2.48** (1.43–4.30)	**.001**	**2.38** (1.37–4.14)	**.002**	**2.29** (1.31–4.00)	**.004**
IAA_{90}	**1.07** (1.01–1.15)	**.041**	**1.07** (1.00–1.15)	**.039**	**1.07** (1.00–1.15)	**.046**

CD = cardiac death; CI = confidence interval; IAA = index of average alternans; SCD = sudden cardiac death.
*Adjusted model includes age, gender, New York Heart Association class, left ventricular ejection fraction < 35%, and diabetes.
†Adjusted model includes covariables in model 1 plus use of beta-blockers, amiodarone, and angiotensin receptor blocker or angiotensin-converting enzyme inhibitors. Statistically significant values are marked in bold.

tients with wide QRS (>120 ms) were more likely to have a TWA+ outcome than patients with narrow QRS (≤120 ms) (29.9% vs 19.4%; $p = .002$). However, IAA was not significantly different in wide vs narrow QRS patients: 3.44 ± 1.45 μV vs 3.16 ± 2.44 μV ($p = .085$).

Survival rate was significantly higher in the TWA– group for primary and secondary end points (Table 2). Univariate Cox analysis revealed that a TWA+ outcome was associated with all-cause mortality, CD, and SCD (Table 3). No association was found between a TWA+ outcome and noncardiac mortality. Multivariate Cox proportional hazards models were constructed by adjusting for (1) age, gender, NYHA class, left ventricular ejection fraction < 35%, and diabetes and (2) use of beta-blockers, amiodarone, and angiotensin-converting enzyme or angiotensin receptor blocker inhibitors in addition to covariables in model 1. For model 1, a TWA+ outcome was the variable most significantly associated with SCD risk, with a hazard ratio of 2.38 (95% confidence interval [CI] 1.37–4.14; $p = .002$), similar to left ventricular ejection fraction < 35% (hazard ratio 2.55; 95% CI 1.35–4.80; $p = .004$). For model 2, a TWA+ outcome was the covariable with the second highest hazard ratio (2.29) after left ventricular ejection fraction < 35% (hazard ratio 2.65; 95% CI 1.39–5.03; $p = .003$). Figure 3 shows the event-free curves for CD and SCD. In patients with maximum HR < 90 beats/min (n = 51), a TWA+ outcome was more predictive of SCD than in the whole population, with a univariate hazard ratio of 6.06 (95% CI 1.10–33.25; $p = .038$).

Univariate Cox analysis was performed for all IAA_X, and only IAA_{90} was found to be associated with SCD. Multivariate analysis confirmed this association (Table 3). IAA_{90} was not associated with all-cause mortality or noncardiac mortality.

The mean value of IMA in the study population was 31.4 ± 25.3 μV, and the 25th, 50th, and 75th percentiles were 17.9, 24.7, and 38.0 μV, respectively (Figure 2). No association with CD or SCD risk was found for IMA as a continuous variable or as a categorical variable after dichotomization with the 75th percentile. The mean values of IMA_X were IMA_{70} = 16.1 ± 13.1 μV, IMA_{80} = 17.2 ± 10.6 μV, IMA_{90} = 17.5 ± 12.1 μV, IMA_{100} = 19.7 ± 12.1 μV, and IMA_{110} = 20.6 ± 22.6 μV. IMA_X were not significantly associated with CD or SCD risk according to Cox univariate and multivariate analyses.

Discussion

This study demonstrates that the quantification of the average TWA activity over long periods is a strong, independent predictor of SCD in patients with CHF. Two indices quantifying the TWA activity in a 24-hour period—IAA and IAA_{90}—independently predicted CD and SCD but did not predict noncardiac mortality. These findings support the hypothesis that elevated TWA activity reflects abnormal cardiac function predisposing to CD.

The results of recent studies involving different types of TWA analysis in similar populations have led to divergent conclusions. In the Sudden Cardiac Death in Heart Failure Trial (SCD-Heft),[15] TWA measured by using the spectral method during submaximal treadmill exercise did not predict arrhythmic events or mortality in patients with symptomatic heart failure and left ventricle systolic dysfunction. On the other hand, results in the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study[16] (EPHESUS) (involving post–myocardial infarction patients with left ventricle dysfunction) and in Sakaki et al [17] (involving patients with left ventricle dysfunction) showed that maximal TWA measured in ambulatory records by using the modified moving average method with posterior visual inspection predicted SCD and CD, respectively. In our study, the average TWA activity in 24 hours (IAA) was the covariable most strongly associated with the risk of SCD.

Only a weak correlation was found between IAA and the patient's HR, which disappeared when the patient's average HR was recomputed only with those segments included in automatic TWA analysis. This indicates that IAA not merely is a surrogate measure of the patient's HR but also

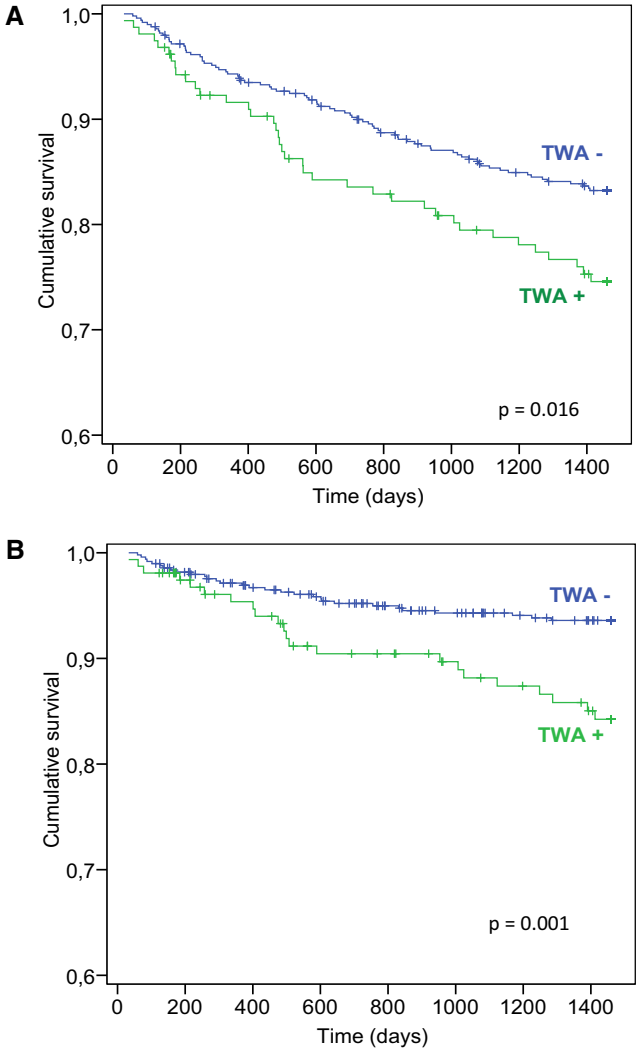

Figure 3 Event-free curves for cardiac death **(A)** and sudden cardiac death **(B)**.

reflects the influence of HR-independent factors in TWA. Therefore, IAA may provide a measure of the extent of cardiac vulnerability, since a higher influence of HR-independent factors in TWA amplitude reflects a higher degree of cardiac electrical instability.[18]

This finding does not contradict the well-described fact that, for a particular patient, instantaneous TWA amplitudes rise with HR (as reflected by IAA_X indices in Figure 2). Let us illustrate it with an example. The first patient enrolled in the study with SCD had an average HR = 76 beats/min, IAA = 3.80 μV, IAA_{70} = 1.68 μV, IAA_{80} = 3.16 μV, IAA_{90} = 4.68 μV, and IAA_{100} = 5.01 μV. On the other hand, the first patient who survived the follow-up period had an average HR = 93 beats/min, IAA = 2.22 μV, IAA_{70} = 1.12 μV, IAA_{80} = 1.57 μV, IAA_{90} = 1.83 μV, and IAA_{100} = 2.38 μV. In both cases, there was an increment of alternans with local HR (increasing IAA_X values), without the correlation between IAA and the average HR being necessarily positive.

The prognostic value of quantitative TWA measurements is increasingly being studied.[6–8] In this study, an index of quantitative TWA (IAA_{90}) independently predicted SCD. Higher magnitudes of TWA are known to predict a greater risk of serious outcomes when measured at moderate heart rates.[3] For TWA to predict cardiovascular events, maximum HR limits ranging from 100 to 125 beats/min are usually considered.[18] In this study, the average TWA activity was associated with SCD when measured at lower rates, between 80 and 90 beats/min (IAA_{90}). A possible explanation for this difference is that heart failure lowers the HR threshold to elicit TWA.[19] This finding was consistent with results by Tanno et al,[20] who demonstrated that higher TWA at HR $\leq$ 90 beats/min were associated with an increasing incidence of cardiac events.

Unsupervised maximum TWA amplitudes (IMA and IMA_X) did not predict cardiac risk. Although the values obtained for IMA were comparable to maximum TWA amplitudes reported in the literature (between 30 and 60 μV), no significant association was found between IMA and the risk of SCD or CD. This was not unexpected, since measuring local TWA amplitudes without testing for its significance, either visually or automatically, can lead to inaccurate results caused by noise and artifacts.[21] In recent studies with ambulatory ECGs,[16,17,22,23] the maximum TWA amplitude in a record was measured with the modified moving average method and then was visually verified.

We found that quantifying the average TWA activity (IAA) instead of the maximum amplitude (IMA) eliminates the necessity of visually discarding erroneous measurements and allows the prediction of CD and SCD in the study population. Long-term averaging of cardiac measurements has been applied to quantify subtle phenomena such as HR turbulence,[24] deceleration capacity,[25] or baroreflex sensitivity.[26] In this study, we applied long-term averaging to produce a reliable and noise-insensitive characterization of TWA in ambulatory recordings. To our best knowledge, the method presented here is the first one that allows a multilead, fully automated computation of TWA markers of cardiac risk in ambulatory ECGs.

Several limitations of this work need to be acknowledged. First, only patients with sinus rhythm were included in the study. Also, although results indicate that the average TWA activity over a 24-hour period provides important prognostic information in patients with CHF, it would be premature to extend our observations to other groups. The use of a 75th percentile cut point for TWA measures is a common starting point when a technique is first tested on a population,[27,28] but additional prospective evaluation is still required, particularly on the applicability of the cut point derived in this study.

Conclusion

Fully automated analysis of TWA in ambulatory ECGs can be a robust tool for risk stratification. The average TWA activity over a 24-hour period provides important prognostic information in patients with mild-to-moderate CHF. Two

novel indices—IAA and IAA_{90}—were proposed to quantify the average TWA activity and were found to be strong independent predictors of SCD.

References

1. Bardy GH, Lee KL, Mark DB, et al; Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
2. Mark DB, Nelson CL, Anstrom KJ, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation 2006;114:135–142.
3. Cutler DS, Rosenbaum MJ. Explaining the clinical manifestations of T wave alternans in patients at risk for sudden cardiac death. Heart Rhythm 2009;6: S22–S28.
4. Verrier RL, Nearing BD, Kwaku KF. Noninvasive sudden death risk stratification by ambulatory ECG-based T-wave alternans analysis: evidence and methodological guidelines. Ann Noninvasive Electrocardiol 2005;10:110–120.
5. Nieminen T, Verrier RL. Usefulness of T-wave alternans in sudden death risk stratification and guiding medical therapy. Ann Noninvasive Electrocardiol 2010;15:276–288.
6. Klingenheben T, Ptaszynski P, Hohnloser SH. Quantitative assessment of microvolt T-wave alternans in patients with congestive heart failure. J Cardiovasc Electrophysiol 2005;16:620–624.
7. Slawnych MP, Nieminen T, Kähönen M, et al. Post-exercise assessment of cardiac repolarization alternans in patients with coronary artery disease using the modified moving average method. J Am Coll Cardiol 2009;53:1130–1137.
8. Minkkinen M, Kähönen M, Viik J, et al. Enhanced predictive power of quantitative TWA during routine exercise testing in the Finnish Cardiovascular Study. J Cardiovasc Electrophysiol 2009;20:408–415.
9. Vázquez R, Bayés-Genís A, Cygankiewicz I, et al. The MUSIC risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. Eur Heart J 2009;30:1088–1096.
10. Cygankiewicz I, Zareba W, Vazquez R, et al. Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction >35%. Am J Cardiol 2009;103:1003–1010.
11. Moody GB, Mark RG. Development and evaluation of a 2-lead ECG analysis program. Comput Cardiol 1982;9:39–44.
12. Meyer CR, Keiser HN. Electrocardiogram baseline noise estimation and removal using cubic splines and state-space computation techniques. Comput Biomed Res 1977;10:459–470.
13. Martínez JP, Olmos S, Wagner G, Laguna P. Characterization of repolarization alternans during ischemia: time-course and spatial analysis. IEEE Trans Biomed Eng 2006;53:701–711.
14. Monasterio V, Clifford GD, Laguna P, Martínez JP. A multilead scheme based on periodic component analysis for T wave alternans analysis in the ECG. Ann Biomed Eng 2010;38:2532–2541.
15. Gold MR, Ip JH, Costantini O, et al. Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. Circulation 2008;11:2022–2028.
16. Stein PK, Sanghavi D, Domitrovich PP, Mackey RA, Deedwania P. Ambulatory ECG-based T-wave alternans predicts sudden cardiac death in high-risk post-MI patients with left ventricular dysfunction in the EPHESUS study. J Cardiovasc Electrophysiol 2008;19:1037–1042.
17. Sakaki K, Ikeda T, Miwa Y, et al. Time-domain T-wave alternans measured from Holter electrocardiograms predicts cardiac mortality in patients with left ventricular dysfunction: a prospective study. Heart Rhythm 2009;6:332–337.
18. Verrier R, Kumar K, Nearing BD. Basis for sudden cardiac death prediction by T-wave alternans from an integrative physiology perspective. Heart Rhythm 2009;6:416–422.
19. Wilson LD, Jeyaraj D, Wan X, et al. Heart failure enhances susceptibility to arrhythmogenic cardiac alternans. Heart Rhythm 2009;6:251–259.
20. Tanno K, Ryu S, Watanabe N, et al. Microvolt T-wave alternans as a predictor of ventricular tachyarrhythmias: a prospective study using atrial pacing. Circulation 2004;109:1854–1858.
21. Nemati S, Abdala O, Monasterio V, Yim-Yeh S, Malhotra A, Clifford GD. A non-parametric surrogate-based test of significance for T-wave alternans detection. IEEE Trans Biomed Eng 2010;58:1356–1364.
22. Maeda S, Nishizaki M, Yamawake N, et al. Ambulatory ECG-based T-wave alternans and heart rate turbulence predict high risk of arrhythmic events in patients with old myocardial infarction. Circ J 2009;73:2223–2228.
23. Stein PK, Sanghavi D, Sotoodehnia N, Siscovick DS, Gottdiener J. Association of Holter-based measures including T-wave alternans with risk of sudden cardiac death in the community-dwelling elderly: the Cardiovascular Health Study. J Electrocardiol 2010;43:251–259.
24. Martínez JP, Cygankiewicz I, Smith D, Bayés de Luna A, Laguna P, Sörnmo L. Detection performance and risk stratification using a model-based shape index characterizing heart rate turbulence. Ann Biomed Eng 2010;30:3173–3184.
25. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006; 367:1674–1681.
26. Di Rienzo M, Castiglioni P, Mancia G, Pedotti A, Parati G. Advancements in estimating baroreflex function: exploring different aspects of autnomic control of the heart through the sequence technique. IEEE Eng Med Biol Mag 2001; 20:25–32.
27. Verrier RL, Nearing BD, La Rovere MT, et al. Ambulatory electrocardiogram-based tracking of T wave alternans in postmyocardial infarction patients to assess risk of cardiac arrest or arrhythmic death. J Cardiovasc Electrophysiol 2003;14:705–711.
28. Nieminen T, Lehtimäki T, Viik J, et al. T-wave alternans predicts mortality in a population undergoing a clinically indicated exercise test. Eur Heart J 2007; 28:2332–2337.