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

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The average TWA activity automatically measured from Holter ECGs predicts SCD in patients with CHF.
Average T-wave alternans activity in ambulatory ECG records predicts sudden cardiac death in patients with chronic heart failure

Short title: Average T-wave alternans and sudden cardiac death

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Keywords
T-wave alternans; Multilead analysis; Holter ECG; Chronic heart failure; Sudden cardiac death

Abbreviations
ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
bpm = beats per minute
CD = cardiac death
CI = confidence interval
CHF = chronic heart failure
HR = heart rate
LV = left ventricle
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
SCD = sudden cardiac death
TWA = T-wave alternans
Introduction

Sudden cardiac death remains an important cause of mortality in patients with mild-to-moderate heart failure (New York Heart Association class II and III). Although previous studies have shown the benefit of ICD implantation in this type of population (1), the cost effectiveness of the therapy is low, as only a minority of patients with implanted ICD benefitted from this therapy during the follow-up period (2). Therefore, finding a more effective risk stratification remain a clinical problem.

T-wave alternans (TWA) is a beat-to-beat alternation in the morphology of the ST segment and the T wave, and reflects 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 semi-automatically quantified using the Modified Moving Average (MMA) method (4), and then compared to a cut point to decide if such TWA level should be considered normal or abnormal. This binary TWA index has been found to be a strong predictor of arrhythmic events and cardiac mortality in different populations (5). In the last years, quantitative analysis of TWA amplitude as a continuous 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 sudden cardiac death (SCD) and cardiac death (CD) in patients with chronic heart failure (CHF). Following the approaches of existing studies (6) (7) (8), we propose two risk indices: a binary index that defines a positive/negative TWA test, and a quantitative continuous index that reflects an increasing degree of cardiac risk.
Methods

Study population

Consecutive patients with symptomatic CHF corresponding to NYHA classes II to 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 as well as medication are listed in the first column of 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 cardiac death (CD) and sudden cardiac death (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: a) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than cardiac was obvious, b) an unwitnessed death (<24 hours) in the absence of preexisting progressive circulatory failure or other causes of death, or c) 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 ECG recordings (XYZ orthogonal leads, 200 Hz sampling rate) were performed using SpiderView recorders (ELA Medical, Sorin Group, Paris, France). Heart beats were detected and labeled with the Aristotle ECG analysis software (11). Baseline wander was cancelled using a cubic-splines technique(12). Automatic TWA analysis was then performed on every ECG recording in three steps: 1) selection of signal segments which were suitable for automatic analysis, 2) estimation of the amplitude of TWA in those segments, and 3) computation of indices that reflect the general alternans activity through the record. These steps are summarized below.

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 HR during the segment was ≤ 20 beats per minute (bpm), 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, a measurement of the TWA amplitude in that segment (denoted as $V_k$) was computed by using a multilead scheme that combines a technique called periodic component analysis (πCA) with the Laplacian Likelihood Ratio method for TWA analysis (13).

First, the ECG segment was low-pass filtered at 15 Hz to eliminate part of the 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 three orthogonal leads of the ECG segment were linearly combined to obtain a new lead in which the visibility of TWA over noise was maximized. This combination of leads was not predetermined, but was specifically computed for each segment with the πCA technique, and depended on how the periodic components of the signal were distributed among the ECG leads. The use of πCA for TWA analysis has been shown to reveal TWA episodes embedded in noise and artifacts that were undetectable if leads were analyzed separately (14). Figure 1b shows the combined lead obtained with πCA for the example ECG segment.

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 the ST-T complexes of even and odd beats was computed by using the LLR method (13). In this way, an estimation of the median TWA waveform in the ECG segment was obtained (Figure 1c). The amplitude of TWA in the segment, denoted as $V_k$, was finally measured as the absolute value of the mean of the estimated TWA waveform (Figure 1c).

**Computation of TWA indices:** two sets of indices were computed after measuring the amplitude of TWA in all the segments of an ECG record. The first set reflected the average amplitude of TWA within the segments under study, and the second set quantified the maximum TWA amplitude in the segments under study.

The first set consisted of the Average Alternans Index (AAI) and the heart-rate-restricted Average Alternans Indices (AAI$_h$). The AAI was computed as the average of all $V_k$ values in the ECG signal, 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 AAI = 3 μV, which means that the AAI cannot be interpreted as a direct measurement of the amplitude of TWA at any single point. Restricted Average Alternans
Indices ($AAI_x$) were computed as the average of only those $V_k$ values measured in segments with average HR ranging from $X-10$ bpm to $X$ bpm, with $X = \{70, 80, 90, 100, 110\}$. For instance, $AAI_{80}$ would reflect the average TWA activity at HR between 80 and 90 bpm in the 24-hour period.

The second set consisted of the Maximum Alternans Index (MAI) and the restricted Maximum Alternans Indices ($MAI_x$). The MAI was computed as the maximum of all $V_k$ values in the ECG signal. Restricted Maximum Alternans Indices ($MAI_x$) were computed as the maximum of the $V_k$ values measured in segments with average HR ranging from $X-10$ bpm to $X$ bpm, with $X = \{70, 80, 90, 100, 110\}$. For instance, $MAI_{90}$ would represent the maximum TWA amplitude at HR between 80 and 90 bpm in the 24-hour period.

**Statistical Analysis**

Data are presented as mean ± standard deviation for continuous variables, and number and percentage for categorical variables. Two-tailed Mann-Whitney and Fisher’s exact tests were used for univariate comparison of quantitative and categorical data respectively. Survival probability was estimated using Kaplan-Meier methods with comparison of cumulative events using log-rank tests. Univariate and multivariate Cox proportional hazards analyses were performed to determine the prognostic value of TWA indices in predicting the end points. Cox regression models were built considering a significance $\leq 0.05$ as the criterion for entry into a model. Linear relations between quantitative TWA indices and HR were evaluated with Spearman’s correlation coefficient. A $p$-value $< 0.05$ was considered statistically significant. Data were analyzed using SPSS software (version 15.0; SPSS Inc. Chicago, IL).

**Results**
The mean value of AAI 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). A very weak negative correlation was found between AAI and mean HR in the Holter recording (ρ = -0.083, p-value = 0.035).

The mean values of AAIx were AAI70 = 2.8 ± 1.9 μV, AAI80 = 3.3 ± 2.3 μV, AAI90 = 3.9 ± 2.4 μV, AAI100 = 5.0 ± 3.1 μV and AAI110 = 6.1 ± 5.5 μV. Not all ECGs presented a HR span from 60 to 110 bpm; 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 AAIx could be computed for every patient. The percentages of indeterminate values for the entire population were 18.1% for AAI70, 9.1% for AAI80, 13.4% for AAI90, 26.1% for AAI100, and 47.2% for AAI110. Figure 2 shows the distributions of AAIx.

Patients were divided into TWA positive (TWA+) and TWA negative (TWA−) groups by setting a cut point for AAI of 3.7 μV, corresponding to the 75th percentile of the distribution of AAI in the population. Of the 650 studied patients, 493 (75.8%) were included in the TWA− group (AAI ≤ 3.7 μV) and 157 (24.2%) in the TWA+ group (AAI > 3.7 μV). No significant differences were found upon comparison of clinical variables in TWA+ and TWA− groups (Table 1). Survival rate was significantly higher in group TWA− for primary and secondary end points (Table 2).

Univariate Cox analysis revealed that a TWA+ outcome was associated with all-cause mortality, with CD, and with SCD (Table 3). No association was found between a TWA+ outcome and non-cardiac mortality. Multivariate Cox proportional hazards model were constructed by adjusting for (1) age, gender, NYHA class, LVEF < 35, and diabetes, and (2) use of beta-blockers, amiodarone and ACE or ARB inhibitors in addition to covariables in model (1). For multivariate model (1), a TWA+ outcome was the variable most significantly associated to SCD risk, with a hazard ratio of 2.38 (95% CI: 1.37-4.14, p=0.002), similar to LVEF < 35 (hazard ratio 2.55, 95% CI: 1.35-4.80, p=0.004). For multivariate model (2), a TWA+ outcome was the
covariable with the second highest hazard ratio (2.29) after LVEF < 35 (hazard ratio 2.65, 95% CI: 1.39-5.03, p=0.003). The event-free curves for CD and SCD are shown in Figure 3.

The mean values of AAl_k increased with local HR, and there were significant differences between indices from all adjacent HR intervals (Figure 2). Univariate Cox analysis was performed for all AAl_k, and only AAl_90 was found to be associated with SCD. Multivariate Cox analysis confirmed this association (Table 3). AAl_90 was not associated to all-cause mortality or non-cardiac mortality.

The mean value of MAI in the study population was 31.4 ± 25.3 μV, and the percentiles 25th, 50th and 75th were 17.9, 24.7 and 38.0 μV respectively (Figure 2). No association to CD or SCD risk was found for MAI as a continuous variable or as a categorical variable after dichotomization with the 75th percentile. The mean values of MAI_k were MAI_70 = 16.1 ± 13.1 μV, MAI_90 = 17.2 ± 10.6 μV, MAI_90 = 17.5 ± 12.1 μV, MAI_100 = 19.7 ± 12.1 μV and MAI_110 = 20.6 ± 22.6 μV. MAI_k were not significantly associated to 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, AAI and AAI_90, were found to independently predict CD and SCD, but did not predict non-cardiac mortality. These findings support the hypothesis that elevated TWA activity reflects abnormal cardiac function predisposing to cardiac death.

The results of recent studies involving different types of TWA analysis in similar populations have led to divergent conclusions. In the SCD-Heft study (15), TWA measured using the Spectral Method during submaximal treadmill exercise did not predict arrhythmic events or mortality in patients with symptomatic heart failure and LV systolic dysfunction. On the other hand, results in the EPHESUS study (16) (involving post-myocardial infarction
patients with LV dysfunction) and in (17) (involving patients with LV dysfunction) showed that maximal TWA measured in ambulatory records using the time-domain Modified Moving Average technique with posterior visual inspection was a predictor of SCD and CD respectively.

In our study, the average TWA activity in a 24-h period, quantified by the AAI, was the covariable most strongly associated to the risk of SCD. In our population, a weak correlation was found between AAI and the patient’s HR, which indicates that AAI is not merely a surrogate measure of the patient’s HR, but also reflects the influence of HR-independent factors in TWA. Therefore, AAI may provide a measure of the extent of cardiac vulnerability, because a higher influence of HR-independent factors in TWA amplitude reflects a higher degree of cardiac electrical instability (18).

The prognostic value of quantitative TWA measurements is increasingly being studied (6) (7) (8). In this study, an index of quantitative TWA (AAI90) independently predicted SCD. When measured at moderate heart rates, higher magnitudes of TWA are known to predict a greater risk of serious outcomes (3). For TWA to predict cardiovascular events, maximum HR limits ranging from 100 to 125 bpm are usually considered (18). In this study, we found that the average TWA activity was associated to SCD when measured at lower rates, between 80 and 90 bpm (AAI90). A possible explanation for this difference is that heart failure lowers the HR threshold to elicit TWA(19).

Unsupervised maximum TWA amplitudes, measured by MAI and MAIX, did not predict cardiac risk. Although the values obtained for MAI were comparable to maximum TWA amplitudes reported in the literature (between 30 and 60 µV), no significant association was found between MAI and risk of SCD or CD. This was not unexpected, since it is known that measuring local TWA amplitudes without testing for its significance, either visually or automatically, can lead to inaccurate results due to noise and artifacts (20). In recent studies with ambulatory ECGs, the maximum TWA amplitude in a record has been measured with the
MMA method, either in the whole record (21)(16)(22) or in segments below a maximum HR (17), and then needs to be visually verified to ensure that they correspond to real TWA.

Long-term averaging of cardiac measurements has been successfully used to quantify subtle phenomena such as heart rate turbulence (23), deceleration capacity (24) or baroreflex sensitivity (25). In this study we applied the concept of long-term averaging to produce a reliable and noise insensitive characterization of TWA in ambulatory recordings, allowing TWA analysis for risk assessment in a fully-automated way.

We found 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 CD and SCD in the study population. To our best knowledge, the method presented in this work is the first one that allows a multilead, fully-automated computation of TWA markers of cardiac risk in ambulatory ECGs.

However, although this study indicates 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 (26)(27), 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 CHF. Two novel indices, AAI and AAI$_{90}$, are proposed to quantify the average TWA activity, and are found to be strong independent predictors of SCD.
References


[16] Stein PK, Sanghavi D, Domitrovich PP, Mackey RA, Deedwania P: Ambulatory ECG-based T-


Table 1: Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Overall Population (n = 650)</th>
<th>TWA – (n = 493)</th>
<th>TWA + (n = 157)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63 ± 12</td>
<td>63 ± 11</td>
<td>64 ± 13</td>
<td>0.091</td>
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<tr>
<td>Gender (men)</td>
<td>462 (71.1%)</td>
<td>350 (71.0%)</td>
<td>112 (71.3%)</td>
<td>0.999</td>
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<tr>
<td>NYHA class III</td>
<td>117 (18.0%)</td>
<td>87 (17.6%)</td>
<td>30 (19.1%)</td>
<td>0.721</td>
</tr>
<tr>
<td>LVEF ≤ 35</td>
<td>356 (54.8%)</td>
<td>262 (53.1%)</td>
<td>94 (59.9%)</td>
<td>0.142</td>
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<td>Diabetes</td>
<td>245 (37.7%)</td>
<td>190 (38.5%)</td>
<td>55 (35.0%)</td>
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<tr>
<td>Beta-blockers</td>
<td>454 (69.8%)</td>
<td>350 (71.0%)</td>
<td>104 (66.2%)</td>
<td>0.273</td>
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<tr>
<td>Amiodarone</td>
<td>59 (9.1%)</td>
<td>43 (8.7%)</td>
<td>16 (10.2%)</td>
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</tr>
<tr>
<td>ARB or ACE inhibitors</td>
<td>573 (88.2%)</td>
<td>441 (89.4%)</td>
<td>132 (84.1%)</td>
<td>0.088</td>
</tr>
<tr>
<td>Average heart rate (bpm)</td>
<td>75 ± 12</td>
<td>76 ± 12</td>
<td>75 ± 12</td>
<td>0.581</td>
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<tr>
<td>Maximum heart rate (bpm)</td>
<td>122 ± 26</td>
<td>123 ± 27</td>
<td>119 ± 25</td>
<td>0.100</td>
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Data are presented as absolute frequencies and percentages, and as mean ± standard deviation.

Table 2: Events during follow-up

<table>
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<th>Overall Population (n = 650)</th>
<th>TWA – (n = 493)</th>
<th>TWA + (n = 157)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>146 (22.5%)</td>
<td>99 (20.1%)</td>
<td>47 (30.0%)</td>
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<tr>
<td>CD</td>
<td>119 (18.3%)</td>
<td>81 (16.4%)</td>
<td>38 (24.2%)</td>
<td>0.033</td>
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<td>SCD</td>
<td>52 (8.0%)</td>
<td>30 (6.1%)</td>
<td>22 (14.0%)</td>
<td>0.003</td>
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</table>

Data expressed as absolute frequencies and percentages.
Table 3. Association of TWA indices with mortality

<table>
<thead>
<tr>
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<th>Multivariate(^{(2)})</th>
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<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>p value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Total mortality AAI &gt; 3.7 μV</td>
<td>1.62 (1.15 – 2.29)</td>
<td>0.006</td>
<td>1.54 (1.09 – 2.19)</td>
</tr>
<tr>
<td>CD AAI &gt; 3.7 μV</td>
<td>1.60 (1.09 – 2.35)</td>
<td>0.017</td>
<td>1.54 (1.04 – 2.26)</td>
</tr>
<tr>
<td>CD AAIm0</td>
<td>1.05 (1.00 – 1.11)</td>
<td>0.051</td>
<td>1.06 (1.00 – 1.13)</td>
</tr>
<tr>
<td>SCD AAI &gt; 3.7 μV</td>
<td>2.48 (1.43 – 4.30)</td>
<td>0.001</td>
<td>2.38 (1.37 – 4.14)</td>
</tr>
<tr>
<td>SCD AAIm0</td>
<td>1.07 (1.01 – 1.15)</td>
<td>0.041</td>
<td>1.07 (1.00 – 1.15)</td>
</tr>
</tbody>
</table>

(1) Adjusted model includes age, gender, NYHA class, LVEF < 35, and diabetes.

(2) Adjusted model includes covariables in (1) plus use of betablockers, amiodarone, and ARB or ACE inhibitors.
Figure 1: Example of TWA amplitude estimation. (a) ECG segment selected for automatic analysis after low-pass filtering and baseline cancellation. (b) New combined lead, computed with the technique of periodic component analysis. (c) Median TWA waveform in the segment, estimated with the Laplacian likelihood ratio method, and absolute TWA amplitude in the segment $V_k = 18.5 \mu V$. 
Figure 2: Top: boxplot of the average alternans indices computed in the 24-h period (AAI), and in intervals with HR in the range of X-10 to X bpm (AAI_X). Bottom: boxplot of the maximum alternans indices computed in the 24-h period (MAI), and in intervals with HR in the range of X-10 to X bpm (MAI_X). The number (and percentage) of records in which indices could be computed is indicated above the boxes. Significant differences between the medians of adjacent AAI_X and MAI_X boxes are indicated by * (p < 0.05) and ** (p < 0.001).
Figure 3: Event-free curves for CD (top) and SCD (bottom)