

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

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**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<sub>90</sub>).

**RESULTS** Patients were divided into TWA positive (TWA+) and TWA negative (TWA-) groups by setting a cut point of 3.7  $\mu$ V 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<sub>90</sub> were associated with SCD with hazard rates of 2.29 ( $p = .004$ ) and 1.07 per  $\mu$ V ( $p = .046$ ), 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

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## 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,<sup>1</sup> the cost-effectiveness of the therapy is low, as only a minority of patients with implantable cardioverter-defibril-

lators benefitted from this therapy during the follow-up period.<sup>2</sup> 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.<sup>3</sup> The utility of TWA testing during ambulatory monitoring has been subject to intense investigation in recent years.<sup>4,5</sup> In ambulatory recordings, the maximum amplitude of TWA has been semiautomatically quantified by using the modified moving average method<sup>4</sup> 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.<sup>5</sup> In the past years, the quantitative analysis of TWA amplitude as a continuous

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**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%)	<b>.002</b>
Nonsustained ventricular tachycardia and > 240 ventricular premature beats in 24 h	164 (25.2%)	102 (20.7%)	62 (39.5%)	<b>&lt;.001</b>

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.<sup>6,7</sup>

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,<sup>6–8</sup> 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.<sup>9</sup> 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.<sup>9,10</sup> 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%)	<b>.012</b>
CD	119 (18.3%)	81 (16.4%)	38 (24.2%)	<b>.033</b>
SCD	52 (8.0%)	30 (6.1%)	22 (14.0%)	<b>.003</b>

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.

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