

# Prediction of Sudden Cardiac Death in Chronic Heart Failure Patients by Analysis of Restitution Dispersion

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## Abstract

*An increase in the dispersion of action potential duration restitution (APDR) has been associated with higher propensity to suffer from ventricular arrhythmias and sudden cardiac death (SCD). Recently, a marker,  $\Delta\alpha$ , was proposed to non-invasively quantify APDR dispersion from the electrocardiogram (ECG) by computing the ratio between differences in the T-peak-to-T-end ( $T_{pe}$ ) and RR intervals at different steady-state conditions. Holter ECG recordings of patients with chronic heart failure divided into two groups, one consisting of victims of SCD and the other of victims of other causes and survivors, were analyzed. ECGs were delineated using a single-lead procedure over the first principal component calculated to emphasize the T-wave.  $\Delta\alpha$  discriminated between the groups formed by SCD and non-SCD victims, respectively, with mean  $\pm$  SEM values of:  $\Delta\alpha = 0.052 \pm 0.013$  for the former and  $\Delta\alpha = 0.026 \pm 0.003$  for the latter ( $p < 0.048$ ). In a survival analysis where a threshold on the third quartile of  $\Delta\alpha$  values was set, statistically significantly different event probabilities were obtained in both strata of the population ( $p = 0.003$ ). The marker  $\Delta\alpha$  stratifies patients according to their risk of suffering from ventricular arrhythmias that could lead to SCD, with larger restitution dispersion indicating lower survival probability.*

## 1. Introduction

Sudden cardiac death (SCD) remains an important cause of mortality in patients with mild-to-moderate heart failure. A number of indices have been proposed as SCD predictors, including left ventricular ejection fraction (currently the only recommended marker to risk stratify patients [1]) and T-wave alternans [2]. Nevertheless, further research is needed to provide an index or a combination of indices with improved capacity to identify patients at risk of SCD.

Heart rate dependence of action potential duration (APD), also called restitution kinetics, is thought to be critical in activation instability and, therefore, provides relevant information for ventricular arrhythmic risk stratification [3]. The dynamic APD restitution (APDR) curve, measured using the so-called dynamic restitution protocol, quantifies the relationship between the APD and the RR interval at steady-state when pacing at different RR values. Heterogeneities in the ventricle lead to non-uniform restitution properties, which makes APDR curves present spatial variations [4]. Dispersion is a measure of that spatial variation. Recent studies have suggested that dispersion in the APDR curves may act as a potent arrhythmogenic substrate and increments in that dispersion have been associated with greater propensity to suffer from ventricular tachycardia/fibrillation [5].

The main limitation on the usability of APDR dispersion as a risk index is that its quantification usually requires invasive procedures. In [6], a method to indirectly estimate dispersion of restitution slopes by making only use of the surface electrocardiogram (ECG) was developed. An ECG index,  $\Delta\alpha$ , that quantifies dispersion in the dynamic APDR slopes by characterizing the relationship between the T-peak-to-T-end ( $T_{pe}$ ) and the RR intervals at different steady-state conditions, was proposed and evaluated.

In this work, we present a fully automated method to analyze APDR dispersion in ambulatory recordings and we show that the ECG index,  $\Delta\alpha$ , proposed in [6], is an independent predictor of SCD in patients with chronic heart failure (CHF).

## 2. Materials

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 [2]. The Holter recordings of 609 patients (48 victims of SCD, 64 of other cardiac causes, 25 of non-cardiac death causes and 472 survivors) with sinus rhythm were available for the present study. Each recording consisted of three orthogonal ECG leads, sampled at 200 Hz. In this study, the population was divided into two groups: SCD victims (group 1) and victims of other cardiac causes, non-cardiac causes and survivors (group 2).

The clinical characteristics of the studied patients and medications are listed in Table 1. No medications were withdrawn during Holter monitoring.

Patients were followed up every 6 months for a median of 48 months. *SCD* 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.

### 3. Methods

#### 3.1. ECG preprocessing and delineation

Preprocessing of the ECG signals included low pass filtering at 40 Hz to remove electric and muscle noise, cubic splines interpolation for baseline wander removal and ectopic beats detection.

Principal Component Analysis was applied over the three leads to emphasize the T-wave and improve delineation. The first principal component was delineated using a single-lead technique [7] and, from the delineation marks, the RR, QT and  $T_{pe}$  interval series were obtained and subsequently interpolated at a sampling frequency  $f_s = 1$  Hz.

#### 3.2. Restitution dispersion from ECG segments with stable heart rate

The  $T_{pe}$  interval reflects differences in the time for completion of repolarization by different cells spanning the ventricular wall. Therefore, the  $T_{pe}$  interval can be expressed in terms of APDs as follows:

$$T_{pe} = APD_{last} - APD_{min} - \Delta AT \quad (1)$$

where  $APD_{min}$  corresponds to the cell with the minimum APD among those repolarizing at the T-wave peak instant and  $APD_{last}$  is the APD of the last cell to repolarize [8].  $\Delta AT$  represents the activation time delay between the two cells associated with  $APD_{min}$  and  $APD_{last}$ .  $\Delta AT$  hardly changes with RR for RR intervals above 600 ms [9]. Therefore, changes in the  $T_{pe}$  interval under variations

of the RR interval, measured at different steady-state heart rate levels, can be obtained as

$$\frac{\partial T_{pe}}{\partial RR} = \frac{\partial APD_{last}}{\partial RR} - \frac{\partial APD_{min}}{\partial RR} \quad (2)$$

If we let  $\alpha_{last}$  and  $\alpha_{min}$  denote the slopes of the dynamic restitution curves at the regions corresponding to  $APD_{last}$  and  $APD_{min}$ , respectively:

$$\alpha_i = \frac{\partial APD_i}{\partial RR}, i = \{last, min\} \quad (3)$$

the spatial difference  $\Delta\alpha = (\alpha_{last} - \alpha_{min})$ , which measures dispersion of restitution slopes, can be estimated from the ECG by introducing (3) into (2), resulting in

$$\Delta\alpha = \frac{\partial T_{pe}}{\partial RR} \quad (4)$$

#### 3.3. Restitution dispersion from ECG segments with unstable heart rate

When ECG segments presenting unstable heart rate are analyzed, the lag of the  $T_{pe}$  interval with respect to the RR interval needs to be considered in the computation of the index  $\Delta\alpha$ . The model shown in Fig. 1, previously proposed to quantify QT rate adaptation [10], was used to characterize the  $T_{pe}$  dependence on RR. The input  $x_{RR}(n)$  and output  $y_{T_{pe}}(n)$  denote the RR and  $T_{pe}$  series of each recording.

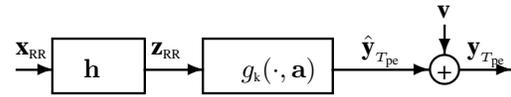


Figure 1. Block diagram describing the  $[RR, T_{pe}]$  relationship consisting of a time-invariant FIR filter (impulse response  $\mathbf{h}$ ) and a nonlinear function  $g_k(\cdot, \mathbf{a})$ .  $\mathbf{v}$  accounts for the output error.

The impulse response  $\mathbf{h} = [h(1), \dots, h(N)]^T$  includes information about the memory of the system, that is, a characterization of the influence of a history of previous RR intervals on each  $T_{pe}$  measurement. Therefore,  $z_{RR}(n)$  represents a surrogate of  $x_{RR}(n)$  with the memory effect of  $T_{pe}$  compensated for. The length  $N$  of vector  $\mathbf{h}$  was set to 150 samples. The function  $g_k(\cdot, \mathbf{a})$ , dependent on the parameter vector  $\mathbf{a} = [a(0), a(1)]^T$ , represents the relationship between the RR interval and the  $T_{pe}$  interval at steady-state conditions. Ten different biparametric regression models ( $k = 1, \dots, 10$ ) were considered for  $g_k(\cdot, \mathbf{a})$ . The estimated output  $\hat{y}_{T_{pe}}(n)$  was defined as

$$\hat{y}_{T_{pe}}(n) = g_k(z_{RR}(n), \mathbf{a}) \quad (5)$$

in which the optimum values of the FIR filter response  $\mathbf{h}$ , vector  $\mathbf{a}$ , and function  $g_k$  were searched for by minimizing the difference between the estimated output  $\hat{y}_{T_{pe}}(n)$  and the

Table 1. Characteristics of patients.

	Overall population ( <i>n</i> = 609)	$\Delta\alpha-$ ( <i>n</i> = 457)	$\Delta\alpha+$ ( <i>n</i> = 152)	<i>p</i> -value
Age (y)	63 ± 0.5	62 ± 0.6	64 ± 1.0	<b>0.040</b>
Gender (men)	426 (70.0%)	333 (72.9%)	93 (61.2%)	<b>0.008</b>
NYHA class III	110 (18.1%)	81 (17.7%)	29 (19.1%)	0.716
LVEF ≤ 35%	324 (53.2%)	242 (53.0%)	82 (53.9%)	0.852
Diabetes	232 (38.1%)	180 (39.4%)	52 (34.2%)	0.289
Beta-blockers	425 (69.8%)	327 (71.6%)	98 (64.5%)	0.104
Amiodarone	55 (9.0%)	30 (6.6%)	25 (16.4%)	<b>0.001</b>
ARB or ACE inhibitors	494 (81.1%)	375 (82.1%)	119 (78.3%)	0.338
Average heart rate [beats/min]	72 ± 0.5	71 ± 0.5	73 ± 1.1	0.600
Maximum heart rate [beats/min]	115 ± 0.8	115 ± 0.9	116 ± 1.8	0.589
Heart rate range [beats/min]	43 ± 0.6	43 ± 0.7	43 ± 1.3	0.426
$t_{90}$ [s] ( $T_{pe}$ )	94 ± 2.3	88 ± 2.7	109 ± 3.8	<b>0.001</b>
QRS > 120 ms	236 (38.8%)	178 (38.9%)	58 (38.2%)	0.924
Nonsustained ventricular tachycardia and > 240 Ventricular premature beats in 24 h	155 (25.5%)	121 (26.5%)	34 (22.4%)	0.335
SCD	48 (7.9%)	27 (5.9%)	21 (13.8%)	<b>0.003</b>

Data are presented as absolute frequencies and percentages and as mean ± standard error of the mean.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association;  $\Delta\alpha+$  = dispersion in the dynamic APDR slopes positive group;  $\Delta\alpha-$  = dispersion in the dynamic APDR slopes negative group. Significant differences between  $\Delta\alpha+$  and  $\Delta\alpha-$  are indicated in bold.

system output  $y_{T_{pe}}(n)$ , for each subject independently using the whole ECG recording.

The series  $z_{RR}(n)$  represents a surrogate of the running RR series as if of a truly steady-state period was present. Therefore, the estimate of restitution dispersion derived in (4) can be replaced with the following equation, obtained by differentiating (5) with respect to  $z_{RR}$ :

$$\Delta\alpha = \left. \frac{\partial \hat{T}_{pe}}{\partial z_{RR}} \right|_{z_{RR}=\bar{z}_{RR}} = \left. \frac{\partial g_k(z_{RR}, \mathbf{a})}{\partial z_{RR}} \right|_{z_{RR}=\bar{z}_{RR}} \quad (6)$$

where the derivative is evaluated at the mean  $z_{RR}$  value,  $\bar{z}_{RR}$ , of the recording.

Additionally, a measure of the time required for  $T_{pe}$  to complete 90% of its rate adaptation, denoted by  $t_{90}$ , was computed by setting a threshold of 0.1 to the cumulative sum of the filter impulse response,  $c(n)$

$$c(n) = \sum_{i=n}^N h(i) \quad (7)$$

leading to

$$t_{90} = \frac{1}{f_s} \arg \max_n (c(n) > 0.1). \quad (8)$$

### 3.4. Statistical analysis

Data are presented as mean ± standard error of the mean (SEM) 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  $\Delta\alpha$  in predicting the end points was determined with univariate and multivariate Cox proportional hazards analyses. Cox regression models were built considering a significance of  $\leq 0.05$  as the criterion for entry into a model. A *p* value of  $< 0.05$  was considered as statistically significant. Data were analyzed by using SPSS software.

## 4. Results and discussion

The mean ± SEM value of  $\Delta\alpha$  in the study population was  $0.028 \pm 0.003$  and the 25th, 50th and 75th percentiles were 0.005, 0.022 and 0.046, respectively. Patients were divided into  $\Delta\alpha$  positive ( $\Delta\alpha+$ ) and negative ( $\Delta\alpha-$ ) groups by setting a cut-off point of 0.046 for  $\Delta\alpha$ , corresponding to the 75th percentile of  $\Delta\alpha$  in the population. Of the 609 patients studied, 457 were thus included in the  $\Delta\alpha-$  group ( $\Delta\alpha \leq 0.046$ ) and 152 in the  $\Delta\alpha+$  group ( $\Delta\alpha > 0.046$ ).

Upon comparison of clinical variables between  $\Delta\alpha+$  and  $\Delta\alpha-$  groups (Table 1), significant differences were found for age, gender, treatment with amiodarone and rate adaptation time  $t_{90}$  for the  $T_{pe}$  series. Patients with longer adaptation time  $t_{90}$  were more likely to have a  $\Delta\alpha+$  outcome.

Survival rate was significantly higher in the  $\Delta\alpha-$  group for SCD end point ( $p = 0.003$ ). Univariate Cox analysis revealed that  $\Delta\alpha+$  outcome was associated with SCD (Table 2). Multivariate Cox proportional hazard models were con-

Table 2. Association of dispersion in the dynamic APDR slopes index,  $\Delta\alpha$ , with sudden cardiac death.

	Univariate		Multivariate 1*		Multivariate 2†	
	Hazard ratio (95% CI)	<i>p</i> -value	Hazard ratio (95% CI)	<i>p</i> -value	Hazard ratio (95% CI)	<i>p</i> -value
$\Delta\alpha > 0.046$	<b>2.54</b> (1.44-4.50)	<b>0.001</b>	<b>2.59</b> (1.46-4.60)	<b>0.001</b>	<b>2.57</b> (1.44-4.58)	<b>0.001</b>

CI = confidence interval;  $\Delta\alpha$  = dispersion in the dynamic APDR slopes.

\* Adjusted model includes age, gender, New York Heart Association class, left ventricular ejection fraction < 35% and diabetes.

† Adjusted model includes variables 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.

structed 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,  $\Delta\alpha+$  was the variable most significantly associated with SCD risk, with a hazard ratio of 2.59 (95% confidence interval [CI] 1.46-4.60;  $p = 0.001$ ), improving the performance of the left ventricular ejection fraction < 35% (hazard ratio 2.92; 95% CI 1.47-5.78);  $p = 0.002$ ). For model 2,  $\Delta\alpha+$  was the variable with the second highest hazard ratio (2.57), after left ventricular ejection fraction < 35% (hazard ratio 2.94; 95% CI 1.48-5.82;  $p = 0.002$ ). Figure 2 shows the event-free curves for SCD, having divided the population into  $\Delta\alpha+$  and  $\Delta\alpha-$  groups.

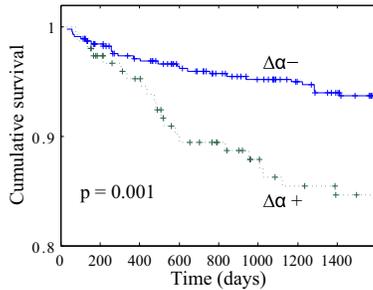


Figure 2. Event-free curves for sudden cardiac death.

## 5. Conclusions

This study demonstrates that dispersion in APD restitution, quantified from Holter ECG recordings, is a strong and independent predictor of SCD in patients with CHF, improving the performance of other markers such as the left ventricle ejection fraction. Our findings support the hypothesis that an increased dispersion in APD restitution reflects abnormal cardiac function predisposing to SCD.

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