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Trabajo Fin de Máster

Arrhythmic Risk Prediction based on the Analysis of Ventricular Repolarization Markers from Surface ECG

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ABSTRACT

Heart rate (HR) dependence of action potential duration (APD), also called restitution kinetics, is critical in activation instability of the heart and provides relevant information for ventricular arrhythmic risk stratification. The dynamic APD restitution (APDR) curve quantifies the relationship between the APD and the RR interval (inverse of HR) 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. Dispersion is a measure of that spatial variation. An electrocardiogram (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 recently proposed.

In this master's thesis a fully automated method to compute $\Delta\alpha$ in ambulatory recordings has been developed and the value of $\Delta\alpha$, as an independent predictor of sudden cardiac death (SCD) in patients with chronic heart failure (CHF), has been evaluated.

Consecutive patients with symptomatic CHF 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. 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. Preprocessing of the ECG signals performed in this master's thesis included low pass filtering at 40 Hz to remove electric and muscle noise, cubic splines interpolation for baseline wander removal and ectopic beats detection. A single-lead-and-rules delineation technique was applied to select the samples from the T-wave and compute principal component analysis. Then, the first principal component was delineated using a single-lead technique and, from the delineation marks, the RR and T_{pe} interval series of the ECG were obtained and subsequently interpolated at a sampling frequency $f_s = 1$Hz. Since each value of the APDR curve represents a stationary state corresponding to a specific HR value, the ECG index $\Delta\alpha$ proposed to estimate APDR dispersion should in principle be computed using ECG segments of stable HR regimes. Those types of segments are difficult to get in clinical practice and thus the dependence of the T_{pe} interval on a history of previous RR intervals was modeled and compensated for the T_{pe} memory lag. The relationship between T_{pe} and RR was then characterized on the whole ECG of the ambulatory recordings and the index $\Delta\alpha$ was calculated.

A threshold set in $\Delta\alpha$>0.046 showed to discriminate patients from high and low SCD risk (p-value = 0.003). The time to recurrence (SCD) was approximately doubled among patients with $\Delta\alpha\leq$0.046 in comparison with those with $\Delta\alpha$>0.046 (p-value = 0.001). By combining $\Delta\alpha$ with other ECG indices, like the index of average T-wave alternans (IAA), stratification of SCD risk was improved (p-value <0.001). This study demonstrates that dispersion in APDR, quantified from Holter ECG recordings, is a strong and independent predictor of SCD in patients with CHF. This findings support the hypothesis that an increased dispersion in APDR reflects abnormal cardiac function predisposing to SCD.

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RESUMEN

La dependencia de la duración del potencial de acción (APD, del inglés "Action Potential Duration") con el ritmo cardiaco (HR, del inglés "Heart Rate"), también conocida como cinética de restitución, es crítica a la hora de generar inestabilidades eléctricas en el corazón y proporciona información relevante en la estratificación del riesgo a sufrir arritmias ventriculares. La curva dinámica de restitución del APD (APDR, del inglés "APC restitution") cuantifica la relación entre el APD y el intervalo RR (inverso de HR) en condiciones estacionarias. Heterogeneidades en el ventrículo dan lugar a propiedades de la restitución no uniformes, haciendo que las curvas APDR presenten variaciones espaciales. La dispersión es una medida de dicha variación espacial. Recientemente se propuso en la literatura un índice derivado del electrocardiograma (ECG), $\Delta\alpha$, que cuantifica la dispersión en las pendientes de las curvas dinámicas de APDR mediante la caracterización de la relación entre los intervalos del pico al final de la onda T (T_{pe}) y RR bajo condiciones estacionarias diferentes.

En este Trabajo Fin de Máster (TFM) se ha desarrollado un método automático para obtener y evaluar, a partir de registros ambulatorios, $\Delta\alpha$, como predictor independiente de muerte súbita cardiaca (SCD, del inglés "Sudden Cardiac Death") en pacientes con fallo cardiaco crónico (CHF, del inglés "Chronic Heart Failure").

Pacientes con CHF sintomático formaron parte del estudio "MUSIC" (MUerte Súbita en Insuficiencia Cardiaca). La base de datos contenía los registros Holter the 609 pacientes (48 víctimas de SCD, 64 de otras causas cardiacas, 25 de causas no cardiacas y 472 supervivientes) con ritmo sinusal. El preprocesado de las señales ECG realizado en este TFM consistió en un filtrado paso bajo a 40 Hz, interpolación de splines cúbicos y un detector de latidos ectópicos. Se aplicó una técnica de delineación "uniderivacional más reglas a posteriori" para seleccionar las muestras pertenecientes a la onda T y realizar un análisis de componentes principales. A continuación, se delineó la primera componente principal mediante una técnica uniderivacional y, a partir de las marcas de delineación, se obtuvieron las series de los intervalos RR y T_{pe}. Posteriormente, se interpolaron a una frecuencia de muestreo $f_s = 1$ Hz. Como cada valor de la curva APDR está medido a un valor específico de RR, el índice de ECG $\Delta\alpha$ debería calcularse usando segmentos de ECG de ritmos cardiacos estables. Dichos segmentos son difíciles de conseguir en la práctica clínica y por lo tanto se modeló la dependencia del intervalo T_{pe} con una historia de intervalos previos de RR y se compensó por el retardo de memoria de T_{pe}. La relación entre T_{pe} y RR se caracterizó en los registros completos de ECG.

Un umbral fijado en $\Delta\alpha{>}0.046$ discriminó los pacientes en alto y bajo riesgo a sufrir SCD (p-valor = 0.003). El tiempo hasta el evento (SCD) fue aproximadamente el doble en los pacientes con $\Delta\alpha{\leq}0.046$ en comparación con los $\Delta\alpha{>}0.046$ (p-valor = 0.001). Al combinar $\Delta\alpha$ con el índice de media de alternancias de onda T se mejoró la estratificación del riesgo a sufrir SCD (p-valor$<$0.001). Este estudio demuestra que la dispersión en APDR, cuantificada a partir de registros ECG Holter, es un predictor de SCD fuerte e independiente en pacientes con CHF. Estos resultados apoyan la hipótesis de que una dispersión de APDR elevada refleja un funcionamiento cardiaco anormal, con predisposición a sufrir SCD.

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Chapter 1

Introduction

1.1. Background

Cardiovascular disease is the leading cause of death in developed countries. In 2010, 201,781 deaths associated with cardiovascular disease occurred in Spain, 92,224 corresponding to men and 109,557 to women. This number represented 54,4 % of the total number of deaths that occurred in Spain that year [1]. A good number of those cardiovascular deaths were produced by *arrhythmias*. An arrhythmia is defined as a deviation from or a disturbance of the normal sinus rhythm. The normal sinus rhythm has a rate between 50 and 100 beats/minute at rest. The rhythm is called sinus *bradycardia* when the rate is below the lower limit and sinus *tachycardia* when it is above the upper limit. A particular case of arrhythmia is *ventricular fibrillation*, which is a totally disorganized rhythm during which the ventricles cease to depolarize in an orderly fashion. As a result, a heart undergoing ventricular fibrillation cannot deliver oxygenated blood to the brain. Ventricular fibrillation leads to cardiac arrest, cessation of respiration, loss of consciousness, and, if no immediate treatment is given, it could lead to *Sudden Cardiac Death* (SCD) and be almost invariably fatal [2].

SCD remains an important cause of mortality in patients with mild-to-moderate heart failure (New York Heart Association [NYHA] classes II and III) [3]. Although previous studies have shown the benefit of implantable cardioverter-defibrillators in this type of population [4], 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 [5]. A number of indices have been proposed as SCD predictors, including left ventricular ejection fraction (currently the only recommended marker to risk stratify patients [6]) and T-wave alternans [7]. Nevertheless, further research is needed to provide an index or a combination of indices with improved capacity to identify patients at risk of SCD.

1.2. The Electrocardiogram

An electrocardiogram (ECG) describes the electrical activity of the heart recorded by electrodes placed on the body surface. The voltage variations measured by the electrodes are caused by the action potentials of the excitable cardiac cells as they make the cells contract. The resulting heartbeat in the ECG is manifested by a series of waves whose morphology and timing

convey information that can be used for diagnosing diseases associated with disturbances of the heart's electrical activity [8].

1.2.1. Electrical Activity of the Heart

The heart is a muscular organ the size of a large fist whose primary function is to pump oxygen-rich blood throughout the body. Its anatomy is divided into two "mirrored" sides, left and right, which support different circulatory systems but which pump in a synchronized, rhythmic manner. Each side of the heart consists of two chambers, the *atrium* where the blood enters and the *ventricle* where the blood is forced into further circulation.

The wall of the heart is called the *myocardium* and is primarily composed of muscle cells which produce mechanical force during contraction of the heart. The myocardium also contains specialized muscle cells which are connected into a network (conduction system) that allows an electrical impulse to rapidly spread throughout the heart. A cardiac cycle is created when such an impulse propagates through the conduction system. The electrical impulse is the event that triggers the mechanical force, and thus the electrical event precedes heart contraction. The initialization of this cardiac cycle occurs in a mass of pacemaker cells with the ability to spontaneously fire an electrical impulse. These cells are collectively referred as the *sinoatrial* (SA) *node* and are situated in the upper part of the right atrium.

Each cardiac cycle is composed of two phases, activation and recovery, which are referred to in electrical terms as *depolarization* and *repolarization* and in mechanical terms as contraction and relaxation. Depolarization is manifested by a rapid change in the membrane potential of the cell and constitutes the initial phase of the cardiac action potential (AP). The rapid change in voltage causes neighbouring cells to depolarize, and, as a result, an electrical impulse spreads from cell to cell throughout the myocardium. Depolarization is immediately followed by repolarization during which the membrane potential of the cells gradually returns to its resting state. The ECG describes the different electrical phases of a cardiac cycle and represents a summation in time and space of the action potentials generated by millions of cardiac cells. Of the millions of individual cells in the heart that depolarize during a cardiac cycle, only groups of cells in the myocardium depolarize at any given instant. Each group of cells simultaneously depolarizing may be represented as an equivalent current dipole source to which a vector is associated, describing the dipole's time-varying position, orientation and magnitude. The related vectors of all these groups can be summed to give a "dominant" vector which describes the main direction of the electrical impulse.

Figure 1.1 illustrates how the AP of different cardiac cells generate the ECG signal, in this example viewed by an exploring electrode which is positioned on the chest. During atrial depolarization, the dominant vector is directed downwards towards the AV node. As a result, an atrial wave with positive polarity ("P" wave) is generated in the ECG recorded at the position of the exploring electrode. The amplitude of the resulting wave is low because the muscle mass of the atria that produces the electrical wavefront is relatively small. Ventricular depolarization begins in the wall between the ventricles (septum) in such a way that the associated vector is directed away from the exploring electrode; hence, the related ECG wave ("Q" wave) has negative polarity. Due to the high conduction velocity of the cells in this part of the heart, the Q wave has short duration. During continued ventricular depolarization, the dominant direction of the vector gradually turns toward the exploring electrode ("R" wave). Depolarization terminates with the dominant vector pointing away from the electrode, and thus a wave with negative polarity ("S"

wave) is produced in the ECG. During ventricular repolarization, a similar sequence of dominant vectors to those during ventricular depolarization appears, and a wave with positive polarity ("T" wave) is produced. Since atrial repolarization is concurrent with ventricular depolarization, the related atrial repolarization wave is masked by the ventricular waves which have much larger amplitudes.

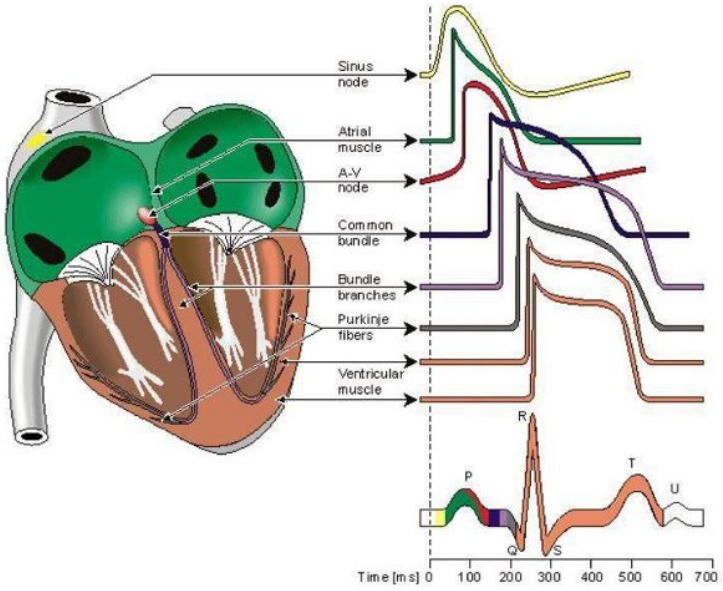


Figure 1.1: The morphology and timing of action potentials from different regions of the heart and the related cardiac cycle of the ECG as measured on the body surface.

1.2.2. Leads

The electrical activity of the heart is measured on the body surface by attaching a set of electrodes to the skin. The electrodes are positioned so that the spatiotemporal variations of the cardiac electrical field are sufficiently well-reflected. For an ECG recording, the difference in voltage between a pair of electrodes is referred to as a *lead*.

A number of lead systems exist today with standardized electrode positions. The two that have received the most attention, namely, the standard 12-lead ECG and the orthogonal lead system producing a *vectorcardiogram* (VCG) are described below.

- **Standard 12-lead ECG**: The standard 12-lead ECG is the most widely used lead system in clinical routine and is defined by a combination of three different lead configurations: the bipolar limb leads, the augmented unipolar limb leads and the unipolar precordial leads. The 12-lead ECG is recorded by placing 10 electrodes at standardized positions on the body surface.
- **Orthogonal leads**: Each standard lead reflects a different point of view of the electrical activity of the heart, depending on the place where the electrode, or pairs of electrodes are located. Sometimes it is interesting to obtain a global ECG which represents the different ECGs obtained from individual leads. Therefore, is is possible to compute an orthogonal

base composed of three leads from the standard 12-lead ECG [9]. This method symbolizes three leads (*Frank leads*) that would be obtained if three electrodes were placed on the x, y and z axis of the heart, which is physically unviable [9]. The three orthogonal leads were available in the database analyzed in this master's thesis.

1.2.3. ECG Waves and Time Intervals

To develop signal processing algorithms, the knowledge of ECG wave characteristics, which are described below, along with the wave-naming convention, is central.

- **P wave**: Reflects the sequential depolarization of the right and left atria.
- **QRS complex**: Reflects depolarization of the right and left ventricles. It is composed of the Q, R and S waves. Since the QRS complex has the largest amplitude of the ECG waveforms, it is the waveform of the ECG which is first identified in any type of computer-based analysis.
- **T wave**: Reflects ventricular repolarization. Substantial changes in T-wave have shown to provide relevant information about the risk of suffering from ventricular arrhythmias. This master's thesis mainly analyzes this wave.

Figure 1.2 shows ECG waves and important time intervals.

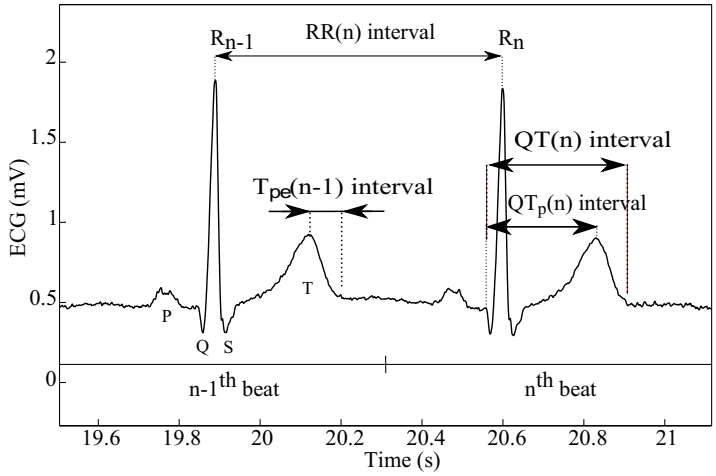


Figure 1.2: Wave definitions of the cardiac cycle and important wave durations and intervals.

- **RR interval**: Represents the length of a ventricular cardiac cycle, measured between two successive R waves, and serves as an indicator of ventricular rate.
- **QT interval**: Represents the time from the onset of ventricular depolarization to the completion of ventricular repolarization.
- $T_{\mathbf{pe}}$ **interval**: Represents the time from the peak to the end of T-wave. It is considered as a ventricular repolarization dispersion marker.

1.3. Electrocardiogram Detection and Delineation

The detection process consists of detecting heartbeats. ECG delineation consists of determining the boundaries of each wave within the PQRST complex so that, with the resulting time instants, wave durations can be computed.

1.3.1. Single-lead Delineation

Single-lead delineation identifies the wave boundaries of a lead, independently from the others. In this work an automatic method based on the Wavelet Transform (WT) has been used [10]. WT describes the signal in both time and frequency domains. Therefore, it allows to represent temporal wave characteristics at different levels (scales) depending on its frequency content. This representation is proportional to the signal derivative, so a zero-crossing represents a peak in the original signal. QRS complex needs a different scale of that used to characterize P and T waves, because its frequency content is substantially different [11].

Firstly, QRS complex *fiducial point* (QRS complex gravity center) is detected and, then, Q, R and S waves are separately delineated. Finally, P and T waves are delineated by sliding the analysis window [10]. Signal to noise ratio constitutes a drawback in single-lead delineation technique because if the noise level is high it is difficult to correctly place the wave boundaries.

1.3.2. Single-lead-and-rules Delineation

This method consists of selecting an annotation mark among the marks obtained using single-lead delineation over the available leads in each heartbeat. If the mark is the onset of a wave, all the onset marks from all the leads are sorted and the first one (which marks the position of the first recorded electrical change) is chosen, since it is the most restrictive. To do so, a protection criteria which states that k leads must have their onset mark within a δ time interval needs to be accomplished. k and δ values are chosen depending on the delineated wave. If the mark is the offset of a wave, the algorithm is the same but choosing the last annotation mark. If the protection criteria is not accomplished, the mark is rejected. If the mark corresponds to the wave peak, the median criteria is used: all the marks are sorted and the one in the middle is selected [12].

1.4. Action Potential Duration Restitution Dispersion

The underlying mechanisms of lethal arrhythmias, which contribute to cardiovascular disease begin the primary cause of death in the industrialized world, are poorly understood [13]. The generation of arrhythmias has been widely studied by dynamically pacing cardiac myocytes, cardiac tissue or whole hearts [14]. These experimental results have revealed that heart rate (HR) dependence of action potential duration (APD), also called restitution kinetics, is critical in activation instability and, therefore, provides relevant information for ventricular arrhythmic risk stratification [15]. The dynamic APD restitution (APDR) curve, measured using the so-called dynamic restitution protocol, quantifies the relationship between the APD and the RR interval (inverse of HR) at steady-state when pacing at different RR values [16] (Figure 1.3).

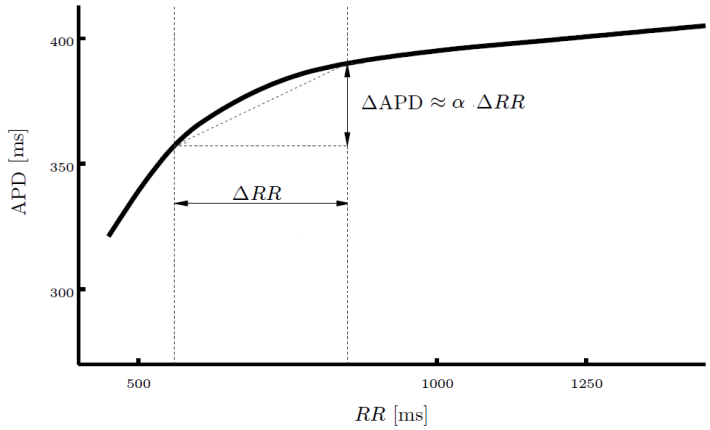


Figure 1.3: APD dynamic restitution (APDR) curve from one particular cardiac cell.

Individual APDR curves have been reported to play an important role in the development of ventricular arrhythmias and APDR curves containing steep slopes are thought to induce alternans of APD and block propagation leading eventually to arrhythmia [17]. On the contrary, for shallow slopes, APD disturbances are smaller and eventually return to a stable activation [16].

Heterogeneities in the ventricle lead to non uniform restitution properties, which makes APDR curves present spatial variations [18]. 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 [19]. Additionally, increments in that dispersion have been associated with greater propensity to suffer from ventricular tachycardia/fibrillation [20] (Figure 1.4). In [21], a method to indirectly estimate dispersion of restitution slopes by making only use of the surface 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.

1.5. Objectives

The main objective in this work is to present a fully automated method to analyze APDR dispersion in ambulatory recordings and to show that the ECG index, $\Delta\alpha$, proposed in [21], is an independent predictor of SCD in patients with chronic heart failure (CHF). To achieve the proposed objective, a number of steps were followed:

- To process the "MUSIC" (MUerte Súbita en Insuficiencia Cardiaca) database, composed of 609 Holter ECG recordings.
- To compute a representative marker of dispersion of APD restitution curves from changes in the heart rate and time intervals measured on the ECG signal.
- To compare the obtained responses and to extract conclusions about the relevance of these results to predict ventricular arrhythmias that could lead to SCD in patients with CHF.

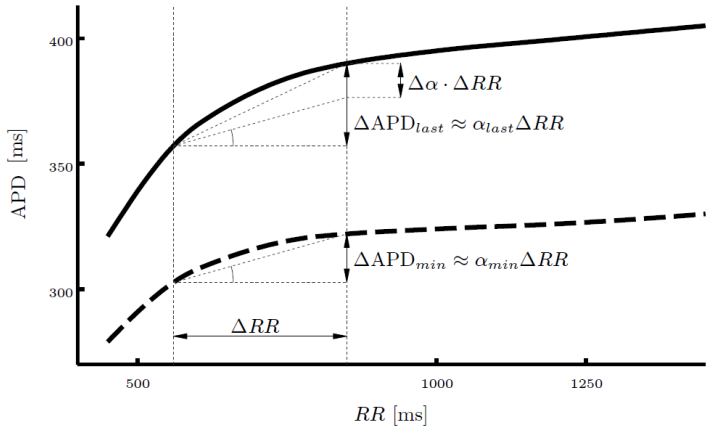


Figure 1.4: Dynamic restitution curves (APDR) for two regions corresponding to APD_{min} (dashed line) and APD_{last} (solid line). Slopes α_{min} and α_{last} are estimated for a change in the RR interval.

1.6. Structure of the document

After this brief introduction, the structure of this document is the following: in chapter 2, the analyzed database and the methods used to reliably compute the risk index, $\Delta\alpha$, are described. In chapter 3, the results obtained by applying the methodology on the studied database are presented and discussed. In chapter 4, the practical training performed during this work is explained. Finally, in chapter 5, the conclusions and future work are presented.

Chapter 2

Materials and Methods

2.1. Materials

2.1.1. 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 [22]. The study protocol was approved by institutional investigation committees and all patients signed informed consent. 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. No medications were withdrawn during Holter monitoring. Each recording consisted of three orthogonal ECG leads, sampled at 200 Hz.

The clinical characteristics of the studied patients and medications are listed in Table 3.1. Measurements of the index of average alternans (IAA), computed in the MUSIC database after evaluation of other clinical variables, were available for this study [7]. Only the values of IAA corresponding to the patients analyzed in this master's thesis were considered.

2.1.2. 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. *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. *Cardiac death* was defined as death from cardiac causes, including SCD, but excluding such vascular causes as pulmonary embolism, aortic aneurysm dissection/aneurysm or stroke. End points were reviewed and classified by the MUSIC Study Endpoint Committee. Table 3.2 summarizes the number of deaths in the study population during the median 48-month period.

2.2. Methods

2.2.1. 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 (PCA) is a method that, based on a signal's statistical content, gathers the information from a group of correlated variables into a group of uncorrelated variables. PCA was applied in this master's thesis as a method to robustly extract temporal and morphological properties from the T wave. One way to implement PCA is by applying *singular value decomposition* (SVD) over the three available leads (**x**, **y** and **z**) to obtain three new leads using the following transformation equation:

$$\mathbf{w}(n) = \mathbf{V}^T \mathbf{l}(n) \tag{2.1}$$

where vector $\mathbf{l}(\mathrm{n}) = [x(n), y(n), z(n)]^T$ and $\mathbf{V}$ is the matrix which contains the right-singular vectors obtained from a training matrix, $\mathbf{L}$. In this master's thesis, $\mathbf{L} = [\widehat{x}(\mathrm{n}),\widehat{y}(\mathrm{n}),\widehat{z}(\mathrm{n})]$, where the circumflex accent indicates that only the samples from the T-waves have been considered on each lead. Therefore,

$$\mathbf{L} = \mathbf{U}\Sigma\mathbf{V}^T \tag{2.2}$$

where $\mathbf{U}$ is a matrix which columns contain the left-singular vectors and Σ is a diagonal matrix containing the eigenvalues of $\mathbf{L}$.

First, a single-lead-and-rules delineation technique (section 1.3.2) was applied to select the samples from the T-wave and compute the matrix $\mathbf{L}$. Then, the first principal component was computed and delineated using a single-lead technique (section 1.3.1). From the delineation marks, the RR, QT and T_{pe} interval series were obtained and subsequently interpolated at a sampling frequency $f_{\mathrm{s}} = 1$ Hz.

2.2.2. Restitution Dispersion from ECG segments with Stable Heart Rate

In [21] a method to indirectly compute ventricular dispersion in dynamic APDR slopes by making only use of the surface ECG was proposed.

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:

$$T_{\mathrm{pe}} = APD_{\mathrm{last}} - APD_{\mathrm{min}} - \Delta AT \tag{2.3}$$

where APD_{min} corresponds to the cell with the minimum APD among those repolarizing at the T-wave peak instant (time instant when the maximum repolarization gradient sum occurs) and APD_{last} is the APD of the last cell to repolarize [19]. ΔAT represents the activation time delay between the two cells associated with APD_{min} and APD_{last}, as shown in Figure 2.1. ΔAT hardly changes with RR for RR intervals above 600 ms [23]. Therefore, changes in the T_{pe} interval

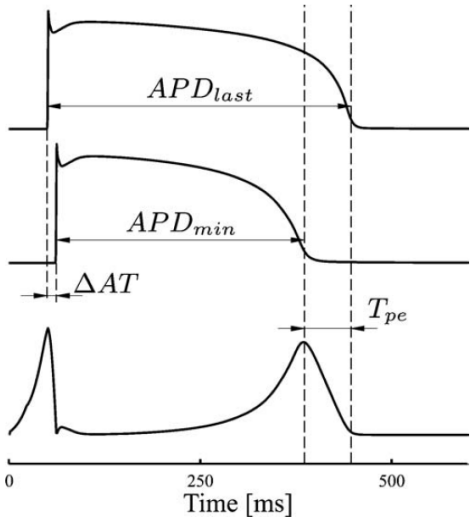


Figure 2.1: Representation of the T_{pe} interval in terms of APDs and delay of activation times (ΔAT).

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

$$\frac{\partial T_{\mathrm{pe}}}{\partial RR} = \frac{\partial APD_{\mathrm{last}}}{\partial RR} - \frac{\partial APD_{\mathrm{min}}}{\partial RR} \tag{2.4}$$

where $\partial\Delta\mathrm{AT}/\partial\mathrm{RR}$ has been neglected, under the premise that RR intervals above 600 ms are considered.

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

$$\alpha_{\mathrm{i}} = \frac{\partial APD_{\mathrm{i}}}{\partial RR}, \qquad i = \{last, min\} \tag{2.5}$$

the spatial difference $\Delta\alpha = (\alpha_{\mathrm{last}} - \alpha_{\mathrm{min}})$ (see Figure 1.3), which measures dispersion of restitution slopes, can be estimated from the ECG by introducing (2.5) into (2.4), resulting in

$$\Delta\alpha = \frac{\partial T_{\mathrm{pe}}}{\partial RR} \tag{2.6}$$

2.2.3. Restitution Dispersion from ECG segments with Unstable Heart Rate

Each value of the APDR curve represents a stationary state corresponding to a specific HR value, and, therefore, the ECG measurement proposed to estimate restitution dispersion should in principle be computed using ECG segments of stable HR regimes. Since those types of segments are difficult to get in clinical practice, in [21] an approach proposed to overcome that restriction by modeling the dependence of the T_{pe} interval on a history of previous RR intervals and compensating for the T_{pe} memory lag.

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. 2.2, previously proposed to quantify QT rate adaptation [24], was used to characterize the T_{pe} dependence on RR. The input $x_{\mathrm{RR}}(\mathrm{n})$ and output $y_{T_{\mathrm{pe}}}(\mathrm{n})$ denote the RR and T_{pe} series of each recording.

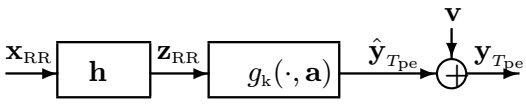


Figure 2.2: Block diagram describing the [RR,T_{pe}] relationship consisting of a time-invariant FIR filter (impulse response $\mathbf{h}$) and a nonlinear function $g_{\mathrm{k}}(\cdot, \mathbf{a})$. $\mathbf{v}$ accounts for the output estimation error.

The impulse response $\mathbf{h} = [h(1), ..., h(N)]^T$ 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, $z_{\mathrm{RR}}(\mathrm{n})$ represents a surrogate of $x_{\mathrm{RR}}(\mathrm{n})$ with the memory effect of T_{pe} compensated for. The length N of vector $\mathbf{h}$ was set to 150 samples. The function $g_{\mathrm{k}}(\cdot, \mathbf{a})$, 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 ($k = 1,...,10$) were considered for $g_{\mathrm{k}}(\cdot, \mathbf{a})$, and the one that best fits the data of each subject was identified.

$$\begin{gathered}
\text{Linear: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1)\mathbf{z}_{\mathrm{RR}} \\
\text{Hyperbolic: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + \frac{a(1)}{\mathbf{z}_{\mathrm{RR}}} \\
\text{Parabolic: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0)(\mathbf{z}_{\mathrm{RR}})^{a(1)} \\
\text{Logarithmic: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1)\ln(\mathbf{z}_{\mathrm{RR}}) \\
\text{Inverse logarithmic: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = \ln(a(0) + a(1)\mathbf{z}_{\mathrm{RR}}) \\
\text{Exponential: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1).e^{-\mathbf{z}_{\mathrm{RR}}} \\
\text{Arctangent: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1)\mathrm{arctag}(\mathbf{z}_{\mathrm{RR}}) \\
\text{Hyperbolic tangent: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1)\mathrm{tgh}(\mathbf{z}_{\mathrm{RR}}) \\
\text{Hyperbolic arcsine: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1)\mathrm{arcsinh}(\mathbf{z}_{\mathrm{RR}}) \\
\text{Hyperbolic arccosine: } \hat{\mathbf{y}}_{T_{\mathbf{pe}}} = a(0) + a(1)\mathrm{arccosh}(\mathbf{z}_{\mathrm{RR}}).
\end{gathered}$$

The estimated output $\widehat{y}_{T_{\mathrm{pe}}}(\mathrm{n})$ was defined as

$$\widehat{y}_{T_{\mathrm{pe}}}(n) = g_{\mathrm{k}}(z_{\mathrm{RR}}(n), \mathbf{a}) \tag{2.7}$$

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 $\widehat{y}_{T_{\mathrm{pe}}}(\mathrm{n})$ and the system output $y_{T_{\mathrm{pe}}}(\mathrm{n})$, for each subject independently using the whole ECG recording. The optimization algorithm seeks to minimize the following function:

$$\boldsymbol{J}(\mathbf{h}, \mathbf{a}) = \|y_{T_{\mathrm{pe}}}(n) - \widehat{y}_{T_{\mathrm{pe}}}(n)\|^2 + \beta^2 \|\mathbf{D}\mathbf{h}\|^2 \tag{2.8}$$

where $\mathbf{D}$ is a regularization matrix that penalizes the fact that $\mathbf{h}$ deviates from having an exponential decay [25] and β is the regularization parameter whose value was obtained by using

the "L-curve" criterion [26]. With the computed value for β, the optimum values $\mathbf{h}$ and $\mathbf{a}$ in 2.8 were determined by using a "quasi-Newton" optimization technique described in [27], subject to two constraints: the sum of the $\mathbf{h}$ components is 1, to ensure normalized filter gain, and all the components of $\mathbf{h}$ are nonnegative, to give a physiological plausible interpretation. Regarding k, in order to account for the inter-subject variability in the [RR, T_{pe}] relationship, the regression function $g_{\mathrm{k}}(\cdot, \mathbf{a})$ was determined as the one that minimizes the mean square error for each subject independently.

The series $z_{\mathrm{RR}}(\mathrm{n})$ 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 (2.6) can be replaced with the following equation, obtained by differentiating (2.7) with respect to z_{RR}:

$$\Delta\alpha = \left.\frac{\partial \hat{T}_{\mathrm{pe}}}{\partial z_{\mathrm{RR}}}\right|_{z_{\mathrm{RR}}=\overline{z}_{\mathrm{RR}}} = \left.\frac{\partial g_{\mathrm{k}}(z_{\mathrm{RR}}, \mathbf{a})}{\partial z_{\mathrm{RR}}}\right|_{z_{\mathrm{RR}}=\overline{z}_{\mathrm{RR}}} \tag{2.9}$$

where the derivative is evaluated at the mean z_{RR} value, $\overline{z}_{\mathrm{RR}}$, 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)

$$c(n) = \sum_{i=n}^{N} h(i) \tag{2.10}$$

leading to

$$t_{90} = \frac{1}{f_{\mathrm{s}}} \arg\max_{n}(c(n) > 0{,}1). \tag{2.11}$$

2.2.4. Automated processing of the database

The previous subsections describe the methodology applied to the ECG recordings to obtain the marker of APDR dispersion, $\Delta\alpha$. In this master's thesis this signal processing has been developed in a fully automated and parallel computing using "Hermes", a high performance computer property of the University of Zaragoza. This parallel computing approach allows to analyse a huge amount of data (in this master's thesis, the ECG recordings from the patients in the database) saving computational time. The methodology described previously was applied at the same time in all the recordings in the database. The computational time required to analyze one ECG recording is 2 hours, meaning a total of around 1200 hours to analyze the whole database. Thanks to this high performance computer, it is possible to analyze the complete database in 2 hours.

2.3. Statistical Analysis

Several statistical tests have been used in this master's thesis, as described in the following.

2.3.1. Quantitative statistical differences between populations

Student's *t*-test

A *t-test* is a statistical hypothesis test used to determine if two sets of data are significantly different from each other, and is most commonly applied when the test statistic would follow a normal distribution. A p value of <0.05 was considered as statistically significant in this master's thesis.

Mann-Whitney U test

The *Mann-Whitney U* test is a non-parametric test of the null hypothesis that two populations are the same against an alternative hypothesis, especially that a particular population tends to have larger values than the other.

It has greater efficiency than the t-test on non-normal distributions, such as a mixture of normal distributions, and it is nearly as efficient as the t-test on normal distributions [28].

Fisher's exact test

Fisher's exact test is a statistical significance test used in the analysis of contingency tables. Although in practice it is employed when sample sizes are small, it is valid for all sample sizes. It is one of a class of exact tests, so called because the significance of the deviation from a null hypothesis can be calculated exactly, rather than relying on an approximation that becomes exact in the limit as the sample size grows to infinity, as with many statistical tests. The test is useful for categorical data that result from classifying objects in two different ways; it is used to examine the significance of the association (contingency) between the two kinds of classification [29].

2.3.2. Classification

A *receiver operating characteristic (**ROC**)* is a graphical plot which illustrates the performance of a binary classifier system as its discrimination threshold is varied. It is created by plotting the fraction of true positives out of the positives (sensitivity) vs. the fraction of false positives out of the negatives (1-specificity), at various threshold settings.

ROC analysis provides tools to select possibly optimal models and to discard suboptimal ones independently from the cost context or the class distribution [30].

If a classifier system is optimal at some threshold, its associated ROC curve would approach to the upper left corner (as a logarithmic function), pointing at the maximized sensitivity and specificity. If, on the contrary, there is no threshold optimizing the classification, its ROC curve would follow a diagonal line.

2.3.3. Survival analysis

Survival analysis is a branch of statistics which deals with death in biological organisms and failure in mechanical systems. Survival analysis attempts to answer questions such as: what

is the fraction of a population which will survive past a certain time? Of those that survive, at what rate will they die or fail? Can multiple causes of death or failure be taken into account? How do particular circumstances or characteristics increase or decrease the odds of survival?

More generally, survival analysis involves the modeling of time to event data. In this context, death or failure is considered as an "event" in the survival analysis literature.

The *hazard function* is defined as the event rate at time t conditional on survival until time t or later. *Censoring* is a form of missing data problem which is common in survival analysis. Ideally, both the birth and death dates of a subject are known, in which case the lifetime is known. The *hazard ratio* is the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable. This explanatory variable would, then, divide the population in two groups and the hazard ratio would measure the proportion of probability survival between both groups. The higher the hazard ratio, the better the survival rate from both groups can be discriminated.

Kaplan-Meier estimator

The *Kaplan-Meier estimator* estimates the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment.

A plot of the Kaplan-Meier estimate of the survival function is a series of horizontal steps of declining magnitude which, when a large enough sample is taken, approaches the true survival function for that population. The value of the survival function between successive distinct sampled observations is assumed to be constant.

An important advantage of the Kaplan-Meier curve is that the method can take into account some types of censored data, which occurs if a patient withdraws from the study, i.e. is lost from the sample before the final outcome is observed. On the plot, small vertical tick-marks indicate losses, where a patient's survival time has been censored [31].

Proportional hazards models

Proportional hazards models are a class of survival models in statistics. Survival models relate the time that passes before some event occurs to one or more covariables that may be associated with that quantity of time. In a proportional hazards model, the unique effect of a unit increase in a covariable is multiplicative with respect to the *hazard rate*.

Survival models can be viewed as consisting of two parts: the underlying hazard function, describing how the hazard (risk) changes over time at baseline levels of covariables, and the effect parameters, describing how the hazard varies in response to explanatory covariables. The *proportional hazards condition* [32] states that covariables are multiplicatively related to the hazard. The effect of covariables estimated by any proportional hazards model can thus be reported as *hazard ratios*. Survival models were built considering a significance of ≤ 0.05 as the criterion for entry into a model.

Logrank test

In statistics, the *logrank test* is a hypothesis test to compare the survival distributions of two samples. It is a nonparametric test and appropriate to use when the data are right skewed and censored. It is widely used in clinical trials to establish the efficacy of a new treatment compared to a control treatment when the measurement is the time to event.

The logrank test statistic compares estimates of the hazard function of the two groups at each observed event time. It is constructed by computing the observed and expected number of events in one of the groups at each observed event time and then adding these to obtain an overall summary across all time points where there is an event [33].

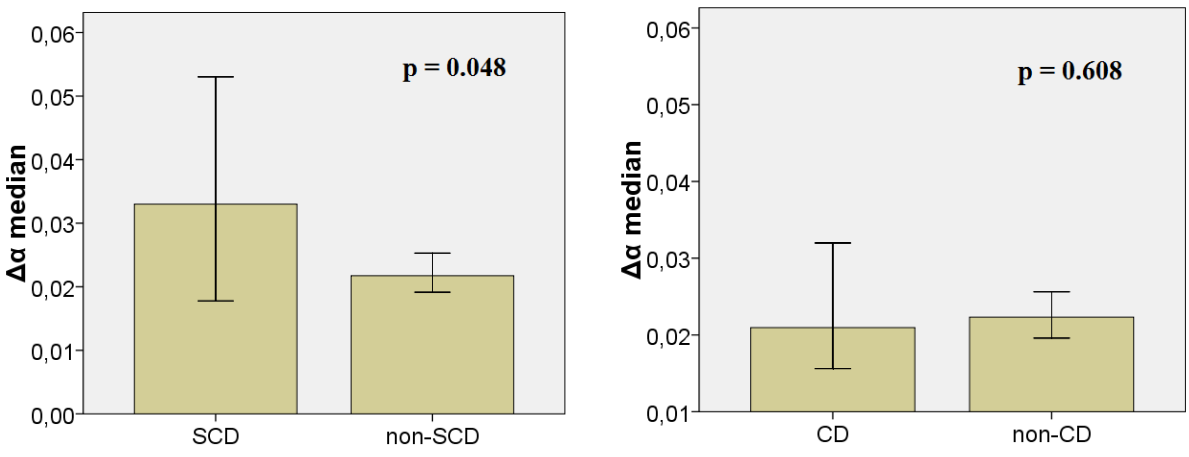
Chapter 3

Results

This chapter presents and discusses the results obtained in this master's thesis regarding the computation of APDR dispersion in ambulatory recordings from CHF patients and its use for prediction of SCD risk. The relevance of this study is supported by the large amount of clinical studies investigating abnormal ventricular behaviour and its relation to SCD. In this study, *Principal Component Analysis* transformation was applied over the three orthogonal leads available in the database and the heartbeats from the first principal component were detected and delineated. From the annotation marks provided by the delineation process, RR and T_{pe} series were computed. The value of $\Delta\alpha$, describing dispersion in APDR slopes, was obtained from the RR and T_{pe} series of each patient in the database. To account for the T_{pe} memory lag with respect to the RR interval, a model that characterizes the T_{pe} dependence on RR was used. The results obtained for $\Delta\alpha$ and their relation to the occurrence of clinical events are described in the following.

3.1. Analysis of the relation between $\Delta\alpha$ and SCD

The risk marker $\Delta\alpha$ did not follow a normal statistical distribution. Therefore, the non-parametric Mann-Whitney U test (section 2.3.1) was applied to determine whether SCD victims (group a1) presented $\Delta\alpha$ values that were significantly different from the rest of patients (cardiac death but non-SCD victims, victims of other causes and survivors) (group a2). The 25th, 50th and 75th percentiles of $\Delta\alpha$ in the study population were 0.005, 0.022 and 0.046, respectively. The median value of $\Delta\alpha$ was 0.033 for group a1 and 0.022 for group a2 ($p = 0.048$) (Figure 3.1(a)). In an equivalent way, the procedure was repeated to determine whether there were statistical differences between CD victims (group b1) and the rest (victims of other causes and survivors) (group b2) $\Delta\alpha$ values. The median value of $\Delta\alpha$ was 0.021 for group b1 and 0.022 for group b2 ($p = 0.608$) (Figure 3.1(b)). Statistically significant differences were found in $\Delta\alpha$ median values between groups a1 and a2 but not in $\Delta\alpha$ median values between b1 and b2 groups. As a result, the idea of the restitution dispersion marker acting as a good SCD predictor may be supported. Increments in $\Delta\alpha$ would indicate higher SCD risk.



(a) (b)

Figure 3.1: $\Delta\alpha$ median $\pm$ 95 % confidence interval for SCD and non-SCD victims (a) and for CD and non-CD victims (b).

3.2. Selection of a risk threshold

Based on the results in section 3.1 showing that increments in $\Delta\alpha$ values are related with SCD, a risk threshold was set on the continuous variable $\Delta\alpha$. A new binary variable was built so that $\Delta\alpha+$ (associated with $\Delta\alpha$ values above the threshold) was composed of patients at higher SCD risk and $\Delta\alpha$- (associated with $\Delta\alpha$ values below the threshold) contained patients at lower SCD risk. To determine the threshold that better discriminated between group a1 and group a2, a ROC curve was computed, as shown in figure 3.2. As it can be seen, the ROC curve did not show a marked logarithmic tendency but curved enough to separate from the diagonal. The threshold that maximized sensitivity and specificity (closest point to the upper-left corner) was $\Delta\alpha$=0.046, which corresponded to the 75th percentile of $\Delta\alpha$ in the population (marked with a red dot in figure 3.2).

3.3. Analysis of the relation between increments in $\Delta\alpha$ and SCD

Patients were divided into $\Delta\alpha$ positive ($\Delta\alpha+$) and negative ($\Delta\alpha$-) groups by setting a cut-off point of 0.046 for $\Delta\alpha$. 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 3.1), significant differences were found for age, gender, treatment with amiodarone and rate adaptation time t_{90} for the T_{pe} series. Data are presented as mean $\pm$ 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 (section 2.3) were used for univariable comparison of quantitative and categorical data, respectively.

Survival rate was significantly higher in the $\Delta\alpha$- group for primary and secondary end points ($p = 0.003$) (Table 3.2).

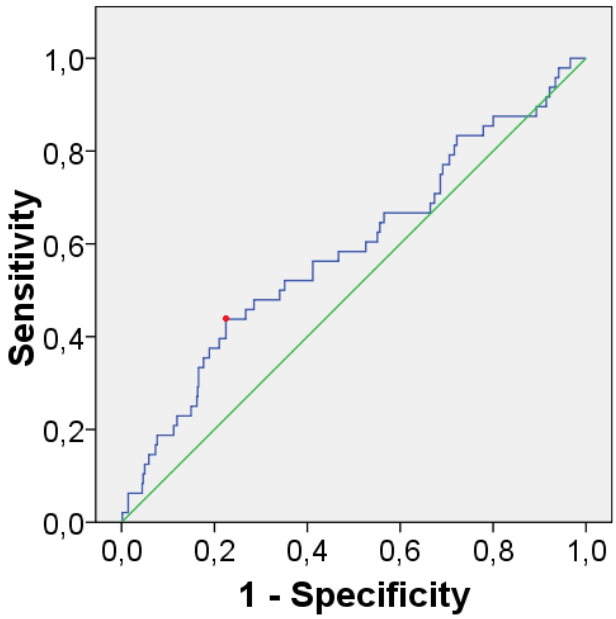


Figure 3.2: ROC curve for $\Delta\alpha$ in the classification of SCD victims. Red dot is associated with the selected threshold.

3.4. Survival analysis

As explained in section 2.3.3, a survival analysis involves predicting the fraction of the population which will survive to SCD past a certain time and how clinical variables increase or decrease the odds of survival.

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 univariable and multivariable Cox proportional hazards analyses.

3.4.1. Influence of $\Delta\alpha$ and other variables on SCD

Use of $\Delta\alpha$

Univariable Cox analysis computes the hazard function and the hazard ratio explained in section 2.3.3 by only taking into account the variable under study. In this master's thesis, $\Delta\alpha$. Univariable Cox analysis revealed that $\Delta\alpha+$ outcome was associated with all-cause mortality, CD and SCD (Table 3.3), however, $\Delta\alpha+$ statistically discriminates better the survival rate to SCD than to CD or total mortality. We can conclude that the time to recurrence was significantly prolonged (approximately doubled) among patients with $\Delta\alpha \leq 0.046$ in comparison with those with $\Delta\alpha > 0.046$.

	Overall population ($n = 609$)	$\Delta\alpha-$ ($n = 457$)	$\Delta\alpha+$ ($n = 152$)	p-value
Age (y)	63 ± 0,5	62 ± 0,6	64 ± 1,0	**0.040**
Gender (men)	426 (70.0 %)	333 (72.9 %)	93 (61.2 %)	**0.008**
NYHA class III	110 (18.1 %)	81 (17.7 %)	29 (19.1 %)	0.716
LVEF $\leq$ 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 %)	**0.001**
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	**0.001**
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
IAA>3.7μV	143 (23.8 %)	108 (23.9 %)	35 (23.5 %)	0.999

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; IAA = Index of maximum alternans; $\Delta\alpha+$ = 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.

Table 3.1: Characteristics of patients

Use of $\Delta\alpha$ in combination with other variables

Although a univariable Cox analysis provides useful information about survival rate, it necessarily ignores the impact of any other factors under investigation, which are known to be associated with SCD end-point, such as left ventricular ejection fraction <35 % [6] or index of average alternans >3.7μV [7]. In clinical investigations, it is more common to have a situation where several covariables potentially affect patient prognosis [34]. By considering all the critical covariables in the adjusted model, it is possible to compute the relative SCD risk prediction of each covariable. Multivariable Cox proportional hazard model was constructed by adjusting for: age, gender, NYHA class, left ventricular ejection fraction < 35 %, index of average alternans >3.7 μV, diabetes, use of beta-blockers, amiodarone and angiotensin-converting enzyme or angiotensin receptor blocker inhibitors. $\Delta\alpha+$ was the variable with the second highest hazard ratio (2.68), after left ventricular ejection fraction < 35 % (hazard ratio 2.87; 95 % CI 1.44-5.69; $p = 0.003$). The index of average alternans had a hazard ratio of 2.33; 95 % CI 1.30-4.20; $p = 0.005$. Table 3.3 shows all the hazard ratios computed in the multivariable Cox analysis. The unadjusted $\Delta\alpha+$ effect (univariable) may be summarized by a time ratio of 2.54 (1.44-4.50), which, having allowed for other covariables (multivariable) increased slightly to 2.68. This fact suggests that joining together more variables instead of using only $\Delta\alpha+$ may improve survival prediction.

	Overall population ($n = 609$)	$\Delta\alpha-$ ($n = 457$)	$\Delta\alpha+$ ($n = 152$)	p-value
Total mortality	137 (22.5 %)	91 (19.9 %)	46 (30.3 %)	**0.010**
CD	112 (18.4 %)	74 (16.2 %)	38 (25.0 %)	**0.021**
SCD	48 (7.9 %)	27 (5.9 %)	21 (13.8 %)	**0.003**

Data are presented as absolute frequencies and percentages.
CD = cardiac death; SCD = sudden cardiac death; $\Delta\alpha+$ = 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.

Table 3.2: Events during follow-up.

3.4.2. Cumulative survival curves

Figure 3.3 (top panels) shows the event-free curves for SCD (a) and CD (b), respectively, having divided the population into $\Delta\alpha+$ (in green) and $\Delta\alpha$- (in blue) groups. As it can be seen from the figure, the survival curves for $\Delta\alpha+$ and $\Delta\alpha$- can be statistically separated for SCD end-point (p-value = 0.001) and CD end-point (p-value = 0.007). Patients belonging to $\Delta\alpha+$ group have a lower survival rate than those from $\Delta\alpha$- group, supporting the idea that higher values of $\Delta\alpha$ indicate higher SCD risk. Values of cumulative survival corresponding to CD end-point are lower, indicating that $\Delta\alpha$ better separates SCD risk than other types of cardiac deaths.

The Kaplan-Meier curves obtained by using IAA>3.7μV as a risk stratifier are shown in Figure 3.3 (middle panels). Both curves can be statistically separated for SCD end-point (p-value = 0.004) and CD end-point (p-value = 0.026). Comparing these p-values and curves visual separation, we can affirm that $\Delta\alpha$ on its own statistically discriminates better from SCD and CD risk than IAA.

This master's thesis uses an ECG-derived marker to predict SCD survival. It would be, then, interesting, to measure the SCD survival prediction rate using the combination of ECG-derived variables. The prediction of $\Delta\alpha+$ was, then, combined with the one provided by Index of average alternans >3.7 μV.

Combining the information provided by $\Delta\alpha$ and IAA and sorting the population by those who meet $\Delta\alpha$>0.046 and IAA>3.7μV and those who do not, it can be seen how both survival curves are more separated with lower p-values (Figure 3.3 (bottom panels)). Therefore, combining $\Delta\alpha$ and IAA improves the stratification of SCD risk.

The results described above can be discussed in terms of sensitivity and specificity. Using only $\Delta\alpha$ as a risk marker, 21 true positives out of 152 are obtained (positive predictive value = 13.82 %). Using the combination of $\Delta\alpha$ and IAA, the population of the risk group is reduced to 35 patients, from which 10 are SCD (positive predictive value = 28.57 %). In clinical practice, it is recommended to implant cardioverter defibrillators to 18 patients if only one is known to suffer from SCD (positive predictive value = 5.56 %). Besides, carrying an implantable cardioverter defibrillator is not comfortable, as it is an invasive device and its discharges are often debilitating. Therefore, minimizing non-necessary cardioverter defibrillator implantations is an important matter. The results obtained in this master's thesis show how $\Delta\alpha$ on its own helps to improve the positive predictive value and how, in combination with another ECG-derived SCD risk marker, such as the index of average alternans, the survival prediction is increased up to 28.57 %.

This study demonstrates that quantification of the dispersion in the dynamic APDR slopes

	Univariable		Multivariable	
	Hazard ratio (95 % CI)	*p*-value	Hazard ratio (95 % CI)	*p*-value
Total mortality				
$\Delta\alpha+$ ($\Delta\alpha$>0.046)	**1.68** (1.18-2.40)	**0.004**	**1.60** (1.11-2.32)	**0.013**
Age	-	-	**1.02** (1.00-1.04)	**0.013**
Gender (men)	-	-	**1.74** (1.15-2.62)	**0.009**
NYHA class III	-	-	**2.42** (1.67-3.50)	**<0.001**
LVEF	-	-	**2.29** (1.56-3.36)	**<0.001**
IAA>3.7μV	**1.59** (1.11-2.29)	**0.012**	**1.53** (1.06-2.21)	**0.025**
Diabetes	-	-	**1.31** (0.92-1.86)	0.129
Beta-blockers	-	-	**0.74** (0.51-1.07)	0.111
Amiodarone	-	-	**1.59** (0.97-2.60)	0.064
ARB or ACE inhibitors	-	-	**1.10** (0.72-1.68)	0.671
CD				
$\Delta\alpha+$ ($\Delta\alpha$>0.046)	**1.70** (1.15-2.51)	**0.008**	**1.65** (1.10-2.49)	**0.016**
Age	-	-	**1.02** (1.00-1.04)	**0.026**
Gender (men)	-	-	**1.92** (1.20-3.07)	**0.006**
NYHA class III	-	-	**2.34** (1.55-3.53)	**<0.001**
LVEF $\leq$ 35 %	-	-	**2.27** (1.48-3.47)	**<0.001**
IAA>3.7μV	**1.58** (1.05-2.36)	**0.028**	**1.53** (1.01-2.31)	**0.043**
Diabetes	-	-	**1.39** (0.94-2.05)	0.097
Beta-blockers	-	-	**0.78** (0.52-1.17)	0.229
Amiodarone	-	-	**1.37** (0.78-2.43)	0.281
ARB or ACE inhibitors	-	-	**1.10** (0.68-1.76)	0.703
SCD				
$\Delta\alpha+$ ($\Delta\alpha$>0.046)	**2.54** (1.44-4.50)	**0.001**	**2.68** (1.50-4.79)	**0.001**
Age	-	-	**1.02** (1.00-1.04)	0.231
Gender (men)	-	-	**2.57** (1.18-5.60)	**0.018**
NYHA class III	-	-	**2.01** (1.07-3.76)	**0.029**
LVEF $\leq$ 35 %	-	-	**2.87** (1.44-5.69)	**0.003**
IAA>3.7μV	**2.26** (1.27-4.04)	**0.006**	**2.33** (1.30-4.20)	**0.005**
Diabetes	-	-	**1.29** (0.71-2.34)	0.402
Beta-blockers	-	-	**1.19** (0.62-2.30)	0.605
Amiodarone	-	-	**1.22** (0.50-2.93)	0.665
ARB or ACE inhibitors	-	-	**0.61** (0.26-1.46)	0.269

CD = cardiac death; CI = confidence interval; SCD = sudden cardiac death; $\Delta\alpha$ = dispersion in the dynamic APDR slopes; IAA = Index of maximum alternans.
Adjusted model includes age, gender, New York Heart Association class, left ventricular ejection fraction < 35 %, Index of maximum alternans >3.7 μV, diabetes and use of beta-blockers, amiodarone and angiotensin receptor blocker or angiotensin-converting enzyme inhibitors. Statistically significant values are marked in bold.

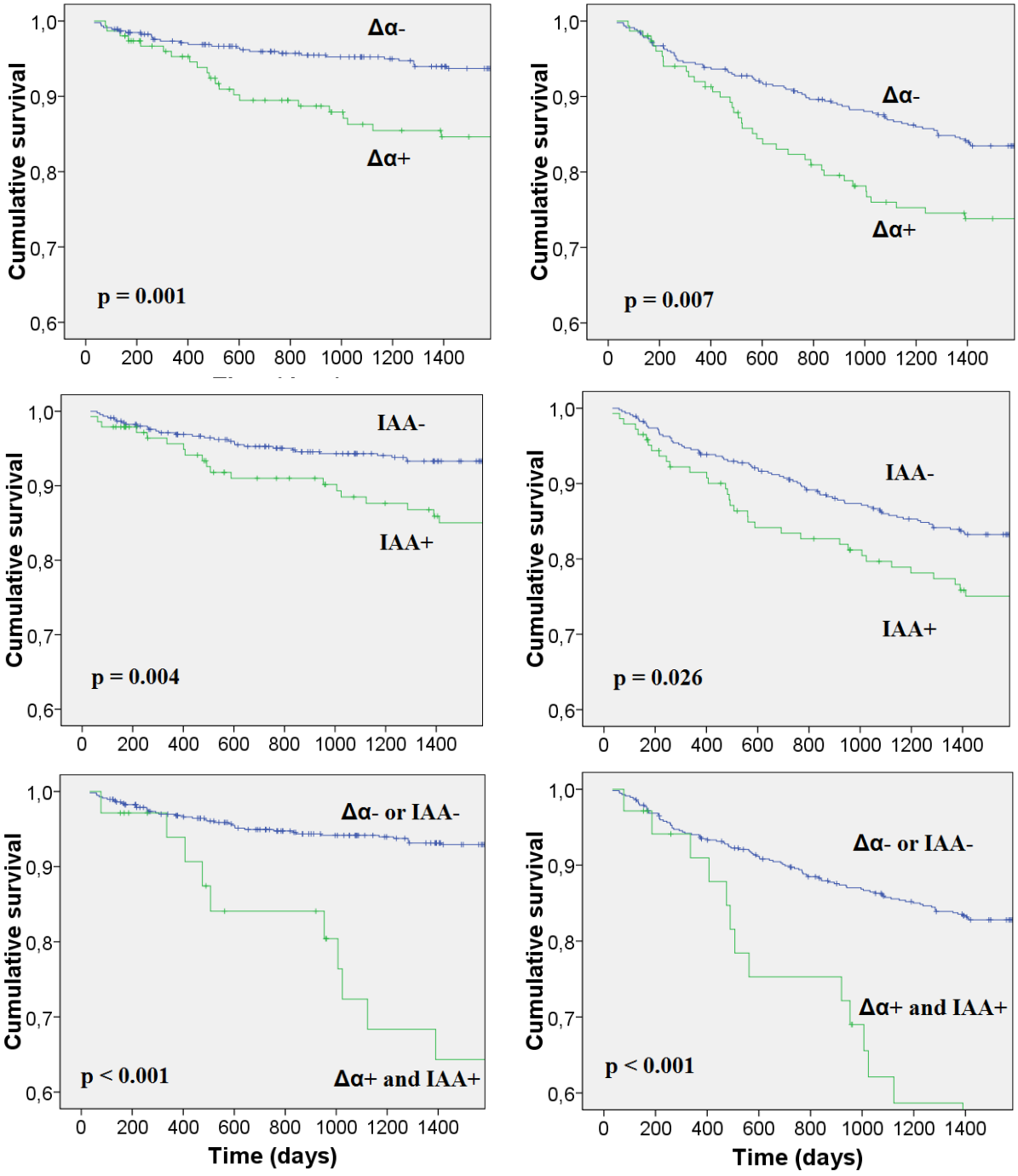
Table 3.3: Association of dispersion in the dynamic APDR slopes index, $\Delta\alpha$, with sudden cardiac death, cardiac death and total mortality.

is a strong, independent predictor of SCD in patients with CHF. The index $\Delta\alpha$ quantifying the dispersion in the dynamic APDR slopes in a 24-hour period independently predicted CD and SCD but did not predict noncardiac mortality (results not shown). These findings support the hypothesis that elevated dispersion in the dynamic APDR slopes reflects abnormal cardiac function predisposing to CD and, more specifically, to SCD.

3.5. Limitations

Some of the limitations of the present work are listed below:

- The number of patients in the "MUSIC" database that died from SCD was relatively low in comparison with the group formed by survivors, victims of non-cardiac causes and victims of cardiac-but-non-SCD causes.
- The quality of the ECG recordings was not optimal. A thorough preprocessing step was necessary to prepare the signals for further analysis.



(a) (b)

Figure 3.3: Event-free curves for sudden cardiac death (a) and cardiac death (b). Above, using $\Delta\alpha+$ on its own; middle, using IAA+ on its own; below, a combination of $\Delta\alpha+$ and IAA+.

Chapter 4

Practical Training

4.1. Introduction

In this master's thesis, I visited the Zentrum für Klinische Forschung (ZKF) (Center for Clinical Trials) of UniversitätsSpital in Zürich (USZ) (Switzerland). I worked in the group of Dr. Laurence Jacobs, in collaboration with FIFA - Medical Assessment and Research Centre (F-MARC), as the required part of the practical training of the master thesis in Biomedical Engineering.

Sports-Related Sudden Cardiac Death (SRSD) is always a devastating event. This is especially true when the victim is an apparently healthy athlete who in the eyes of the public epitomizes health itself. Among athletes a tragedy like SRSD becomes a powerful symbol, one that is vigorously fueled by the media. However, SRSD remains fundamentally mysterious in medical terms, in the sense that no practical diagnosis of its risk exists, and an understanding of the mechanisms involved is lacking. A large amount of research into SRSD has been generated over the past decade, most of it with mixed results as far as identifying plausible causes. In this practical training I learnt new hypotheses about the field and, especially, methodologies and techniques that have never before been brought to bear on this problem.

4.2. Hypothesis

The central hypothesis of our study is that SRSD will not occur unless there is an associated impairment in the dynamics of the Autonomic Nervous System (ANS). Based on this idea, an external stimulus, a trigger, will generate an arrhythmia, which, under normal circumstances, is quickly arrested by an ANS response. When the ANS is impaired, however, the arrhythmia is not arrested and SRSD ensues. While the response system associated with inter- and intracardiac rhythms, mediated through various nonlinear feedback loops, is highly complex, it is undoubtedly deterministic. This forms the basis for the proposed analysis, namely, the concept that deterministic complexity [35] is essential for long-term dynamical stability of the cardiovascular system. The degree of deterministic complexity might be the basis of a diagnosis of health and risk associated with the ANS.

4.3. Objectives

The first objective in this study was to explore the hypothesis described in 4.2 by evaluating and analyzing the dynamics of the QT, T_{pe} and other intra-beat intervals in highly physically conditioned and apparently healthy subjects. The APDR risk marker, $\Delta\alpha$, measured in this master's thesis over recordings from CHF patients, showed to significantly stratify SCD risk. Therefore, the second objective was to measure $\Delta\alpha$ in the database composed of recordings from professional athletes provided by F-MARC, and analyze potentially high $\Delta\alpha$ values in the investigated population.

4.4. Methods

4.4.1. ECG acquisition and processing

Electrocardiographic data from the subjects of the study were collected and analyzed during the pilot phase of the study performed in collaboration with F-MARC. To do this, a three-lead electrocardiograph that generates ECG data at the time and voltage resolution required by the analytical methods was used (Figure 4.1). The selected electrocardiograph was provided by "Schiller" [36].

Figure 4.1: The electrograph used for the recording of the electrocardiographic data.

The analysis proceeded through the calculation of various metrics, including the deterministic complexity metrics mentioned above, as well as methods for determining the degree of nonlinearity in the time series, including the QT and T_{pe} interval series. These metrics were

used to estimate the degree and stability of autonomic function [35]. The extended phase of the project is currently under development. ECG signals will be acquired through the FIFA centers collaborating on the project and they will be subsequently analyzed in our studies.

4.4.2. Study Population

ECG data for the pilot phase of the project was acquired, and continues to be acquired, from approximately 150-200 male soccer athletes drawn from 4 clubs. The extended phase of the project will involve on the order of 10 FIFA Medical centers of Excellence, each acquiring 150-200 additional recordings in their respective areas of operation.

Any healthy male member of the selected clubs in the age range of 18-36 years who signs an informed consent form can be included in the study. The selection process will be done in consultation with the medical officers of each selected soccer club. The only possible exclusion criteria are highly unlikely in this population: (1) overt diagnosed cardiovascular disease and (2) use of either beta-blockers or any other medication known to affect the ANS function.

4.4.3. Protocol

During the pilot phase, project staff performed subject preparation and data acquisition at the club venue. Three measurements sessions were run in parallel. For the extended study, project staff will acquire the ECG recordings together with the cardiology staff of the FIFA Medical Center in question. Detailed data management protocols and specialized software will be provided to the center's cardiology service to facilitate data management and transfer to ZKF to ensure consistency of the procedure.

4.5. Conclusions

In this practical training I learned about the relationship between deterministic complexity and ANS, and how a variability in such deterministic complexity can be a SCD risk marker.

I also participated on the data acquisition from the pilot phase, by attending to an introductory training course to know how the electrocardiograph works.

Chapter 5

Conclusions and Future Work

5.1. Conclusions

In this master's thesis the performance of an ECG index proposed to measure APDR dispersion, $\Delta\alpha$, has been evaluated. A database composed of patients with chronic heart failure has been analyzed. The information provided by the index $\Delta\alpha$ has been correlated to clinical information obtained during patients' follow-up.

Dispersion in APDR, quantified from Holter ECG recordings through the index $\Delta\alpha$, is shown to be a strong and independent predictor of SCD in patients with chronic heart failure. $\Delta\alpha$ improves up to three times the predictability recommended for an index to be used in the assessment of cardioverter-defibrillator implantation. When $\Delta\alpha$ is combined with other ECG indices, like the index of average T-wave alternans, the predictability rises up to six times. Our findings support the hypothesis that an increased dispersion in APDR reflects abnormal cardiac function predisposing to SCD.

5.2. Future Work

To improve and extend the results of the present master's thesis, the following future work is proposed:

- In [37] a method to perform multilead delineation of the VCG on a beat-to-beat basis was proposed. The method was shown to remove side effects in ECG series computed from the delineation marks, such as postural changes that could be misunderstood with repolarization phenomena. Future work could include the delineation of the three orthogonal leads ($\mathbf{x}$, $\mathbf{y}$ and $\mathbf{z}$) available in the "MUSIC" database with the *multilead* technique proposed in [37], by searching for the onsets, peaks and offsets of the ECG waves on a beat-to-beat basis, following the electrical movement of the VCG to remove inherent postural change effects.
- The work started during the clinical training (chapter 4) will be continued. The methodology described in this master's thesis will be evaluated on the whole database composed of professional athletes, whose ECG recordings have been and continue to be acquired in collaboration with FIFA.

- The cellular and sub-cellular mechanisms that could explain the origin of the different observed patterns in the analyzed ventricular repolarization indices remain to be elucidated. An electrophysiological modeling investigation is proposed to be carried out to better understand action potential duration restitution dynamics and their eventual relationship with arrhythmic risk and sudden cardiac death.

The results obtained in this master's thesis have been published in the following conferences:

- J. Ramírez, A. Mincholé, J. Bolea, P. Laguna, E. Pueyo. "Sudden Cardiac Death Survival Prediction from Restitution Dispersion Analysis". II Reunión Jóvenes Investigadores del Instituto de Investigación en Ingeniería de Aragón (I3A). 16 Mayo 2013.
- J. Ramírez, A. Mincholé, P. Laguna, E. Pueyo. "Analysis of Repolarization Dispersion to Predict Sudden Cardiac Death Survival". PGBiomed. 9th-11th July 2013.
- J. Ramírez, A. Mincholé, J. Bolea, P. Laguna, E. Pueyo. "Prediction of Sudden Cardiac Death in Chronic Heart Failure Patients by Analysis of Restitution Dispersion". Computers in Cardiology 2013. Accepted for the Young Investigators Awards plenary session. 22th-25th September 2013.

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APPENDIX

Sudden Cardiac Death Survival Prediction from Restitution Dispersion Analysis

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Abstract

Increase in the dispersion of action potential duration restitution (APDR) has been associated with sudden cardiac death (SCD). A marker, Δα, was proposed to quantify APDR dispersion from the electrocardiogram (ECG). 609 ECG recordings were analysed. The marker Δα stratified patients according to their risk of suffering from SCD.

Introduction

APDR measures the relationship between the action potential duration and the RR interval at steady-state pacing. Due to heterogeneities in the ventricles, APDR presents spatial variations generally termed APDR dispersion. An increase in APDR dispersion has been associated with higher propensity to suffer from ventricular arrhythmias and SCD. Recently, a marker, Δα, which accounts for the rate normalized differences of the T_{pe} interval, was proposed to quantify APDR dispersion from the ECG at steady-state conditions [1].

Materials and methods

Materials

Consecutive patients 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. 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 3 ortogonal ECG leads, sampled at 200 Hz. In this study, the population in the database was splitted into two groups: SCD victims (group 1) and victims of other cardiac causes, non-cardiac causes and survivors (group 2).

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.

Methods

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 T-wave energy and improve delineation. A Single-Lead-and-rules delineation technique was applied to mark the onsets and offsets of the T-wave. From the annotation marks, RR, QT and Tpe series were obtained and subsequently interpolated at a sampling frequency of 1 Hz.

The spatial dispersion of APDR slopes was estimated from the ECG as

$$\Delta\alpha = \frac{\partial Tpe}{\partial RR}$$

measured at steady-state RR intervals [1].

Results and discussion

The mean value of Δα in the study population was 0.028 ± 0.076 and the 25th, 50th and 75th percentiles were 0.005, 0.022 and 0.046, respectively.

Δα discriminated between the group formed by SCD victims (group 1) and the group composed of the other patients (group 2), with mean ± SEM values of: Δα = 0.052 ± 0.013 for the former and Δα = 0.026 ± 0.003 for the latter (p = .048). Patients were divided into Δα positive (Δα+) and negative (Δα-) groups by setting a cut-off point of 0.046 for Δα, corresponding to the 75th percentile of the distribution of Δα in the population. Of the 609 patients studied, 457 (75.0%) were included in the Δα- group (Δα ≤ 0.046) and 152 (25%) in the Δα+ group (Δα > 0.046). A two-tailed Fisher exact test showed an existing effect of being a SCD victim on having Δα>0.046 (p = .003), with a survival rate higher in the Δα- group for SCD endpoint. In a survival analysis, Cox regression revealed that a Δα+ outcome was associated with SCD (p = .001), as shown in Figure 1.

Conclusions

This study demonstrates that quantification of APDR from the ECG is a strong predictor of SCD. This finding supports the hypothesis that elevated APDR dispersion reflects abnormal cardiac function predisposing to SCD.

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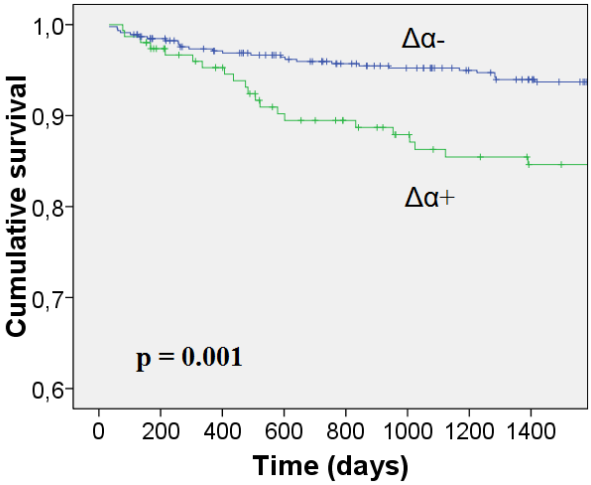

Fig 1: Event-free curves for SCD

Analysis of Repolarization Dispersion to Predict Sudden Cardiac Death Survival

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Abstract - Enhancement of dynamic restitution of the action potential duration (APDR) dispersion has been associated with higher propensity to suffer from ventricular arrhythmias and sudden cardiac death (SCD). Recently, a marker, Δα, was proposed to quantify APDR dispersion from the electrocardiogram (ECG) by computing the ratio between T-peak-to-T-end (T_{pe}) and RR intervals. Holter ECG recordings of 609 subjects were analysed. RR and T_{pe} series were computed and the risk marker Δα was derived. The marker Δα stratified patients according to their risk of suffering from ventricular arrhythmias that could lead to SCD, with larger repolarization dispersion indicating lower survival probability.

I. INTRODUCTION

APDR measures the relationship between the action potential duration and the RR interval at steady-state pacing. Due to heterogeneities in the ventricles, APDR presents spatial variations generally termed APDR dispersion. Enhancement of APDR dispersion has been associated with higher propensity to suffer from ventricular arrhythmias and SCD. A marker, Δα, was recently published to non-invasively estimate the quantification of APDR dispersion from the ECG by computing the ratio between differences in the T_{pe} and RR intervals at different steady-state conditions [1].

II. METHODS

Holter ECG recordings of 609 subjects (48 victims of SCD, 64 of other cardiac causes, 25 of non-cardiac death causes and 472 survivors) from the ``MUSIC'' database were analysed. ECGs were delineated using a single-lead procedure over the first principal component calculated to emphasize the T-wave. RR and T_{pe} series were computed and T_{pe}/RR dynamics was estimated using a nonlinear system with memory [2], from which the risk marker Δα was derived, by applying the following equation:

$$\Delta\alpha = \frac{\partial T_{pe}}{\partial RR}$$

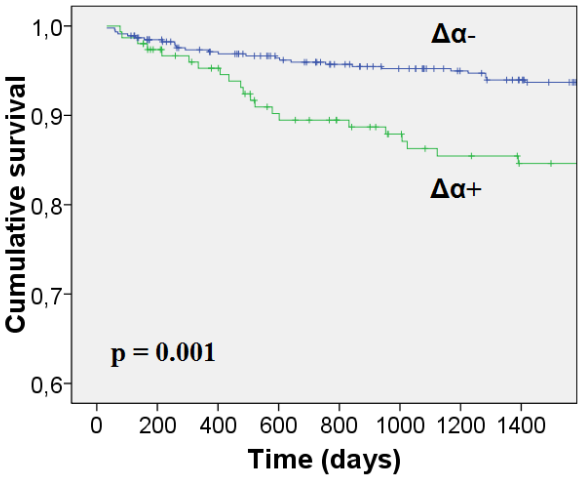

Figure 1.Event-free curves for SCD.

III. RESULTS AND DISCUSSION

Δα discriminated between the group formed by SCD victims and the group composed of the other subjects, with mean ± SEM values of: Δα = 0.052 ± 0.013 for the former and Δα = 0.026 ± 0.003 for the latter (p = 0.026). Following the hypothesis that an enhancement of APDR dispersion has been associated with higher propensity to suffer from SCD, a threshold on the third quartile of Δα values was set in a survival analysis. Statistically significantly different event probabilities were obtained in both strata of the population (p = 0.001), as shown in Figure 1.

IV. CONCLUSIONS

The marker Δα stratifies patients according to their risk of suffering from ventricular arrhythmias that could lead to SCD, with larger repolarization dispersion indicating lower survival probability. Future research involves applying this method over a database composed of professional athletes, to predict sports-related sudden cardiac death.

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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 stratas 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 arrhtymogenic 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 and Methods

2.1. 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 [7]. 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.

2.2. Methods

2.2.1. 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 [8] 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.

2.2.2. 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 [9]. ΔAT represents the activation time delay between the two cells associated with APD_{min} and APD_{last}. ΔAT hardly changes with RR for RR intervals above 600 ms [10]. 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 α_{last} and α_{min} denote the slopes of the dynamic restitution curves at the regions corresponding to APD_{last} and APD_{min}, respectively:

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

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

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

2.2.3. 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 [11], 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.

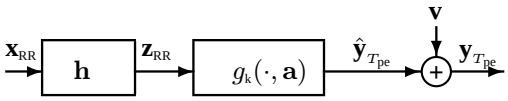

Figure 1. Block diagram describing the [RR,T_{pe}] relationship consisting of a time-invariant FIR filter (impulse response **h**) and a nonlinear function $g_k(\cdot, \mathbf{a})$. **v** accounts for the output error.

The impulse response **h** =[$h(1), ..., h(N)]^T$ 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 **h** was set to 150 samples. The function $g_k(\cdot, \mathbf{a})$, dependent on the parameter vector **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,...,10) were considered for $g_k(\cdot, \mathbf{a})$. The estimated output $\widehat{y}_{T_{pe}}$(n) was defined as

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

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

	Overall population ($n = 609$)	$\Delta\alpha-$ ($n = 457$)	$\Delta\alpha+$ ($n = 152$)	*p*-value
Age (y)	63 ± 0.5	62 ± 0.6	64 ± 1.0	**0.040**
Gender (men)	426 (70.0%)	333 (72.9%)	93 (61.2%)	**0.008**
NYHA class III	110 (18.1%)	81 (17.7%)	29 (19.1%)	0.716
LVEF $\leq$ 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%)	**0.001**
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	**0.001**
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%)	**0.003**

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.

Table 1. Characteristics of patients

derived in (4) can be replaced with the following equation, obtained by differentiating (5) with respect to z_{RR}:

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

where the derivative is evaluated at the mean z_{RR} value, $\overline{z}_{RR}$, 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

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

2.2.4. 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.

3. Results and Discussion

The mean ± SEM value of $\Delta\alpha$ in the study population was 0.028 ± 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 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, $\Delta\alpha$+ was the variable most significantly

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

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.

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

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.

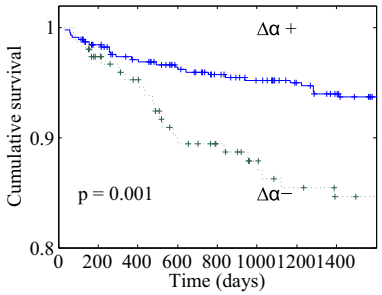

Figure 2. Event-free curves for sudden cardiac death

4. 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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