Ischemic risk stratification by means of multivariate analysis of the heart rate variability

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Ischemic risk stratification by means of multivariate analysis of the heart rate variability

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Abstract
In this work, a univariate and multivariate statistical analysis of indexes derived from heart rate variability (HRV) was conducted to stratify patients with ischemic dilated cardiomyopathy (IDC) in cardiac risk groups. Indexes conditional entropy, refined multiscale entropy (RMSE), detrended fluctuation analysis, time and frequency analysis, were applied to the RR interval series (beat-to-beat series), for single and multiscale complexity analysis of the HRV in IDC patients. Also, clinical parameters were considered. Two different endpoints after a follow-up of three years were considered: (i) analysis A, with 151 survivor patients as a low risk group and 13 patients that suffered sudden cardiac death as a high risk group; (ii) analysis B, with 192 survivor patients as a low risk group and 30 patients that suffered cardiac mortality as a high risk group. A univariate and multivariate linear discriminant analysis was used as a statistical technique for classifying patients in risk groups. Sensitivity (Sen) and specificity (Spe) were calculated as diagnostic criteria in order to evaluate the performance of the indexes and their linear combinations. Sen and Spe values of 80.0% and 72.9%, respectively, were obtained during daytime by combining one clinical parameter and one index from RMSE, and during nighttime Sen = 80% and Spe = 73.4% were attained by combining one clinical factor and two indexes from RMSE. In particular, relatively long time scales were more relevant for classifying patients into risk groups during nighttime, while during

7 Author to whom any correspondence should be addressed.
daytime shorter scales performed better. The results suggest that the left atrial size, indexed to body surface and RMSE indexes are those that allow enhanced classification of ischemic patients in their respective risk groups, confirming that a single measurement is not enough to fully characterize ischemic risk patients and the clinical relevance of HRV complexity measures.

Keywords: ischemic dilated cardiomyopathy, risk stratification, heart rate variability, complexity analysis, multivariate analysis

(Some figures may appear in colour only in the online journal)

1. Introduction

Cardiovascular diseases represent the most common cause of death worldwide (Heron et al 2009) and their high incidence has motivated the development of quantitative markers, in order to identify the presence of cardiac pathologies and the risk of suffering cardiac death. Clinical markers as the left ventricular ejection fraction (LVEF), the New York Heart Association (NYHA) functional classification, and the increment in left atrium size have been associated with heart failure and ischemia in heart tissue (Bayés-Genis et al 2007, Voss et al 2008).

Additionally, several studies used heart rate variability (HRV) analysis as a non-invasive method for diagnosis of a large number of cardiovascular diseases (Task force 1996), which may involve changes in the autonomic nervous system modulation and tone, thus facilitating the diagnosis and prognosis of cardiopathies and neuropathies.

Methods for quantifying HRV by means of the RR series (time intervals between consecutive heart beats) are categorized as time domain, frequency domain, geometric and nonlinear techniques (Task force 1996). While time domain measures assess the magnitude of the RR variations, frequency domain analysis decomposes heart period changes into different contributions according to their frequency content. However, given the intrinsic nonlinear nature in cardiac regulatory mechanisms, a more insightful description of the dynamical changes of HRV becomes inaccessible if only linear methods of analysis are employed (Wessel et al 2000). In addition, the nonlinear methods provide a reliable quantification of the complexity of RR variability, a powerful marker of pathological situations (Moraru et al 2005).

Healthy subjects and heart failure patients can be clearly distinguished using conventional clinical measures and more sophisticated indexes (Guzzetti et al 2000, Costa et al 2002, Voss et al 2007, Porta et al 2007a). Unfortunately, the stratification of risk groups in patients with heart failure is an issue that has yet to be resolved, and, probably, a single measurement is not sufficient to fully characterize the risk groups, being necessary to use a combination of parameters derived from different techniques. Several nonlinear analyses have been proposed to distinguish the patients with high risk, especially for cardiovascular diseases (Maestri et al 2007). Also and considering that the cardiovascular control is carried out by several regulatory mechanisms interacting across multiple temporal scales, multiscale analysis has showed to be an adequate technique in the HRV analysis (Costa et al 2007, Ho et al 2011).

In this work, linear time and frequency domain parameters and nonlinear complexity indexes derived from HRV were evaluated with traditional clinical indexes in different groups of heart failure patients. Specifically, parameters derived from multiscale analysis, based on entropies and detrended fluctuation analysis, were selected in order to characterize the intrinsic multiscale behavior of the HRV. Univariate and multivariate statistical analyses were carried out to determine which index was helpful to classify different groups and which combination
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of parameters improved risk stratification of patients with ischemic dilated cardiomyopathy (IDC) at risk for cardiac death.

2. Methods

2.1. Analyzed data and preprocessing

Patients from MUSIC (MUerte Subita en Insuficiencia Cardiaca, Sudden Death in Heart Failure) study were analyzed in the present work. All these patients had symptomatic chronic heart failure (NYHA class II-III) and were treated according to institutional guidelines. The MUSIC study included patients with either depressed (<45%) or preserved (≥45%) LVEF. Patients were excluded from MUSIC study if they had recent acute coronary syndrome or severe valvular disease amenable for surgical repair. Also those patients with severe pulmonary, hepatic or renal disease or other concomitant non-cardiovascular disease expected to reduce life-expectancy to less than three years were excluded. The investigation was conforming to the recommendations of the Declaration of Helsinki, the study was approved by the Ethical Committee of the institution and all subjects gave their written informed consent before participation.

A total of 212 patients with IDC were enrolled in the present work. The inclusion criteria were: sinus rhythm, symptomatic chronic heart failure with NYHA functional class II or III, and ischemic etiology of heart failure. Most patients were taking angiotensin-converting enzyme inhibitors (75.6%), blockers (76.8%), and diuretics (60.8%).

Two different end-points after a follow-up of three years were considered: (i) analysis A, with 151 survivor patients (SV) as a low risk group (aged 64.7 ± 0.60 years, 91.4% male) and 13 patients that suffered sudden cardiac death (SCD) as a high risk group (aged 63.5 ± 1.66 years, 92.3% male); (ii) analysis B, with 192 survivor patients (SV) as a low risk group (aged 63.0 ± 0.60 years, 87.0% male) and 30 patients that suffered cardiac mortality (CM) due to SCD, progressive heart failure or myocardial infarction, as a high risk group (aged 64.5 ± 1.55 years, 86.7% male). SCD and CM patients were aged-matched with SV groups. Death was defined as ‘sudden’ if it was: (1) a witnessed death occurring within 60min from the onset of new symptoms, unless a cause other than cardiac was obvious; (2) an unwitnessed death (<24 h) in the absence of pre-existing progressive circulatory failure or other causes of death; or (3) a death during attempted resuscitation (Tapanainen et al 2004).

The RR series, intervals between consecutive beats, were obtained from 24h ECG-Holter recordings with a sampling frequency of 200 Hz (Spiderview recorders, ELA Medical, Sorin Group, Paris). An adaptive filter (Wessel et al 2000) was applied to the RR series in order to replace ectopic beats and artifacts by interpolated RR intervals. Percentages of corrections were less than 1.5%. The 24h RR series were analyzed in two periods, during daytime (16:00 to 21:00h) and during nighttime (23:00 to 5:00h), and 10 000 cardiac beats were considered for each period.

2.2. Methods

2.2.1. Clinical and traditional analysis. The following clinical parameters, which were reported in previous studies as important markers in the classification of subjects according to the risk of cardiac death (Bayés-Genis et al 2007, Voss et al 2008), were considered in this work: LVEF, NYHA (functional classification system), NT-proBNP (N-terminal pro b-type natriuretic peptide), Indexed_LA (left atrial size indexed to body surface) and Indexed_LVEDD (left ventricular end diastolic diameter indexed to body surface).
The time domain and frequency domain indexes were selected based on recommendations given in (Task force 1996). In spectral analysis, the RR series of 10,000 beats were analyzed according to frames of 300 beats with an overlap of 50%. Each frame was interpolated and resampled at 5 Hz. Power spectrum was estimated over each frame using an AR approach (Burg method) with order 12: total power \( P_{\text{tot}} \) (ms\(^2\)); power in the high frequency band \( \text{HF} \) (ms\(^2\), 0.15–0.4 Hz); power in the low frequency band \( \text{LF} \) (ms\(^2\), 0.04–0.15 Hz); power in the very low frequency band \( \text{VLF} \) (ms\(^2\), below 0.04 Hz); LF and HF in normalized units (LFn and HFn); and the LF/HF ratio.

2.2.2. Conditional entropy. Conditional entropy (Porta et al 1998) was computed using a nonuniform quantization of the phase space (Valencia et al 2009a) following a criterion (1) based on symbolic dynamics (Voss et al 2007):

\[
S_i = \begin{cases} 
0 & \text{if } \bar{x} < x(i) \leq (1 + a)\bar{x} \\
1 & \text{if } (1 + a)\bar{x} < x(i) < \infty \\
2 & \text{if } (1 - a)\bar{x} < x(i) \leq \bar{x} \\
3 & \text{if } 0 < x(i) \leq (1 - a)\bar{x}
\end{cases} 
\quad i = 1, \ldots, N
\]  

(1)

where \( N \), \( \bar{x} \) and \( a \) are the number of samples, the mean value and a constant that quantifies the standard deviations of the series \( x = \{x(i), i = 1, \ldots, N\} \), respectively. \( S_i \) represents the symbolic series that is obtained. Parameter \( a \) was set to 0.07 according with previous studies of the HRV by means of symbolic dynamics (Valencia et al 2007). With this criterion (1), the series \( x \) was divided into four non-uniformly spaced regions. A pattern of \( L \) consecutive symbols \( S_i \) represents one point in the \( L \)-dimensional phase space, where each symbol \( S_i \) denotes the value of \( x(i) \) properly quantized \( \hat{x}(i) \). Therefore, the \( L \)-dimensional phase space is reconstructed as \( \hat{u}_L(j) = [\hat{x}_i, \ldots, \hat{x}_{i+L-1}] \) and the conditional entropy \( H_C \) is calculated using the definition given in (2):

\[
H_C\left(\frac{u_L}{u_{L-1}}\right) = \frac{1}{1 - q} \sum_{k=1}^{N_k} p(u_{L-1}(k)) \log \left( \sum_{j=1}^{N_j} \left( \frac{p(u_L(j)/u_{L-1}(k))}{u_{L-1}(k)} \right)^q \right)
\]

(2)

where \( N_k = N - (L - 2) \), \( N_j = N - (L - 1) \), \( u_L(j) \) represents a pattern of \( L \) consecutive samples, \( p(u_{L-1}(k)) \) denotes the joint probability of the pattern \( u_{L-1}(k) \), \( p(u_L(j)/u_{L-1}(k)) \) symbolizes the conditional probability of a pattern \( u_L(j) \) of \( L \) samples given a pattern \( u_{L-1}(k) \) of \( L-1 \) samples. The parameter \( q \) is a real number, \( q > 0 \) and \( q \neq 1 \), that determines the manner in which the probabilities of the vectors \( u_L(j) \) are weighted. This definition (2) includes the use of the Rényi entropy in the computation of \( H_C \) and therefore, it is a generalization of the conditional entropy given in (Porta et al 1998) which is based solely on the Shannon entropy. In this study, it was taken into account different values of parameter \( q = \{0.1, 0.15, 0.25, 1, 2, 4\} \), where \( q = 1 \) indicates that the definition of the Shannon entropy was used, and the parameter \( L \) was fixed to \( L = 2 \) (Valencia et al 2009a). The conditional entropy \( H_C \) will be indicated as \( H_C(L)_q \), with \( L = 2 \), in the following sections. In the computation of \( H_C(L) \), during daytime and nighttime, the RR series were divided into non-overlapped windows of length \( N = 1000 \) beats.

2.2.3. Multiscale entropy. Refined multiscale entropy (RMSE) (Valencia et al 2009b) was applied as a technique of multiscale analysis in which an entropy rate (SampEn(\( \tau \))) is computed on different time scales of the RR series, given information of the regularity of the HRV in each one of the time scales. SampEn(\( \tau \)) represents the sample entropy computed in the time scale \( \tau \). RMSE provides two refinements of MSE (multiscale entropy —(Costa et al 2005)):
(i) it offers a way to improve the procedure devised to eliminate fast time scales, avoiding the aliasing effects; (ii) it modifies the coarse graining procedure in such a way that reduction of the variance in the RR series, because the elimination of fast time scales, do not tend to artificially decrease entropy rate as a function of the time scale. The result is a more reliable method for the assessment of entropy-based complexity as a function of the temporal scale.

2.2.4. Detrended fluctuation analysis. As an alternative to standard analysis using detrended fluctuation analysis (DFA) in the RR series (Peng et al. 1995), in this work it was proposed a previous transformation of the RR series into series of symbols. Concretely, HRV was analyzed by applying DFA to: (a) RR series; (b) RR increment series (△RR); (c) magnitude of △RR series (|△RR|); (d) sign of △RR series (△RRsign); (e) symbolic series obtained from △RR series (△RRsymbol). The following criteria (3) were applied to transform the △RR series into symbols:

\[
S_i = \begin{cases} 
3 & \text{if } (\overline{\triangle RR} + \text{sd}) < \triangle RR_i < \infty \\
2 & \text{if } \triangle RR < \triangle RR_i \leq (\overline{\triangle RR} + \text{sd}) \\
1 & \text{if } (\overline{\triangle RR} - \text{sd}) < \triangle RR_i \leq \overline{\triangle RR} \\
0 & \text{if } -\infty < \triangle RR_i \leq (\overline{\triangle RR} - \text{sd}) 
\end{cases} 
\]

where N, \(\overline{\triangle RR}\) and sd are the length, the mean value and the standard deviation of the △RR series. This transformation allows more information about the magnitude and the sign of the RR increment series to be included. Thus, symbols 0 and 1 represent a ‘negative sign’ (the present RR interval is shorter than the previous one) and symbols 2 and 3 represent a ‘positive sign’ (the present RR interval is larger than the previous one), and additionally, symbols 0 and 3 indicate a strong variation between consecutive RR intervals whereas symbols 1 and 2 indicate a weak variation.

Two scaling exponents were calculated according with the regions proposed in Peng et al. (1995): \(\alpha_1\) corresponding to the region given by \(4 < n < 16\) and \(\alpha_2\) corresponding to the region given by \(16 < n < 64\), where \(n\) is a parameter of DFA that is used to indicate the length of the boxes in which the series is divided.

Due to the limitation in accuracy of DFA when scaling exponents \(\alpha\) are computed in series with strong anticorrelation (\(\alpha\) values close to zero), as △RR series and △RRsymbol series have proven to be (Ashkenazy et al. 2001), series were doubly integrated (Kantelhardt et al. 2002). Thus, the scaling exponent \(\alpha\) must be interpreted considering the following ranges: (i) \(1 < \alpha < 1.5\) for series with anticorrelation; (ii) \(\alpha = 1.5\) for uncorrelated series; (iii) \(1.5 < \alpha \leq 2\) for series with long range correlation; (iv) \(\alpha = 2\) for \(1/f\) noise; (v) \(2 < \alpha \leq 2.5\) for series with long range correlation that not follow a power law.

2.2.5. Statistical analysis. A statistical analysis based on Anova test was used to assess the significance of the differences between continuous variables from clinical parameters, classical indexes, RMSE indexes and DFA exponents derived during daytime or nighttime inside the same high risk groups in analysis A and B. Indeed, Levene’s test for homogeneity of variance was used to confirm homoscedasticity. Indexes that no fulfill homoscedasticity were statistically analyzed by applying the Mann–Whitney U test. The Fisher exact test was used in case of categorical variables. Statistical analysis based on repeated measure analysis of variance was applied to \(H(x)\) indexes calculated on each window of length \(N = 1000\) beats. A significance level \(p < 0.05\) was considered as significant.

A discriminant linear function was built for every individual index (univariate analysis) and for their combination (multivariate analysis) in order to classify the subjects. The sensitivity
Table 1. Discriminant analysis of clinical parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Analysis A</th>
<th>Analysis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>TL-proBNP (ng L⁻¹)</td>
<td>SV (n = 151) SCD (n = 13) p</td>
<td>SV (n = 192) CM (n = 30) p</td>
</tr>
<tr>
<td>NT-proBNP (ng L⁻¹)</td>
<td>154.7 ± 20.4 566.6 ± 198.8 0.0108 38.5 88.8 0.714</td>
<td>165.7 ± 21.2 571.6 ± 131.2 &lt;0.0005 40.0 89.2 0.744</td>
</tr>
<tr>
<td>NYHA (% patients in class III)</td>
<td>15.2 46.2 0.0052 46.2 84.8 0.655</td>
<td>14.6 53.3 &lt;0.0005 53.3 85.4 0.694</td>
</tr>
<tr>
<td>Indexed_LA (mm m⁻²)</td>
<td>22.7 ± 0.26 24.8 ± 0.84 0.0278 61.5 64.9 0.684</td>
<td>35.5 ± 0.80 30.7 ± 1.38 0.0338 53.3 59.4 0.620</td>
</tr>
</tbody>
</table>

SV, survivors; SCD, sudden cardiac death; CM, cardiac mortality. Mean ± standard error are indicated in continuous variables and percentage is indicated in categorical variables. (Sen), the specificity (Spe) and the area under the curve (AUC) were taken into account in this statistical analysis using leave-one-out cross-validation. To test the association between clinical parameters and indexes derived from analysis of the RR series, a two tailed Pearson correlation coefficient (r) was calculated. Finally, Cox regression has been applied to the multivariate function that best has discriminated the groups.

3. Results

3.1. Univariate statistical analysis

3.1.1. Clinical parameters, time and frequency indexes. Clinical parameters that showed significant statistical differences with \( p < 0.05 \), comparing low and high risk groups in analysis A and B, are included in table 1. In this table, mean ± standard error for continuous variables (or percentages for categorical variables), significance level (p), Sen, Spe and AUC values are indicated. Clinical parameters exhibited similar changes in both analyses, A and B. Indeed, the value of NT-proBNP, NYHA and Indexed_LA was higher in high risk groups in comparison with low risk groups. Conversely, the value of LVEF factor was lower in the high risk group in comparison with the low risk group. Although parameters as NT-proBNP and NYHA were highly significant, especially in analysis B, these indexes had poor Sen values. The unique clinical factor with simultaneously values of Sen and Spe higher than 60%, in both analysis A and B, was the Indexed_LA factor. The best AUC values were obtained with TL-proBNP (AUC = 0.714) in analysis A and with indexed_LA (AUC = 0.745) in analysis B.

Time domain indexes and frequency domain indexes with \( p < 0.05 \) are included in table 2 when low and high risk groups were compared (analysis B), both during the daytime and the nighttime. The mean value of the indexes sdNN, LF/HF during daytime and the mean value of the index LFH during nighttime was lower in the high risk group in comparison with the low risk group. The Sen and Spe of these indexes were not simultaneously higher than 60%. In analysis A, none of the time and frequency domain indexes allowed a statistical differentiation between low and high risk groups neither during daytime or nighttime.

3.1.2. Measures with conditional entropy. Table 2 also includes the conditional entropy indexes that showed \( p < 0.05 \) when low and high risk groups were compared during nighttime in both analysis A and B. In the daytime, none of the proposed conditional entropy indexes allowed a statistical differentiation between low and high risk groups neither during analysis A or analysis B. During the nighttime in analysis A and B, the mean value of all the \( H_{c(q)} \) indexes was lower in the high risk group in comparison with the low risk group, indicating an
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Table 2. Statistical and discriminant analysis of IDC patients: analysis A and B.

<table>
<thead>
<tr>
<th>Analysis A</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexes</td>
<td>SV (n = 151)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>(H_C(2)_{q=0.1})</td>
<td>1.055 ± 0.012</td>
</tr>
<tr>
<td>(H_C(2)_{q=0.15})</td>
<td>1.017 ± 0.012</td>
</tr>
<tr>
<td>(H_C(2)_{q=0.25})</td>
<td>0.947 ± 0.012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis B</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexes</td>
<td>SV (n = 192)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>62.37 ± 2.269</td>
</tr>
<tr>
<td>LF/HF</td>
<td>57.31 ± 1.047</td>
</tr>
<tr>
<td>SampEn(5)</td>
<td>1.185 ± 0.025</td>
</tr>
<tr>
<td>SampEn(7)</td>
<td>1.293 ± 0.205</td>
</tr>
<tr>
<td>SampEn(13)</td>
<td>1.397 ± 0.205</td>
</tr>
<tr>
<td>(\alpha_1(\Delta RR))</td>
<td>1.148 ± 0.016</td>
</tr>
<tr>
<td>(\alpha_1(\Delta RR_{sign}))</td>
<td>1.472 ± 0.006</td>
</tr>
<tr>
<td>(\alpha_1(\Delta RR_{symbol}))</td>
<td>1.317 ± 0.009</td>
</tr>
<tr>
<td>(\alpha_2(\Delta RR_{symbol}))</td>
<td>1.381 ± 0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis B</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexes</td>
<td>SV (n = 192)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>57.71 ± 1.136</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.058 ± 0.011</td>
</tr>
<tr>
<td>SampEn(5)</td>
<td>1.021 ± 0.011</td>
</tr>
<tr>
<td>SampEn(7)</td>
<td>0.953 ± 0.011</td>
</tr>
<tr>
<td>SampEn(13)</td>
<td>1.427 ± 0.025</td>
</tr>
<tr>
<td>SampEn(10)</td>
<td>1.448 ± 0.025</td>
</tr>
<tr>
<td>SampEn(11)</td>
<td>1.446 ± 0.025</td>
</tr>
<tr>
<td>SampEn(13)</td>
<td>1.447 ± 0.026</td>
</tr>
<tr>
<td>(\alpha_1(\Delta RR))</td>
<td>1.891 ± 0.005</td>
</tr>
<tr>
<td>(\alpha_1(\Delta RR_{sign}))</td>
<td>1.456 ± 0.006</td>
</tr>
<tr>
<td>(\alpha_1(\Delta RR_{symbol}))</td>
<td>1.353 ± 0.008</td>
</tr>
</tbody>
</table>

SV, survivors; SCD, sudden cardiac death; CM, cardiac mortality. Mean ± standard error is indicated.

increment in the regularity of the RR series belonging to patients at increased risk of cardiac death. Unlike time and frequency domain measures, it was possible to obtain \(H_C(2)\) indexes with simultaneously values of Sen and Spe higher than 60% but only in analysis A, using \(q = \{0.1, 0.15, 0.25\}\). The best result in analysis A was obtained with \(H_C(2)_{q=0.1}\) (Sen = 61.5%, Spe = 77.5% and AUC = 0.666).

3.1.3. Measures with refined multiscale entropy. Figure 1 shows the course of RMSE calculated over the RR series in IDC patients classified in low (SV) and high (SCD or CM) risk groups, according with analysis A and B. Risk groups in analysis A are compared during daytime (figure 1(a)) and nighttime (figure 1(b)). In these figures, the RMSE curves exhibited a minimum at short time scale followed by an exponential increment as function of the scale factor \(\tau\). Even if entropy seems to be larger in the low risk group than in the high risk group, there are no significant statistical differences in any of the time scales. In analysis B, risk groups are compared during daytime (figure 1(c)) and nighttime (figure 1(d)). Again, the RMSE curves exhibited a minimum at short time scale followed by an exponential increment as function of the scale factor \(\tau\). Contrary to analysis A, in analysis B risk groups showed significant differences over a large interval of scales both during daytime (figure 1(c) at \(\tau = 4–15\)) and during nighttime (figure 1(d) at \(\tau = 3–16\)), the entropy-based complexity being
Figure 1. Mean values (± standard error) of RMSE as a function of the scale factor derived from the RR series in IDC patients classified in low (SV) and high (SCD) risk of sudden cardiac death (analysis A), and in low (SV) and high (CM) risk of cardiac death (analysis B). SV and SCD were compared during daytime (a) and during nighttime (b). Also, SV and CM were compared during daytime (c) and during nighttime (d). Significant statistical differences with \( p < 0.05 \) are marked with *.

smaller in the CM group than in the SV group. Indeed, table 2 contains the sample entropy indexes that are calculated in the different time scale given by \( \tau \), SampEn(\( \tau \)), which showed \( p < 0.05 \) and simultaneously values of Sen and Spe higher than 60% when low and high risk groups were compared in analysis B. The largest statistical differentiation was obtained at the time scale \( \tau = 7 \) during daytime, and at the time scale \( \tau = 8 \) during nighttime.

3.1.4. Measures with detrended fluctuation analysis. Table 2 shows results relevant to detrended fluctuation analysis for all the proposed different transformation of the RR series both during daytime and nighttime. Only scaling exponents with \( p < 0.05 \) were reported when low and high risk groups were compared. In analysis A, none of the scaling exponent indexes allowed a statistical differentiation between low and high risk groups neither during daytime or nighttime. In analysis B, during daytime scaling exponents \( \alpha_1 \) of \( \Delta \text{RR} \) and \( \Delta \text{RR}_{\text{symbol}} \), and \( \alpha_2 \) of \( \Delta \text{RR}_{\text{sign}} \) and \( \Delta \text{RR}_{\text{symbol}} \) allowed a significant separation between low and high risk groups. On the other hand, during nighttime in analysis B, scaling exponents \( \alpha_2 \) of \( \text{RR}, \Delta \text{RR}_{\text{sign}} \) and
Table 3. Multivariate statistical analysis of IDC patients.

<table>
<thead>
<tr>
<th>Analysis A</th>
<th>Sen(%)</th>
<th>Spe(%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night</td>
<td>$f_L$ (Indexed_LA, $H_C(2)q = 0.1$)</td>
<td>69.2</td>
<td>75.5</td>
</tr>
<tr>
<td>Analysis B</td>
<td>Sen(%)</td>
<td>Spe(%)</td>
<td>AUC</td>
</tr>
<tr>
<td>Day</td>
<td>$f_L$ (Indexed_LA, SampEn(7))</td>
<td>80.0</td>
<td>72.9</td>
</tr>
<tr>
<td></td>
<td>$f_L$ (Indexed_LA, $\alpha_1(\triangle RR)$)</td>
<td>70.0</td>
<td>76.0</td>
</tr>
<tr>
<td></td>
<td>$f_L$ (Indexed_LA, $\alpha_2(\triangle RR_{symbol})$)</td>
<td>73.3</td>
<td>74.0</td>
</tr>
<tr>
<td>Night</td>
<td>$f_L$ (Indexed_LA, SampEn(8))</td>
<td>76.7</td>
<td>71.9</td>
</tr>
<tr>
<td></td>
<td>$f_L$ (Indexed_LA, SampEn(8), SampEn(13))</td>
<td>80.0</td>
<td>73.4</td>
</tr>
</tbody>
</table>

$f_L(x,y,z)$, discriminant function using indexes $x$, $y$ and $z$.

$\triangle RR_{symbol}$ significantly varied between the two groups. For all these series, including analysis during daytime and nighttime, the mean value of the scaling exponent $\alpha_1$ was higher in the low risk group than in the high risk group, whereas the scaling exponent $\alpha_2$ showed the opposite behavior, i.e. the mean value of $\alpha_2$ was lower in the low risk group than in the high risk group. In general: (i) the RR series showed the same behavior as the $1/f$ noise, with $\alpha$ values about 2; (ii) the $\triangle RR$ series had a strong anticorrelation behavior with $1 < \alpha < 1.5$; (iii) the $\triangle RR_{sign}$ series had a weak anticorrelation behavior, tending to be similar to white noise with $\alpha$ values about 1.5; (iv) $\triangle RR_{symbol}$ series showed a less anticorrelation behavior in comparison with the original $\triangle RR$ series, with $1 < \alpha < 1.5$. It must be noted that the $\triangle RR_{symbol}$ series is the only RR series transformation that showed scaling exponents (i.e. $\alpha_2$) with simultaneously values of Sen and Spe higher than 60% in both daytime and nighttime.

3.2. Multivariate statistical analysis

Table 3 contains the best combinations of the indexes with $p < 0.05$, Sen > 60% and Spe > 60%, simultaneously, obtained by applying a multivariate discriminant analysis in analysis A and B. During nighttime, the linear combination $f_L$ (Indexed_LA, $H_C(2)q = 0.1$) was the best in analysis A. In analysis B, the linear combination $f_L$ (Indexed_LA, SampEn(7)) was the best during daytime, while the linear combination during nighttime was $f_L$ (Indexed_LA, SampEn(8), SampEn(13)). These results were confirmed by their AUC statistics, where AUC = 0.804 for analysis A during nighttime, AUC = 0.803 and AUC = 0.793 for analysis B during daytime and nighttime, respectively. It is observed that linear combinations in analysis B include the clinical factor Indexed_LA and one or more entropy rates given by SampEn($\tau$) as proposed in the RMSE methodology. In particular, relatively long time scales ($\tau = 8, 13$) were more relevant in classifying patients into risk groups during the nighttime, while for the daytime shorter scales ($\tau = 7$) showed a better classification of patients. Pearson’s correlation coefficients between Indice.AI and indexes $H_C(2)q = 0.10$, SampEn(7), $\alpha_1(\triangle RR)$, $\alpha_2(\triangle RR_{symbol})$, SampEn(8) and SampEn(13) were $r = -0.114$, $r = -0.093$, $r = -0.211$, $r = 0.210$, $r = -0.032$ and $r = -0.015$, respectively, indicating that Indice.AI and the studied indexes contain independent information.

The estimated survival functions using the Cox regression analysis and considering the covariates Indexed_LA, $f_L$ (Indexed_LA, $H_C(2)q = 0.1$), $f_L$ (Indexed_LA, SampEn(7)) and $f_L$ (Indexed_LA, SampEn(8), SampEn(13)) are plotted in figure 2. The baseline functions are included. Table 4 shows the $-2LL$ ($-2$ log-likelihood), $\chi^2$ (chi-square) and $p$ statistics comparing the estimated survival functions with the baseline functions. When tested in the multivariate Cox model, the $f_L$ functions were the most powerful independent predictor of cardiac mortality compared with Indexed_LA index, as it is seen in figure 2 and table 4. This is more evidenced during nighttime, as it is observed in figure 2(a) for the analysis A and figure 2(c) for the analysis B.
4. Discussion

An increase in NT-proBNP, NYHA or Indexed_LA and a reduction in LVEF is directly related to cardiac system dysfunction (Bayés-Genis et al 2007). Even though heart failure is present in all analyzed patients, it is clear that the value of NT-proBNP, NYHA, Indexed_LA and LVEF indicates a greater cardiac system dysfunction in patients that were included in the high risk groups of suffering cardiac death and sudden cardiac death. Although clinical parameters such as NT-proBNP and NYHA were highly significant in analysis B, the Sen values of these parameters in the classification of patients using univariate linear discriminant analysis were lower than 60% (Sen = 40.0% for NT-proBNP and Sen = 53.3% for NYHA). These results are consistent with previous studies (Bayès-Genis et al 2007, Voss et al 2008) confirming that the major shortcoming of these clinical parameters, which reflect the severity of heart failure, is its low Sen as it only identifies about 50% of risk group subjects. Particularly in (Voss et al 2008), 509 patients with heart failure, belonging to the MUSIC database, were classified
Table 4. Cox regression analysis.

<table>
<thead>
<tr>
<th>Analysis A</th>
<th>$-2LL$</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hazard function</td>
<td>131.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed_LA (mm m$^{-2}$)</td>
<td>126.6</td>
<td>4.7</td>
<td>0.0299</td>
</tr>
</tbody>
</table>

**Night**

| $f_1$ (Indexed_LA, $H_C(2)_{q=0.1}$) | 118.1  | 13.2     | $<0.0005$ |

**Analysis B**

<table>
<thead>
<tr>
<th>$-2LL$</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hazard function</td>
<td>320.0</td>
<td></td>
</tr>
<tr>
<td>Indexed_LA (mm m$^{-2}$)</td>
<td>303.4</td>
<td>16.6</td>
</tr>
</tbody>
</table>

**Day**

| $f_1$ (Indexed_LA, SampEn(7)) | 300.5  | 19.5    | $<0.0005$ |

**Night**

| $f_1$ (Indexed_LA, SampEn(8), SampEn(13)) | 295.4  | 24.7    | $<0.0005$ |

$F_x(y,z)$, discriminant function using indexes $x$, $y$ and $z$. $-2LL$ ($-2$ log-likelihood function), $\chi^2$ (chi-square), $p$ value.

between low and high risk groups of cardiac death, with a $\text{Sen} = 44.0\%$ and $\text{Spe} = 80.0\%$ by means of a combination of clinical parameters such as: gender, age, LVEF, NYHA and LVDD (left ventricular diastolic diameter). On the other hand, in the present work the only clinical factor with values of Sen and Spe simultaneously higher than 60%, in both analysis A and B, was the factor Indexed_LA. Similar results were obtained in (Bayés-Genis et al 2007) where the factor Indexed_LA showed a $\text{Sen} = 58.0\%$ and $\text{Spe} = 74.0\%$ studying 494 patients with heart failure, belonging to the MUSIC database and classifying in low and high risk groups of sudden cardiac death.

The analysis in time and frequency domains of the RR series has indicated that none of the proposed indexes allowed a statistical differentiation between low and high risk groups in analysis A, neither during daytime or nighttime. However, in analysis B, which includes patients from analysis A and patients with others causes of death, the indexes $sdNN$, $LF_n$ and $LF/HF$ have indicated that the magnitude of RR changes ($sdNN$) and the sympathetic modulation ($LF_n$ and $LF/HF$) were significantly higher in SV group than in CM during daytime. Spectral analysis of the RR series suggests that the capability to modify RR is more preserved in the SV group than in the CM one, even though both groups were characterized by a high sympathetic tone. Various pathophysiological mechanisms were proposed to explain this finding (i.e. a reduction in sinus node response, central abnormality in autonomic modulation, limitation in responsiveness to high levels of cardiac sympathetic activation, depressed baroreflex, and increased chemoreceptor sensitivity (Guzzetti et al 2005)). The risk classification of patients using only the traditional indexes of time domain and frequency domain has not provided satisfactory results. The Sen and Spe values of the indexes $sdNN$, $LF_n$ and $LF/HF$ were not simultaneously higher than 60%, underlining the lack of predictive power of these measures in the classification of IDC patients at risk of cardiac death (Tapanainen et al 2002). Although the study in Tapanainen et al 2002 was performed on patients who suffered acute myocardial infarction and not only on IDC patients, the Sen in indexes of the time and frequency domain was less than 60%, with the exception of $LF/HF$ (Sen $= 61\%$), when patients were classified into risk groups.

In contrast to the analysis of traditional measures, which indicated that none of the proposed traditional indexes allowed statistical discrimination among the risk groups in the analysis A, conditional entropy indexes $H_C(2)_{q=0.1}$, $H_C(2)_{q}=0.15$ and $H_C(2)_{q}=0.25$ showed significant differences between risk groups during the nighttime for both analysis A and analysis B. The value of these conditional entropy indexes was lower in high risk groups than in low risk groups, indicating an increase in the regularity of HRV, at short time scales,
in patients who suffered SCD and CM in comparison with SV patients. Besides that, the proposed conditional entropy index $H_C(2)_q$ was the only one, with the exception of the clinical factor Indexed_LA, which achieved both Sen and Spe values greater than 60% in analysis A. This result emphasizes the importance of a proper partitioning of the phase space in the calculation of the entropy rates as discussed in Valencia et al 2009a. Because the regularity of the HRV is controlled by the sympathetic branch (Porta et al 2007b), an increase in regularity might indicate that the high risk patients have higher levels of sympathetic tone, suggesting the implementation of more aggressive therapy to reduce sympathetic overactivity in patients at high risk.

The multiscale analysis by means of entropy rates has indicated that several indexes obtained with RMSE (SampEn($\tau$)) allowed simultaneous values of Sen and Spe higher or equal than 60% in analysis B, during both daytime and nighttime. These SampEn($\tau$) indexes have been obtained for time scales in the medium range ($\tau = \{5, 6, 7, 13\}$ for daytime and $\tau = \{8,10,11,13\}$ for nighttime), being the entropy-based complexity smaller in the CM than in the SV group. These results indicate a reduction of the HRV complexity in patients with a high degree of disease. In contrast, there are not significant differences in the shortest and largest time scales when the risk groups were compared using the SampEn($\tau$) indexes. These results reinforce the need for a multiscale analysis to adequately characterize the behavior of HRV in IDC patients (Valencia et al 2009b, Costa et al 2005). Other authors (Costa et al 2007, Ho et al 2011) have used cumulative MSE values from different values of $\tau$, representing the complexity exhibited in short and long time scales. However in our study, generalize parameters, as use in Ho et al 2011, lose the local scaling information as given by SampEn(7), SampEn(8) and SampEn(13) and present non statistical differences. Furthermore, RR series of IDC patients seem to exhibit complexity differences in the mid-scale locations $\tau = \{7, 8, 13\}$ rather than short or long time scales.

In the reported results, significant differences were found between daytime and nighttime periods for the low risk group in analysis B, particularly when indexes SampEn(13), $\alpha_2 (\Delta RR_{sign})$ and $\alpha_2 (\Delta RR_{symbol})$ were compared ($p < 0.05$). Considering the index SampEn(13), it is possible to indicate that entropy-based complexity was significantly larger during nighttime than daytime, and that the low risk group presents circadian variations more evident than in the high risk group.

The multivariate statistical analysis based on linear discriminant analysis, including clinical parameters, traditional measures from time and frequency domains, entropy rates indexes and scaling exponents, suggests that Indexed_LA, $H_C(2)_q = 0.1$ and SampEn($\tau$) indexes in middle time scales are those that allow better classification of patients in their respective risk groups. In analysis A, a linear combination of indexes $f_L$ (Indexed_LA, $H_C(2)_q = 0.1$) improved the classification of patients in the high risk groups compared with the individual variables, obtaining a Sen = 69.2%. On the other hand, a better classification was obtained in the analysis B with a linear combination $f_L$ (Indexed_LA, SampEn(7)) during daytime and $f_L$ (Indexed_LA, SampEn(8), SampEn(13)) during nighttime, reaching values up to Sen = 80% and Spe = 73.4%. This suggests that the clinical factor Indexed_LA and entropy rates ($H_C$ and SampEn($\tau$)) have a great relevance in the statistical differentiation and in the risk stratification of cardiac death in IDC patients. The predictive ability of these measures was higher in analysis B, which considers SCD, progressive heart failure and myocardial infarction as a cause of mortality, than analysis A which only considers SCD as a cause of mortality. This behavior was also evidenced by the Cox regression analysis and by the cumulative survival curves. Although the reduced physical activity in patients with heart failure influence the results in relation to a population of healthy subjects (Guzzetti et al 2000), all the patients that were included in analysis A and B are in class II or III of the NYHA classification system, and
therefore it could be considered that the intensity of physical activity during the day is not very different between the patients, hence its effect on the results is less important.

5. Conclusions

The results presented in this work have confirmed the multiscale regulation of HRV and suggested that the degree of complexity of this multiscale regulation depends on the physiological state of the subject (daytime versus nighttime) and on the severity of pathological condition. The comparison between groups at different risks of cardiac death in the ischemic cardiomyopathy population has shown that entropy-based HRV complexity decreases with the severity of the disease, thus confirming the paradigm that pathology reduces the complexity of the cardiovascular control. The univariate and multivariate statistical analyses applied to stratify patients with ischemic cardiomyopathy in low and high risk groups of suffering cardiac death indicated that a single measurement is not enough to fully characterize the groups at risk and the importance of introducing complexity measures in clinics.

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