

**Title proposed:**

Symbolic dynamics to discriminate healthy and ischemic dilated cardiomyopathy populations: an application to the variability of heart period and QT interval

**Short Title proposed:**

Symbolic dynamics of RR and QT intervals

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### **Abstract (Summary)**

Myocardial ischemia is hypothesized to stimulate the cardiac sympathetic excitatory afferents and therefore, ischemic dilated cardiomyopathy (IDC) patients should exhibit greater sympathetic tone than healthy subjects. However, given the nonlinear nature of cardiac regulatory mechanisms, a detailed description of the dynamical changes in RR intervals is not feasible if only linear methods of analysis are employed. Symbolic dynamics (SD) is a nonlinear and powerful tool for extraction and classification of pattern in time series analysis, which implies a transformation of the original series into symbols and the construction of patterns with the symbols. The aim of this work was to investigate whether SD transformations of RR and QT cardiac series can improve the separation ability between IDC patients and healthy subjects (NRM) compared with traditional linear measures. The variability of these cardiac series was studied during daytime and nighttime periods and also the complete 24h recording over windows of short data sequences of 5 minutes approximately. IDC group was characterized by an increase of the occurrence rate of patterns without variations (P0%) and a reduction of the occurrence rate of patterns with one variation (P1%) and two variations (P2%). Concerning to RR variability during daytime, the highest number of patterns belonged to P0%, while P1% and P2% values were lower. While during nighttime, P1% and P2% increased their values at the expense of diminishing P0%. Patterns with and without variations between consecutives symbols were able to increase the separation between IDC and NRM groups, allowing accuracies higher than 80%. Related to entropy measures, an increase of heart rate regularity was associated to the cardiac disease described with  $Acc > 70\%$  in RR series and  $Acc > 60\%$  in QTc series. These results could be associated to an increase of the sympathetic tone in IDC patients.

### **Key index words or phrases (3-6 choices)**

Complexity, Heart Rate Variability, Ischemic dilated cardiomyopathy, QT, Symbolic Dynamics

## 1. INTRODUCTION

Hyperactivity of the sympathetic nervous system is triggered by both central and peripheral pathways that are associated with abnormal cardiovascular reflexes observed in a variety of disease states such as cardiac ischemia, ventricular dysfunction, renal failure, and obstructive sleep apnea [1]. Patients with congestive heart failure (CHF) have evidence of increased activation of the sympathetic nervous system as reflected by the increase in plasma norepinephrine levels [2,3]. Also, ischemia can produce a rapid and massive increase in the concentration of endogenous catecholamines such as norepinephrine, epinephrine, endothelin and dopamine in the myocardial interstitial fluid, with a deleterious effect on the cardiac myocytes [4,5]. Ischemic dilated cardiomyopathy (IDC) is a type of cardiomyopathy that is due to ischemic myocardial damage, that is, damage caused by insufficient coronary arterial flow, usually as a result of atherosclerotic coronary artery disease (CAD). In particular, the presence of CAD may accelerate the progression of CHF, explaining the higher mortality among ischemic CHF patients compared with nonischemic CHF patients [4]. CAD is the initiating cause of approximately 70% of all cases of CHF [6]. Because its relation with CHF, this suggests the hypothesis that IDC patients should exhibit sympathoexcitation which may result from either an increase in excitatory influences or a decrease in inhibitory influences on brainstem cardiovascular centers [3]. Abnormalities in cardiac parasympathetic tone may be one factor that contributes to the increase in cardiac sympathetic activity seen in the setting of CHF [1,7].

Heart rate variability (HRV) has become a relevant indicator for cardiovascular risk in humans [8]. The effects of sympathetic and vagal modulation on normal HRV have been well characterized, as has the marked reduction in autonomically mediated HRV associated with CHF and myocardial infarction [8,9]. In general, healthy subjects show a more pronounced HRV than subjects with heart diseases. Berger et al. [9] found that patients with dilated cardiomyopathy had a higher mean heart rate and lower HRV compared with control subjects, suggesting that this probably reflects withdrawal of parasympathetic tone accompanying CHF. Autonomic influences on ventricular repolarization have been also studied by means of QT interval analysis [10-12]. In the healthy heart, variability of the QT interval is intimately linked to that of heart rate, reflecting the rate-adaptation of action potential duration of ventricular myocytes, which is influenced by the autonomic nervous system (ANS) and repolarization reserve [10]. Ventricular repolarization abnormalities may vary over time as the result of changes in the myocardial substrate, in response to changes in ANS, changes due to circadian variations or presence of ischemia [11]. In ECG recordings from patients with CHF, the temporal myocardial repolarization inhomogeneity can be accentuated due to the

sympathetic hyperactivity and reduced cardiac vagal control [13]. An increased QT duration and increased variability of QT dispersion reflecting variations in T-wave morphology was observed in patients with dilated cardiomyopathy [11].

A number of studies have been carried out aiming to characterize HRV and repolarization variability based on linear and nonlinear analysis. One commonly used non-invasive mode of autonomic function testing is based on power spectral analysis of HRV and quantification of low frequency (LF) and high frequency (HF) power. It is generally accepted that HF power reflects respiratory sinus arrhythmia, which is mediated by the parasympathetic cholinergic system [14]. However, the origins and clinical significance of LF power have aroused persistent controversy [15]. Although, it was suggested initially that LF power provides an index of cardiac sympathetic outflow, more recent studies support that LF power seems to provide a measure not of cardiac sympathetic tone but of baroreflex function, as indicated in [16]. Concerning the ventricular repolarization, QT intervals are more under sympathetic control especially if the sympathetic drive is relevant [17].

Symbolic dynamics (SD) is a nonlinear and powerful tool for pattern extraction and pattern classification in time series analysis, including series from physiological systems. This technique implies a transformation of the original time series into symbols and the creation of patterns with the symbols. Different criteria can be applied to transform series into symbolic representation and create patterns. The analysis and identification of a particular performance of the patterns provide information about signal complexity without a priori assumption of the signal behavior and system process. These features guarantee the generality of SD as a method for studying complex systems [8,18]. Although the analysis of SD applied to physiological time series has included different approaches in order to obtain the symbols, two of them are widely used: one approach uses equidistant levels which are obtained by dividing the span (range between the minimum and the maximum) of the time series in a fixed number of equal regions [19], and the other approach uses non-equidistant levels based on the amount of deviation from the average of the time series [20]. The complexity of the resulting symbolic patterns has been quantified using metrics as probability of occurrence, information entropies, forbidden patterns, classification according to the amount of variations in the patterns, and others. These measures have shown complementary information to the spectral analysis of RR series [21-23].

The aim of the present work was to investigate whether patterns derived from SD transformations, and applied to cardiac repolarization series regarding HRV, are able to improve separation ability

compared with traditional linear time-domain and frequency-domain analysis between IDC patients and a control group.

## **2. METHODOLOGY**

### **2.1. Analyzed database**

The analyzed experimental data set belongs to the IDEAL (Intercity Digital ECG Alliance) database which was organized by University of Rochester Medical Center, Rochester, USA [24]. Two groups of subjects have been selected for the present study, 64 healthy subjects (NRM) and 44 patients with IDC. All subjects gave their written informed consent before study participation.

Healthy subjects had no previous history of any heart disease or other chronic disorders. They were symptom free, off-drugs, with normal physical examination and normal 12-leads ECG. In case of suspicion of any ECG changes, a normal electrocardiogram and normal exercise test were required. IDC patients were identified based on left ventricular dysfunction with a left ventricular ejection fraction  $\leq 40\%$  in the absence of ischemic or valvular heart disease (angiographically confirmed). All IDC patients had to remain in sinus rhythm to be eligible for enrolment. The demographic characteristics of the subjects included in the study are shown in Table 1, age, gender, etiology, comorbidities and therapies are described.

Three-orthogonal-lead Holter ECG was recorded (Burkid-Spacelab, Milton, Wi, USA) during 24-hour with a sampling frequency of 200 Hz. RR intervals, time interval between consecutive heart beats of normal sinus rhythm, and QT intervals in each consecutive beat were obtained using a wavelet-based ECG detection algorithm [25]. The QT interval was defined as the time interval between the beginning of QRS complex and the end of the T wave. This system has proven to be quite robust against noise and morphological variations, even in the problematic T wave delineation. Also, algorithms based on robust template matching approach have been recommended for beat-to-beat variability measurement of QT interval in body surface ECG [26].

The ECG lead with the best signal-to-noise ratio was selected for the analysis. All analyzed subjects had less than 10% ectopic beats. Therefore, a possible alteration of the results produced by the filtering process can be discarded. In this way, RR and QT series were filtered by replacing beat abnormalities if their deviation was more than a programmed tolerance of 15% and 10%, respectively, from the mean values of the previous five beats. In order to analyze QT values with a reduced effect of heart rate, we obtained the corrected QT (QTc) intervals. Calculation of QTc values was according to Bazett's formula [27] using preceding RR interval.

Beat-to-beat RR, QT and QTc intervals were divided into windows of length  $w=300$  samples, without overlapping. This was nearly the average data length in 5 min short-term RR interval series [14]. Besides that, awake (daytime) and sleep (nighttime) periods were selected from the 24h ECG recordings. Approximately, nighttime correspond to the interval time from 12:00 a.m. to 6:00 a.m., and daytime from 9 a.m. to 9 p.m.

Table 1. Subject demographic characteristics, baseline clinical status and treatments

	NRM	IDC
N (subjects)	64	44
Age (years, mean $\pm$ SD)	46.1 $\pm$ 16.8	50.3 $\pm$ 14.6
Female sex	38 (60.3%)	5 (11.6%)
Etiology		
VT	0 (0.0%)	18 (41.9%)
LVEF		24.0%
Co-morbidities		
Hypertension	1 (1.61%)	9 (20.9%)
Diabetes Mellitus	1 (1.61%)	4 (9.4%)
Therapy		
Digoxin	0 (0.00%)	19 (44.2%)
Beta-blockers	0 (0.00%)	11 (25.6%)
ACE inhibitors	1 (1.61%)	37 (86.0%)
Antiarrhythmics	0 (0.00%)	18 (41.9%)
Diuretics	0 (0.00%)	21 (48.8%)

LVEF, left ventricular ejection fraction; VT, ventricular tachycardia

## 2.2. Linear time domain and frequency domain analysis

The standard temporal and spectral RR measures were calculated according to the guidelines reported in [14]. The following linear time domain measures were obtained: mean of the RR intervals (meanNN) and standard deviation of the NN intervals (SDNN); mean of the QT intervals (meanQT) and standard deviation of QT intervals (SDQT); mean of the QTc intervals (meanQTc) and standard deviation of QTc intervals (SDQTc). The power spectral measures of RR variability were: HF<sub>n</sub>, normalized power in high frequency band (0.15-0.4 Hz); LF<sub>n</sub>, normalized power in low frequency band (0.04-0.15 Hz); and VLF, power in very low frequency band ( $\leq 0.04$  Hz). Moreover, the ratio between low-frequency and high-frequency power (LF/HF) was calculated.

## 2.3. Symbolic dynamics analysis

The method of SD is a non-linear approach based on the transformations of a series into symbolic sequences with symbols from a given alphabet, for investigating the dynamic aspects of a time series. It provides simplified information of complex systems by means of a limited number of

symbols [23]. Some detailed information is lost in this process, but the obtained symbolic sequence has not redundant information useful to describe the dynamic behavior of the original series [28]. In the present study, two different approaches to transform cardiac series into a symbolic series are applied. These consist of dividing the cardiac series into equidistant levels (EQ) and into non-equidistant (NEQ) levels.

### 2.3.1. Transformation of the cardiac series into symbols: equidistant levels (EQ)

In this approach, given a temporal series  $x=\{x(i), i = 1, \dots, N\}$ , the full range of dynamics of the series  $x(i)$  is divided into  $\xi$  quantization bins of size  $\ell=(\max(x(i))-\min(x(i)))/\xi$  in order to obtain a symbolic cardiac series  $S_{\max-\min,i}$ , as it is derived from the following algorithm (1):

$$S_{\max-\min,i} = \begin{cases} 1 & : \quad \min(x(i)) \leq x(i) < 1 \cdot \ell \\ 2 & : \quad 1 \cdot \ell \leq x(i) < 2 \cdot \ell \\ & \vdots \\ \xi & : \quad (\xi - 1) \cdot \ell \leq x(i) < \max(x(i)) \end{cases} \quad (1)$$

Therefore, the transformation have the symbols  $A=\{1, \dots, \xi\}$ . In this work, the number of quantization levels is set to  $\xi=4$  and  $\xi=6$  [21].

### 2.3.2. Transformation of the cardiac series into symbols: non-equidistant levels (NEQ)

This approach transforms the cardiac series  $x(i), i=1, \dots, N$ , into the symbol sequence  $S_{\alpha,i}$  using quantization with non-equidistant levels [20], which are function of the deviation from the average of  $x(i)$ , as is indicated as follows (2):

$$S_{\alpha,i} = \begin{cases} 4 & : \quad (1 + \alpha) \cdot \mu < x(i) < \infty \\ 3 & : \quad \mu < x(i) \leq (1 + \alpha) \cdot \mu \\ 2 & : \quad (1 - \alpha) \cdot \mu < x(i) \leq \mu \\ 1 & : \quad 0 < x(i) \leq (1 - \alpha) \cdot \mu \end{cases} \quad (2)$$

This transformation uses four non-equidistant quantization levels where the set of symbols is  $A=\{1,2,3,4\}$ ,  $\mu$  denotes the average of  $x(i)$ , and  $(1+\alpha)\cdot\mu$  and  $(1-\alpha)\cdot\mu$  are thresholds respectively above and below the average according to the parameter  $\alpha$ . In this study  $\alpha$  is set to 0.07. That

means, the upper and lower threshold is respectively 7% above and below the average. This choice has proven to yield reliable results if applied to cardiac series [29].

### 2.3.3. Patterns of symbolic sequences

Words of length  $k = 3$  consecutive symbols with an overlapping of two symbols are generated.

Figure 1 shows an example of a QTc series quantized using  $\xi = 6$  equidistant levels.

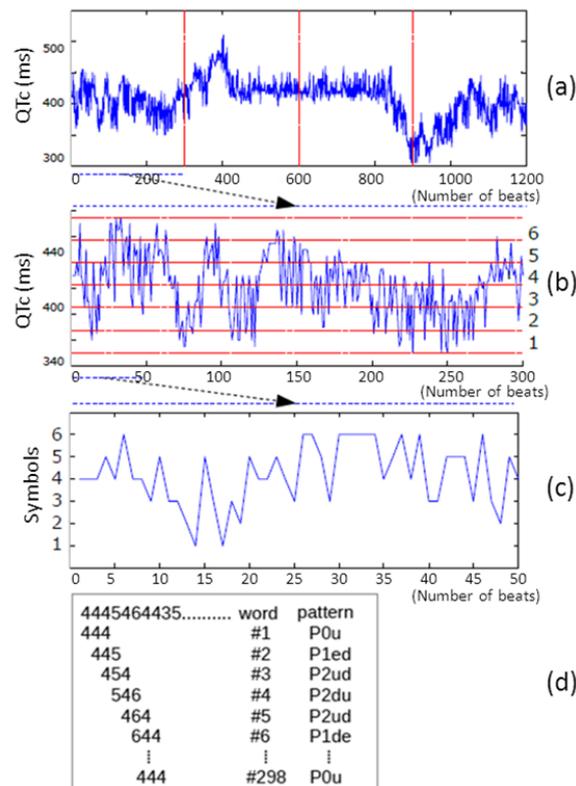


Figure 1. (a) A cardiac series QTc is divided into windows of length  $w=300$  samples without overlapping. (b) The amplitude of the signal is uniformly divided into  $\xi=6$  equidistant levels. (c) Each level corresponds to a symbol, and the value of the cardiac series in each of the level is replaced by the assigned symbol. (d) Words of length  $k = 3$  consecutive symbols with an overlapping of two symbols are generated. Finally, a pattern is constructed according to the consecutive variation of the symbols into the word.

The words of length  $k$  are categorized in patterns according to their amount of variations between successive symbols as follows [21]:

- No variation (0V) between successive symbols (pattern P0)
- One variation (1V) between successive symbols (pattern P1)

- Two like (2LV) or two unlike (2UV) variations between successive symbols (pattern P2). That is, two successive increases or decreases or one decrease followed by an increase, or vice versa.

This categorization has been applied to the symbolic series  $S_{\max-\min,i}$  and  $S_{\alpha,i}$  obtaining  $\xi^k$  different sequences of symbols. The categorization of the  $6^3=216$  different sequences results in: 6 with 0V sequences,  $P0=\{P0d, P0u\}$  with  $P0d=\{111,222,333\}$  and  $P0u=\{444,555,666\}$ ; 60 with 1V sequences,  $P1=\{P1eu,P1ue,P1de,P1ed\}$ ; 40 with 2LV sequences and 110 with 2 UV sequences,  $P2=\{P2du,P2ud,P2dd,P2uu\}$ . An example of how these sequences of  $k=3$  symbols with  $\xi=6$  vary is shown in Figure 2. The categorization of the  $4^3=64$  different sequences results in: 4 with 0V sequences,  $P0=\{P0d, P0u\}$  with  $P0d=\{111,222\}$  and  $P0u=\{333,444\}$ ; 24 with 1V sequences,  $P1=\{P1eu,P1ue,P1de,P1ed\}$ ; 8 with 2LV sequences and 28 with 2UV sequences,  $P2=\{P2du,P2ud,P2dd,P2uu\}$ .

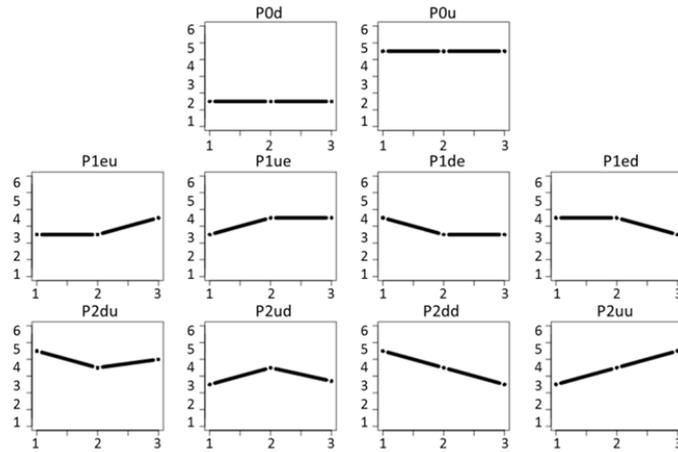


Figure 2. Example of symbol variation (V) in different patterns obtained from  $\xi=6$  equidistant levels and words of  $k=3$  symbols: 0V in symbol sequences,  $P0=\{P0d,P0u\}$ ; 1V in symbol sequences,  $P1=\{P1eu,P1ue,P1de,P1ed\}$ ; 2LV and 2UV in symbol sequences,  $P2=\{P2du,P2ud,P2dd,P2uu\}$ .

#### 2.3.4. Assessment of the regularity of the patterns

In the present study, the following measures have been proposed to measure the regularity of the design patterns:

- Occurrence rate of each pattern:  $P0\%$ ,  $\{P0d\%, P0u\%\}$ ;  $P1\%$ ,  $\{P1eu\%, P1ue\%, P1de\%, P1ed\%\}$ ;  $P2\%$ ,  $\{P2du\%, P2ud\%, P2dd\%, P2uu\%\}$ .
- Number of patterns (PTHy) with probability higher than or equal to a threshold (THy), where  $THy=\{1\%, 3\%, 5\%, 10\%, 50\%\}$ .

c) Number of forbidden words (fw01), defined as patterns with probability lower than 0.1%.

d) Shannon entropy (SH) (3) and Rényi entropy (Hq) (4).

$$SH = - \sum_{i=1}^z p_i \log_2 p_i \quad (3)$$

$$Hq = \frac{1}{1-q} \log_2 \left( \sum_{i=1}^z p_i^q \right) \quad (4)$$

where the probability  $p_i = \{P_0, P_1, P_2\}$ , being the number of patterns  $z=3$ . Large probabilities dominantly influence Hq if  $q>1$  and small probabilities mainly determine the value of this entropy if  $0<q<1$  [30]. When  $q$  tends to unity, Rényi entropy converges to Shannon entropy. In this study, Rényi entropy was estimated for different values of the control parameter  $q=\{0.1, 0.15, 0.20, 0.25, 2, 4, 6\}$ .

e) Conditional entropy (Hc) [19, 31], calculated in a window of length  $w$  using the definition given in (5).

$$Hc \left( \frac{u_k}{u_{k-1}} \right) = \frac{1}{1-q} \sum_{z=1}^{N_z} p(u_{k-1}(z)) \log \left( \sum_{j=1}^{N_j} \left( p \left( \frac{u_k(j)}{u_{k-1}(z)} \right) \right)^q \right) \quad (5)$$

where  $N_z=w-(k-2)$ ,  $N_j=w-(k-1)$ ,  $u_k(j)$  represents a pattern of  $k$  consecutive samples,  $p(u_{k-1}(z))$  denotes the joint probability of the pattern  $u_{k-1}(z)$ ,  $p(u_k(j)/u_{k-1}(z))$  symbolizes the conditional probability of a pattern  $u_k(j)$  of  $k$  samples given a pattern  $u_{k-1}(z)$  of  $k-1$  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  $u_k(j)$  are weighted. In this study, different values of parameter  $q=\{0.1, 0.15, 0.25, 1, 2, 4\}$  are taken into account, where  $q=1$  indicates that the definition of Shannon entropy was used, and the parameter  $k$  was fixed to  $k=3$  [32]. The conditional entropy  $H_C$  will be indicated as  $H_C(k)_q$ , with  $k=3$ . Entropy  $H_C(3)_q$  was computed using the quantization based on dividing the amplitude of the cardiac series in equidistant levels (1) and in non-equidistant levels (2).

## 2.4. Statistical Analysis

All measures from linear and non-linear methodologies were expressed by the arithmetical mean $\pm$ std. The separation ability between measures derived from NRM and IDC populations inside the same period of analysis (24 hours, daytime and nighttime) was analyzed using the Mann-

Whitney U-test. The level of significance was set at  $p\text{-value} < 0.05$ . In order to select the best measures able to separate IDC patients from control group, a linear discriminant function was built for each individual measure with  $p\text{-value} < 0.05$ , using leave-one-out cross-validation procedure. In this statistical analysis, sensitivity (Sen), specificity (Spe) and accuracy (Acc) were taken into account. Correlations were assessed by Spearman's rank correlation coefficients ( $\rho$ ) selected for those measures with the highest Acc values.

### 3. RESULTS

#### 3.1. Time-domain and frequency-domain analysis

Table 2 contains the results corresponding to the measures obtained from time-domain and frequency-domain analysis for 24h period, daytime and nighttime, when NRM and IDC groups were compared. This table only contains the measures with Acc higher than 60% in at least one of the periods of analysis (24h, daytime or nighttime). Although the measure meanNN was not significant, it was also included.

Table 2. Significant statistical measures for the time-domain (TD) and frequency-domain (FD) analysis

measure			64 (NRM)	44 (IDC)	p-value	Acc (%)
			(mean±std)	(mean±std)		
24h period						
TD	RR	meanNN (ms)	777.3±99.5	89.3±112.4	n.s.	54.5
		SDNN (ms)	147.9±48.9	118.5±45.9	0.0015	65.2
	QT	meanQT (ms)	371.6±27.8	417.8±41.9	<0.0005	75.0
	QTc	meanQTc (ms)	420.4±22.2	467.8±49.8	<0.0005	73.4
FD	RR	LFn (n.u.)	48.2±7.0	41.6±8.8	<0.0005	58.8
		LF/HF	1.23±0.376	1.02±0.335	0.014	57.0
Daytime						
TD	RR	meanNN (ms)	703.4±92.9	729.2±110.4	n.s.	53.7
		SDNN (ms)	86.3±26.1	71.8±30.3	0.0015	61.3
	QT	meanQT (ms)	354.6±28.4	403.9±39.0	<0.0005	75.8
	QTc	meanQTc (ms)	420.2±15.9	466.8±49.7	<0.0005	74.8
FD	RR	LFn (n.u.)	51.1±7.33	42.0±10.9	<0.0005	69.6
		LF/HF	1.38±0.410	1.08±0.445	<0.0005	67.8
Nighttime						
TD	RR	meanNN (ms)	959.5±158.9	913.0±152.6	n.s.	52.6
		SDNN (ms)	98.9±35.5	82.2±38.7	0.0092	60.6
	QT	meanQT (ms)	393.6±32.4	441.6±48.8	<0.0005	70.6
	QTc	meanQTc (ms)	421.25±19.1	470.0±50.2	<0.0005	70.3
FD	RR	LFn (n.u.)	44.7±8.58	40.8±9.24	n.s.	48.0
		LF/HF	1.057±0.431	0.964±0.340	n.s.	49.6

NRM, healthy group; IDC, ischemic dilated cardiomyopathy group; Acc, accuracy.

Regarding with the results in Table 2, it can be observed that: a) meanNN has not significant differences in none of the analyzed periods; b) SDNN is statistically significant for all periods, being the 24h period the one with the highest Acc value (65.2%). The value of SDNN is higher in NRM, suggesting that a significant decreased variability is presented in the IDC group in all the analyzed periods in relation with the NRM group; c) meanQT and meanQTc measures has Acc values higher than 70% in all analyzed periods. The values of meanQT and meanQTc are higher in the IDC group, suggesting a significant lengthening of the repolarization intervals of the IDC patients; d) In relation to the results obtained from frequency-domain analysis, LFn and LF/HF have presented Acc values higher than 60% but only in daytime. In this case, the values of LFn and LF/HF are significantly lower in the IDC group compared with the NRM group.

### 3.2. Symbolic dynamics

Many of the proposed measures derived from the application of SD in the cardiac series showed significant differences ( $p\text{-value} < 0.05$ ) with levels of sensitivity, specificity and accuracy higher than 60% ( $\text{Sen} > 60\%$ ,  $\text{Spe} > 60\%$  and  $\text{Acc} > 60\%$ ). The number of measures that meet these conditions is indicated in Table 3. The results are grouped by periods of time (24h, daytime and nighttime), by type of series (RR, QT and QTc), and by the quantization methods (6EQ, 6 equidistant levels; 4EQ, 4 equidistant levels; and 4NEQ, 4 non-equidistant). The information contained in this table indicates that similar behavior is observed in RR series in 24h and daytime periods. For these RR series, the higher number of measures was obtained with the quantization method 4NEQ, while it was 4EQ for nighttime period. The number of measures was lower in QTc series than those obtained in RR series, being the quantization 6EQ where more measures were obtained for 24h and also for daytime and nighttime. None of the proposed measures resulting from SD in QT series showed  $p\text{-value} < 0.05$ ,  $\text{Sen} > 60\%$ ,  $\text{Spe} > 60\%$  and  $\text{Acc} > 60\%$  simultaneously.

Table 3: Number of best measures ( $p\text{-value} < 0.05$ ,  $\text{Sen} > 60\%$ ,  $\text{Spe} > 60\%$  and  $\text{Acc} > 60\%$ ) using algorithms based on equidistant (EQ) and non-equidistant (NEQ) levels

Periods	Series	Levels		
		6EQ	4EQ	4NEQ
24h	RR	12	19	21
	QT	0	0	0
	QTc	8	3	--
daytime	RR	13	18	24
	QT	0	0	0
	QTc	13	11	2
nighttime	RR	9	21	6
	QT	0	0	0
	QTc	5	3	--

**a) 24h period**

Table 4 includes the measures derived from the SD in RR and QTc intervals for the 24h period. Only measures, from 4NEQ levels for RR intervals and 6EQ levels for QTc intervals, with p-value<0.05, Sen>60% and Spe>60% were included. In relation with RR intervals, all the measures obtained with SD showed Acc values higher than 68%, being all superior to the Acc values obtained with the measures obtained from time-domain and frequency-domain analysis. The measure P1ed(%) had the highest Acc value (80.9%), which is an important improvement compared with the 65.2% obtained with the linear measure SDNN. Also, three of the measures obtained in QTc intervals with SD (P1de(%),P1eu(%) and pTH1) showed higher Acc values than linear measures obtained in time domain analysis, being 80.6% the highest Acc value. In general, the results in Table 4 showed that: a) the occurrence of patterns without variations (P0%) was lower in NRM than in IDC group for RR intervals. This measure was not included in QTc series; b) from the P0 pattern family, the measure P0u% was higher in NRM than in IDC group, while the measure P0d% showed a contrary behavior; c) the rate of patterns with one variation (P1%, including P1de%, P1ed%, P1eu% and P1ue%), was higher in NRM than in IDC group for RR and QTc intervals; d) the number of patterns with probability higher than or equal to a threshold (PTH3, PTH5 and PTH10 for RR intervals, and PTH1 and PTH3 for QTC intervals) was higher in NRM than in IDC group; e) entropy measures, including Shannon (SH), Rényi (Hq) and conditional entropy (Hc) showed higher value in NRM than in IDC group.

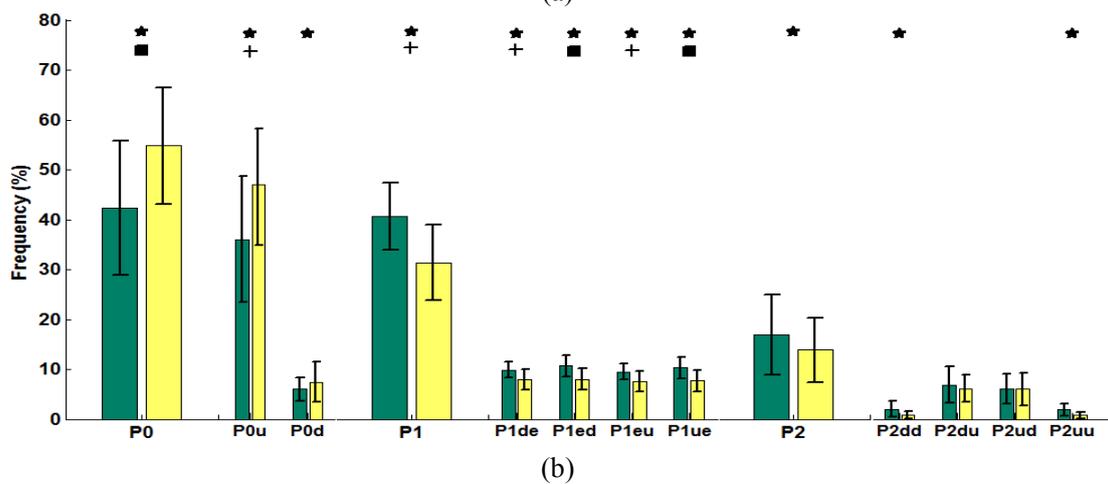
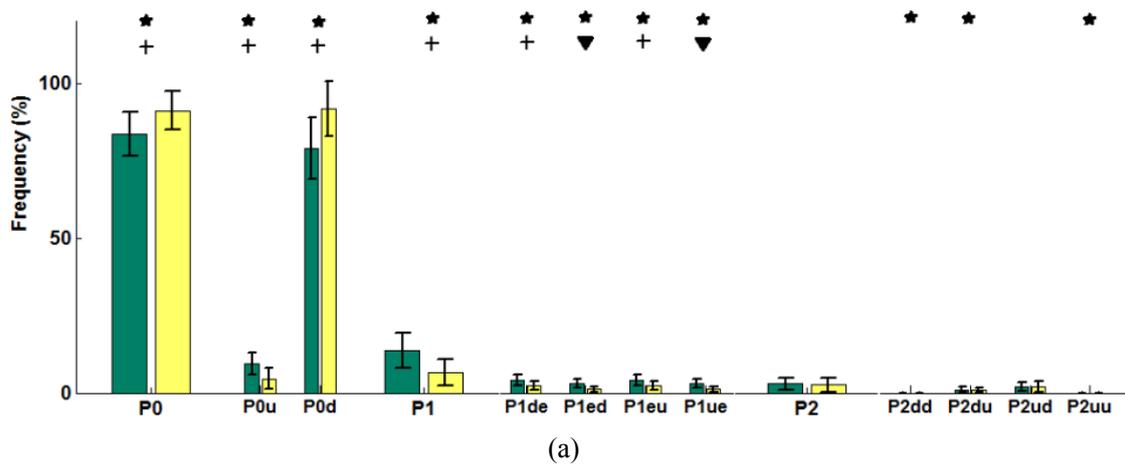
Table 4: Measures derived from the symbolic dynamics: 24h period

Series/ Levels	Measures	64 (NRM) (mean±std)	44 (IDC) (mean±std)	Acc (%)
RR/ 4NEQ	P0(%)	82.4±7.43	90.2±6.51*	73.6
	P0u(%)	7.96±2.85	4.64±2.99*	69.5
	P0d(%)	74.4±9.26	85.6±8.36*	73.5
	P1(%)	14.3±5.78	6.95±4.19*	76.2
	P1de(%)	4.13±1.69	2.31±1.52*	69.5
	P1ed(%)	3.00±1.24	1.17±0.78*	80.9
	P1eu(%)	4.13±1.69	2.31±1.52*	68.9
	P1ue(%)	3.00±1.25	1.17±0.78*	80.3
	SHw	0.717±0.225	0.459±0.225*	69.5
	Hqw2	0.501±0.205	0.281±0.176*	74.2
	pTH3	4.25±1.42	2.48±1.05*	74.2
Hc(3) <sub>a1</sub>	0.696±0.126	0.549±0.116*	70.2	
QTc/ 6EQ	P1(%)	42.5±2.05	39.4±2.98*	74.6
	P1de(%)	11.2±0.61	10.1±0.888*	79.1
	P1eu(%)	11.2±0.668	9.9±0.839*	80.6
	P1ue(%)	10.0±0.737	9.6±0.712†	62.7
	pTH1	9.70±0.144	9.38±0.391*	79.1
	Hc(3) <sub>a4</sub>	0.764±0.057	0.718±0.114†	67.6

NRM, healthy group; IDC, ischemic dilated cardiomyopathy group  
EQ, equidistant levels; NEQ, non-equidistant levels; \*, p-value<0.0005; †, p-value<0.05

## b) Daytime and nighttime periods

The results derived from SD applied to the cardiac intervals during daytime and nighttime are shown in Figures 3 and 4. Only the measures from 4NEQ and 4EQ levels are presented for RR intervals during daytime and nighttime periods, respectively, and 6EQ levels for QTc intervals during daytime as the most representative (as it was seen in Table 3). Figure 3 contains the occurrence rate of the patterns P0%, P1%, P2%, and their respective pattern variability (P0d%, P0u%, P1eu%, P1ue%, P1de%, P1ed%, P2du%, P2ud%, P2dd%, P2uu%). Figure 4 shows the results of the patterns with probability higher than or equal to a threshold (PTH1, PTH3, PTH5, PTH10, PTH30 and PTH50) and the patterns with probability lower than 0.1% (fw01). The results corresponding to entropy measures (SH, H<sub>q</sub> and H<sub>c</sub>) are included in Table 5.



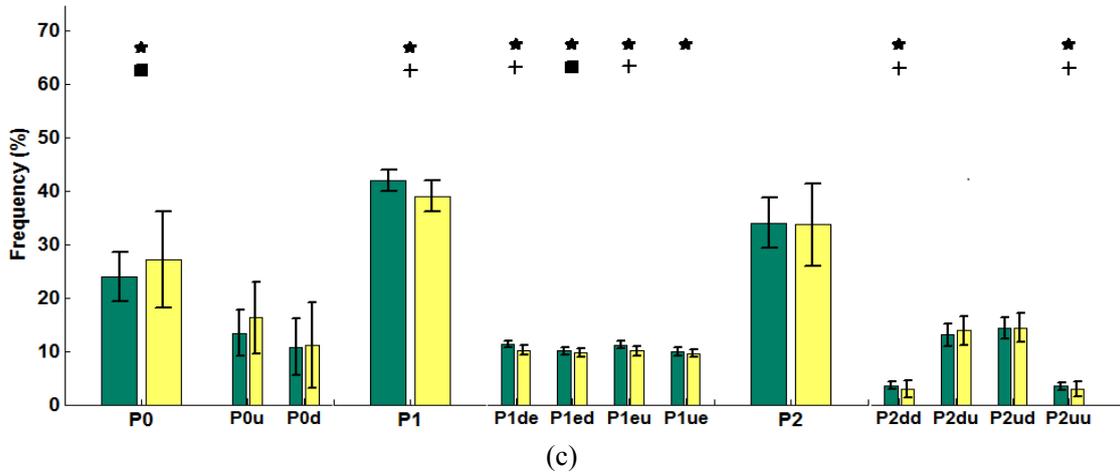
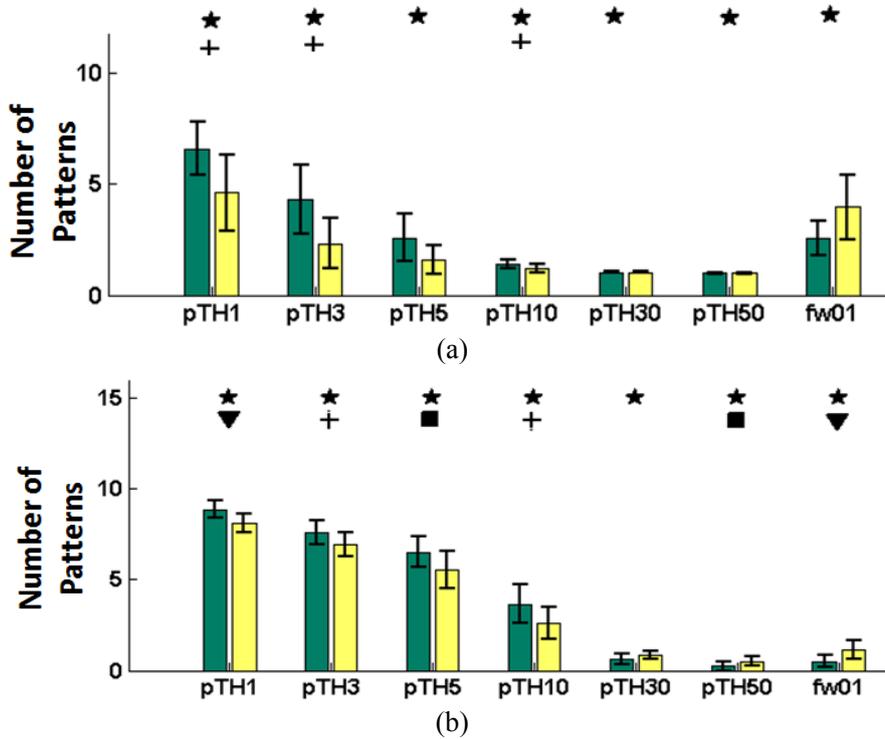


Figure 3. Occurrence rate of patterns without variation (P0%), one variation (P1%) and two variations (P2%) between consecutive symbols, and their respective pattern variability (P0d%, P0u%, P0d%, P1eu%, P1ue%, P1de%, P1ed%, P2du%, P2ud%, P2dd%, P2uu%). a) RR interval in daytime using 4NEQ; b) RR interval in nighttime using 4EQ; c) QTc interval in daytime using 6EQ. The behavior of QTc interval in nighttime was similar to daytime. Green and yellow bars correspond to NRM and IDC groups, respectively. \*, p-value<0.05; ■, 60%≤Acc<70%; +, 70%≤Acc<80%; ▼, Acc≥80%.



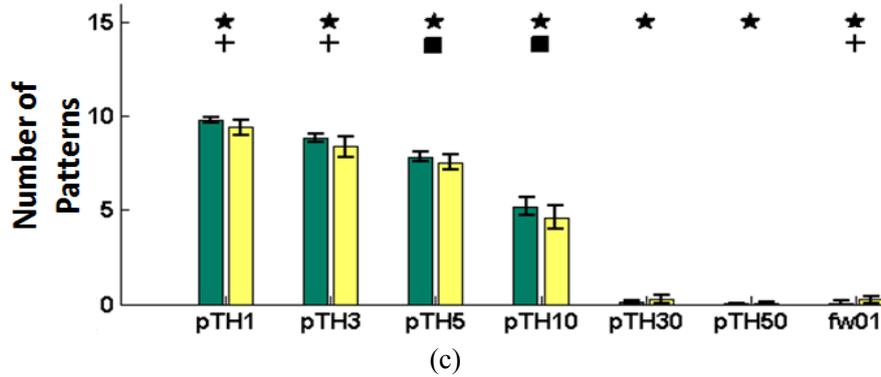


Figure 4. Number of patterns with probability higher than or equal to a threshold (PTH1, PTH3, PTH5, PTH10, PTH30 and PTH50) and number of patterns with probability lower than 0.1% (fw01). a) RR interval in daytime using 4NEQ; b) RR interval in nighttime using 4EQ; c) QTc interval in daytime using 6EQ. The behavior of QTc interval in nighttime was similar to daytime. Green and yellow bars correspond to NRM and IDC groups, respectively. \*, p-value<0.05; ■, 60%≤Acc<70%; +, 70%≤Acc<80%; ▼, Acc≥80%.

Table 5: Entropy measures derived from the symbolic dynamics: daytime and nighttime

Series/ Levels	Measures	64 (NRM) (mean±std)	44 (IDC) (mean±std)	Acc (%)
Daytime				
RR/ 4NEQ	SHw	0.696±0.226	0.435±0.221*	75.1
	Hqw4	0.356±0.167	0.188±0.137*	76.5
	H <sub>C</sub> (3) <sub>q2</sub>	0.537±0.141	0.386±0.116*	75.1
QTc/ 6EQ	H <sub>C</sub> (3) <sub>q4</sub>	0.777±0.061	0.720±0.137†	66.4
Nighttime				
RR/ 4EQ	Hqw4	1.081±0.1436	0.9346±0.181*	65.3
	H <sub>C</sub> (3) <sub>q1</sub>	0.719±0.110	0.596±0.106*	71.6

\*, p-value<0.0005; †, p-value<0.05

Comparing Acc values between nonlinear measures (symbolic dynamics) and linear measures (time and frequency domains), it is possible to see (as it was shown during 24h period) that nonlinear measures show better Acc values than linear measures computed in daytime and nighttime. Indeed, the highest Acc value (81.8%) from RR intervals during daytime was obtained with the measures P1ed(%) and P1ue(%), which is superior to the best Acc value (69.6%) obtained with linear measures in the same period of analysis. QTc intervals during daytime have the highest Acc value (78.0%) if the nonlinear measure is P1(%), while Acc is 74.8% with linear measures. In relation with RR intervals from nighttime, the highest Acc value with nonlinear measures is 80.8% (pTH1, fw01), while it was 60.6% with the linear measure SDNN. The intervals of QTc during nighttime

present highest Acc values similar for both nonlinear and linear measures, P1eu(%) with 70.5% and meanQTc with 70.3% respectively.

In general, the behavior of the nonlinear measures during daytime and nighttime is similar to the behavior observed during 24h period, in both RR and QTc intervals. Indeed: a) the occurrence of patterns P0% was lower in NRM than in IDC group; b) the occurrence rate of pattern P1% (including P1de%, P1ed%, P1eu% and P1ue%), was higher in NRM than in IDC group; c) measures PTH1, PTH3, PTH5 and PTH10 were higher in NRM than in IDC group; d) entropy measures (SH, Hq and HC) show higher values in NRM than in IDC group; e) measure fw01 is lower in NRM than in IDC group. However, the measures P0u% and P0d% have different behavior in daytime compared with nighttime. While P0u% presents higher values and P0d% lower values in NRM than in IDC group during daytime, P0u% and P0d% present lower values in NRM than in IDC group during nighttime.

#### **4. DISCUSSION**

The analysis in time-domain showed that the standard deviation of heart period (SDNN) and the mean of QT (meanQT) and QTc intervals (meanQTc) were the only measures able to discriminate ( $p$ -value<0.05) and classify (Acc>60%) subjects in NRM and IDC groups. The measure SDNN is an overall index of the HRV, where a lower value of SDNN is related with a reduction of the HRV [14]. The results obtained in this work indicate a reduction of the HRV in IDC patients due to the lower SDNN value in IDC group than in NRM group. This behavior was observed in all analyzed periods (24h, daytime and nighttime). A similar response was reported in [32,33] where SDNN presented statistical differences during both 24h and daytime, when low and high risk groups of IDC were compared. Analyzing the meanQT and the meanQTc measures, the results indicate that IDC patients showed longer QT and QTc intervals than healthy subjects, suggesting that the repolarization of the myocardium is slower in patients with dilated cardiomyopathy. In agreement with our finding, other studies [10,11,34] have also shown an increased QTc interval evaluated in patients with dilated cardiomyopathy, where the lengthening of QTc intervals have been considered as a marker of bad prognosis in different substrates of patients. SDQT or SDQTc, measuring variability of QT in absolute terms was not significantly different between groups despite significantly different mean QTc duration. One limitation of this study is given by the relatively low sampling rate of 200Hz, which produce an intrinsic error of 5ms in the detection of cardiac intervals. Risk et al. [35] verified that sampling rate affects the measurements of QT interval and

duration of QRS complex, in both cases these variables were overestimated at ECG sampling rates below 300 Hz.

Considering CAD can be the initiating cause of heart failure [6], and patients with CHF have an increased cardiac sympathetic outflow [3], it is expected that IDC patients follow similar responses. It has been reported that conditions such as CHF, hypertension, and myocardial infarction are associated with baroreflex-cardiovagal failure and associated with low LF power [15]. Notarius et al. [36] also reported, in patients with moderate and severe CHF, an absence rather than an enhancement of the spectral power in the low-frequency range, which was very closely associated with the resting muscle sympathetic nerve activity. These evidences are in accordance with our results where LFn and LF/HF were able to statistically discriminate subjects in NRM and IDC groups, being the lowest value in IDC group for both measures. The main statistical differences of LFn and LF/HF were during daytime, similarly as was reported in [32,33]. The measures extracted from time-domain and frequency-domain analysis of HRV have been shown to contain useful information [14,22]. However, these measures only describe linear features of the systems involved in heart rate control and may not capture the non-linear features of such control.

The reported results showed in a clear way that nonlinear measures derived from SD, according with the proposed methods, have provided improved separation ability between ischemic dilated cardiomyopathy (IDC) patients and a control group (NRM), compared with linear measures obtained from the standard temporal and spectral RR measures. Many of the measures derived from SD, in RR or QTc intervals, were able to discriminate between NRM and IDC groups. These measures showed a better performance than the measures derived from time and frequency domain, allowing percentages higher than 80% in accuracy. The occurrence rate of patterns without variations and patterns with variations between successive symbols has been associated with sympathetic and parasympathetic modulations [18,22,37]. Indeed, Guzzetti et al [22] reported that an increase in sympathetic modulation and a vagal withdrawal elicited a significant increase in patterns without variations and a decrease in patterns with variations between successive symbols, whereas parasympathetic dominance induced the opposite, reflecting a reciprocal sympathovagal balance. For all analyzed periods (24h, daytime and nighttime), our findings similarly showed an increase of patterns P0(%) (without variations) and a decrease of P1(%) (occurrence rate of patterns with one variation) in IDC group suggesting a reduction of the variability in RR and QTc intervals, which can be associated with an increment in the sympathetic activity in this group. Although, the P2(%) (occurrence rate of patterns with two like or two unlike variations between successive symbols) is also associated with a higher variability, these patterns had a lower performance than

P1% (Acc<60%). All the patterns with one variation (P1eu(%), P1ue(%), P1de(%), P1ed(%)) exhibited a similar tendency, being the number of this patterns higher in NRM than in IDC group. This means that the result is almost the same without matter if the variation is in up or down direction or if the variation occurs after or before a period without variation, and therefore, all these measures are appropriate to indicate a reduction of the RR or QT variability in IDC patients.

During daytime period of the RR series, the highest number of patterns (more than 80%) belongs to the family P0%, while the families P1% and P2% contain lower frequencies of patterns (less than 13%). During nighttime, families P1% and P2% increased their frequency values at the expense of diminishing P0%. Similar results were observed in Porta et al. [37], where a clear day-night variation of 0V(%) and 2UV(%) with 0V(%) decreasing and 2UV(%) increasing during the nighttime was reported. These observations lead to a higher regularity of the RR series during daytime period with the presence of P0 patterns and a losing of regularity during nighttime period with the increasing of instable patterns as P1. This behavior was followed by both NRM and IDC groups, suggesting differences between daytime and nighttime following a circadian pattern.

Similarly, the results from entropy measures, based on the occurrence probability of patterns, also showed a reduction of the variability in IDC group compared with NRM group. Indeed, all the entropy measures (SH, Hq and H<sub>C</sub>) reported in Tables 4 and 5 had a higher value in NRM group, suggesting an increase in the regularity of the RR and QTc intervals in IDC group. In Porta et al. [19] it was pointed out that a reduced complexity through a reduction of the number of different patterns is associated with a sympathetic activation. Therefore, the obtained reduced entropy values in IDC patients also can be associated with a sympathetic activation in those patients. Comparable results using entropy measures have been reported in [32,33] where an increase of HRV regularity was associated to the evolution of cardiac disease severity. Measure H<sub>C</sub>, which assesses the distribution of the pattern with length k=3 conditioned on the distribution of the pattern with length k=2, was one of the best entropies since it could describe the NRM and IDC groups in all analyzed periods with Acc>70% in RR series and Acc>60% in QTc series. While Shannon and Rényi entropies only depend on pattern distribution, conditional entropy also considers the dynamic relations between patterns, given more information about the regularity of the RR or QTc intervals. Entropy rates as H<sub>C</sub> can be affected by the short length of the series or the long length of the patterns, which can reduce artificially the value of conditional entropy, indicating a false impression of determinism and requiring a correction factor [19]. Since the length of series was enough larger w=300 samples and the length of the patterns enough shorter k=2 and k=3, the effect of including a correction factor on the computation of H<sub>C</sub> is not significant in the results of this entropy [38].

Besides that, in Valencia et al. [32] was demonstrated that a non-uniform quantization of the dynamic range of the RR series, as applied in this work, can also improve the performance of  $H_C$  even with a few number of quantization regions.

The correlation analysis between the measures with highest accuracy values obtained from nonlinear measures (P0%, P1%, PTH1) and linear measures (meanQTc) has shown a weak correlation with rho values between 0.2 and 0.5 (p-value<0.05). Furthermore, no correlation was found between the nonlinear measures and measures from frequency-domain analysis. Finally, consistent with Heitmann et al. [8], we have confirmed that indices from linear methods only demonstrate a weak differentiation between healthy subjects and heart disease patients. In contrast, nonlinear indices have proven to have more significant discriminatory power. In relation to QT and QTc intervals, the nonlinear measures of the individual QT have demonstrated that could not statistically differentiate the groups, but significant statistics were obtained for QT corrected (p-value< 0.05 and Acc> 60%). Considering the individual QT dependence on past RR intervals, the traditional approach for rate correction of the QT interval used was the Bazett correction. It is known that this correction and any other approach using fixed formula will clearly over- or underestimate the true and individual QT/RR relationship and will lead to imprecise QTc values [39,40]. Furthermore, the QT/RR relationship is much more complicated when QT is analyzed in different, nonstandard conditions, as it happens during 24h ECG. Some studies have driven their efforts to apply nonlinear dynamics methods to analyze the QT/RR, providing additional markers of repolarization instability. Indeed, Baranowski et al [12] applied joint symbolic dynamics to the relation of QT on RR interval dynamics in healthy women and men. Similar nonlinear method was applied in [10], where the effect of aging on QT/RR relationship was assessed in healthy subjects. The results of the univariate symbolic dynamics applied to ECG cardiac intervals of IDC and NRM in the present work open a further study based on joint symbolic dynamics to investigate the QT/RR relation of those patients.

## 5. CONCLUSION

This work investigated whether symbolic dynamics (SD) transformations applied to cardiac repolarization series, regarding heart rate variability (HRV), can improve the separation ability between ischemic dilated cardiomyopathy (IDC) patients and a control group (NRM), compared with traditional linear time-domain and frequency-domain analysis. Two different approaches to transform cardiac series into a symbolic series, consisting of dividing the cardiac series into equidistant levels and non-equidistant levels, were applied to RR and QTc intervals belonging to

NRM and IDC subjects. Although measures extracted from the time-domain and frequency-domain of the HRV were able to evidence some statistical differences between IDC and NRM groups, the measures derived from SD showed a better performance and were able to classify with more than 80% in accuracy. Indeed, the occurrence of patterns without variation and with one variation showed a reduction of the complexity in RR and QTc intervals for IDC patients compared with healthy subjects. Also, entropy measures, computed over the patterns, indicated an increase in the regularity (reduction of the complexity) of the HRV in IDC patients. These results suggest that SD is a useful method to obtain diagnostic information in IDC patients, and the pattern analysis generates measures that can relate a high sympathetic tone in IDC patients.

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## APPENDIX

### A1. Dependency of the conditional entropy values with the pattern length

Figure A1 shows the conditional entropy ( $H_c(k)_q$ ) values as function of the  $k$  consecutive samples in the defined patterns. This study was done on 30 random series of 10000 samples with a Gaussian distribution with zero mean and unitary standard deviation. In this figure,  $H_c$  was calculated using Shannon entropy over windows of length  $w=300$  samples and  $w=1000$  samples. The windows were considered without overlapping. It can be observed that  $H_c(k)_q$  remained stable from  $k=1$  to  $k=3$  even when windows of  $w=300$  samples were taken into account.

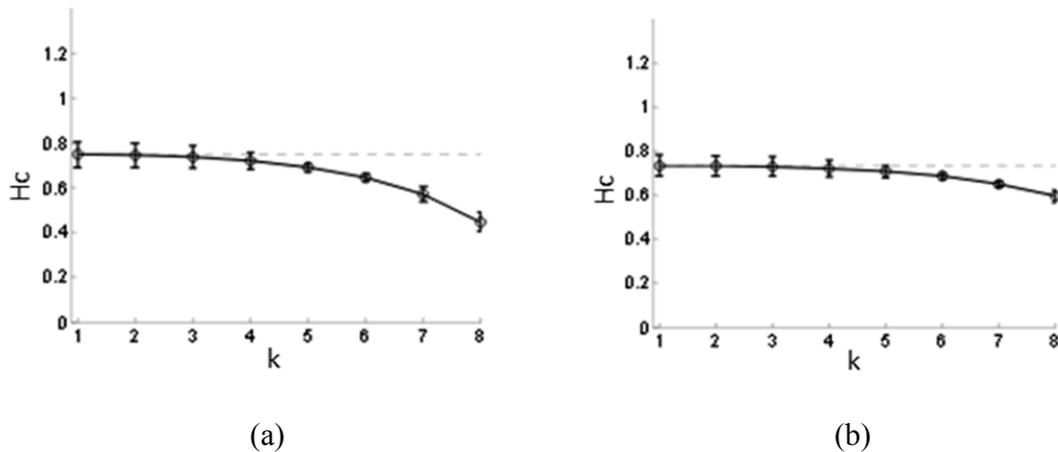
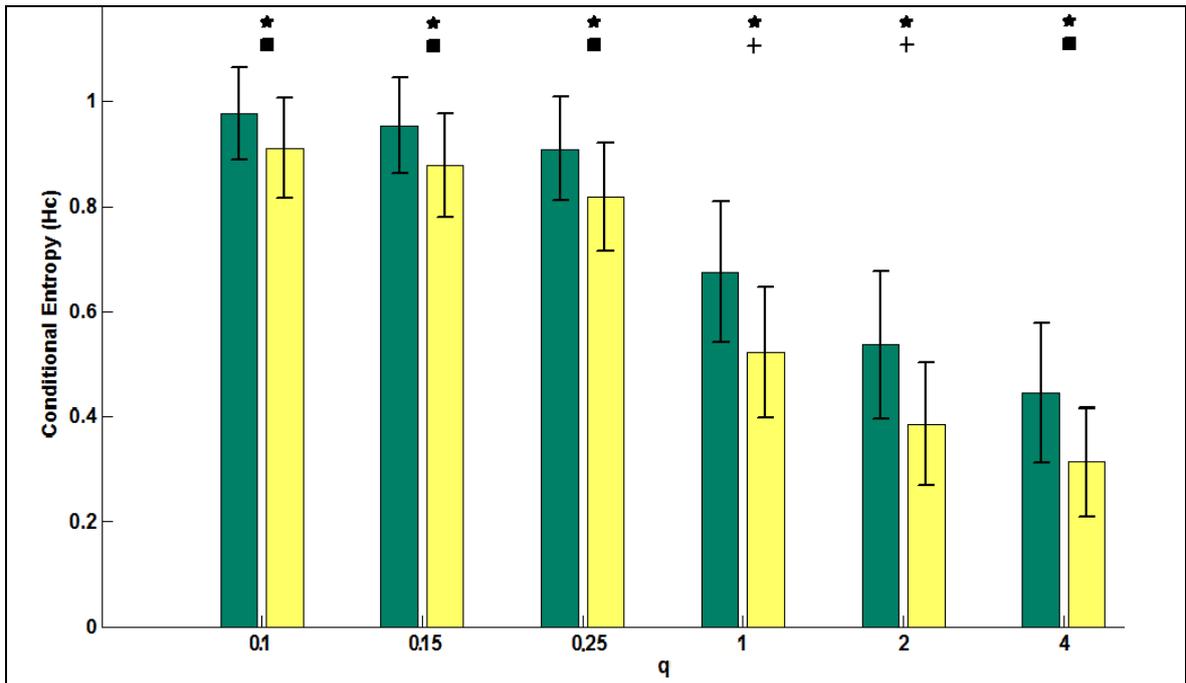


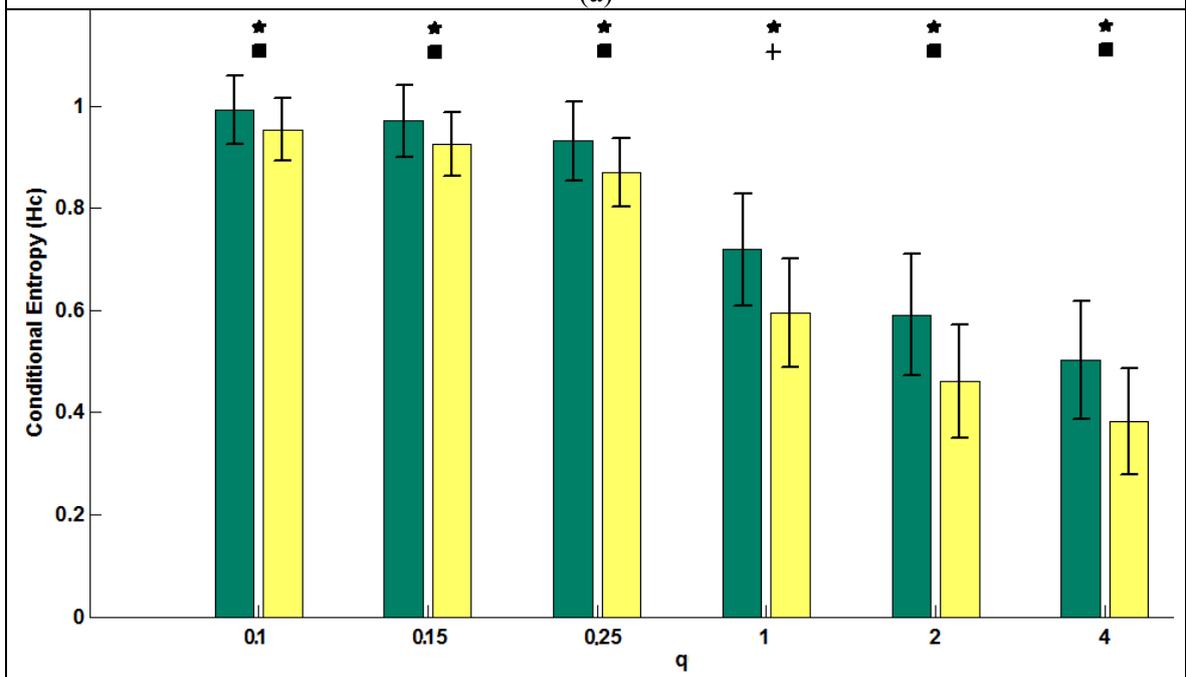
Figure A1. Mean and the standard deviation values of  $H_c(k)_q$  obtained from 30 random series of 10000 samples with a Gaussian distribution. a) windows of  $w=300$  samples; b) windows of  $w=1000$  samples.

### A2. Dependency of the conditional entropy values with the parameter $q$

Figure A2 shows the conditional entropy ( $H_c(k)_q$ ) values as function of the parameter  $q$ . The value of parameter  $k$  was set to 3 [32]. This study was done on RR and QTc intervals of 64 healthy subjects (NRM) and 44 patients with ischemic dilated cardiomyopathy (IDC). Results of  $H_c(3)_q$  from daytime and nighttime periods are presented. It can be observed that during daytime the best results of  $H_c(3)$  correspond to  $q=\{1,2\}$  and nighttime to  $q=1$  for RR series, but  $q \geq 2$  for QTc series.



(a)



(b)

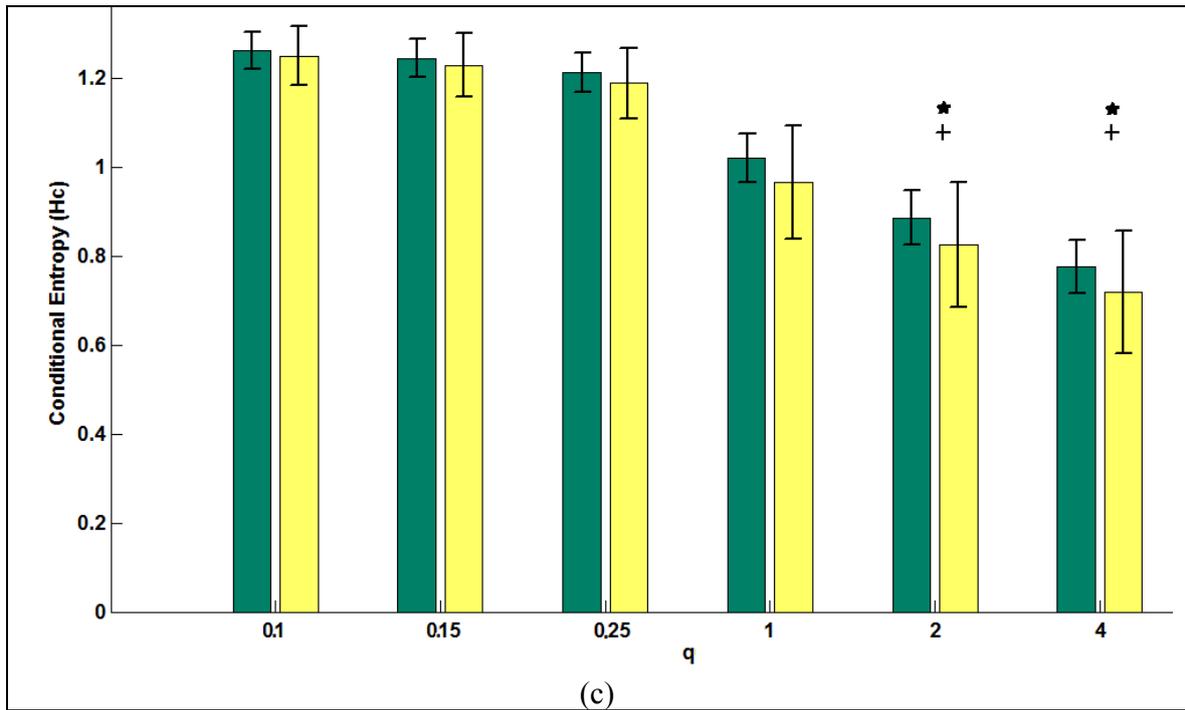


Figure A2. Behavior of the conditional entropy  $H_c(3)$  varying the parameter  $q$ . Green and yellow bars correspond, respectively, to NRM and IDC groups: (a) RR series during daytime period; (b) RR series during nighttime period; (c) QTc series during daytime period. \*,  $p\text{-value} < 0.05$ ; ■,  $60\% \leq \text{Acc} < 70\%$ ; +,  $70\% \leq \text{Acc} < 80\%$ .