Symbolic Dynamics of QT Interval Series in Ischemic Cardiomyopathy

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Abstract

Repolarization dynamics may be of increasing interest in analyzing ECG-Holter for characterization of myocardial ischemic events related to cardiac death. The quantification of the dynamics of the beat-to-beat QT interval fluctuations, representing changes in repolarization duration, may be another emerging marker of cardiac events. Based on these arguments, we propose a symbolic analysis series to quantify the dynamics of the beat-to-beat QT interval fluctuations, representing changes in repolarization duration, and the prevalence of sympathetic or parasympathetic cardiac modulation in the RR series. This analysis decomposes the series in patterns of length L=3 beat and classify them into three categories: non-variable, variable, and very variable patterns referred to as P0, P1 and P2 patterns. The present work analyses QT and RR series obtained from 24-hour ECG-Holter recordings in order to obtained patterns able to stratify high (HRG) and low risk (LRG) of suffer cardiac mortality in patients with symptomatic myocardial ischemia. Comparing LRG and HRG, results showed that pattern P0 could better quantify QT series and pattern P2 the RR series. These findings suggest a decreased cardiac vagal function with a relative increase in sympathetic cardiac modulation, and more complex pattern of ventricular repolarization in the HRG.

1. Introduction

Cardiovascular responses to ischemic cardiomyopathy may extend from minor changes in heart rhythm to induction of cardiac death. Ischemic cardiomyopathy is the initiating cause of approximately 70% of all cases of heart failure [1]. Therapies for patients who have survived a cardiac death episode or have a high risk of developing lethal ventricular arrhythmia are now well established, but strategies such as the application of an implantable cardioverter-defibrillator depend mainly on risk stratification.

Several studies have been performed to investigate the usefulness of clinical application of linear and non-linear heart-rate analysis for physiological interpretation and risk stratification in cardiac diseases [2-5]. However, the problem of cardiac death risk stratification in patients with ischemic cardiomyopathy still remains of paramount importance. In this way, we analyze the heart rate by the RR consecutive intervals and QT duration, which reflects the cumulative effects of the preceding beats and the patient-specific adaptation rate to change in heart rate.

A symbolic dynamics methodology to study QT and RR variability is applied. In this regards, QT and RR series are transformed to a series of symbols according to equidistant amplitude-levels. All possible patterns referred to three-beat variation will be analyzed and we hypothesized that these patterns can stratify high of low risk cardiac mortality in patients with ischemic cardiomyopathy.

2. Methods

2.1. Study population

Time series obtained from 24-hour ECG-Holter recordings and belonging to MUSIC (MUerte Subita en Insuficiencia Cardiaca, Sudden Death in Heart Failure) database were analyzed. They consisted of three orthogonal leads (X, Y, Z), acquired at a sampling rate of 200Hz (Spiderview recorders, ELA Medical, Sorin Group, Paris).

A total of 146 patients with ischemic heart failure were analyzed. Twenty-five patients who suffered cardiac death were considered as high risk group (HRG) and 121 survivor patients as low risk group (LRG). The mean age

was 61.6±9.6, and 79.3% of the subjects were males in group LRG and 84% in HRG.

Inclusion criteria were: New York Heart Association index *NYHA II* or *III*, left ventricular diastolic diameter *LVDD* > 60mm, left ventricular hypertrophy *LVH* > 14mm and sinus rhythm. Patients with severe valvular disease, severe hepatic, pulmonary or renal disease and other criteria influencing the autonomic regulation were excluded. All ischemic heart failure patients were optimal treated with drugs as ACE inhibitors (74%), beta blockers (70%), diuretics (65%) and digitalis (21%). The investigation was conforming to the recommendations of the Declaration of Helsinki, the ethical committee of the respective institutions approved the study protocol and all patients gave their written informed consent before participation.

2.2. Signal preprocessing

RR time series (interval between consecutive heartbeats) and QT series (interval between Q wave and end of T wave) were obtained from the lead with lowest noise, using wavelet-based software for automatic ECG delineation [6]. RR and QT time series were filtered by replacing artifacts or ectopic beats if they deviated more than a programmed tolerance of 15% from the mean values of the previous five ones. Finally, all series were consecutively partitioned into windows of 300-samples without overlapping.

2.3. Symbolic dynamics

Nonlinear dynamic behavior within RR and QT time series can be characterized by measures from nonlinear symbolic dynamics. The symbolic dynamics method based on [3] was applied to RR and QT series previously partitioned into windows of 300-samples without overlapping. Both, series were uniformly spread on 6 levels. That was done calculating the distance between minimum and maximum value for each signal [4]. After that, the distance was divided by the number of levels (n=6) and each level was determined by the equation (1).

$$l_i = l_{i-1} + \frac{max - min}{n} \quad (1)$$

where l_i is the i-th level and i=1,2,…,n. When i=1, l_{i-1} is the minimum value of the signal. In this regards, QT and RR series were transformed to a series of symbols according to six-equidistant amplitude-levels.

Finally, patterns of length L=3 consecutive symbols with an overlapping of two symbols were constructed. All possible patterns were grouped into 3 families referred to as: *P*0, patterns with no variation (all 3 symbols were equal); *P*1, patterns with one variation (2 consequent symbols were equal and the remaining symbol was different); *P*2, patterns with 2 variations (all symbols were different from the previous one).

For each family, different kinds of variations were defined as it can be seen in Figure 1. In the case of *P*0, one pattern can have all values at the highest level ($P0_u$, 0 variation, up) or at the lowest level ($P0_d$, 1 variation, down). In *P*1 case, there are 4 different kinds of variations: $P1_{eu}$, $P1_{ue}$, $P1_{de}$, $P1_{ed}$, where *e* means equal (i.e., two consequent beats are in the same level), *u* is for up (i.e., next beat is in a level higher than the previous one), and *d* means down (i.e., next beat is in a lower level than the previous one). Finally, pattern *P*2 is characterized by 4 variants: $P2_{du}$, $P2_{ud}$, $P2_{dd}$, $P2_{uu}$.

There are several measures that can characterize such patterns. In this study, we analyze the frequency distribution of each of the three-symbol patterns (*P*0, $P0_u$, $P0_d$; *P*1, $P1_{eu}$, $P1_{ue}$, $P1_{de}$, $P1_{ed}$; *P*2, $P2_{du}$, $P2_{ud}$, $P2_{dd}$, $P2_{uu}$). Also, Shannon entropy *SH* and Renyi entropy H_q (equations 2 and 3), which are the classic measures for the complexity in time series, were calculated from the distribution of patterns of *P*0, *P*1 and *P*2 (z=1,..,3).

$$SH = -\sum_{i=1}^{z} p_i \, log_2 p_i \quad (2)$$

$$H_q = \frac{1}{1-q} log_2 \left(\sum_{i=1}^{z} p_i^q \right) \quad (3)$$

Large probabilities dominantly influence the Renyi entropy if q > 1 and small probabilities mainly determine the value of this entropy if 0 < q < 1 [2]. When q tends to unity, Renyi entropy converges to Shannon entropy. In this study, Renyi entropy was estimated for different values of q parameter, q ={0.1, 0.15, 0.20, 0.25, 2, 4, 6}.

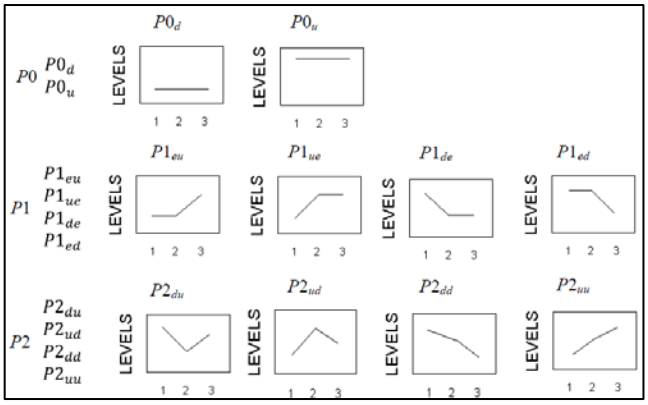

Figure 1. Classification of patterns: *P*0, *P*1 and *P*2 represent three beats with no variation, with one variation and with two variations, respectively.

2.4. Statistical analysis

Univariate statistical analysis based on Mann-Whitney U-test (p-value<0.05) and descriptive statistics (mean

values and standard deviations) were determined for all proposed measures (clinical, time-domain and nonlinear). A linear discriminant function was constructed on each defined measure with p-value<0.05, comparing low and high risk groups, and leave-one-out cross-validation method was applied. A multivariate statistical analysis will be applied to defined new variables containing uncorrelated measures of non-linear information of RR and QT series. Finally, diagnostic specificity (Spe) and sensitivity (Sen) were calculated. By means of the receiver operating characteristic (ROC) methodology pairs of true and false positives were estimated and plotted across the full range of possible cut-off values. The area under the curve (AUC) was estimated.

3. Results

The measures described in the preceding sections were calculated for both the LRG and HRG of RR and QT series and test then for equality of the averaged values obtained from both groups. The statistical analysis of the clinical and traditional time domain parameters are presented in Table 1. Only *LVEF* and *NYHA* lead to a significant separation of both groups (p-value). All other measures presented non-significant differences between the groups. On the contrary, parameters of symbolic dynamics (Table 2) indicate significant differences between both groups, in the analysis of RR and QT series.

Table 1. Clinical and time-domain measures: RR and QT series

(mean±sd)	LRG	HRG	p-value
Clinical measures:			
LVEF (%)	35.2±10.2	30.5±7.24	0.037
Gender (F/M)	25/96	4/21	n.s.
Age (years)	62.7±9.19	65.9±10.5	n.s.
NYHA	2.17±0.374	2.44±0.507	0.02
LVDD (mm)	62.8±8.71	64.32±6.65	n.s.
Time-domain measures:			
SD RR (ms)	124±47.9	104±48.9	n.s.
MeanRR (ms)	808±127	788±106	n.s.
SD QT (ms)	38.7±16.9	35.8±10.2	n.s.
MeanQT (ms)	393±61.6	388±30.5	n.s.

HRG, high risk group: ischemic heart failure patients who suffered cardiac death; LRG, low risk group; survivor ischemic heart failure patients.

The complexity analysis of the RR series, have shown that the probability distribution of the patterns is mainly concentrated in $P0$, $P0_u$, $P0_d$, $P1$ and $P2$ (see Figure 2), for both LRG and HRG. The highest probability value is in the pattern $P0$ and decreasing to $P1$ going to $P2$. It is observed in Figure 2, that pattern $P0$ is more influenced by pattern $P0_d$ than $P0_u$. The pattern $P0$ with cero variation in its definition is slightly higher in LRG than HRG (p-value =0.028) as it is presented in Table 2. However, $P2$ with two beat variation in its pattern has higher values in HRG (p-value=0.010). The frequency in $P2$ is due more to $P2_{du}$ and $P2_{ud}$ than the frequencies of $P2_{dd}$ and $P2_{uu}$, as observed in Figure 3. Patterns with low probabilities are which effect in Renyi entropy with parameter $q<1$, $\{H_{01}, H_{015}, H_{020}, H_{025}\}$. All this entropy values were lower in LRG.

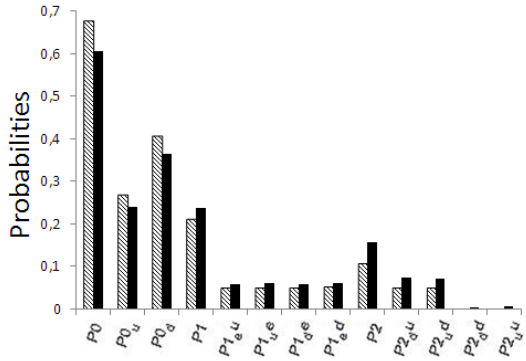

Figure 2. Probability distribution of the *pattern*s during 24-hour RR series for LRG (gray columns) and HRG (black columns).

Table 2. Symbolic dynamics results

(mean±sd)	LRG	HRG	p-value
RR series:			
$P0$	0.679±0.0010	0.606±0.0068	0.028
$P2$	0.108±0.0005	0.155±0.0044	0.010
$P2_{du}$	0.053±0.0002	0.074±0.0018	0.012
$P2_{ud}$	0.052±0.0003	0.072±0.0017	0.009
$P2_{dd}$	0.0015±0.000	0.0037±0.0004	0.023
H_{01}	1.53±0.0003	1.55±0.0012	0.029
H_{015}	1.51±0.0004	1.53±0.0018	0.029
H_{020}	1.48±0.0005	1.51±0.0024	0.028
H_{025}	1.46±0.0006	1.49±0.0029	0.029
QT series:			
$P0_u$	0.208±0.0011	0.145±0.0063	0.0073
$P0_d$	0.216±0.0014	0.325±0.0073	0.0049

HRG, high risk group: ischemic heart failure patients who suffered cardiac death; LRG, low risk group; survivor ischemic heart failure patients.

Figure 3 contains the probability distribution of the patterns obtained in QT series. Patterns $P0$, $P0_u$, $P0_d$, $P1$ and $P2$ have the maximum probabilities for both LRG and HRG. The global behavior is similar to the observed in RR series (Figure 2), but with a more homogeneous distribution in QT series than in RR series. Particularly, the behavior of $P0_d$ between HRG and LRG is contrary in RR series (Figure 2) that in QT series (Figure 1). The patterns $P0_u$ and $P0_d$, with no variations in their definitions, could statistically differentiate LRG and HRG. Pattern $P0_u$ presented higher values in LRG (p-

value = 0.0073), and the values of $P0_d$ were higher in HRG (p-value = 0.0049).

Table 3 includes those patterns that have statistical significant level (p-value < QT series. In RR series, the pattern $P2_{ud}$ with two beat variations (up and down) stratified risk groups with AUC = 0.621, and the entropies $\{H_{01}, H_{015}, H_{020}, H_{025}\}$ with AUC ≥ 0.645. In QT series, both patterns with no-beat variation, $P0_u$ (AUC = 0.643) and $P0_d$ (AUC = 0.679), were able to classify both risk groups. A new variable containing the combination of $P2_{ud}$ constructed on RR series and $P0_u$ constructed on QT series was obtained by constructing a discriminant function. This new variable improved the discriminatory power with a Spe = 73.5%, Sen = 72% and AUC = 0.718.

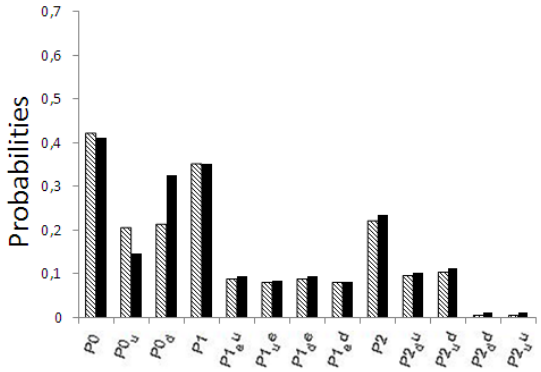

Figure 3. Probability distribution of the *pattern*s during 24-hour QT series for LRG (gray columns) and HRG (black columns).

Table 3. Discriminant analysis

	Spe (%)	Sen (%)	AUC (ROC)
RR series:			
$P2_{ud}$	65.3	60.0	0.621
H_{01}	67.8	68.0	0.660
H_{015}	66.9	68.0	0.657
H_{020}	66.9	68.0	0.651
H_{025}	66.1	68.0	0.645
QT series:			
$P0_u$	60	73	0.643
$P0_d$	64.5	60	0.679
RR and QT series: $P2_{ud}$(RR), $P0_u$(QT)			
	73.5	72.0	0.718

4. Discussion and conclusions

The non-linear heart-rate indexes obtained from RR and QT series have permitted to better classify HRG and LRG than classical time-domain or clinical indexes. This has permitted to obtain a measure of the behavior of the QT dynamics be different in HRG and LRG. Both, RR and QT patterns seem to be associated to non-linear risk marker in cardiac death.

An increase in the tendency of *P*0 dynamics was detectable in LRG both RR and QT series, and in contrast *P*2 value decreased. This behavior seems to be due to an increased sympathetic modulation and vagal withdrawal [4]. The global behavior of the patterns in RR and QT series (*P*0, *P*1, *P*2) were similar (Figures 2 and 3) but with a more homogeneous distribution of the probability in QT series. However, comparing RR and QT series there were local differences in the behavior of pattern P0d between HRG and LRG which was contrary.

In conclusion, the results of this study show that patterns based on symbolic dynamics of the RR and QT series may contribute to a better risk stratification in ischemic cardiomyopathy patients.

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