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Refined Multiscale Entropy Analysis of Heart Period and QT Interval Variabilities in Long QT Syndrome Type-1 Patients

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Abstract— **This study assesses complexity of cardiovascular control in patients affected by type-1 variant of long QT (LQT1) syndrome. Complexity was assessed by refined multiscale entropy of heart period (HP) and QT interval variabilities. HP was taken as the time distance between two consecutive R peaks (RR) and QT interval was approximated as the time distance between the R-peak and T-wave apex (RTa) and between R-peak and T-wave end (RTe). RR, RTa and RTe intervals were automatically extracted from 24h Holter recordings and the daytime period was analyzed (from 02:00 to 06:00 PM). Non mutation carrier (NMC) individuals (n=11), utilized as a control group, were taken from the same family line of the mutation carrier (MC) subjects (n=26). We found that, while NMC and MC groups were indistinguishable based on time domain and complexity analyses of RR dynamics, complexity analysis of RTa and RTe variabilities clearly separates the two populations and suggests an impairment in the cardiac control mechanisms acting on the ventricles.**

I. Introduction

Long QT (LQT) syndrome is an inherited disease whose patients are characterized by longer QT interval, as measured from the surface electrocardiogram (ECG), because of a delayed repolarization of cardiac myocytes [1].

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The increasing interest in LQT syndrome is due to the dramatic clinical manifestations leading to arrhythmias, such as torsades de pointes, often resulting in sudden death. So far, twelve different genetical mutations leading to LQT syndrome have been discovered. The most common mutation is the one occurring on KCNQ1 gene, defined as type-1 variant of LQT (LQT1) syndrome [2,3]. Situations determining a sympathetic overactivation (e.g. physical exercise) are the main triggering factors leading to arrhythmias in LQT1 patients. As a consequence, LQT1 patients are usually treated with β-blockers.

The state of the autonomic nervous system is commonly assessed through spectral analysis of the beat-to-beat series of heart period (HP). The amplitude of the HP changes about the mean, especially in the high frequency (from 0.15 to 0.5 Hz) band [4] has been related to vagal modulation [5]. More recently, it has been proposed that also the temporal distance between Q wave onset and T wave offset (i.e. QT interval) can be fruitfully exploited to assess the state of the autonomic nervous system. Indeed, it was demonstrated that the amplitude of the oscillations of QT variability in the low frequency (from 0.04 to 0.15 Hz) band [4] is linked to sympathetic modulation [6]. While spectral analysis of HP variability can provide information about neural influences directed to the sinus node, spectral analysis of QT variability can provide information about those directed to ventricles (i.e. mainly on sympathetic modulation).

Although spectral analysis provides important information about the autonomic nervous system governing cardiovascular control, this tool is inherently limited in characterizing the variety of mechanisms concurring to the cardiovascular regulation (i.e. the complexity of the cardiovascular control) [7]. It was proposed that the larger the complexity, the more flexible the cardiovascular system in reacting to risky situations because a wider set of control mechanisms could concur to deal with a life-threatening situation [8].

We hypothesize that complexity of cardiovascular control is different when computed in non mutation carrier (NMC) and mutation carrier (MC) individuals belonging to the same family originating the mutation. In this study we analyzed individuals with founder effect (i.e. many individuals share a mutation identical by descent) originating in South Africa in approximately 1700 and segregating the same KCNQ1 mutation [2,3].

Therefore, the aim of the study is to evaluate complexity of cardiovascular control from HP and QT variability series derived from 24h Holter recordings in NMC and MC subjects. We exploited the refined multiscale entropy

(RMSE) [9], a refined version of the multiscale entropy (MSE) originally proposed in [10]. We selected this technique, instead of a more traditional entropy-based approach (see [11] for a review), because MSE (and RMSE) assesses complexity of a times series at different time scales. This feature is extremely helpful because it is well-known that HP dynamics is regulated by several mechanisms operating along different time scales [12]. This consideration holds even for the QT dynamics: indeed, for example, QT interval suddenly adapts to HP changes [13] but also adjustments with longer time constants are present [14].

II. Multiscale Entropy Analysis

A. RMSE

Given a time series $x=\{x(i), i=1,\ldots,N\}$, where i is the sample counter and N is the series length, the calculation of MSE [10] is based on three steps: i) elimination of fast temporal scales; ii) undersampling; iii) entropy calculation. In the original method, proposed in [10], the series was filtered using a FIR filter with τ coefficients (for $\tau=1$, the time series is simply the original time series). This procedure allowed the elimination of fast temporal scales according to the scale factor τ. The filtered series was undersampled with a factor τ, thus reducing the length of the series to N/τ samples at each scale factor τ. Complexity of the filtered signals was assessed using sample entropy (SampEn) [15]. The process was iterated with scale factors ranging from 1 to 20 and SampEn was plotted as a function of τ.

The procedure to calculate RMSE [9] is similar to that to compute MSE except for two substantial variations. The parameter r setting the tolerance for the calculation of the SampEn was continuously adapted with the scale factor τ, thus preventing the dependence of RMSE on the change of variance induced by the procedure of elimination of the temporal scales. In addition, the suboptimal FIR filter, leading to aliasing during undersampling, was substituted with an optimal low-pass Butterworth filter limiting as much as possible aliasing at any scale factor. We made reference to [9] for specific details on the method.

B. SampEn

In MSE [10] SampEn [15] was calculated with tolerance $r=0.15*SD$, where SD was the standard deviation assessed over the original time series and it was kept fixed as a function of factor τ. Conversely, in RMSE [9] SD was the standard deviation of the filtered version of the time series and it was adapted during the process of elimination of the temporal scales. In the SampEn calculation the pattern length of the conditioning pattern, m, was set to 2 and the time shift between adjacent samples forming a pattern was set to 1.

III. Experimental Protocol and Data Analysis

A. Study Population and Experimental Protocol

Twenty-four hours Holter 12 lead ECG (Mortara Instrument Inc., Milwaukee, WI, USA) were recorded from 26 MC LQT1 patients and 11 NMC control subjects with founder effect (i.e. the subjects, belonging to 22 different families, are all descendants of an original founding couple settled in South Africa in approximately 1700) [2,3]. The sampling rate was 180 Hz. Analysis was carried out on the lead with the best signal-to-noise ratio. All subjects did not take any drug, including β-blockers at the moment of recording. All the subjects gave their written informed consent. The study is in keeping with the principles of the Declaration of Helsinki for medical research involving human subjects. The human research and ethical review boards of the University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia approved the protocol.

B. Beat-to-beat Variability Series Extraction

After detecting the QRS complex on the ECG, the temporal distance between two consecutive R peaks (RR interval) was computed and utilized as an approximation of HP. QT interval was approximated as the temporal distance between R-peak and T-wave apex (RTa) and as the time distance between R-peak and T-wave end (RTe) [16]. RR, RTa and RTe intervals were automatically computed from 24h Holter ECG recordings. The apexes of the QRS complex and T-wave were fixed with minimum jitters using parabolic interpolation. The T-wave end was located according to a threshold on the first derivative set as a fraction of the absolute maximal first derivative value computed on the T-wave downslope. The T-wave was searched on the ECG in a time window whose length depended on the previous HP duration. All the parameters for the evaluation of RTa and RTe are continuously updated during the analysis of 24h Holter ECG recordings. The R-peak delimiting the i-th RTa and RTe measures is the R-peak defining the end of the i-th RR. All the R-wave peak detections were carefully checked to avoid erroneous identifications or missed beats. RR and RT series were not corrected or filtered except in correspondence of premature ventricular contractions or evident arrhythmias. In this case cubic spline interpolation technique was applied over the RR and RT values that were directly influenced by arrhythmias. The number of corrected values was smaller than 3% of the series length. Analyses were carried out during daytime (from 02:00 to 06:00 PM). In this period sequences of 5000 beats were selected. After calculating RR, RTa and RTe mean (μ_{RR}, μ_{RTa} and μ_{RTe}) the RR, RTa and RTe series were linearly detrended before any further analysis to limit effects of non stationarities. RR, RTa and RTe variance (σ^2_{RR}, σ^2_{RTa} and σ^2_{RTe}) were calculated from detrended series. RMSE was assessed over RR, RTa and RTe series.

C. Statistical Analysis

We performed unpaired t-test (or Mann-Whitney rank sum test when appropriate) to check the significance of the difference between NMC and MC groups. A $p<0.05$ was always considered as significant.

IV. Results

Table I shows mean and variance computed from RR, RTa, RTe series in the two populations. No significant difference was found in terms of RR mean and variance between NMC and MC individuals. Although mean RR was

TABLE I
MEAN AND VARIANCE OF THE RR, RTA AND RTE INTERVALS IN NMC AND MC INDIVIDUALS

	NMC	MC
μ_{RR} [ms]	698±110	750±91
σ^2_{RR} [ms^2]	1041±586	1446±1383
μ_{RTa} [ms]	235±33*	324±40
σ^2_{RTa} [ms^2]	70±58*	41±20
μ_{RTe} [ms]	311±30*	400±46
σ^2_{RTe} [ms^2]	130±151	132±87

Values are expressed as mean ± standard deviation. μ = mean; σ^2 = variance; NMC = non mutation carrier; MC = mutation carrier. The symbol * indicates a between-group difference with $p<0.05$.

similar, RTa and RTe mean were longer in MC subjects. This result reflects the phenotype of the pathology leading to a lengthening of the ventricular repolarization duration. Furthermore, RTa variance was significantly higher in NMC individuals compared to MC subjects.

Figure 1 shows RMSE course of RR series for the two populations. Mean value of RMSE (±standard deviation) are presented as a function of the scale factor. Both functions were monotonically increased with the scale factor. Even though in MC subjects RMSE was always higher than in NMC individuals, no significant difference between the two populations was detected, thus suggesting that the complexity of the RR dynamics is similar in the two groups.

Figure 2 shows RMSE computed from RTa series for NMC and MC subjects. Mean value of RMSE (±standard deviation) are presented as a function of the scale factor. After an initial increase from τ=1 to τ=2, the two functions monotonically decreased. At τ=1 (i.e. SampEn of the original series), RMSE of RTa series was significantly higher in NMC individuals than in MC subjects, while the opposite trend was observable for τ higher than 2. RMSE of RTa series assessed from MC subjects became significantly larger than that calculated from NMC subjects for τ larger than 5.

While the course of RMSE computed from RTe series (Fig.3) in NMC individuals was similar to that of the RTa series assessed from the same population (i.e. an initial increase followed by a gradual decrease, see Fig.2), the course of RMSE of RTe series calculated in MC individuals (Fig.3) was remarkably different from that of RTa series recorded in the same group (see Fig.2). Indeed, the RMSE of RTe series in MC subjects monotonically decreased as a function of the scale factor. As a consequence, RMSE of the RTe series at τ=1 (i.e. SampEn of RTe series) in MC group was significantly larger than that in the NMC group and remained larger at higher scale factors.

V. DISCUSSION

The major findings of this study can be summarized as follows: i) time domain indexes derived from RR variability was not able to distinguish between NMC and MC subjects; ii) time domain indexes derived from RTa and RTe variabilities suggested that MC individuals exhibited an impairment of the cardiovascular control; iii) complexity analysis of RR variability was not able to separate NMC group from MC population; iv) complexity analysis of RTa variability indicates a loss of complexity of cardiovascular

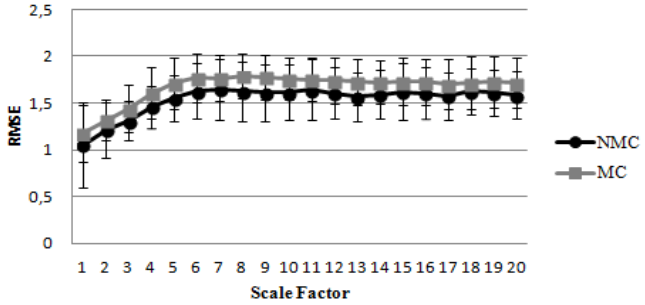

Fig.1. RMSE (mean ± standard deviation) of RR series assessed in NMC (black symbols and line) and MC (gray symbols and line) subjects as a function of the scale factor.

control at short temporal scale (i.e. τ=1) in MC individuals, while the opposite situation was detected at longer time scales in both RTa and RTe series.

This study originally compares 24h Holter ECG recordings of HP and QT variabilities in a group of subjects affected by LQT1 syndrome (i.e. MC) and in a control group (i.e. NMC) belonging to the same family line with founder effect [2,3]. Measures of HP and QT were approximated as RR and RT (RTa and RTe) respectively and automatically performed on 24h Holter ECG recordings. Comparison was carried out based on time domain indexes (i.e. mean and variance) and information domain parameters (i.e. RMSE).

While time domain analysis of RR variability was unable to differentiate the two populations, the same analysis carried out over RTa and RTe variabilities can separate MC subjects from the NMC individuals. This is remarkable given that the resolution of the 24h Holter ECG recordings is extremely low. Indeed, in addition to the expected lengthening of the RTa and RTe interval in MC group, the reduction of the variance of RTa in MC group compared to NMC individuals suggests an impairment of the autonomic nervous system, and, more specifically, a loss of sympathetic modulation directed to the ventricles [6]. The unaltered variance of the RTe might be ascribed to the larger sensitivity to broad band noise of this measure with respect to the RTa one [16].

Complexity analysis of RR variability was unable to distinguish NMC group from MC population, thus suggesting that complexity of regulatory mechanisms directed to the sinus node are not affected by LQT1 syndrome. Conversely, complexity analysis of RTa and RTe series was able to separate the two populations, thus indicating that complexity of control mechanisms directed to the ventricles was modified by LQT1 syndrome. More specifically, analysis of RTa series suggested that complexity of mechanisms operating over short time scales (i.e. τ=1) was reduced in MC subjects. This result is in agreement with the paradigm suggesting that pathological conditions might lead to a decrease of complexity of the cardiovascular control [8]. However, it is worth remarking that this finding is observable only at the level of RTa variability, while the complexity of RR dynamics was not affected. This finding corroborates previous observations that RTa variations cannot be explained only in terms of adaptation to RR

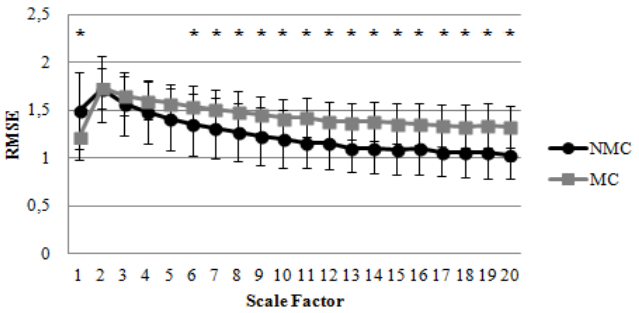

Fig.2. RMSE (mean ± standard deviation) of RTa for NMC (black symbols and line) and MC (gray symbols and line) subjects, plotted as a function of the scale factor. The symbol * indicates a significant between-group difference with $p<0.05$.

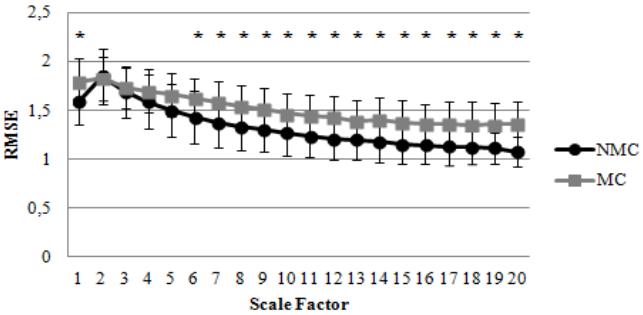

Fig.3. RMSE (mean ± standard deviation) of RTe for NMC (black symbols and line) and MC (gray symbols and line) subjects, plotted as a function of the scale factor. The symbol * indicates a significant between-group difference with $p<0.05$.

changes and influences independent of RR play a role in contributing to the RTa dynamics [6,17]. This result is not confirmed over RTe series as a possible result of the larger influence of broad band noise on the RTe interval [16].

The two populations were clearly separable at scale factor larger than 5. Indeed, RMSE assessed from both RTa and RTe variabilities was significantly larger in MC subjects than in NMC individuals. Since the effect of noise should be limited by the procedure responsible for the elimination of fast temporal scales, it is not surprising to find out that the two series behaved similarly at high scale factor. We can speculate that the larger complexity of mechanisms operating at ventricular level at high temporal scales in MC subjects might be related to the alteration of mechanisms adjusting QT interval over temporal scales of few minutes or to slow humoral regulations acting at time scales longer than those characterizing the fast neural reflexes (i.e. baroreflex).

VI. Conclusion

Complexity analysis of QT variability carried out over RTa and RTe measures provided important information about cardiovascular control in LQT1 patients. It is worth noting that the same analysis over RR variability was inconclusive. This result is remarkable because it was obtained from ECG traces recorded under uncontrolled conditions and during daily life activities (i.e. 24h Holter ECG recordings) and because these recordings had a very low temporal resolution. The proposed analysis suggests that differences between NMC and MC groups depend on scales factor, thus suggesting that regulatory mechanisms operating over different time scales can be differently affected by LQT1 syndrome. More specific studies should be performed to link the observed differences to an impairment of specific cardiac control mechanisms influencing ventricular repolarization dynamics.

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