Effect of Diurnal Rhythm on RR Interval Correlations of Long QT Syndrome Patients

Matias Kanniainen, Teemu Pukkila, Matti Molkkari, Esa Räsänen

Tampere University, Tampere, Finland

Abstract

We studied the effect of diurnal rhythm in RR interval (RRI) correlations of long QT syndrome (LQTS) patients. We focused on discrimination of healthy controls and LQTS subjects based on the variation of the HRV between the day and the night. We used 24-hour Holter recordings from Telemetric and Holter ECG Warehouse *with 149 healthy controls and 88 genetically confirmed LQTS patients (LQT1 = 70, LQT2 = 18, LQTS without beta blocker (BB) medication = 54, LQTS with BB medication = 29). The data was split into daytime (hours 15–19) and night-time (00–04). We assessed the RRI correlations with detrended fluctuation analysis (DFA) and its dynamical extension (DDFA) by considering time- and scale-dependent scaling exponents $\alpha(t, s)$. We observed reduced diurnal variability in the RRI correlations of LQTS patients, resulting in greater divergence from healthy controls during the day for all subsets. The effect was increased in the BB-treated subgroup (ROC-AUC 0.88, $p = 3.7 \times 10^{-5}$), but the results persisted in the absence of BBs (ROC-AUC 0.83, $p = 3.6 \times 10^{-7}$) with statistical significance ($p > 0.05$). The overall reduction in both the RRI correlations and their diurnal variability could potentially be exploited in QT-free risk assessment of LQTS.*

1. Introduction

Long QT syndrome (LQTS) is a genetic cardiac condition, where the QT interval and corrected QT interval (QTc) values of the electrocardiogram (ECG) are prolonged due to the delayed repolarization of the myocardia [1]. LQTS is divided in several subtypes based on the mutations affecting the sodium and potassium channels in different genes. The three main subtypes (LQT1, LQT2, LQT3) account for around 75 % of all the LQTS cases [1]. Sudden cardiac death can be the first symptom of the underlying LQTS for up to 10 % of the cases [2]. Therefore, early detection and prevention of LQTS are vitally important. Currently, LQTS is diagnosed with Schwartz criteria [3] and confirmed with genetic testing. Even though the main implication of LQTS is prolonged QTc, the criteria includes several other factors, such as the clinical history and family history, which are unrelated to prolonged QTc. There are certain conditions with resembling symptoms [4], which can be misdiagnosed as LQTS due to ambiguous diagnostic criteria. Additionally, the criteria have been confirmed to have poor diagnostic specificity [5].

The diurnal variation of QT intervals in LQTS subjects has been previously studied from 24-hour Holter recordings, and it has been shown that the intervals are prolonged during night [6]. However, this effect prevails in the healthy population [7], where the night-time QTc values are inclined to surpass the healthy limit of 450 ms. This underlines the importance of the clinical context of the QTc analysis.

Heart rate variability (HRV) metrics, and in particular detrended fluctuation analysis [8] (DFA), have potential for supplementing the diagnostic criteria [9]. The HRV is also known to exhibit diurnal variation [10]. Here, we utilize DFA and recently introduced dynamical DFA (DDFA) [11] to examine the diurnal variation in RR interval (RRI) correlations of healthy controls and LQTS subjects with an aim to further improve the diagnosability.

2. Data and Preprocessing

We used two large datasets, Healthy (E-HOL-03-0202-003) and Congenital Long QT Syndrome (E-HOL-03-0480-013) from Telemetric Holter and ECG Warehouse [12,13]. The datasets consist of Holter recordings with 2 or 3 leads. The healthy dataset contains 202 recordings from as many individuals and the LQTS dataset contains 480 recordings from 307 individuals. The LQTS dataset includes many infants and children, so the age distributions are significantly imbalanced. Thus, infants and children were excluded from the LQTS dataset, leading to similar age distributions for the datasets. Beta blockers (BBs) are the most common treatment for LQTS, and to control for their effect we limited ourselves to subjects without any medication or exclusively on BBs.

We defined the daytime as hours 15–19 and night-time as hours 00–04. These segments are included in the most

recordings, and the most subjects could be reasonably assumed to be awake or sleeping/resting during these segments, respectively. Furthermore, the starting point of the recording varied between the subjects, so hours 15–19 were chosen to include the majority of the measurement. The samples that did not contain data for both daytime and night-time segments were discarded.

The RRIs were extracted from the ECG with an in-house algorithm (QRS detection specificity 99.5 % and sensitivity 99.6 % with 30 ms threshold for the MIT-BIH Arrhythmia Database). The following filtering procedure was applied to the RRIs to assure consistent data for further analysis: (i) local median in windows of 21 RRIs is computed; (ii) the RRIs with differences $\geq$ 500 ms to the preceding RRI are removed; (iii) RRIs outside of the range 0.75–1.50 times the local median are removed. The samples with a removal rate larger than 5 % were discarded.

After the data selection and preprocessing, we ended up with 149 healthy controls and 88 LQTS samples (LQT1: 70, LQT2: 18). Out of the LQTS samples, 54 have no medication and 29 are on BBs. The remaining 5 subjects have a medication different from BBs. The basic information about the studied subsets is summarized in Table 1.

Table 1. Summary of the analyzed subsets of the data. For the number of samples N, the number of unique subjects is shown in parenthesis. The gender is shown as males (m) / females (f), and the rest are shown as the mean ± standard deviation.

	Healthy	LQT1	LQT2	LQTS (no BB)	LQTS (BB)
N (subjects)	149 (149)	70 (55)	18 (15)	54 (50)	29 (25)
gender (m/f)	68/75	30/40	5/13	25/29	8/21
age (years)	38 ± 14	37 ± 16	37 ± 15	39 ± 16	31 ± 11
RR (ms)	774 ± 177	854 ± 209	769 ± 183	843 ± 208	828 ± 205

3. Methods

Previously, conventional DFA α_1 and its scale-dependent extension showed enhanced discernibility for LQTS from other common HRV measures, particularly at higher DFA orders [9]. We complement the scale-dependent DFA with dynamical detrended fluctuation analysis (DDFA) [11]. DDFA extends conventional DFA [8] to the study of dynamical behavior of RRI correlations with time and scale-dependent scaling exponents $\alpha(t, s)$ [11]. We investigated the diurnal variation of HRV with only 2nd order DFA and DDFA.

The statistical significance of the differences in the scaling exponents α in the different groups was assessed by Welch's t-test. We evaluated the distinguishability of the different groups by area under curve (AUC) of receiver operating characteristic (ROC) [14].

4. Results

First, we utilize conventional second-order DFA α_1 and focus on short scales (4–16), which has been shown to yield a powerful discrimination for LQTS [9]. We analyze the statistical significance of the discrimination between healthy and different LQTS subgroups including LQT1 ($p_{\mathrm{day}} = 2.0 \times 10^{-9}, p_{\mathrm{night}} = 3.5 \times 10^{-5}$), LQT2 ($p_{\mathrm{day}} = 8.3 \times 10^{-3}, p_{\mathrm{night}} = 4.1 \times 10^{-2}$), LQTS with BB medication ($p_{\mathrm{day}} = 3.7 \times 10^{-6}, p_{\mathrm{night}} = 3.1 \times 10^{-4}$) and LQTS without BB medication ($p_{\mathrm{day}} = 3.6 \times 10^{-7}, p_{\mathrm{night}} = 1.1 \times 10^{-3}$), where all the differences are statistically significant (limit $p < 0.05$). In Fig. 1 the p-values of Welch's t-test are plotted as a function of ROC-AUC scores of the α_1 results between the healthy and LQTS subgroups. Since the datasets are imbalanced due to smaller sizes of the LQTS subsets, a corresponding number of healthy subjects is randomly selected to match the size of each LQTS subset. The procedure is repeated 100 times, and the mean values of both p-value and ROC-AUC score are taken to average the randomization of the samples.

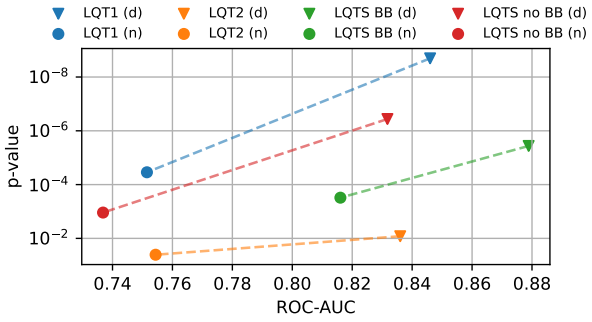

Figure 1. ROC-AUC scores and Welch's t-test p-values for the studied subsets and their diurnal separations in day (d) and night (n) for second-order DFA α_1.

Figure 1 shows that the discrimination of LQTS during the day compared to the night is considerably and systematically stronger. The discrimination persists at night, but with lower performance. The effect of the BBs can be easily seen, and the ROC-AUC score of the day-segments reaches a high value of 0.88. Furthermore, during the night the BB effect is observable with higher discrimination. There is little difference between LQT1 and LQT2, and the LQTS subjects without medication have the lowest ROC-AUC scores. However, the situation without medication is the most promising for practical diagnostic purposes, since a previous medication with BBs already implies the existence of a heart condition.

Next we focus on DDFA to demonstrate the real-time differences between healthy and LQTS subjects. Figure 2 shows examples of DDFA results for RRIs of a healthy and

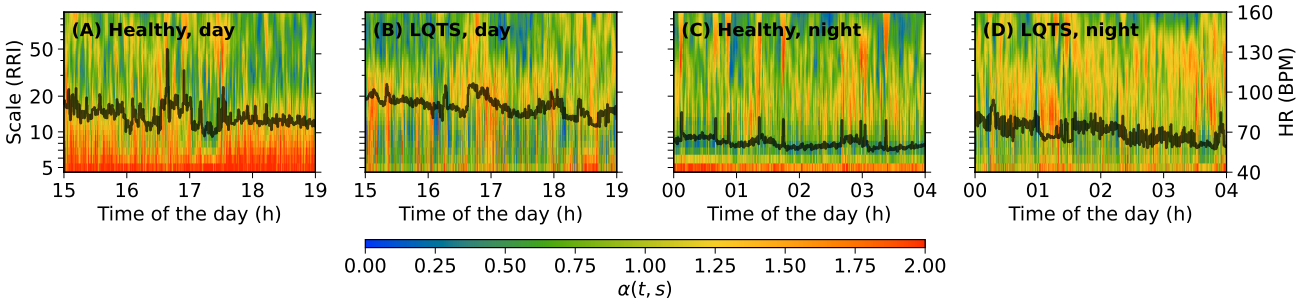

Figure 2. Examples of dynamical detrended fluctuation analysis for RR intervals of healthy and LQTS subjects in day- and night-time. The black line corresponds to the moving average HR computed in 30-second segments.

LQTS subject (LQT1, no BB) during the daytime (**A**, **B**) and night-time (**C**, **D**). It is evident that $\alpha(t, s)$ in short scales (4–16) during the day is considerably higher for the healthy subject compared to the LQTS subject, even though the HR range is similar in both cases. The differences are diminished during the night, where the $\alpha(t, s)$ behavior is relatively similar in both cases.

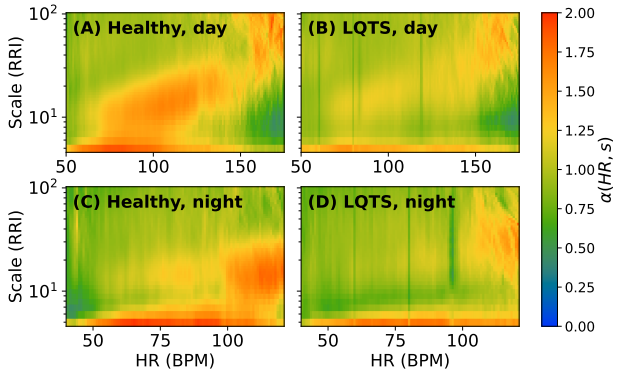

Figure 3. Aggregate plots of the DDFA results for RR intervals of healthy and LQTS subjects in day- and night-time computed for the full datasets.

To study the differences and similarities between healthy and LQTS subjects for the complete dataset we construct an aggregate plot of $\alpha(t, s)$ for all the samples as a function of HR. This is shown in Fig. 3 for healthy and LQTS groups, and for daytime and night-time, respectively. The figure shows that the phenomenon observed within Fig. 2 is conserved across the whole dataset. The most distinguishable difference is once again visible during the day, where $\alpha(\mathrm{HR}, \mathrm{s})$ is considerably higher for healthy than for LQTS subjects across a large range of HR (70–120 BPM), especially for the short scales (4–16), but also extending to scales up to 30. Moreover, during the night, the healthy subjects exhibit higher $\alpha(\mathrm{HR}, \mathrm{s})$, especially for higher HR values. However, the short-scale differences are reduced, potentially leading to reduced discrimination power. It is also noteworthy that the maximal HRs found at night are considerably lower than during the day, and thus the different axes between the day- and night-time are not directly compatible.

In Fig. 4, the density of the DDFA α over the whole dataset is plotted as a function of the RRI scale. Inspecting the figure, it is evident that the discrimination between healthy and LQTS is considerably better during the day than during the night. Furthermore, we find that the most prominent differences between the healthy and LQTS subjects for both day and night occur in short scales (4–16), where the differences are highlighted with the different mode of the distributions. However, detailed analysis using *scale-dependent* DFA is required.

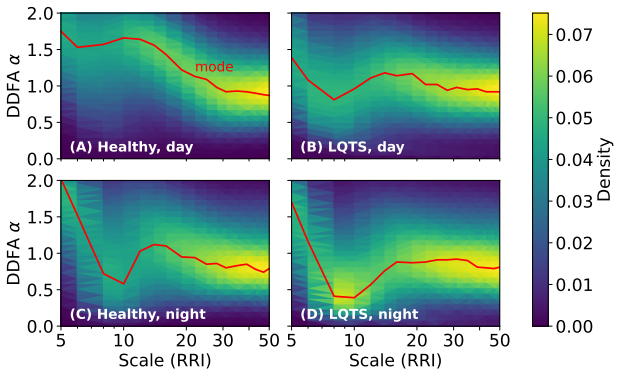

Figure 4. Mean densities of DDFA scaling exponents and their modes as a function of the scale during the day and the night for healthy controls and LQTS patients.

Finally, we point our that a healthy heart is known to exhibit fractal properties in the RR fluctuations, corresponding to higher values of scaling exponent α [15]. These fluctuations reflect the adaptive and flexible nature of the cardiac regulation system, which can adjust to changing internal and external conditions. Therefore, reduction of α implies reduction in the adaptivity, which may cause arrhythmias or altered heartbeats as known symptoms of

LQTS [2]. The conducted analysis shows significantly reduced scaling exponents for LQTS compared to healthy, especially during the daytime. During the night the scaling exponents are reduced in both groups (at the lowest HRs), and the differences between the groups are less prominent than during the day.

5. Conclusion

DFA and DDFA provide a promising tool for QT-free analysis of the LQTS. The discrimination between the LQTS and healthy subjects is enhanced with the consideration of the diurnal variation. In particular, the distinguishability is significant during the day compared to the night. Further insights could be obtained by considering scale-dependent DFA as well as rigorous statistical analysis of the DDFA results, which was here limited to a survey of the aggregate landscapes and densities of the time- and scale-dependent scaling exponents. Nevertheless, (D)DFA could already be potentially exploited in the diagnosis of LQTS along with the prevalent diagnostic criteria, taking also the diurnal variation into account.

Acknowledgments

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Address for correspondence:

Matias Kanniainen

Computational Physics Laboratory, Tampere University, P.O. Box 692, FI-33014 Tampere, Finland

matias.kanniainen@tuni.fi