Reduced RR Interval Correlations of Long QT Syndrome Patients

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Abstract

We study RR interval (RRI) correlations in subjects with long QT syndrome (LQTS). We aim to find distinctive differences in nonlinear heart rate variability (HRV) measures between the LQTS subjects and healthy controls.

We analyze 24-hour Holter recordings from 127 healthy controls and 115 LQTS samples with unified age distributions. Beta blockers (BB), which are known to affect HRV, are a common treatment for LQTS, and that is the primary confounding factor to be accounted for. We compute conventional short-scale (4–16 RRIs) detrended fluctuation analysis (DFA) scaling exponents α_1 at various degrees of detrending and compare the results to other common HRV measures. We complement the study by investigating scale-dependent exponents $\alpha(s)$.

We find statistically significant reduction in the short-scale α_1 of LQTS for subjects with (Welch's t-test $p = 2.5 \times 10^{-13}$) and without ($p = 3.2 \times 10^{-8}$) BBs. These DFA-2 results yield considerable improvement over the linear detrending of DFA-1. Among other common HRV features the DFA α_1 is the best indicator for LQTS. Despite the clear differences in the mean behavior, the predictive power of the measures is diminished by large individual variability. The scale-dependent picture may aid in finding optimal HRV indicators for LQTS diagnosis.

1. Introduction

Long QT syndrome (LQTS) is a genetic condition delaying myocardial repolarization, which can be detected as prolonged QT intervals on the electrocardiogram (ECG). Typical symptoms of LQTS are syncope and cardiac arrest, which can cause sudden cardiac death even in young asymptomatic patients. The first clinical manifestation of LQTS is sudden death in 10 % of the cases, so accurate and early detection of the condition is vital [1].

LQTS is caused by gene mutations affecting the ion channels responsible for the action potential of the heart. LQTS has several genotypes, but the 3 most common types (LQT1, LQT2, and LQT3) account for about 90 % of the cases [1]. Genetic testing is neither always easily available nor cost effective, so initial screening of LQTS patients is based on the duration of the QT intervals and Schwartz criteria. The Schwartz criteria are a scoring system consisting of heart rate-corrected QT values, a few other ECG findings such as notched T wave, clinical history, and family history [1]. Problems with calculating proper corrected QT values and misinterpretation of symptoms result in diagnostic miscues [2].

Heart rate variability (HRV) analysis could potentially assist in diagnosing LQTS. Our main analysis tool is detrended fluctuation analysis (DFA), which was originally introduced to study long-range power-law correlations in DNA sequences based on the theory of random walks [3]. By computing the mean fluctuations $F(s)$ around the local polynomial trends at multiple scales s, DFA is applied to assess the power-law scaling $F(s) \propto s^{\alpha}$ characterized by a scaling exponent α [4,5]. The method was quickly adopted for studying non-stationary physiological time series and the beat-to-beat fluctuations of the heart [4]. Previous studies of LQTS with DFA have been inconclusive [6], possibly due to the limited number and short duration of the data. Here, we utilize a large amount of 24-hour recordings to overcome this limitation together with advances in the DFA methodology [7, 8].

2. Data and preprocessing

We utilize two large databases from the Telemetric and Holter ECG Warehouse (THEW) [9, 10]. Healthy controls from (E-HOL-03-0202-003) database and Congential Long QT syndrome patients from (E-HOL-03-0480-013) database. Both databases contain 24-hour Holter ECG recordings with multiple leads. RR intervals were extracted from the ECG using an in-house algorithm (QRS-detection specificity 99.5 % and sensitivity 99.6 % with 30 ms threshold for the MIT-BIH Arrhythmia Database).

The original LQTS database contains 420 recordings from 307 subjects mostly from the 3 most common genotypes. Studying the differences between the genotypes is outside the scope of this paper, but the LQTS group is further split into two groups based on whether they were on beta blocker (BB) therapy or were untreated. The medication is a primary confounding factor due to how BBs affect the heart rate and HRV. BBs are usually the first choice of

Table 1. Basic statistics of the studied groups. The number of subjects (N) is shown separately for males (m) and females (f), and for the rest mean $\pm$ standard deviation.

	Healthy	LQTS no BB	LQTS BB
N (m/f)	127(57/70)	73(27/46)	42(10/32)
age (years)	40 ± 14	40 ± 14	33 ± 12
RR (ms)	766 ± 81	813 ± 101	897 ± 90
QT (ms)	399 ± 29	451 ± 49	499 ± 44

treatment for LQTS for their efficiency at reducing cardiac events [11]. Age is also known to affect HRV [12] and over a third of the LQTS samples are from young subjects (< 16 years) compared to just a few from the healthy controls. Limiting the analysis to $\geq$ 16-year-old subjects results in approximately similar age distributions for the studied groups.

Due to the nature of the 24 h Holter recordings measuring different daily activities, there are always some outliers and samples with poor data quality. We perform a simple filtering to limit our analysis to the samples with consistent data: (i) we apply a rolling median filter with 31 RRI kernel to the data, (ii) RRIs are discarded if they fall outside the interval $0.75\eta \leq \text{RRI} \leq 1.5\eta$, where η is the local median, and (iii) RRIs are also discarded if the difference between subsequent intervals is greater than 200 ms.

Samples, where more than 1 % of RRIs are discarded, are excluded from the analysis to ensure high data quality. After the data selection, we have 127 healthy controls and 115 LQTS samples, of which 42 are on BBs and 73 are untreated. The LQTS genotypes are as follows: 68 LQT1, 33 LQT2, 3 LQT3, and 11 others. Table 1 summarizes the basic statistics about the studied groups.

3. Theory and methods

Our main tool for HRV analysis is detrended fluctuation analysis (DFA) [3–5]. We compute conventional short-scale (4–16 RRIs) scaling exponents α_1 [4] with DFA detrending orders 1–3 (the degree of the local detrending polynomial). We utilize maximally overlapping windows in the computations for increased statistical accuracy [7]. The DFA scaling exponents describe the *collective* correlations over the studied range of scales in contrast to the *pointwise* correlations of the autocorrelation function [8]. We complement the analysis by studying a spectrum of scale-dependent exponents $\alpha(s)$ [8].

For comparison, we also compute other conventional HRV measures: mean RR, standard deviation (SD), the root mean square of successive differences (RMSSD) and the percentage of successive differences over 20 ms (pRR20) from the time domain, Poincaré plot indices (SD2, SD2/SD1), and frequency domain high- (HF) and low-frequency power (LF) and the HF/LF ratio. For the frequency domain analysis, the time series are detrended using smoothness priors method (with the smoothing parameter $\lambda = 500$) [13] and transformed into frequency domain with Lomb–Scargle periodogram [14].

We study the statistical significance of the differences in the location parameters of the HRV measure distributions among the different groups with Welch's t-test p-values (which does not assume equal variances in contrast to Student's t-test). For diagnostic purposes, differences in the mean behavior are not sufficient, but the distributions must be distinct enough such that a randomly chosen sample can be assigned to one of the groups with sufficient certainty. We study this distinguishability with the receiver operating characteristic (ROC) [15]. The ROC is a plot of the true positive rate versus the false positive rate of a single threshold binary classifier when the threshold is varied across all the observed values. The area under the curve (AUC) can be intuitively interpreted as the probability of the classifier correctly distinguishing two randomly chosen samples from both groups.

4. Results and discussion

The short-scale DFA scaling exponents α_1 indicate reduced RRI correlations for LQTS patients in Fig. 1. The correlations are further reduced by BB treatment. Increasing the DFA detrending order broadens the distributions of the α_1 values. However, at the same time, the distributions are shifted such that the medians and interquartile ranges of the LQTS groups become more clearly separated from those of the healthy cases. The differences in the mean α_1 are statistically significant already with DFA-1 (healthy vs. LQTS no BB: $p = 4.5 \times 10^{-4}$, healthy vs. LQTS BB: $p = 7.5 \times 10^{-8}$), but are notably elevated with the non-linear detrending of DFA-2 (healthy vs. LQTS no BB: $p = 3.2 \times 10^{-8}$, healthy vs. LQTS BB: $p = 2.5 \times 10^{-13}$). With DFA-3 the statistical significances remain approximately similar to those of DFA-2. No statistically significant differences were found in the α_1 between the LQT1/2 genotypes, and for the other genotypes there is insufficient data to draw conclusions. Therefore, we focus on the combined genotype data in this study of RRI correlations.

For comparison, we also computed other common HRV measures. The statistical significance of their differences and the diagnostic power between the healthy and LQTS cases are illustrated in Fig. 2 by p-values and ROC-AUC scores, respectively. In Fig. 2(a) we find that the higher order DFA α_1 are the best indicators for LQTS in the absence of BB treatment. For diagnosing LQTS this is the most interesting case, as the prescription of BBs implies an already known heart condition. The heart rate itself is known to affect HRV, and indeed the differences in the mean RR level alone result in medial distinctiveness be-

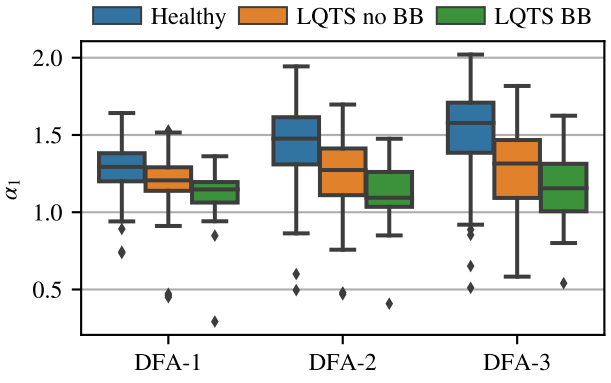

Figure 1. Box plots of short-scale DFA scaling exponents α_1 for different DFA detrending orders.

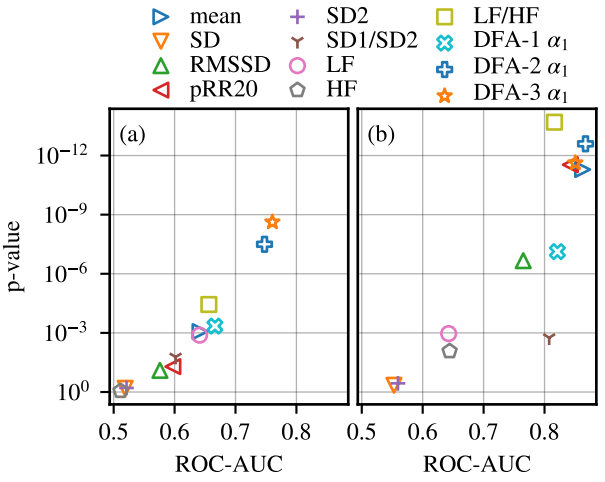

Figure 2. Welch's-t test p-values versus ROC-AUC for different HRV measures. Comparison between healthy and LQTS without (a) and with (b) beta blocker therapy.

tween these two groups. Despite this trivial confounding factor the DFA-2&3 α_1 clearly outperform the other HRV measures with known heart rate dependence.

Beta blockers are known to decrease the heart rate and thus are expected to have an effect on HRV. This is manifested in Fig. 2(b) where the mean RR has become a prominently distinctive measure, along with other measures with trivial RR dependence. Notably, while the distinctiveness of α_1 of DFA-1, 2, and 3 is also increased, the beat rate dependent measures are affected to a greater extent, suggesting that the reduction of the short-scale RRI correlations is a characteristic of LQTS beyond the beat rate effect.

More in-depth insights into the RRI correlations are obtained by studying the scale-dependent $\alpha(s)$ in Fig. 3. The results for DFA-2 in Fig. 3(a) demonstrate common qualitative features among all the studied DFA orders: (i) bias for increased $\alpha(s)$ at the very shortest scales, (ii) the mean

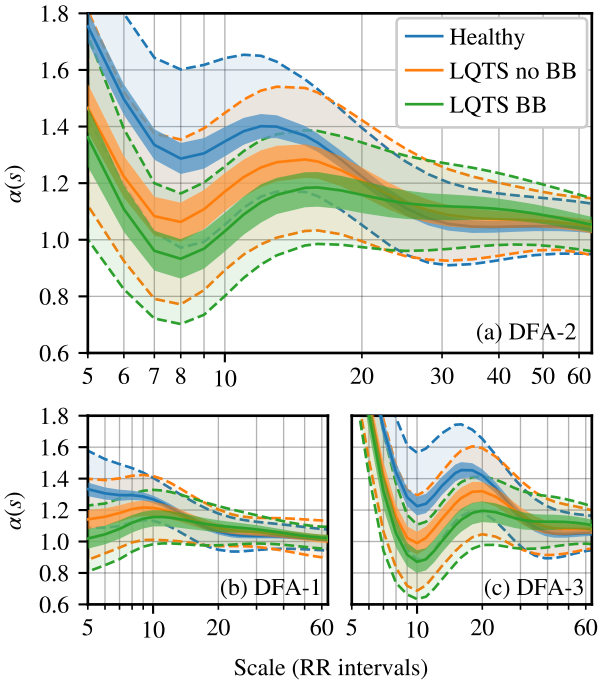

Figure 3. Scale-dependent DFA results with mean $\alpha(s)$ (solid line) and its bootstrapped 95 % confidence intervals (strong shading) and standard deviation (light shading + dashed line) for DFA-2 (a), DFA-1 (b), and DFA-3 (c).

$\alpha(s)$ remain distinct for healthy and LQTS from the shortest scales until a longer threshold scale with BBs raising the threshold, (iii) after the threshold the $\alpha(s)$ for all the groups converge towards unity, and (iv) despite statistically significant differences in the mean $\alpha(s)$ the distributions have substantial overlap.

The $\alpha(s)$ results for DFA-1&3 are shown in Figs. 3(b,c), which reveal the following quantitative differences among the common features with increasing DFA detrending order: (i) magnitude of the short-scale bias and the scales it affects are increased, (ii) the threshold at which the confidence intervals of the mean $\alpha(s)$ for healthy and LQTS begin to overlap shifts to longer scales (DFA-1: 9, DFA-2: 15, DFA-3: 20), (iii) the beginning of the mutual convergence towards unity is similarly shifted to larger scales (DFA-1: $\approx$15, DFA-2: $\approx$25, DFA-3: $\approx$35), and (iv) the overall $\alpha(s)$ distributions broaden, but the standard deviations become slightly more separated from the means of the other groups and remain so through longer scales.

The final point may not be visually obvious but is made rigorous by the study of the scale-dependent ROC-AUC scores for $\alpha(s)$ in Fig. 4. There is a notable improvement in the AUC score for the higher order methods over linear DFA-1 (with the exception of the dip at the shortest scales due to the bias). The distinguishability also remains

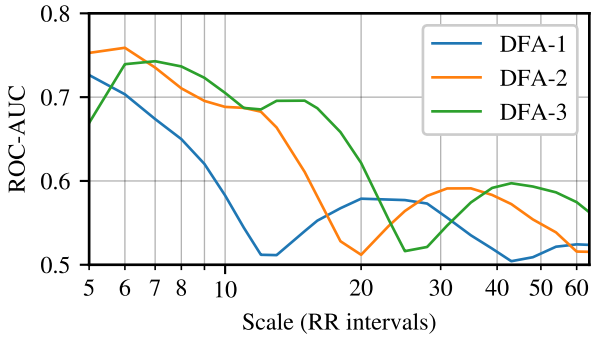

Figure 4. Receiver operating characteristic area under curve (ROC-AUC) values for $\alpha(s)$. Comparison between healthy and LQTS without beta blocker therapy.

at higher levels through longer scales with increasing DFA order. The AUC bouncing through the value 0.5 of random chance corresponds to the mean levels of $\alpha(s)$ for healthy and LQTS crossing each other.

The AUC values suggest that the standard α_1 fitting range of 4–16 RRIs extends to the scales too long for DFA-1 to provide optimal results. This could be due to possible short-term trends in LQTS that are not sufficiently accounted for by the linear detrending, resulting in the enhanced performance of the higher order methods. Additional insights could be gained by taking into account the circadian rhythm in the 24-hour recordings and analyzing shorter segments. This could lead to more viable data by not discarding entire recordings for data quality, permitting more careful study of the different genotypes.

5. Conclusions

Short-scale RRI correlations, measured by DFA α_1, are reduced in LQTS and further with BB treatment. DFA scaling exponents, especially with higher-order detrending, are superior indicators for LQTS compared to other conventional HRV measures. A combination of novel scale-dependent DFA measures could potentially be utilized for enhancing the LQTS scoring system [1] for improved diagnosability.

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