Combination of QTc and RR Analysis in the Detection of Long QT Syndrome

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Abstract

Conventionally, long QT syndrome (LQTS) is diagnosed from the prolonged corrected QT (QTc) interval. Recently it has been shown that also RR intervals can be used to discriminate LQTS patients with a reasonable accuracy. Here, we examine a combination of these approaches, that is, analysis of (i) Bazett's QTc interval length and (ii) RR interval sequences analyzed with detrended fluctuation analysis (DFA) to improve the classification of LQTS subjects from healthy controls. We utilize segments of 24-hour Holter recordings from Telemetric and Holter ECG Warehouse with 143 healthy control samples and 113 genetically confirmed LQTS samples. The beta blocker (BB) treatment and different LQTS subtypes are accounted for. A support vector machine pipeline is utilized in the classification. Independent QTc analysis yields a classification accuracy of 0.84, and independent DFA analysis of RR intervals yields an accuracy of 0.76. A combination of these two approaches leads to a high accuracy of 0.88. Hence, LQTS discrimination can be improved by combining QTc evaluation and RR interval analysis with DFA. The DFA approach can be used also as a prediagnostic tool by monitoring the RR intervals with wearable devices before thorough ECG measurements including QT intervals.

1. Introduction

Long QT syndrome (LQTS) is a genetic cardiac condition, which can lead to arrhythmias and a sudden cardiac death (SCD) if untreated. The main manifestation of the LQTS is the prolongation of the corrected QT (QTc) interval in the electrocardiogram (ECG). SCD can be the first symptom of the underlying LQTS for up to 10 % of the cases [1]. Therefore, early detection and prevention of LQTS is vitally important. Currently, LQTS is diagnosed with Schwartz criteria [2] and confirmed with genetic testing. However, the criteria have been confirmed to yield poor diagnostic specificity [3]. Also, there are certain conditions with resembling symptoms [4], which can be misdiagnosed as LQTS due to ambiguous diagnostic criteria.

Along with the prevalent diagnostic criteria, nonlinear heart rate variability (HRV) analysis has been used in the discrimination of LQTS. In particular, detrended fluctuation analysis (DFA) [5] has been recently utilized to discriminate LQTS subjects from healthy controls with an accuracy which is superior to conventional HRV metrics [6, 7]. In essence, the scaling properties portraying the internal correlations of RRI's for LQTS subjects are inherently different from those of the healthy population, which enables a reliable discrimination of the LQTS.

Here, both QTc and RR analyses are used to classify the LQTS subjects, and their combinatory classification power is evaluated. The use of DFA is found to improve the classification, and its use alone (without QTc) provides reasonable results. Hence, DFA is proposed to supplement the current diagnostic criteria of LQTS as a potential early detection tool. Due to the utilization of only RRI's, the DFA approach would be directly applicable in wearable smartwatches and heart rate monitors.

2. Data and Preprocessing

We employ two datasets, Healthy (E-HOL-03-0202-003) and Congenital Long QT Syndrome (E-HOL-03-0480-013) from Telemetric Holter and ECG Warehouse [8, 9]. They contain 202 and 480 long-term ECG recordings, respectively, measured with two or three leads. The healthy and LQTS datasets include 5 and 74 infants and children (age < 16), respectively. As the age significantly affects the QT intervals [10] and HRV [11], the infants and children were removed from the analysis to ensure similar age distributions in the groups.

The long-term Holter recordings are usually 24 hours long including several different types of physical activity. It has been shown that the discriminatory power of DFA is increased during daytime (physical activity) compared to the night-time (deep rest, sleep) [7]. Therefore, we restrict the analysis to the daytime (15h-19h) akin to Ref. [7].

The RRI's 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). To ensure high-quality data for the analysis, we utilized the following preprocessing scheme: (i) local medians in windows of 21 RR intervals and QT intervals were computed; (ii) the intervals with differences

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RR $\geq$ 500 ms & QT $\geq$ 250 ms to the preceding intervals were removed; (iii) the intervals outside of the range 0.75–1.50 times the local median were removed. If more than 5% of the data were removed, the sample was discarded.

After the restrictions and preprocessing, we were left with 143 healthy samples and 113 LQTS samples, from which 49 had a BB medication and 64 had no medication. The basic information of the samples is shown in Table 1.

Table 1. Summary of the datasets used in this study: the number of ECG samples N, age distribution in years (mean $\pm$ standard deviation), gender distribution (M/F) by samples, LQTS subtype (LQT1/LQT2/other) beta-blocker medication (YES/NO) by samples and both RR and QT distributions in milliseconds (mean $\pm$ standard deviation).

	Healthy	**LQTS**
ECGs	143	113
Age	39 ± 14	36 ± 15
Gender (M/F)	68/75	47/66
LQTS subtype	-	69/39/5
BB (YES/NO)	-	49/64
RR (ms)	723 ± 146	762 ± 203
QT (ms)	388 ± 54	435 ± 81

3. Methods

The QT interval has a complex relationship with the heart rate, i.e., RRI's. The QT-RR dependency is treated with QT correction (QTc) with an aim to remove the RRI-dependence from the QT interval. Several QTc methods have been proposed [12], including simple formulae, individual corrections [13], and recently also those based on the actual information transfer [14] between the RRI's and QT intervals [15]. Here, we utilize most commonly used method of Bazett, which is defined as $\mathrm{QTc} = \mathrm{QT}/\sqrt{\mathrm{RR}}$ [16]. For the RRI analysis, we utilize the DFA short-scale (scales 4-16) scaling exponent α_1. At DFA orders > 1 (beyond linear detrending), DFA α_1 has been shown to yield enhanced discrimination for LQTS compared to the conventional HRV measures [6]. Here, we utilize DFA with second-order polynomial detrending. We point out that alternative QTc and HRV methods for the discrimination of LQTS are examined in Ref. [17].

As the features for the classification, we utilize the mean values and standard deviations (SD) of DFA α_1 and Bazett's QTc values over the individual measurements. For the classification task, we employ a support vector machine (SVM) classifier [18] with a split of 80% and 20% for the training and test sets, respectively. The classification is done 100 times, and the optimal parameters of SVM for each iteration are calculated using grid search with cross validation [19]. The parameter grid of the grid search cross validation consists of three parameters: C is the SVM regularization parameter (values 0.1, 1, 10, 100), γ is the SVM kernel coefficient (values 10^{-3}, 10^{-4}, 10^{-5}, scale), and $kernel$ corresponds to the SVM kernel type (linear, polynomial). In γ, the 'scale'-parameter corresponds to a special value of $(N_X$ * Variance$(X))^{-1}$ for X features. The mean values and SDs of precision, recall, accuracy and balanced accuracy of each classification iteration are then analyzed.

4. Results

First, we calculate the classification results for the whole LQTS dataset and the healthy controls using DFA α_1 and Bazett's QTc values. They are used both individually and in a combined fashion by assigning both DFA α_1 and QTc features to the classifier. In Fig. 1, the precision, recall and accuracy scores are shown for the DFA, QTc and for the combination of the methods. The mean values and SDs are shown with the bar plots and error bars, respectively.

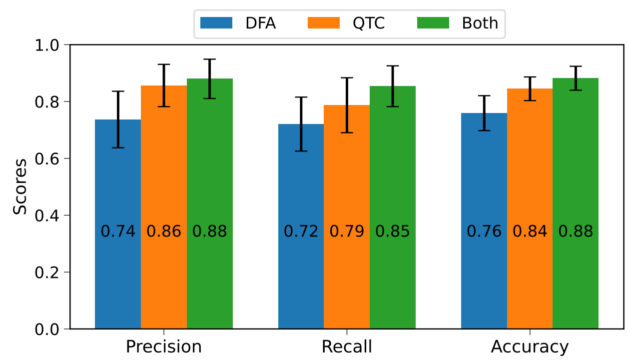

Figure 1. Precision, recall and accuracy scores of the classification results for DFA and QTc methods, and for the combination of the methods. The bars correspond to the mean values and the black lines show to the standard deviations of the iterations.

Both DFA and QTc methods yield good scores individually. DFA yields precision=0.74, recall=0.72, and accuracy=0.76, and the QTc method yields the respective scores of 0.86, 0.79, and 0.84. However, the combination of the methods yields the highest precision, recall and accuracy scores with 0.88, 0.85, and 0.88, respectively. In particular, the combination of the methods enhances the recall score of the classification compared to DFA and QTc, leading to fewer false positives.

To study the classification results in more detail, we consider the corresponding confusion matrices in Fig. 2. Here, it is reassured that the combination of the methods yields the best classification power compared to the DFA and QTc methods individually. The sensitivities of both DFA and QTc (0.79, 0.89) are relatively good, and the sensitivity of the combination of methods (0.90) only slightly exceeds the one of the QTc method. However, the specificity of the combination of the methods (0.85) is enhanced considerably compared to the specificities of the DFA (0.72) and QTc (0.79) methods individually. Therefore, the classification is more reliable when considering both DFA-based RRI and conventional QTc analysis, since both sensitivity and specificity of the classification are increased.

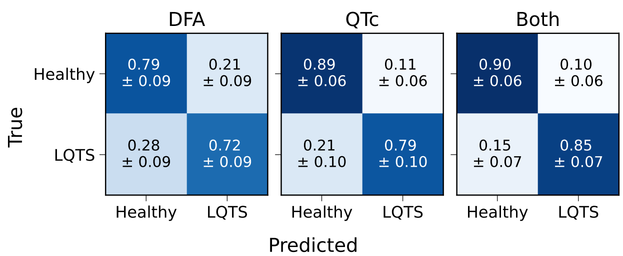

Figure 2. Confusion matrices of DFA and QTc methods and their combination for the classification. The predictions are shown as mean ± standard deviation of the individual confusion matrix results from each iteration.

The LQTS dataset contains several different subsets, e.g., subjects with and without beta-blocker (BB) medication, and subjects with different LQTS subtypes, such as type 1 (LQT1) and type 2 (LQT2). LQTS is commonly treated with BB's, but they are known to affect both the HR and its variability [20], as well as the QTc interval length [21]. Therefore, it is also worthwhile to study the classification of such subgroups individually. We point out that the subsets are not mutually exclusive. For example, a subject can belong to both BB and LQT1 subsets. Here, we resort to the balanced accuracy (BA), since the subsets have a considerable data imbalance compared to the healthy dataset.

In Fig. 3 we show the balanced accuracies of the classification results of LQTS subjects (i) with and (ii) without BB medication, (iii) LQT1 subjects, and (iv) LQT2 subjects against the healthy controls computed using DFA, QTc and their combination, respectively. Here, the BA distributions are the highest for the BB subset. All the methods perform well in the classification, and there is no significant difference between the QTc method and the combination of the QTc and DFA methods in the BB subset, as the methods yield median BAs of 0.88 and 0.87, respectively. Regarding the subgroup without BB medication, DFA and QTc yield median BAs of only 0.68 and 0.80, respectively, but the combination of the methods improves the classification with a median BA of 0.85. The analysis for subjects without medication is especially fruitful, since the presence of BBs already implies a presence of a cardiac condition. Thus, it is important to be able to distinguish LQTS from the subjects without medication. In the LQT1 and LQT2 subsets, the combination of the methods yields the best median BAs (LQT1=0.84, LQT2=0.87) compared to the individual DFA (LQT1=0.73, LQT2=0.80) and QTc (LQT1=0.81, LQT2=0.85) methods.

To summarize, for the overall LQTS population the classification of LQTS from healthy controls is enhanced by using the combination of DFA α_1 and the conventionally utilized Bazett's QTc formula. By employing a classification pipeline utilizing the features of both methods, we can achieve the best overall classification accuracy compared to individual application of the methods. We point out that RRI analysis with DFA could be utilized in wearable devices, such as smartwatches or HR monitors, for porediagnostic screening and early guidance to care. Furthermore, in the long Holter recordings, both DFA and QTc analysis could be employed together to evaluate the possibility of an existing LQTS condition.

5. Conclusion

DFA provides a promising diagnostic tool for the LQTS alongside the conventional QTc analysis. When classifying LQTS subjects from healthy controls, both DFA and QTc analysis yield considerable distinguishability for LQTS, but the overall classification accuracy is enhanced when utilizing features from both DFA and QTc analysis in the classification. The combination of DFA and QTc also increases the balanced accuracy of the classification compared to the individual analysis of the methods when considering different subgroups such as LQTS subjects without beta-blocker medication, or LQT1 and LQT2 subtypes. For the subjects with beta-blocker medication, the balanced accuracy of the combination of the methods does not improve the classification compared to that of individual QTc analysis. As a conclusion, DFA can be a useful tool in early stage prevention of LQTS and guidance to care through consumer devices measuring RRIs. Furthermore, the inclusion of DFA in the diagnostic criteria of LQTS should be considered.

Acknowledgments

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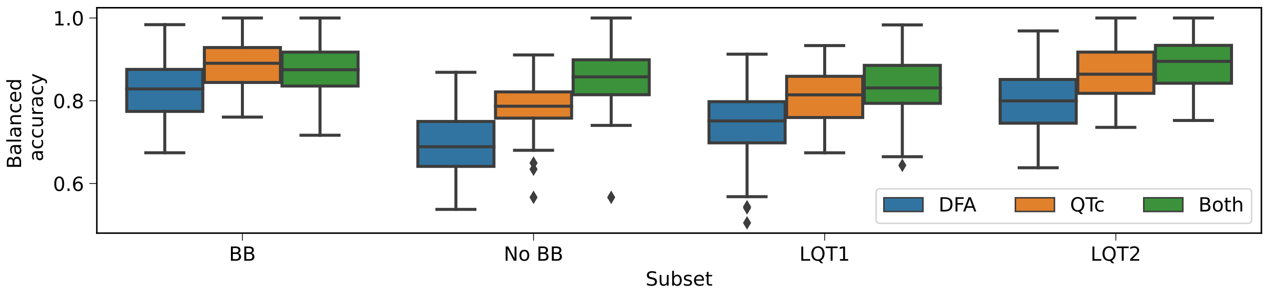

Figure 3. Distributions of balanced accuracies over 100 classification iterations for subjects with beta blocker (BB) medication, without BB medication, LQT1, and LQT2 computed using DFA, QTc and their combination.

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