

Transfer Entropy between RR and QT Intervals in Long QT Syndrome

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Abstract

Healthy subjects exhibit strong information transfer from RR to QT intervals. In this study, we assess the dynamic coupling between RR and QT intervals for subjects with long QT syndrome (LQTS) - a potentially fatal genetic cardiac disease characterized by delayed myocardial repolarization. We use transfer entropy (TE) to quantify the magnitude and direction of the information exchange between the RR and QT intervals. Using 24-hour Holter ECGs, we calculate TE as a function of RR and QT histories up to 50 beats and compare the results between the healthy controls and the subjects of LQTS type 1 and 2.

Asymmetry between $TE_{RR \rightarrow QT}$ and $TE_{QT \rightarrow RR}$ was observed for the LQTS subjects. Compared to the healthy, the LQTS subjects had significantly smaller $TE_{RR \rightarrow QT}$ at RR history lengths longer than about 18 beats, while $TE_{QT \rightarrow RR}$ was significantly larger at all RR and QT history lengths. The average characteristic RR history length that maximized $TE_{RR \rightarrow QT}$ was 27 beats for the healthy subjects, which was significantly longer than 21 and 22 beats for LQT1 and LQT2, respectively. Aging had no significant effect on $TE_{RR \rightarrow QT}$, but reduced $TE_{QT \rightarrow RR}$ for the LQTS subjects, whereas the gender and beta blocker were found to have relatively small effects on the TE. In conclusion, the dynamic coupling between RR and QT intervals is altered by LQTS.

1. Introduction

In an electrocardiogram (ECG), the RR and QT intervals have been shown to have a relationship [1, 2]. A useful measure to describe the relation is transfer entropy (TE), which quantifies the information transfer from the source to the destination in a coupled process [3]. TE from RR to QT is formally defined in Eq. (1) of Ref. [4]. The study showed that there is a bidirectional information flow between RR and QT intervals in healthy individuals. The information flow from RR to QT is more prominent, indicating an asymmetry, which becomes stronger when more previous values of RR and QT are taken into account. This effect is related to the QT-RR hysteresis, which has been studied especially in the context of QT correction [5].

In this study, we investigate the information transfer between RR and QT intervals in long QT syndrome (LQTS) subjects. LQTS is a genetic condition, characterized by prolonged QT intervals, caused by delayed ventricular repolarization. LQTS affects approximately 1 in every 5000 people [6], and the symptoms range from seizures to potentially lethal arrhythmias [7]. In this study, we consider the subjects of LQTS types LQT1 and LQT2, where the mutation is altering the functionality of the myocardial potassium channels in genes *KCNQ1* and *KCNH2*, respectively [6].

2. Data and Method

We use the Healthy (E-HOL-03-0202-003) and the congenital long QT syndrome (E-HOL-03-0480-013) database from the Telemetric and Holter ECG Warehouse (THEW), administrated by the University of Rochester Medical Center [8, 9]. Both databases consist of 24-hour Holter ECG recordings with 2-3 leads. To extract the RR and QT intervals from the ECGs, we utilize an in-house algorithm (QRS-detection specificity 99.5% and sensitivity 99.6% with a 30 ms threshold for the MIT-BIH Arrhythmia Database [10]). In order to remove any non-physiological changes, the interval data is filtered with a moving average procedure with a window size of 100 intervals and the maximum deviation from the mean of 150 ms and 500 ms for QT and RR, respectively.

Table 1. Statistics of the studied groups. The total number of subjects (N) and the male-to-female ratio are shown. The age is shown with the mean \pm standard deviation, and the number of RR-QT interval pairs per dataset is specified in millions (M).

	Healthy	LQT1	LQT2
N (Male/Female)	202 (102/100)	227 (96/131)	127 (57/70)
Age (years)	38 \pm 16	28 \pm 18	24 \pm 17
Interval pairs	20,1M	19,9M	11,3M

The original database contains 202 Holter recordings for the healthy and 480 recordings for the LQTS, from which 246 are of the subtype LQT1, and 145 of LQT2. We consider only the subjects with a history of using beta blockers

or no medication at all. We also discard a few subjects with undefined or less than one year of age. Table 1 summarizes the statistics and the metadata of the studied groups.

To calculate the TE, we use the Java Information Dynamics Toolkit (JIDT) [11] with the Kraskov-Stögbauer-Grassberger (KSG) probability estimation. To balance the statistical and systematic errors in the KSG, we use 4 nearest neighbors, as suggested in [12]. The other parameters are set to the default values. We calculate the TE up to history lengths of 50 RR and QT intervals. For statistical analyses, we use Welch’s t-test to compare the averages between the independent samples.

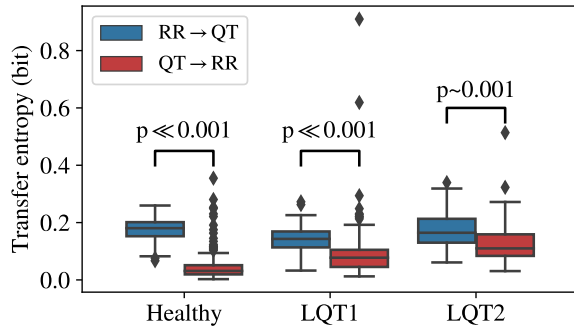


Figure 1. Distributions of TE in the healthy and LQTS subjects (over 20 years old). The asymmetry between the two directions is evident in each group.

3. Results

We first consider the information transfer from a single preceding RR or QT interval as the source. Distributions of the TE from RR to QT ($TE_{RR \rightarrow QT}$) and from QT to RR ($TE_{QT \rightarrow RR}$) for the healthy and LQTS are shown in Fig. 1. In all three groups, there is a clear asymmetry of the TE, in which the $RR \rightarrow QT$ transfer is significantly larger than the $QT \rightarrow RR$ ($p \leq 0.001$). The average $TE_{RR \rightarrow QT}$ is significantly different between the healthy and LQT1 and between LQT1 and LQT2. The average $TE_{QT \rightarrow RR}$ differs significantly in all the pairs ($p \ll 0.001$ between the healthy and either type of LQTS, $p < 0.01$ between LQT1 and LQT2).

When more than one RR and QT history value are taken into account, the gap between the $RR \rightarrow QT$ and $QT \rightarrow RR$ transfer increases with RR history length, as shown in Fig. 2. On the other hand, $TE_{RR \rightarrow QT}$ declines with increasing QT history length, regardless of the presence of LQTS, while $TE_{QT \rightarrow RR}$ persists, becoming larger than the opposite transfer. The results are well in line with the previous study with the healthy subjects [4] and further confirm that the dominance of the $RR \rightarrow QT$ transfer over the opposite direction is still prominent in the presence of LQTS.

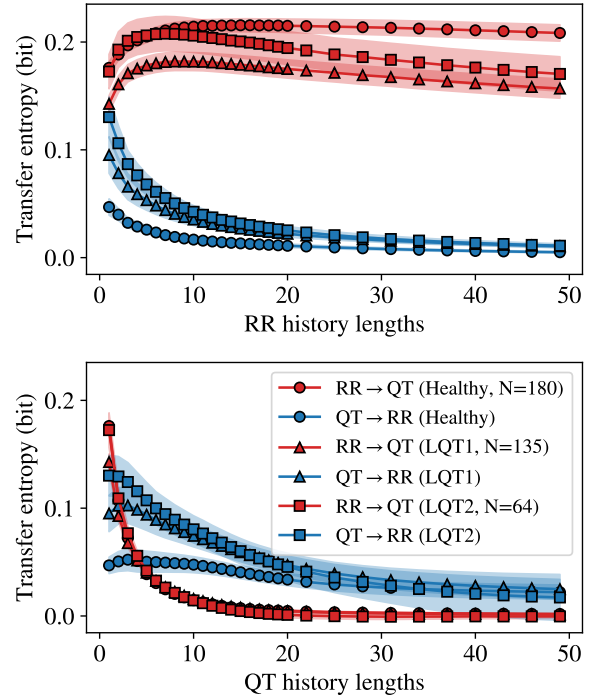


Figure 2. Average TE as functions of RR and QT history lengths for the healthy and LQT1 and LQT2 subjects (over 20 years old). The shaded bands represent the 95% confidence intervals.

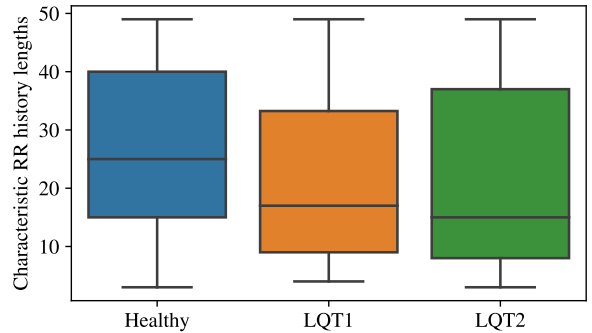


Figure 3. Distributions of characteristic RR history lengths, n_{char} , which maximize the TE from RR to QT. The healthy subjects have a significantly longer average n_{char} than the LQTS.

The mean $TE_{RR \rightarrow QT}$ of the LQTS subjects diverge significantly from that of the healthy for RR history length longer than 18 beats ($p < 0.001$). On the other hand, the mean $TE_{QT \rightarrow RR}$ of the LQTS are significantly larger than that of the healthy at all RR and QT history lengths ($p \ll 0.001$).

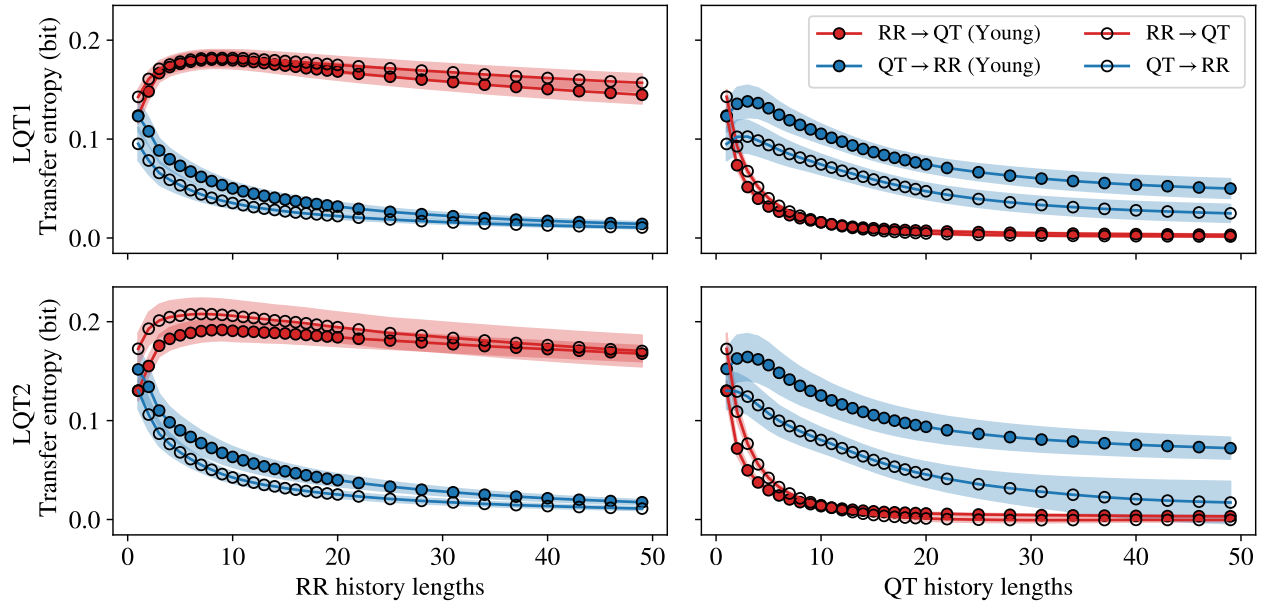


Figure 4. Average TE as functions of RR and QT history lengths for age groups younger and older than 20 years, with 95% confidence intervals as shaded bands.

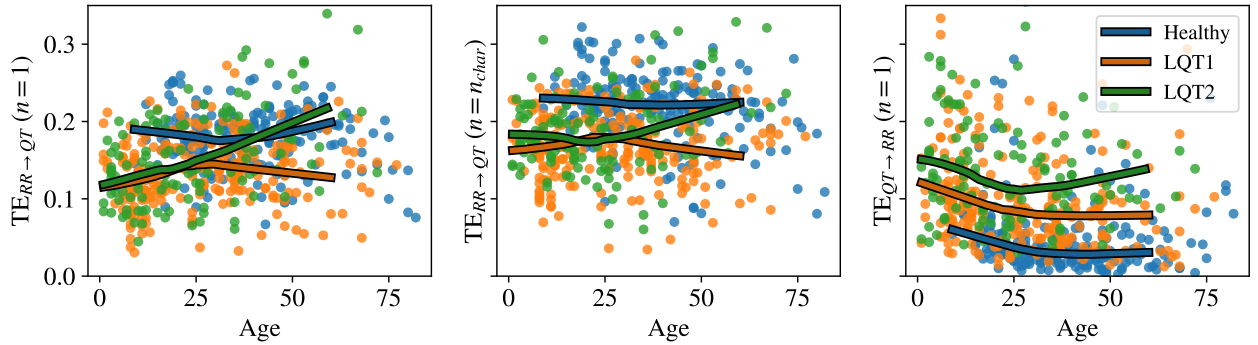


Figure 5. TE from preceding RR to QT (left) and at characteristic RR history lengths (center) and TE from preceding QT to RR (right) as functions of age. Only the ages < 60 years are used for computing the LOWESS.

The declining trends in $TE_{RR \rightarrow QT}$ as a function of RR history length that clearly deviate from that of the healthy, which has a flat profile, may be a unique feature of LQTS. In particular, the critical history length n_{crit} , after which TE remains constant [4], is absent in LQT1 and LQT2. A further calculation of TE for RR history length up to 100 beats shows that $TE_{QT \rightarrow RR}$ does not reach a plateau for LQT1 or LQT2. Therefore, we define a different characteristic RR history length, n_{char} , as the RR history length at which $TE_{RR \rightarrow QT}$ is maximized. Distributions of n_{char} for the healthy and LQTS individuals are shown in Fig. 3. The average n_{char} is 27 ± 14 beats for the healthy subjects, which is significantly larger than 21 ± 14 , 22 ± 16 for LQT1

($p \ll 0.001$) and LQT2 ($p < 0.01$), respectively.

Next we investigate the age effect on TE. We first divide the subjects into two age groups, younger and older than 20 years. For the healthy, age has little effect on the TE at any given RR or QT history length ($p > 0.001$). However, as shown in Fig. 4, for the LQTS subjects, $TE_{QT \rightarrow RR}$ is reduced significantly, especially as a function of QT history length ($p < 0.001$ for QT history > 5 beats). $TE_{RR \rightarrow QT}$ has a crossover at QT history of about 10 beats, after which the $TE_{RR \rightarrow QT}$ of the younger group dominates over that of the older.

Figure 5 shows the TE values at a few chosen RR and QT history lengths ($n = 1, n_{char}$) as a function of age.

Due to large variation among the individuals, the locally weighted scatter plot smoothing (LOWESS) curves are used to depict the age dependency. The healthy group exhibits a flat trend in $TE_{RR \rightarrow QT}$ at $n = 1$, n_{char} . For the LQT1 and LQT2, very different trends are suggested. In particular, LQT2 subjects exhibit a prominent positive slope as a function of the age > 20 years, diverging from the negative slope of the LQT1. All three groups share a similar age dependency of $TE_{QT \rightarrow RR}$ at $n = 1$, in which the TE declines in those younger than about 20 years.

Females who are healthy or have LQTS exhibit longer QT intervals (see e.g., [13]), compared to males. However, we do not find any significant differences in the average TE between the male and female subjects. We also studied the effect of beta blockers, which are the most commonly used medication for LQTS, as it increases the QT intervals at a resting heart rate (e.g., [14]). For the analysis, 40 subjects with LQT1 ($N = 28$) and LQT2 ($N = 12$) with a pair of recordings, before and after the use of beta blockers were analyzed. However, we do not find any significant differences in the average TE.

4. Conclusion

We have used transfer entropy (TE) to show that the dynamic coupling between RR and QT is altered by the LQTS. In particular, on average, TE from RR to QT is reduced, while TE to the opposite direction is enhanced compared to the TE of the healthy. However, the asymmetry of the information flow previously observed in healthy subjects is preserved. Due to the large variation among the individuals, further systematic studies are necessary to make the implications clear. However, the altered dynamics between RR and QT in LQTS provides insights, which may influence the current models and methods in QT correction and in the detection of LQTS.

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