Information Theory Based Evaluation of Interactions Between RR and QT Intervals in the Normal and People with High Risk for Cardiac Arrhythmias

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Abstract

This project is purposed to evaluate autonomic nerve system (ANS) through the coupling of RR interval (RRI) and QT interval (QTI) using information theory as well as Spearman correlation coefficient (Spearman CC). And the possible changes of their coupling in ESRD (those with high risk for cardiac arrhythmias and sudden cardiac death).The Holter data with 189 Normal and 43 ESRD were provided by THEW. 5min episodes at rest were selected both in daytime and on night. Let predictive information (PI) measure the information that carried by QTI can be predicted by the knowledge of the past of itself and RRI. The information storage and internal information of QT variability (QTV) were determined respectively as the self-entropy of the QTI series and the self-entropy of the series conditioned to the knowledge of RRI. The information transfer and cross information from RRI to QTV were assessed as the coupling of them two. PI on night (PI_n) was significantly smaller in ESRD compared with that in Normal (0.258±0.137 vs 0.322±0.142). However, no significant difference was found between PI in daytime (PI_d) in Normal and in ESRD. And the decreased PI_n led the loss of PI diurnal variation in ESRD(0.275±0.170 vs 0.258±0.137). While in Normal, there were significant difference between PI_d and PI_n (0.223±0.102 vs 0.322±0.142). Since the decreased PI_n in ESRD was mostly due to the changes in transfer entropy, meaning the reduction of RRI and QTI coupling. At the same time, the decreased conditioned self-entropy of QTI revealed less predictability of the past QTI to its present. All the above reflected the loss of sympathetic inhibition in ESRD, especially on night when the vagal activity is dominant and sympathetic activity should be withdrawn. The information theory based approach is not only feasible for assessing ANS activity through the coupling of RRI and QTI, but also provides a measure to characterize QTV related to HRV as well as those unrelated to HRV from nonlinear view.

1. Introduction

The modulation of autonomic nerve system (ANS) to sinus node results in the dynamic changes of RR interval (RRI) and heart rate variability (HRV). QT interval (QTI) is defined as the temporal difference between the QRS complex onset and the T wave end. In addition to its main dependency on RRI, QTI is directly influenced by ANS and other factors [1,2]. The coupling within and between RRI and QTI can be linear or nonlinear. However, this coupling can be changed by physiological factors (such as day and night alternation) and autonomic neuropathy caused by diseases, such as myocardial infarction, heart failure, diabetes, hypertension and so on [3-5].

In our previous study [6], we applied cross-spectrum method, measuring the linear coupling of RRI and QTI, to characterize alterations in ANS behaviors of those with high risk for cardiac arrhythmias and sudden cardiac death. We have shown that by directional correlation analysis of RRI and QTI based on transfer function. In the present study, an analysis of nonlinear coupling dynamics of RRI and QTI was conducted using information theory, which has proven to be useful to assess directional interactions between time series [7-9]. Information decomposition was used to assess information storage and internal information of QTV, and information transfer and cross information from HR to QTV. It is hypothesized that information theory based measures may reveal altered ANS behaviors with high risk for cardiac arrhythmias. Additionally, linear coupling of RRI and QTI is assessed by Spearman correlation coefficient (Spearman CC).

2. Materials and methods

The flow diagram of our study is presented in Fig1. The date for this analysis were based on Holter data of database Normal and ESRD in Telemetric and Holter ECG Warehouse (THEW, http://www.thew-project.org). 5 min episodes in resting state were selected from each Holter recording both in day and on night. RRI and QTI were extracted from each selected episode. For the extracted RRI and QTI, the mean and standard deviation of these interval series as well as the Spearman CC between the RRI and QTI were calculated. Let RRI as the driving process and QTI as the target process, an

information decomposition method based on information theory was applied to selected RRI and QTI series to get predictive information of target process as well as indicators that reflect the internal dynamics of target process and interactions from driving process to target process. The relevant indices results were compared to verify whether there were statistical differences among the Normal and ESRD in terms of circadian rhythm.
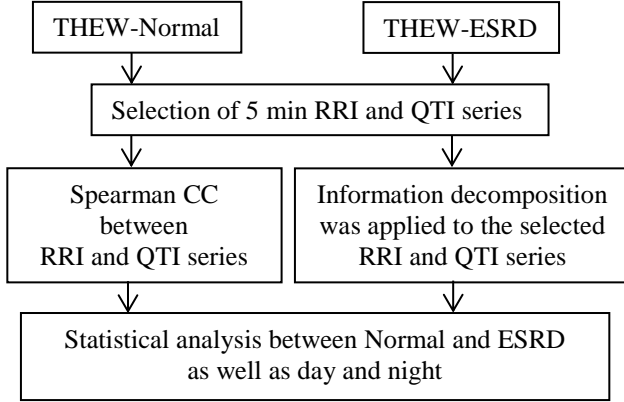

Fig1. The flow diagram of our study

2.1. Data source

In THEW, Database Normal (E-HOL-03-0202-003, ranging from 9~82 y) contains 24 h Holter recordings of 202 healthy subjects. The other database is ESRD (E-HOL-12-0051-016, more than 40 y), including 48 h Holter recordings of 51 end stage renal disease patients with high risk for cardiac arrhythmias and sudden cardiac death. With the exclusion of those incomplete records, 189 records from Normal and 43 records from ESRD were finally selected.

For each selected recording, 2 episodes (each lasting 5min) in resting state were extracted, one in the period of 7:00~20:00(day), the other in 0:00~6:00 (night). RRIs and QTIs corresponding to the selected episodes were obtained using a complex algorithm validated with the records in Physionet QT Database (http://www.physionet.org/ physiobank/database/qtdb/)[10]. Ectopic beats were removed before further analysis.

2.2. Information Decomposition

Information theory has proven to be useful to assess directional interactions between cardiorespiratory time series [11]. Considering a system consisting of two interacting subsystems X and Y, let X as the driving process and Y as the target process. Assuming that the evolution of the systems over time is described by the

dynamic bivariate process $\{X,Y\}$. Setting a time reference point and n is the present time. X_n and Y_n are the univariate variables describing the present of the processes X and Y, and $X_n^- = [X_{n-1}, X_{n-2}, \cdots]$ and $Y_n^- = [Y_{n-1}, Y_{n-2}, \cdots]$ are the multivariate variables describing the past of the processes.

Then, the effect of the joint process $\{X,Y\}$ on the target process Y is measured by the predictive information(PI):

$$PI_Y = H(Y_n) - H(Y_n| X_n^-, Y_n^-) \quad (1)$$

Where $H(Y_n) = -\sum p(y_n)\ln p(y_n)$ is the Shannon entropy, and $H(Y_n| X_n^-, Y_n^-)$ is conditional entropy. Predictive information PI_Y quantifies the part of the information carried by the present of the target process Y that can be predicted by the past of the joint process $[X_n^-, Y_n^-]$, i.e. how much of the information carried by Y_n can be predicted by the knowledge of the past of X and Y.

In the framework of information dynamics, the temporal evolution of coupled systems can be studied by decomposing the predictive information about an assigned target system into amounts quantifying the information stored inside the system and the information transferred to it. Therefore, the prediction information PI_Y can be decomposed as:

$$PI_Y = H(Y_n) - H(Y_n| Y_n^-) + H(Y_n| Y_n^-) - H(Y_n| X_n^-, Y_n^-) \quad (2)$$

The former two items $S_Y = H(Y_n) - H(Y_n| Y_n^-)$ in the formula is the self-entropy, which is a measure of information storage, quantifying the part of the information carried by Y_n that can be predicted by its own past. The latter two $T_{X \rightarrow Y} = H(Y_n | Y_n^-) - H(Y_n | X_n^-, Y_n^-)$ is the transfer entropy, a measure of information transfer quantifying the part of the information carried by Y_n that can be predicted by the past of X on condition that Y_n^- is known. $T_{X \rightarrow Y}$ describes the additional predictability that the past of X brings about the present of Y that was not brought already by the past of Y.

Alternatively, the prediction information PI_Y can be decomposed by first considering the past of X:

$$PI_Y = H(Y_n) - H(Y_n| X_n^-) + H(Y_n| X_n^-) - H(Y_n| X_n^-, Y_n^-) \quad (3)$$

The former two items $C_{X \rightarrow Y} = H(Y_n) - H(Y_n| X_n^-)$ in the formula is the cross-entropy, quantifying the part of the information carried by Y_n that can be predicted by the past of X. The latter two $S_{Y/X} = H(Y_n| X_n^-) - H(Y_n| X_n^-, Y_n^-)$ is the conditional self-entropy, quantifying the part of the information carried by Y_n that can be predicted by its own past on condition that X_n^- is known. $S_{Y/X}$ describes the additional predictability that the past of Y brings about the present of Y that was not brought already by the past of X.

2.3. Statistic analysis

All indices are expressed as mean ± standard deviation (SD). The Wilcoxon rank sum test was applied to detect

differences between the Normal and ESRD and differences of the circadian indices in two groups.

The statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, USA). Statistical significance was accepted at the level of $P < 0.05$.

3.　Results

The results of our study are shown in Table 1. It could be seen from the time-domain indices that diurnal variation of RRI and QTI exists in both Normal and ESRD, and the value was significantly smaller at day. In addition, there were significant differences of almost all RRI and QTI between Normal and ESRD except for QTI at night. Specifically, RRI by day in Normal was smaller than that in ESRD while the situation is reversed for RRI at night.

The Spearman CC of RRI and QTI during daytime was significantly higher than that at night in Normal. For ESRD, no diurnal variation of that was observed. And for this indice, there was significantly decreased in ESRD compared with Normal.

For the results of information decomposition, when RRI as the driving process and QTI as the target process, PI on night (PI_n) was significantly smaller in ESRD compared with that in Normal (0.258 ± 0.137 vs 0.322 ± 0.142). However, no significant difference was found between PI in daytime (PI_d) in Normal and in ESRD. While in Normal, there were significant difference between PI_d and PI_n (0.223 ± 0.102 vs 0.322 ± 0.142). The self-entropy and the cross-entropy showed the same change as the PI between the two groups. PI was significantly increased from day to night in Normal, but this diurnal variation did not exist in ESRD. The decreased PI_n led the loss of PI diurnal variation in ESRD (0.275 ± 0.170 vs 0.258 ± 0.137). Several entropy measures of information decomposition had the same diurnal variation as that of PI.

Table 1 The analysis results in Normal and ESRD

Index	Normal (n=189)		ESRD (n=43)	
	Day	*Night*	*Day*	*Night*
RRI (ms)	733±113*#	948±154#	799±119*	869±123
QTI (ms)	371±27*#	419±33	403±40*	423±40
$\rho_{RRI,QTI}$	0.264±0.168*#	0.179±0.144	0.206±0.256	0.129±0.179
S_{QTI}	0.061±0.042*	0.090±0.072#	0.097±0.104	0.067±0.050
$T_{RRI \rightarrow QTI}$	0.162±0.076*	0.232±0.105#	0.178±0.110	0.191±0.119
$C_{RRI \rightarrow QTI}$	0.083±0.049*	0.098±0.063	0.117±0.118	0.084±0.054
$S_{QTI|RRI}$	0.139±0.079*	0.224±0.115#	0.159±0.100	0.174±0.120
PI_{QTI}	0.223±0.102*	0.322±0.142#	0.275±0.170	0.258±0.137

Note: Data are expressed as mean ±SD；*P<0.05 Day vs Night within a group；#P<0.05 Normal vs ESRD during the same period of one day.

4.　Discussion

Based on the Spearman CC and information decomposition, we investigated the coupling of RRI and QTI from linear and nonlinear aspects. Differences were revealed between Normal and ESRD concerning their ANS behaviors. Significant circadian differences existed in all indexes both in Normal, but were lost in ESRD for both Spearman CC and PI.

In the study of Seethala et al [12], they sought to assess β-adrenergic stimulation effects on QTI response to HR (or RRI) change with normal subjects (except for supraventricular tachycardia). They described QTI response to RRI change as two distinct phases, an immediate response (IR) followed by a gradual monoexponential course to the new steady state value. And the IR is based on the assumption of an approximately linear relationship between immediate changes of QTI to RRI. Their results showed that β-adrenergic stimulation increased the immediate QT response to RRI change, that is the enhanced sympathetic activity might increase IR magnitude of RRI change. Our results are in accordance with the above ones. In Normal, the Spearman CC of QTI and RRI in daytime is significantly larger than that on night due to higher sympathetic activity in daytime. As for ESRD, though there is the tendency for Spearman CC to decrease from day to night, no significant difference emerges. In ESRD, though RRI on night is obviously smaller than that in Normal, the QTIs of them two are almost at the same level. The prolonged QTI in ESRD reflects insufficient withdrawal of sympathetic activity on night.

In contrast to the reduction of Spearman CC in night in Normal, PI increased on night compared with that in daytime. The significant increase in PI means the better prediction of QTI, or the less variability of QTI (QTV) [13].While in ESRD, the PIs in daytime and on night are almost at the same level. From linear and nonlinear aspects, we found different coupling behaviors of RRI and QTI about circadian rhythm in normal people and those with high risk for cardiac arrhythmias.

In this study, information dynamics was used to assess information storage and internal information of QTV, and information transfer and cross information from heart rate to QTV. Furthermore, the composition of QTV could be

obtained upon this kind of analysis. Transfer entropy in Equation (2) measures the information transferring from the driver to the target process and will always be zero in the absence of a causal link from driver to target. Here, $T_{\mathrm{RRI}\rightarrow\mathrm{QTI}}$ represents the QTV that is related to HRV. On the other hand, the conditional self-entropy in Equation (3) reflects the internal information in the target process because it will always be zero in the absence of internal dynamics in the target, and it is not influenced by the dynamics of the driver process. So, $S_{\mathrm{QTI}\|\mathrm{RRI}}$ indicates the QTV that is unrelated to HRV. Not only the interaction between sympathetic modulation and the coupling of HRV and QTV, but also the influence of sympathetic modulation on ventricular repolarization, can be interpreted by information decomposition analysis. For Normal, increased PI (more predictive information) for QTI on night means the decrease in QTV that is in line with situation represented by QTVi in Ref [14]. Furthermore, the decreased PI_n in ESRD was mostly due to the changes in transfer entropy, meaning the reduction of RRI and QTI coupling. At the same time, the decreased conditioned self-entropy of QTI revealed less predictability of the past QTI to its present. All the above reflected the loss of sympathetic inhibition in ESRD, especially on night when the vagal activity is dominant and sympathetic activity should be withdrawn.

5. Conclusion

The information theory based approach is feasible for assessing ANS activity through the coupling of RRI and QTI. Moreover, this method provides a measure to characterize QTV related to HRV as well as those unrelated to HRV from nonlinear view.

Acknowledgements

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