

# Assessment of Cardiac Autonomic State Based on RR and QT Interval Series and Symbolic Analysis

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## Abstract

*This paper is aimed to explore the possibility in evaluating the state of cardiac autonomic nerve based on paired short-term heart rate variability (HRV) and QT variability (QTV) indexes. Fantasia Database and Normal Sinus Rhythm Database were used as data source. Using short-term symbolic analysis and mutual information (MI) estimation, the consistency of HRV and QTV and its influencing factors were investigated. The MI of paired HRV and QTV indexes had no significant difference according to age, sex and circadian rhythm, while there were significant differences in most HRV indexes at the same time. The proposed measure is expected to reduce the influence of individual difference and highlight that of some pathological states.*

## 1. Introduction

Analysis of heart rate variability (HRV) provides an indication of cardiac autonomic regulation that has provided pathophysiological, clinical, and prognostic relevance to heart diseases. HRV analysis, with its low cost, effective and noninvasive nature, encourages the development of new HRV analysis methods to broaden and improve its applications [1].

Most of the studies on HRV have investigated its prognostic value for sudden death. At present, only the time domain parameters derived from 24 h Holter are available in clinic application. In the non-time-domain analysis, normal controls are selected as those with similar age and the same sex with the patients under investigation. The indexes of HRV tend to be influenced by age, sex and circadian rhythm [2], it requires a large amount of samples to get satisfying confidence interval of the indexes. Besides, many disease states have influence on the indexes of HRV as well. So it is motivating in cardiac autonomic state evaluation to reduce the influence of age, sex and circadian rhythm and highlight the influence of certain pathological states, which have more

potential to find clinical application.

The electrocardiographic QT interval (QTI), the temporal difference between the QRS complex onset and the T wave end, is currently considered as a global measure of ventricular repolarization time, in spite of including the total ventricular electrical activity. Despite the fact that heart rate is a major determinant of the duration of the QTI, direct influences of cardiac autonomic nerve over ventricular repolarization or non-autonomic influence were reported [3,4]. For example, hypoxia, acidosis and elevation in extracellular potassium  $K^+$  accompany ischemia and lead to changes in the amplitude of resting membrane potential and the duration of the action potential [5]. Therefore, the QTI variations not driven by the RR interval, especially in pathological state, can itself have clinical meaning.

Murabayashi et al investigated in time domain the beat-to-beat QT variability (QTV) associated with acute myocardial ischemia [6]. They found increase in  $QTV_{norm}$  and decrease in  $HRV_{norm}$  during ischemia, where  $QTV_{norm}$  and  $HRV_{norm}$  were determined by the QTI and RRI data in the 5 min epoch and *a priori* knowledge for each patient derived from a learning phase lasting for a few hours. Nahshoni et al investigated the change of complexity in patients after acute anterior wall myocardial infarction [7]. Pointwise correlation dimension (PD2) was chosen as a nonlinear measure of complexity for QTI and RRI series. They found that the patients after acute myocardial infarction had a significantly higher ventricular repolarization and lower heart rate complexities than that of normal controls. They attributed the decoupling of the complex control between heart rate and ventricular repolarization to the autonomic imbalance caused by acute myocardial infarction.

It is suggested that the coupling of RRI and QTI, or the consistency of HRV and QTV indexes in normal physiological situation, has the possibility to change under certain pathological states. Thus, the correlation analysis of paired QTV and HRV indexes has the possibility to evaluate the state of cardiac autonomic nerve.

One important characteristic of QTI and RRI variations is that their dynamics are nonlinear and nonstationary [8]. Recently, nonlinear measures provide additional prognostic information and complementing traditional time and frequency domain analyses [9]. Moreover, short-term nonlinear analysis, such as symbolic dynamics [10], provides the possibility of analyzing the short-term series where the dynamics are regarded as proximately stationary.

Since severe and sudden arrhythmic events might follow the abnormality of cardiac autonomic nerve, the evaluation of the state of cardiac autonomic nerve is of great importance. Our study was designed to check the feasibility of evaluating the consistency of short-term HRV and QTV indexes of symbolic analysis based on mutual information estimation, and at the same time, to reduce the influence of age, sex and circadian rhythm.

## 2. Method

Fantasia Database (40 records in all. 10 old males, 10 old females, 10 young males, 10 young females. <http://www.physionet.org/physiobank/database/fantasia/>) was used to test the age and sex influences. Each record in the Database lasts 2 h. Normal Sinus Rhythm Database (18 records in all. 5 males, 25~45 yr; 13 females, 20~50 yr. <http://www.physionet.org/physiobank/database/nsrdb/>) for the circadian rhythm difference. Two episodes lasting 2 h were to be selected in the same record, one in the period of 7:00~20:00, the other in 0:00~6:00.

For each 2 h episode, RRI and QTI were extracted using a complex algorithm [11] to form long-term RRI and QTI series. And, the preprocessing of removing ectopic beats was performed at the same time. Then, 2000 short term RRI series with length of 100 beats were selected randomly from each long-term RRI series. Symbolic dynamic analysis was used in short-term RRI series and its corresponding QTI series to get paired HRV and QTV indexes. Then, mutual information (MI) of the paired indexes was estimated. Differences in age, sex and circadian rhythm were analyzed respectively using paired *t* test. Statistical significance was accepted at the  $P < 0.05$  level

The method for short-term symbolic analysis was conducted referring [10, 12]. In the construction of symbol words, the length of series ( $N$ ), the number of level ( $\xi$ ) and the length of each symbol word ( $L$ ) should satisfy the following relationship:

$$N \geq (\xi - 1) \sum_{i=0}^{L-1} \xi^i \quad (1)$$

We selected  $L=3$ , and the length of series in our analysis was 100 beats ( $N=100$ ), so we got  $\xi=4$ . In our short-term (100 beats) symbolic dynamic analysis, the full range of the sequences was uniformly spread on 4

levels, and each symbol word was composed of 3 heart beats. All possible patterns describing the changing of heart beat in symbol words were grouped into 4 families. 1) patterns with no variation (0V, all the three symbols were equal forming a three-beat plateau); 2) patterns with one variation (1V, two symbols were equal and consecutive forming a two-beat plateau, while the remaining one was different); 3) patterns with two like variations (2LV, the three symbols formed an ascending or descending ramp); and 4) patterns with two unlike variations (2UV, all symbols are different from the previous one). Among them, 0V and 2UV are selected. And the percentages of each of them two (indicated as 0V% and 2UV%), representing the activation of sympathetic branch and parasympathetic branch [13], were selected as indexes for analysis.

For each 2 h RRI series, the data flow for MI estimation consists of following stages (a-d).

a. 2000 short-term segments with a preset length (100 RRIs) were randomly selected and the corresponding QTI series were selected as well.

b. Each segment was input into a short-term symbolic analysis. The indexes 0V% and 2UV% were calculated to get the paired HRV and QTV indexes.

c. The 2-D probability density functions of each paired HRV and QTV indexes were formed.

d. The consistency properties of paired HRV and QTV indexes, represented by MI, were estimated based on the 2-D probability density functions.

## 3. Results

With the data in Fantasia Database, Table 1 is the result for symbolic analysis indexes of RRI and QTI series concerning the differences in age and sex. For the RRI series in the same sex groups, 0V% increased significantly with age, while 2UV% decreased significantly with age. While for the QTI series in the same group, there are no significant age differences for these indexes but with the same changing trend.

For the RRI series in the same age groups, there is significant difference between 0V% in old male and female groups. There are no sex differences in the other cases. As for QTI series, there are no significant sex differences for all the indexes but with the same changing trend as those in RRI series.

With the data in Normal Sinus Rhythm Database, Table 2 shows the result for indexes of RRI and QTI series concerning the circadian rhythm difference. For both RRI and QTI series, 0V% is stronger in day time than that in night time, 2UV% is weaker in day time than that in night time.

The values of MI for the paired HRV and QTV indexes are showed in Table 3. There are no significant difference according to age, sex and circadian rhythm.

Table 1 Indexes of HRV and QTV concerning the age and sex differences (mean  $\pm$  SD)

Index	RRI Series		QTI Series	
	Male	Female	Male	Female
0V%-old (%)	41.16 $\pm$ 8.21 <sup>*#</sup>	33.91 $\pm$ 9.43 <sup>*</sup>	24.21 $\pm$ 9.98	19.38 $\pm$ 3.87
0V%-young (%)	19.70 $\pm$ 5.58	19.36 $\pm$ 7.01	17.44 $\pm$ 3.52	17.59 $\pm$ 2.63
2UV%-old (%)	13.25 $\pm$ 4.02 <sup>*</sup>	16.35 $\pm$ 5.88	28.94 $\pm$ 7.08	33.01 $\pm$ 3.23
2UV%-young (%)	21.57 $\pm$ 7.17	20.67 $\pm$ 4.12	31.29 $\pm$ 3.98	33.10 $\pm$ 3.18

<sup>\*</sup> $P < 0.05$  compared with the indexes of the young in male group

<sup>#</sup> $P < 0.05$  compared with the indexes of the old in female group

Table 2 Indexes of HRV and QTV concerning the circadian rhythm difference (mean  $\pm$  SD)

Index	RRI Series		QTI Series	
	Day	Night	Day	Night
0V% (%)	25.22 $\pm$ 6.37 <sup>*</sup>	21.97 $\pm$ 5.63	21.43 $\pm$ 5.45 <sup>*</sup>	18.80 $\pm$ 5.48
2UV% (%)	19.09 $\pm$ 2.79 <sup>*</sup>	22.54 $\pm$ 4.40	26.54 $\pm$ 6.23 <sup>*</sup>	29.50 $\pm$ 5.34

<sup>\*</sup> $P < 0.05$  compared with the indexes of night

Table 3 Mutual information (MI) of paired HRV and QTV indexes (mean  $\pm$  SD)

Paired Index	MI		MI		MI	
	Young	Old	Male	Female	Day	Night
0V%	1.998 $\pm$ 0.514	1.311 $\pm$ 0.370	1.799 $\pm$ 0.667	1.587 $\pm$ 0.602	2.359 $\pm$ 1.160	1.998 $\pm$ 0.835
2UV%	1.547 $\pm$ 0.550	0.771 $\pm$ 0.280	1.287 $\pm$ 0.695	1.086 $\pm$ 0.586	1.842 $\pm$ 1.234	1.447 $\pm$ 0.911

## 4. Discussion

It is revealed in our investigation that there exist significant differences in indexes of symbolic analysis for RRI series, according to age, sex and circadian rhythm for normal subjects under physiological state. These results are in agreement with other ones from the literatures [14]. While the MI for paired indexes of symbolic dynamic analysis has no significant differences, meaning that the paired HRV and QTV indexes maintain consistent in some degree even they are influenced by the same factors.

There are usually significant differences in HRV indexes according to age, sex and circadian rhythm. But there is certain consistency of HRV and QTV indexes due to the coupling of RR and QT intervals under normal physiological state, despite the influence of these individual differences. And damage of autonomic nervous system caused by pathological state might decouple the RRI and QTI, thus decrease the consistency of HRV and QTV indexes. Our previous study found the weakened coupling between QTI and RRI during acute myocardial ischemia [15], suggesting the decreased influence from sinoatrial node on QTI modulation during ischemia. Thus it is of importance, for evaluating the state of cardiac autonomous nerve, to explore the method for evaluating the consistency of HRV and QTV indexes and its influencing factors. This kind of measures is expected to reduce the influence of individual difference of the

normal and highlight the influence of certain pathological states, providing more potential to find clinical applications.

Instead of concerning only one kind of time interval series, we propose to explore the possibility in evaluating the state of cardiac autonomous nerve by joint analysis of RRI and QTI series. The method for assessing cardiac autonomous nerve, with less data length and short-term HRV and QTV indexes, is expected to develop.

Among the records in Physionet, Fantasia Database can be used to test the age and sex difference, and Normal Sinus Rhythm Database for circadian rhythm difference. The feasibility of our proposed method was investigated preliminarily based on the data in these two databases. But there are limited samples and deficiency in age distribution in these two databases. Especially in Normal Sinus Rhythm Database, in addition to limited samples, there are imbalances both in sex and age distribution. More data are needed for a further systemic study.

## 5. Conclusions

The consistency of paired HRV and QTV indexes in healthy subjects, represented by mutual information estimation of paired symbolic analysis indexes, was found to be less influenced by factors such as age, sex and

circadian rhythm, providing a potential way in weakening the individual differences. The proposed method, integrating signal processing and mutual information analysis, is expected to make quantitative analysis on correlation of HRV and QTV indexes in ambulatory ECG. Moreover, the usage of short-term signal processing adapts to the nonstationary characteristic of QTI and RRI variations.

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