# An Evaluating Method for Autonomic Nerve Activity by Means of Estimating the Consistency of Heart Rate Variability and QT Variability

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Abstract—The imbalance of autonomic nervous system (ANS) has a close relationship to cardiac mortality. The noninvasive assessment of ANS is of great importance and remains challenging. A new method, characterizing the consistency of short-term nonlinear indexes of heart rate variability (HRV) and QT variability (QTV), is proposed and validated. Holter records from two databases in Telemetric and Holter ECG Warehouse were used, 43 records from one database (named ESRD) as typical subjects of ANS dysfunction and 118 records from the other database (named Normal) as normal controls. The consistency of HRV and QTV was characterized by estimating mutual information (MI) of paired short-term recurrence quantification analysis (RQA) indexes in resting state. The influence of physiological differences on MIs of paired RQA indexes in Normal was investigated as well. Results showed that there were significant differences in MI-DET (day: 0.283 ± 0.070 versus 0.133 ± 0.055 and night: 0.258 ± 0.061 versus 0.117 ± 0.055) and MI-LAM (day: 0.439 ± 0.053 versus 0.293 ± 0.073 and night: 0.361 ± 0.079 versus 0.241 ± 0.087) between Normal and ESRD, much reduced consistency in ESRD. For MI-DET in Normal, sex had no influence, and there was age related alternations by day but not at night. There was no influence of sex and age on MI-LAM in Normal. The sensitivity, specificity, and total accuracy for discriminating Normal and ESRD were 88.37%, 95.76%, and 93.79%, respectively. The proposed measures are shown to have the advantage in reducing the influence of physiological differences and highlighting the pathological influence, providing a promising method to find clinical application for noninvasive assessment of ANS state.

Index Terms—Autonomic nervous system (ANS), heart rate variability (HRV), mutual information (MI), QT variability (QTV), recurrence quantification analysis (RQA).

## I. Introduction

THE autonomic nervous system (ANS), with its sympathetic–parasympathetic interaction, plays a critical role in the physiological control of the heart. The autonomic dysfunction, or the autonomic imbalance, has the possibility in causing cardiac instability, arrhythmia, and heart failure [1], [2]. Since severe cardiac events might follow autonomic dysfunction, the assessment of ANS is of great importance and remains challenging as well.

As known to all, the modulation of 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 dependence on RRI, QTI is directly influenced by ANS and nonautonomic factors [3], [4]. The coupling of RRI and QTI, as well as HRV and QT variability (QTV), might change under different physiological and pathological conditions. Porta et al. found that the RT variability (a measure of QTV) and the amount unrelated to HRV and respiration in RT variability increased with the magnitude of the sympathetic drive directly related to tilt table inclination in the head tilt-up experiment [5]. Baumert et al. [6] revealed that the resting norepinephrine (NE) spillover into the coronary sinus (the direct indicator of sympathetic activity) and QTV index (QTVi) was significantly increased in essential hypertensive patients compared with normotensive subjects. And the elevated QTVi was due to the increase in QTV and the decrease in HRV. Nahshoni et al. [7] showed that the patients after acute myocardial infarction (AMI) had a significantly higher ventricular repolarization and lower heart rate (HR) complexities than the normal controls, using the measure of pointwise correlation dimension (PD2). They attributed the decoupling of the complex control between HR and ventricular repolarization to the autonomic imbalance caused by AMI. The earlier studies suggest that the coupling between the indexes of HRV and QTV may contain valuable information on the assessment of ANS state.

The analysis of HRV provides valuable information to assess ANS [8], [9]. But HRV can be significantly affected not only by many diseases but also physiological differences, such as age, sex, and the period of measurement [10], [11]. Controls in almost all the studies are selected as self-controls or those with matched age, sex, and experimental time during a day, making difficult to find clinical application. The same situation exists in QTV analysis [12]. But there is certain consistency of HRV and QTV indexes because of the main dependence of QTI on RRI under normal resting state. Damage of ANS caused by pathological state might decouple RRI and QTI, thus decreasing the consistency of HRV and QTV indexes. We hypothesize that

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the abnormal autonomic function might result in greater changes in the consistency of paired HRV and QTV indexes than those caused by physiological differences.

We proposed a new method to quantify the consistency of short-term nonlinear dynamic indexes of HRV and QTV by mutual information (MI) estimation. The proposed method is expected to reduce the influence of physiological differences and highlight the pathological state of ANS, evaluating ANS state without specially selected normal controls. One important characteristic of RRI and QTI variations is that their dynamics are nonstationary and nonlinear [13]–[15]. Short-term recurrence quantification analysis (RQA) [16], [17] provides the possibility of analyzing the short-term series where the dynamics are regarded as proximately stationary. And the consistency of short-term nonlinear dynamic indexes is estimated by MI based on the distribution of these indexes in long-term nonstationary RRI and QTI series. The proposed method is evaluated using the data in Telemetric and Holter ECG Warehouse (THEW, http: //www. thew-project.org) [18]. Comparative study is performed between two databases in THEW, one (named Normal) contains Holter recordings of healthy subjects, and the other (named ESRD) contains Holter recordings of end-stage renal disease patients with high risk for cardiac arrhythmias and sudden cardiac death (SCD).

The enrollment criteria for ESRD are those hemodialysis patients with confirmed history of hypertension or diabetes requiring treatment. Hemodialysis patients often experience a substantial risk for abnormal autonomic function resulting in increased risk for coronary disease (CAD) and SCD [19], [20]. Sympathetic activity is increased in end-stage renal disease patients from a direct effect of the diseased kidneys [21], [22]. Moreover, increased sympathetic activity is observed in patients with hypertension or diabetes [6], [23]. So, the records in ESRD provide us typical population with ANS dysfunction for the comparison with normal people.

Instead of concerning only one kind of time-interval series (such as HRV analysis), our proposed measures, estimating the consistency of short-term HRV and QTV indexes, are shown to reduce the influence of physiological differences and highlight the influence of pathological states, providing a promising method for noninvasive assessment of ANS for the evaluation of cardiac safety.

## II. Methods

The flow diagram of our study is presented in Fig. 1. The data for this analysis were based on Holter data of database Normal and ESRD in THEW. For each Holter recording, 2-h long-term episodes were extracted from day and night, respectively. Measures of RQA and QTVi were calculated based on the short-term RRI and QTI series extracted from the selected long-term episodes. MI was estimated on the 2-D probability density function (PDF) of paired short-term HRV and QTV RQA indexes. And mean short-term QTVi (MQTVi) in each long-term episode was calculated as well. Statistical analysis and discriminant analysis were used to investigate the difference between Normal and ESRD for the assessment of ANS state.

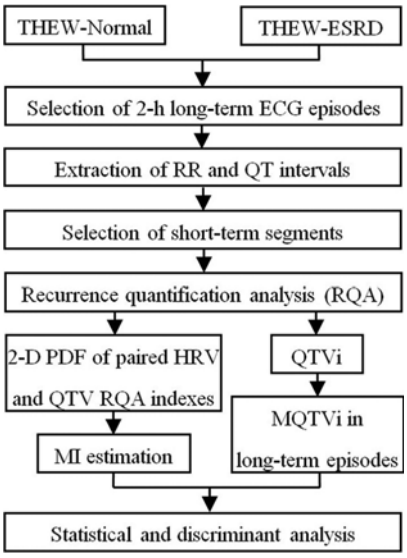


Fig. 1. Flow diagram of our study.

### A. Data Source

Normal in THEW contains 24-h Holter recordings of 202 healthy subjects (E-HOL-03-0202-003, age ranging from 9 to 82 years), and ESRD contains 48-h Holter recordings of 51 end-stage renal disease patients with high risk for cardiac arrhythmias and SCD (E-HOL-12-0051-016, age greater than 40 years). In addition to ECG data, beat annotations are available in both databases.

With the exclusion of those incomplete records, 189 records were left in Normal, and 43 records in ESRD using post hemodialysis data. Since those at the age of 30 or more are typical samples in need for ANS evaluation, for the 189 left records in Normal, those who are no younger than 30 years old were selected. Finally, we got 118 records in Normal for analysis. For each selected record, two episodes in resting state lasting 2 h were selected, one in the period of 7:00–20:00 (day) and the other in 0:00–6:00 (night).

RRIs of the selected 2-h episodes were derived from the beat annotations in the databases, while QTIs corresponding to the selected episodes were obtained using a complex algorithm [24]–[26]. Biorthogonal spline wavelet filters were used for the P–Q junctions detection, then the T wave ends were detected using a waveform-area algorithm independent of any threshold. The complex algorithm was validated with the records in Physionet QT Database (http://www.physionet.org/physiobank/database/qtdb/). Ectopic beats were removed before further analysis.

### B. RQA

RQA characterized the dynamic properties by quantifying the structure in a recurrence plot (RP), which is based on the analysis of the trajectories under an appropriate reconstruction method of the dynamics by the time delay-embedding method [27].

Five RQA indexes, Determinism (DET), Entropy (ENT), $\varepsilon$ under a given Recurrence Rate (REC), VMAX, and Laminarity (LAM), are used in this paper.

1) DET: DET is defined as the percentage of the recurrent points that form upward diagonal line segments. The diagonal lines in an RP represent the dynamics repeating themselves in the phase space:

$$\mathrm{DET} = \frac{\sum_{s=s_{min}}^{N} sP_s(s)}{\sum_{i,j=1}^{N} R(i,j)} \times 100\% \quad (1)$$

where $P_s(s)$ is the number of the diagonal line with the length of $s$ in the RP and $s_{min}$ is the minimum length of the diagonal line counted for the DET value. $N = M - (m - 1)\tau$; $M$ is the length of the data series under analysis; $m$ is the embedding dimension; and $\tau$ is the time delay. $R(i,j)$ is an element in $N \times N$ binary array, $i,j = 1,2,3,\ldots,N$. Usually, $R(i,j) = 1$, if point $(i,j)$ is a recurrence point, $R(i,j) = 0$, if point $(i,j)$ is a nonrecurrent point.

2) ENT: The Shannon information entrophy of all diagonal line lengths distributed over integer bins in a histogram, a measure of signal complexity

$$\mathrm{ENT} = -\sum_{l=s_{min}}^{s_{max}} p(l)\ln p(l) \quad (2)$$

where $p(l)$ is the histogram estimation of the probability distribution of the diagonal line at the length of $l$, $s_{max}$ is the maximum length of the diagonal line in an RP.

3) Euclidean threshold $\varepsilon$ under a given REC: REC is defined as the density of the recurrent points in an RP, when $\varepsilon$ is given

$$\mathrm{REC} = \frac{1}{N^2}\sum_{i,j=1}^{N} R(i,j) \times 100\%. \quad (3)$$

Thus, the euclidean threshold $\varepsilon$ can be inversely calculated from a given REC and used as an output variable. The $\varepsilon$ calculated out by a given REC value representing a dynamic range in which the specifically defined recurrences fall. Since this range is determined by the intrinsic dynamic properties, it provides valuable data for the dynamic analysis. In this case, the REC is used to set up the RQA. In this paper, we set up 2% as given REC.

4) VMAX: The length of longest vertical or horizontal structure in an RP.

5) LAM: The percentage of recurrent points comprising vertical or horizontal line structures, a measure of relatively "quiet" dynamics of the signal:

$$\mathrm{LAM} = \frac{\sum_{v=v_{min}}^{N} vP_v(v) + \sum_{u=u_{min}}^{N} uP_u(u)}{\sum_{i,j=1}^{N} R(i,j)} \times 100\% \quad (4)$$

where $P_v(v)$ is the histogram of the vertical line at the length of $v$; $P_u(u)$ is the histogram of the horizontal line at the length of $u$; $v_{min}$ is the minimum length of the vertical line counted for the LAM value; and $u_{min}$ is the minimum length of the horizontal line counted for the LAM value.

In this paper, we set $M = 100, m = 10, \tau = 1, s_{min} = v_{min} = u_{min} = 2$.

## C. MI Calculation

MI [28] was used to measure the dependence of paired RQA indexes of RRI and QTI.

If $x$ denotes the measurement of a system $X$, and $p(x)$ denotes the probability of $x$, the average amount of information calculated from the measurement $x$ is the entropy $H$ of the system $X$, and this is defined as follows:

$$H(X) = -\sum_{i=1}^{n} p(x_i)\log_2 p(x_i). \quad (5)$$

In a similar way, for a system $Y$, its entropy is defined as follows:

$$H(Y) = -\sum_{j=1}^{m} p(y_j)\log_2 p(y_j). \quad (6)$$

According to the chain rule, for a general coupled system $(X,Y)$, $I(X,Y)$ is expressed as follows:

$$I(X,Y) = H(X) + H(Y) - H(XY) \quad (7)$$

where $H(X,Y)$ is the entropy of the joint probability and is defined as follows:

$$H(XY) = -\sum_{i=1}^{n}\sum_{j=1}^{m} p(x_i,y_j)\log_2 p(x_i,y_j) \quad (8)$$

where $p(x_i,y_i)$ is the joint probability of $(x_i,y_i)$. The $I$ also satisfies $I(X,Y) = I(Y,X)$. $I$ is maximum if $X = Y$, and is zero, if and only if $X$ and $Y$ are completely independent.

In this paper, the paired HRV and QTV RQA indexes are input as $X$ and $Y$. The MI of the two indexes represents the dependence of two nonlinear dynamic properties.

According to the range from minimum to maximum values of $X$ and $Y$, each of the two is divided evenly into $2^B$ intervals. And the 2-D area formed by $X$ and $Y$ is divided into $2^{2B}$ blocks, each block can be labeled as (1, 1),(1, 2),. . .,(2, 1),. . .,$(i,j)$,. . .,$(2^B,2^B)$, $i,j = 1, 2,\ldots,2^B$.

Then, 2-D PDF of $X$ and $Y$ for estimating joint probability is expressed as follows:

$$p(x_i,y_j) = n(i,j)/n, (i,j = 1,2,\ldots,2^B) \quad (9)$$

where $n$ is the length of $X$ or $Y$.

The probability of $x_i$ and $y_j$ can be estimated as follows:

$$p(x_i) = \sum_{j} n(i,j)/n = n(i)/n \quad (10)$$

$$p(y_j) = \sum_{i} n(i,j)/n = n(j)/n. \quad (11)$$

Here, we choose $B = 5$, $n = 2000$. $I$ values range from 0 to $2B$, that is, from 0 to 10. MI is defined as normalized $I$ value as $I/2B$, so MI ranges from 0 to 1.

For each 2-h RRI series, 2000 short-term segments with a length of 100 beats were randomly selected and the corresponding QTI series were selected as well. Then, the short-term RQA indexes were calculated and 2000 paired HRV and QTV indexes were got to form a 2-D PDF. Finally, the consistency of paired HRV and QTV indexes, represented by MI, were estimated based on the 2-D PDF.

TABLE I
MEASURES IN NORMAL AND ESRD

| Measuress | Normal ($n$=118) | | ESRD ($n$=43) | |
|---|---|---|---|---|
| | *Day* | *Night* | *Day* | *Night* |
| RRI (ms) | 737±113 | 945±142 | 773±116 # | 870±113 # |
| QTI (ms) | 394±37 | 435±38 | 410±44 # | 442±46 |
| MI-DET | 0.283±0.070 | 0.258±0.061 | 0.133±0.055 # | 0.117±0.055 # |
| MI-ENT | 0.448±0.017 | 0.453±0.017 | 0.447±0.016 | 0.440±0.024 |
| MI-$\varepsilon$ | 0.562±0.028 | 0.550±0.030 | 0.572±0.032 | 0.554±0.040 |
| MI-VMAX | 0.013±0.007 | 0.014±0.005 | 0.014±0.004 | 0.014±0.006 |
| MI-LAM | 0.439±0.053 | 0.361±0.079 | 0.293±0.073 # | 0.241±0.087 # |
| MQTVi | −0.091(0.636) | −0.590 (0.849) | 0.228 (0.872) # | −0.243 (0.798) # |

*Notes:* # $P$<0.05 Normal versus ESRD.

TABLE II
RESULTS OF ONE-WAY ANOVA WITH NEWMAN–KEULS MULTIPLE POST-TEST COMPARISONS FOR AGE GROUPS

| *Measures* | *Age(y)* | | | | *Between group analyses (Newman-Keuls)* |
|---|---|---|---|---|---|
| | 30~39 (1) | 40~49 (2) | 50~59 (3) | ≥60~ (4) | |
| Number of people (F) | 36(14) | 46(22) | 18(11) | 18(11) | … |
| RRI-D | 733±91 | 722±113 | 739±94 | 783±157 | NS |
| RRI-N | 964±122 | 936±156 | 935±147 | 938±148 | NS |
| MI-DET-D* | 0.27±0.04 | 0.28±0.08 | 0.29±0.09 | 0.33±0.07 | S |
| MI-DET-N | 0.25±0.06 | 0.25±0.06 | 0.27±0.06 | 0.28±0.08 | NS |
| MI-LAM-D | 0.43±0.03 | 0.44±0.05 | 0.44±0.06 | 0.45±0.09 | NS |
| MI-LAM-N | 0.34±0.09 | 0.36±0.08 | 0.37±0.07 | 0.39±0.06 | NS |

*Notes:* *$P$<0.05, one-way ANOVA for all age groups.
S: significant differences existed between group 4 and any of other three groups.
NS: no significant differences between four age groups.

In addition, 2000 short-term indexes of RRI were averaged as the feature indexes (indicated as MDET-D: mean DET by day, etc.) of this episode.

### D. QTVi

QTVi [29] was determined with the following formula:

$$QTVi = \log_{10}[(QT_v/QT_m^2)/(RR_v/RR_m^2)] = \log_{10}(QTVN/RRVN) \quad (12)$$

where the numerator (QTVN) contains the variance of all QTIs ($QT_v$) divided by the square of the mean QTI ($QT_m$). The denominator (RRVN) contains the variance of RRIs ($RR_v$) divided by the squared mean RRI ($RR_m$). For each 2-h period, a sliding window with width of 100 beats was moved according to time sequence. QTVi was calculated in each window. Indexes of each sliding window within the episode were averaged as the feature indexes (MQTVi) of this episode.

### E. Statistical Analysis

Except for MQTVi, data are expressed as mean ± SD. MQTVi is expressed as median and interquartile range (75th–25th). Mann–Whitney U test was used to compare the corresponding measures in Normal and ESRD. In Normal, four age groups were divided as 30–39, 40–49, 50–59, and ≥ 60 years. Mann–Whitney U test was used to compare the MIs of male and female in the same age group. One-way ANOVA with Newman–Keuls multiple post-test comparisons was used to compare indexes between the four age groups. Fisher linear discriminant analysis and leave-one-out methods were employed for the classification of Normal and ESRD as well as accuracy test. The statistical analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, USA). Statistical significance was accepted at the level of $P < 0.05$.

## III. RESULTS

Table I shows the measures in Normal and ESRD. There were significant differences in RRI both by day and at night, while significant difference only existed in day QTI. Significant differences were found in MI values of DET (MI-DET) and LAM (MI-LAM), while the MI values of ε (MI-ε) and ENT (MI-ENT) were high both in Normal and ESRD with no significant difference. And for the MI values of VMAX (MI-VMAX), low correlation remains in Normal and ESRD with no significant difference either. There existed significantly increased MQTVi in ESRD compared with that in Normal.

For RRI, MI-DET and MI-LAM, which had significant difference between Normal and ESRD, there were no significant differences between male and female. Concerning the measures of RRI, MI-DET, and MI-LAM in Normal, results of one-way ANOVA with Newman–Keuls multiple post-test comparisons for four age groups are shown in Table II. There were no significant differences between four age groups in RRI and MI-LAM both by day (RRI-D and MI-LAM-D) and at night (RRI-N and MI-LAM-N). Also, there were no significant differences between four age groups in night MI-DET (MI-DET-N). But for day MI-DET (MI-DET-D), significant differences existed between group 4 and any of other three groups.

Fig. 2 shows the box plots of MQTVi in Normal and ESRD. Though there were significant differences for MQTVi in Normal

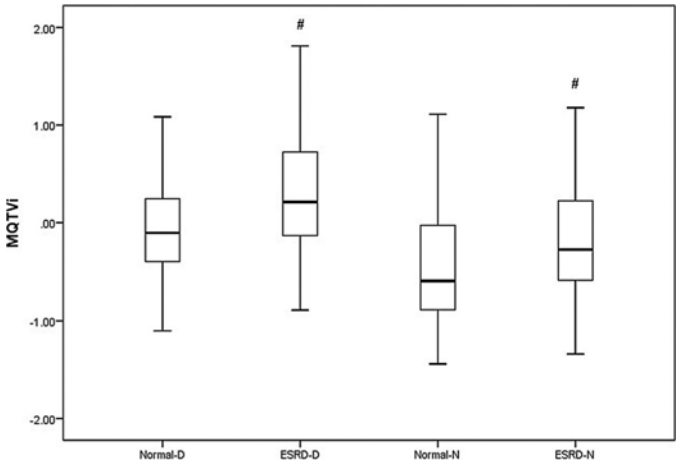


Fig. 2. Box plots of MQTVi in Normal and ESRD. (In the box plots, the central line represents the median distribution. Each box spans from 25th to 75th percentile points, and error bars extend from 10th to 90th percentile points. D: by day and N: at night. # $P < 0.05$ Normal versus ESRD.)

and ESRD, the ranges of the two compared measures overlapped a lot, leading to some difficulty in discriminating them two. While as showed in Fig. 3, the means of corresponding measures of Normal and ESRD (MI-DET and MI-LAM) were much apart with small standard deviations as well. Moreover, in the same figure, compared with corresponding MIs, normalized MDET and MLAM displayed almost the same situation as MQTVi. So, the discriminating power of Normal and ESRD could be much improved using MIs of paired HRV and QTV RQA indexes.

Table III shows the results of Fisher linear discriminant analysis and the accuracy test. Let MI-DET-N, MI-LAM-N, and RRI-N be input parameters, the sensitivity was 88.37%, the specificity was 95.76%, and the total accuracy for discriminating Normal and ESRD was 93.79%.

## IV. Discussion

In this study, we proposed to assess the ANS state by characterizing the consistency of HRV and QTV. Using the Holter data in normal people and those patients with high risk for cardiac arrhythmias and SCD, we found the significant difference of them two in correlation of short-term HRV and QTV indexes based on their distribution in long-term series. In addition, in normal subjects, there exist MI measures on which the influence of physiological differences (such as sex and age) is nonexistent. The results of our study lead to much improvement of power to discriminate the normal and ANS dysfunction.

Sympathetic activation, rather than being a consequence, is an early event in the pathophysiology of chronic renal failure [30]. In 1992, Converse et al. reported that muscle sympathetic nerve activity (MSNA), as assessed by microneurography, was increased in patients undergoing hemodialysis [31]. And direct measurement indexes of cardiac sympathetic activity suggested that hypertension and diabetes are associated with increased cardiac and vascular sympathetic activity as well as with an increased risk for arrhythmia [12], [16], [22]. Moreover, Grassi et al. found that MSNA values of patients with stable moderate chronic renal failure and hypertension were significantly and markedly greater than those only with hypertension, showing that the double influence of renal failure and hypertension would lead to higher risk of arrhythmia [32]. In addition, different direct measures of ANS activity confirmed the relation of increased QTVi to pathological elevation of sympathetic activity. Except for aforementioned Baumert's work [6], Piccirillo et al. provided direct evidence showing an association between augmented sympathetic activity and the increased QTVi in dogs with pacing-induced congestive heart failure [33]. In our study, significantly elevated QTVi in ESRD compared with Normal confirmed the abnormal ANS activity of the patients enrolled in ESRD. So, the records in ESRD are expected to provide us relatively typical population with ANS dysfunction for the comparison with normal people.

The interrelated fractals and chaos are concepts of nonlinear dynamics. Normal HR and QT dynamics are characterized by chaotic behavior [13], especially in resting state. The interaction of sympathetic and parasympathetic nervous systems is a main factor determining HRV. There exists reciprocal changes in this interaction, that is the activation of sympathetic nerve is accompanied by the withdrawal of parasympathetic nerve, and vice versa [34], [35]. In Tulppo's study based on a short-term fractal scaling exponent analysis and direct MSNA measurement [36], it was found that the loss or reduction of reciprocal changes, represented by coactivation of sympathetic and vagal outflow, resulted in changed fractal HR organization from chaotic toward more random dynamics. In fact, reduction of reciprocal changes is one of the reflections of pathological sympathetic activation. In our study, the reduction of reciprocal changes was indicated by sharp contrast of RRI between day and night in Normal and much smaller contrast in ESRD, displaying much lower RRI on night (insufficient sympathetic withdrawal when vagal outflow should be predominant at night). MI-DET and MI-LAM measure the similarity in chaotic and relative "quite" characteristics of RR and QT dynamics, respectively. For ESRD in our study, elevated sympathetic activation (verified by the significantly increased QTVi) in pathological situation is directly associated with repolarization lability, resulting in less part of QTV driven by HRV. In addition, the more random RRI and QTI dynamics tended to decrease MI-DET and MI-LAM, measuring the correlation of the dynamic characteristics of HR and QT dynamics. For the similarity of complexity measured by MI-ENT, there is decreasing trend but not significant, possibly due to the distinction in sensitivity of different measures. In our study on RQA behavior during acute ischemia [17], we found that the changes of $\varepsilon$ (under the given REC of 2%) for paired RRI and QTI series were almost on the same proportion. The synchronization of $\varepsilon$ might give an explanation for the maintainability of high MI-$\varepsilon$ both in Normal and ESRD. The sensitivity of MI-$\varepsilon$ under different REC levels could be investigated in further study. VMAX is an index concerning the line length in an RP plot. It inclines to display more uncertainty in a short-term series (such as 100 beats in this paper) than that in a long-term series. So, MI-VMAX estimation tends to be low in Normal and remain low in ESRD.

The linear discriminant analysis based on MI-DET-N, MI-LAM-N, and RRI-N reaches the accuracy of 93.75%. Since the

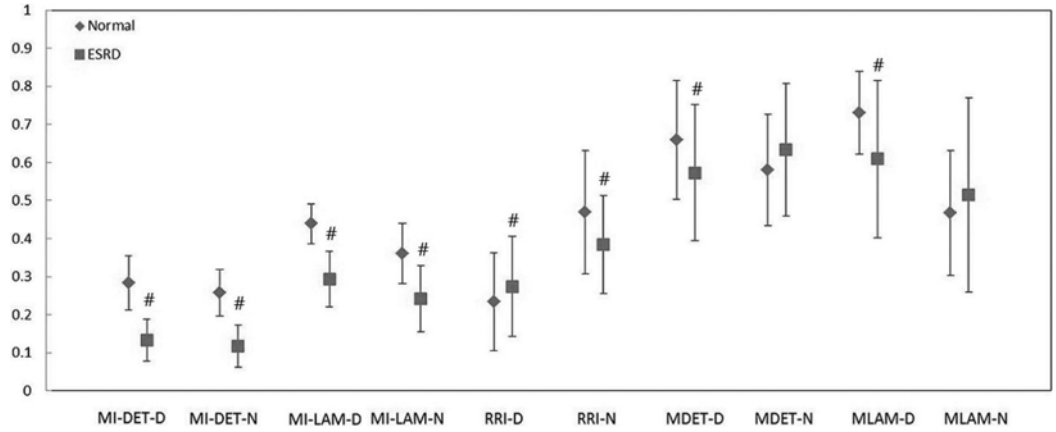


Fig. 3. Line charts of MI-DET, MI-LAM, normalized RRI, normalized MEDT, and normalized MLAM. (The central symbols represent the means. Error bars span 2 SD. D: by day and N: at night. # $P < 0.05$ Normal versus ESRD.)

TABLE III
RESULTS OF FISHER LINEAR DISCRIMINANT ANALYSIS AND ACCURACY TEST

| | *Measures* | | | *Intercept* |
|---|---|---|---|---|
| | ***MI-DET-N*** | ***MI-LAM-N*** | ***RRI-N*** | |
| Coefficient for ESRD | 65.139 | 63.221 | 0.077 | –46.172 |
| Coefficient for Normal | 115.885 | 71.695 | 0.094 | –72.378 |
| Sensitivity (%) | 88.37 (38/43) | | | |
| Specificity (%) | 95.76 (113/118) | | | |
| Total accuracy (%) | 93.79 (151/161) | | | |

coefficient of variation (CV) of Normal is small and the means of Normal and ESRD are apart far enough, there are only five (out of 118) discriminating errors in Normal. While in ESRD, differences in ANS damage might result in different degree of changes in the consistency of MI-DET-N and MI-LAM-N, leading to higher (CV) in these two indexes than those in Normal. The higher error rate for discrimination in ESRD, to a certain extent, can be attributed to its higher CV. The inclusion of night RRI for discriminant analysis is a reflection of autonomic imbalance in ESRD. In ESRD, though the level of day RRI is comparable to that in Normal, much smaller night RRI compared with that in Normal indicated the reduction of reciprocal changes in ANS, especially on night when parasympathetic activity is prominent without sufficient sympathetic withdrawal. QTVi, though normalized by both the QT duration and the magnitude of HR fluctuations, is still influenced by physiological differences [12]. Compared with the QTVi method, our proposed measures, characterizing the consistency of HRV and QTV estimated by MI, gain much improvement in discriminating power.

Our study is the first work, to our best knowledge, to explore the possibility in evaluating the ANS state by characterizing the consistency of QTV and HRV using MI of paired short-term RQA indexes. Since the characteristics of nonstationarity reflect the complex equilibrium control activities within ANS, the use of short-term analysis in our study might provide valuable information in assessing ANS. Furthermore, through combining HRV and QTV indexes, our proposed measures are expected to reduce the influence of physiological difference and highlight the influence of pathological states, providing more potential to find clinical application. In addition, it provides a way to make use of Holter data to investigate the distribution of short-term indexes in long-term series, complying with the ubiquitous nonstationarity of HR dynamics.

There are two limitations to this study. First, the data in ESRD do not include the direct measures of sympathetic activity. Though Holter is becoming more and more popular, there has been no database including both Holter data and direct measurement of ANS activity by now. As the aforementioned, elevated sympathetic activity was proved based on direct measurement in end-stage renal disease patients resulted from a direct effect of the diseased kidneys, and increased sympathetic activity is observed in patients with hypertension or diabetes. Moreover, significantly increased QTVi in ESRD in our study is in accord with the results in other studies in which elevated QTVi was accompanied by direct measurement of augmented sympathetic activity. We might regard database ESRD as a reasonable model for ANS dysfunction. Second, the number of subjects in ESRD was relatively low. Besides the enrollment criteria for ESRD, its exclusion criteria are those with class I antiarrhythmic, pacemaker, ICD device, cardiac resynchronization therapy device or having a history of chronic atrial fibrillation. So the enrolled patients in ESRD could be considered to be in the similar state of ANS dysfunction, without other clear comorbidities and experiences of severe arrhythmia. And this kind of population is expected to be in need for cardiac risk assessment and drug effect verification. However, a much larger database would be needed for the validation of practical use.

## V. Conclusion

Our proposed method provides a new way to assess the ANS state. Short-term RQA indexes are used to overcome the nonstationary interference on the quantification of nonlinear properties in ECG time interval series. MI of paired HRV and QTV RQA indexes, based on the distribution of short-term indexes in long-term series, reflects the consistency of HRV and QTV indexes. With the application to Normal and ESRD databases in THEW, the results reveal the reduced consistency of HRV and QTV indexes in typical population of ANS dysfunction. Furthermore, our proposed measures are shown to have the advantage in reducing the influence of physiological differences (such as sex and age) and highlighting the pathological influence, providing valuable information in noninvasive assessment of ANS state.

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