Comparative Analysis of Short-Term Variability of RR and QT Intervals for the Assessment of Autonomic Nerve Activity

Yi Zhu, Xiaolin Yang, Zhigang Wang, Yi Peng

Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences &
School of Basic Medicine, Peking Union Medical College, Beijing, China

Abstract

The purpose of this study is to investigate the behavior of autonomic nervous system (ANS), reflected by short-term variability (STV), in the hemodialysis patients with high risk for cardiac arrhythmias and sudden cardiac death. Comparison was performed with normal people. The data were provided by THEW (database ESRD and Normal). STV of RR intervals (STV_{RR}) and QT intervals (STV_{QT}) as well as the ratio of them ($STV_{QT/RR}$) were calculated using 30 consecutive beats. Two resting episodes lasting 1 h were selected in each Holter record, one by day, the other at night. For each 1 h interval series, a sliding window with width of 30 beats was implemented and indexes of each sliding window within the episode were averaged as the feature indexes ($MSTV_{RR}$, $MSTV_{QT}$ and $MSTV_{QT/RR}$) of this episode. Results showed that MSTVRR in ESRD was much lower than that in Normal. Though the level of $MSTV_{QT/RR}$ by day was comparable in these two groups, there existed significantly increased $MSTV_{QT/RR}$ at night in ESRD. The decreased heart rate variability (HRV) and increased $MSTV_{QT/RR}$ at night suggest the sympathetic overactivity in ESRD. Comparative analysis of HRV and QT variability using Holter data might be a potential approach to get information of ANS modulation.

1. Introduction

The time interval series from ECG, such as RR intervals and QT intervals, contain a plenty of information about autonomic nerve system (ANS) modulation to heart rate and ventricular repolarization. Heart rate variability (HRV) refers to subtle changes in duration of cardiac cycle. It has been used as a non-invasive clinical tool for assessing sympathetic-parasympathetic balance and as a sensitive marker of the relationship between the ANS and cardiac mortality [1]. The QT interval, expressing global depolarization and repolarization in the ventricular myocardium, manifests the intrinsic adaptation of the action potential duration to changes in cycle length. QT variability (QTV) reflects ANS activities as well. Cardiac norepinephrine (NE) spillover is the 'gold-standard' of cardiac sympathetic activity. Baumert et al [2] measured NE spillover directly and assessed beat-to-beat QTV. They revealed the association between QTV and sympathetic activation.

The corresponding process for QT interval to RR interval is complex, including an immediate adaptation and a slow adaption (called QT/RR hysteresis) [3]. Though QTV is mainly driven by HRV, the relationship between them can be inflected by ANS modulation. It was reported on the tilt experiment that HRV and QTV showed a gradual uncoupling tendency following transition of ANS status induced by shifted tilt table [4]. Investigation of the changes in the relationship of HRV and QTV might provide useful information about ANS modulation.

Short-term variability (STV) was introduced as a measure of HRV and QTV. It has been used in some researches, such as heart failure in animals [5] and structural heart disease in humans [6]. The greatest advantage of this index is its no special requirement to the data size. So, this kind of analysis can make full use of short-term data, which is more likely to comply with non-stationary characteristics of time interval series of heart.

End stage renal disease (ESRD) patients are often with a substantial risk for abnormal autonomic function [7-8]. Therefore, our analysis concentrates on the performance of STV in characterizing the behaviour of ANS in normal people and ESRD patients.

2. Methods

The data for this analysis were accessed by the Telemetric and Holter ECG Warehouse (THEW, http://www.thew-project.org), among which two databases were extracted. One contains 24 h Holter recordings of 202 healthy subjects (Normal, E-HOL-03-0202-003, ranging from 9~82 y), the other contains 48 h Holter recordings of 51 end stage renal disease patients with high risk for cardiac arrhythmias and sudden cardiac death (ESRD, E-HOL-12-0051-016, more than 40 y). In addition to ECG data, beat annotations are available in both databases.

With the exclusion of those incomplete records and age matching according to ESRD, we got 43 records from ESRD and 82 records from Normal for analysis For each selected record, 2 episodes (each lasting 1 h) in resting state were extracted, one in the period of 7:00~20:00 (day), the other in 0:00~6:00 (night).

RR intervals of the selected 1 h episodes were derived from the annotations in the databases, while QT intervals corresponding to the selected episodes were obtained using a complex algorithm [9] validated with the records in Physionet QT Database (http://www.physionet.org/physiobank/database/qtdb/). Ectopic beats were removed before further analysis.

The short-term variability (STV) defined as the mean orthogonal distance from the diagonal to the points of the Poincaré plot [10-11]. We measured the STV of RR and QT intervals using 30 consecutive beats. The formulas used were as follows:

$$\mathrm{STV_{RR}} = \sum \frac{|\mathrm{RR}_{i+1} - \mathrm{RR}_i|}{30\sqrt{2}} \quad (1)$$

$$\mathrm{STV_{QT}} = \sum \frac{|\mathrm{QT}_{i+1} - \mathrm{QT}_i|}{30\sqrt{2}} \quad (2)$$

$$\mathrm{STV_{QT/RR}} = \frac{\mathrm{STV_{QT}}}{\mathrm{STV_{RR}}} \quad (3)$$

where RR_i and QT_i are the duration of *i*th RR and QT interval. For each 1 h period, a sliding window with width of 30 beats was moved according to time sequence. $\mathrm{STV_{RR}}$, $\mathrm{STV_{QT}}$ and $\mathrm{STV_{QT/RR}}$ were calculated in each window. Indexes of each sliding window within the episode were averaged as the feature indexes ($\mathrm{MSTV_{RR}}$, $\mathrm{MSTV_{QT}}$ and $\mathrm{MSTV_{QT/RR}}$) of this episode.

Intervals are expressed as mean ± standard deviation. $\mathrm{MSTV_{RR}}$, $\mathrm{MSTV_{QT}}$ and $\mathrm{MSTV_{QT/RR}}$ are given as median and interquartile range (75th percentile – 25th percentile). Student's t-test was used to compare the RR and QT intervals between day and night. Wilcoxon signed rank tests were applied to detect differences in feature indexes between day and night. Mann-Whitney U tests were used to compare the differences between Normal and ESRD. The statistical analysis was performed using SPSS 19.0 (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.

There were significantly increased RR intervals in night compared with that by day both in Normal and ESRD. And there were obvious differences for the same index between Normal and ESRD in the corresponding period. For QT intervals, the situation was almost the same except that there was no significant difference for QT intervals at night between Normal and ESRD.

Compared with Normal, there were significantly decreased HRV and QTV measured by $\mathrm{MSTV_{RR}}$ and $\mathrm{MSTV_{QT}}$, respectively. We can also see it from Figure 1 which shows representative examples of QT and RR interval Poincaré plots from a normal person and patient with ESRD in day and night. Both for Normal and ESRD, $\mathrm{MSTV_{RR}}$ increased from day to night, while $\mathrm{MSTV_{QT}}$ changed in the opposite direction, which indicates the parasympathetic activation and the sympathetic withdrawal due to circadian rhythm. In the meantime, the fluctuations of these two indexes during day and night were smaller in ESRD. At resting state by day, $\mathrm{MSTV_{QT/RR}}$ was almost at the same level for Normal and ESRD, while there was significantly increased $\mathrm{MSTV_{QT/RR}}$ at night in ESRD compared with Normal.

Table 1. The results of analysis in Normal and ESRD

Index	Normal (*n*=82)		ESRD (*n*=43)	
	Day	Night	Day	Night
RR interval (ms)	732±119$^{*\#}$	931±151$^{\#}$	775±118*	866±113
QT interval (ms)	398±42$^{*\#}$	439±45	410±44*	440±43
$\mathrm{MSTV_{RR}}$ (ms)	11.16(8.98)$^{*\#}$	14.86(11.76)$^{\#}$	5.48(5.56)*	8.05(5.61)
$\mathrm{MSTV_{QT}}$ (ms)	14.04(11.65)$^{*\#}$	8.96(7.69)$^{\#}$	7.82(8.23)*	5.59(4.64)
$\mathrm{MSTV_{QT/RR}}$	1.56(1.40)*	0.64(0.85)$^{\#}$	1.61(2.16)*	0.92(1.08)

Notes: Data are expressed as mean ± SD or median and interquartile range (75th–25th).
$^{*}P<0.05$ Day *vs* Night; $^{\#}P<0.05$ Normal *vs* ESRD.

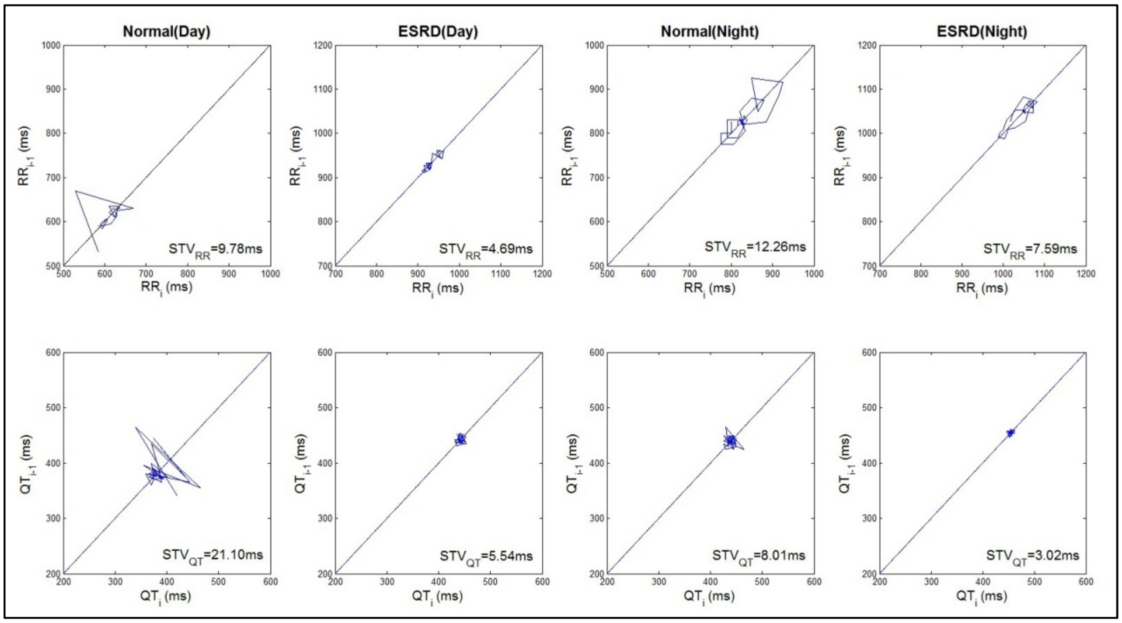

Figure 1. Representative Poincaré plots of QT and RR intervals in a normal person and patient with ESRD in day and night. In all plots, the diagonal line is for illustration purposes. i=RR or QT interval of beat i of each subject; i-1=RR or QT interval of the previous beat.

4. Discussion

In present study, we used STV as a measure of HRV and QTV to assess the autonomic nerve activities. $MSTV_{RR}$ is an index reflecting the modulation of sympathetic and parasympathetic activities. $MSTV_{QT}$ represents repolarization activity. The relative relationship between STV_{RR} and STV_{QT} is expressed as $STV_{QT/RR}$. Our results demonstrate that these measures of STV are highly associated with autonomic nerve activities.

The enrollment criteria for database ESRD in THEW are those hemodialysis patients with high risk for cardiac arrhythmias and sudden cardiac death. Their ages are greater than 40 and with confirmed history of hypertension or diabetes requiring treatment. At the same time, the exclusion criteria are those with class I antiarrhythmic, pacemaker, ICD device, cardiac resynchronization therapy (CRT) device or having a history of chronic atrial fibrillation. The exclusion criteria make sure that the enrolled patients in ESRD are almost in the similar state of ANS dysfunction, without other clear comorbidities and experiences of severe arrhythmia. The sympathetic activity is increased in end stage renal disease patients from a direct effect of the diseased kidneys. Moreover, increased sympathetic activity is observed in patients with hypertension or diabetes [12, 13]. So, the records in ESRD database provide us typical population with ANS dysfunction for the comparison with normal people.

The major conclusions of Celik's and Oikawa's studies [14-15] are that autonomic function deteriorates in ESRD paitents presented by all of the decreased HRV indexes. Our results coincide with theirs on this point. The magnitudes of $MSTV_{RR}$ are much lower in ESRD regardless of nearly the same heart rate level as Normal. The relatively low $MSTV_{QT}$ is another potent proof.

The differences of HRV and QTV between day and night are resulted from reciprocal function of ANS. Usually, the activation of sympathetic nerve is accompanied by the withdrawal of parasympathetic nerve, and *vice versa*. $STV_{QT/RR}$ is a measure representing the interaction of RR and QT intervals. Sharp contrast of $MSTV_{QT/RR}$ between day and night in Normal reveals their clear circadian rhythm. While in ESRD, though the level of $MSTV_{QT/RR}$ is the same with that in Normal, increased $MSTV_{QT/RR}$ at night showed the weakened circadian rhythm. The declining magnitude for $MSTV_{QT}$ from day to night is less in ESRD than that in Normal, resulting in the higher $MSTV_{QT/RR}$ in ESRD. Sympathetic overactivity often leads to increased QTV, indicating less RR interval's impact on QT interval [16-17]. Our finding from non-invasive ECG detection is in accordance with those from direct measurement of sympathetic activity. For example, Converse, JR. et al [18] recorded postganglionic sympathetic nerve discharge. Their results demonstrate substantially higher discharge in ESRD patients than that in normal controls. Since the autonomic imbalance has the possibility in causing cardiac instability, arrhythmia and even sudden cardiac death, non-invasive monitoring of ANS is very important but remains challenging by now.

The ambulatory Holter is a universal and non-invasive tool to record electric activities physiology in the heart. It is an important data resource to research ANS activity. However STVs are calculated on the basis of absolute differences between consecutive intervals of beats, which makes them sensitive to immediate changes in nature. Unlike other HRV and QTV indexes, there is no requirement to the number of beats to be calculated. These two merits make us believe that STVs are potential indexes to evaluate the state of ANS using Holter data.

5. Conclusions

Short-term variability is a useful tool in characterizing autonomic nerve activity. Comparative analysis of HRV and QTV using Holter data might be a potential approach to get information of ANS modulation.

Acknowledgements

This work received financial support from the National Natural Science Foundation of China through the project 81071225.

References

[1] Xhyheri B, Manfrini O, Mazzolini M, Mazzolini M, Pizzi C, Bugiardini R. Heart rate variability today. Progress in Cardiovascular Diseases 2012;55:321-31.

[2] Baumert M, Schlaich MP, Nalivaiko E, Lambert E, Sari CI, Kaye DM, Elser MD, Sanders P, Lanbert G. Relation between QT interval variability and cardiac sympathetic activity in hypertension. Am J Physiol Heart Circ Physiol 2011;300:H1412-7.

[3] Seethala S, Shusterman V, Saba S, Mularski S, Němec J. Effect of β-adrenergic stimulation on QT interval accommodation. Heart Rhythm 2011;8(2):263-70.

[4] Porta A, Bari B, Badilini F, Tobaldini E, Gnecchi-Ruscone T, Montano N. Frequency domain assessment of the coupling strength between ventricular repolarization duration and heart period during graded head-up tilt. Journal of Electrocardiology 2011;44:662-8.

[5] Prccirillo G, Magrì D, Pappadà MA, Ogawa M, Han S, Joung B, Rossi P, Nguyen BL, Lin SF, Chen PS. Autonomic nerve activity and the short-term variability of T_{peak}-T_{end} interval in dogs with pacing-induced heart failure. Heart Rhythm 2012;9(12):2044-50.

[6] Oosterhoff P, Tereshchenko LG, Heyden MAG, Ghanem RN, Fetics BJ, Berger RD, Vos MA. Short-term variability of repolarization predicts ventricular tachycardia and sudden cardiac death in patients with structural heart disease: A comparison with QT variability index. Heart Rhythm 2011;8(10):1584-90.

[7] Ranpuria R, Hakk M, Chan CT, Untuh M. Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. Nephrol Dial Transplant 2008;23:444-9.

[8] Oikawa K, Ishihara R, Maeda T, Yamaguchi K, Koike A, Kawaguchi H, Tabata Y, Murotani N, Itoh H. Prognostic value of heart rate variability in patients with renal failure on hemodialysis. International Journal of Cardiology 2009; 131: 370-7.

[9] Sun ZW, Peng Y. Study on a complex algorithm for detecting QT interval. Biomedical Engineering and Clinical Medicine 2009;13:184 - 8.

[10] Hinterseer M, Thomsen MB, Beckmann B-M, Pfeufer A, Schimpf R, Wichmann H-E, Steinbeck G. Beat-to-beat variability of QT intervals is increased in patients with drug-induced long-QT syndrome: a case control pilot study. European Heart Journal 2008;29:185-90.

[11] Nishi I, Sugiyama A, Takahara A, Kuroki K, Igawa M, Enomoto T, Iida K, Koseki S, Aonuma K. Utility of short-term variability of repolarization as a marker for monitoring a safe exercise training program in patients with cardiac diseases. Int Heart J 2011;52(5):304-7.

[12] Baumert M，Schlaich MP, Nalivaiko E，Lambert E, Sari CI, Kaye DM, Elser MD, Sanders P, Lambert G. Relation between QT interval variability and cardiac sympathetic activity in hypertension. Am. J Physiol Heart Circ Physiol 2011;300: 1412-7.

[13] Vinik AL, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26: 1553-9.

[14] Celik A, Melek M, Yuksel S, Onrat E, Avsar A. Cardiac autonomic dysfunction in hemodialysis patients: The value of heart rate turbulence. Hemodialysis International 2011;15:193-9

[15] Oikawa K, Ishihara R, Maeda T, Yamaquchi K, Koike A, Kawaquchi H, Tabata Y, Murotani H, Itoh H. Prognostic value of heart rate variability in patients with renal failure on hemodialysis. International Journal of Cardiology 2009;13:370-7.

[16] Piccirillo G, Magrì D, Ogawa M, Song J,Chong VJ, Han S, Joung B, Choi EK, Hwang S, Chen LS, Lin SF, Chen PS. Autonomic nervous system activity measured directly and QT interval variability in normal and pacing-induced tachycardia heart failure dogs. J American College of Cardiology 2009; 54(9):840-50.

[17] Berge RD. QT interval variability Is it a measure of autonomic activity?. J of American College of Cardiology 2009;54(9):851-2.

[18] Converse RL Jr, Jsvondrn TN, Jacibseb TN, Toto RD, Jost CMY, Cosentino DOF, Fouad-Tarazi F, Victor RG. Sympathetic overacitvity in patients with chronic renal failure. The New England of Medicine 1992;327(27):1912-8.

Address for correspondence.

Yi Peng
Dept. of Biomedical Engineering
Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences
School of Basic Medicine, Peking Union Medical College
5 Dong Dan San Tiao, Beijing 100005, China
pengyi@pumc.edu.cn