Assessment of Autonomic Nerve Activity by Circadian Rhythm at Different Stages after Acute Myocardial Infarction Based on Holter Data

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Abstract

This project is aimed to perform study concerning the state of autonomic nerve system (ANS) at different stages after acute myocardial infarction (AMI), as well as the comparison with normal controls. The analysis was based on the assessment of circadian rhythm reflected by heart rate variability (HRV). The data were provided by the Telemetric and Holter ECG Warehouse (THEW), among which two databases were extracted. 61 Holter recordings were selected from database AMI (E-HOL-03-0160-001), containing the recordings of two stages for a patient after AMI, one between 24-48 h after AMI (AMI-I) and the other between 5th and 10th day after AMI (predischarge, AMI-II). And 189 Holter recordings were selected from database Normal (E-HOL-03-0202-003) as normal controls. Two episodes in resting state lasting 2 h were selected in each Holter record, one in the period of 7:00~20:00 (day), the other in 0:00~6:00 (night). Non-Gaussianity indexes (λ) with the scale at 100 beats were calculated in each 2 h RR interval series, including the λ of day (λ_d) and night (λ_n), as well as the ratio of them (λ_d/λ_n).

Results showed that there were significant differences between λ_d and λ_n for Normal, AMI-I and AMI-Ⅱ. For λ_d/λ_n, there were significant differences between Normal (0.57(0.42-0.81)) and AMI-I as well as AMI-I (0.80(0.57-1.18)) and AMI-II (0.60(0.45-0.79)), but not between Normal and AMI-II . The results suggest the loss of Circadian Rhythm at AMI-I and the regain of it at AMI-Ⅱ. Since the loss of circadian rhythm is revealed to be a typical symbol of autonomic dysfunction, further monitoring and assessment of circadian rhythm is necessary for post-AMI patients.

Key words: Heart rate variability; Circadian rhythm; Non-Gaussianity index; Acute myocardial infarction (AMI); Autonomic nervous system.

1. Introduction

Cardiovascular diseases, especially in the acute stage, recovery stage and the following up stage of acute myocardial infarction (AMI), result in high risk of sudden cardiac death (SCD). In the acute stage (within 72 h after AMI), the SCD risk could reach 15%~20%; While in the recovery stage (within 3 days ~ 8 weeks after AMI), the SCD risk could be even higher for those with previous ventricular tachycardia (VT) or ventricular fibrillation (VF). For those with higher SCD risk, the mortality could be 50%~80% during 6~12 months after AMI [1-3]. Intervention and the evaluation of intervention are of great importance for reducing mortality in patients after AMI.

Experimental models for SCD after AMI indicated that sympathetic stimulation under impaired reflex vagal antagonism provoked ventricular vulnerability to fibrillation during transient myocardial ischemia. Evidence from experimental and clinical studies revealed that a fall in vagal activity increased the risk of death. So the balance of ANS is critical in reducing the risk of arrhythmia and SCD [4, 5].

Usefulness of the detection of autonomic dysfunction by heart rate variability (HRV) has been proposed for post-AMI risk stratification [6, 7]. HRV is affected by both vagal and sympathetic modulation of the sinus node.

The non-Gaussian analysis was introduced as a measure of intermittent heart rate increment [8, 9].The properties of non-Gaussian “fat” tails in the probability density function (PDF) of heart rate increments indicates increased variability of heart rate with intermittent large deviations [10]. It was used in such researches as the predictor of mortality in patients with chronic heart failure (CHF) [11] and post-AMI [3]. The greatest advantages of this index are its no special requirement to the data size.

This project is aimed to perform study concerning the state of autonomic nerve system (ANS) at different stages after acute myocardial infarction (AMI), as well as the comparison between the normal individuals and the patients after AMI. Our analysis was based on the assessment of circadian rhythm reflected by heart rate variability (HRV).

2. Methods

The data for this analysis were provided by the Telemetric and Holter ECG Warehouse (THEW, http://www.thew-project.org), among which two

databases were extracted. 67 Holter recordings were selected from database AMI (E-HOL-03-0160-001, ranging from 27-90y), containing the recordings of two stages for a patient after AMI, one between 24-48 h after AMI (AMI-I) and the other between 5th and 10th day after AMI (predischarge, AMI-II). And 202 Holter recordings were selected from database Normal (E-HOL-03-0202-003, ranging from 9-82y) as normal controls. In addition to ECG data, beat annotations are available in both databases.

With the exclusion of those incomplete records, we got 61 records from AMI containing the recordings of two stages, and 189 records from Normal for analysis. For each selected record, two episodes in resting state lasting 2 h were to be extracted in each Holter record, one in the period of 7:00~20:00 (day), the other in 0:00~6:00 (night).RR intervals of the selected 2 h episodes were derived from the annotations in the databases.

The intermittent behaviour of HRV is related to non-Gaussian probability distribution [8, 9]. If the λ is close to zero, the probability density function (PDF) is close to a Gaussian distribution. On the other hand, the greater λ indicates the fatter non-Gaussian tail and the sharper peak of the PDF. The λ of day (λ_d) and night (λ_n), as well as the ratio of them (λ_d/λ_n), was calculated for each selected 2 h RR series.

The first step is to integrate and detrend RR interval series to yield series $b(t)$, which are interpolated with a cubic spline function and resampled at an interval (Δt) of 250 ms (4 Hz). After subtracting average interval b_{ave} , integrated times series $\boldsymbol{B}(\boldsymbol{t})$are obtained by integrating $b(t)$ over the entire length.

$$B(t)=\sum_{i=1}^{t/\Delta t}\{b(i\Delta t)-b_{ave}\} \qquad (1)$$

Using third-order polynomial fit to eliminate the local trend of { $\boldsymbol{B}(\boldsymbol{t})$} within moving windows of length 2*s*, where *s* is the scale of analysis. Intermittent deviation $\Delta_{\boldsymbol{s}}\boldsymbol{B}(\boldsymbol{t})$ is measured as the increment with a time lag *s* of the detrended time series. So, the increments are calculated as

$$\Delta_s\boldsymbol{B}(\boldsymbol{t})=\left\{\boldsymbol{B}(\boldsymbol{t}+\boldsymbol{s}/2)-\boldsymbol{f}_{\mathbf{fit}}\left(\boldsymbol{t}+\frac{\boldsymbol{s}}{2}\right)\right\}-\left\{\boldsymbol{B}(\boldsymbol{t}-\boldsymbol{s}/2)-\boldsymbol{f}_{\mathbf{fit}}\left(\boldsymbol{t}-\frac{\boldsymbol{s}}{2}\right)\right\} \qquad (2)$$

where $T-s/2\le t\le T+s/2$ and $\boldsymbol{f}_{\mathbf{fit}}(\boldsymbol{t})$ is the polynomial representing the local trend of $\boldsymbol{B}(\boldsymbol{t})$, of which the elimination assures the zero-mean probability density function. $\Delta_{\boldsymbol{s}}\boldsymbol{B}$ is normalized by the SD to quantify the PDF. Then, the non-Gaussianity index λ_s is estimated as

$$\lambda_s=\sqrt{\frac{2}{q(q-2)}\left[\ln\left(\frac{\sqrt{\pi}\langle|\Delta_sB|^q\rangle}{2^{q/2}}\right)-\ln\Gamma\left(\frac{q+1}{2}\right)\right]} \qquad (3)$$

Where $\langle|\Delta_sB|^q\rangle$ denotes an estimated value of the *q*-th order absolute moment of $\{\Delta_sB\}$. The λ_s is based on the 0.25th order moment (*q*=0.25) to emphasize the center part of PDF and to reduce the effects of large outliers such as those by ectopic beats, if any, even after the correction [9]. Based on previous findings [10], the difference of λ_s, at scale100 beats, is dominant between day-time and night-time. We measured the non-Gaussianity index (λ) with the scale at 100 beats in each 2 hours RR interval series.

Spectral analysis was performed via a parametric approach exploiting the autoregressive (AR) model [12].The important aspect for the use of AR method is the selection of the order *p*. Much work has been done on this problem. So, in this study, the order of the AR model *p*=16 can be taken [13].

Paired *t* test was used to compare λ_d and λ_n for each subject in Normal and Wilcoxon signed ranks test for post-AMI. The differences between two stages after AMI were compared by means of Mann-Whitney rank sum test. The data were expressed as mean ± SD and the median (25th-75th percentiles) .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 at night compared with that by day in Normal, AMI-I and AMI-II. For λ, the situation was almost the same. For λ_d/λ_n, there were significant differences between Normal and AMI-I as well as AMI-I and AMI-II, but not between Normal and AMI-II. Except for λ_d between Normal and AMI-II, significant differences existed in all indexes of λ in the corresponding period of a whole day. Among them, λ_n in AMI-I was much lower than that in Normal and AMI-II. As for LF/HF, there were significant differences between day and night both in Normal and AMI-II, but not in AMI-I.

Figure 1 are typical examples of PDF representing different values of λ in a normal control and a patient with AMI in day and night. Dissimilarity in the shape of PDF by day and at night could be seen in Normal and AMI-II, while similarity of them was shown in AMI-I.

Table 1. The results of analysis in Normal and AMI

Index	Normal (n=189)		AMI-I (n=61)		AMI-II(n=61)	
	Day	Night	Day	Night	Day	Night
RR interval(ms)	732±119[abc]	931±151[bc]	782±113[ad]	880±144[d]	844±124[a]	1005±127
λ	0.28(0.23-0.33)[ab]	0.54±0.13[bc]	0.32(0.25-0.39)[ad]	0.40±0.14[d]	0.28(0.23-0.35)[a]	0.48±0.14
λ_d/λ_n	0.57(0.42-0.81)[b]		0.80(0.57-1.18)[d]		0.60(0.45-0.79)	
LF/HF	3.50(2.27-5.17)[abc]	1.55(0.94-2.35)	2.15(0.97-3.11)	1.57(1.00-3.02)	1.81(1.17-2.71)[a]	1.69(0.97-2.71)

Notes: Data are expressed as mean±SD or median and interquartile range (75th-25th)
[a]P <0.05 Day *vs* Night; [b]P <0.05 Normal *vs* AMI-I; [c]P <0.05 Normal *vs* AMI-II; [d]P <0.05 AMI-I *vs* AMI-II

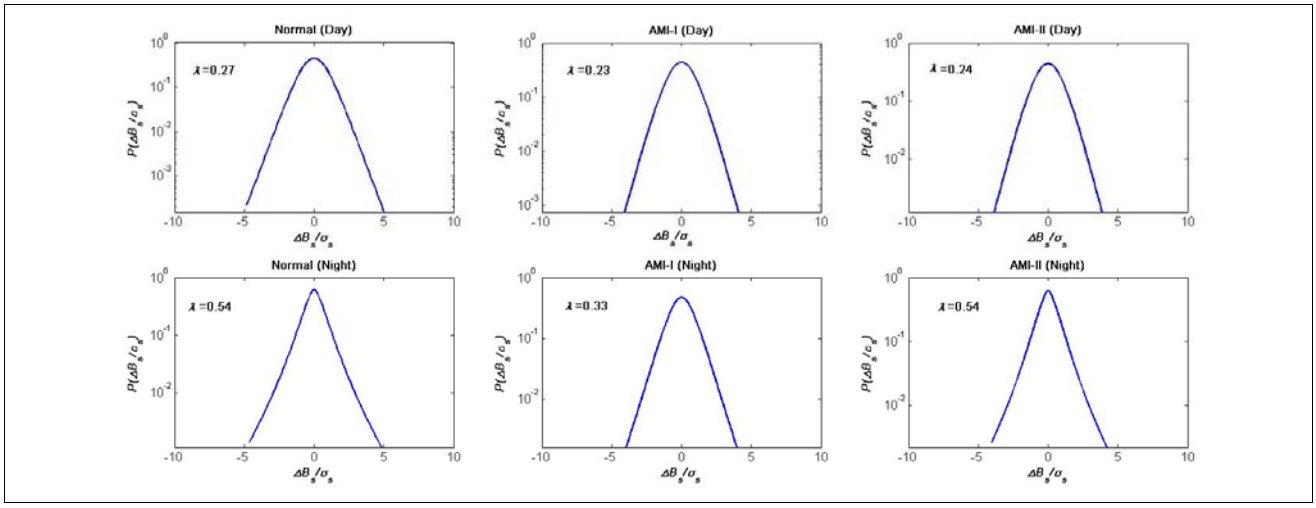

Figure 1. Typical examples of PDF representing non-Gaussian heart rate fluctuation with λ at 100 beat scale in a normal person and a patient with AMI in day and night.

4. Discussion

In this study, non-Gaussianity indexes (λ) with the scale at 100 beats were used to assess autonomic nerve activities at the two stages after AMI. We focused on characterizing the circadian rhythm of HRV. We compared the λ between day and night intraperson and the ratio of them (λ_d/λ_n) between normal people and AMI patients, as well as two stages after AMI for the same group of people. We found the differences among them.

The loss of circadian rhythm is usually accompanied by the dysfunction of ANS [14]. λ with the scale of 100 beats is more sensitive to the difference caused by circadian rhythm than other scales. Though there exist significant differences between λ_d and λ_n for normal controls, AMI-I and AMI-II, situation for λ_d/λ_n is somewhat different. The result, significant difference between Normal and AMI-I as well as nonsignificant difference between Normal and AMI-II, suggest the recovery of circadian rhythm for predischarge AMI patients. In other words，the ratio of λ_d to λ_n provides the possibility to estimate the degree of the loss of circadian rhythm, which is helpful for the quantitative analysis on assessing the circadian rhythm using HRV.

61 patients with two Holter records just after AMI and predicharge were selected from database AMI. Patients with AMI were identified based on clinical symptomatic: sudden chest pain (typically radiating to the left arm or left side of the neck), shortness of breath, nausea, vomiting, palpitations, sweating, and anxiety. All selected patients are supposed to be in sinus rhythm. The exclusion criteria for the AMI patients were: patients in non-sinus rhythm, patients with major co-morbidity such as malignancy, severe hepatic, renal or cerebral disease, etc. The patients whom had prior CABG were also excluded (but not the patient with history non-CABG coronary revascularization). The exclusion criteria make sure that the changes in Holter records for enrolled patients are mainly caused by AMI and the following treatments. So there might be less uncertain or unknown factors when we made comparison between these patients and the normal controls.

From Table 1, we can see that the significant increase of λ_d/λ_n in AMI-I is mainly caused by the decrease of λ_n compared to Normal. We can attribute this kind of

decrease to the overactivity of sympathetic branch in AMI-I [1]. The reciprocal function of ANS means that the activation of sympathetic branch is accompanied by the withdrawal of parasympathetic branch, and *vice versa*. While in AMI-I, though the activation of parasympathetic branch exists in night, but the withdrawal of sympathetic branch is not enough due to the impaired ANS during AMI. After several days of recovery, we can find increased λ_n in AMI-II, indicating the improvement of ANS function. The improved ANS can also be reflected by evolution of LF/HF in our results. There are significant differences for LF/HF between day and night in Normal and AMI-II, but not in AMI-I. Though similar in evolution behavior, λ_d/λ_n has more potential to be an index for practical use with its much smaller coefficient of variation.

5. Conclusions

Since the loss of circadian rhythm is revealed to be a typical symbol of autonomic dysfunction, it is suggested that further monitoring and assessment of circadian rhythm is necessary for post-AMI patients.

Acknowledgements

This work received financial support from the National Natural Science Foundation of China through the project 81471746 and 81071225.

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