Assessment of autonomic nervous system activity by heart rate recovery response*

MENG Zhaohui and BAI Jing**

(Department of Biomedical Engineering, School of Medicine, Tsinghua University, Beijing 100084, China)

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Abstract The assessment of autonomic nervous system (ANS) activity is a tool for diagnosing or predicting cardiovascular diseases, while heart rate recovery response (HRRR) after exercise has been promoted as a process under the regulation of ANS (sympathetic and parasympathetic nervous systems). Therefore, assessment of ANS activity was performed by HRRR in this study. Firstly, HRRR signal was extracted based on wavelet decomposition and difference curve of coarse component from heart rate signal. Then, HRRR was divided into quickly descending interval (QDI) and slowly descending interval (SDI). Finally, 3 groups of indexes (Difference, Exponential and Quadratic Groups) from QDI and SDI were compared between 50 normotensive and 61 hypertensive subjects. The results showed that the indexes of Difference Group were better choices than others in analyzing the features of HRRR. Furthermore, parasympathetic activity is dominant in QDI, while sympathetic and parasympathetic activities affect SDI together. In conclusion, the proposed method was effective to assess ANS activity.

Keywords: **heart rate recovery, exercise testing, autonomic nervous system, sympathetic activity, parasympathetic activity.**

The autonomic nervous system (ANS) plays a central role in regulating cardiovascular function in both healthy subjects and patients. Quantitative analysis of ANS activity has been proved as an approach to diagnosing or predicting cardiovascular diseases. Analysis of heart rate variability (HRV) has become a popular and noninvasive tool recommended to assess the influence of ANS on heart since the 1970s[1]. The common methods to analyze HRV are based on frequency domain because the frequency feature of HRV signal has a strong correlation with the control of ANS[2].

In recent years, exercise testing is widely used to detect cardiovascular diseases or abnormalities that are not apparent at rest. Heart rate recovery response (HRRR) after exercise has been proposed as a process reflecting ANS activity with important clinical implications. Many reports noted that a delayed heart rate (HR) decrease in HRRR was a powerful predictor of overall mortality, and the results were explained with chronotropic incompetence[3~8]. It is well known that ANS consists of two independent subsystems: sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). After stopping exercise, HR will recover from peak HR to rest level within several minutes. HRRR process is considered as the reflection of decreased SNS and increased PNS activities[9]. The changes in SNS and PNS activities are often associated with myocardial function and exercise capacity[10]. However, previous studies have effectively assessed PNS activity, but not for SNS activity[11].

Usually HRRR signal is fitted by a first order exponential decay curve to obtain decay constant[11]. In recent studies, the difference in HR from peak to 1- or 2- minute after exercise was used as a simple index[5,12]. However, the computed decay constant is affected by the selection of time interval of curve fitting. The index based on the change in HR between peak HR and recovery HR at specific time cannot represent the characteristic of whole HRRR.

We present a method to decompose HRRR signal and extract novel indexes to assess ANS activity (not only PNS, but also SNS) in this article. These indexes were compared between normotensive (NTN) and hypertensive (HTN) subjects to verify the validity of this method.

1 Methods

Our study was performed in NTN and HTN subjects at age of $30\sim65$. The consent was obtained

* Supported by Beijing Natural Science Foundation

** To whom correspondence should be addressed. E-mail: deabj@tsinghua.edu.cn

from all participants after they were informed of the purpose of this study. NTN subjects were free of diabetes, hypertension and other cardiovascular diseases. HTN subjects were told not to take any antihypertensive medicine for one week before the exercise testing.

Exercise testing was performed according to YMCA 1-Minute Step Test protocol[13], and the procedure was up and down a stair climber for 1 minute. The stair climber was 30 cm in height. Usually the exercise testing procedure ended within 15 minutes. Firstly, after putting on the electrodes, the subject was asked to take a rest by sitting on a chair for about 5 minutes. Then the subject began to perform stair climber exercise testing at the speed of 30 steps/minute following the hint of an auditory metronome. The exercise lasted 1 minute. When the exercise stopped, the subject was asked to sit down on a chair and electrocardiogram (ECG) from lead II was recorded synchronously. The sampling frequency of ECG was 200 Hz. R-waves were detected sequentially using the method of adapting threshold[14]. The positions of sequential R-waves were continuously detected and recorded until HR returned to pre-exercise level. The interval of two adjacent R-waves was defined as the value of R-R interval. The time series of R-R intervals was regarded as heart period signal, $HP(t)$.

$HP(t)$ derived directly from ECG was uneven and should be converted into fixed time series with a uniform interval using resampling method. Cubic splines interpolation[15] was applied to the original $HP(t)$ and 1 Hz was used as the resampling frequency. Then fixed $HP(t)$ was converted into HR signal ($HR(t)$) that was calculated as follows:

$$HR(t) = 60000/HP(t). \quad (1)$$

Fig. 1 (a) illustrates a typical observation of $HR(t)$, and the curves in Fig. 1 (b) ~ (d) are all analyzed based on $HR(t)$ shown in Fig. 1 (a).

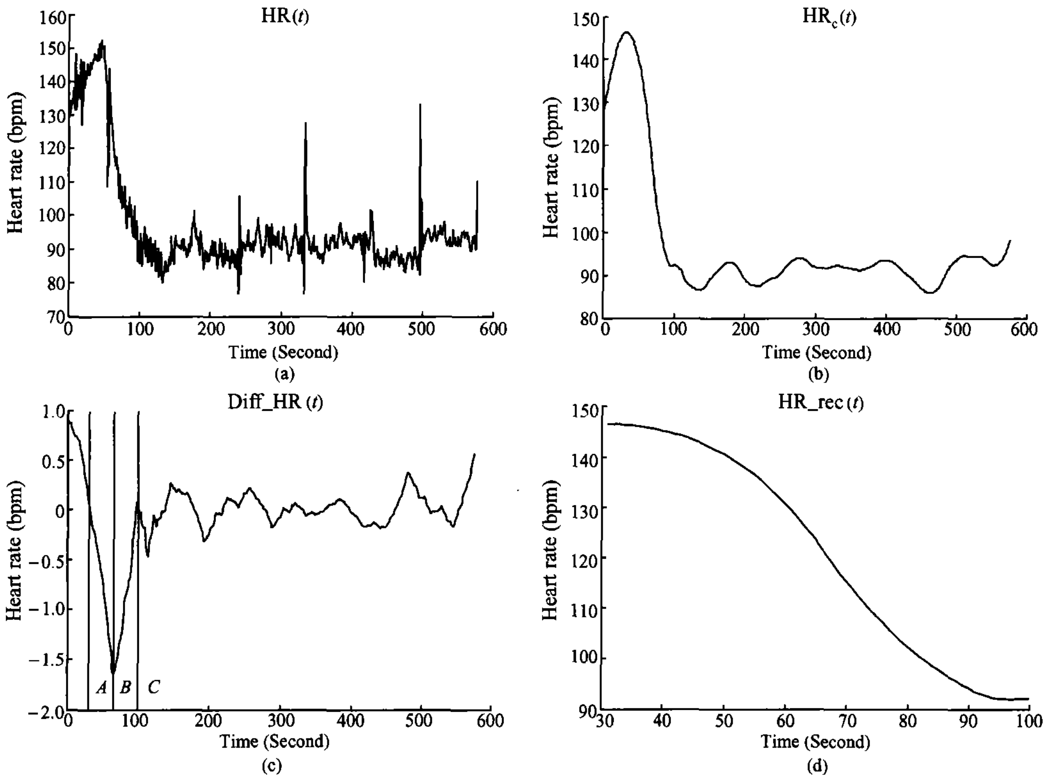

Fig. 1. Extraction of heart rate recovery response signal. (a) $HR(t)$; (b) $HR_c(t)$; (c) Diff_HR(t); (d) HR_rec(t).

We suppose that $HR(t)$ consists of two components, which can be represented by

$$HR(t) = HR_c(t) + HR_d(t), \quad (2)$$

where $HR_c(t)$ is the coarse component and $HR_d(t)$ the detail component. $HR_d(t)$ is related with HRV analysis. Only $HR_c(t)$ is used in the following analysis of HRRR.

Multi-resolution wavelet decomposition was adopted to derive $HR_c(t)$ from $HR(t)$. The decomposition procedure was equivalent to a series of filtering banks decomposing signal into multiple sub-band components[16]. HR(t) was decomposed into 5 sub-bands employing Daubechies wavelet *db5* in this study. With 1 Hz as the resampling frequency, these sub-bands were divided into the frequency bands as [0.25, 0.5], [0.125, 0.25], [0.0625, 0.125], [0.03125, 0.0625] and [0, 0.03125] Hz respectively. We chose [0, 0.03125] Hz as frequency band of coarse component. Then $HR_c(t)$, as shown in Fig. 1 (b), was reconstructed from the wavelet decomposition coefficients of HR(t) at frequency band of [0, 0.03125] Hz.

$HR_c(t)$ did not descend immediately after exercise stopped. In order to find the start-point and end-point of HRRR, the difference of $HR_c(t)$ is defined as

$$\text{Diff\_HR}(t) = HR_c(t+1) - HR_c(t), \quad 1 \leqslant t \leqslant N-1, \tag{3}$$

where N is the signal length of $HR_c(t)$. Diff_HR(t) (see Fig. 1 (c)) kept decreasing after exercise stopped until reaching a minimum, and then began to increase to a steady level. According to Diff_HR(t), we divided $HR_c(t)$ into 4 intervals using the following steps:

Step 1: Find time B when Diff_HR(t) reaches the minimum. The minimal value is named $\text{diff}_{\min}$.

Step 2: Search backward from time B until Diff_HR(t) ascends to 0. This time is named time A.

Step 3: Search forward from time B until Diff_HR(t) ascends to 0. This time is named time C.

Step 4: Based on the time set $\{A, B, C\}$, the $HR_c(t)$ is thus divided into 4 intervals:

Interval_1: ([0, A)): $HR_c(t)$ keeps in exercise status.

Interval_2: ([A, B)): $HR_c(t)$ descends quickly.

Interval_3: ([B, C)): $HR_c(t)$ descends slowly.

Interval_4: ([C, Time_end]): $HR_c(t)$ recovers to pre-exercise status.

Time_end was the time when the ECG record was stopped. The results of interval division were also shown in Fig. 1 (c). We named Interval_2 and Interval_3 quickly descending interval (QDI) and slowly descending interval (SDI) respectively. The time lengths of QDI and SDI were calculated as $Interval_{\text{QDI}}$ and $Interval_{\text{SDI}}$. The part of $HR_c(t)$ during $A \leqslant t \leqslant C$ was regarded as HRRR signal including QDI and SDI and named HR_rec(t) as shown in Fig. 1 (d). We named the mean value of $HR_c(t)$ in Interval_4 Rest HR, and named HR_rec(A) Peak HR that was the maximum of HR_rec(t).

We extracted 3 groups of indexes from HRRR signal in order to find the effective indexes for assessment.

Difference Group: The change pattern of Diff_HR(t) in QDI and SDI were approximately linear as shown in Fig. 1 (c). Therefore, we defined $|\text{diff}_{\min}|/Interval_{\text{QDI}}$ and $|\text{diff}_{\min}|/Interval_{\text{SDI}}$ as quickly descending rate (QDR) and slowly descending rate (SDR) respectively.

Exponential Group: The HR_rec(t) was modeled to fit the following first order exponential curve[11]:

$$\text{HR\_rec}(t) = \begin{cases} \text{HR\_rec}(B) + (\text{HR\_rec}(A) - \text{HR\_rec}(B)) * e^{-(t-A)/\alpha_{\text{QDI}}} & (A \leqslant t \leqslant B), \\ \text{HR\_rec}(C) + (\text{HR\_rec}(B) - \text{HR\_rec}(C)) * e^{-(t-B)/\alpha_{\text{SDI}}} & (B < t \leqslant C), \end{cases} \tag{4}$$

where α_{QDI} and α_{SDI} are HR decay constants representing the time reaching 63% of HR to recover in QDI and SDI respectively. The standard deviations of residuals in two intervals ($Residual^{\alpha}_{\text{QDI}}$ and $Residual^{\alpha}_{\text{SDI}}$) were computed to evaluate the curve fitting.

Quadratic Group: It was also supposed that HR_rec(t) in QDI and SDI fitted quadratic curves:

$$\text{HR\_rec}(t) = \begin{cases} C1_{\text{QDI}} * (t-A)^2 + C2_{\text{QDI}} * (t-A) + C3_{\text{QDI}} & (A \leqslant t \leqslant B), \\ C1_{\text{SDI}} * (t-B)^2 + C2_{\text{SDI}} * (t-B) + C3_{\text{SDI}} & (B < t \leqslant C). \end{cases} \tag{5}$$

The standard deviations of residuals in two intervals ($Residual^{C}_{\text{QDI}}$ and $Residual^{C}_{\text{SDI}}$) were also calculated.

Results were expressed as mean ± SD and Student's unpaired t test was used for comparison between NTN and HTN subjects. The bivariate correlation procedure was also performed to compute Pearson's correlation coefficient and find the linear relationships among the indexes mentioned above. A value $p<0.05$ was considered significant in Student's unpaired t test. Strong correlation was considered if the absolute value of correlation coefficient was >0.90 in correlation analysis. All curves were fitted using Matlab software (version 6.5, Maths Works Inc.).

2 Results

Among the subjects examined by exercise testing, the age-matched 51 NTN and 60 HTN subjects had similar average values of age and Rest HR (Table 1). NTN subjects had remarkably lower Peak HR than that of HTN subjects. There was no significant difference between the $Interval_{QDI}$ for NTN and HTN subjects. However, the mean $Interval_{SDI}$ of NTN subjects was much shorter than that of HTN patients.

Table 1. Basal characteristics of heart rate recovery response

Index	NTN ($n=51$)	HTN ($n=60$)	p value
Age (year)	49.73±9.14	51.33±9.60	0.371
Rest heart rate (bpm)	84.54±9.97	84.19±8.26	0.841
Peak heart rate (bpm)	123.17±14.46	130.59±11.18	0.003
$Interval_{QDI}$ (second)	26.35±14.64	27.52±17.88	0.711
$Interval_{SDI}$ (second)	37.47±30.21	70.38±40.66	<0.001

Data expressed as mean ±SD.

The comparison of indexes in 3 groups is shown in Table 2. For indexes of Difference Group, no significant difference existed in QDR between NTN and HTN subjects while mean SDR of NTN subjects was much quicker. NTN subjects had significantly greater absolute value of $diff_{min}$. For indexes of Exponential Group, NTN and HTN subjects had similar α_{QDI}, and NTN subjects also had shorter α_{SDI} than HTN patients. The standard deviations of residuals were significantly smaller in QDI and greater in SDI for HTN subjects. For indexes of Quadratic Group, $C1_{SDI}$ and $C2_{SDI}$ were significantly different between NTN and HTN subjects, but $C1_{QDI}$ and $C2_{QDI}$ were not. $C3_{QDI}$ represented the level of Peak HR while $C3_{SDI}$ represented the HR level at time B. Both $C3_{QDI}$ and $C3_{SDI}$ were similar between NTN and HTN subjects, and $Residual^{C}_{SDI}$ of NTN subjects was significantly smaller than that of HTN subjects. The standard deviations of residuals in Quadratic Group were much smaller than that in Exponential Group both in NTN and HTN subjects.

Table 2. Three groups of indexes from heart rate recovery response

Index	NTN ($n=51$)	HTN ($n=60$)	p value
Difference Group			
QDR (bpm/second)	0.06±0.04	0.06±0.04	0.274
SDR (bpm/second)	0.05±0.03	0.02±0.03	<0.001
$diff_{min}$ (bpm)	−1.32±0.48	−1.02±0.36	<0.001
Exponential Group			
α_{QDI} (second)	14.04±10.21	13.92±9.65	0.949
$Residual^{e}_{QDI}$	2.70±1.54	2.04±1.02	0.008
α_{SDI} (second)	10.11±10.08	18.78±11.09	<0.001
$Residual^{e}_{SDI}$	1.51±0.72	2.31±1.29	<0.001
Quadratic Group			
$C1_{QDI}$	−0.04±0.02	−0.03±0.03	0.371
$C2_{QDI}$	0.05±0.19	0.00±0.23	0.198
$C3_{QDI}$	128.29±14.51	130.83±11.25	0.301
$Residual^{C}_{QDI}$	0.20±0.25	0.22±0.23	0.582
$C1_{SDI}$	0.02±0.01	0.01±0.01	<0.001
$C2_{SDI}$	−1.24±0.45	−0.86±0.37	<0.001
$C3_{SDI}$	111.60±14.57	116.58±13.28	0.063
$Residual^{C}_{SDI}$	0.36±0.38	0.63±0.59	0.005

Data expressed as mean ±SD.

From the results of correlation analysis, there were strong linear correlations respectively between $Interval_{QDI}$ and α_{QDI} ($r=0.970$), $Interval_{SDI}$ and α_{SDI} ($r=0.961$), QDR and $C1_{QDI}$ ($r=-0.978$), SDR and $C1_{SDI}$ ($r=0.976$) in all 111 tested subjects.

3 Discussions

We divided HRRR signal into 2 parts (QDI and SDI) in the present study, then extracted and compared 3 groups of indexes from HRRR signal between NTN and HTN subjects.

The HRRR process is influenced by age[9]. Therefore, the exercise testing was only performed for the age-matched subjects (Table 1) in order to avoid the effect of age on the results. The means and standard deviations of Rest HR were similar, which indicated that there was no significant difference in HR at rest status between NTN and HTN subjects. Generally, both NTN and HTN have similar Rest HR, but NTN subjects had smaller change of HR than HTN subjects (38.63 vs. 46.40 bpm) under the same load of exercise.

Exponential and quadratic models were used to fit curves respectively. As shown in Table 2, the standard deviations of residuals with quadratic model were near zero and much smaller than that with exponential model, no matter whether for NTN subjects or HTN subjects, and no matter whether in QDI or in SDI. Exponential model was used widely in previous studies because HRRR process was not divided into QDI and SDI. Therefore, quadratic model was a satisfying model to fit HRRR curve under the premise of interval division. However, for 6 indexes in quadratic model ($C1_{QDI}$, $C2_{QDI}$, $C3_{QDI}$, $C1_{SDI}$, $C2_{SDI}$ and $C3_{SDI}$), $C3_{QDI}$ and $C3_{SDI}$ should be approximated to HR_rec(A) and HR_rec(B) respectively that could be obtained from HR_rec(t). $C1_{QDI}$ was always negative and $C1_{SDI}$ was always positive. Thus, the greater were the absolute values of $C1_{QDI}$ and $C1_{SDI}$, the quicker was the HR recovery. Nevertheless, $C2_{QDI}$ and $C2_{SDI}$ had no such property. In addition, according to Eq. (5) and the definition of QDR (SDR), the relationship between $C1_{QDI}$ ($C1_{SDI}$) and QDR (SDR) was calculated as follows:

$$\frac{d^2 HR\_rec(t)}{dt^2} = \begin{cases} 2 * C1_{QDI} \approx - QDR & (A \leqslant t \leqslant B), \\ 2 * C1_{SDE} \approx SDR & (B < t \leqslant C). \end{cases} \quad (6)$$

This relationship was validated with the data shown in Table 2 and the correlation coefficients between QDR and $C1_{QDI}$($r = -0.978$), SDR and $C1_{SDI}$($r = 0.976$). We recommended using QDR and SDR instead of $C1_{QDI}$ and $C1_{SDI}$. Here, QDR and SDR represent the features in QDI and SDI respectively and can directly be estimated from HR_rec(t) without any process of curve fitting.

$Interval_{QDI}$ was the time interval of HR to recover while α_{QDI} was the time interval reaching 63% of HR to recover in QDI. Thus, there might be a linear relationship between $Interval_{QDI}$ and α_{QDI}. The correlation coefficient proved that the linear relationship was strong between $Interval_{QDI}$ and α_{QDI} ($r = 0.970$). Therefore, $Interval_{QDI}$ could be used to assess HRRR process replacing α_{QDI}. So did $Interval_{SDI}$ and α_{SDI} ($r = 0.961$). In this way, only simple indexes in Difference Group were necessary to calculate in HRRR analysis. It was unnecessary to fit HRRR signal to any model. The effective indexes in Exponential and Quadratic Groups could be estimated from the indexes in Difference Group.

Imai et al. used HR decay constant during early HRRR (30 seconds) as the independent and specific index to assess PNS activity because HR decay constant during late HRRR (120 seconds) would be affected by SNS activity[17]. In other words, the increased PNS activity played a dominant role immediately after exercise stopped. However, the decline of SNS activity started a while after exercise stopped. Therefore, the whole HRRR process included two intervals. In the first interval, HR descended quickly only due to the increased PNS activity. In the second interval, HR still descended slowly, which was the result of decreased SNS and increased PNS activities. The decreasing rate of HR in the first interval was quicker than that in the second interval (Table 2) because the SNS and PNS activities were near to the steady status in the second interval. We named the first and second intervals QDI and SDI respectively. Thus, the HRRR process in QDI would become slow if the PNS was impaired. The abnormity would appear in SDI if the SNS was wounded. Certainly, the whole HRRR process (both in QDI and SDI) would be affected if both SNS and PNS were injured. Unfortunately, previous studies only emphasized that the delayed HR decrease in QDI was a powerful predictor of the mortality[3~8], which might mislead us into merely using QDI and omiting SDI in HRRR analysis. In fact, PNS was dominant in cardiovascular regulation at rest status[11] and the abnormal PNS activity perhaps was the primary inducement of death. However, assessment of SNS should be performed in HRRR because the SNS activity out of normal range was also related to cardiovascular diseases, such as hypertension. Many reports noted that the SNS activity of HTN subjects was enhanced at rest[18,19]. Our data of NTN and HTN subjects in QDI and SDI agreed with these conclusions (Tables 1 and 2). Since no significant difference in PNS activity was found between NTN and HTN subjects[18,19], almost all of the extracted indexes from QDI demonstrated a similarity in both NTN and HTN groups ($Interval_{QDI}$, α_{QDR}, $C1_{QDI}$, $C2_{QDI}$ and $C3_{QDI}$). As expected, significantly different indexes in SDI were identified between NTN and HTN subjects ($Interval_{SDI}$, SDR, α_{SDI}, $C1_{SDI}$ and $C2_{SDI}$). In QDI, HR for both NTN and HTN subjects decreased with a steady rate because the enhanced PNS activity in HTN subjects was the same as that of NTN subjects. In SDI, the SNS activity declined along with the increase of PNS activity. We considered that HTN subjects had a higher SNS activity at rest (recovered) status, thus in these subjects the decrease in SNS activity was less than NTN subjects, which led to a slower decreasing rate in HR. Thus, HTN subjects had a slower recovery process in SDI, not in QDI when compared with

NTN subjects.

4 Conclusions

We describe a method to extract HRRR signal based on wavelet decomposition and difference curve of coarse component from HR signal in the present study. Then, the HRRR signal was divided into QDI and SDI. Three groups of indexes were defined as Difference, Exponential and Quadratic Groups respectively, compared between 50 NTN and 61 HTN subjects.

The results showed that there were strong correlations between some indexes of Difference, Exponential and Quadratic Groups. Therefore, only simple indexes in Difference Group were calculated to represent the features of HRRR process and the procedure of curve fitting was needless.

Furthermore, PNS activity is dominant in QDI, while SNS and PNS activities affect SDI together. The SNS and PNS activities could separately be assessed by the interval division of HRRR. The greater were the absolute values of QDR and SDR, the better were the functions of PNS and SNS. In conclusion, the proposed method using HRRR was verified by the data from HTN subjects and could assess effectively the activity of ANS.

References

1 Hyndman, B. W. et al. Spontaneous rhythms in physiological control systems. Nature, 1971, 233: 339.

2 Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. Circulation, 1996, 93: 1043.

3 Lauer, M. S. et al. Impaired heart rate response to graded exercise-Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation, 1996, 93(8): 1520.

4 Lauer, M. S. et al. Impaired chronotropic response to exercise stress testing as a predictor of mortality. Journal of the American Medical Association, 1999, 281(6): 524.

5 Cole, C. R. et al. Heart-rate recovery immediately after exercise as a predictor of mortality. The New England Journal of Medicine, 1999, 341: 1351.

6 Nishime, E. O. et al. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. Journal of the American Medical Association, 2000, 284 (11): 1392.

7 Watanabe, J. et al. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality—The case of stress echocardiography. Circulation, 2001, 104: 1911.

8 Desai, M. Y. et al. Abnormal heart rate recovery after exercise as a reflection of an abnormal chronotropic response. The American Journal of Cardiology, 2001, 87: 1164.

9 Fletcher, G. F. et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation, 2001, 104: 1694.

10 Tavel, M. E. Stress testing in cardiac evaluation—Current concepts with emphasis on the ECG. Chest, 2001, 119(3): 907.

11 Pierpont, G. L. et al. Heart rate recovery post-exercise as an index of parasympathetic activity. Journal of the Autonomic Nervous System, 2000, 80: 169.

12 Shetler, K. et al. Heart rate recovery: Validation and methodologic issues. Journal of the American College of Cardiology, 2001, 38 (7): 1980.

13 Myers, C. R. The Official YMCA Physical Fitness Handbook. New York: Popular Library, 1975, 99~102.

14 Bai, J. et al. Portable ECG and blood pressure telemonitoring system. IEEE Engineering in Medicine and Biology, 1999, 18(4): 63.

15 Aubert, A. E. et al. Analysis of heart rate variability in unrestrained rats. Validation of method and results. Computer Methods and Programs in Biomedicine, 1999, 60(3): 197.

16 Mallat, S. A theory for multiresolution signal decomposition: the wavelet representation. IEEE Pattern Analysis and Machine Intelligence, 1989, 11(7): 674.

17 Imai, K. et al. Vagally mediated heart-rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart-failure. Journal of the American College of Cardiology, 1994, 24 (6): 1529.

18 Huikuri, H. V. et al. Heart rate variability in systemic hypertension. The American Journal of Cardiology, 1996, 77(2): 1073.

19 Piccirillo, G. et al. Heart rate variability in hypertensive subjects. International Journal of Cardiology, 1996, 53(3): 291.