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New Methodology to Develop Multi-parametric Measure of Heart Rate Variability Diagnosing Cardiovascular Disease

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Abstract

The main purpose of our study is to propose a new methodology to develop the multi-parametric measure including linear and nonlinear measures of heart rate variability diagnosing cardiovascular disease. We recorded electrocardiogram for three recumbent postures; the supine, left lateral, and right lateral postures. Twenty control subjects (age: 56.70 ± 9.23 years), 51 patients with angina pectoris (age: 59.98 ± 8.41 years) and 13 patients with acute coronary syndrome (age: 59.08 ± 9.86 years) participated in this study. To develop the multi-parametric measure of HRV, we used the multiple discriminant analysis method among statistical techniques. As a result, the multiple discriminant analysis gave 75.0 % of goodness of fit. When the linear and nonlinear measures of HRV are individually used as a clinical tool to diagnose cardiac autonomic function, there is quite a possibility that the wrong results will be obtained due to each measure has different characteristics. Although our study is a preliminary one, we suggest that the multi-parametric measure, which takes into consideration the whole possible linear and nonlinear measures of HRV, may be helpful to diagnose the cardiovascular disease as a diagnostic supplementary tool.

Keywords: Multiple discriminant analysis, Linear analysis, Nonlinear analysis, Multi-parametric measure of heart rate variability

Introduction

Heart rate variability (HRV) analysis has been used extensively to assess autonomic control of the heart under various physiological and pathological conditions, and used as a clinical tool to diagnose cardiac autonomic function.[1-3] Various measures and explanations have been used to analyze the HRV. For example, simple linear time domain analysis, such as mean, standard deviation, and root mean square of successive RR interval (RRI) differences have been widely employed in quantification of the overall variability of the heart rate (HR).[1] Frequency-domain variable provide markers of the cardiac autonomic regulation, i.e. the sympatho-vagal balance.[4,5] In addition, there are several nonlinear measures. The nonlinear interaction between the various regulatory systems of the heart rate gives rise to clinically useful concepts of variability and regularity. Nonlinear analysis include the complexity estimation, the fractal scaling analysis such as exponent α of the 1/f spectrum, Hurst exponent, and detrended fluctuation entropy, and deterministic chaos methods such as the correlation dimension and the largest Lyapunov exponent, etc.

The reason why these kinds of various measures have been used is that each measure has the different characteristics and physiological meanings. Another reason is that there is not a master measure that explains the whole characteristics of HRV at one time, unfortunately. Thus, researchers must select to use among various measures of HRV according to circumstances. If a multi-parametric measure of HRV

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with relable accuracy be developed, it will be helpful to diagnose the cardiovascular disease. Therefore, in the present study, we propose a new methodology to develop the multi-parametric measure of HRV diagnosing cardiovascular disease using various linear and nonlinear measures.

According to the previous study, there is a relationship between recumbent posture and HRV in patients with coronary artery disease (CAD). In the previous studies using linear analysis, it has been found to increase parasympathetic activity and decrease sympathetic modulation in the right lateral posture.[6-9] In the nonlinear analysis, the right lateral posture induced an increased complexity and irregularity of the dynamic system, and also induced the highest vagal modulation and the lowest sympathetic modulation among the three recumbent postures in patients with severe CAD.[10] Because of the effect of the recumbent posture on HRV, we considered that it is worthwhile to include the linear and nonlinear characteristics of HRV for three recumbent postures; the supine, left lateral, and right lateral postures in patients with CAD.

We used several time- and frequency-domain measures of HRV as linear measures. As nonlinear measures, Poincare plots, the fractal scaling measures and complexity estimations were used. Multiple discriminant analysis was used to discriminate among three groups, i.e. control, angina pectoris (AP) and acute coronary syndrome (ACS), using various linear and nonlinear measures.

Material

Subjects

Patients with stenosis of the luminal narrowing > 50% were recruited as the CAD group, the others were classified as the control group. After then, the CAD group was divided into two groups. One is AP, and the other is acute coronary syndrome (ACS) which consists of unstable AP and myocardial infarction. Patients who had atrial fibrillation or those using class I antiarrhythmic medication were excluded from this study. Informed consent was obtained from the subjects before study. The subjects' clinical characteristics are represented in Table 1.

Table 1 Characteristics of the study population.

Group	N	Male/Female	Age (years)
control	20	10 / 10	56.70 ± 9.23
AP	51	25 / 26	59.98 ± 8.41
ACS	13	6 / 7	59.08 ± 9.86

Values are means ± standard deviation

Study protocol

All subjects were instructed not to drink caffeinated beverages for ≥ 12 hours before electrocardiogram (ECG) recording. Any metal products including ring, watch, necklace, coins, etc. were taken out to prevent inducing electric noise. Cellular phones were turned off, and the environment kept silent to prevent emotional stimulation. To prevent circadian variation of cardiac autonomic nervous activity, HRV measurements were carried out during a certain period of daytime: from 9: 30 a.m. to 11: 30 a.m. All patients were instructed to stay awake during the experiments. According to the experimental protocol, each subject lied in 3 recumbent postures: the supine, left lateral decubitus, and right lateral decubitus postures, in random order. After 5 minutes' rest in each posture, the ECG signals were recorded by electrocardiograph (CardioTouch3000, Bionet Inc., Korea), and were transmitted immediately to a personal computer for recording for 5 minutes. During the rest and recording periods, the patients were asked to keep awake. The sampling frequency for ECG signals was 500 Hz.

The recorded ECG signals were retrieved afterward to measure the consecutive RRIs by using software for the detection of the R waves. We extracted the R-peaks from the ECG recordings based on Thomkin's algorithm.[11] Sinus pause and atrial or ventricular arrhythmia were deleted, and the last 256 stationary RRIs were obtained in each recumbent posture for HRV analysis. If the percentage of deletion was > 5 %, the patient was excluded from the study. We analyzed data from each 5-min supine, right, and left lateral postures. We edited all RRIs manually in order to exclude all ectopicbeats or artifacts, and RRIs time series were resampled at a rate of 4 Hz to obtain power spectral density.

Analysis methods

Time domain analysis

In the present study, several time-domain measures of HRV were selected. In a continuous ECG record, each QRS complex is detected, and the so-called normal-to-normal intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations, normal RRIs), or the instantaneous heart rate is determined. Simple time-domain variables that can be calculated include the mean RRI (RRm), the standard deviation of all RRIs (SDRR), and the standard deviation of differences between adjacent RRIs (SDSD).

Frequency domain analysis

We used fast Fourier transformation to obtain the power spectrum of RRIs. We then defined the various areas of spectral peaks as follows: the total power (TP), 0 Hz to 0.4 Hz; very low frequency (VLF) power, 0 Hz to 0.04 Hz; low frequency (LF) power, 0.04 Hz to 0.15 Hz; and high frequency (HF) power, 0.15 Hz to 0.4 Hz. We used the normalized LF (nLF = 100 x LF/(TP-VLF)) power as an index of sympathetic modulation, the normalized HF (nHF = 100 x HF/(TP-VLF)) power as an index of vagal modulation, and the LF and HF ratio (LF/HF) as an index of sympathovagal balance. The spectral component values such as nLF, nHF power are presented in normalized units (nu).

Poincare plots

The Poincare plot is a diagram, where each RRI is plotted as a function of delayed RRI signal. The length and width of the Poincare plot have been regarded as indicative of the levels of long- and short-term variability, respectively.[12] The Poincare plot may be analyzed quantitatively by calculating the standard deviations of the distances of the RRI (i) to the lines $y = x$ and $y = -x + 2RRI_m$, where RRI_m is the mean of all RRI (i). The parameters SD1 and SD2 refer to these standard deviations, respectively. SD1 is related to the instantaneous beat-to-beat variability of the data, while SD2 describes the longer-term variability of RRI.[13,14] The parameters SD2/SD1, and SD1·SD2 describing the relationship between SD1 and SD2 were also computed in our study.

Exponent α of the 1/f Spectrum (f_α)

Self-similarity is the most distinctive property of fractal signals. Fractal signals usually have a power spectrum of the inverse power law form, $1/f^{\alpha}$, where f is frequency, since the amplitude of the fluctuations is small at high frequencies and large at low frequencies. The exponent α is calculated by a first least-squares fit in a log-log spectrum, after finding the power spectrum from RRI time series. The exponent α is clinically significant because it has different values for healthy and heart rate failure patients.[16,17]

Hurst Exponent (H)

Hurst Exponent H is the measure of the smoothness of a fractal time series based on the asymptotic behavior of the rescaled range of the process. The Hurst Exponent H is defined as $H = \dfrac{\log(R/S)}{\log(T)}$, where T is the duration of the sample of data and R/S the corresponding value of rescaled range. If $H = 0.5$, the behavior of the time series is similar to a random walk. If $H < 0.5$, the time series cover less distance than a random walk. But if $H > 0.5$, the time series covers more distance than a random walk.[15]

Detrended fluctuation analysis (DFA)

A modification of the random walk model analysis has been used to quantify the fractal-like correlation properties by calculating the scaling property of the root-mean-square fluctuation of the integrated and detrended time series data.[18] The detailed algorithm and equations are presented elsewhere.[18,19] We followed the equations based on earlier studies, and we considered computing the exponent α separately for short-term (< 11 beats) and intermediate-term (> 11 beats) scales, yielding the scaling exponents α_1 and α_2, respectively.[18,19]

Approximate entropy (ApEn)

ApEn quantifies the regularity of the RRI. The more regular and predictable the RRI series, the lower will be the value of ApEn.[20] The detailed algorithm and equations are presented elsewhere,[20-22] so we dose not present the derivation of the equations. We followed the equations based on earlier studies.[21] The embedding dimension, m, and the tolerance, r are fixed at m = 2 and $r = 0.2 \times SD$ in physiological time series data.[21,22]

All variables used in our study were summarized in Table 2.

Table 2. Description of HRV Variables.

	Variable	Description
Linear measures	nLF	Normalized low frequency power
	nHF	Normalized high frequency power
	LF/HF	The ratio of low- and high-frequency power
	RRm	The mean of RRI
	SDRR	Standard deviation of all RRIs
	SDSD	Standard deviation of differences between adjacent RRIs
Nonlinear measures	SD1	Standard deviation of the distance of RR(i) from the line y = x in the Poincare plot
	SD2	Standard deviation of the distance of RR(i) from the line $y = -x + 2RRI_m$ in the Poincare plot
	SD2/SD1	The ratio of SD2 and SD1
	SD1SD2	SD1 x SD2
	f_α	Exponent α of the 1/f Spectrum
	ApEn	Approximate Entropy
	H	Hurst Exponent
	α_1	Short-term scale of detrended fluctuation analysis
	α_2	Long-term scale of detrended fluctuation analysis

Multiple discriminant Analysis

The objective of discriminant analysis is to use the information from the independent variables to achieve the clearest possible separation or discrimination between or among groups.[23] In other words, discriminant analysis gives an answer the question that how groups differ with respect to the underlying variables. Discriminant analysis is an analysis of dependence method that is a special case of canonical correlation.[23] With more than two groups, there will potentially be more than one discriminant function that can be used to explain the differences among groups. For example, if we want to discriminate among three groups, two canonical discriminant functions will be derived. The first discriminant function separates group 1 from groups 2 and 3, and the second discriminant function separates group 2 from group 3.

In addition, we can obtain classification function for prediction through the discriminant analysis. Classification function is generated for each group. If new case we have to classify comes into existence, this subject will belong to a group that has the highest value of classification function.

A hit rate serves the measure of goodness of fit in the discriminant analysis, and it corresponds to R^2 in regression analysis. Hit rate, the percentage of time the actual group membership of an observation, corresponds to the group membership as fitted by the discriminant function.[23] In this study, we performed the multiple discriminant analysis using SPSS (version 12.0). Fig. 1 presents the flow chart summarizing individual steps used when recording and processing the ECG signal in order to obtain the multi-parametric measure of HRV diagnosing cardiovascular disease.

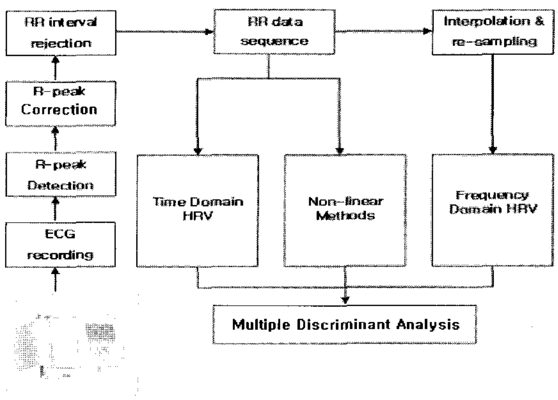

Figure 1 Flow chart summarizing individual steps of recording and processing the ECG signals in order to obtain the multi-parametric measure of HRV diagnosing cardiovascular disease.

Results and Discussion

We obtained two canonical discriminant functions and three classification functions as a result. Table 3 and 4 show coefficients of each function, respectively. Variables of each function include several linear and nonlinear measures. Among various linear measures, nLF, LF/HF, RRm, SDRR and SDSD were selected as the variables in the canonical discriminant and classification functions. As nonlinear measures, the regularity measure and the fractal scaling measures such as f_α, H, α_1 and α_2 were included in the canonical discriminant and classification functions.

Table 3 Coefficients of canonical discriminant functions.

Posture	Variable	Function 1	Function 2
Supine	nLF	-5.661	3.685
	LF/HF	0.114	-0.308
	RRm	0.010	-0.002
	SDRR	0.907	-0.261
	SDSD	-0.235	-0.020
	SD2	-0.548	0.202
	f_α	0.713	0.642
	H	3.035	3.110
	α_1	1.348	-0.937
	α_2	-0.856	-1.347
Right	nLF	6.526	2.792
	LF/HF	-0.612	0.656
	RRm	-0.014	0.007
	SDRR	-0.092	-0.173
	SDSD	0.190	-0.006
	SD1SD2	-0.002	0.003
	f_α	-0.762	-0.543
	ApEn	2.282	-0.697
	H	0.729	-5.788
	α_1	1.702	-1.816
Left	nLF	1.649	2.642
	SDRR	-0.969	-5.915
	α_1	-0.425	2.099
Constant		-6.904	1.018

Table 4. Coefficients of classification functions

Posture	Variable	classify Control	AP	ACS
Supine	nLF	39.742	32.599	46.328
	LF/HF	2.740	3.215	2.910
	RRm	-0.038	-0.031	-0.056
	SDRR	26.344	27.022	24.862
	SDSD	-2.949	-3.001	-2.452
	SD2	-17.808	-18.281	-16.969
	f_α	11.115	10.447	8.851
	H	160.392	157.011	150.262
	α_1	26.069	27.854	24.577
	α_2	-2.965	-1.345	0.502
Right	nLF	-169.674	-171.421	-186.402
	LF/HF	22.539	21.401	22.918
	RRm	0.3826	0.367	0.401
	SDRR	-2.940	-2.726	-2.530
	SDSD	3.355	3.429	2.981
	SD1SD2	-0.026	-0.031	-0.027
	f_α	-8.602	-8.090	-6.368
	ApEn	543.736	545.498	540.058
	H	132.578	141.032	138.624
	α_1	96.881	100.032	95.819
Left	nLF	12.624	9.437	5.883
	SDRR	9.4801	17.539	19.101
	α_1	43.205	40.085	41.334
Constant		-670.494	-673.870	-659.222

AP = angina pectoris; ACS = acute coronary syndrome

Fig. 2 shows the real estimate data plotted in discriminant function space. The scatter plot shows a fairly clear separation between ACS and other groups on the first dimension. The separation between control and AP groups on the second dimension is much less clear.

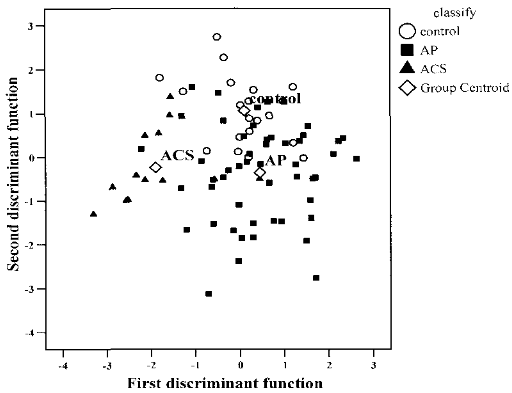

Figure 2. Plot of real estimate data for control (O), AP (■), ACS (▲) groups in discriminant function space. The scatter plot shows a fairly clear separation between ACS and other groups on the first dimension. The separation between control and AP groups on the second dimension is much less clear.

Table 5 records the accuracy of our classification in a hit-and-misses table. The results are reasonably good: 15 control subjects, 37 AP patients, and 11 ACS patients are correctly classified using the multiple discriminant analysis. The hit rate for control, AP, and ACS groups are 75.0 %, 72.5 %, and 84.6 %, respectively. Totally, the hit rate is 63/84 = 75.0 %, i.e. 63 cases among 84 original grouped cases are correctly classified. We can obtain the multi-parametric measure of HRV through the proposed procedures, from the calculation of each measure to multiple discriminant analysis.

Table 5 Classification results for control, angina pectoris (AP), and acute coronary syndrome (ACS) groups

	Classify*	Predicted Group Membership Control	AP	ACS	Total
Original Count	control	15	4	1	20
	AP	9	37	5	51
	ACS	0	2	11	13
%	control	75.0	20.0	5.0	100
	AP	17.6	72.5	9.8	100

ACS	0	15.4	84.6	100

* 75.0% of original grouped cases correctly classified

Sensitivity and specificity for each AP group and ACS group are shown in Table 6. Sensitivity refers to the proportion of people with disease who have a positive test result, and specificity refers to the proportion of people without disease who have a negative test result. Therefore, we can calculate the sensitivity and specificity for AP and ACS groups from classification results. The sensitivity and specificity for AP group are 72.5 % and 81.8 %, respectively. In the case of ACS group, the sensitivity and specificity are 84.6 % and 91.5 %, respectively.

Table 6 Sensitivity and specificity for angina pectoris (AP) group and acute coronary syndrome (ACS) group.

	AP	ACS
Sensitivity	$\frac{37}{51}\times 100 = 72.5\%$	$\frac{11}{13}\times 100 = 84.6\%$
Specificity	$\frac{27}{33}\times 100 = 81.8\%$	$\frac{65}{71}\times 100 = 91.5\%$

We expected that the use of the measures for three recumbent postures will produce the more effective tool than the use of the measures for each recumbent posture. To address this expectation, we presented the accuracy of classification results for three recumbent postures in Table 7. In the supine posture, 9 control subjects, 26 AP patients, and 10 ACS patients are correctly classified. The hit rate for control, AP, and ACS groups are 45.0 %, 51.0 %, and 76.9 %, respectively. Totally, the hit rate is 45/84 = 53.6 %.

In the right lateral posture, 11 control subjects, 29 AP patients, and 9 ACS patients are correctly classified, so the hit rate for three groups are 55.0 %, 56.9 %, and 69.2 %, respectively. Totally, the hit rate is 45/84 = 58.3 %.

In the left lateral posture, 11 control subjects, 30 AP patients, and 7 ACS patients are correctly classified, so the hit rate for three groups are 55.0 %, 58.8 %, and 53.8 %, respectively. Totally, the hit rate is 45/84 = 57.1 %.

Table 7 Classification results for each posture.

Posture		classify	Predicted Group Membership			Total
			Control	AP	ACS	
Supine [a]	Original Count	control	9	7	4	20
		AP	15	26	10	51
		ACS	2	1	10	13
	%	control	45.0	34.0	20.2	100
		AP	29.4	51.0	19.6	100
		ACS	15.4	7.7	76.9	100
Right [b]	Original Count	control	11	5	4	20
		AP	13	29	9	51
		ACS	2	2	9	13
	%	control	55.0	25.0	20.0	100
		AP	25.5	56.9	17.6	100
		ACS	15.4	15.4	69.2	100
Left [c]	Original Count	control	11	5	4	20
		AP	10	30	11	51
		ACS	3	3	7	13
	%	control	55.0	25.0	20.0	100
		AP	19.6	58.8	21.6	100
		ACS	23.1	23.1	53.8	100

[a] 53.6% of original grouped cases correctly classified.

[b] 58.3% of original grouped cases correctly classified.

[c] 57.1% of original grouped cases correctly classified.

The highest hit rate among three recumbent postures is 58.3 %, however, this hit rate is much lower than the hit rate (75.0 %) obtained from multi-parametric measure of HRV considering all three postures. This result means that to include the linear and nonlinear measures of HRV for all three postures gives more effective results to discriminate among groups.

Fig. 3 represents diagrams showing the relative pattern of elements of the canonical discriminant function. Each mean value is normalized to the corresponding mean value of control group in order to estimate the relative quantities. The reason why we depict these diagrams is useful in understanding the relative relationship between the characteristics of control group and those of other groups at a glance. For example, the α_1 value of AP group is similar to that of control group in the supine posture, but higher in the right lateral posture.

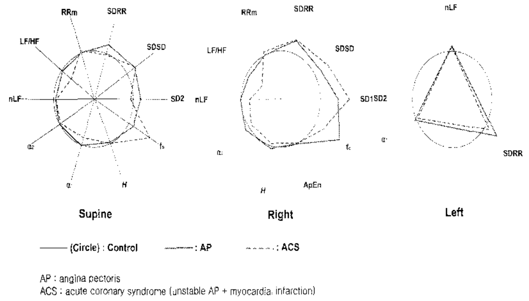

Figure 3 Diagram showing the relative pattern of elements of the canonical discriminant function. Each value corresponds to the mean of each variable, and it is normalized to the corresponding mean value of control group.

Conclusion

The main purpose of our study is to propose a new methodology to develop the multi-parametric measure of HRV diagnosing cardiovascular disease. To achieve this aim, we used the multiple discriminant analysis method among statistical techniques. In the present study, the multiple discriminant analysis gave 75.0 % of goodness of fit.

When the linear and nonlinear measures of HRV are individually used as a clinical tool to diagnose cardiac autonomic function, there is quite a possibility that the wrong results will be obtained due to each measure has different characteristics. In other words, the same subject can be classified as a normal or a patient according to the selected measure. However, we suggest a possibility that multi-parametric measure taking into consideration the whole possible measures of HRV may be helpful to diagnose the cardiovascular disease as a diagnostic supplementary tool.

The extension of the proposed method with the use of enormous number of study population would lead to a better multi-parametric measure of HRV diagnosing cardiovascular disease.

References

1. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Guidelines of Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354-381.
2. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death: experimental basis and clinical observations of post-myocardial infarction risk stratification. Circulation 1992;85(suppl I):177-191.
3. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59(4): 256-262.
4. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. Cardiovasc Res 1996;32(2):208-216.
5. Mezzacappa E, Kindlon D, Earls F, Saul JP. The utility of spectral analytic techniques in the study of the autonomic regulation of beat-to-beat heart-rate-variability. Int J Methods Psychiatr Res 1994;4(April(1)):29-44.
6. Miyamoto S, Fujita M, Sekiguchi H, Sekiguchi H, Okano Y, Nagaya N, Ueda K, Tamaki S, Nohara R, Eiho S, Saayama S. Effects of posture on cardiac autonomic nervous activity in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1788-1793.
7. Miyamoto S, Fujita M, Tambara K, Sekiguchi H, Eiho S, Hasegawa K, Tamaki S. Circadian variation of cardiac autonomic nervous activity is well preserved in patients with mild to moderate chronic heart failure: effect of patient position. Int J Cardiol 2004;93:247-252.
8. Kuo CD, Chen GY. Comparison of Three recumbent position on vagal and sympathetic modulation using spectral heart rate variability in patients with coronary artery disease. Am J Cardiol 1998;81:392-396.
9. Chen GY, Kuo CD. The effect of the lateral decubitus position on vagal tone Anaesthesia. 1997;52:653-657.
10. Kim WS, Yoon YZ, Bae JH, Soh KS. Nonlinear characteristics of heart rate time series: influence of three recumbent positions in patients with mild or severe coronary artery disease. Physiol Measurement 2005;26:517-529.
11. Tompkins WJ. Bimedical digital signal processing. Prentice Hall PTR, Upper Saddle River, New Jersey 07458, 1995.

12. Moraru L, Tong S, Malhotra A, Geocadin R, Thakor N, Bezerianos A. Investigation of the effects of ischemic preconditioning on the HRV response to transient global ischemia using linear and nonlinear methods. Med Eng & Physics 2005;27(6):465-473.
13. Tulppo MP, Makikallio TH, Takala TE, Seppanen T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol 1996;271:H244-252.
14. Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincare plot geometry reflect nonlinear features of heart rate variability?. IEEE T Bio-Med Eng 2001;48(11):1342-1347.
15. Kannathal N, Acharya UR, Lim CM, Sadasivan PK. Characterization of EEG-A comparative study. Comput Meth Prog Bio 2005;80:17-23.
16. Signorini M G, Guzzetti S, Manzoni C, Milani S, Cerutti S. Multiparametric analysis of HRV signal by linear and nonlinear methods in heart failure patient population. Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society 1998;20:322-325.
17. Calcagnini G, Censi F, Cesarini A, Lino S, Cerutti S. Self-similar properties of long term heart rate variability assessed by discrete wavelet transform. Comput Cardiol 1998;25:333-336.
18. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heart-rate time series. Chaos 1995;5: 82-87.
19. Ho KK, Moody GB, Peng CK, Mietus JE, Larson MG, Levy D, Goldberger AL. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. Circulation 1997;96(3); 842-848.
20. Tulppo MP, Hughson RL, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Huikuri HV. Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics. Am J Phyisol Heart Circ Physiol 2001;280: H1081-H1087.
21. Pincus SM. Approximating Markov chains. Proc Natl Acad Sci USA 1992;89:4432-4436.
22. Pincus SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify?. Am J Physiol 1994;266:H1643-56.
23. Lattin J, Carroll JD, Green PE. Analyzing multivariate data. Thomson Learning, Inc., Canada, 2003.