Nonlinear Methods to Assess Changes in Heart Rate Variability in Type 2 Diabetic Patients

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Abstract

Background: Heart rate variability (HRV) is an important indicator of autonomic modulation of cardiovascular function. Diabetes can alter cardiac autonomic modulation by damaging afferent inputs, thereby increasing the risk of cardiovascular disease. We applied nonlinear analytical methods to identify parameters associated with HRV that are indicative of changes in autonomic modulation of heart function in diabetic patients.

Objective: We analyzed differences in HRV patterns between diabetic and age-matched healthy control subjects using nonlinear methods.

Methods: Lagged Poincaré plot, autocorrelation, and detrended fluctuation analysis were applied to analyze HRV in electrocardiography (ECG) recordings.

Results: Lagged Poincaré plot analysis revealed significant changes in some parameters, suggestive of decreased parasympathetic modulation. The detrended fluctuation exponent derived from long-term fitting was higher than the short-term one in the diabetic population, which was also consistent with decreased parasympathetic input. The autocorrelation function of the deviation of inter-beat intervals exhibited a highly correlated pattern in the diabetic group compared with the control group.

Conclusion: The HRV pattern significantly differs between diabetic patients and healthy subjects. All three statistical methods employed in the study may prove useful to detect the onset and extent of autonomic neuropathy in diabetic patients. (Arq Bras Cardiol. 2013;101(4):317-327)

Keywords: Heart Failure; Diabetes Mellitus, Type 1; Systole; Measurements, Methods and Theories; Statistics as Topic.

Introduction

Heart rate is dynamically regulated by intrinsic and extrinsic control systems, maintaining homeostasis. The major extrinsic control is provided by the autonomic nervous system. Heart rate variability (HRV) is a measure of the fluctuation in the interval between sequential sinus heartbeats, and reflects cardiac autonomic regulation1-3. Diabetes leads to autonomic neuropathy4, thereby disrupting a major component of cardiovascular regulation and contributing to an increased incidence of cardiovascular diseases in diabetic patients, such as heart attack, sudden cardiac death, and silent ischemia5-8. Early diagnosis of autonomic diabetic neuropathy is difficult and the detection methods available, e.g., the Ewing Test Battery, are cumbersome and have poor sensitivity and reproducibility. In contrast, HRV analysis is noninvasive and the input data are easily obtained by conventional electrocardiography (ECG)9-12. However, because of the nonlinear heart dynamics, conventional time and frequency domain parameters of HRV may not always represent the nonstationary characteristics of ECG. Nonlinear methods such as the Poincaré plot, detrended fluctuation analysis (DFA), tone/entropy analysis and HR complexity analysis are newly developed tools used for identifying nonlinear patterns within ECG data13-18.

In this study, we used nonlinear analytical methods to study the differences in HRV patterns between diabetic and healthy individuals. The purpose of this study was to identify new parameters useful for detecting autonomic dysregulation in diabetes.

Methods

The patient group consisted of 23 type 2 diabetes mellitus patients with no history of cardiac, neurological, psychiatric, or sleep disorders. Patients on heart rate-altering medications were excluded from the study. The study was approved by the ethical committee of the Indian Institute of Technology, Kharagpur, India. A total of 23 healthy subjects were selected as a control group using the same exclusion criteria. All participants provided
written informed consent prior to inclusion in the study. Subjects were instructed to avoid caffeine, alcohol, and physical exertion the day before the study was performed. A 10-min ECG recording was acquired from the patients while on supine position following a 15-min relaxation period. All ECGs were recorded at a fixed time of day to avoid the effects of diurnal variations on HRV.

Matlab and SPSS software packages were used for statistical analysis. For comparative analysis between the groups, unpaired t-tests were applied as appropriate. Other statistical methods are individually described in details.

**Poincaré Plot**

The Poincaré plot is a scatter plot of \( R_R \) vs. \( R_{R_{n+m}} \), where \( R_R \) is the time between two successive R peaks and \( R_{R_{n+m}} \) is the time between the next two successive R peaks. When the plot is adjusted by the ellipse-fitting technique, the analysis provides three indices: the standard deviation of instantaneous beat-to-beat interval variability (SD1), the continuous long-term RR interval variability (SD2), and the SD1/SD2 ratio (SD12). On the Poincaré plot, SD1 is the width and SD2 the length of the ellipse. In addition to this conventional plot (\( R_{R_{n+m}} \) vs. \( R_R \)), we also used the generalized Poincaré plot with different intervals, including the m-lagged Poincaré plot (the plot of \( R_{R_{n+m}} \) versus \( R_R \)). The values of SD1 and SD2 were calculated for lag = m from the relations

\[
SD1 = \langle \Phi(m) - \Phi(0) \rangle^{1/2} \quad \text{and} \quad SD2 = \langle \Phi(m) + \Phi(0) \rangle^{1/2},
\]

where the autocovariance function \( \Phi(m) \) is given by

\[
\Phi(m) = E[R_R^n R_R^{n+m} - \langle R_R \rangle \langle R_R \rangle]
\]

and \( \langle R_R \rangle \) is the mean \( R_R \). For the purpose of our study, we set \( m = 1, 5, \) and 9. We then extended our analysis to reveal the association between these standard deviation (SD) values and \( m \) by using the Padé approximation 9. We assumed a simple form of the Padé approximation for SD values as the ratio of polynomial in \( M \) of degree one.

\[
Y = \frac{a + bM}{c + dM} = \chi \frac{1 + BM}{1 + \gamma M}
\]

Here \( Y = SD1, SD2, \) or \( SD12 \) and \( \chi = a/c \). The terms \( \beta = b/a \) and \( \gamma = d/c \) are the new unknown parameters. In order to determine if these parameters are of value for assessing cardiovascular health, we considered eq. (1) for the case of small \( m \). In this limit, equation (1) can be approximated as \( Y = C + LM + QM^2 \), where the slope is \( L = \chi (\beta - \gamma) \) and the curvature is \( Q = \gamma L \). The slope and curvature of the plot of SD vs. \( m \) were determined by the fitted parameters \( \chi, \beta, \) and \( \gamma \).

**Detrended Fluctuation Analysis**

Another analytic method to assess long-term correlation in the R–R–time sequence is based on DFA 20. The measure of correlation was given by a scaling exponent \( \alpha \) of the fluctuation function \( F(t) = t^\alpha \). The fluctuation function \( F(t) \) was computed as follows. For a given time sequence \( R(t) \), \( t_i = i \delta t \), where \( \delta t \) is the characteristic time interval for the sequence and \( i = 1, N \) is an integrated time series, \( r(t) \) was defined as \( r(t) = \sum_i [R(t_i) - \langle R \rangle] \), where \( \langle R \rangle \) is the mean of \( R \). The integrated series was divided into segments of equal duration, \( \tau = n \delta t \) and a linear function used to fit the data within each segment. The fluctuation function \( F(t) \) was calculated as the root mean square fluctuation relative to the linear trend and alpha was obtained by fitting the data to a power law function. It has been observed that an acceptable estimate of the scaling exponent alpha (from DFA) can be obtained from analysis of data sets with 256 samples or longer (equivalent to approximately 3.5 min of RR data at a heart rate of 70 beats/min). The analysis of RR data from an ECG recording period of 10 min was therefore expected to provide an adequate measure of the scaling exponent 21. However, the alpha value obtained from this calculation may be under the mixed influence of both short-term scaling, reflecting parasympathetic control, and long-term scaling, reflecting sympathetic control, and thus may fail to fully distinguish parasympathetic and sympathetic influences. A separate analysis of both short- and long-term scaling is supposed to nullify the mutual effect and reveal the exact scaling variation 22. Thus, we analyzed separate alpha values, short-term \( \alpha_s \) and long-term \( \alpha_l \). For \( \alpha_s \), data from 25 beats were included, whereas for \( \alpha_l \), data from 30 to N/4 beats were included.

**Correlation between successive differences in \( R_Rn \) interval**

The coherence of the RRn interval can be assessed from the map of interval variation:

\[
rr_{n+1} = \frac{RR_{n+2} + RR_{n+1}}{RR_n} \quad \text{VS.} \quad rr_n = \frac{RR_{n+1} - RR_n}{RR_n}
\]

where \( <RR_n> \) is the mean interval. This plot is expected to show the correlation between the variability of three consecutive R–R intervals.

**Autocorrelation of fluctuation of RRn**

We explored the autocorrelation of the deviation of \( RR_n \) from the mean \( <RR_n> \). The autocorrelation function \( C(m) \) of a particular subject was calculated from

\[
C(m) = \sum_{n=1}^{N} \Delta RR_{n+m} \Delta RR_n / \sum \Delta RR_n^2
\]

where the deviation is \( \Delta RR_n = RR_n - <RR_n> \) and \( N \) is the total number of RR intervals.

**Results**

The mean heart rate was 74.7 ± 6.1 beats/min in the diabetic group and 72.4 ± 6.7 beats/min in the healthy control group. Mean age in the diabetic group was 46.3 years (range, 36–56 years) and 47.4 years (range, 39–57 years) in the control group. All study subjects were non-smokers.

In the Poincaré plot analysis, plot scatter increased with lag number, yielding higher width (SD1) and length (SD2)
Figure 1 – Poincaré plot of \(RR_{n+m}\) vs. \(RR_n\) from HRV analyses of one diabetic (D, left panels) and one nondiabetic subject (ND, right panels). In the upper panel, the lag factor \(m = 1\), in the middle panel, \(m = 5\), and in the bottom panel, \(m = 9\). Note the greater scatter in the ND subjects, particularly as the lag factor is increased.
The incremental increase in width of the plot $RR_{n+m}$ vs. $RR_n$ as $m$ increased was smaller in the diabetes group (Figure 1, D) than in the control group (Figure 1, ND). Differences in the values of SD1, SD2, and SD12 between the diabetes group and the control group were statistically significant ($p < 0.001$ for all). The values of SD1 and SD12 were higher in the control group, whereas SD2 was higher in the diabetic group. The difference in SD12 increased with lag number (Figure 2).

An excellent fit of the data with equation (1) ($R^2 = 0.999$) was found with the $\chi$, $\beta$, $\gamma$ value sets listed in Table 1. The values for $L$ and $Q$ as obtained by fitting of the data to eq. (1) are also presented in Table 1. The general features were that the slope ($L$) was positive but curvature ($Q$) was negative for all parameters and curvature was nearly one order of magnitude smaller than the slope.

From DFA, the mean value of alpha in the control group was smaller than that in the diabetic group ($0.88 \pm 0.17$ vs. $1.02 \pm 0.13$; $p < 0.001$) (Figure 3). In control subjects, $\alpha_s$ was slightly larger than $\alpha_l$ ($1.01 \pm 0.14$ vs. $0.80 \pm 0.19$), whereas $\alpha_s$ was larger than $\alpha_l$ for the diabetic group ($\alpha_s = 1.09 \pm 0.17$; $\alpha_l = 0.80 \pm 0.19$).
Table 1 - The values of parameters $\chi$, $\beta$, $\gamma$ obtained by fitting the data to eq. (1), as well as respective $R^2$ values. The $L$ and $Q$ parameters are the coefficients of the linear and quadratic terms in expansion of $Y$ in terms of $m$. Values of $\chi$, $L$ and $Q$ for SD1 and SD2 are expressed in seconds.

|     | $\chi \times 10^{-2}$ | $\beta \times 10^{-2}$ | $\gamma \times 10^{-2}$ | $R^2 \times 10^{-2}$ | $L \times 10^{-3}$ | $-Q \times 10^{-4}$ |
|-----|------------------------|-------------------------|--------------------------|----------------------|-------------------|---------------------|
| SD1 | ND                     | 1.3 ± 0.03              | 39.1 ± 2.0               | 3.2 ± 0.2            | 99.9              | 4.7 ± 0.4            |
|     | D                      | 1.0 ± 0.02              | 38.2 ± 1.4               | 2.0 ± 0.1            | 99.9              | 3.6 ± 0.08           |
| SD2 | ND                     | 3.2 ± 0.06              | 20.3 ± 1.1               | 3.5 ± 0.2            | 99.9              | 5.4 ± 0.4            |
|     | D                      | 3.1 ± 0.07              | 26.4 ± 1.6               | 4.4 ± 0.3            | 99.9              | 6.8 ± 0.6            |
| SD12| ND                     | 40.2 ± 0.5              | 25.0 ± 1.8               | 12.2 ± 0.9           | 99.9              | 51.3 ± 6.4           |
|     | D                      | 33.0 ± 0.3              | 15.3 ± 0.8               | 6.5 ± 0.4            | 99.9              | 29.0 ± 2.6           |

Figure 3 - The DFA exponent $\alpha$ for healthy (nondiabetic) and diabetic subjects.

$q_1 = 1.18 \pm 0.19$. When $q_1$ was plotted against $q_s$ (Figure 4), the diabetic and nondiabetic populations tended to form two separate clusters.

In the correlation plot, points were crowded around the origin for diabetic patients. In contrast, there was greater scattering about the origin and more asymmetry in the plot of control subjects (Figure 5, ND1, ND2). The strength of heart rhythm correlation was estimated by considering the autocorrelation of fluctuation in $R_T$. Representative results from one control and one diabetic patient are plotted in Figure 6. The autocorrelation functions for diabetic and control patients were distinct. For diabetic subjects, the correlation function $C(m)$ decreased slowly (black and green curve in the upper figure) with lag time. The time dependence was close to the sum of the two exponentials with superimposed small amplitude oscillation of low frequency. On the other hand, $C(m)$ from the healthy subjects demonstrated a more rapid (exponential) fall as correlation time decreased compared with the diabetic cases. To confirm this difference in correlation pattern between control and diabetic subjects, we shuffled the actual time series of $R$–$R$ interval using Matlab software and the autocorrelation functions of the shuffled data (red and blue for subjects 1 and 2 respectively) were plotted in Figure 6. The autocorrelation functions of the shuffled data from all subjects (2 diabetics and 2 healthy controls) were nearly identical.
We also characterized properties of $\Delta RR_n$ by the probability distribution function $P(\Delta RR_n)$ (Figure 7). For diabetic patients, the probability distribution was almost symmetrical and could be fit by a Gaussian function ($R^2 = 0.93$) with width = 0.023. For healthy subjects, the probability distribution $P$ was asymmetrical with positive mean and higher width = 0.036 as obtained by the Gaussian fit ($R^2 = 0.93$).

**Discussion**

We found marked differences in HRV pattern between diabetic and healthy control subjects using nonlinear analyses. Subjects were matched for both mean age and resting heart rate, the two major determinants of HRV \(^{23}\), so that the difference in distribution would reflect changes in cardiovascular regulation resulting from the diabetic condition only.

Several modifications of the simple Poincaré plot have been proposed to more effectively reveal changes in HRV patterns, including the lagged plot. The concept of this m lagged plot emerged from the recognition that any given R–R interval can influence up to eight subsequent R–R intervals \(^{24,25}\). It has been shown that SD1 correlates with the short-term variability of heart rate and is mainly influenced by parasympathetic modulation, whereas SD2 is a measure of long-term variability \(^{14,26}\) and reflects sympathetic activation. The lower SD1 in diabetic subjects indicates that parasympathetic regulation is weakened by the disease, presumably by peripheral neuropathy, whereas higher SD2 in diabetic patients indicates increased long-term variability because of compensatory sympathetic input.

The results from Poincaré plot analysis are further revealed by the slope (L) and curvature (-Q) of the plot. In the diabetic group, L and -Q for SD1 and SD12 were smaller, whereas L and -Q values for SD2 were higher than in the control group. The difference in Q was larger than the difference in L. In particular, the Q value for SD12 in the control group was >3 times greater than that for diabetic group. Low values of curvature are found in patients with cardiovascular disease \(^{24}\). These data strongly suggest decreased parasympathetic activity and excessive influence of sympathetic activity in the diabetic heart. In addition, this result provides indirect support for the notion that higher sympathetic influence over cardiovascular function is correlated with cardiac morbidity \(^{27,28}\). An increased SD12 is considered a good indicator of healthy heart dynamics, and the lower value in diabetic patients again supports altered sympathovagal balance in diabetes.

Previous reports using DFA showed that $\alpha_s > \alpha_l$ in healthy subjects, whereas the reverse was the case for subjects with cardiovascular disease \(^{20}\). We found a similar trend in this study, again confirming the adverse effect of diabetes on the heart.

In the absence of external modulation, the correlation plot is expected to scatter close to the point of origin, whereas random input will produce a uniform distribution. We observed a high density of points around the origin with greater symmetry in diabetic patients when compared with controls. Plots from
healthy controls were generally asymmetrically scattered with large RRn values. These results suggest that mechanisms for decelerating and accelerating HR over different time frames are substantially impaired in diabetic patients.

Application of autocorrelation to HRV analysis is a recent idea that regards HRV as the outcome of the interaction between coupled oscillators of various frequencies. The degree of autocorrelation can also reflect on the embedded time scales within the HRV pattern. It is thought that each of these time scales in the coupled oscillator is represented by a separate self-oscillator, interacting with other oscillators with different physiological functions. The lack of exponential fall in C(m) indicates the presence of a long-term memory effect in the diabetic condition and strongly suggests that mechanisms for short-term variation in heart rate are weakened or lacking in diabetic patients.

Heart rate variability analysis based on nonlinear dynamics has been shown to be superior to conventional methods for identifying hidden changes in cardiac autonomic modulation in various disease conditions. Previous reports have demonstrated

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**Figure 5** - Plot of rrn+1 and rrn for two subjects from each group. Subjects were age matched (1 from each group in their mid-fifties, one from each group in their late thirties). The quantity rm is the relative difference between RRn+1 and RRn normalized to the mean RRn of all intervals.
Figure 6 - Plot of the correlation function $C(m)$ with $m$ for two diabetic (D) (left) and two control (ND) subjects. The lower curves were obtained from shuffled RRn intervals.

Figure 7 - The plot of probability distribution $P$ as a function of $r_{n}$ for the two groups (upper panel is the diabetic group and the lower is the nondiabetic healthy group). Continuous Guassian curves are fitted to the distributions.
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Conclusions

In summary, we have shown the effectiveness of nonlinear analytical methods to study differences in HRV patterns between diabetic patients and healthy-matched controls. We also emphasized the novelty of autocorrelation analysis to assess changes in the autonomic regulation of the diabetic heart. To our knowledge, this is the first attempt to distinguish normal from diabetic heart function using autocorrelation analysis. We believe these methods have the potential to identify diagnostic and prognostic markers for cardiac autonomic neuropathy in diabetes.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Roy, B, Ghatak S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Contreras P, Canetti R, Migliaro RE. Correlations between frequency-domain HRV indices and lagged Poincaré plot width in healthy and diabetic subjects. Physiol Meas. 2007;28(1):85-94.

2. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput. 2006;44(12):1031-51.

3. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(1):2850-5.

4. Viskin P, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553-79.

5. Gemtens J, Dekker JM,tenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, et al. Impaired autonomic function is associated with increased mortality especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. Diabetes Care. 2001;24(10):1793-8.

6. Liao D, Carnethon M, Evans CW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes. 2002;51(12):3524-1.

7. Kataoka M, Ito C, Sasaki H, Yamaneb K, Kohno N. Low heart rate variability is a risk factor for sudden cardiac death in type 2 diabetes. Diabetes Res Clin Pract. 2004;64(1):51-8.

8. Alina JK, Agata MG, Torzska K, Kramer L, Sowinska A, Moczkio J, et al. Diabetes abolishes the influence of revascularization on heart rate variability in patients with stable angina. Assessment by novel mathematical models. [abstract]. J Electrocardiol. 2007;40:S32-S33.

9. Ewing DJ, Martyn CM, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care. 1995;8(5):491-8.

10. Pagani M. Heart rate variability and autonomic diabetic neuropathy. Diabetes Nutr Metab. 2000;13(6):341-6.

11. Rolim LC, Sa JR, Chacra AR, Dib SA. Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis. Arq Bras Cardiol. 2008;90(4):e24-31.

12. Spallone V, Menzinger G. Diagnosis of cardiovascular autonomic neuropathy in diabetes. Diabetes. 1997;46 Suppl 2:567-76.

13. Tulppa MP, Makikallio TH, Takala TE, Seppapan T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol. 1996;271(1 Pt 2):H4244-52.

14. Brennan M, Palaniswami M, Karen P. Do existing measures of Poincaré plot geometry reflect nonlinear features of heart rate variability? IEEE Trans Biomed Eng. 2001;48(11):1342-7.

15. Woo MA, Stevenson WG, Moser DK, Trelease RB, Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. Am Heart J. 1992;123(3):704-10.

16. Khandoker A, Jelinek HE, Moritani T, Palaniswami M. Association of cardiac autonomic neuropathy with alteration of sympatho-vagal balance through heart rate variability analysis. Med Eng Phys. 2010;32(2):161-7.

17. Khandoker A, Jelinek HE, Palaniswami M. Identifying diabetic patients with cardiac autonomic neuropathy by heart rate complexity analysis. Biomed Eng Online. 2009;8:3.
18. Khovanov IA, Khovanova NA, McClintock PV, Stefanovska A. Intrinsic dynamics of heart regulatory systems on short time-scales: from experiment to modeling. [Cited on 2012 Jan 10]. Available from: http://arxiv.org/PS_cache/arxiv/pdf/0912/0912:2237v1.pdf.

19. Ghatak SK, Roy B, Choudhuri R, Bandopadhaya R. Modulation of autonomous nervous system activity by gyrosound stimulation; 2010. [Cited on 2012 Feb 20]. Available from: http://arxiv.org/abs/1003.2075

20. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos. 1995;5(1):82-7.

21. Coronado AV, Carpena P. Size effects on correlation measures. J Biol Phys. 2003;31(1):121-33.

22. Blazquez MT, Anguianoa M, De Saavedra FA, Lallena AM, Carpenaet P. Study of the human postural control system during quiet standing using detrended fluctuation analysis. Physica A: statistical Mechanics and its Applications. 2009;388:1857-66.

23. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman Cl, et al. Determinants of heart rate variability. J Am Coll Cardiol. 1996;28(6):1539-46.

24. Thakre TP, Smith ML. Loss of lag-response curvilinearity of indices of heart rate variability in congestive heart failure. BMC Cardiovasc Disord. 2006;6:27.

25. Lerma C, Infante O, Perez-Groux H, Jose MV. Poincaré plot indexes of heart rate variability capture dynamic adaptations after haemodialysis in chronic renal failure patients. Clin Physiol Funct Imaging. 2003;23(2):72-80.

26. Brennan M, Palaniswami M, Kamen P. Poincaré plot interpretation using a physiological model of HRV based on a network of oscillators. Am J Physiol Heart Circ Physiol. 2002;283(5): H1873-86.

27. Julius S, Nesbitt S. Sympathetic overactivity in hypertension: a moving target. Am J Hypertens. 1996;9(11):113S-120S.

28. Triposkiadis F, Karayannis G, Giarmouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure: physiology, pathophysiology, and clinical implications. J Am Coll Cardiol. 2009;54(19):1747-62.

29. Stefanovska A, Bracic M. Physics of the human cardiovascular system. Contemp Phys. 1999;40:31-55.

30. Javorka M, Javorkova J, Tonhajerova I, Calkovska A, Javorka K. Heart rate variability in young patients with diabetes mellitus and healthy subjects explored by Poincaré and sequence plots. Clin Physiol Funct Imaging. 2005;25(2):119-27.
