ORIGINAL ARTICLE

Comparative effect of bisoprolol and losartan in the treatment of essential hypertension

Goran Keković, Branislav Milovanović[1], Dragomir Davidović, Dejan Raković[2], Milka Ćulić

Laboratory of Radiation and Environmental Protection, Vinča Institute of Nuclear Sciences, University of Belgrade, [1]Department of Cardiology, Neurocardiology Laboratory, Clinical Hospital Centre "Bežanijska Kosa", Belgrade, Medical Faculty, University of Belgrade, [2]Department of Microelectronics and Engineering Physics, Faculty of Electrical Engineering, University of Belgrade, Serbia

Objective: We investigated the effects of bisoprolol and losartan on subjects with essential hypertension, by conducting heart rate variability (HRV) analysis of ECG signals. Our intention was to establish the set of linear and nonlinear heart rate variability parameters, which could be used as a noninvasive markers in the treatment of hypertension. **Materials and Methods:** Sixty subjects with essential hypertension included in this study were divided in two groups. During the four weeks medical treatment, the first group was administered with daily oral dose of 5 mg of bisoprolol and the second with daily oral dose of 50 mg of losartan. We recorded ECG signals, and performed HRV analysis of consecutive RR time intervals, before and after a month of pharmacological therapy. **Results:** In the case of bisoprolol, statistically the most significant changes of HRV parameters were: TP (1814.1 ± 1731.3 ms^2 vs. 761.3 ± 725.0 ms^2, $P < 0.0001$), RR (870.2 ± 105.7 ms vs. 1027.2 ± 150.0 ms, $P < 0.0001$), HR (70.81 ± 8.42 bp/min vs. 60.10 ± 9.52 bp/min, $P < 0.0001$). In the case of losartan, the most significant changes were: SDNN (43.16 ± 17.27 ms vs. 237.98 ± 118.54 ms, $P = 0.002$), rmSDD (27.09 ± 18.27 ms vs. 46.82 ± 37.71 ms, $P = 0.003$), SD2 (55.18 ± 20.6 vs. 70.67 ± 26.12, $P < 0.019$) and DF2 (0.69 ± 0.21 vs. 0.86 ± 0.25, $P < 0.014$). **Conclusion:** Effects of bisoprolol and losartan were especially manifested among the set of linear HRV parameters. As a consequence of effect of losartan, we singled out the nonlinear parameters SD2 and DF2.

Key words: Bisoprolol, heart rate variability, hypertension, losartan

INTRODUCTION

Heart rate variability (HRV) analysis has become a very popular noninvasive tool of accessing to the function of the autonomic nervous system (ANS).[1] There are number of studies dedicated to impact of hypertension on the HRV parameters.[2-4] We compared the effects of losartan and bisoprolol, which belong to the different classes of drugs for hypertension. Losartan is an effective angiotensin II receptor blocker (ARB) that prevents vasopressor effects of circulating angiotensin II at receptor site on blood vessels, which results in decreased blood pressure.[5,6] This drug is also effective in the treatment of heart failure and in preventing kidney failure. On the other hand, bisoprolol is a beta-blocker and blocks adrenalin and noradrenalin stimulation of β_1 receptors decreasing contractility and heart rate of heart muscle.[7] That results in a reduction of blood pressure, but can also be used as a preventive measure for heart attack and cardiac ischemia.[8] It is known that in most subjects with essential hypertension, the cause of hypertension cannot be detected, but this is usually accompanied by appearance of cardiac autonomic neuropathy (CAN), which manifests itself with impaired function of blood pressure.[9,10] Ewing battery of tests[11] is a reliable tool for determining the presence of CAN, but HRV analysis[12] can also detect the first signs of impaired sympathovagal balance. The linear methods in time and frequency domain could be very efficient. For example, the increase in the values of spectral power in HF band (in normalized units) and mean length of consecutive RR intervals are considered as an improved function of parasympathetic nervous system and good direction in treatment. Taking into account the property of non-stationarity of biosignals, the nonlinear methods were also applied in HRV analysis.[13,14] It was shown that in case of abnormal blood pressure, there exists a decrease in the values of nonlinear parameters, which reflects the loss of complexity in disease.[15,16] Inspired by these studies, we examined the properties of HRV parameters typical for hypertension under both drugs and we have highlighted their similarities and differences.

Access this article online	
Quick Response Code:	Website: www.journals.mui.ac.ir/jrms
	DOI: ***

Address for correspondence: Dr. Goran Keković, Laboratory of Radiation and Environmental Protection, Institute of Nuclear Sciences, "Vinča", University of Belgrade, P.O. Box 522, 11001, Belgrade, Serbia. E-mail: astra678@yahoo.com

Received: 22-11-2011; **Revised:** 28-06-2012; **Accepted:** 12-08-2012

MATERIALS AND METHODS

Subjects and data acquisition

In this quantitative medical study, 60 essential hypertensive subjects with age ranging from 26 to 75 years were included. In both groups, representation of men and women was equal and all subjects were from Serbia, Belgrade region. The first group was treated with bisoprolol (STADA-Hemofarm, Serbia and Germany) and second with losartan (Galenika, Serbia). In all patients, the first recording of ECG signals was performed during supine rest position, without the drug. Thereafter, the daily oral dose 5 mg of bisoprolol was administered to the patients in the first group and daily oral dose of 50 mg of losartan to the patients in the second group. The medical treatment continued and ECG recording was performed after a month in the supine rest position. All recorded time series lasted 12-15 min and we calculated the standard set of linear HRV parameters in time and frequency domain and nonlinear parameters. The Task Force (CNSystems, Graz, Austria) system with 12 leads at sampling frequency of 1000 Hz, was used to monitor beat-to-beat heart rate (HR). Also, we performed 24 h ambulatory blood pressure monitoring in order to identify changes in blood pressure more accurately. The study was approved by the Scientific Ethical Committee of the Clinical Hospital Center "Bežanijska kosa" and all the participants gave written consent in accordance with declaration of Helsinki.

HRV analysis

In this study, we calculated a set of linear HRV parameters by analyzing the file containing the equidistant sampled values of consecutive RR intervals, resampled at 1 Hz with linear interpolation. The calculated parameters in time domain were: Mean ($\overline{RR}$) and standard deviations (SD) of RR intervals, percentage of RR intervals that vary more than 50 ms (pNN50) and square root of the mean of the squares of differences between consecutive RR intervals (rMSSD). Also, we obtained power spectra of consecutive RR intervals by using fast fourier transform (FFT) of 256 points, (this corresponds to 256 s in time domain and overlap between gliding Hamming windows was 50%). Three characteristic frequency bands were analyzed: VLF band (0.003 Hz-0.04 Hz), LF band (0.04 Hz-0.15 Hz) and HF band (0.16 Hz-0.5 Hz). The spectral power of these frequency bands LF (%), HF (%) was expressed in normalized units,[10] and ratio *LF*/*HF* was calculated as an important marker of sympathovagal balance. Also, we determined the average spectral power in the corresponding frequency bands: VLF (ms^2), LF (ms^2), HF (ms^2) and total spectral power, TP (ms^2). The nonlinear properties of recorded ECG signals were analyzed by the various nonlinear parameters: Approximate entropy (ApEn), SD1 and SD2, which defines Poincaré plot, as well, DF1 and DF2 parameters obtained from detrended fluctuation analysis (DFA) method. The parameter ApEn[17] indicates the degree of regularity and predictability of time series. The lower values of ApEn usually refer to more predictable and regular time series, while more random time series lead to higher values of ApEn. Detrended fluctuation analysis[18] describes fractal properties of time series. Both scaling exponents: Short term DFA_1 (3-16 beats) and long term DFA_2 (>16 beats) point to short and large correlations of the signals. The higher values of scaling exponents indicate higher degree of self-similarity of time series.

Finally, we calculated ratio SD1/SD2 defined on Poincaré plot, as another measure of sympathetic modulation. The parameter SD1 is related to fast changes between two consecutive heart beats, while SD2 describes long-term variability in time series.

Statistical analysis

All results in this work were expressed as a Mean ± SD and nonparametric Mann-Whitney U-test was used to perform pair-wise testing for significant differences of HRV parameters between two groups.[19] The standard value of $P < 0.05$ was considered significant. In order to perform statistical tests, we used the commercial software SPSS (IBM software, USA, version 11.5).

RESULTS

We summarized all the relevant results concerning the values of linear HRV parameters in Table 1, while the values of nonlinear HRV parameters are given in Table 2. The group averaged values of the HRV parameters are given in these tables. The values before the administration of bisoprolol and losartan are given in the second and third column. The values of corresponding HRV parameters after a month of therapy with bisoprolol and losartan are given in the fifth and sixth column, respectively. The values of statistical probability ('*P*' value) obtained from Mann-Whitney test are given in the fourth, seventh and eighth column. The values of blood pressure were obtained by Holter monitoring. The group averaged values of systolic and diastolic blood pressure were: (137.85 ± 12.20 mmHg, 82.79 ± 8.58 mmHg) before and (126.65 ± 11.71 mmHg, 77.29 ± 9.02 mmHg) after the treatment in the case of bisoprolol. In the case of losartan, those values were (130.91 ± 12.39 mmHg, 81.00 ± 9.25 mmHg) before and (124.15 ± 12.25 mmHg, 77.27 ± 9.15 mmHg) after the treatment.

DISCUSSION

The first and logical step in conducting the effects of bisoprolol and losartan is the analysis of linear HRV parameters in the frequency domain, since, they represent

Table 1: The average values of linear HRV parameters and *P* values of statistical test

HRV parameter	Before bisoprolol	Before losartan	'*P*' value between groups before intervention	After a month of treatment with bisoprolol	After a month of treatment with losartan	'*P*' value in the case of bisoprolol (before and after follow up)	'*P*' value in the case of losartan (before and after follow up)
RR (ms)	870.2±105.7	856.93±144.77	0.99	1027.2±150.0	876.68±125.76	<0.0001	0.11
HR (bp/min)	70.81±8.42	73.21±12.97	0.96	60.10±9.52	70.29±10.35	<0.0001	0.45
HF (%)	37.21±24.46	31.35±18.45	1.0	48.97±16.73	40.74±31.35	0.025	0.23
LF (%)	62.79±24.46	69.65±21.56	0.38	51.03±16.73	59.26±23.68	0.025	0.23
VLF (ms^2)	127.23±81.75	73.62±42.78	0.73	54.44±44.77	90.93±47.86	0.0008	0.59
LF (ms^2)	357.96±251.37	183.32±160.78	0.49	182.39±125.68	163.52±115.26	0.12	0.15
HF (ms^2)	783.00±173.75	124.99±105.71	0.54	311.6±275.4	280.16±213.44	0.8	0.17
TP (ms^2)	1814.1±1731.3	1044.6±955.7	0.81	761.3±725.0	863±774.6	<0.0001	0.1
LF/HF	2.76±2.22	3.26±1.99	0.36	1.32±0.97	2.46±2.01	0.025	0.21
SDNN (ms)	80.25±59.51	43.16±17.27	0.1	133.22±103.46	237.98±118.54	0.094	0.002
pNN50 (%)	5.98±5.19	2.49±1.60	0.23	9.50±10.03	4.23±3.98	0.38	0.049
rmSDD (ms)	88.77±82.31	27.09±18.27	0.1	66.32±59.09	46.82±37.71	0.59	0.003

Values are reported as Mean±SD. RR, mean length of RR intervals, HR= Heart rate, rMSSD, square root of the mean of the sum of squares of successive differences between adjacent normal-to-normal intervals, HF: high frequency band, LF= Low frequency band; the average spectral power in the corresponding frequency bands: Very low-VLF (ms^2), low-LF (ms^2), high-HF (ms^2) and total power-TP (ms^2), LF/HF ratio of spectral power of low and high frequency bands, SDNN, standard deviation of the RR intervals, pNN50, percentage of RR intervals that vary more than 50 ms. *P* values of Mann-Whitney test (before and after treatment) for each group separately (bisoprolol, column seven and losartan column eight), $P<0.05$ was considered significant

Table 2: The average values of nonlinear HRV parameters and *P* values of statistical test

HRV parameter	Before bisoprolol	Before losartan	'*P*' value between groups before intervention	After a month of treatment with bisoprolol	After a month of treatment with losartan	'*P*' value in the case of bisoprolol (before and after follow up)	'*P*' value in the case of losartan (before and after follow up)
ApEn	0.75±0.13	0.73±0.12	0.14	0.66±0.11	0.70±0.20	0.018	0.75
SD1 (ms)	62.81±59.47	18.09±13.90	0.1	46.92±41.81	38.45±33.20	0.59	0.11
SD2 (ms)	88.43±44.22	55.18±20.68	0.09	79.17±35.13	70.67±26.12	0.53	<0.019
SD1/SD2	0.56±0.43	0.32±0.17	0.25	0.57±0.31	0.51±0.34	0.28	<0.015
DF1	1.00±0.38	1.23±0.30	0.18	0.93±0.23	0.99±0.40	0.33W	0.11
DF2	0.72±0.23	0.69±0.21	0.74	0.69±0.17	0.86±0.25	0.71	<0.014

Values are reported as Mean±SD. ApEn, aproximate entropy, SD1 and SD2 are parameters (deviations) taken from Poincaré plot, SD1 describes beat to beat (short-term) fluctuation, while SD2 refers to long-term variability of data, DF1 and DF2 are parameters obtained from detrended fluctuation analysis (DFA) method; *P* values of Mann-Whitney test (before and after treatment) for each group separately (bisoprolol, column seven and losartan column eight), $P<0.05$ was considered significant

promising indicators in the treatment of hypertension.[20,21] We calculated set of linear HRV parameters listed in Table 1. The values of parameter LF (%) were reduced in the earliest stages of therapy with both drugs, with statistically significant differences manifested after a month of medical treatment. The group averaged values of this parameter after a month of therapy were lower, in the case of bisoprolol (51.03 ± 16.73%, $P < 0.025$), as well as in the case of losartan (59.26 ± 23.68%, $P = 0.23$) compared to the corresponding baseline values (62.79 ± 24.46%, 69.65 ± 21.56%). In the case of parameter HF (%), the values after a month of administration with bisoprolol (48.97 ± 16.73%, $P < 0.025$) and losartan (40.74 ± 31.35%, $P = 0.23$) were higher than the values before the treatment (37.21 ± 24.46%, 31.35 ± 18.45%). Increasing the values of this parameter improves the function of parasympathetic nervous system,[22] which can be considered, roughly speaking, as a good sign of the medical treatment. Increasing the value of this parameter in the case of bisoprolol is greater than in the case losartan, which can be explained by their different effects on the autonomic nervous system. As an effective beta blocker bisoprolol is blocking secretion of adrenaline and noradrenaline, which directly affects the heart muscle and reduce heart rate. It was reflected in the mean length of RR time series, which is significantly higher after a month of therapy with this drug, (1027.2 ± 150.0 ms, $P < 0.001$), than baseline values (870.2 ± 105.7 ms). Statistically significant differences in this parameter and heart rate did not exist in the case of losartan. The similar result was obtained in the study,[23] where arterial blood pressure, heart rate and dose-response effects on renal perfusion in hypertensive dogs were examined. After 6 weeks of administration with losartan, reduction in arterial pressure, about 10 mm Hg-15 mmHg was found, with no effect on heart rate. This is understandable, having in mind that minor changes in luminal diameter of a vessel has exponential effect on blood flow resistance (Poiseuilles law). As a consequence of the effect of bisoprolol, we noted significant changes in power spectrum of analyzed RR time series, expressed in the values of corresponding HRV parameters. In accordance with this, there was drastic reduction in values of parameter TP that represented total spectral power of RR time series. Its values after one month of bisoprolol therapy (761.3 ± 725.0 ms^2, $P < 0.0001$), were reduced compared to baseline (1814.1 ± 1731.3 ms^2). We

compared the group averaged values of the systolic and diastolic blood pressure after using both drugs. In the case of bisoprolol, the reductions of systolic (~11 mmHg) and diastolic (~6 mmHg) blood pressure were significantly higher than in the case of losartan (~7 mmHg, 3 mmHg). These values of blood pressure were comparable with values reported,[24] where one-daily oral dose of losartan was evaluated in patients from mild to moderate hypertension. As expected, the changes of ratio LF/HF were consistent with changes in parameters related to the power spectrum of the signal. During the administration of bisoprolol the values of this parameter after a month of therapy (1.32 ± 0.97, $P < 0.025$), were significantly lower than the baseline values (2.76 ± 2.22). These facts indicate the possibility of using this parameter, as a possible indicator of efficiency of therapy with bisoprolol. During administration with losartan, the ratio LF/HF after a month (2.46 ± 2.04, $P = 0.34$), were also lower than the initial (3.40 ± 1.89), but without statistical significance.

The HRV parameters in time domain were especially interesting, because they indicated the differences between bisoprolol and losartan. The parameter SDNN represents variability of RR time series without distinguishing short-term and long-term fluctuations.[14] In the case of bisoprolol, the baseline values of parameter SDNN before therapy (80.25 ± 59.51 ms) were lower than the values after a month (133.22 ± 103.46 ms, $P = 0.094$) of administration of this drug, but without significant differences. On the other hand, after using losartan, the statistical significant differences in the value of this parameter were manifested after a month (237.89 ± 118.54 ms, $P < 0.002$) of administration of this drug and they were higher compared to values before therapy (43.11 ± 17.27 ms). It indicates that the effects of losartan were more pronounced in improving variability of RR intervals. The changes of parameter SDNN in the case of losartan were significantly higher than in the case of bisoprolol. This effect could be explained by role of renin-angiotensin-aldosterone (RAS) system[25,26] responsible for renin secretion, which leads to formation of angiotensin II. It was shown that in the short term regulation of blood pressure RAS reacted through vasoconstrictor mechanisms, while in the long term regulation of blood pressure released aldosterone. Losartan is angiotensin II antagonist, so it is obvious that this drug has significant impact on variability of blood pressure. The changes of parameter pNN50, referred to fast changes between heart beats. The group averaged values of this parameter in the case of losartan were significantly higher (4.23 ± 3.98%, $P < 0.049$), after a month of therapy, compared to baseline values (2.49 ± 1.60%). To the contrary, the significant differences were not manifested after using bisoprolol. Further, the properties of parameter rmSDD depended on the type of applied drug. The group averaged value of this parameter before the administration with bisoprolol (88.77 ± 82.31 ms) was higher then the value after a month (66.32 ± 59.09 ms) of therapy with this drug, without statistical significance. On the other hand, after using losartan the group averaged value of parameter rmSDD after a month (46.82 ± 27.71ms, $P < 0.0027$) was higher than the value before the administration (27.08 ± 18.27 ms). The increase of this parameter and other HRV parameters in time domain was a sign of improving parasympathetic activity[27] (in literature often portrayed as parasympathetic indices). Improving parasympathetic activity indicated efficiency of applied medical treatment of losartan in improving adaptability of patients. In favor of this thesis are the results obtained in the study,[28] where it was proven that losartan attenuated age-related mitochondrial dysfunction of rats, improving the adaptability of living organism.

The statistical significant differences were manifested in the values of approximate entropy ApEn after using the bisoprolol. Namely, after a month of administration of this drug, the final outcome was different, because the values of this parameter were significantly lower (0.66 ± 0.11, $P < 0.018$) compared to value before therapy (0.75 ± 0.13). The decreasing of values of ApEn was a good sign of improving function of autonomic nervous system during treatment with cardiac autonomic neuropathy and diabetes mellitus.[29,30] The effects of losartan was manifested in the values of parameter SD2. This parameter is a marker of long-term variability.[31,32] The group averaged value of this parameter was significantly higher after a month of therapy (70.67 ± 26.12 ms, $P < 0.019$), compared to baseline (55.18 ± 20.68 ms). Also, the values of ratio SD1/SD2 obtained form Poincaré plot were significantly higher after a month of therapy, implicating influence of losartan on the short and long-term variability of RR time series. Another evidence of influence of losartan in long-term variability is the parameter DF2. Increased values of this parameter indicate improving function of ANS.[33] In our case, the group averaged values of parameter DF2, after a month (0.86 ± 0.25, $P < 0.014$), was higher than baseline (0.69 ± 0.21).

CONCLUSIONS

The results presented in this study indicate that HRV analysis is a promising noninvasive method of accessing to the function of ANS. It must be pointed out, that the values of HRV parameters in the treatment of hypertension were highly dependent on the type of the applied drug. In the case of bisoprolol, HRV parameters in frequency domain dominated. We emphasized parameters LF (%), HF (%), LF/HF, RR (ms) and HR (bp/min), because they exhibited statistically significant differences after a month of medical treatment. Also, there is a drastic reduction of spectral total power TP (ms^2) which was detected regardless of the applied drug. On the other hand, under the effects of

losartan HRV parameters in time domain were dominant. These parameters were: SDNN (ms), pNN50 (%) and rmSDD (ms). The changes of these parameters were evidence of improving short an long-term variability of RR series and adaptability of the patients. The effects of both drugs on blood pressure were comparable and very effective, after a month of medical treatment. The group averaged value of systolic blood pressure was decreased about 11 mmHg and about 6 mmHg of diastolic blood pressure, in the case of bisoprolol, while in the case of losartan these values were 7 mmHg and 3 mmHg. Among the cohort of nonlinear parameters, we emphasized approximate entropy (ApEn). The values of this parameter were significantly reduced after a month of medical treatment with bisoprolol. In the case of losartan, statistically significant changes were manifested in the values of parameter DF2 which is the marker of parasympathetic activity.

Both drugs effectively regulate blood pressure, through different HRV markers due to different mechanism of action in the treatment of hypertension. The obtained results should be tested in various groups of essential hypertensive patients depending on gender, age, obesity-related hypertension, other types of diseases, etc.

ACKNOWLEDGMENT

This study was supported by the Ministry of Science and Technological Development of Republic of Serbia (Project 171028).

REFERENCES

1. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.
2. Sevre K, Lefrandt JD, Nordby G, Os I, Mulder M, Gans RO, *et al*. Autonomic function in hypertensive and normotensive subjects: The importance of gender. Hypertension 2001;37:1351-6.
3. Ding W, Zhou L, Bao Y, Zhou L, Yang Y, Lu B, *et al*. Autonomic nervous function and baroreflex sensitivity in hypertensive diabetic patients. Acta Cardiol 2011;66:465-70.
4. Milovanovic B, Trifunovic D, Djuric D. Autonomic nervous system adjustment (ANSA) in patients with hypertension treated with enalapril. Acta Physiol Hung 2011;98:71-84.
5. Schiffrin EL, Park JB, Intengan HD, Touyz RM. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. Circulation 2000;101:1653-9.
6. Carr AA, Prisant LM. Losartan: First of a new class of angiotensin antagonists for the management of hypertension. J Clin Pharmacol 1996;36:3-12.
7. Amabile G, Serradimigni A. Comparison of bisoprolol with nifedipine for treatment of essential hypertension in the elderly: Comparative double-blind trial. Eur Heart J 1987;8:65-9.
8. Konishi M, Haraguchi G, Kimura S, Inagaki H, Kawabata M, Hachiya H, *et al*. Comparative effects of carvedilol vs bisoprolol for severe congestive heart failure. Circ J 2010;74:1127-34.
9. Salo TM, Viikari JS, Antila KJ, Voipio-Pulkki LM, Jalonen JO, Välimäki IA. Antihypertensive treatment and heart rate variability in diabetic patients: Role of cardiac autonomic neuropathy. J Auton Nerv Syst 1996;60:61-70.
10. Khandoker AH, Jelinek HF, Palaniswami M. Identifying diabetic patients with cardiac autonomic neuropathy by heart rate complexity analysis. Biomed Eng Online 2009;8:3.
11. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8:491-8.
12. Kors JA, Swenne CA, Greiser KH. Cardiovascular disease, risk factors, and heart rate variability in the general population. J Electrocardiol 2007;40:19-21.
13. Yeh RG, Chen GJ, Shieh JS, Kuo CH. Parameter investigation of detrended fluctuation analysis for short-term human heart rate variability. JMBE 2009;30:277-82.
14. Yulmetyev R, Hänggi P, Gafarov F. Quantification of heart rate variability by discrete nonstationary non-Markov stochastic processes. Phys Rev E 2002;5:1-15.
15. Goldberger AL. Fractal variability versus pathologic periodicity: Complexity loss and stereotypy in disease. Perspect Biol Med 1997;40:543-61.
16. Vaillancourt DE, Newell KM. Changing complexity in human behavior and physiology through aging and disease. Neurobiol Aging 2002;23:1-11.
17. Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender- and age-related differences in heart rate dynamics: Are women more complex than men? J Am Coll Cardiol 1994;24:1700-7.
18. Xu L, Ivanov PCh, Hu K, Chen Z, Carbone A, Stanley HE. Quantifying signals with power-law correlations: A comparative study of detrended fluctuation analysis and detrended moving average techniques. Phys Rev E Stat Nonlin Soft Matter Phys 2005;71:051101.
19. Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Stat 1947;18:50-60.
20. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability: The Atherosclerosis Risk in Communities (ARIC) study. Hypertension 2003;42:1106-11.
21. Terathongkum S, Pickler RH. Relationships among heart rate variability, hypertension, and relaxation techniques. J Vasc Nurs 2004;22:78-82; quiz 83-4.
22. Burr RL. Interpretation of normalized spectral heart rate variability indices in sleep research: A critical review. Sleep 2007;30:913-9.
23. Bovee KC, Wong PC, Timmermans PB, Thoolen MJ. Effects of the nonpeptide angiotensin II receptor antagonist DuP 753 on blood pressure and renal functions in spontaneously hypertensive PH dogs. Am J Hypertens 1991;4:327-33.
24. Mallion JM, Bradstreet DC, Makris L, Goldberg AI, Halasz S, Sweet CS, *et al*. Antihypertensive efficacy and tolerability of once daily losartan potassium compared with captopril in patients with mild to moderate essential hypertension. J Hypertens Suppl 1995;13:35-41.
25. Campbell DJ, Lawrence AC, Towrie A, Kladis A, Valentijn AJ. Differential regulation of angiotensin peptide levels in plasma and kidney of the rat. Hypertension 1991;18:763-73.
26. Kim S, Tokuyama M, Hosoi M, Yamamoto K. Adrenal and circulating renin-angiotensin system in stroke-prone hypertensive rats. Hypertension 1992;20:280-91.
27. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, *et al*. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: The SUDEP-7 Inventory. Epilepsy Behav 2010;19:78-81.
28. de Cavanagh EM, Piotrkowski B, Basso N, Stella I, Inserra F,

Ferder L, *et al*. Enalapril and losartan attenuate mitochondrial dysfunction in aged rats. FASEB J 2003;17:1096-8.
29. Ahamed VI, Dhanasekaran P, Naseem A, Karthick GN, Jaleel TK, Joseph KP. Quantification of heart rate variability: A measure based on unique heart rates. Int J Biol Sci 2008;4:201-4.
30. Kitlas A, Oczeretko E, Kowalewski M, Borowska M, Urban M. Nonlinear dynamics methods in the analysis of the heart rate variability. Roczniki AMB 2005;50:46-7.
31. Kamen PW, Krum H, Tonkin AM. Poincaré plot of heart rate variability allows quantitative display of parasympathetic nervous activity in humans. Clin Sci (Lond) 1996;91:201-8.
32. Javorka M, Javorková J, Tonhajzerová 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;25:119-27.
33. Acharya UR, Kannathal N, Sing OW, Ping LY, Chua T. Heart rate analysis in normal subjects of various age groups. Biomed Eng Online 2004;3:24.

How to cite this article: Keković G, Milovanović B, Davidović D, Raković D, Ćulić M. Comparative effect of bisoprolol and losartan in the treatment of essential hypertension. J Res Med Sci 2012;17:1027-32.

Source of Support: Nil, **Conflict of Interest:** None declared.