EFFECT OF SPIRONOLACTONE ON HEART RATE VARIABILITY (HRV) IN DIABETIC PATIENTS

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Abstract

INTRODUCTION: Diabetes mellitus is the most common metabolic and endocrine disease. Depressed Heart Rate Variability (HRV) is an early warning sign of diabetic neuropathy. In numerous studies, spironolactone improved HRV and decreased mortality in Congestive Heart Failure (CHF). This study was performed to assess the effect of spironolactone on HRV in diabetic patients.

METHODS: This prospective, randomized, double-blind clinical trial was performed on 62 diabetic patients with autonomic neuropathy at Isfahan Cardiovascular Research Center. Baseline HRV was measured with time domain and frequency domain methods using a Valiance system manufactured by US Biomedical Systems Inc. (2000). The patients were then randomly placed in case and control groups. The control group was given placebo and the case group was given 25mg spironolactone twice daily for two months. HRV was measured at the end of this period and data were analyzed using SPSS. HRV before and after medication was compared with t-test, paired t-test, Wilcoxon test, and Mann-Whitney test.

RESULTS: Twenty-nine patients in the control group and thirty-three patients in the case group were assessed. HRV was measured before and after the study. T-test and Mann-Whitney test revealed no significant difference between HRV in the two groups. Paired t-test and Wilcoxon test did not show any significant difference of HRV within the two groups.

DISCUSSION: In this study, spironolactone did not improve HRV in diabetic patients.

Keywords • Heart Rate Variability (HRV) • Congestive Heart Failure (CHF) • Diabetes Mellitus • Mortality • Neuropathy

ARYA Journal, 2005, 1(2): 80-84

Introduction

Diabetes, formerly thought of as a problem of glucose metabolism, produces most of its harm by effects on the cardiovascular system. In the coming decades, the burden of cardiovascular diseases (CVD) related to diabetes will increase substantially.[1-3]

Cardiovascular Autonomic Neuropathy (CAN) probably contributes to the poor prognosis of CVD in both type I and type II diabetes mellitus.

Patients with CAN come to clinical attention with complaints of postural hypotension, resting tachycardia, exercise intolerance, or painless myocardial ischemia.[4]

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The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death.[5-8] Experimental evidence for an association between propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity has spurred efforts for the development of quantitative markers of autonomic activity.[9] Heart Rate Variability (HRV) represents one of the most promising such markers.[10] In a large group of type I and II diabetic subjects, HRV on 24-hour ambulatory EKG showed abnormalities in nearly 50 percent of diabetics.[11] Loss of HRV in diabetic autonomic neuropathy is associated with up to 50% mortality rate within five years of the onset of clinical symptoms.[12] HRV has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals.

The variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the Time Domain Methods, which include these parameters: Standard deviation of NN interval (SDANN), standard deviation of average NN interval (SD ANN), square root of the mean squared difference of successive NN intervals (RMSSD), and HRV triangular index.

Other methods are Frequency Domain Methods, which include the following: High frequency (HF), Low Frequency (LF), Very Low Frequency (VLF), and Ultra Low Frequency (ULF). The results of the frequency domain analysis are equivalent to those of the time domain analysis, which is easier to perform. Numerous studies have shown that spironolactone improves HRV in CHF, but the effect of spironolactone on HRV in diabetic patients is not well-defined. This study was performed to assess the effect of spironolactone on HRV in diabetic patients.

Materials and methods

This prospective, randomized, double-blind, clinical trial was performed at Isfahan Cardiovascular Research Center between August 2004 and November 2004. One-hundred diabetic patients with fasting plasma glucose (FBS) ≥ 126 mg/dl were screened for diabetic neuropathy. A variety of tests can assess autonomic neuropathy, the simplest of which are as follows: Immediate heart rate response to standing is tested by measuring the R-R interval at the 15th and 30th beats after the patient rises from a supine to an upright posture. The result is reported as the 30th:15th ratio. Normal ratio is ≥ 1.04, borderline ratio is 1.01-1.03, and a ratio ≤ 1 suggests autonomic neuropathy.[13] Inclusion criteria were the presence of diabetic neuropathy, serum potassium levels lower than 5 mmol/l, serum creatinine levels lower than 2 mg/dl, no arrhythmias such as supraventricular tachycardia (SVT), no premature atrial complex (PAC) > 6 minutes, no premature ventricular complex (PVC) > 6 minutes, no atrial fibrillation (AF) in EKG, no bundle branch block (BBB) in EKG, ejection fraction (EF) ≥ 55% in echocardiography, and no myocardial infarction (MI) within the last year as evidenced by EKG.

Eighty diabetic patients (61 females, 19 males) with autonomic neuropathy (30th:15th RR ratio≤1) between the ages of 23 and 74 years were selected. Their cardiovascular risk factors, hypertension, hyperlipidemia, cigarette smoking, positive family history of ischemic heart disease (IHD) and insulin therapy were evaluated. The patients continued their other drugs.

Baseline HRV was measured using a Valiance system manufactured by US Biomedical Systems (BMS) (2000) under equivalent conditions (supine position) using time domain and frequency domain methods. The patients were then randomly placed in case and control groups.

The control group (32 females, 8males) was given placebo and the case group (29 females, 11 males) was given 25 mg spironolactone twice daily for two months. HRV was measured at the end of the study and data were analyzed in SPSS. HRV was compared by t-test and Mann Whitney test between two groups. HRV was compared by paired t-test and Wilcoxon test within each of the two groups. Age was compared by t-test; cardiovascular risk factors and sex were compared by chi-square test and the observed difference was significant (P<0.05).

Results

HRV of 29 patients in the control group and 33 patients in the case group were measured and followed up. Eighteen patients were not referred for HRV measurement due to interrupting their medication. Baseline demographic characteristics and cardiovascular risk factors are presented in table 1. The two groups were not significantly different, except in insulin therapy.

TABLE 1. Baseline demographic characteristics and cardiovascular risk factors of patients

characteristics	Spironolactone group N= 33(%)	Placebo group N=29(%)	P Value
Age(mean ±SD)	54±9.51	51.20 ± 11/03	* 0.148
Male	9 (27.3%)	7 (24.1%)	** 0.77
Female	24 (72.7%)	22 (75.9%)	** 0.77
Hypertension	13 (39.4%)	14 (48.3%)	** 0.48
Hyperlipidemia	21 (63.6%)	14 (48.3%)	** 0.22
History of cigarette smoking	2 (6.1%)	2 (6.9%)	** 0.89
Family history of (IHD)	7 (21.2%)	8 (27.6%)	** 0.55
Insulin therapy	6 (18.2%)	14 (48.3%)	** P<0/05

(IHD: Ischemic Heart disease), * by t-test, ** by chi-square test

TABLE 2. Comparison of mean HRV parameters between two groups before and after medication

Methods	HRV parameters	Spironolactone group	Placebo group	T test	Mann-Whitney test
		mean	mean	P value	P value
Time domain	$SDNN_1$	112.6 ± 183.36	57.05 ±57.60	0.06	0.23
	$SDNN_2$	61.36 ±48.51	66.67 ±74.92	0.36	0.19
	$RMSSD_1$	127.86 ±236.03	58.96 ±78.36	0.06	0.35
	$RMSSD_2$	67.58 ±69.62	78.86 ±10.4.66	0.30	0.40
	HRV triangular $index_1$	8.98 ±5.98	8.61 ±4.09	0.38	0.26
	HRV triangular $index_2$	8.80 ±4.45	8.05 ±5.02	0.26	0.09
Frequency domain	LF_1	157.89 ±65.24	141.22 ±46.05	0.12	0.15
	LF_2	139.51 ±112.77	141.76 ±67.11	0.44	0.28
	HF_1	163.51 ±112.77	147.17±99.98	0.27	0.31
	HF_2	153.72 ±88.41	159.53 ±93.31	0.40	0.37
	$LF.HF_1$	1.57 ±1.69	1.77 ±1.93	0.38	0.2
	$LF.HF_2$	1.12 ±1.05	1.94 ±3.81	0.12	0.11

1: before medication
2: after medication
SDNN: Standard Deviation of NN interval
RMSSD: Square root of the mean squared difference of successive NN intervals
LF: Low Frequency
HF: High Frequency

TABLE 3. Analysis of t-pair test and Wilcoxon test in HRV parameters within two groups

HRV parameters	t-pair test		Wilcoxon-test	
	Spironolactone group	Placebo group	Spironolactone group	Placebo group
	P value	P value	P value	P value
SDNN	1.51	0.26	0.26	0.33
RMSSD	1.38	0.18	0.39	0.08
HRV triangular index	0.19	0.21	0.43	0.13
Lf	1.40	0.48	0.06	0.32
Hf	0.38	0.31	0.32	0.20

T-test showed no significant difference in mean HRV between the two groups before medication (table 2). At the end of the study, t-test and Mann-Whitney test showed no significant difference in mean HRV between the two groups. Paired t-test and Wilcoxon test showed no significant difference in mean HRV within the two groups (tables 2, 3).

T-test revealed no significant difference of HRV in patients with hypertension, hyperlipidemia, and positive family history of IHD ($P>0.05$). However, t-test showed an increase in Lf/Hf from 2.31±2.12 to 2.41±4.47 ($P<0.05$) in patients receiving insulin. T-test also showed an increase in mean RMSSD from 24.70±16.43 ms to 180.58±107.99 ms in patients with history of cigarette smoking ($P<0.05$).

Discussion

In neuropathy associated with diabetes mellitus characterized by alteration of small nerve fibers, a reduction in time domain parameters of HRV seems not only to carry negative prognostic value, but also to precede the clinical expression of autonomic neuropathy.[14-17] In diabetic patients without evidence of autonomic neuropathy, reduction of the absolute power of Lf and Hf under a controlled condition was also reported.[16]

HRV was found to be an indicator for long term prognosis after an acute myocardial infarction. The relative risk of death was 5.3 times higher in patients with poor HRV (SDNN<50 ms) than in the patients with good HRV (SDNN>50 ms).[18]

Recent data show that blockage of aldosterone receptors by spironolactone reduces the risk of morbidity and death among patients with severe heart failure.[19] In the Randomized Aldactone Evaluation Study (RALES), 1663 patients with symptomatic heart failure were randomly assigned to spironolactone or placebo groups. Under standard care, the overall risks of death, death due to progressive heart failure, and sudden cardiac death were reduced by approximately 30% in the spironolactone group.[20]

Mehmet Emin Korkmaz et al and Kok-Meng Yee et al, reported that spironolactone improved HRV in patients with CHF.[19,21] The effects of spironolactone on HRV in diabetic patients are not well defined.

In our study, spironolactone decreased mean HRV parameters and placebo increased mean HRV, both by time domain and frequency domain. However, these differences were not significant (table 2). These results are unlike those of previous studies in CHF patients. This can be due to wide dispersion of HRV parameters. Nonetheless, spironolactone increased RMSSD in patients with history of cigarette smoking ($P< 0.05$) and increased Lf/Hf in patients receiving insulin ($P<0.05$).

This study suggests that spironolactone may have a positive effect on HRV in cigarette smoking diabetics and insulin therapy or probably spironolactone can be harmful in diabetic patients and may increase the rate of mortality or sudden cardiac death. Further studies with larger sample sizes are warranted.

References

1. Libby P, Rabbanil, Brogi E, et al: The challenge of diabetic vascular disease. In Bagdade J(ed): Year Book of Endocrinology. St Louis, Mosby, 1993.

2. Grundy SM, Benjamin IJ, Burke GL, et al: diabetes and cardiovascular disease: A statement for healthcare professionals From the American Heart Association. Circulation 1999; 100:1134-1146.

3. Friesinger GC 2nd, Gavin JA 3rd: Diabetes and cardiologists: A call to action. J Am coll cardiol 2000;35:1130-1133.

4. Richard W, Nesto Peterlibby. Diabetes Mellitus and the cardiovascular system A text book of cardiovascular medicine 6th Edition Philadelphia: WB Saunders company 2001;2133-2150.

5. Lown B, Verrier RL. Neural activity and ventricular fibrillation. N Engl J Med. 1976;294:1165-1170.

6. Corr PB. Yamado KA, Withkowski FX, Mechanisms controlling cardiac autonomic Function their relation to arrhythmogenesis. In: Fozzard HA, Haber E, Jennings RB, Katz AN, Morgan HF, eds. The Heart and cardiovascular system. New York, Nr: Raven press; 1986:1343-1403.

7. Schwortz PJ, Priori SG, sympathetic nervous system and cardiac arrhythmias. In: Zipes DP. Jalife J, eds. Cardiac Electrophysiology: From cell to Bedside. Philadelphia, pa: WB Saunders CO; 1990:330-343.

8. Levy MN, Schwartz PJ, eds. Vagal control of the Heart: Experimental Basis and clinical Implications. Armonk, NY: Futura:1994.

9. Task Force of the European society of cardiology, and the North American Society of pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043-65.

10. Dreifus LS, Agarwal JB, Botvinick EM, et al. Heart rate variability for risk stratification of life threatening arrhythmias. J Am coll cardiol. 1993;22:948-950.

11. Ewing DJ, Neilson JM, Shapiro CM, et al: twenty four hour heart rate variability: Effects of posture, sleep and time of day in healthy controls and comparison with bedside tests of autonomic Function in diabetic patients. Br Heart J 1991;65:230-244.

12. Ewing DJ, Campbell IW, Clarke BF: The Natural History of Diabetic Neuropathy. Quarterly Journal of Medicine 1980;49(193):65-108.

13. Dyberg T, Benn J, Christiansen JS, et al. Prevalence of diabetic autonomic neuropathy measured by simple bedside test 1981;20:190-194.

14. Ewing DJ, Neilson JMM, Traus P. New method for assessing cardiac parasympathetic activity using 24. hour electro cardiogram. Br Heart J. 1984;52:396-402.

15. Kitney RI, Byrne S, Edmonds ME, Watkins PJ, Roberts VC Heart rate variability in the assessment of autonomic diabetic neuropathy. Automedica. 1982;4:155-167.

16. Pagan M, Malfatto G, Pierine S et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. J Auton Nerv syst 1988;23:143-153.

17. Freeman R, Saul JP, Roberts MS et al. Spectral analysis of heart rate in the diabetic neuropathy. Arch Neurol. 1991;48:185-190.

18. Bigger JT, Steinman RC, Rolnitzky LM et al. Power Law behavior of RR-interval variability in healthy middle- aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. Circulation. 1996;63:2142-51.

19. Mehmet Emin Korkmaz, Haldun Muderrisoglu, Melek Ulucam, Bulent Ozin. Effects of spironolactone on heart rate variability and left ventricular systolic Function in sever ischemic heart failure. AM J Cardiol. 2000;86:649-653.
20. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with sever heart Failure. N Engl J Med 1993;341:709-717.
21. Kok-Meng Yec, MR CP, Stuart D, Pringle MD, FRCP, Allan D, Struthers, MD, FRCP, FESC. Circadian variation in the effects of Aldosterone blockade on heart rate variability and QT Dispersion in congestive heart failure. AM J coll cardiol. 2001;37:1800-7.