

Heart Rate Variability Non-Linear Analysis by Poincare Plot in the Complete Glycemic Spectrum

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ABSTRACT

Background: Prevalence of autonomic dysfunction in diabetes imposes marked cardiovascular risk in them. Heart rate variability (HRV) denotes the status of cardiovascular health. The present study was undertaken to study HRV using Poincare plot in the complete glycemic spectrum.

Materials and Method: We grouped the participants of either gender in the age group of 30-50 years based on their glycemic status and family history into four groups - 1. Normoglycemic subjects without family history of diabetes (control), 2. First degree relatives of diabetes, 3. Prediabetes, and 4. diabetes. We measured anthropometric variables, blood pressure and heart rate. We recorded lead II ECG and analyzed the RR interval using Poincare plot method. Groups were compared using one-way ANOVA followed by Bonferroni correction post-hoc analysis

Results : We observed that Poincare plot values such as SD1, SD2, SD1/SD2 ratio and S showed decreasing order as follows Control > FDRD > prediabetes > diabetes

Conclusion: heart rate variability decreases as the blood glucose value increases or even if you at risk for diabetes as with first degree relatives of diabetes.

Keywords: HRV, Poincare plot, autonomic dysfunction, glycemic spectrum, diabetes, T2DM

INTRODUCTION

Diabetes is a prevalent disease and major medical health burden. The incidence of type 2 diabetes mellitus is increasing globally. It is predicted that by the year 2025, diabetes incidence will increase two times than the year of 2000 ⁽¹⁾. Diabetes has been associated with cardiovascular autonomic dysfunction in the form of vagal withdrawal and increased sympathetic tone

subsequently causing sympathetic denervation ⁽²⁻⁴⁾.

Heart rate variability (HRV) is a non-invasive tool to assess the cardiac autonomic function ⁽⁵⁾. Conventionally, there are two methods for HRV analysis, linear and non-linear methods. Heart rate (HR) regulation by autonomic nervous system engages complex interactions between electrophysiological, humoral and hemodynamic parameters ⁽⁶⁾. In this view, heart rate is known to have nonlinear trends ⁽⁷⁻⁹⁾. Nonlinear analysis of HRV have been documented to evaluate the quality, scaling and correlation characteristics of the signals of variability and they do not assess the magnitude of variability ⁽¹⁰⁾. Non-linear method reflects interactions of central neural and autonomic nervous system ⁽⁵⁾. Poincare plot is a non-linear component which reflects the non-linear dynamics of HRV ⁽¹¹⁾ and entire RR time series in a single

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diagram⁽¹²⁾. This approach of HRV quantification have recently emerged to disclose the non-linear alterations in heart rate which is not obvious. Many method of calculation have been suggested by many researchers for calculating Poincare plot⁽¹³⁻¹⁵⁾. But, in this study we will present the Poincare plot scatter gram of our study group.

Many studies have assessed the linear methods in glycemic spectrum⁽¹⁶⁻¹⁸⁾ but, no studies have assessed the nonlinear dynamics of HRV in complete glycemic spectrum. Therefore, in this study, we assessed especially the nonlinear dynamics of HRV using Poincare plot in complete glycemic spectrum.

MATERIALS METHOD

The present study is cross-sectional comparative study. After obtaining scientific and ethics committee approval. We screened volunteer subjects willing to participate in our study for their glycemic status using oral glucose tolerance test after obtaining written informed consent. Subjects with age between 30 to 50 years of either gender has been included for our study. We classified the participants into four groups based on their glycemic status and family history of diabetes – 1. normoglycemic non-first-degree relatives of diabetes (n=50), 2. first-degree relatives of diabetes (n=50), 3. Prediabetes (Fasting plasma glucose >100mg/dL and <125 mg/dL) (n=50) and 4. diabetes (n=50). We excluded subjects with any organic disease or smoking or overweight or morbid obesity or hypertension or under insulin treatment. Recording for female subjects was done during follicular phase of their reproductive cycle to avoid the influence of sympathetic overactivity during luteal phase^(19,20).

Patient preparation: Subjects were requested to report to Obesity research laboratory of physiology department at between 8 AM- 11AM. On the day of recording, we have asked the subject to come with light breakfast, we also instructed them to avoid caffeinated beverages (12 hours before the test), nicotine (12 hours before the test) and vigorous physical activity. We maintained thermoneutral temperature (25°C) throughout the procedure. The procedure of recording lead II ECG was explained, and lab orientation was given prior to the recording to alleviate anxiety.

We measured their height (cm), weight (Kg), resting heart rate, systolic blood pressure (SBP) and diastolic

blood pressure (DBP). We measured subjects, height (cm) using wall mounted stadiometer (VM electronics Hardware Ltd), weight (Kg) using digital weighing machine (Charder Electronic Co Ltd, Taichung, Taiwan 2013) and they were asked to take rest for 10 minutes in sitting position. Following which, we recorded resting heart rate and blood pressure using automated blood pressure monitor (Omron, HEM 7203 model, (Omron Healthcare Co., Kyoto, Japan).

Poincare plot: We followed guidelines formulated by Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology⁽⁵⁾. After 5 minutes of supine rest, lead II electrocardiography (ECG) was recorded for 5 minutes. The conversion of analog to digital signal was done using 16 bit, 16- channel data acquisition system with Acqknowledge 3.8.2 software (Biopac MP36, USA). The sampling rate was 500 Hz and band pass filter of 2 Hz to 40 Hz was used. From the RR tachogram Poincare plot analysis was computed using Kubios 1.0 software (Bio-signal analysis Group, Finland) and the following parameters were noted.

SD1 is the standard deviation of short-term instantaneous beat-to- beat RR interval variability (minor axis of the ellipse in the diagram)

SD2 is the standard deviation of the long-term R-R interval variability (major axis of the ellipse in the diagram)^(21,22)

S: is the area of the ellipse which is the product of π , SD1, SD2. This reflects the overall dispersion and thereby the total HRV⁽²³⁾

SD1/SD2: Represents randomness of HR^(24,25)

SD2/SD1: Correlates with LF/HF ratio. The ratio was positively correlated with Low Frequency (LF) and negatively correlated with High Frequency (HF)⁽²⁶⁾.

Statistical analysis: All the data were tested for normality. All parameters were normally distributed and are expressed as mean \pm standard deviation. Comparison between groups were done using One-way ANOVA followed by posthoc test using bonferroni correction. All analyses were two-tailed and a significance level of $p < 0.05$ was used in the study.

RESULTS

Table 1: Comparison cardiovascular parameters across the glycemc spectrum

	Control	FDRD	Prediabetes	Diabetes	p value
	Mean ±SD	Mean ± SD	Mean ± SD	Mean ± SD	
HR (beats per minute)	72.60 ± 9.15	75.60 ± 9.90	79.88 ± 12.38	80.12 ± 9.63	.001
SBP (mm Hg)	105.24 ± 8.02	103.14 ± 9.22	104.34 ± 8.97	104.18 ± 9.85	.715
DBP (mm Hg)	80.76 ± 3.59	81.04 ± 3.53	80.20 ± 3.26	80.26 ± 3.72	.581

Values are expressed in Mean ± SD. Statistical analysis was done using one-way ANOVA.FDRD-First degree relatives of diabetes, HR-Heart rate, SBP- Systolic blood pressure, DBP- Diastolic blood pressure.

Table 2: Comparison of nonlinear dynamics of heart rate variability across the glycemc spectrum

Poincare plot parameters	Control	FDRD	Prediabetes	Diabetes	p value
	Mean ±SD	Mean ± SD	Mean ± SD	Mean ± SD	
SD1	52.80±42.80	31.72±18.66	24.40 ± 19.13	17.75 ± 14.40	<.001
SD2	86.21 ± 43.17	63.66 ± 30.57	48.49 ± 28.60	44.94 ± 27.24	<.001
SD1/SD2	0.57 ± 0.18	0.49 ± 0.11	0.48 ± 0.18	0.39 ± 0.14	<.001
SD2/SD1	1.92 ± 0.60	2.18 ± 0.56	2.35 ± 0.80	2.99 ± 1.30	<.001
S	19480.50 ± 31205.73	7936.67 ± 8174.51	5094.41 ± 6292.97	3570.16 ± 6499.01	<.001

Values are expressed in Mean ± SD. Statistical analysis was done using one-way ANOVA. SD1: minor axis of ellipse, SD2: Major axis of ellipse, S is area of the ellipse.

Table 3: Post hoc analysis using Bonferroni correction test for Poincare plot variables

		FDRD	Prediabetes	Diabetes
control	SD1	.001	<.001	<.001
	SD2	.005	<.001	<.001
	SD1/SD2 ratio	.046	.033	<.001
	SD2/SD1 ratio	.821	.087	<.001
	S	.004	<.001	<.001
FDRD	SD1		.989	.051
	SD2		.136	.030
	SD1/SD2 ratio		1.000	.011
	SD2/SD1 ratio		1.000	<.001
	S		1.000	1.000
Prediabetes	SD1			1.000
	SD2			1.000
	SD1/SD2 ratio			.016
	SD2/SD1 ratio			.002
	S			1.000

FDRD-First degree relatives of diabetes, HR-Heart rate, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, SD1:minor axis of ellipse, SD2: Major axis of ellipse. Comparison between the group was done using Bonferroni correction test.

Table 1: Groups were comparable based on systolic and diastolic blood pressure. Heart rate was significantly different among groups based on One-way ANOVA. On post hoc analysis it was observed that HR of control was significantly higher than prediabetes ($p = .003$) and diabetes ($p = .002$) while it was comparable with that of FDRD ($p = .891$). All the other groups were comparable based on HR.

Table 2: Groups were significantly different in all the parameters of Poincare plot analysis (SD1, SD2, SD1/SD2, SD2/SD1, and S) based on one-way ANOVA. We observed that SD1, SD2, S and SD1/SD2 values decrease and SD2/SD1 value increase as we progress in the order of Control group, FDRD, prediabetes and diabetes.

Table 3: On post hoc analysis SD1, SD2, SD1/SD2 ratio, S was significantly higher in control as compared to FDRD, prediabetes and diabetes group, while SD2/SD1 was significantly lower in control group as compared to diabetes alone.

FDRD and prediabetes groups were comparable based on all the parameters. SD1, SD2, SD1/SD2 ratio was significantly higher and SD2/SD1 was significantly lower in FDRD as compared to diabetes group.

SD1/SD2 ratio was significantly higher and SD2/SD1 was significantly lower in prediabetes as compared to diabetes group, while other parameters were comparable.

DISCUSSION

In this study, among the baseline cardiovascular parameters (HR and blood pressure), HR was significantly elevated in prediabetes and diabetes compared to control group. The increase in resting heart rate denotes vagal tone deterioration, because resting HR regulation is influenced by vagal tone⁽²⁷⁾. Comparable blood pressure across the groups denotes sympathetic denervation, across the group is yet to progress, as blood pressure is predominantly regulated by sympathetic tone⁽²⁸⁾.

In the present study, we found that control group

have shown higher S, which is positively correlated with total HRV and SDNN (time-domain variable which reflects parasympathetic activity) among the four groups indicates physiological autonomic homeostasis. A similar finding was reported by Toichi et al⁽²⁶⁾. The significantly lesser S among FDRD, prediabetes and diabetes than control group emphasizes the autonomic dysregulation in these groups.

Bernnan M et al have documented positively association between SD1 and RMSSD (time-domain analysis parameter, which reflects parasympathetic activity) because there was similar mathematical equivalent for these two parameters in spite of their different origin⁽²⁹⁾. Hence, SD1 is similar to RMSSD, which is proven as an index of short-term HRV^(5, 30, 31). We observed higher SD1 in the following order control> FDRD> prediabetes> diabetes, which signifies that parasympathetic tone decreases with hyperglycemia in graded manner⁽³²⁾.

SD2 can be used as a surrogate marker of sympathetic activity because the relationship between SD2 and Low Frequency (LF) (Frequency domain parameter, which denotes sympathetic activity) is double the relationship of SD2 with High Frequency (HF) (Frequency domain parameter, which denotes parasympathetic activity)⁽³³⁾. We observed SD2 decreases in the following order control> FDRD> prediabetes> diabetes, which signifies that sympathetic tone decreases with hyperglycemia in graded manner. This is the consequence of progressive reduction of total HRV as evident by decreased S in the same order, which displays future cardiovascular risk in FDRD, prediabetes and diabetes. This is further supported by SD1/SD2 ratio which also decreases in the following order control> FDRD> prediabetes> diabetes. This shows that decrease in SD1 (parasympathetic) is more than decrease in SD2 (sympathetic) as hyperglycemia progresses resulting in relative sympathetic overactivity.

We found reduced SD1 in FDRD, prediabetes diabetes than apparently healthy subjects and the similar findings (reduced SD1 in diabetes alone) have been documented in a study carried out in UAE⁽³⁴⁾. Also, our study demonstrates higher SD2 in FDRD, prediabetes and diabetes than control group which reflects sympathetic overactivity. Roy Bhaskar et al reported lower SD1 and higher SD 2 in diabetes which is in agreement with our findings⁽³⁵⁾.

Available evidences have reported the similarity of SD2/SD1 ratio with LF/HF ratio (marker of sympathovagal balance) ^(26, 36). Our findings suggest that, SD2/SD1 is significantly more in diabetes than FDRD, prediabetes and control group which indicates sympathetic over activity or vagal tone attenuation. Few researchers use reciprocal of these variables as a tool to assess randomness of the heart rate over sympathovagal balance ^(24, 25). Whereas, in our study, we found significant reduction in SD1/SD2 ratio in FDRD, prediabetes and diabetes than control group which could be due to reduced variability of heart rate among these groups indicating risk for future cardiovascular event. Many studies have demonstrated Poincare plots in diabetes and healthy subject ^(34, 35, 37), but these studies did not studied the entire glycemic spectrum which could have helped to identify the point of deterioration of autonomic homeostasis.

CONCLUSION

Total HRV(s), parasympathetic tone (SD1) and sympathetic tone (SD2) progressively decreases and relative sympathetic tone (SD2/SD1 and SD1/SD2) increases as we progress from normoglycemic controls, positive family history of diabetes, prediabetes to diabetes.

Limitations: Firstly, we studied only modest sample size. Secondly, our study is cross-sectional comparative study. Thirdly, we have done the nonlinear analysis using short-term HRV hence, our findings may not be applicable for long-term recording. Fourth, subgroup analysis was not done based on gender.

Ethical Clearance: We have obtained Institute Ethics committee clearance from JIPMER, Puducherry.

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Conflict of Interest: None declared

Disclosure: We are presenting here only a part of a larger PhD project

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