

## EVALUATION OF ASSOCIATION BETWEEN TIME DOMAIN ANALYSIS OF HEART RATE VARIABILITY WITH GLYCATED HEMOGLOBIN AND DURATION OF TYPE II DIABETES MELLITUS

Aswathy Lloyds<sup>1</sup>, Jiya Michael<sup>2</sup>, Ramesh Sangayya Hiremath<sup>3</sup>, Sruthy Velangupara<sup>4</sup>, Sabu Augustine<sup>5</sup>

Received : 12/05/2023  
Received in revised form : 08/06/2023  
Accepted : 19/06/2023

### Keywords:

cardiac autonomic neuropathy, blood sugar levels, heart rate variability.

### Corresponding Author:

**Dr. Sruthy Velangupara,**  
Email: drsruthyvp@gmail.com

DOI: 10.47009/jamp.2023.5.3.403

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

*Int J Acad Med Pharm*  
2023; 5 (3); 2047-2050



<sup>1</sup>Associate Professor, Department of Physiology, Dr.Somervell Memorial CSI medical College, Thiruvananthapuram, Kerala, India.

<sup>2</sup>Associate Professor, Department of Physiology, Believers Church Medical College Hospital, Thiruvalla, India.

<sup>3</sup>Associate Professor, Department of General Medicine, Rajarajeshwari medical college and Hospital, Bangalore, India.

<sup>4</sup>Assistant Professor- CONS & Endodontics, Department of Dental Surgery, Dr. Somervell Memorial CSI medical College, Thiruvananthapuram, Kerala, India.

<sup>5</sup>Associate Professor, Department of General Medicine, Dr. Somervell Memorial CSI medical College, Thiruvananthapuram, Kerala, India.

### Abstract

**Background:** To evaluate association between time domain analysis of heart rate variability with glycated hemoglobin and duration of type II diabetes mellitus. **Materials and Methods:** Fifty- six adult patients of type II diabetes mellitus of either gender and equal number of healthy controls was selected. As recommended by the task group, HRV values were obtained from a 24-hour Holter electrocardiogram. We examined RR intervals, standard deviations of RR intervals (SDNN), the square root of the mean squared difference of succeeding RR intervals (RMSSD), and the proportion of neighbouring NN intervals that differed by more than 50 ms (pNN50) in the time domain. **Results:** Group I comprised of 36 males and 20 females and group II 29 males and 27 females. The mean HbA1C level in group I was 9.6% and in group II was 5.3%, SBP was 142.6 mm Hg and 118.2 mm Hg, DBP was 76.4 mm Hg and 80.8 mm Hg in group I and II respectively. The mean heart rate was 86.2 beats/min and 74.2 beats/min in group I and II respectively. SDNN was 21.4 ms and 32.5 ms, RMSSD was 18.2 per minute and 22.1 per minute and pNN50 was 1.6% and 3.4% in group I and II respectively. The difference was significant (P< 0.05). There was positive correlation in mean heart rate with both duration of diabetes and HbA1C. **Conclusion:** The detection and screening of cardiac autonomic neuropathy, which is brought on by persistently elevated blood sugar levels, can be done using heart rate variability.

## INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by high blood sugar levels resulting from the body's inability to properly use or produce insulin.<sup>[1]</sup> Insulin is a hormone produced by the pancreas that helps regulate blood sugar (glucose) levels.<sup>[2]</sup> In type 2 diabetes, the body either becomes resistant to the effects of insulin, meaning it does not respond properly to insulin, or it does not produce enough insulin to maintain normal blood sugar levels. This leads to a condition known as hyperglycemia, where blood glucose levels remain consistently elevated.<sup>[3]</sup>

Cardiovascular autonomic neuropathy (CAN) affects many type 2 diabetics yet is occasionally disregarded.<sup>[4]</sup> About 50% of persons with type 2 diabetes have this impairment of the autonomic regulation of the cardiovascular system. Clinically, it could manifest as a myocardial infarction that is quiet. It is well recognised that hypoglycemia can cause cardiovascular problems.<sup>[5]</sup> Although traditional cardiovascular reflex tests remain the gold standard for the evaluation of cardiovascular autonomic neuropathy, measuring heart rate variability (HRV) is one of the simplest and most accurate approaches to evaluate cardiac autonomic neuropathy.<sup>[6]</sup> The HRV measures the difference between two successive heartbeats; the greater the difference, the greater the parasympathetic

activity.<sup>[7]</sup> A high HRV indicates that a person is capable of continual adaptation to microenvironmental changes. Low HRV is a sign of cardiovascular risk as a result.<sup>[8]</sup> We performed this study to assess association between time domain analysis of heart rate variability with glycated hemoglobin and duration of type II diabetes mellitus.

## MATERIALS AND METHODS

A sum total of fifty- six adult patients of type II diabetes mellitus of either gender was selected in this prospective, observational study after seeing the usefulness of the study and gaining endorsement from ethical review committee. Patients' consent was obtained beforehand starting the study.

Data such as name, age, gender etc. was recorded. All patients were selected in group I and group II comprised of equal number of healthy controls. As recommended by the task group, HRV values were obtained from a 24-hour Holter electrocardiogram. We examined RR intervals, standard deviations of RR intervals (SDNN), the square root of the mean squared difference of succeeding RR intervals (RMSSD), and the proportion of neighbouring NN intervals that differed by more than 50 ms (pNN50) in the time domain. While the SDNN is correlated with low-frequency power (LF), the RMSSD and pNN50 are associated with high-frequency power (HF) and therefore parasympathetic activity. By using high performance liquid chromatography, HbA1c levels were calculated. The results were compiled and subjected for statistical analysis using Mann Whitney U test. P value less than 0.05 was set significant.

## RESULTS

**Table 1: Patients distribution**

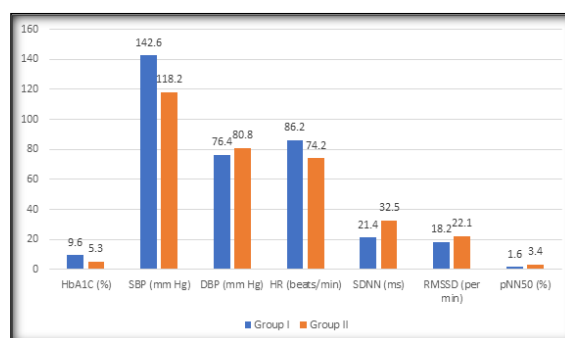
	Group I	Group II
Status	Type II DM	Healthy
Male:Female	36:20	29:27

Group I comprised of 36 males and 20 females and group II 29 males and 27 females (Table I).

**Table 2: Assessment of heart rate variability parameters**

Parameters	Group I	Group II	P value
HbA1C (%)	9.6	5.3	0.01
SBP (mm Hg)	142.6	118.2	0.04
DBP (mm Hg)	76.4	80.8	0.04
HR (beats/min)	86.2	74.2	0.02
SDNN (ms)	21.4	32.5	0.01
RMSSD (per min)	18.2	22.1	0.03
pNN50 (%)	1.6	3.4	0.001

The mean HbA1C level in group I was patients was 9.6% and in group II was 5.3%, SBP was 142.6 mm Hg and 118.2 mm Hg, DBP was 76.4 mm Hg and 80.8 mm Hg in group I and II respectively. The mean heart rate was 86.2 beats/min and 74.2 beats/min in group I and II respectively. SDNN was 21.4 ms and 32.5 ms, RMSSD was 18.2 per minute and 22.1 per minute and pNN50 was 1.6% and 3.4% in group I and II respectively. The difference was significant ( $P < 0.05$ ) (Table II, graph I).



**Table 1: Assessment of heart rate variability parameters**

**Table 3: Correlation of heart rate variability parameters with HbA1C**

Parameters	HR	SDNN	RMSSD	pNN50
HbA1C	0.47	-0.41	-0.46	-0.37
Duration	0.39	-0.26	-0.04	-0.23

There was positive correlation in mean heart rate with both duration of diabetes and HbA1C (Table II).

## DISCUSSION

Heart rate variability (HRV) is the term used to describe the variation in the space between successive heartbeats.<sup>[9]</sup> The interaction between the sympathetic and parasympathetic branches of the autonomic nervous system affects this measurement of the beat-to-beat variations in heart rate.<sup>[10]</sup> Due to a variety of physiological reasons, the heart rate is not constant but rather varies constantly. HRV analysis entails analysing these variations to learn more about how the autonomic nervous system and cardiovascular system are functioning.<sup>[11]</sup>

Hypoglycemia has been proposed to have immediate impacts on inflammation, enhanced platelet and neutrophil activation, endothelial function, and sympathoadrenal activation, all of which have the potential to have negative cardiovascular effects.<sup>[12]</sup> The increased risk of cardiovascular disease (CVD) in hypoglycemic people may also be brought on by cardiac ischemia or lethal arrhythmia during hypoglycemia. Therefore, especially in older patients with type 2 diabetes, hypoglycemia may directly contribute to an elevated risk of CVD and death.<sup>[13]</sup> We performed this study to assess association between time domain analysis of heart rate variability with glycated hemoglobin and duration of type II diabetes mellitus.

In our study, group I comprised of 36 males and 20 females and group II 29 males and 27 females. Benichou T et al.<sup>[14]</sup> included twenty-five case-control studies with 2,932 patients: 1,356 with T2DM and 1,576 healthy controls. T2DM patients had significantly ( $P < 0.01$ ) lower RR-intervals (effect size =  $-0.61$ ; 95%CI  $-1.21$  to  $-0.01$ ), lower SDNN ( $-0.65$ ;  $-0.83$  to  $-0.47$ ), lower RMSSD ( $-0.92$ ;  $-1.37$  to  $-0.47$ ), lower pNN50 ( $-0.46$ ;  $-0.84$  to  $-0.09$ ), lower total power ( $-1.52$ ;  $-2.13$  to  $-0.91$ ), lower LF ( $-1.08$ ;  $-1.46$  to  $-0.69$ ), and lower HF ( $-0.79$ ;  $-1.09$  to  $-0.50$ ). LF/HF did not differ between groups. Levels of blood glucose and HbA1c were associated with several HRV parameters, as well as Time from diagnosis of T2DM.

In our study, the mean HbA1C level in group I was 9.6% and in group II was 5.3%, SBP was 142.6 mm Hg and 118.2 mm Hg, DBP was 76.4 mm Hg and 80.8 mm Hg in group I and II respectively. The mean heart rate was 86.2 beats/min and 74.2 beats/min in group I and II respectively. SDNN was 21.4 ms and 32.5 ms, RMSSD was 18.2 per minute and 22.1 per minute and pNN50 was 1.6% and 3.4% in group I and II respectively. Jaiswal et al.<sup>[15]</sup> in their study, based on their mean A1c over time, subjects were divided into four glycemic control groups: Group 1, optimal (mean A1c, 7.4%); Group 2, average (mean A1c, 7.5-8.4%); Group 3, average (mean A1c, 8.5-9.4%); and Group 4, bad (mean A1c, 9.5%). A linear trend was investigated among these groups. Independent of demographic and conventional CVD risk

variables, there was a 5% drop in the SD of the normal RR interval (SDNN) and a 7% decrease in the root mean square successive difference of the RR interval (RMSSD) for every 1% increase in the average A1c over a six-year period. It was discovered that measures of overall lower HRV and categories of poor glucose control exhibited a dose-response association.

There was positive correlation in mean heart rate with both duration of diabetes and HbA1C. Yun et al.<sup>[16]</sup> investigated whether patients with type 2 diabetes who have a history of prior cardiovascular disease (CVD) are more likely to experience severe hypoglycemia (SH). 60 patients (9.6%) of the 624 participants who underwent follow-up had a history of CVD. Patients with past CVD were older, had longer histories of diabetes and hypertension, required more insulin, and had more diabetic microvascular problems at baseline compared to patients without CVD. 62 individuals (9.9%) had at least one SH episode during follow-up. After correcting for sex, age, the length of diabetes, hypertension, haemoglobin A1c levels, complications from diabetes, cardiovascular autonomic neuropathy, and insulin use, the development of SH was linked to a history of CVD.

## CONCLUSION

The detection and screening of cardiac autonomic neuropathy, which is brought on by persistently elevated blood sugar levels, can be done using heart rate variability.

## REFERENCES

1. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1.9 million people. *Lancet Diabetes Endocrinol.* 2015;3: 105–113.
2. Ponto KA, Koenig J, Peto T, Lamparter J, Raum P, Wild PS, et al. Prevalence of diabetic retinopathy in screening-detected diabetes mellitus: results from the Gutenberg Health Study (GHS). *Diabetologia.* 2016;59: 1913–1919.
3. Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM, et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). *Am J Cardiol.* 2000;86: 309–312.
4. Kim JT, Oh TJ, Lee YA, Bae JH, Kim HJ, Jung HS, Cho YM, Park KS, Lim S, Jang HC, Lee HK. Increasing trend in the number of severe hypoglycemia patients in Korea. *Diabetes Metab J* 2011;35:166-72.
5. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410-8.
6. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 2013;347:4533.
7. Mirza et al. The Association Between Time Domain Analysis Of Heart Rate Variability With Glycated Hemoglobin And Duration Of Type 2 Diabetes Mellitus. *International Journal of Health and Clinical Research,* 2021;4(10):167-170.

8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: A patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;55:1577-96.
9. Ko SH, Kim SR, Kim DJ, Oh SJ, Lee HJ, Shim KH, Woo MH, Kim JY, Kim NH, Kim JT, Kim CH, Kim HJ, Jeong IK, Hong EK, Cho JH, Mok JO, Yoon KH; Committee of Clinical Practice Guidelines, Korean Diabetes Association. 2011 Clinical practice guidelines for type 2 diabetes in Korea. *Diabetes Metab J* 2011;35:431-6.
10. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 2002; 45:937-48.
11. Bloomfield HE, Greer N, Newman D, MacDonald R, Carlyle M, Fitzgerald P, Rutks I, Wilt TJ. Predictors and consequences of severe hypoglycemia in adults with diabetes: a systematic review of the evidence. Washington, DC: Department of Veterans Affairs; 2012. 12.
12. Ginde AA, Espinola JA, Camargo CA Jr. Trends and disparities in U.S. emergency department visits for hypoglycemia, 1993-2005. *Diabetes Care* 2008;31:511-3.
13. Ziegler D, Zentai CP, Perz S, Rathmann W, Haastert B, Döring A, et al. Prediction of mortality using measures of cardiac autonomic dysfunction in the diabetic and nondiabetic population: the MONICA/KORA Augsburg Cohort Study. *Diabetes Care*. 2008;31: 556–561.
14. Jaiswal M, Fingerlin TE, Urbina EM, Wadwa RP, Talton JW, D'Agostino Jr RB, Hamman RF, Daniels SR, Marcovina SM, Dolan LM, Dabelea D. Impact of glycemic control on heart rate variability in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes technology & therapeutics*. 2013 Dec 1;15(12):977-83.
15. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, Dutheil F. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS one*. 2018 Apr 2;13(4):0195166.
16. Yun JS, Ko SH, Ko SH, Song KH, Yoo KD, Yoon KH, Park YM, Ahn YB. Cardiovascular Disease Predicts Severe Hypoglycemia in Patients with Type 2 Diabetes. *Diabetes Metab J*. 2015; 39:498-506.