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Research Article

Heart rate variability in type 2 diabetics

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Abstract

Aim: To assess the autonomic function in type 2 diabetics by evaluating Heart Rate Variability.

Methods: The study was conducted in 80 diabetics and 80 healthy controls, to assess the autonomic control of the heart rate using short term Heart Rate Variability in respect of time domain and frequency domain parameters.

Results: The HRV values such as SDNN, RMSSD, NN50; pNN50; LF; HF, LF/HF were significantly($p<0.05$) reduced in diabetics compared to healthy controls.

Conclusion: This demonstrates that the subclinical autonomic neuropathy may be prevalent in asymptomatic diabetics. Parasympathetic regulation appears to be more significantly affected in the early asymptomatic diabetics. However, this study does not correlate HRV changes with various degrees of glycemic control and different durations of diabetes. More prospective studies in large diabetic populations are required to validate this inference.

Keywords: Heart Rate Variability (HRV), Diabetics, cardiovascular autonomic neuropathy (CAN).

1. Introduction

Thereare 371 million known diabetics at present in the world and by 2030, it is estimated that the numbers will increase to552 million, according to the International Diabetes Federation (IDF). The fact that half the diabetics are undiagnosed yet is more alarming[1]. India is now estimated to have 62.4 million people with diabetes and 77.2 million people with prediabetes.[2] Increased incidence of diabetes has become a major health concern in the modern day society, probably as a by-product of rapid industrialization and sedentary lifestyle.

Cardiovascular autonomic neuropathy (CAN) more strongly predicts major cardiac events than Silent Myocardial Infarction (SMI) itself[3].Patients with type 2 diabetes mellitus, having higher resting heart rate reflecting the deranged autonomic function, have a greater incidence of progressive nephropathy and retinopathy [4]. CAN might be subclinical for several years until the patient develops resting tachycardia, postural hypotension, exercise intolerance, cardiac dysfunction and diabetic cardiomyopathy[5].

Reduced heart rate variability reflects impairment in cardiovascular autonomic function. It is strongly associated with an increased risk of silent myocardial ischemia and mortality[6]. HRV evaluation is a simple and reliable test that reflects autonomic regulation of heart rate.

In the present study, we conducted the HRV evaluation in asymptomatic diabetics and their healthy controls.

2. Materials and Methods

2.1 Study design

80 Type 2 Diabetic males were enrolled in the study from Hoskote, Bangalore rural district. A well informed written consent was obtained after explaining the entire procedure of the study in their own language. Biochemical tests were conducted as per the inclusion and exclusion criteria. Similarly, 80 healthy male control subjects were included in the study after taking their well informed written consent .These study and control subjects were chosen based on the following Inclusion and Exclusion criteria.

2.1 Study Group:

Inclusion Criteria:

1. Males with BMI 22 TO 25.
2. Age: 50 -55 years.
3. Diabetes of < 5years duration.
4. HbA1 c : 7-8%
5. Resting heart rate: 60-80 beats per min.

Exclusion Criteria:

1. Hypertensives.
2. Smokers and / alcoholics.
3. Cardiac complications (arrhythmias , history of Myocardial Infarction)
4. Nephropathy (serum creatinine> 2mg/dl)
5. Endocrine disorders (thyroid, adrenal etc)
6. Those with injuries and painful conditions such as arthritis.
7. Epileptics
8. Psychiatric disorders(depression, manic depressive illness etc)
9. Treatment with drugs like antidepressants, B blockers, antiarrhythmics, ACE inhibitors, thyroid stimulants, anti thyroid drugs.
10. Symptomatic diabetic autonomic neuropathy.
11. Trained athletes.

2.2 Control group

Inclusion Criteria

1. Males with BMI 22 TO 25.
2. Age: 50 -55 years.
3. Resting heart rate: 60-80 beats per min.

Exclusion Criteria

1. Hypertensives.
2. Diabetics.
3. Smokers and / alcoholics.
4. Cardiac complications (arrhythmias , history of Myocardial Infarction)
5. Nephropathy (serum creatinine> 2mg/dl)
6. Endocrine disorders (thyroid, adrenal etc)
7. Those with injuries and painful conditions such as arthritis.
8. Epileptics
9. Psychiatric disorders(depression, manic depressive illness etc)
10. Treatment with drugs like antidepressants, B blockers, antiarrhythmics, ACE inhibitors, thyroid stimulants, anti thyroid drugs.
11. Symptomatic diabetic autonomic neuropathy.
12. Trained athletes.

Ethical clearance for the study was obtained from the institutional ethical committee.

2.3 Methodology

The HRV of the subjects was assessed 2 hours after food and without any caffeinated drinks or strenuous exercise meanwhile. Anthropometric measurements such as height (m), weight (kg) were recorded. Resting blood pressure was measured using a mercury sphygmomanometer. Resting heart rate was recorded. The resting ECG of 5 minutes was recorded in supine posture for all subjects, in lead II, in a state of physical and mental rest in a quiet, adequately illuminated and well ventilated lab. HRV values are derived by the software.

Similar procedure was followed for control subjects.

The HRV equipment used was: RMS, VAGUS .MODEL:

The following HRV parameters were recorded in each subject.

SDNN : Standard Deviation of the Normal to Normal beat R-R interval.

RMSSD : Root Mean Square of the Standard Deviations of the Normal to Normal beat R-R intervals.

NN50 : Successive Normal to Normal beat R-R intervals> 50 milliseconds.

pNN50 : Proportion of Normal to Normal beat R-R intervals> 50 milliseconds out of total Normal to Normal beat R-R intervals.

RR interval series was used to estimate the power spectral density (PSD) for the frequency domain methods.

VLF : Very Low Frequency (<0.04Hz): physiological significance unclear yet

LF : Low Frequency (0.04 – 0.1 Hz): reflects both sympathetic as well parasympathetic tone

HF : High Frequency (0.15-0.4): Mainly depicts the parasympathetic component.

For each frequency band, measurements from the PSD Estimate consisted of both absolute and relative power of VLF, LF, and HF bands. LF and HF power bands were normalized

LF / HF : depicts the sympatho- vagal balance.

In short-term HRV recordings, Frequency domain methods are preferred to the time domain methods[6].

2.3 Statistical Analysis

Student t test was used for the statistical analysis of the results obtained. Software used statistical analysis was: Open Epi.

3. Results

Time Domain and .Frequency Domain Parameter values are listed in Tables 1 and 2, respectively.

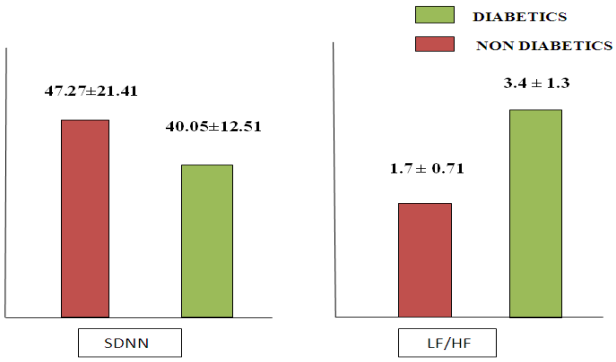
Table 1.Time Domain Parameters

	Diabetics(80)	Controls(80)	Significance
SDNN (ms)	40.05±12.51	45.27±21.41	P<0.05
RMSSD (ms)	22.28±8.74	34.14± 14.72	P<0.01
NN50 (count)	9.02± 1.52	14.91± 3.27	P<0.01
pNN50 (%)	17.34± 2.02	24.51± 4.17	P<0.01

Table 2 .Frequency Domain Parameters

	Diabetics(80)	Controls(80)	Significance
LF (n.u)	69.21±20.72	65.29±19.03	P<0.05
HF(n.u)	21.43± 2.55	34.37± 3.88	P<0.01
LF/HF	3.4 ± 1.3	1.7 ± 0.71	P<0.01

Figure 1.Comparison of SDNN and LF/HF values in Diabetics and Non Diabetics.



The difference in Time Domain and Frequency Domain Parameter values between the diabetics and controls were found to be of statistical significance (p< 0.01).

4. Discussion

Heart rate variability is defined as the oscillation in the intervals between consecutive heart beats. "Time domain" or "frequency domain" methods of measuring the variation in HRV are used. These techniques are complementary to each other. The measures of HRV reflect specific physiological autonomic regulatory activities. For example, the SDNN denotes the total power; both RMSSD and pNN50 reflect the parasympathetic tone as they detect oscillations of high frequency. Parasympathetic blockade reduces all HRV measures significantly.

The HF component is thought to reflect the respiration induced modulation of vagus nerve discharge. The LF and VLF components reflect the variation in R-R interval influenced by more gradual co-ordination between sympathetic and parasympathetic systems[7]. In this study, we have observed that the SDNN values in Diabetics, signifying the total HRV, was significantly reduced ($p<0.05$) as compared to that of the controls. This can be attributed to the greater reduction in the indices signifying the parasympathetic tone such as the RMSSD; NN50; pNN50 ($p<0.01$)as well as the reductions in index reflecting the sympathetic tone, LF ($p<0.05$). This is in concurrence with some of the earlier studies[4] that have shown that there was a decrease in parasympathetic discharge even at rest in diabetics.

Sympathovagal balance is reflected in the ratio of absolute LF to HF power. LF and LF/HF power are increased and time domain measures of HRV are decreased in upright tilt, due to an increased sympathetic tone. It is known that Beta-blockade blunts these changes. Spectral analysis of HRV, using nu or LF-to-HF ratio can quantitatively evaluate graded changes in the Sympathovagal balance[8]. In our study, LF and LF/ HF were significantly increased in diabetics, indicating altered sympathovagal balance due to increased sympathetic activity and decreased parasympathetic tone. The decrease in parasympathetic activity was more significant than altered sympathetic activity.

Many theories have been put forth to explain the pathophysiology of the inflammatory processes in the various sites including the neuronal tissues causing the sympathovagal imbalance in diabetes. A few of them are mentioned here.

Peroxynitrite, produced from the diffusion-controlled reaction between NO (nitric oxide) and, the superoxide anion, another free radical, interacts with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms. These reactions lead to cellular responses of subtle modulations of cell signalling or even overwhelming oxidative injury, causing cellular necrosis or apoptosis. It is also postulated that peroxynitrite generation represents a crucial pathogenic mechanism in conditions such as stroke, chronic heart failure, myocardial infarction and diabetes[9].

Julius *et al* have stated that monocyte nitrosylated protein expression is a new biomarker of metabolic control and inflammation in diabetic subjects with macroangiopathy[10]. It was also found that subclinical inflammation is associated with diabetic polyneuropathy and neuropathic impairments. High levels of C-reactive protein and interleukin (IL)-6 were most consistently associated with diabetic polyneuropathy[11]. It was found that parasympathetic input to adipose tissue clearly modulates its insulin sensitivity and thus, its glucose and Free Fatty Acid metabolism in an anabolic way[12].

Patients with diabetes with cardiac autonomic neuropathy have increased levels of superoxide and peroxynitrite which are few of the markers of oxidative stress in plasma. Adiponectin deficiency and hyperleptinaemia favour sympathetic over activity in diabetics, according to some studies[13]. The protective association between decreased heart rate, increases in HRV indices and incidence of diabetes due to lifestyle changes was found in one of the studies[14].

Autonomic imbalance in the subclinical and asymptomatic stages could be established by analyzing the patterns of heart rate variability. Sympathovagal balance may be affected by Glycaemic Variability (GV) due to increased oxidative stress and also proinflammatory cytokines. Establishing a GV risk profile could be useful in risk factor identification in diabetes patients[15]. It was found that diabetics have significantly lower vagal activity than non-diabetics. Even in non diabetics, serum insulin, and, to a lesser degree, serum glucose level was inversely associated with vagal function, which suggests a role in the pathogenesis of diabetic neuropathy[16].

Rodica *et al* have explained the pathophysiology of autonomic disturbance in CAN in Diabetics as the initial augmentation in cardiac sympathetic activity with subsequent abnormal norepinephrine signalling and metabolism, calcium dependent apoptosis[17] and increased mitochondrial oxidative stress [18]. These may contribute to myocardial injury [19] and may cause cardiac events and sudden death. The sympathetic imbalance associated with CAN may critically influence myocardial substrate utilization[20] and contribute to mitochondrial uncoupling[21] regional ventricular motion abnormalities, functional deficits, and cardiomyopathy[22]. This is probable pathology of CAN in diabetics.

Kotecha *et al* have observed that reduced LF power in HRV strongly associated with angiographic coronary disease[23]. Diabetic CAN, which affects one third of type 2 diabetic patients, results in increased mortality and silent myocardial ischemia and also predicts the development of stroke. CAN was found to be associated with results in postural hypotension, exercise intolerance, severe orthostasis, enhanced intraoperative instability, and a greater incidence of silent MI and ischemia and hence has a poor prognosis[24].

Reduced HRV obtained from short-term predischarge ECG recordings predict increased risk of Sudden Cardiac Death. When considered with depressed LVEF, such predictive power was greatly increased. This would be effective as a simple screening method to identify high risk subjects[25].

The study by Rashba *et al* finds that the nonischemic dilated cardiomyopathy patients with preserved HRV have very good prognosis. It was also noted that patients withseverely depressed HRV and those excluded from HRV analysis because of atrial fibrillation and frequent ventricular ectopy, have the highest risk of mortality[26].

Andrew *et al*, in their meta-analysis study demonstrated that those with decreased heart rate variability (HRV), indicating reduced cardiovascular autonomic function, are at ahigh risk of silent myocardial ischemia and mortality[27].

The DCCT (Diabetes Control and Complications Trial) documented that intensive therapy can slow the progression and the development of abnormal autonomic tests[28]

HRV analysis can detect early subclinical alterations of the autonomic nervous system in asymptomatic patients with IDDM, which seem to consist mainly in a parasympathetic impairment. Autonomic dysfunction is associated both with the duration and an inadequate metabolic control of the disease[29]. Thus short term HRV test could be used as a screening tool for early detection of cardiac autonomic dysfunction at the diabetic clinics. Further studies to validate these inferences in large diabetic populations using short term HRV are required.

5. Conclusion

1. Subclinical cardiac autonomic neuropathy might be prevalent in asymptomatic diabetic individuals as demonstrated by short term HRV tests.
2. Parasympathetic regulation appears to be more significantly affected in the early asymptomatic diabetics.

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References

1. http://www.theglobeandmail.com › Life › Health & Fitness › Health.
2. Anjana RM1, Pradeepa R, Deepa M *et al*, Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research–INdiaDIABetes (ICMR–INDIAB) study. *Diabetologia*. 2011 Dec; 54(12):3022-7. doi: 10.1007/s00125-011-2291-5. Epub 2011 Sep 30.
3. Pual Velensi, Regis Nessim, Sachs *et al*. Predictive Value of Cardiac Autonomic Neuropathy in Diabetic Patients With or Without Silent Myocardial Ischemia**.** *Diabetes Care*. February 2001 vol. 24 no. 2 339-343.

4. Graham S Hillis, Jun Hata, Mark Woodward.Epidemiology: Resting Heart Rate and the Risk of Microvascular Complications in Patients with Type 2 Diabetes Mellitus. *J Am Heart Assoc*.2012**;** 1: e002832
5. Gerasimos Dimitropoulos, Abd A Tahrani, and Martin J Stevens. Cardiac autonomic neuropathy in patients with diabetes mellitus. *World J Diabetes*. Feb 15, 2014; 5(1): 17–39.
6. Aaron I. Vinik, Raelene E. Maser, Braxton D. Mitchell, and Roy Freeman, Diabetic Autonomic Neuropathy. *Diabetes Care* May 2003 vol. 26 no. 5 1553-1579.
7. Marek Malik, Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology: Task Force of Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. *Circulation*. 1996; 93: 1043-1065.
8. N Montano, T G Ruscone, A Porta. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation*. 1994; 90: 1826-1831.
9. Pal Pacher, Joseph S. Beckman, and Lucas Liaudet. Nitric Oxide and Peroxynitrite in Health and Disease. *Physiol Rev*. Jan 2007; 87(1): 315–424.
10. Julius U., Drel V.R., Grabler J., and Obrosova I.G.. Nitrosylated Proteins in Monocytes as a new Marker of Oxidative-Nitrosative Stress in Diabetic Subjects with Macroangiopathy. *Exp Clin Endocrinol Diabetes*. Feb 2009; 117(2): 72–77.
11. Christian Herder, Mark Lankisch, Dan Ziegler, Wolfgang Rathmann Wolfgang Koenig, Thomas Illig *et al*. Subclinical Inflammation and Diabetic Polyneuropathy. *Diabetes Care*. Apr 2009; 32(4): 680–682.
12. Felix Kreier, Eric Fliers, Peter J. Voshol, Corbert G. Van Eden, Louis M. Havekes, Andries Kalsbeek *et al*. Selective parasympathetic innervation of subcutaneous and intra-abdominal fat — functional implications. *J Clin Invest*. Nov 1, 2002; 110(9): 1243–1250.
13. Vinik A I, Maser R E and Ziegler D. Autonomic imbalance: prophet of doom or scope for hope? *Diabet Med*. Jun 2011; 28(6): 643–651.
14. Mercedes R. Carnethon, Ronald J. Prineas, Marinella Temprosa, Zhu-Ming Zhang, Gabriel Uwaifo *et al*. The Association Among Autonomic Nervous System Function, Incident Diabetes, and Intervention Arm in the Diabetes Prevention Program. *Diabetes Care*. Apr 2006; 29(4): 914–919.
15. Fleischer J. Diabetic autonomic imbalance and glycemic variability. *J Diabetes Sci Technol*. 2012 Sep 1; 6(5):1207-15.
16. Liao D, Cai J, Brancati FL, Folsom A, Barnes RW, Tyroler HA, Heiss G. Association of vagal tone with serum insulin, glucose, and diabetes mellitus--The ARIC Study. *Diabetes Res Clin Pract*. 1995 Dec; 30(3):211-21.
17. Iwai-Kanai E, Hasegawa K, Araki M, Kakita T, Morimoto T, Sasayama S. alpha- and beta-adrenergic pathways differentially regulate cell type-specific apoptosis in rat cardiac myocytes. *Circulation* 1999; 100: 305– 311
18. Givertz MM, Sawyer DB, Colucci W. Antioxidants and myocardial contractility: illuminating the "Dark Side" of beta-adrenergic receptor activation? *Circulation* 2001; 103: 782– 783.
19. Paulson DJ, Light KE .Elevation of serum and ventricular norepinephrine content in the diabetic rat. *Res Commun Chem Pathol Pharmacol* 1981; 33: 559– 562.
20. Drake-Holland AJ, Vand V, Roemen TH, Hynd JW, Mansaray M, Wright ZM, Noble MI.Chronic catecholamine depletion switches myocardium from carbohydrate to lipid utilisation. *Cardiovasc Drugs Ther* 2001; 15: 111– 117.
21. Schrauwen P, Hoeks J, HesselinkMK. Putative function and physiological relevance of the mitochondrial uncoupling protein-3: involvement in fatty acid metabolism? *Prog Lipid Res* 2006; 45: 17– 41.
22. Pop-Busui R, Kirkwood I, Schmid H, Marinescu V, Schroeder J, Larkin D, Yamada E, Raffel DM, Stevens MJ. Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. *J Am Coll Cardiol* 2004; 44: 2368– 2374.
23. Kotecha D., New G, Flather M D.Five-minute heart rate variability can predict obstructive angiographic coronary disease**.** *Heart* 2012; 98:395-401.
24. Aaron I Vinik, Dan Ziegler. Diabetic Cardiovascular Autonomic Neuropathy. *Circulation*. 2007; 115:387-397.
25. La Rovere M T, Pinna G D, Maestri R Capomolla S, Febo O, Ferrari R *et al*. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients.*Circulation*. 2003 Feb 4; 107(4):565-70.
26. Rashba EJ, Estes NA, Wang P, Schaechter A *et al*. Preserved heart rate variability identifies low-risk patients with nonischemic dilated cardiomyopathy: results from the DEFINITE trial. *Heart Rhythm*. 2006 Mar; 3 (3):281-6.
27. Andrew J.M. Boulton, Arthur I. Vinik, Joseph C. Arezzo. Diabetic Neuropathies**:** A statement by the American Diabetes Association. *Diabetes Care* April 2005 vol. 28 no. 4 956-962.
28. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia*. Apr 1998; 41(4): 416–423.
29. Chessa M, Butera G, Lanza GA, Bossone E, Delogu A, De Rosa G, *et al*. Role of heart rate variability in the early diagnosis of diabetic autonomic neuropathy in children. *Herz*. 2002 Dec; 27(8):785-90.