Heart rate variability in type 2 diabetics

V. Pramodh*1, M. Prashanth Kumar2 and B. A. Krishna Prasad3

1Associate Professor, Department of Physiology, M.V.J.M.C & R.H, Hoskote, Bangalore.
2Professor, Department of Physiology, R.R.M.C & R.H, Mysore Road, Bangalore.
3Professor, Department of Physiology, M.V.J.M.C & R.H, Hoskote, Bangalore.

*Correspondence Info:
Dr. V. Pramodh,
Associate Professor,
Department of Physiology, M.V.J.M.C & R.H, Hoskote, Bangalore.
E-mail: drvpramodh@gmail.com

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, N50; 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
There are 371 million known diabetics at present in the world and by 2030, it is estimated that the numbers will increase to 552 million, according to the International Diabetes Federation (IDF). The fact that half the diabetics are undiagnosed yet is more alarming1. 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) itself3. Patients with type 2 diabetes mellitus, having higher resting heart rate reflecting the deranged autonomic function, have a greater incidence of progressive nephropathy and retinopathy4. CAN might be subclinical for several years until the patient develops resting tachycardia, postural hypotension, exercise intolerance, cardiac dysfunction and diabetic cardiomyopathy5.
Reduced heart rate variability reflects impairment in cardiovascular autonomic function. It is strongly associated with an increased risk of silent myocardial ischemia and mortality6. 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 < 5 years duration.
4. HbA1c: 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, antihypertensives, ACE inhibitors, thyroid stimulants, anti thyroid drugs.
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.
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 sphygmonanometer. 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.

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.
- **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

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

| 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±4.13       | 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 systems1. 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 studies4 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 balance3. 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 modulation 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 diabetes2. Julius et al have stated that monoxy nitrosylated protein expression is a new biomarker of metabolic control and inflammation in diabetic subjects with macroangiopathy5. 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 polyneuropathy13. 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 way14.

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 studies15. 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 studies14.

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 in risk factor identification in diabetes patients15. 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 neuropathy16.

Rodia 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 apoptosis17 and increased mitochondrial oxidative stress8. These may contribute to myocardial injury19 and may cause cardiac events and sudden death. The sympathetic imbalance associated with CAN may critically influence myocardial substrate utilization26 and contribute to mitochondrial uncoupling27 regional ventricular motion abnormalities, functional deficits, and cardiomyopathy28. This is the probable pathology of CAN in diabetics.

Kotecha et al have observed that reduced LF power in HRV strongly associated with angiographic coronary disease29. 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 in diabetics with history of hypertension or exposure to hypoglycemia, severe hyperglycemia, enhanced intraoperative instability, and a greater incidence of silent MI and ischemia and hence has a poor prognosis30. 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 subjects31. The study by Rishiha et al finds that the nonischemic dilated cardiomyopathy patients with preserved HRV have very good prognosis. It was also noted that patients with severely depressed HRV and those excluded from HRV analysis because of atrial fibrillation and frequent ventricular ectopy, have the highest risk of mortality26.

Andrew et al, in their meta-analysis study demonstrated that those with decreased heart rate variability (HRV), indicating reduced cardiovascular autonomic function, are at high risk of silent myocardial ischemia and mortality32. The DCCT (Diabetes Control and Complications Trial) documented that intensive therapy can slow the progression and the development of abnormal autonomic tests30.

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 disease39. 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 regulatory appears to be more significantly affected in the early asymptomatic diabetics.

Acknowledgement

We acknowledge the immense support and help of the teaching and non teaching staff of the Department of Physiology, M.V.J. Medical College, Hoskote, Bangalore. We also thank the management of M.V.J. Medical College, for their support to this project.

References

Epidemiology:


