Original Article
Cardiac autonomic dysfunctions in type 2 diabetes mellitus: an investigative study with heart rate variability measures

Anu Panackal Purackal John1*, Kaviraja Udupa1*, Santhosh Avangapur1, Magadi Umeshchandra Sujan1#, Ganagarajan Inbaraj1, Prathyusha Parthipulli Vasuki2, Anita Mahadevan3, Rudramunisetty Anilkumar4, Mysore AnkeGowda Shekar4, Talakad Narasappa Sathyaprabha1

1Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bangalore, India; 2Department of Biostatistics, National Institute of Mental Health and Neurosciences, Bangalore, India; 3Department of Neuropathology, National Institute of Mental Health and Neurosciences, Bangalore, India; 4Karnataka Institute of Endocrinology and Research (KIER), Diabetology, Bangalore, India; #Current affiliations: Department of Yoga, JSS Academy of Higher Education & Research, Mysuru (Deemed to be University), India.
*Equal contributors and co-first authors.

Abstract: Cardiac autonomic neuropathy (CAN) is a common yet underdiagnosed complication of Type 2 diabetes mellitus (T2DM). Heart rate variability (HRV), a sensitive diagnostic marker of cardiovascular risk, could help detect CAN at its earliest stage. However, the progression of CAN based on age and disease duration in T2DM is lacking. In this study, we propose to explore the occurrence of CAN in patients with varying stages and duration of T2DM. This cross-sectional study involves participants with T2DM (n = 160) and healthy volunteers (n = 40) with an age range of 30-60 years of both genders. Patients in the T2DM group were further subdivided into four subgroups based on their disease duration [Prediabetes, disease duration <5 yrs (D1), 5-10 yrs (D2), and >10 yrs (D3)]. All participants underwent short-term HRV recording for 20 minutes and analyzed for both time and frequency domain measures. The study results showed a significant increase in Heart Rate (HR) in D1 (P = 0.031) and D3 (P = 0.001) groups compared to healthy controls. The time-domain measures of HRV were significantly reduced in the T2DM group compared to healthy controls. Furthermore, this reduction is more intense in the D3 group than in D2 and D1. Correspondingly, in frequency domain parameters: total power, high-frequency power, and low-frequency power were significantly reduced in all the T2DM groups compared to healthy controls. The study concludes that the overall HRV (as determined by total power), sympathetic activity (low frequency power) and parasympathetic activity (time domain measures and high frequency power) were significantly reduced in all the diabetic subgroups except prediabetes as compared to the healthy controls, implying that both sympathetic and parasympathetic limbs are symmetrically affected in T2DM patients even in the earliest stages (<5 yrs) implying subclinical cardiac autonomic dysfunction in the earliest stages.

Keywords: Autonomic nervous system, type 2 diabetes mellitus, heart rate, heart rate variability, cardiac autonomic neuropathy, sympathetic and parasympathetic activity

Introduction

Diabetes Mellitus (DM) is a chronic, widely prevalent metabolic disorder marked by increased blood glucose levels, leading to severe complications of vital organs such as the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), heart (cardiopathy and other vascular complications) [1]. Further, diabetes can cause impairment of the autonomic nervous system functioning, leading to cardiac autonomic neuropathy (CAN). Cardiovascular autonomic neuropathy (CAN) is defined as abnormalities associated with heart-rate control and vascular dynamics. CAN is the result of complex interactions involving numerous mechanisms and pathways that contribute to neuronal ischemia and, eventually, neuronal death [2]. This Diabetic CAN, is a serious complication that affects one-third of patients with T2DM and is associated with five-fold increased risk of developing cardiovascular mortality [3].
Alteration of HRV by duration of diabetes

toms of CAN range from resting tachycardia and a fixed heart rate (HR) to the development of “silent” myocardial infarction. The common risk markers associated with CAN are age, duration of DM, glycemic control, hypertension, dyslipidemia, and microvascular complications. Multiple studies have shown the varying incidence and prevalence of CAN in diabetes ranging from as low 1.6% in well-controlled diabetic patients to as high as 90% in those with uncontrolled longstanding diabetics undergoing pancreas transplantation [4, 5]. CAN is often under-diagnosed, whereas the cardiovascular mortality, associated with CAN was found to be the primary cause of death in patients with T2DM [6, 7].

The under diagnosis of CAN is due to the lack of standardized diagnostics in the typical hospital context. According to published studies, the prevalence of CAN varies from 2% to 91% in type 1 diabetic mellitus (T1DM) and 25% to 75% in type 2 diabetes (T2DM), this wide range in prevalence is due to this lack of standardized diagnostic criteria and under diagnosis at the hospitals. The early detection of CAN could improve prognosis and prevent cardiovascular complications [8].

CAN prevalence vary greatly depending on the diagnostic procedures utilized, the population analyzed, and the stage of the disease. Studies show that the duration of diabetes is an independent factor for developing CAN irrespective of diabetes type [9-11]. Despite the fact that CAN is associated with a longer duration of disease, certain studies indicate that it may also be present in newly diagnosed diabetic individuals, but at a much lower frequency [11]. CAN is discovered in around 7% of patients with type 1 or type 2 DM at the time of diagnosis, and the risk is projected to increase by approximately 2% to 6% annually [4, 11]. Other risk factors that influence CAN on DM are poor glycemic control, age, obesity, smoking, hypertension, hypercholesterolemia, distal polyneuropathy, nephropathy, and retinopathy [12].

Recent evidence suggests that multiple complex pathways are involved in CAN, whereas its entire pathogenesis is obscure. CAN occurs in a range of subclinical and clinical manifestations, from resting tachycardia to cardiomyopathy. According to the Toronto Consensus Panel on Diabetic Neuropathy, all diabetic patients, especially those with a history of poor glycemic control, macro/microvascular problems, and elevated cardiovascular risk, should be evaluated for CAN [10]. In clinical practice, CAN assessment methods include symptom and sign assessment, HR and BP-based cardiovascular reflex tests, short-term electrocardiography (ECG), QT interval prolongation, HR variability (24 h, classic 24 h Holter ECG), ambulatory BP monitoring, HR turbulence, baroreflex sensitivity, catecholamine assessment and cardiovascular sympathetic tests, heart sympathetic imaging [3]. Whereas, CAN is traditionally determined by cardiovascular reflex testing [13]. The initial preclinical sign of this issue is reduced Heart-Rate Variability (HRV), which refers to changes in the time intervals between R waves of the QRS complexes [14]. HRV is a quick, economical, and authenticated tool to help diagnose CAN at a subclinical stage, providing a significant association between cardiovascular morbidity and the autonomic nervous system [15, 16].

Further, Ewing et al. in 1970’s proposed a five simple tests to assess autonomic functions [17]. Which include, (1) the R-R changes in paced deep breathing (expiration:inspiration ratio and E:I ratio); (2) HR response to standing:30:15 ratio-is the ratio of the greatest R-R interval (between the 20th and 40th beat) to the shortest interval (between the 5th and 25th beat) induced by a shift in position from horizontal to upright; (3) the HR response to the Valsalva maneuver; (4) the BP response to standing; and (5) the BP response to a continuous handgrip produced by muscle contraction via a handgrip dynamometer [15]. Further studies have also attested that HRV aids in diagnosing CAN at a subclinical stage, consequently providing the possibility for better prevention and treatment as low HRV is related to the progression of diabetes, predicting the early onset of metabolic syndrome and diabetic CAN [2].

Despite these measures available CAN is often under diagnosed due to the lack of standardized diagnostics in the typical hospital context. Moreover, no comprehensive studies have focused on the progression of CAN based on age and disease duration. Hence, the objective of the present study was to compare the HRV of T2DM patients with healthy controls based on their disease duration, (i) prediabetes, (ii) diabetes for less than five years, (iii) between five
to ten years, and (iv) more than ten years. This study would help understand the severity of CAN, which varies with age and disease duration. Also, this study would help detect CAN-associated severe complications early and aid in planning treatment strategies in the early stages of the disease.

Materials and methods

Study population

This cross-sectional study involves participants with T2DM (n = 160) and healthy volunteers (n = 40) with an age range of 30-60 years of both genders. Subjects in the T2DM group (n = 160) were further subdivided into four groups covering different disease duration: (i) prediabetes, (ii) diabetes with onset less than five years (D1), (iii) diabetes ranging from 5-10 years (D2), and (iv) more than ten years (D3). Patients were recruited from Karnataka Institute of endocrinology and research (KIER), Bangalore, India and were escorted to National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India for HRV analysis.

Exclusion criteria

Patients on medications known to affect autonomic functions (Beta-Blockers, anticholinergics, antidepressants and antipsychotics), patients with psychiatric illness like anxiety and depression and psychosis known to affect autonomic functions, patients with uncontrolled long term hypertension more than 5 years in spite of medication, patient with Hypothyroidism/Hyperthyroidism, patients with any recent history of fever, meningitis or encephalitis that may significantly influence CNS function or structure, patients with alcohol/substance abuse, patients with a cardiac pacemaker or other implanted or external electrical device, as well as pregnant or lactating female patients, were excluded from the study.

Inclusion criteria

Subjects ranging from 30 to 60 years of both genders were recruited for the study. Prediabetic patients with no co-morbidities and who were not on oral hypoglycemic agents/other medications are included in the study.

Patients with T2DM were recruited from the Karnataka Institute of Diabetology and healthy controls matching for age and gender were recruited from NIMHANS. The study was explained to all participants, and their written informed consent was obtained. Following recruitment, the patients underwent complete clinical examination with short-term HRV recording for 20 minutes. The temporal and frequency domains of HRV were measured in T2DM patients and compared to age- and gender-matched healthy controls (n = 40).

HRV analysis

For HRV recording patients should refine from smoking, caffeine intake for 2 hours and alcohol intake for 36 hours. They should have had adequate rest, at least 8 hours of uninterrupted sleep on the night before the assessment of HRV and regular breakfast on the day of assessment. They were made to lie quietly in a couch in supine position for 5 min to alleviate the anxiety in a sound attenuated room with dim lighting and the temperature ranging from 20 to 25°C. After explaining the procedure to the subject, HRV was analyzed as per the guidelines of the Taskforce report of 1996 [18]. Patients were attached with Lead II ECG and the signals were conveyed through an analogue digital converter (Power lab, 16 channels data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz. The data was stored in a personal computer and analyzed offline using an automatic programme that allowed visual checking of the raw ECG and breathing signal to obtain the HRV parameters in time-domain and frequency-domain, known as ‘linear methods’. Twenty-minute basal recordings were stored and later analyzed to obtain both time and frequency domain parameters of HRV using HRV Analysis Software LabChart pro version 8 (Powerlab AD instruments). An artifact-free 5-minute segment was analyzed to obtain time and frequency domain parameters.

Time-domain analysis: In this method, a descriptive statistical tool will be applied to quantify the variations in RR intervals and the following parameters are computed; (a) Standard Deviation of RR intervals which is sensitive to all sources of variation (SDNN); (b) Root mean square of the standard deviation of RR intervals - (RMSSD); (c) Number of successive NN intervals that vary by more than 50 ms (NN50); and (d) Percentage of NN50 counts which are more sensitive to the highest fre-
Alteration of HRV by duration of diabetes

Frequency component and best predictors of parasympathetic activity (pnn50).

**Frequency-domain analysis:** For frequency-domain analysis the machine uses Fast Fourier Technique (FFT), which transforms R-R intervals into waves with three essential components: very low frequency ≤0.04 Hz (VLF), low frequency 0.04-0.15 Hz (LF), and high frequency 0.15-0.4 Hz (HF). HF describes the vagal activity, whereas LF blends the effect of sympathetic and parasympathetic influence. The signals were further used to calculate LF normalized unit (LF nu) and HF normalized unit (HF nu), which represents the relative value of each component in proportion to the total power minus the very low frequency component and LF/HF Ratio reflects the sympathovagal balance and sympathetic modulation. Literature suggest a decrease in HF (a sign of parasympathetic dysfunction) with increased LF (sympathetic predominance) is observed in the early stages of autonomic dysfunction in diabetes, leading to an increase in LF/HF [18].

Furthermore, the fasting and post prandial blood sample was taken for estimation of plasma glucose by hexokinase method. HBA1c was measured by the high-performance liquid chromatography method using the Bio-Rad Variant 2 turbo analyzer. Prediabetes was diagnosed by FPG 100 to 125 mg/dl, 2-hour PPPG 140 to 199 mg/dl and HBA1c 5.7 to 6.4%. Diabetes was diagnosed by using American diabetes association (ADA) criteria that recommends Fasting plasma glucose ≥126 mg/dl and HBA1c ≥6.5% (Table 1). The American Diabetes Association is a United States-based non-profit organization that seeks to manage, cure and prevent diabetes.

**Statistical analysis**

Data were analyzed using IBM SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). All the parameters in this study were not normally distributed. Hence, the data is expressed using descriptive statistics such as median, quartiles for continuous variables, frequency and percentages for categorical variables. Continuous variables were tested for normality and the differences between the subgroups were analyzed using non-parametric tests with P<0.05 was considered statistically significant.

**Results**

A total of 200 volunteers of all the groups have undergone the HRV test Analysis. The values are exhibited in terms of Median (25th-75th percentile) = [M (Q1, Q3)]. Kruskal-Wallis test with Dunn’s Correction was employed to compare the multiple groups of the study population. The statistical significance was set at a p-value <0.05. Analysis of Time domain and Frequency domain HRV parameters have presented in Table 2. HR of prediabetes and the diabetes groups showed higher values than healthy control group, but statistical significance was found with D1 and D3 groups compared to healthy controls. The values of SDNN in prediabetes and diabetes groups showed

| Table 1. Demographic details of the subjects included in this study |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variables       | HC (n = 40)     | Pred (n = 40)   | D1 (n = 40)     | D2 (n = 40)     | D3 (n = 40)     |
| Age (years)     | 49.53 ± 5.70    | 50.08 ± 6.46    | 49.43 ± 6.44    | 49.83 ± 5.18    | 51.65 ± 4.53    |
| DM Duration     | NA              | 0.45 ± 0.22     | 3.13 ± 0.91     | 7.33 ± 0.97     | 13.7 ± 1.65     |
| Weight (Kg’s)   | 69.70 ± 9.95    | 70.7 ± 10.47    | 71.67 ± 11.39   | 71.20 ± 8.52    | 71.02 ± 10.98   |
| Height (cm’s)   | 2.58 ± 0.31     | 2.60 ± 0.26     | 2.67 ± 0.26     | 2.71 ± 0.27     | 2.75 ± 0.24     |
| BMI (Kg/m²)     | 27.31 ± 4.39    | 27.50 ± 5.17    | 26.90 ± 3.78    | 26.41 ± 3.45    | 25.94 ± 3.72    |
| Waist Hip Ratio | -               | 0.95 ± 0.06     | 0.96 ± 0.06     | 0.97 ± 0.04     | 0.97 ± 0.05     |
| FPG (mg/dL)     | -               | 109.37 ± 16.14  | 145.15 ± 37.31  | 164.37 ± 51.93  | 175.44 ± 56.51  |
| PPPG (mg/dL)    | -               | 150.26 ± 30.59  | 224.53 ± 69.95  | 232.20 ± 69.48  | 251.38 ± 94.73  |
| HbA1c (%)       | -               | 6.08 ± 0.24     | 7.93 ± 1.45     | 8.24 ± 1.74     | 8.58 ± 1.74     |

*All demographic data are presented as Mean ± Standard deviation (SD). None of these variables showed any difference between the various stages of diabetes: FPG = Fasting plasma glucose, PPPG = Post prandial plasma glucose, Pred = Pre-diabetes, D1 = Diabetes <5 years, D2 = Diabetes from 5-10 years, D3 = Diabetes >10 years (as per ADA-American diabetes association guidelines).
### Table 2. Time domain and Frequency domain parameters of heart rate variability (HRV) measures

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data represented as Median (Q1, Q3)</th>
<th>Kruskal-Wallis test</th>
<th>Multiple comparison with Dunn’s correction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC (n = 40)</td>
<td>Pred (n = 40)</td>
<td>D1 (n = 40)</td>
</tr>
<tr>
<td>HR (BPM)</td>
<td>71.39 (66.1, 82.1)</td>
<td>78 (72.2, 85.4)</td>
<td>80 (75.9, 90.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>42.34 (28.2, 57.25)</td>
<td>34.99 (22.13, 45.97)</td>
<td>29.29 (19.04, 42.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSSD</td>
<td>30.05 (22.5, 39.3)</td>
<td>23.05 (9.7, 34.0)</td>
<td>19.41 (11.9, 27.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NN50</td>
<td>28 (9, 60.5)</td>
<td>12 (0.75, 45)</td>
<td>5.5 (0, 24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NN50%</td>
<td>8.08 (2.1, 19.3)</td>
<td>2.96 (0.1, 12.2)</td>
<td>1.49 (0.6, 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total_Power (ms(^2))</td>
<td>1661.3 (899.3, 2943.4)</td>
<td>1115.9 (464.5, 2188.3)</td>
<td>748.2 (349.1, 1732.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (ms(^2))</td>
<td>312.7 (206.7, 563.92)</td>
<td>250.13 (67.23, 416.31)</td>
<td>228.76 (72.44, 397.24)</td>
</tr>
<tr>
<td>HF (ms(^2))</td>
<td>355.50 (209.7, 588.53)</td>
<td>197.91 (39.65, 413.80)</td>
<td>92.61 (46.25, 258.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF_NU</td>
<td>44.32 (33.91, 54.96)</td>
<td>41.54 (27.08, 51.43)</td>
<td>39.59 (31.74, 49.44)</td>
</tr>
<tr>
<td>LF/HF Ratio</td>
<td>1.12 (0.69, 1.65)</td>
<td>1.2 (0.72, 2.15)</td>
<td>1.32 (0.78, 1.86)</td>
</tr>
</tbody>
</table>

Abbreviations: HC = Healthy Controls; Pred = Pre-diabetes; D1 = Diabetes <5 years; D2 = Diabetes from 5-10 years; D3 = Diabetes >10 years; HR = Heart Rate (BPM); SDNN = Standard Deviation of N-N intervals, in milliseconds; RMSSD = Root Mean square of successive differences between adjacent R-R intervals, in milliseconds; NN50% = Percentage of consecutive N-N intervals that differ by >50 milliseconds; TP = Total Power (The variations of NN intervals over the temporal segment, ms); LF = Low Frequency (ms\(^2\)); HF = High Frequency (ms\(^2\)); LF_NU = Low Frequency (Normalized Units); HF_NU = High Frequency (Normalized Units); LF/HF Ratio = Ratio of Low and High Frequency power; P-Value = Probability value; *Statistical Significance = P-value <0.05. **p<0.01; ***p<0.001.
lower values compared to healthy control group. However, statistical significance was found with D1 and D3 group in comparison with Healthy controls. The values of RMSSD, NN50 count, NN50% and HF values of prediabetes and diabetes groups showed lower values than the healthy controls and were also found to be statistically significant with all three diabetic groups compared to healthy controls. The values of Total power of Prediabetes and all the diabetes groups were lower in comparison with the healthy control, but the statistical significance was found with D1 and D3 groups in comparison with healthy controls. The values of LF of prediabetes and all the diabetes groups were lower in comparison with healthy control groups, yet found the statistical significant only with D3 group in comparison with healthy controls. The normalized units of HF of the D3 group were lower among all the groups and were found to be statistically significant compared to healthy controls. The LF/HF ratio of the D3 group showed greater values among all the groups and was statistically significant compared to Healthy controls.

Discussion

The autonomic nervous system is one of the major homeostatic regulatory systems of the body. HRV is making a valuable contribution to the diagnosis of cardiovascular autonomic dysfunction and CAN by exhibiting reduced HRV. Further, the measures of short-term resting HRV were found to be more accurate in diagnosis tests for detecting CAN [19]. The present study confirms the evidence of CAN in all subgroups of T2DM compared to healthy controls. HRV measures reveal that sympathetic and parasympathetic activity than healthy controls. The time and frequency domain characteristics of HRV and CAN development in T2DM patients were found to be associated independently [24]. The present study results were similar to the findings of Park et al., who reported subjects with diabetes had lower HRV values than normal subjects (SDNN; 36.2 ± 15.5 vs. 30.1 ± 14.4, p-value = .024) [25]. Furthermore, the standardized testing of HRV for autonomic function tests in the diabetes group with poor glycemic control as assessed by HbA1c levels of ≥8% showed lower (SDNN; 26.57 (14.11, 34.07) vs. 42.34 (28.2, 57.25), p-value = .001) compared with healthy controls [25]. The main findings of our study were that T2DM patients had significantly lower HRV in both sympathetic and parasympathetic activity than healthy controls, which can be explained by the adverse metabolic consequences of high blood glucose levels on HRV.

In this study, T2DM participants in the subgroups D1 (3.13 ± 0.91), D2 (7.33 ± 0.97), and D3 (13.7 ± 1.65) had a statistically significant
Alteration of HRV by duration of diabetes

reduction in RMSSD, NN50% and HF (ms²) compared to healthy controls. At the same time, a significant reduction in HR (BPM), SDNN, LF (ms²) and Total Power (ms²) occurred in D1 and D3 compared to HC. There was no significant change in the LF/HF ratio between DM subgroups and HC except for D3, which increased significantly. These findings match a previous population-based study that identified HF power to be lower in people with diabetes than in normal subjects [15].

In most clinical circumstances, parasympathetic activity decreases while sympathetic activity increases [26]. However, the present investigation indicated that both parasympathetic and sympathetic activities were decreased in T2DM patients. A possible explanation is that T2DM affects both sympathetic and parasympathetic fibres in the heart, causing cardiac autonomic neuropathy. The fact that the LF/HF ratio did not alter among the patients in this study could be attributed to changes in both the LF and HF components that have undergone similar alterations.

In an earlier study, Verma et al. [27] showed that patients with T2DM showed a reduction of HRV and increased LF nu and LF/HF ratio. These impairments were significantly higher for the group. However, there was no difference in these measures regarding disease duration (<5 vs. 5-10 vs. >10 years). On the other hand, duration of diabetes was strongly associated with a decrease in HRV similar to present study in another trial by Tarvainen et al., 2014 which has demonstrated that the most significant decrease in HRV was observed within the first 5-10 years of the disease and negative correlations of blood glucose level and HbA1c with most of the HRV parameters [28]. In T2DM with onset less than five years (D1), the early stage of CAN could cause damage to the vagus nerve, thus leading to sympathetic predominance. This increase in sympathetic tone could continue until advanced CAN when sympathetic denervation also occurs.

This is the first population-based study to examine multiple HRV variables (SDNN, LF and HF power, LF/HF ratio) across the spectrum of different subgroups of DM with varying disease durations. Our findings extend the previous observation made in selected studies with diabetic patients compared with healthy volunteers [29]. Thus, in this cross-sectional study of autonomic dysfunction assessed by HRV measures, correlation of disease duration and autonomic dysfunctions: RMSSD and HF power have a significant negative correlation with disease duration (p<0.05), indicating a decrease in both these measures with increased disease duration. Moreover, glycemic control assessed by HbA1c showed a negative correlation with RMSSD. Thus, our study confirms the earlier review by Helleputte et al., 2020 [30], which found a significant negative correlation between HRV measures and clinical measures such as glycemic variability (HbA1c) and disease duration. Thus, these HRV measures (RMSSD and HF power) could be used as predictors of glycemic control in patients with diabetes.

The present study finding of a reduction in HRV measures in pre-diabetes compared to HC was similar to a large study (Coopmans et al., 2000) involving more than 2000 subjects showed cardiac autonomic dysfunction even in the pre-diabetes stage of the disease as assessed by HRV measures [31]. Since the objective of our study is to detect autonomic abnormality through HRV measures and not to follow these patients with any changes in autonomic balance, as studied by Jun et al. 2019 [23], recovery from these dysfunctions was not assessed by subsequent follow-ups. Nevertheless, this prospective design might be the future direction of research and provide more details about the clinical significance of HRV measures in prognostication, especially the cardiovascular domain.

Our study has the strength that three disease groups were assessed with a varied duration of disease ranging from <5, 5-10 and >10 years, thus providing longitudinal changes with time. Although Cha et al. (2018) [24] have demonstrated longitudinal follow-up in same cohort of patients for around 8 years and evaluated cardiac autonomic and cardiovascular morbidity measures, our study showed similar cardiac autonomic dysfunctions in patients with different disease duration by examining their CAFT in a cross-sectional study design. Nevertheless, it would be imperative to conclude the importance of cardiac autonomic dysfunction analysis in patients with DM and look for cardiovascular morbidity in these patients. Further, patients with T2DM who have subclinical CAN,
Alteration of HRV by duration of diabetes

which precedes clinically evident CAN, may have reduced HRV but go undiscovered by standard autonomic tests. Whereas short-term HRV appears to be a good approach for detecting pre-diabetic CAN [32].

Conclusion

We found substantial evidence of a significant drop in HRV among T2DM patients across all study groups. Assessing and monitoring the severity of T2DM using HRV could be a potential non-invasive, reliable, and pain-free measurement strategy to detect any diabetes-induced CAN and other complications. Both sympathetic and parasympathetic activity were reduced, possibly as a result of the negative effects of altered glucose metabolism on HRV. Further, the reduction in Time- and frequency-domain measures of HRV could also independently predict cardiovascular outcomes in patients with T2DM. Hence, ECG and HRV evaluation should be considered early in patients with diabetes.

Acknowledgements

This study was supported by funding from the Indian Council of Medical Research (ICMR), and all authors acknowledge this funding support 5/4/5-11/Diab.-16-NCD-II.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kaviraja Udupa, Additional Professor, Department of Neurophysiology, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, India. ORCID: 0000-0001-6906-5193. Tel: 91-80-26995914; E-mail: kaviudupa@gmail.com; kaviudupa.nimhans@nic.in

References

[16] Thayer JF and Brosschot JF. Psychosomatics and psychopathology: looking up and down


