Impact of disease control and co-existing risk factors on heart rate variability in Gujarati type 2 diabetics: An observational study

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a proven threat of cardiac dysautonomia with paucity of studies from India. Poor disease control makes it further worse with co-existence of hypertension in majority. Heart rate variability (HRV) is a validated noninvasive tool to assess cardiac autonomic status. Aim: We studied HRV parameters of type 2 diabetics looking for effects of disease control and other co-existing risk factors. Materials and Methods: Ninety-eight hypertensive and forty normotensive under-treatment, Gujarati type 2 diabetics were evaluated for disease control and risk stratification. Five minutes resting, HRV was measured by Variowin HR, software-based instrument, using standard protocols to record time domain, frequency domain, and Poincare plot HRV parameters. They were compared between subgroups for the difference with \( P < 0.05 \) defining statistical significance. Results: All HRV parameters were reduced in type 2 diabetics, having mean age 56 years, mean duration 6 years with poor glycemic but comparatively better pressure control. HRV parameters were significantly not different in good compared to poor glycemics or in subjects with optimum pressure control than those without it. Results did not differ significantly, by the presence of individual cardiovascular risk factor in diabetics except resting heart rate. Conclusion: Our findings of HRV suggest that type 2 diabetics with poor glycemic control do not have a significant difference of cardiac dysautonomia by pressure control, glycemic control, and absence of risk cardiovascular factor. It suggests diabetes as a major cause for cardiac dysautonomia, residual risk despite treatment and need for HRV screening, strict glycemic control, and further studies.

Keywords: Dysautonomia, heart rate variability, hypertension, normotensive, type 2 diabetes

Introduction

In India, type 2 diabetes mellitus (T2DM) is now reaching potentially epidemic proportion and showing association with a spectrum of complications, that too at relatively young age.[1] Cardiovascular complications are well-documented in type 2 diabetes, but cardiac autonomic neuropathy (CAN) is neglected.[2] Cardiac dysautonomia is one of these known entities, which can be measured by heart rate variability (HRV).[3] Reduced HRV is an independent cardiovascular risk factor.[4] In type 2 diabetics, the presence of other risk factors and disease control may affect this cardiac autonomic balance. However, only few Indian studies have assessed it, so we tried to study the same.

Materials and Methods

Study design and subjects

A community-based observational study was conducted by Physiology Department on medicine outdoor patients of a Tertiary
Care Teaching Government Hospital, affiliated to a Government Medical College from 15th October 2014 to 15th January 2015. We enrolled from medicine outpatient department, 138 under-treatment type 2 diabetics with or without hypertension (HTN) with minimum 1-year of the duration of diabetes by random sampling. After taking approval for the study from the institutional review board, sample size was calculated by Raosoft software (Raosoft, Inc., free online software, Seattle, WA, USA). To have 95% confidence level and 5% precision, a sample size of 138 for population of the city 6 lakhs with 7.33% prevalence of T2DM in our region was adequate.

We included type 2 diabetic patients, with duration of disease more than 1-year and having reports of recent disease control, aged 30–70 years, of either sex, taking regular treatment, not taking insulin, and ready for written consent. We excluded patients taking irregular treatment, not ready for written consent, diagnosed newly (<6 months), having previous neurological or cardiovascular intervention, and using pacemaker or taking drugs that directly affect autonomic nervous system. We excluded subjects with arrhythmia after HRV measurement for analysis.

**Initial assessment**

All subjects underwent personal interview in the form of questionnaires including general features, demographic characteristics, investigations done, and treatment taken. Specific emphasis was given to identify the following cardiovascular risk factors: (1) HTN, (2) hyperlipidemia (based on current reports of lipidemic control), (3) smoking, (4) cardiovascular disease (CVD), (5) family history of type 2 diabetes, (6) age >52 years, (7) female gender, (8) fasting blood sugar (FBS) >130 mg/dL, (9) body mass index (BMI) >25 kg/m², (10) T2DM, (11) duration of disease >5 years, and (12) HR >86.

Systolic blood pressure (SBP) <140 mm of Hg and diastolic blood pressure (DBP) <90 mm of Hg were defined as controlled blood pressure. Glycemic control was defined as per American Diabetes Association (ADA) guidelines 2014th and good glycemic control was defined as (1) glycosylated hemoglobin (HbA1c) ≤7 mg%, (2) FBS ≤126 mg%, and (3) postprandial blood sugar (PP2BS) ≤180 mg%.

**Measurements**

Sitting blood pressure was measured with a random-zero mercury sphygmomanometer after a 5-min rest. We defined HTN as per self-reported use of medications for high blood pressure during the 2 weeks preceding the clinic examination. Subjects also brought to the examination all medications they had been taking.

The time domain, frequency domain variables, and nonlinear parameters were measured by window-based software VarioWin HR (HRV Analysis system, Genesis Medical System Pvt. Limited, Hyderabad, Telangana, India) and taken for comparison. Assessment of HRV was carried out between 8.30 and 12.00 am in a separate examination room. Patients were requested to avoid coffee, tea, cola drinks, and smoking for 12 h and alcoholic beverages for 24 h before the procedure. We recorded electrocardiogram (ECG) for the analysis of beat-to-beat HRV after supine rest for at least 5 min, the subject being in supine position and breathing freely. The ECG was recorded from the precordial leads and transferred online to a microcomputer for the analysis of HRV. Only stationary time series of approximately 5-min durations free of arrhythmia and artifacts were used.

**Statistical analysis**

The data were transferred on Excel spreadsheet, and descriptive analysis was expressed as mean ± standard deviation (SD). All calculations were done by GraphPad in Stat 3 software (demo version free software of GraphPad software, Inc., California, USA). We calculated the statistical significance of differences in the mean distribution of various parameters among various subgroups by Mann–Whitney test or unpaired Student’s t-test for quantitative data. Difference with $P < 0.05$ was considered statistically significant.

**Results**

The study group had mean age 56 years, mean duration 6 years with the representation of both genders, and high average BMI. Glycemic control was seen in one-fifth only for HbA1c and one-third only for FBS and PP2BS. Ninety-eight out of 138 type 2 diabetics were hypertensives, and they had comparatively better pressure control probably due to use of antihypertensive drugs [Table 1].

| Table 1: Demographic and Clinical characteristics of study subjects (n=138) |
|---------------------|------------------------|------------------------|------------------------|------------------------|
| **Mean±SD**         | **General features**   | **Gender ‑male/female/total** | **Age (years)** | **55.5±9.09** |
|                     |                        |                          |                     | **68/70/138** |
|                     |                        |                          | **Duration of DM (years)** | **5.66±5.15** |
|                     |                        |                          | **Height (cm)** | **160.58±9.74** |
|                     |                        |                          | **Weight (kg)** | **67.50±10.68** |
|                     |                        |                          | **BMI**         | **26.31±4.51** |
|                     | **Glycemic control value (%)** |               |                      | **8.10±0.93** |
|                     | **HbA1c (mg)**            |                          |                      | **106/138 (77)** |
|                     | **FBS (mg)**              |                          |                      | **120/138 (87)** |
|                     | **PP2BS (mg)**            |                          |                      | **89/138 (64)** |

$SD$: Standard deviation; $DM$: Diabetes mellitus; $BMI$: Body mass index; $HbA1c$: Glycosylated hemoglobin; $FBS$: Fasting blood sugar; $PP2BS$: Postprandial blood sugar; $SBP$: Systolic blood pressure; $DBP$: Diastolic blood pressure
We compared time domain, frequency domain, and Poincare plot derived HRV parameters among groups based on the presence of glycemic control (defined as per ADA guidelines 2014) for all three means of glycemic triad namely – FBS (≤126 mg/dL), PP2BS (≤180 mg/dL), and HbA1c (≤57 mg/dL). Good glycemic had better profile of frequency domain parameters than poor glycemic with reference to HbA1c (low frequency normalized unit [LFnu] 0.53 vs. 0.58, high frequency normalized unit [HFnu] 0.44 vs. 0.40, LF:HF ratio 1.54 vs. 0.39, HR 79 vs. 83), FBS (LFnu 0.60 vs. 0.56, HF nu 0.37 vs. 0.43, LF:HF ratio 1.18 vs. 1.36, HR 81 vs. 84), and PP2BS (LFnu 0.63 vs. 0.56, HFnu 0.37 vs. 0.43, LF:HF ratio 1.72 vs. 1.57, HR 79 vs. 85). Similarly, good glycemic had better profile of time domain parameters than poor glycemic with reference to HbA1c (scatter index [SI] 0.49 vs. 0.50), with evident statistical significance for all [Table 3]. On evaluating the effect of the presence of individual cardiac risk factor (except HTN) on HRV parameters in type 2 diabetics, we found no significant difference in results, in presence or absence of individual risk factor except HR. Diabetics with HR higher than mean had reduced HRV parameters than those with HR less than mean (LFnu 0.60 vs. 0.55, HFnu 0.39 vs. 0.44, LF:HF ratio 2.20 vs. 1.18, SDNN 18 vs. 33, NN50 8 vs. 13, high titer inhibitor 5 vs. 8, Scatter Index (SI) 0.49 vs. 0.50), with evident statistical significance for almost all results [Table 4].

Discussion

T2DM is potential epidemic in India with threatening future prediction.11,12 CAN is a common but overlooked complication of it, which can be diagnosed preclinically by HRV.13 Our previous studies have documented a high prevalence of macrovascular complication such as vasculopathy and ectopic body fat in type 2 diabetics of our region, who usually had poor disease

| Table 2: Effect of glycemic control on heart rate variability parameters among type 2 diabetes mellitus |
|-----------------------------------------------|
| HRV parameter | Glycemic control | Mean±SD | P | Mean±SD | P | Mean±SD |
|----------------|-------------------|---------|----|---------|----|---------|
|                | HbA1c ≤7 | HbA1c >7 | FBS ≤126 | FBS >126 | PP2BS ≤180 | PP2BS >180 |
| VLF power      | 407.65±308.59 | 430.1±333.93 | 0.92 | 598.1±522.77 | 351.4±304.34 | 0.01* | 653.4±597.9 | 429.5±401.01 |
| LF power       | 219.69±273.35 | 359.6±572.41 | 0.89 | 311.1±487.43 | 282.8±685.89 | 0.44 | 290.6±300.84 | 314.0±690.99 |
| HF power       | 195.73±227.86 | 216.8±488.57 | 0.55 | 306.6±676.92 | 346.6±795.35 | 0.56 | 267.9±501.98 | 378.2±821.78 |
| LF (nu)        | 0.53±0.195 | 0.58±0.109 | 0.41 | 0.6±0.18 | 0.56±0.2 | 0.3 | 0.63±0.17 | 0.56±0.2 |
| HF (nu)        | 0.44±0.16 | 0.4±0.18 | 0.52 | 0.37±0.16 | 0.45±0.23 | 0.13 | 0.37±0.17 | 0.45±0.19 |
| Maximum LF     | 0.15±0.2 | 0.07±0.19 | 0.42 | 0.11±0.15 | 0.19±0.91 | 0.14 | 0.09±0.12 | 0.17±0.84 |
| Maximum HF     | 0.29±0.17 | 0.25±0.08 | 0.55 | 0.25±0.11 | 0.29±0.1 | 0.1 | 0.29±0.098 | 0.26±0.1 |
| LF/HF ratio    | 1.54±2.29 | 0.39±0.46 | 0.04* | 1.98±2.22 | 1.36±1.64 | 0.2 | 1.72±1.6 | 1.57±1.95 |
| Heart rate     | 78.76±17.74 | 83.3±12.46 | 0.3 | 81.2±15.71 | 84.4±15.47 | 0.31 | 79.4±15.22 | 85.4±15.12 |
| Mode value     | 768.65±155.18 | 737.0±129.16 | 0.46 | 762.6±174.85 | 719.1±122.67 | 0.17 | 748.6±150.87 | 724.0±136.03 |
| Triangular HRV index | 5.4±2.14 | 8.06±1.26 | 0.64 | 8.07±1.13 | 5.76±2.76 | 0.44 | 6.43±3.42 | 6.81±0.83 |
| SDNN           | 23.96±14.3 | 24.05±17.08 | 0.87 | 27.02±18.49 | 27.73±43.25 | 0.23 | 27.59±18.51 | 28.18±39.38 |
| RMSSD          | 30.27±4.17 | 20.41±25.46 | 0.51 | 26.39±35.36 | 19.82±21.24 | 0.71 | 28.08±37.36 | 19.95±19.74 |
| SDSD           | 19.21±20.37 | 17.85±26.31 | 0.62 | 18.72±24.02 | 17.37±22.33 | 0.94 | 28.08±37.36 | 17.55±20.82 |
| NN50 count     | 19.89±18.78 | 6.12±10.14 | 0.87 | 12.64±26.11 | 7.88±14.44 | 0.78 | 15.85±42.32 | 10.04±17.58 |
| PNN50%         | 3.4±6.55 | 4.14±15.9 | 0.99 | 4.1±9.69 | 3.91±12.41 | 0.88 | 4.55±11.83 | 4.24±11.76 |
| R-R interval   | 788.14±165.87 | 726.52±160.25 | 0.13 | 769.02±173.75 | 728.76±127.3 | 0.21 | 781.63±163.55 | 722.12±128.39 |
| SI              | 15.94±17.18 | 12.7±13.93 | 0.82 | 15.09±18.25 | 13.02±12.76 | 0.89 | 16.19±19.59 | 13.01±11.65 |
| Scatter index  | 26.43±14.21 | 25.56±14.84 | 0.95 | 29.99±28.28 | 24.17±13.51 | 0.11 | 29.94±17.09 | 26.02±14.76 |

VLF: Very low frequency; LF: Low frequency; HF: High frequency; SDNN: Standard deviation of NN interval; RMSSD: Root mean square of standard deviation; SDSD: Standard deviation of standard deviation; HRV: Heart rate variability; T2DM: Type 2 diabetes mellitus; HbA1c: Glycosylated hemoglobin; FBS: Fasting blood sugar; PP2BS: Postprandial blood sugar; SD: Standard deviation
Table 3: Effect of pressure control on heart rate variability parameters among type 2 diabetes mellitus

| HRV parameter                  | Mean±SD | Pressure control | P     | Mean±SD | Pressure control | P     |
|--------------------------------|---------|------------------|-------|---------|------------------|-------|
|                                | SBP ≤140| SBP >140         |       | SBP ≥90 | SBP >90          |       |
| VLF power                      | 442.5±146.84 | 435.9±142.9     | 0.88  | 438.4±453.07 | 358.3±177.74   | 0.71  |
| LF power                       | 390.37±70.6 | 268.9±56.79     | 0.82  | 270.3±544.33 | 234.9±644.2    | 0.38  |
| HF power                       | 309.59±70.6 | 268.9±56.77     | 0.94  | 302.7±670.75 | 137.5±188.1    | 0.75  |
| LF (nu)                        | 0.58±0.2  | 0.56±0.22       | 0.54  | 0.57±0.19   | 0.66±0.12      | 0.12  |
| HF (nu)                        | 0.42±0.2  | 0.4±0.16        | 0.67  | 0.42±0.19   | 0.34±0.12      | 0.17  |
| Maximum LF                    | 0.14±0.7  | 0.06±0.03       | 0.57  | 0.13±0.63   | 0.06±0.02      | 0.7   |
| Maximum HF                    | 0.27±0.1  | 0.26±0.08       | 0.8   | 0.27±0.1    | 0.29±0.07      | 0.4   |
| LF/HF ratio                   | 1.82±1.87 | 1.43±1.14       | 0.75  | 1.64±1.76   | 1.7±1.38       | 0.63  |
| Heart rate                    | 85.87±15.97 | 81.65±12.41     | 0.21  | 85.03±15.53 | 79.73±13.02    | 0.27  |
| Mode value                     | 724.34±139.4 | 726.9±139.82    | 0.93  | 722.25±139.65 | 747.72±114.6   | 0.56  |
| Triangular HRV index           | 6.3±6.5  | 5.92±4.93       | 0.67  | 6.15±6.31  | 5.99±1.82      | 0.38  |
| SDNN                           | 23.47±14.28 | 36.43±62.97     | 0.84  | 23.47±13.33 | 49.18±93.94    | 0.51  |
| RMSSD                          | 19.93±18.23 | 21.4±26.18      | 0.89  | 19.95±20.22 | 16.14±7.27     | 0.75  |
| SDSL                           | 17.4±19.49 | 19.1±21.71      | 0.82  | 17.51±21.35 | 12.83±9.29     | 0.97  |
| NN50 count                     | 11.76±27.93 | 8.19±13.33      | 0.47  | 11.01±25.82 | 3.94±5.26      | 0.88  |
| PNN50%                         | 3.578±9.2 | 5.03±15.26      | 0.48  | 3.88±10.75  | 1.15±1.48      | 0.62  |
| R-R interval                   | 720.72±140.31 | 757.03±118.72   | 0.15  | 728.58±141.16 | 762.83±112.77  | 0.29  |
| SD1                            | 13.85±13.97 | 14.16±14.56     | 0.62  | 13.7±14.19  | 10.76±4.87     | 0.79  |
| SD2                            | 25.59±14.03 | 27.14±16.82     | 0.9   | 25.58±14.73 | 25.48±8.03     | 0.44  |
| Scatter index                  | 0.51±0.31 | 0.49±0.19       | 0.4   | 0.49±0.29   | 0.41±0.15      | 0.82  |

Table 4: Effect of presence of individual cardiac risk factor (except hypertension) on heart rate variability parameters in type 2 diabetics (mean±standard deviation)

| Risk factor (prevalence) | HRV parameter | LF | HF | LF/HF ratio | HR | SDNN | SHTI | SI |
|--------------------------|---------------|----|----|-------------|----|------|------|----|
| Hyperlipidemia Present   | n=27          | 0.54±0.21 | 0.44±0.19 | 1.78±1.44 | 82.04±14.29 | 25.67±17.36 | 10.27±18.41 | 5.91±2.77 | 0.51±0.30 |
| Absent n=111             |               | 0.59±0.19 | 0.40±0.18 | 2.09±1.73 | 85.49±15.73 | 25.63±33.14 | 10.57±26.58 | 5.71±2.83 | 0.49±0.28 |
| Reduced HRV is established fact in T2DM and we found the same as evidenced by reduced HRV parameters for all three methods, namely frequency domain, time domain, or Poincare control and high prevalence of risk factors, many of which were modifiable. Reduced HRV is established fact in T2DM and we found the same as evidenced by reduced HRV parameters for all three methods, namely frequency domain, time domain, or Poincare.
plot analysis, in line with other previous studies. An unpublished part of a study on same subjects has revealed that HRV parameters did not differ much between normotensive or under-treatment hypertensive type 2 diabetics indicating hyperglycemia as main culprit. Hyperglycemia is the key risk factor for CAN,[1,3,11] but we found in known under-treatment type 2 diabetics, no significant effect of glycemic control as evidenced by HRV. This can be due to: (1) Suboptimum glycemic control,[2] (2) one recent finding that CAN due to hyperglycemia preceded,[3,5] T2DM, which itself can be a forerunner of HTN, (3) ethnic vulnerability of Indian population, (4) metformin itself causes neuropathy by Vitamin B12 deficiency,[16] and in our case group all but two were taking it, (5) the fact that intensive glycemic control has more prognostic effect on CAN in type 1 diabetes mellitus (T1DM)[12,15,18] and not much in T2DM,[12,16] (6) CAN is early in the course of T2DM than T1DM[10,17,18] and our case group has mean duration of diabetes 6 years, (7) insulin therapy which benefits CAN[9,16] was not given to our subjects with T2DM, (8) concept of glycemic variability,[29] (9) glycemic control decreases risk of reduced HRV in T1DM than T2DM,[15,21] and (10) lack of multifactorial intervention with lifestyle modifications.[2]

Similarly, HTN alone is a proven cause of reduced HRV,[22] and optimum pressure control is beneficial. However, in T2DM, HTN is seen mostly as an aftermath of uncontrolled hyperglycemia and perhaps as an effect and not the cause of CAN. This could support our result of lack of significant impact of blood pressure control on HRV results. Control of HTN is more effective to reduce the risk of reduced HRV in T1DM and not in T2DM,[21] in line with our result. We could not find any significant impact of risk factors such as hyperlipidemia, smoking, age, female gender, high BMI, duration of diabetes more than 5 years individually on HRV in type 2 diabetes. This is in contrast to other studies,[22,23,29] and perhaps it underscores the importance of hyperglycemia, which was common to all. However, HR was a significant factor that affected HRV result, and same was documented by Tang et al.[24] Diabetics with higher than mean HR had few HRV parameters significantly lower than those with lower than mean HR. In the early stage of CAN, there is a loss of vagal tone leading to tachycardia which is followed by loss of even sympathetic tone[10] which slightly blunts the tachycardia, which may be possible in our subjects having mean HR in 80 s and not much higher than that. This indicates involvement of both components of the autonomic nervous system and a possible dysfunction that had been present for a while in these diabetics, as supported by another Indian study.[25] Resting HR is the index of cardiovascular health[24] and this better profile is due to use of antihypertensive health[24] and this better profile is due to use of antihypertensive drugs, which were offered to hypertensive cases that were predominant in our study group of type 2 diabetics. This discloses the importance of resting HR on cardiac autonomic balance and perhaps same can be achieved by lifestyle modifications.[2]

CVD is the leading cause of morbidity and mortality in diabetics, and subsequently, the primary goal of its treatment is to reduce the burden of CVD as well as the vascular complications associated with diabetes.[27-28] A healthy heart is not a metronome, and physiological variability in HR is a sign of healthy heart.[29] It is recommended that HRV testing should be done in each newly diagnosed individual[9] that can detect even sub-clinical cardiac autonomic balance even at normal HR.[31] This simple procedure does not require much expertise and can be used as a screening tool. No impact of risk factors other than hyperglycemia, pressure or glycemic control suggests early screening for diabetes itself in at-risk patients as CAN can precede clinical diagnosis of even type 2 diabetes itself. Strict disease control and use of lifestyle modification along with low resting HR are there to be offered for primary prevention.

Limitations of study
The study was limited by small sample size, horizontal design, use of 5 min short-term recording, presence of confounding factors, lack of concept of blood pressure variability, absence of controls, reliance on manually measured blood pressure, unavailability of all reports of glycemic control in each subject, and fact that cause-effect relationship can be set only by vertical study. Still, it underscored relatively less importance most of the co-existing risk factors for reduced HRV in type 2 diabetes and need of early diagnosis, optimum control, and further work.

Conclusion
Type 2 diabetics with high co-existence of HTN and poor glycemic control of our sample population showed reduced HRV parameters which were unaffected by optimum pressure or glycemic control, being significantly no different by the presence of other cardiac risk factors. It suggests more supportive work and highlights impact of hyperglycemia of type 2 diabetes, which has to be tackled by early diagnosis and optimum control before significant cardiac dysautonomia ensues.

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Conflicts of interest
There are no conflicts of interest.

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