Comparative study of cardiac autonomic status by heart rate variability between under-treatment normotensive and hypertensive known type 2 diabetics

Jayesh D. Solanki*, Sanket D. Basida, Hemant B. Mehta, Sunil J. Panjwani, Bhakti P. Gadhavi

Department of Physiology, Govt Medical College, Bhavnagar, Gujarat, India

1. Introduction

India stands second globally in type 2 diabetes mellitus (T2DM) with an alarming future prediction and there is co-existence of hypertension (HTN) and T2DM in 75% cases. Taken together they have a threatening synergistic effect with majority having sub-optimal disease control. Cardiac autonomic neuropathy is common yet overlooked complication which contributes to residual risk for cardiovascular morbidity and mortality. Heart rate variability (HRV), measured by simple 5 min recording provides reliable status of cardiac autonomic balance. Reduced HRV is seen in both HTN and T2DM individually and known to be an independent risk factor for cardiovascular health. But only few studies like Takahashi et al. have focused their synergistic effect, perhaps none from India. Indian hypertensives are very peculiar and we undertook this study to assess the effect of coexisting hypertension on HRV in known type 2 diabetics.

2. Materials and methods

2.1. Study design

This case control study was conducted in the Department of Medicine with the help of Department of Physiology, Government Medical College, Bhavnagar, Gujarat, India during a period from 15th October 2014 to 15th January 2015.
2.2. Study subjects

After approval from the Institutional ethical Committee and written informed consent from each subject, volunteers were recruited for this study. Of total number of subjects that attended the Out Door Clinic, all the adult subjects were screened for presence of type 2 diabetes. Subjects coming to clinic with record of treatment of diabetes were also included in this screening for confirmation. Of total number of patients with type 2 diabetes, observed during the recruitment period \(n = 300\), 138 patients were randomly selected for this study. Sample size was calculated by software Raosoft (Raosoft, Inc, free online software, Seattle, WA, USA). A sample of 138 subjects for a population of 6 lakhs with 7.3% prevalence of type 2 diabetes mellitus in our region gave us 95% confidence level, leaving 5% margin of error.

2.3. Inclusion and exclusion criteria

We included type 2 diabetic patients, with minimum duration of one year and known glycaemic control, aged 30–70 years, of either sex, taking regular treatment (through chart review), not taking insulin, ready for written consent.

Exclusion criteria were: those patients with less than one year duration of diabetes \(n = 12\), taking irregular treatment of diabetes \(n = 18\), age more than 70 years \(n = 127\), patients having cancer \(n = 0\), chronic dysentery \(n = 0\), chronic renal failure \(n = 3\), type 1 diabetes \(n = 9\), on pace maker \(n = 0\), past history of intervention, drug therapy influencing autonomic function \(n = 11\) and non-volunteers \(n = 1\) were excluded.

2.4. Collection of data

All the data were collected by a personal interview by a trained physician via validated questionnaires that included symptoms of cardiac autonomic neuropathy, investigations done, treatment received, salt, alcohol and tobacco intake and physical activity.

Specific emphasis was given to identify following 10 risk factors including diabetes itself: (1) hypertension, (2) hyperlipidaemia, (3) smoking, (4) cardiovascular disease (CVD), (5) family history, (6) age > 52 years, (7) male gender, (8) fasting blood sugar (FBS) >130 mg/dL, (9) body mass index (BMI) ≥ 25 kg/m², (10) type 2 diabetes mellitus.

Salt intake was the sum of the salt used during preparation of food and added at the table by each subject.\(^{11,12}\) Added ingestion was from salt added to manufactured foods was taken into account. The physician also measured body weight on each visit after removing shoes of the subjects. Height was measured without shoe.

After a 5-min rest, a blood pressure was recorded in a sitting position, on the right arm with a standard mercury manometer. Every subject had two readings, with the average of these reading reflected the HRV in a non-linear manner.

Scatter index was represented as ratio of SD1 to SD2 which deviation of RR interval along major and minor axis respectively.\(^{15}\)

The data was transferred on Excel spreadsheet and descriptive analysis was expressed as mean ± standard deviation. All calculations were accomplished by Graph Pad in Stat 3 software (demo version free software of GraphPad Software, Inc. California, USA). We calculated the statistical significance of difference in mean distribution of various parameters amongst various subgroups by Mann–Whitney test or unpaired student t test for quantitative data and by Fisher’s exact test for qualitative data. Difference was considered statistically significant with \(p < 0.05\).
3. Results

Two groups did not significantly differ in gender distribution, height, weight, BMI and glycaemic control. However, hypertensive diabetics (HTDM) had older age (57 years vs 52 years, \( p = 0.005 \)), blood pressure (systolic 136 vs 124, diastolic 83 vs 79, mean 101 vs 94, \( p < 0.05 \) for all) and duration of type 2 diabetes (6 years vs 4 years, \( p = 0.018 \)) as compared to normotensive ones (NTDM) yet pressure control was comparatively good (half having normal mean blood pressure) in former group (Table 1).

HTDM and NTDM groups had statistically insignificant difference of distribution of risk factors where high BMI, female gender, older age, positive family history and poor glycaemic control were present in large proportion of subjects in both groups (Table 2).

Comparison of time domain, frequency domain and non-linear parameters of heart rate variability revealed that there is reduced HRV in hypertensive (HTDM) and normotensive (NTDM) type 2 diabetics. Though reduced in both groups, NTDM group had better profile of frequency domain parameters than HTDM group (LFnu – 283 ms vs 262 ms, HFnu – 360 ms vs 262 ms, LF:HF ratio 2.61 vs 1.29, \( p > 0.05 \) for all) although they had higher heart rate (88 vs 83). Except for LF:HF ratio (\( p = 0.002 \)) all parameters did not differ between HTDM and NTDM groups (\( p > 0.05 \)) (Table 3).

Similarly, NTDM subjects, like HTDM subjects had reduced values but no significantly better profile of time domain HRV parameters (SDNN 24 vs 26, RMSSD 20 vs 21, SDSD 18 vs 17, NN50 13 vs 9, Triangular HRV index 13 vs 9, \( p > 0.05 \) for all) (Table 3).

Similarly, comparison of HRV parameters based on Poincare plotting revealed almost reduced but comparable results in NTDM and HTDM group (SD1 14 vs 13, SD2 26 vs 25, scatter index 0.48 vs 0.52, \( p > 0.05 \) for all), with all lacking statistical significance (Table 3).

4. Discussion

Type 2 diabetes mellitus (T2DM) has reached epidemic proportion in India and hypertension (HTN) is prevailing in nearly one out of three urban Indian. Co-existence of T2DM and

### Table 1
Demographic and clinical characteristics of type 2 diabetic subjects under study (\( n = 138 \)).

| General features | HT group | NT group | HT vs NT | Total |
|------------------|----------|----------|----------|--------|
|                  | mean ± SD | mean ± SD | \( p \) value | mean ± SD |
| Age (years)      | 57.07 ± 8.36 | 51.61 ± 9.61 | 0.005* | 55.5 ± 9.09 |
| Gender – male/female/total | 47/51/98 | 21/19/40 | 0.71 | 68/70/138 |
| Duration of DM (years) | 6.21 ± 3.58 | 3.97 ± 4.05 | 0.018* | 5.66 ± 5.15 |
| Height (cm)      | 159.5 ± 9.23 | 160.8 ± 9.54 | 0.083 | 160.58 ± 9.74 |
| Weight (kg)      | 67.5 ± 10.67 | 67.35 ± 10.31 | 0.76 | 67.50 ± 10.68 |
| BMI (kg/m²)      | 26.63 ± 4.59 | 25.59 ± 4.15 | 0.22 | 26.31 ± 4.51 |

### Table 2
Prevalence of various known risk factors for cardiovascular disease in hypertensive and normotensive type 2 diabetics (absolute number and percentage).

| Risk factors       | Prevalence (number) | Hypertensive (\( n = 98 \)) | P value |
|--------------------|---------------------|----------------------------|---------|
| Present            | Absent              | Present                   | Absent  |
| Gender – male      | 73/27               | 4/48                      | 0.09    |
| Smoking            | 85                  | 9/18                      | 0.203   |
| Alcohol            | 95                  | 2/3                       | 0.62    |
| Known heart disease| 69                  | 9/31                      | 0.52    |
| Family history of DM| 63                  | 10/30                     | 0.24    |
| Age > 52 years     | 30                  | 19/21                     | 0.02*   |
| Female gender      | 47                  | 19/21                     | 0.71    |
| BMI > 25 kg/m²     | 40                  | 21/19                     | 0.57    |
| FBS > 126 mg%      | 54                  | 16/24                     | 0.7     |

* Indicates statistical significance.

Abbreviations: HT, hypertensive; NT, normotensive; BMI, body mass index; HbA1c, glycosylated haemoglobin A1c; FBS, fasting blood sugar; PP2BS, post prandial blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.
parameters of HRV. This is well supported by previous studies done in type 2 diabetics with or without hypertension had in general interventions in our middle aged study group. We found that pressure control and lack of use of lifestyle modification the autonomic dysfunction. myocardial infarction, and thus increased overall mortality and exercise intolerance, enhanced intraoperative cardiovascular are linked to decreased heart rate variability, postural hypotension, autonomic neuropathy may cause abnormalities in heart rate has revealed no difference of HRV profile in type 2 diabetics with or the onset of the regimen. An unpublished part of this same work has revealed no difference of HRV profile in type 2 diabetics with or without glycaemic or pressure control indicating that residual cardiac risk remains despite control of these two parameters and cardiac autonomic status must be screened and targeted for better cardiovascular outcome. CAN cannot be overlooked in type 2 diabetics, having poor glycaemic control as major risk that can be reduced by early diagnosis and strict glycaemic control and residual risk can be further reduced by lifestyle interventions like weight reduction and exercise. 

HRV screening is suggested to be used in all type 2 diabetics and it can help in primary prevention of abnormal aftermath of CAN in T2DM. HRV can be used even by family physicians who are treating majority of type 2 diabetics and who can offer benefit of HRV screening to type 2 diabetics at the inception of disease and put appropriate preventive remarks in treatment as a whole.

5. Limitation of study

There were few limitations which are needed to be mentioned. First, the cross-sectional nature of study and moderate sample size warrants prospective vertical study with larger sample in subjects starting with baseline measurement followed serially. Present form of study cannot establish cause effect relationship. Second, we used five minute HRV that reveals only short term changes in cardiac autonomic status and 24 h HRV is required to further consolidate the results. Third, presence of confounding factors, absence of control and eu glycaemic hypertensives, and reliance on manually measured blood pressure were also limiting our study. Still it underscored relatively small impact of co-existing scenario of these two diseases could be different. CAN is seen even before inception of T2DM and a recent study of HRV screening suggests that diabetics can be differentiated from normal controls on the basis of reduced HRV. Similarly, T2DM itself could be the for-runner of HTN wherein anti-hypertensive could cure only one affected variable–blood pressure. The same is indicated in our study, as mean age of hypertensives was 51 against that of normotensive diabetics 57 years and mean duration of T2DM was 4 years in normotensive vs 6 years in hypertensives. However, LF/HF ratio which signifies sympatho-vagal balance was significantly higher in normotensives compared to hypertensives though a recent study shows this ratio to be of less significance. Result can be due to fact that hypertensive T2DM patients were offered calcium channel blockers or angiotensin converting enzyme inhibitor, both of which have anti-sympathetic effect that checks sympathetic over-activity. Benefit of anti-hypertensive therapy can be evident if there is reduced resting heart rate that was not much different in either group, being in 80s. Beta blockers have definite benefit as a drug restoring autonomic balance but it is usually not given as monotherapy and was not given to any of our hypertensives. This may also explain lack of significant HRV difference between diabetics taking or not taking other anti-hypertensive monotherapy. Resting heart rate has a prognostic value as a risk factor and its higher value indicates poor control of cardiovascular risk.

Autonomic functions are determined by sympathetic and parasympathetic nerves, the pituitary and pineal glands and the suprachiasmatic nucleus. Western diet, exercise, tobacco and alcoholism can also cause autonomic dysfunction which may be associated with sympathetic activation predisposing atherosclerosis, end-organ damage, and hypertension. It seems that diet and lifestyle factors can also influence autonomic function and may have an influence on HRV. Experimental studies indicate that high-fat-induced weight gain in rats elevates plasma leptin by 1–3 days after the onset of calorie-dense diets, and that diet-induced overfeeding may increase sympathetic activity within 1 week after the onset of the regimen. An unpublished part of this work has revealed no difference of HRV profile in type 2 diabetics with or without glycaemic or pressure control indicating that residual cardiac risk remains despite control of these two parameters and cardiac autonomic status must be screened and targeted for better cardiovascular outcome. CAN cannot be overlooked in type 2 diabetics, having poor glycaemic control as major risk that can be reduced by early diagnosis and strict glycaemic control and residual risk can be further reduced by lifestyle interventions like weight reduction and exercise. HRV screening is suggested to be used in all type 2 diabetics and it can help in primary prevention of abnormal aftermath of CAN in T2DM. HRV can be used even by family physicians who are treating majority of type 2 diabetics and who can offer benefit of HRV screening to type 2 diabetics at the inception of disease and put appropriate preventive remarks in treatment as a whole.

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hypertension on cardiac autonomic status in type 2 diabetics and need of optimum control of later.

6. Conclusion

We found reduced HRV parameters in type 2 diabetics having poor glycaemic control which was not significantly affected by presence of its co-existing aftermath hypertension, though controlled and use of antihypertensive treatment excluding beta blockers. It suggests that reduced HRV can precede type 2 diabetes which itself is a fore-runner of hypertension and cardiac autonomic balance is not affected much by good pressure control but can be by good glycaemic control which along with residual cardiac risk despite it, are still left unexplored.

Conflicts of interest

The authors have none to declare.

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