RESEARCH ARTICLE

Time Domain Measures of Heart Rate Variability during Acute Mental Stress in Type 2 Diabetics: A Case Control Study

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ABSTRACT

Background: Cardiovascular Autonomic Diabetic Neuropathy (CADN) is one of the most important diabetes- associated complications. Reduced heart rate variation (HRV) is the earliest indicator of CADN. The prospect of using time domain analysis of HRV using mental arithmetic as a stressor has for early diagnosis of CADN has not been studied so far.

Aims & Objective: To compare time domain parameters of HRV at rest and during acute mental stress between Type 2 diabetics and non- diabetics.

Materials and Methods: 30 male asymptomatic, Type 2 diabetics with duration of diabetes of 2-8 yrs with RBS ≥ 200 mg/dl or FBS ≥ 126 mg/dl in the age group of 30-65 yrs were chosen as subjects. 30 age and sex matched healthy non-diabetics were chosen as controls. HRV analysis was done using ECG recorded at rest in supine position for 5 min and during 5 min of acute mental stress testing.

Results: At rest standard deviation of all R-R intervals (SDNN), root mean square of successive RR- interval differences (RMSSD), number of intervals differing by > 50ms from adjacent interval (NN50) and percentage of NN50 (pNN50) were significantly less in diabetics as compared to non-diabetics. Mental stress showed increases in HR, SBP and DBP in non-diabetics as well as diabetics but SDNN was significantly less in diabetics as compared to non- diabetics during stress.

Conclusion: Data from the study demonstrated that diabetics with 8-10 yrs history had already developed parasympathetic autonomic neuropathy. Time domain analysis of HRV during mental stress can be used as a valuable tool for early diagnosis of autonomic neuropathy to prevent further complications.

Key Words: Heart Rate Variability; Time Domain Analysis; Cardiovascular Diabetic Autonomic Neuropathy

INTRODUCTION

Diabetic Autonomic Neuropathy (DAN) is among the least recognized and understood complications of diabetes, despite its significant negative impact on survival and quality of life in people with diabetes.[1] DAN may be either clinically evident or subclinical.[2] Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. Subclinical autonomic dysfunction can however, occur within a year of diagnosis in type 2 diabetes patients and within two years in type 1 diabetes patients. Because of its association with a variety of adverse outcomes including sudden death, cardiovascular autonomic neuropathy (CADN) is the most clinically important and well-studied form of DAN.[3] An important prerequisite for therapeutic intervention to CADN is to identify it as early as possible, since cardiac denervation seems to be reversible at the beginning of the disease.[4]

Reduced heart rate variability is the earliest indicator of CAN.[5] Though cardiovascular reflex tests of heart rate variability standardized by Ewing et al are non- invasive, they require patient co- operation to a greater extent.[6] They may not be sensitive enough to reveal subtle effects of interventions on autonomic nerve function.[7] Time domain analysis is the simplest method to perform HRV analysis and yields valuable information regarding both sympathetic and parasympathetic components of autonomic nervous system (ANS). 24 hr time domain analysis of HRV done in diabetic patients with or without autonomic neuropathy has revealed reduced HRV in them.[6,8-11] However data of short term HRV analysis by time domain is less in diabetics.

Stress testing unveils autonomic dysfunction even before it develops at rest. It also helps us to know the branch of ANS that is affected. Few studies have been done to assess HRV during stress in diabetics. Stress in these studies has been induced by Valsalva maneuver, deep breathing or by tilt table.[12,13] But these require lot of cooperation from the patient and the amount of discomfort experienced by patients is more. Mental stress testing is easier to administer and can be precisely regulated by the investigator.[14] Though Stroop colour word test[15], mensa test stressful interview[16] are different methods of inducing stress used in studies, mental arithmetic using serial subtraction is the most widely used method.[14] Locatelli et al had used mental arithmetic stress as a test for evaluating diabetic sympathetic autonomic neuropathy, but they evaluated skin temperature change and heart rate response.[17] No study has been done to assess ANS in diabetics using time domain analysis of HRV during mental stress. In this context the present study was undertaken.

MATERIALS AND METHODS

Thirty male asymptomatic, Type 2 diabetics with duration of diabetes of two to eight yrs with random blood glucose concentration (RBS) ≥ 200 mg/dl or FBS ≥ 126 mg/dl in the age group of 30-65 yrs were chosen, from the Medicine OPD. The 30 controls chosen from medical college campus were healthy non-diabetics who were matched with the study group for age and sex. Both cases and controls had completed their high school education, this was one inclusion criteria as they had to do mental arithmetic test. Institutional Ethical Committee clearance was taken. Athletes, those who practice yoga or exercises, those with history of cardiovascular, respiratory, psychiatric diseases and consumption of alcohol and tobacco or any medications that affect the autonomic nervous activity were excluded. Subjects reported to study after refraining from food for two hrs.[18] Subjects were asked to abstain from caffeine for at least 12 h. Informed consent was taken from them. Height was measured to the nearest 0.1 cm without footwear using vertically movable scale. Weight was measured to the nearest 100 grams using a digital scale and BMI was calculated.

HRV analysis was done using ECG recorded at rest in supine position for five min and then during five min of acute mental stress testing. ECG was recorded using disposable Ag/AgCl electrodes. ECG data in standard lead II configuration was acquired using portable ECG data acquisition equipment (Niviqure Meditech Systems, Bangalore India).The data gathered was edited manually for artifacts. Time domain analysis was done using Kubios HRV analysis software. HR and BP were recorded at rest and during mental stress.

Mental stress was induced by arithmetic mental challenge under time pressure. The subjects were asked to rapidly subtract seven from a three- or four- digit number. Throughout the test, they were encouraged by investigators to work as fast as possible.[19] Parameters recorded during time domain analysis were the mean heart rate (MHR), standard deviation of all R-R intervals (SDNN), root mean square of successive RR-interval differences (RMSSD), number of intervals differing by > 50ms from adjacent interval (NN50) and percentage of NN50 (pNN50).[20]

Statistical Analysis was done using IBM SPSS 20. Comparison of the data between Type 2 diabetics and non- diabetic groups was done by independent t test. Within the groups comparison of the data at rest and during acute mental stress was done by paired 't' test. A p value < 0.05 was considered significant.

RESULTS

Table 1 gives a comparison of anthropometric indices between diabetics and non- diabetics. Age, Ht. and Wt. did not differ significantly between diabetics and non- diabetics. BMI was significantly higher in diabetics (p< 0.05). At rest SDNN, RMSSD, NN50, pNN50 were less in diabetics as compared to non- diabetics. (p< 0.05) [Table 2]. HR, SBP and DBP were similar in both the groups [Table 2]. SBP, DBP and MHR were increased and MRR interval decreased in both the groups during acute mental stress [Table 3 & 4]. SDNN increased significantly during mental stress only in non-diabetics [Table 3]. SBP was more and RMSSD, NN50 and pNN50 were significantly less in diabetics during mental stress [Table 5].

Table-1: Comparison of Anthropometric Indices in Type 2 Diabetics and Non-Diabetics

Indices	Diabetics (n=30)	Non-Diabetics (n=30)
Age (yrs)	52.63 ± 9.0	48.9 ± 6.53
Height (m)	1.66 ± .07	1.67 ± 0.06
Weight (kg)	70.93 ± 13.23	65.9 ± 10.39
BMI (kg/m²)	25.68 ± 4.05	23.69 ± 3.56*

Values presented as Mean ± SD. BMI- Body Mass Index, *p< 0.05

Table-2: Comparison of Heart Rate, Systolic BP, Diastolic BP and Time Domain Parameters of HRV between Type 2 Diabetics and Non- Diabetics at Rest

Indices	Diabetics (n=30)	Non-Diabetics (n=30)
HR (bpm)	78.33 ± 1.69	73.4 ± 2.05
SBP (mm Hg)	128.10 ± 1.35	125.8 ± 1.73
DBP (mm Hg)	79.37 ± 1.65	78.8 ± 1.18
SDNN (ms)	28.86 ± 1.77	42.73 ± 4.58*
RMSSD (ms)	24.19 ± 1.11	39.91 ± 4.7*
NN_{50}	5.63 ± 1.27	25.13 ± 4.75*
pNN_{50}	3.85 ± 0.86	17.76 ± 3.42*

Table-3: Comparison of Heart Rate, Systolic BP, Diastolic BP and Time Domain Parameters of HRV at Rest and during Mental Stress in Non- Diabetics (N=30)

Indices	Resting	Mental Stress
HR (bpm)	73.4 ± 2.05	84.53 ± 2.13**
SBP (mm Hg)	125.8 ± 1.73	134.0 ± 1.83**
DBP (mm Hg)	78.8 ± 1.18	85.37 ± 1.81**
SDNN (ms)	42.73 ± 4.58	50.57 ± 4.3*
RMSSD (ms)	39.91 ± 4.7	39.2 ± 3.46
NN_{50}	25.13 ± 4.75	25.83 ± 3.83
pNN_{50}	17.76 ± 3.42	16.82 ± 2.59

Table-4: Comparison of Heart Rate, Systolic BP, Diastolic BP and Time Domain Parameters of HRV at Rest and during Mental Stress in Type 2 Diabetics (N=30)

Indices	Resting	Mental Stress
HR (bpm)	78.33 ± 1.69	81.53 ± 1.38*
SBP (mm Hg)	128.10 ± 1.35	141.63 ± 3.09**
DBP (mm Hg)	79.37 ± 1.65	85.57 ± 1.71**
SDNN (ms)	28.86 ± 1.77	31.23 ± 1.97
RMSSD (ms)	24.19 ± 1.11	24.10 ± 0.99
NN_{50}	5.63 ± 1.27	7.3 ± 1.21
pNN_{50}	3.85 ± 0.86	4.64 ± 0.83

Table-5: Comparison of Heart Rate, Systolic BP, Diastolic BP and Time Domain Parameters of HRV between Type 2 Diabetics and Non- Diabetics during Acute Mental Stress

Indices	Diabetics (n=30)	Non-Diabetics (n=30)
HR (bpm)	81.53 ± 1.38	84.53 ± 2.13
SBP (mm Hg)	141.63 ± 3.09	134.0 ± 1.83*
DBP (mm Hg)	85.57 ± 1.71	85.37 ± 1.81
SDNN (ms)	31.23 ± 1.97	50.57 ± 4.3**
RMSSD (ms)	24.10 ± 0.99	39.2 ± 3.46**
NN_{50}	7.3 ± 1.21	25.83 ± 3.83**
pNN_{50}	4.64 ± 0.83	16.82 ± 2.59**

Values are presented as Mean ± S.E. HR- Heart rate, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, SDNN- Standard deviation of all R-R intervals, RMSSD- root mean square of successive RR interval differences, NN50- number of intervals differing by > 50ms from adjacent interval and pNN50- percentage of NN50. * p< 0.05, **p< 0.01

DISCUSSION

At rest SDNN which is considered a global variability indicator was low in asymptomatic Type 2 diabetics as compared to non-diabetics. RMSSD, NN50 and pNN50 which are indicative of parasympathetic activity were less in diabetics. Mean heart rate was more, though not statistically significant in diabetics. This indicates a reduced autonomic modulation of heart rate in diabetics at rest. Study done by Kudat, Akkaya et al in diabetics also has shown significantly reduced time domain parameters in diabetics.[6] However in their study, time domain analysis was done using 24 hr ECG recording. Another study using 24 hr ECG showed that these parameters were reduced in diabetics with or without symptoms of autonomic neuropathy, but reduction was more pronounced in those with symptoms and those with micro vascular complications.[8] Time domain measures using short term ECG recording has not been widely studied. One study where time domain analysis was done using 20 min ECG recording has shown that the parameters were less in Type 2 diabetics and were negatively correlated with blood glucose levels and duration of diabetes.[21]

In accordance with few other studies[15,22,23], in our study also acute mental stress increased HR, SBP and DBP and this happened in both groups. However parameters indicative of parasympathetic activity (RMSSD, NN50 and pNN50) did not decrease during stress. This indicates that increased HR and BP were because of increased sympathetic activity. Mental stress in the form of mental arithmetic has been shown to increase muscle sympathetic nerve activity[15,24] and LF (low frequency) component of the spectrum[22], thus shifting the sympathovagal balance towards sympathetic excess. In contrast a study attributed parasympathetic withdrawal to be the cause of increased HR and BP observed during mental stress, in their study pNN50 had reduced during stress, but their method of inducing mental stress was different.[25]

In diabetics though HR and BP increased during mental stress, SDNN which indicates overall variability did not increase. Further, in them SBP was high and RMSSD, NN50 and pNN50 were significantly lower than non-diabetics during mental stress indicating relatively high sympathetic activity in them. These results indicated that asymptomatic Type 2 diabetics in our study have subclinical autonomic neuropathy predominantly of parasympathetic branch. This is in accordance with the view that early in the natural history of Type 2 diabetes there is impairment of parasympathetic function, with a relative increase of sympathetic function causing an imbalance of the sympathetic/ parasympathetic tone.[26,27] However in Type 1 diabetics there may be early and frequent development of sympathetic neuropathy.[27] Though HR, BP response to mental stress has been studied in diabetics, this is the first time where HRV response using time domain measures has been studied.

Frequency domain analysis of HRV in diabetics has shown LF (low frequency) power, HF (high frequency) power and LF/HF ratio to be reduced in diabetics.[6,10,28,29] Short term recordings of ECG are preferably analyzed by frequency domain analysis.[30] However SDNN, RMSSD, NN50 and pNN50 have also been measured reliably from short term recordings of 5 min[31] and time domain analysis is much easier as compared to frequency domain analysis. In a study by Mukherji S et al time domain measures were more sensitive and reliable to mental effort load.[32]

Limitations of our study were that we did not measure HbA1c and thus chronic glycemic control was not taken into account. We also did not use scale for rating perceived mental stress as a study has indicated that effect of mental stress depends on perceived mental stress.[17]

CONCLUSION

We conclude that HRV analysis brings to fore subtle yet important changes in the autonomic nervous system. Time domain analysis of HRV during induced acute mental stress in addition to resting HRV can be used as a simple yet powerful non-invasive tool for early diagnosis of cardiovascular autonomic neuropathy in asymptomatic Type 2 diabetic patients.

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