Research Article

Cardiovascular autonomic response in children with parental history of diabetes mellitus: A comparative study

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Abstract

Introduction: The autonomic nervous system regulates the electrical and contractile activity of myocardium via interplay of sympathetic and parasympathetic activity. Diabetes leads to development of cardiovascular & cerebrovascular diseases. Increased risk of mortality is strongly associated with the presence of cardiovascular autonomic neuropathy in individual with diabetes. **Aims and objectives:** To study and compare cardiovascular autonomic response in children of diabetic and non diabetic parents in the age group 18- 25 years **Material s and method:** The study procedure was carried out on healthy volunteer medical students of age group 18 to 25 years. They were first categorized into two groups, control (without parental history of diabetes mellitus) and subject (with parental history of diabetes mellitus) .The sample size was 70 in the control group and 70 in the subject group. All participants were examined after explaining the study procedure. The cardiovascular tests to measure cardiovascular autonomic response were performed. These tests were explained and demonstrated to the participants before performing on them. Tests Done for Assessing Parasympathetic Activity were Heart rate variation with breathing test, Valsalva ratio test and 30:15 ratio test. Tests Done For Assessing Sympathetic Activity were Blood pressure response to standing (Orthostasis) test, Hand grip test and QTc interval test. The mean and standard deviation (S D) was calculated for all the parameters. The data was entered using Microsoft Excel (2007). Statistical analysis was done using SPSS version 10.The statistical test used were (as per the requirement of the data). **Results:** Average age of 19.29 years in both the group, which was same and difference was not statistically significant ($p>0.05$). In control group 64.30% were males and 35.70% were females whereas in study group 57.10% were males and 42.30% were females. The mean resting pulse rate was 77.80 beats per minute among control group, which was comparable with 78.87 beats per minute among study group. The mean SBP among study group was 111.86 ± 7.61 mm of Hg, whereas among control group was 110.26 ± 7.92 mm of Hg. The mean DBP of study and control group was 75.66 ± 05.05 mm of Hg and 74.66 ± 04.32 mm of Hg respectively and difference observed in these groups was statistically not significant (>0.05). Out of the three tests done for assessing parasympathetic activity, mean valsalva ratio and mean 30:15 ratio showed statistically significant difference in study and control group whereas mean E/I ratio showed no statistically significant difference. While assessing sympathetic activity Orthostasis and Mean QTc interval test showed no statistically significant difference in study and control group whereas sustained handgrip test showed statistically significant difference in study and control group. **Conclusion:** Children of diabetic parents are more prone to cardiovascular autonomic neuropathy in future, compared with children of non diabetic parents. It may be part of a genetic syndrome rather than a secondary complication of diabetes.

Key Word: autonomic cardiovascular Function, diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common phenotype of hyperglycemia. It is a complex disorder that develops as a result of interplay between the genetics and environmental factors and prognosis may depend on the genetic load and relevant environmental exposure specific to each individual [1]. Prevalence of diabetes in India was

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31.7 million in 2000 & it is expected to increase to 79.4 million in 2030[2]. The autonomic nervous system regulates the electrical and contractile activity of myocardium via interplay of sympathetic and parasympathetic activity[3]. Sympathetic nerves of heart are derived from the upper thoracic 5 segments of the spinal cord. Parasympathetic nerves reach the heart via vagus. Both the sympathetic & parasympathetic nerves form the superficial and deep cardiac plexuses, the branches of which run along the coronary arteries to reach the myocardium. Diabetes leads to development of cardiovascular & cerebrovascular diseases[4]. Increased risk of mortality is strongly associated with the presence of cardiovascular autonomic neuropathy in individual with diabetes[5]. Diminished vagal tone is early manifestation of cardiovascular autonomic neuropathy in diabetes, which is shown by resting tachycardia and decreased beat to beat variation at rest and during deep breathing[6]. Many studies have identified autonomic neuropathy in patients with DM, so that health care providers who treat patients with diabetes can evaluate and treat the patient with cardiovascular autonomic neuropathy even if the patient is asymptomatic. It has been observed that type 2 DM has a strong genetic component. Risk of having diabetes increases in the individuals having parents with type 2 DM. Thus there could be possibility to inherit susceptibility genes for autonomic neuropathy. These genes could be expressed before or may be even without the subject developing diabetes. Different factors (including hyperglycemia) could subsequently affect the expression of genes and influence the progression of neuropathy. Thus the present study was conducted in the young healthy individuals with parental history of diabetes mellitus to study the cardiovascular autonomic response.

AIMS AND OBJECTIVES

To study and compare cardiovascular autonomic response in children of diabetic and non diabetic parents in the age group 18- 25 years.

MATERIALS AND METHOD

The study was carried out on volunteer medical students in the department of physiology in tertiary health care institute. After receiving the approval from the Committee for

Academic Research and Ethics (CARE), Medical students of age group 18 – 25 years fulfilling the inclusion criteria were included. For the purpose of study two groups were formed.

Group I (Study group): with parental history of diabetes mellitus

Group II (Control group): without parental history of diabetes mellitus.

Following inclusion and exclusion criteria was used to select the study subjects.

Inclusion criteria

- Students with parental history of diabetes mellitus
- General good health as determined by history and routine physical examination.
- Both males and females in the age group 18-25 years were included.
- Individuals who did not have any abnormal findings on his/her history and clinical examination and who did not complain of any symptoms were included.

Exclusion criteria

- Individuals suffering with diabetes mellitus, hypertension, known cardiovascular disease, or any other known endocrine or known systemic disorders.
- Individuals with acute illness such as respiratory tract infection, gastroenteritis.
- Individuals under any pharmacological treatment, drugs, hormones, alcohol ingestion.

Same inclusion and exclusion criteria were used for students without parental history of diabetes mellitus. Thus by using above mentioned inclusion and exclusion criteria total 70 subjects were selected for study and control group each. Proper consent was obtained from the volunteer individuals before the procedure. History taking, general examination and systemic examination were done before the procedure and the findings were entered in the prestructured profrorma. All the participants were asked to take rest for 10 minutes in supine position then pulse rate and blood pressure was measured by using standard protocol. Three readings were taken and the average of the three was taken as the resting pulse rate and blood pressure.

The cardiovascular tests to measure cardiovascular autonomic response were performed. These tests were explained and demonstrated to the participants before performing on them.

Tests Done For Assessing Parasympathetic Activity

1) Heart rate variation with breathing:
2) Valsalva ratio:
3) 30:15 ratio:

Tests Done For Assessing Sympathetic Activity

1) Blood pressure response to standing (Orthostasis):
2) Hand grip test:
3) QTc interval:

After performing the tests, the results were calculated by measuring the R-R intervals directly from the electrocardiogram record. Then the data was entered using Microsoft Excel (2007). Statistical analysis was done using SPSS version 10.

RESULTS

Table 1: Distribution according to Age, sex and cardiovascular parameter

Variable		Study group	Control group
Age		19.29 ± 1.49	19.29 ± 1.36
Sex	Male	40(57.1%)	45(64.3%)
	Female	30(42.3%)	25(35.7%)
mean resting pulse		78.87 ± 3.83	77.80 ± 4.20
Mean SBP		111.86 ±7.61	110.26 ±7.92
Mean DBP		75.66 ± 05.05	74.66 ± 04.32

It was observed that mean age of the participants was ranging from 18-24 years with average age of 19.29 years in both the group, which was same and difference was not statistically significant ($p>0.05$). In control group 64.30% were males and 35.70% were females whereas in study group 57.10% were males and 42.30% were females. The mean resting pulse rate was 77.80 beats per minute among control group, which was comparable with 78.87 beats per minute among study group and the difference was statistically insignificant ($p>0.05$). The mean SBP among study group was 111.86 ± 7.61 mm of Hg, whereas among control group was 110.26 ±7.92 mm of Hg and the difference was statistically not significant ($p> 0.05$). The mean DBP of study and control group was 75.66 ± 05.05 mm of Hg and 74.66 ± 04.32 mm of Hg respectively and difference observed in these groups was statistically not significant (>0.05).

Table 2: Distribution according to parasympathetic cardiovascular activity tests

	Study group	Control group	t value	P value	Significance
E:I ratio	1.50 ± 0.19	1.51 ± 0.15	0.3456	0.7302	Not significant
Valsalva Ratio	1.57 ± 0.13	1.64 ± 0.13	3.1856	0.0018	Significant
30:15 Ratio	1.08 ± 0.06	1.11 ± 0.05	3.2137	0.0016	Significant

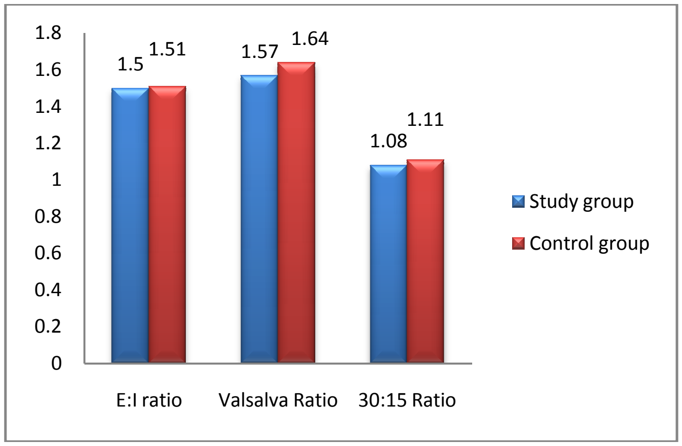

Figure 1: Parasympathetic cardiovascular activity tests

Mean E/I ratio among study group was 1.50 ± 0.19 whereas in control group was1.51 ± 0.15 and the difference was statistically not significant ($p >0.05$). It is evident from the table that, mean valsalva ratio was 1.57 ± 0.13 among the study group and 1.64 ± 0.13 among the control group. The mean valsalva ratio of study group was significantly lowered as compared to control group ($p<0.05$). The mean 30:15 ratio was 1.08 ± 0.06 among study group whereas 1.11 ± 0.05 among control group and ratio was significantly lowered in study group as compared to control group ($p<0.05$).

Table 3: Distribution according to Sympathetic cardiovascular activity tests

	Study group	Control group	t value	P value	Significance
Orthostasis	6.00 ± 2.75	6.37 ± 2.95	0.7676	0.444	Not significant
Sustained handgrip	15.01 ± 4.46	18.81 ± 5.08	4.7031	0.000	Significant
Mean QTc interval	0.38 ± 0.01	0.38 ± 0.02	0	1.0	Not significant

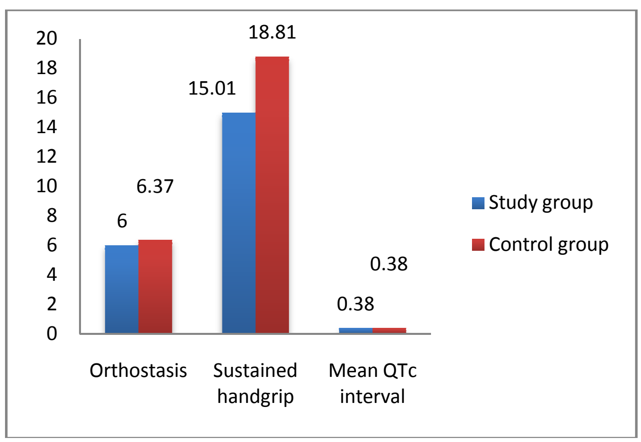

Figure 2: Sympathetic cardiovascular activity tests

Above statistical analysis reveals that to both the groups mean blood pressure response to standing (**Orthostasis**) was within normal range (10 mm of Hg). Mean blood pressure response to standing (orthostasis) was 6.00 ± 2.75 mm of Hg among study group whereas 6.37 ± 2.95 mm of Hg among control group and the difference was statistically not significant (p>0.05). It was observed that mean blood pressure in response to sustained handgrip was 15.01 ± 4.46 mm of Hg among study group whereas 18.81 ± 5.08 mm of Hg among control group. The difference in the mean blood pressure in response to sustained handgrip between both the groups was statistically significant (p<0.05). Mean QTc interval was 0.38 sec among both study and control group which was within normal range (0.35-0.43 sec). The difference in mean QTc interval between these groups was statistically not significant (p>0.05).

DISCUSSION

Diabetes mellitus is an important risk factor for development of cardiovascular autonomic neuropathy in individuals with diabetes which is presented by resting tachycardia and beat to beat variation even at rest. Against this background, present study was conducted to evaluate cardiovascular autonomic response in non diabetic offsprings of diabetic parents and to compare it with non diabetic offsprings of non diabetic parents. This was evaluated in total 140 participants, 70 control and 70 as study group. In the study participants in both control and study group were having same mean age (yrs.) i.e.19.29±1.36 and 19.26±1.49 respectively. Male participants were 64.3% in control group and 57.1% in study group. Female participants were 35.7% in control group and 42.3% in study group. The difference in these factors among the two groups was statistically not significant (P>0.05). Age and gender are the important factors influencing autonomic nervous system activity[7]. Thus the age and sex were matched in the present study to prevent the confounding effect. It is evident from the results that mean resting pulse rate, mean systolic blood pressure and mean diastolic blood pressure had no significant difference (p>0.05) between control and study group. Similar to our findings, previous studies also observed no significant difference in the cardiac autonomic modulation between first degree relatives of diabetic patients and control group in basal unstimulated condition [8,9,10,11]. It was seen that that E: I ratio in the study and control groups was within normal range (1.21). There was no significant statistical difference (p>0.05) found in the mean heart rate response to deep breathing in E: I ratio between study and control groups. Mean valsalva ratio was 1.57 ± 0.13 among the study group and 1.64 ± 0.13 among the control group. The mean valsalva ratio of study group was significantly lowered as compared to control group (p<0.05). Valsalva maneuver involves forced expiration through closed glottis. When forced expiration is started (phase I), blood pressure rises for a few beats along with decrease in heart rate (increase R-R interval), With continued strain (phase II) at 40mm Hg, pressure in the thorax is higher than the pressure in the great veins. As a result the venous return becomes very low. This leads to drop in the blood pressure. The drop in the pressure is sensed by the baroreceptors in the aortic arch and carotid sinus. The baroreceptor reflex is initiated leading to vagal withdrawal and sympathetic stimulation. As a result the heart rate increases (R-R interval decreases). The blood pressure keeps falling during the early phase II despite increase in the heart rate due to falling stroke volume. However, in the late phase II the blood pressure may show increase. On the release of the respiratory strain (phase III), the blood pressure drops suddenly for few beats and then rises again (phase IV). The rise in blood pressure is due to sudden increase in the venous return leading to overshoot above the baseline values. Due to baroreflex, this rise is associated with the decrease in heart rate (increase in the R-R interval). The changes in the blood pressure in phase I and phase III are purely mechanical events. Rise in heart rate during the phase II is mediated initially with vagal withdrawal and subsequently by increase in the sympathetic outflow. The decrease in the heart rate in response to overshoot in phase IV is mediated by baroreflex (vagal)[12,13]. The mean 30:15 ratio was 1.08 ± 0.06 among study group whereas 1.11 ± 0.05 among control group and ratio was significantly lowered in study group as compared to control group (p<0.05). During the change from lying to standing a characteristic immediate rapid increase in heart rate occurs which is maximal at about the 15th beat after standing. A relative overshoot bradycardia then occurs, maximal at about the 30th beat. This response is mediated by the vagus nerve[12,13]. Thus it can be said that the 30:15 ratio, a measure of cardiac parasympathetic activity is educed in subject group. Mean blood pressure response to standing (orthostasis) was 6.00 ± 2.75 mm of Hg among study group whereas 6.37 ± 2.95 mm of Hg among control group and the difference was statistically not significant (p>0.05). On standing peripheral pooling of the blood in the legs causes a fall in blood pressure, which is normally rapidly corrected by peripheral vasoconstriction. In the patients with autonomic dysfunction the blood pressure falls on standing and remains lower than in the lying position. A difference of systolic blood pressure (SBP) more than 30 mm Hg between the standing and lying position is considered positive for autonomic involvement[14]. Here, both groups showed normal responses to this test, also it is said that this test becomes abnormal only with severe autonomic dysfunction[15,16,17]. The mean blood pressure in response to sustained handgrip was 15.01 ± 4.46 mm of Hg among study group whereas 18.81 ± 5.08 mm of Hg among control group and the difference in the mean blood pressure in response to sustained handgrip between both the groups was statistically significant ($p<0.05$). During handgrip exercise test, sustained muscle contraction causes a sharp rise in blood pressure ≥16 mm of Hg. due to heart rate dependent increase in cardiac output with unchanged peripheral vascular resistance. In control group during sustained handgrip exercise, a mean rise in blood pressure was ≥16 mm Hg. However in the study group rise in blood pressure was found to be significantly reduced as compared to control group. Previous studies done on diabetic patients have shown reduced blood pressure response to sustained handgrip similar to present study findings [18,19,20]. No significant difference was found ($p>0.05$) in the mean QTc interval between control and subject group. In both the groups QTc interval was found to be within normal range. According to literature, QTc interval may be prolonged in conditions like Hypocalcaemia, Acute MI, Hypertrophic cardiomyopathy, Hypothermia, cerebral injury, advanced AV block, side effect of certain drugs like Quinidine, Procainamide, Tricyclic antidepressants and in certain congenital diseases like Jarvell- Lange Neilson syndrome etc[21]. Previous studies have also observed that there is an association between an abnormal QTc interval and sudden cardiac death in diabetic patients with severe autonomic neuropathy; it may be because of sympathetic imbalance, as left efferent cardiac sympathetic fibers influence QT interval [22,23,24,25,26]. But in present study as the participants were in general good health on examination and history taking, QTc interval in both the groups was found to be within normal range. Thus, it can be inferred that none of the autonomic function test shows abnormal response but the mean heart rate variation to Valsalva maneuver, 30:15 ratio and mean blood pressure response to handgrip exercise is significantly reduced in subject group with parental history of type2 DM compared with those in control group without parental diabetes. Findings of our study are comparable with the previous studies where they found a higher prevalence of cardiac autonomic neuropathy in the nondiabetic subjects with parental type2 diabetes compared with those without parental diabetes[9,27,28,29,30]. It is generally accepted that autonomic neuropathy is a consequence of long – term hyperglycemia [31,32]. Studies have shown that dysregulation of diabetes affects the progression of autonomic neuropathy in a negative way[33,34]. But in our study, long term hyperglycemia is not a plausible cause of autonomic neuropathy as subjects participated in the study were in good health on examination. The differences in mean values of the cardiovascular reflex tests between nondiabetic children with parental diabetes and control are significant even with two groups having same mean age. Our observations are supported by the previous studies, which indicate that subclinical autonomic neuropathy may develop without the presence of long term hyperglycemia in family members of type 2 diabetic subjects; thus, it is not simply a complication of the hyperglycemia in these subjects. An explanation could be that it is possible to inherit susceptibility genes for autonomic neuropathy, and that these genes could be expressed before or may be even without the subject developing diabetes. Different factors (including hyperglycemia) could subsequently affect the expression of genes and influence the progression of neuropathy [29].

CONCLUSION

Thus Findings of our study conclude that children of diabetic parents are more prone to cardiovascular autonomic neuropathy in future, compared with children of non diabetic parents. It may be part of a genetic syndrome rather than a secondary complication of diabetes. Thus it is necessary to evaluate autonomic function tests in each and every diabetic patient and also in their children for prevention, early detection and management of the cardiovascular autonomic neuropathy even if the individual is asymptomatic.

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