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RESEARCH ARTICLE

Frequency-domain analysis of heart rate variability during rest and stress in adolescents with parental history of diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is a polygenic disorder in which hereditary, environmental factors, lifestyle, and other factors play a role. Among this genetic factor plays a crucial role in that, risk of developing DM increases with a strong parental history almost up to 70%. **Aims and Objectives:** Evaluation of frequency domain analysis of Heart rate variability (HRV) during rest and stress in adolescents with a parental history of DM. **Materials and Methods:** A total of 150 adolescents were involved in the study. They were in three groups based on the parental history of DM; Group I - negative parental history (controls); Group II - one parent diabetic; and Group III - both parents diabetic. HRV analyzed by Kubios software. To induce stress, subjects were made to subtract digit by 7 under pressure. **Results:** During rest, there is a statistically significant reduction in frequency-domain parameters such as total power and high frequency (HF) (nu) ($P = 0.00$ and $P = 0.00$) demonstrating decrease in parasympathetic activity. Low frequency (LF) (nu) ($P = 0.00$) and Lebanon Humanitarian Fund ratio ($P = 0.00$) were increased demonstrating elevated sympathetic activity in adolescents of Group III when compared to Groups I and II. Subjects having both the parents diabetic show exaggerated response to acute stress in terms of significant reduction in total power ($P = 0.00$), HF (nu) ($P = 0.00$), and LF (ms^2) ($P = 0.00$) and a significant increase in LF (nu) ($P = 0.00$) and LF/HF ratio ($P = 0.00$). **Conclusion:** Reduced autonomic modulation was seen in adolescents having a strong parental history of DM. Even during rest, they showed sympathetic predominance and withdrawal of parasympathetic component. During stress, there is an exaggerated response seen in adolescents of both parents diabetic.

KEY WORDS: Heart Rate Variability; Time Domain Analysis; Diabetes Mellitus; Glucose Intolerance; Mental Stress

INTRODUCTION

The global prevalence of diabetes mellitus (DM), which is the most common metabolic disorder in all the age group, will be 4.4% by 2030.[1] Genetic component and environmental factors play a role in the development of DM. Population-based Framingham study shows that the risk of developing offspring diabetes is greater when both parents are diabetic and risk increases when mother is diabetic.[2] Twin-based population study demonstrates the role of genetic factor and non-genetic factors in the development of DM.[3] Role of various genes in the development of DM was established.[4]

The study shows that the development of DM is more in monozygotic twins when compared to dizygotics, also genetic component plays an important role in the development of type I DM (T1DM) than type II.[5] Development of T1DM is more in offspring's with positive sibling and parental

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history of DM.[6] Interaction between multiple genes and environmental factors might lead to the development of DM which is not clearly understood. The common disease-common variant hypothesis proposes that there can be multiple common genetic variants of small effect and also multiple rare variants of large effect.[7,8]

Diabetic cardiac autonomic neuropathy leads to defect in vascular dynamics with features such as orthostasis, postural hypotension, exercise intolerance, and increased incidence of silent myocardial infarction.[9,10]

Beat-to-beat variation in either heart rate or R-R interval is heart rate variability (HRV). It is a practical, non-invasive tool to investigate cardiac autonomic dysfunction and is an indicator of increased risk for cardiac mortality.[11] Reduced HRV with low-frequency (LF) power has strong association with sudden deaths in heart failure patient.[12] One of the complications seen in chronic diabetics with poor glycemic status is autonomic neuropathy.[13] Autonomic function tests such as deep breathing difference, lying-to-standing ratio, and Valsalva ratio were assessed in children with a parental history of diabetes (PHD) by Goel *et al.* which showed altered response in parasympathetic function tests even before they developed diabetes. These tests mainly assess vagal component of the autonomic activity. The study was not able to prove the sympathovagal balance.[14] Tarek *et al.* demonstrated sympathovagal imbalance in subjects with family history of T2DM which was explained by dyslipidemia.[15] None of the above study showed the effect of single parent or having both parent diabetics on autonomic balance in the offspring's. Hence, the following was conducted to assess the cardiac autonomic balance in children with PHD.

Mental stress might lead to work-related illness due to alteration in cardiac autonomic activity.[16] Research has shown increased risk of cardiovascular mortality in those who fail to cope up with stress.[17] As there is less work done to assess the response to stress in offspring's of DM, so one more objective of our study is to assess cardiac autonomic balance during acute mental stress in adolescents with a parental history of DM.

MATERIALS AND METHODS

The study was conducted in the Physiology Department, SDMCMS and H, Dharwad, from July to September 2017. Before starting study, the ethical clearance was obtained from the institutional ethical committee. HRV procedure was explained to all participants and written consent was taken. Based on PHD, participants were divided into three groups.

Group I: Controls (negative PHD), Group II: Positive PHD (single-parent diabetic), and Group III: Positive PHD (both parent diabetics).

Exclusion Criteria

Subjects with a history of smoking, those who are currently using medications which can alter autonomic functions, those who have parental H/O hypertension were excluded from the study.

Inclusion Criteria

Sample size was decided based on previous references. 50 subjects in each group (n = 50) (total n = 150) in the age group of 18–25 years participated who were randomly selected.

Study Design

Participants were instructed not to consume coffee, tea, or cola which can alter autonomic activity at least 12 h before the test. Participants attended physiology laboratory at 9 am after having a light breakfast and limited exertion. A standard pro forma was prepared on which sociodemographic details were taken.

HRV Measurement

Electrocardiography (ECG) data acquisition equipment (Niviqure Meditech Systems, Bengaluru, India) was used to collect the ECG data in lead II later HRV analyzed using Kubios software based on non-parametric method of fast Fourier transform. Frequency-domain values such as LF power, high-frequency (HF) power, and total spectral power were recorded. Mental stress was induced by arithmetic mental challenge in which participants were made to rapidly subtract 7 from a three- or four-digit number under time pressure and HRV recorded.

Statistical Analysis

SPSS software version 20 was used for analysis. Student's paired t-test was used to compare the data between rest and mental stress levels. ANOVA was used for intergroup analyses of variables.

RESULTS

The study involves 50 participants with positive PHD with one parent diabetic (n = 50), 50 participants with positive PHD having both parent diabetics (n = 50), and 50 healthy control participants without PHD (n = 50). HRV parameters at rest in participants with a parental history and without PHD are shown in Table 1 (n = 150). Total power (P = 0.00) and HF (nu) (P = 0.00) were significantly reduced and LF (nu) (P = 0.00) and LF/HF ratio (P = 0.00) were significantly increased in subjects with positive PHD in comparison to those without PHD. Frequency-domain HRV parameters during acute mental stress in subjects with and without PHD are shown in Table 2. Total power (P = 0.00), HF (nu) (P = 0.00), and LF (ms^2) (P = 0.00) were significantly reduced and a significant increase in LF (nu) (*P* = 0.00) and LF/HF ratio (*P* = 0.00) were found in subjects with positive PHD in comparison to those without PHD.

Frequency-domain HRV parameters during rest and stress in subjects with negative PHD are shown in Table 3 (*n* = 50). LF (ms^2) (*P* = 0.00) is significantly increased and HF (nu) (*P* = 0.01) is significantly reduced during stress when compared to rest. Frequency-domain HRV parameters during rest and stress in subjects with one parent diabetic are shown in Table 4 (*n* = 50). LF (ms^2) (*P* = 0.00) is significantly increased and HF (nu) (*P* = 0.01) is significantly reduced during stress when compared to rest.

HRV parameters during rest and stress in subjects with both parent diabetics are shown in Table 5 (*n* = 50). Total power (*P* = 0.041), HF (ms^2) (*P* = 0.00), and HF (nu) (*P* = 0.00) were significantly reduced and LF (ms^2) (*P* = 0.02), LF (nu) (*P* = 0.003), and LF/HF ratio (*P* = 0.00) significantly increased during stress when compared to rest.

DISCUSSION

This study assesses frequency-domain analysis of HRV during rest and stress in adolescents with a parental history of DM. Our study demonstrates reduced total power (ms^2) (*P* = 0.00) and HF nu (HF) (*P* = 0.00) during rest in adolescents of both the parent diabetics when compared to controls having negative PHD, which is statistically significant showing altered cardiac autonomic modulation during rest with reduced parasympathetic activity. The study also demonstrates elevated LF nu (LF) during rest in

Table 1: Frequency-domain HRV parameters recorded during rest in adolescents with and without a parental history of DM (*n*=150)

HRV parameters	Group I (*n*=50)	Group II (*n*=50)	Group III (*n*=50)	F value	*P* value
Total power (ms^2)	3714.94±101.39	3084.91±52.67	2139.96±94.78	2180.76	0.000*
LF (ms^2)	1035.32±24.14	1060.87±53.73	547.96±44.73	3.05	0.039*
LF (nu)	43.52±2.94	45.90±0.63	46.53±1.02	303.586	0.00*
HF (ms^2)	2086.28±75.12	1985.16±800.12	946.52±360.12	3.073	0.062
HF (nu)	56.54±4.44	53.83±5.11	53.03±0.52	232.65	0.00*
LF/HF ratio	0.76±0.18	0.858±0.01	0.877±0.02452	456.172	0.00*

*P<0.05: Statistically significant difference, Group I: Negative PHD, Group II: Positive PHD one parent DM, Group III: Positive PHD both parents DM, Values expressed as mean±SD. DM: Diabetes mellitus, HRV: Heart rate variability, PHD: Parental history of diabetes, LF: Low frequency, HF: High frequency, SD: Standard deviation

Table 2: Frequency-domain HRV parameter recorded during acute stress in adolescents with and without a parental history of DM (*n*=150)

HRV parameters	Group I (*n*=50)	Group II (*n*=50)	Group III (*n*=50)	F value	*P* value
Total power	3398.00±101.23	2868.15±194.42	965.54±116.91	3665.653	0.00*
LF (ms^2)	1310.35±75.59	1543.67±675.34	664.34±56.78	350.957	0.00*
LF (nu)	45.28±2.98	46.67±1.08	56.94±4.06	350.957	0.00*
HF (ms^2)	1593.43±94.23	987.34±563.98	275.56±12.11	2567.98	0.00*
HF (nu)	51.43±8.69	45.79±1.2	42.82±4.06	203.663	0.00*
LF/HF ratio	0.88±0.012	1.02±0.04	1.3419±0.16055	337.207	0.00*

**P<0.05: Statistically significant difference, Group I: Negative PHD, Group II: Positive PHD one parent DM, Group III: Positive PHD both parents DM, DM: Diabetes mellitus, HRV: Heart rate variability, PHD: Parental history of diabetes, LF: Low frequency, HF: High frequency

Table 3: Frequency-domain HRV parameters during rest and stress in adolescents with negative parental history of DM using paired *t*–test (*n*=50)

HRV parameters	Rest	Stress	*t* value	*P* value
Total power	3714.94±101.39	3398.00±101.23	0.263	0.609
LF (ms^2)	1035.32±24.14	1310.35±75.59	63.92	0.00*
LF (nu)	43.52±2.94	45.28±2.98	2.635	0.108
HF (ms^2)	2086.28±75.12	1593.43±94.23	0.530	0.468
HF (nu)	56.54±4.44	51.43±8.69	6.667	0.011*
LF/HF ratio	0.76±0.18	0.88±0.012	−27.66	0.062

*P<0.05: Statistically significant difference. DM: Diabetes mellitus, HRV: Heart rate variability, LF: Low frequency, HF: High frequency

Table 4: Frequency-domain HRV parameters during rest and stress in adolescents with one parent diabetic (*n*=50)

HRV parameters	Rest	Stress	*t* value	*P* value
Total power	3084.91±52.67	2868.15±194.42	7.609	0.000*
LF (ms²)	1060.87±53.73	1543.67±675.34	−27.66	0.062
LF (nu)	45.90±0.63	46.67±1.08	−4.35	0.02*
HF (ms²)	1985.16±800.12	987.34±563.98	2.635	0.108
HF (nu)	53.83±5.11	45.79±1.2	43.58	0.00*
LF/HF ratio	0.858±0.01	1.02±0.04	−26.78	0.000*

*$P<0.05$: Statistically significant difference. HRV: Heart rate variability, LF: Low frequency, HF: High frequency

Table 5: Frequency-domain HRV parameters during rest and stress in adolescents with both parent diabetics (*n*=50)

HRV parameters	Rest	Stress	*t* value	*P* value
Total power	2139.96±94.78	965.54±116.91	64.572	0.041*
LF (ms²)	547.96±44.73	664.34±56.78	−4.35	0.02*
LF (nu)	46.53±1.02	56.94±4.06	9.499	0.003*
HF (ms²)	946.52±360.12	275.56±12.11	7.609	0.00*
HF (nu)	53.03±0.52	42.82±4.06	17.609	0.000*
LF/HF ratio	0.877±0.02452	1.3419±0.16055	−20.211	0.000*

*$P<0.05$: Statistically significant difference. HRV: Heart rate variability, LF: Low frequency, HF: High frequency

adolescents of both the parent diabetics when compared to controls having negative PHD and also adolescents having single-parent diabetic, which is statistically significant showing increased sympathetic activity ($P = 0.00$).

The results are comparable to the study done by Tarek *et al.* who assessed frequency-domain HRV parameters in dyslipidemic adults with PHD which showed frequency-domain indices such as total power and HF (nu) were significantly ($P = 0.05$) decreased and LF (nu) and LF/HF ratio were significantly ($P = 0.05$) increased.[15] Goel compared the parasympathetic functions using deep breathing difference, immediate response to standing, and Valsalva ratio in adults whose parents are diabetics. Even though the study shows a decrease in parasympathetic function tests in adults with PHD, results were not statistically significant.[14] Tuppad studied parasympathetic function tests in subjects with a parental history of DM in relation to glycemic status. They found subclinical cardiac dysfunction in adults with PHD, which is not related to glycemic level.[18] Foss *et al*. also observed subjects with PHD showed reduced HRV in relation to altered diurnal variation of BP.[19] The possible mechanism behind parasympathetic dysfunction associated with increased cardiovascular morbidity is its association with insulin resistance and increased glucose production, leading to atherosclerosis.[14] Our study also demonstrates frequency-domain HRV parameters recorded during rest and acute stress in adolescents with parents having diabetes. Our study demonstrates that total power ($P = 0.00$) and HF (nu) ($P = 0.00$) are significantly reduced and LF (nu) ($P = 0.00$) is significantly elevated in subjects with positive PHD in comparison to those without PHD, which is statistically significant showing altered cardiac autonomic modulation, reduced parasympathetic activity, and also increased sympathetic activity which is augmented response to stress in offspring's having both parents diabetic. We compared the HRV parameters in all three groups during rest and stress. Our study shows that total power and HF (nu) are significantly reduced and LF nu is significantly increased during stress when compared to rest in both the adolescents with one parent and both parents diabetic, but augmented response was seen in them having both parents diabetic. In response to chronic stress, inadequate activation of stress system can lead to altered milieu interieur. After hypoglycemia, HRV recorded during rest and stress showed reduced baroreflex sensitivity and sympathetic activity.[20] Reduced HRV is seen in patients recovered from acute myocardial infarction due to increased sympathetic and reduced parasympathetic activity.[21] The above studies explain that reduced cardiac autonomic modulation is a better predictor of increased cardiovascular mortality.[22] Risk of developing CAN is also more in adolescents with a parental history of DM as they show altered HRV which can be due to elevated blood glucose levels, dyslipidemia, and obesity.[23]

Strength of Study

This is the first study to record the influence of parental DM on frequency-domain HRV parameters during acute stress.

Limitation of Study

Blood glucose levels of the adolescents with a parental history of DM were not estimated. The study can be further extended by assessing blood glucose levels and insulin resistance and correlating its value with the autonomic function tests.

CONCLUSION

Adolescents having a strong parental history of DM exhibit an altered cardiac autonomic modulation even before they develop the disease. They exhibit sympathetic overdrive and reduced parasympathetic activities during rest. They also exhibit an augmented response to acute mental stress when compared to those who have negative parental history of DM.

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